VOLUME 40 FEBRUARY 21, 1975 NUMBER 4 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

For years you've been using 'Baker Analyzed'® Reagents for their quality.

Now try Baker organics for their availability and delivery, too.

That's the "one-two" value package you'll get when you use Baker organics.

They're the "workhorse" line of organics you can rely on: intermediates, reagents for organic synthesis and analysis, solvents, biochemicals.

And if you're thinking about quality, think about the fact that if you ever received one defective bottle of J. T. Baker reagent, the record shows you'd have to live two lifetimes to have it happen again.

Baker organics are available two ways. Through a broad network of distributors, or from J. T. Baker direct. Either way, you're assured of fast and professional service.

Want additional information on Baker Analyzed® Reagents and organics? And a new packet of product grids listing popular organic intermediates? Just fill out and mail the coupon. We'll speed the information to you. J. T. Baker Chemical Co., Phillipsburg, N.J. 08865.

J. T. Baker Chemical Co., 222 Red School Lane
Phillipsburg, New Jersey 08865. Dept.: OCP

J.T.Baker®

- ☐ Send all available Baker organic intermediate grids.
- ☐ Send me your existing catalog listing Baker organic and inorganic chemicals.
- ☐ Put me on your mailing list for the 1975 Baker Laboratory Chemicals Catalog.
- ☐ Please send me an order form for Baker organics.

Name _____ Position _____

Company _____

Address _____

City _____ State _____ Zip _____

THE JOURNAL OF Organic Chemistry

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

BOOKS AND JOURNALS DIVISION

John K Crum *Director*

Virginia E. Stewart
Assistant to the Director

Charles R. Bertsch *Head, Editorial Processing Department*

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

Bacil Guiley *Head, Graphics and Production Department*

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

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

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

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

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

Business and Subscription Information

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

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

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

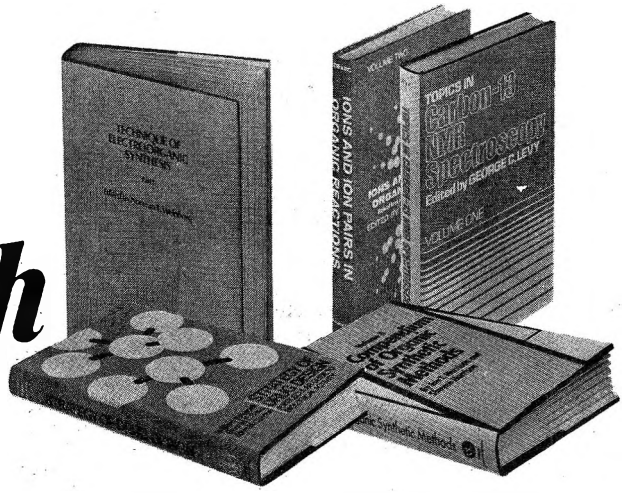
Subscription rates (hard copy or microfiche) in 1975: $20.00 to ACS members, $80.00 to nonmembers. Extra postage $6.00 in Canada and PUAS, $6.50 other foreign. Supplementary material (on microfiche only) available on subscription basis, 1975 rates: $15.00 in U.S., $19.00 in Canada and PUAS, $20.00 elsewhere.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

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

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

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

13 New Ways to Save Research Time!



1. IONS AND ION PAIRS IN ORGANIC REACTIONS: Roles of Ions and Ion Pairs in Chemical Reactions, Vol. 2.
Edited by Michael Szwarc, State University of New York, Syracuse

Reviews electron transfer, proton-transfer, electrophile substitution, and propagation of ionic polymerization—showing how chemical reactions are affected by the nature of ionic species, or by the state of their solvation and aggregations.

1974 566 pages $28.50

Vol. 1, Pairs in Organic Reactions, Available. $20.75

2. STRATEGY OF DRUG DESIGN: A Molecular Guide to Biological Activity.
By William P. Purcell and George E. Bass, both of the University of Tennessee Medical Units in Memphis, and John M. Clayton, National Center for Toxicological Research of the Food and Drug Administration

A convenient desk reference helping you apply mathematical models to the design of molecules with special biological properties. Especially useful to researchers with limited math backgrounds.

1973 193 pages $11.00

3. TECHNIQUES OF ELECTROORGANIC SYNTHESIS, Part 1.
Edited by Norman L. Weinberg. Volume 5 in the Wiley Techniques of Chemistry Series (A. Weissberger, Editor)

A ready-reference with extensive tables showing you the reaction pathways available to compounds, depending on the chemical and electrochemical variables. Also gives data on electrochemical cells, instrumentation, electrodes, solvents, and supporting electrolytes available for carrying out synthesis.

1974 917 pages $47.50

4. COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. 2.
By Ian T. Harrison and Shuyen Harrison, both of Syntex Research, Palo Alto, California

Up-dates volume 1, while expanding coverage to bi-functional compounds. Details the preparation of acetylenes, carboxylic acids, alcohols and phenols, amides, esters, olefins, disfunctional compounds, and much more! Ends tedious searches for synthetic methods.

1974 437 pages $13.95

Vol. 1, Compendium of Organic Synthetic Methods, Available. $15.95

5. TOPICS IN CARBON-13 NMR SPECTROSCOPY, Vol. 1.
Edited by George C. Levy, Florida State University

Volume 1 in a new series presenting all the latest Carbon-13 spectroscopy—including such previously unpublished materials as the first advanced treatment of the theory of ^{13}C chemical shifts and reaction mechanisms. Also contains new accounts of rapidly developing fields, among them the effects of substituents on ^{13}C chemical shifts, ^{13}C spin-lattice relaxation processes, problems and opportunities in ^{13}C nmr unique to synthetic high polymers, and the advantages and limitations of ^{13}C nmr spectroscopy using high-field spectrometers.

1974 294 pages $17.50

6. PROGRESS IN BIOORGANIC CHEMISTRY, Vol. 3.
Edited by E. T. Kaiser and F. J. Kezdy, both of the University of Chicago. A Volume in the Wiley Progress in Bioorganic Chemistry Series (E. T. Kaiser and F. J. Kezdy, Editors)

Helps you keep up with research in this burgeoning field by showing you current applications of spin labeling to structure-conformation studies of enzymes, "half-of-the-sites" reactivity and the role of subunit interactions in enzyme catalysis, and advances in the chemical modification and covalent structural analysis of proteins.

1974 274 pages $19.95

7. REAGENTS FOR ORGANIC SYNTHESIS, Vol. 4.
By Mary Fieser and Louis F. Fieser, both of Harvard University. A Volume in the Wiley Reagents for Organic Synthesis Series (M. Fieser and L. F. Fieser, Editors)

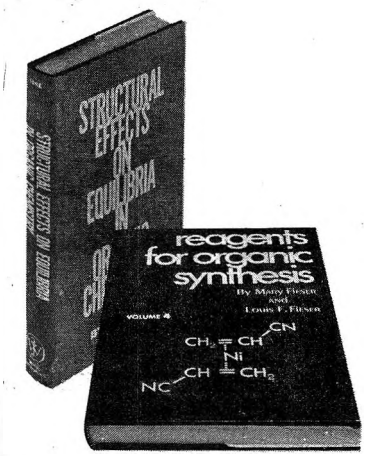
A new, fast reference to reagent literature published in 1970-1972, with some references to literature published in 1973. Here are references to 297 reagents reviewed by the Fiesers for the first time, as well as new references to 380 reagents previously published.

1974 660 pages $24.95

8. ORGANOMETALLIC REACTIONS, Vol. 5.
Edited by Ernest I. Becker, University of Massachusetts, and Minoru Tsutsui, Texas A & M University. A Volume in the Wiley Organometallic Reactions Series (Becker & M. Tsutsui, Editors)

Covers the synthesis and reactions of organothallium, bimetallic organometallic, unsaturated organaluminum, and compounds with carbon dioxide.

1975 448 pages (tent.) $39.95



Get all the latest research findings, experimental results—some never published before—in these 13 new books from Wiley.

And actually read and use any of these published books—FREE for 10 days. See the coupon below for details.

9. STRUCTURAL EFFECTS ON EQUILIBRIA IN ORGANIC CHEMISTRY.
By Jack Hine, Ohio State University

Announcing a new guide to help predict the structural effects on equilibria. Covers the Hammett and Taft equations, equilibrium in conformational and cis-trans isomerization, additions to and migrations of multiple bonds, ring and free radical formations, and more.

1975 352 pages (tent.) $17.50

10. ORGANIC REACTIONS, Vol. 22.
Edited by William G. Dauben, University of California, Berkeley. A Volume in the Wiley Organic Reactions Series (W. Dauben, Editor)

An up-to-the-minute reference work detailing the Claisen and Cope rearrangements, substitution reactions using organocopper reagents, and the Reformatsky Reaction.

1975 496 pages (tent.) $24.95

11. TECHNIQUE OF ELECTROORGANIC SYNTHESIS, Part 2.
Edited by Norman L. Weinberg. Volume 5 in the Wiley Techniques of Chemistry Series (A. Weissberger, Editor)

The companion volume to Part 1, with many "recipe-style" examples and an extensive compilation of oxidation and reduction potentials in aqueous and nonaqueous solutions. Topics include: electrochemical halogenation of organic compounds and oxidation and reduction potentials.

1975 1088 pages (tent.) $45.00

FORTHCOMING...

CARBENES, Vol. 2.
Edited by Robert A. Moss, Rutgers University, and Maitland Jones, Jr., Princeton University. A Volume in the Wiley Reactive Intermediates in Organic Chemistry Series (G. Olah, Editor)

A collection of definitive statements on the status of the field by Mackay, Hartzler, Seyferth, Closs, Trozzolo, Wasserman, Gaspar, and Hammond. Some topics include: unsaturated carbenes, spin states in carbene chemistry, applications of physical methods to the study of carbene reactions in solutions, and others.

1975 384 pages (tent.) $24.95

ORGANIC SYNTHESES VIA BORANES.
By Herbert C. Brown, with Gary W. Kramer, Alan B. Levy, and Mark Midland, all of Purdue University

How to work with hydroboration and organoborane chemistry from the man who orchestrated its discovery. Here are scores of procedures for hydroboration with borane and borane derivatives, organoborane conversions, carbon bond formation via organoboranes, as well as the latest laboratory operations with air-sensitive substances.

1974 320 pages (tent.) $17.50

Wiley-Interscience
Dept. 549
Post Office Box 4569
Grand Central Station
New York, N.Y. 10017

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

1a. ☐ IONS AND ION PAIRS IN ORGANIC REACTIONS, Vol. 2, (0-471-84308-3), $28.50
1b. ☐ IONS AND ION PAIRS IN ORGANIC REACTIONS, Vol. 1, (0-471-84307-5), $20.75
2. ☐ STRATEGY OF DRUG DESIGN, (0-471-70236-6), $11.00
3. ☐ TECHNIQUES OF ELECTROORGANIC SYNTHESIS, (0-471-93271-X), $47.50
4a. ☐ COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. 2, (0-471-35551-8), $13.95
4b. ☐ COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. 1, (0-471-35550-X), $15.95
5. ☐ TOPICS IN CARBON-13 NMR SPECTROSCOPY, (0-471-53154-5), $17.50
6. ☐ PROGRESS IN BIOORGANIC CHEMISTRY, (0-471-45487-7), $19.95
7. ☐ REAGENTS FOR ORGANIC SYNTHESIS, Vol. 4, (0-471-25881-4), $24.95
8. ☐ ORGANOMETALLIC REACTIONS, Vol. 5, (0-471-06146-8), $39.95
9. ☐ STRUCTURAL EFFECTS ON EQUILIBRIA IN ORGANIC CHEMISTRY, (0-471-40035-1), $17.50
10. ☐ ORGANIC REACTIONS, Vol. 22, (0-471-19623-1), $24.95
11. ☐ TECHNIQUE OF ELECTROORGANIC SYNTHESIS, Part 2, (0-471-93272-8), $45.00

☐ My check (money order) for $_____ is enclosed.
☐ Please bill me. (Restricted to the continental United States.)
☐ Please send me a list of local bookstores carrying your titles.

Name _____
Address _____
City State Zip

Please add state and local taxes where applicable.
Prices subject to change without notice.
A 4909-WI

JOCEAH 40 (4) 393-544 (1975)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 4 FEBRUARY 21, 1975

NOTES

COMMUNICATIONS

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

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

AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 4

FEBRUARY 21, 1975

Mechanism of the Acyloin Condensation

Jordan J. Bloomfield* and Dennis C. Owsley*

Corporate Research Department, Monsanto Company, St. Louis, Missouri 63166

C. Ainsworth and R. E. Robertson

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

Received August 1, 1974

Anomalous results found in the acyloin condensation do not fit into the currently acceptable mechanistic schemes for this reaction. A new mechanism is proposed for the acyloin condensation that does not involve α-diketones as intermediates. This mechanism satisfactorily accounts for the wide variety of reaction products obtained in acyloin condensations conducted under different conditions.

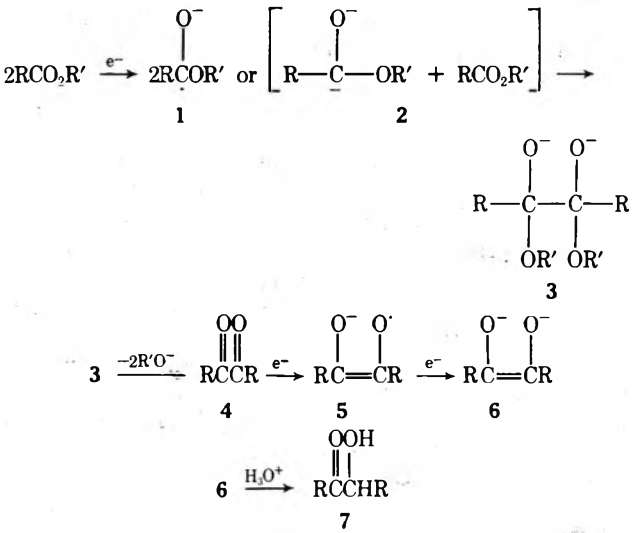
The acyloin condensation is a particularly valuable synthetic tool in the construction of large rings[1a-g] and in the manufacture of perfumes.[1h] A thorough review of the literature concerning the acyloin condensation as a cyclization method was published in 1964.[2] More recently, Rühlmann has reviewed much of the work on the acyloin condensation conducted in the presence of trimethylchlorosilane.[3] During the preparation of an article on the acyloin condensation,[4] a number of anomalous results were found which were not explained by the published mechanistic schemes for the reaction.[1a,2,5-7] The mechanism(s) for any reaction should account for all reported results but, in the case of the acyloin condensation, the anomalous results have not been fitted into a coherent mechanistic scheme. This paper presents some conclusions as to the mechanism of the acyloin condensation in order to stimulate thought and experimentation on this reaction. We are presently unable to carry out any further work toward this end.

Currently Accepted Mechanistic Schemes

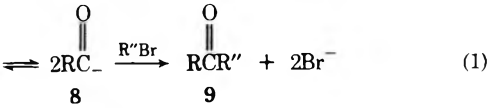
The currently accepted mechanism for the acyloin condensation involves production of the dianion **3** either (a) by coupling of two initially formed radical anions **1**[1a,2,5] or (b) by two-electron reduction of an ester to a dianion **2** followed by its addition to a second molecule of ester (Scheme I). The diketone **4** has been presumed to be an intermediate produced by loss of alkoxide from **3**. Subsequent two-electron reduction produces the acyloin enediolate **6** *via* the semidione **5**.[8] Neutralization of **6** gives the free acyloin **7**. The overall process requires two electrons for each molecule of ester reduced.

For simplicity in presentation e^- is used as the indicated reductant in the mechanistic schemata. The metal employed certainly has some effect on the course of the reduction, partly through differences in ease of electron release to the ester and partly through differences in stability of intermediate salts and their degree of association. At present, however, there are no experimental data available on the latter effect and only inferences may be made about the former effect (*vide infra*).

Scheme I

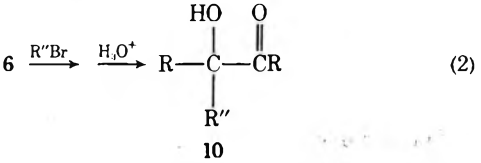


Alkylation experiments on several acyloin reaction mixtures in liquid ammonia produced ketone derivatives of the starting esters.[7] This result caused speculation that the enediolate **6** was in equilibrium with an acyl anion **8** (eq 1).



(1)

Despite the fact that others have obtained **10**, the normal product of simple enolate alkylation (eq 2),[9] the acyl anion



(2)

(or an alkoxide adduct of it), has been uncritically accepted by authors of reference works.[10] Furthermore, other experi-

mental work suggests that compounds of structure **10** may have decomposed under the drastic work-up conditions in use at that time,[7] which included base extractions in air and atmospheric pressure distillation.[11] Moreover, although no data are available to substantiate or disprove it, entropy considerations in an equilibrium between **6** and **8** in acyloin condensations of *diesters* should ultimately lead to polymer and not to the cyclic products which are observed.

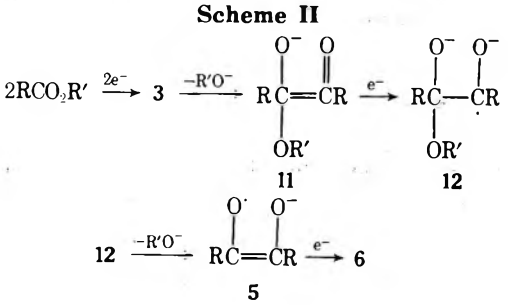
Evidence against the Mechanism of Scheme I

Perhaps the most compelling evidence against this mechanism is found in the reduction of esters in the presence of trimethylchlorosilane. Trimethylchlorosilane is an excellent trap for any alkoxides formed in the reaction. Although no kinetic data are available from the literature on the rate of reaction of Me_3SiCl with alkoxides, a second-order rate constant of 10^2–10^4 l. mol^{-1} sec^{-1} can be estimated for the rate of its reaction with alkoxide.[12] If intermediate **3** of Scheme I has any lifetime, it should be trapped when the acyloin condensation is conducted in the presence of Me_3SiCl. This has not been observed and therefore it is unlikely that **3** is an intermediate.

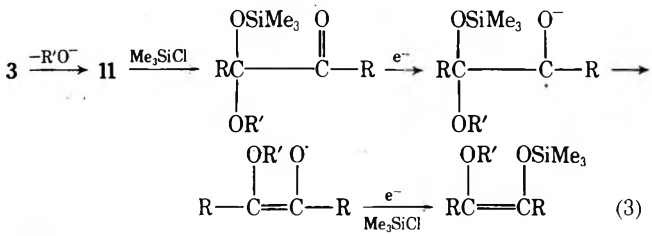
Furthermore, diketone **4** is excluded by the following experimental data. (1) Diketones are not found when oxygen is carefully excluded from reaction mixtures and work-up procedures.[3] (2) Diketones are reduced by sodium in the presence of Me_3SiCl to give mixtures which contain silylated **6** as only one of many products,[3,15] although α-diketones having no enolizable hydrogens reduce normally.[16a] Some diketones are not reduced at all in the absence of Me_3SiCl.[17] (3) Reduction of a mixture of methyl pivalate (1 mol) and di-*tert*-butyl diketone (1 mol) with 2 g-atoms of sodium (enough to reduce all the ester or all the dione but not both) in the presence of Me_3SiCl gave only trimethylsilylated enediolate and diketone with no recovered ester.[16] Reduction of methyl pivalate (1 mol) with 1 g-atom of sodium (enough to reduce only half the ester all the way or all of it to dione) gave recovered ester and silylated enediolate as the only products.[16] These two experiments should show the relative rates of reduction of ester and diketone if diketone were truly an intermediate. If diketone reduced faster or at the same rate as ester, then unreacted ester should have been found in the first experiment; or, alternatively, if ester is reduced faster than diketone, then diketone should have been found in the second experiment. These data strongly suggest that diketones **4** are not intermediates in the acyloin condensation.

An alternative mechanism to that of Scheme I is shown in Scheme II. Scheme II involves no diketone intermediates but assumes stepwise loss of alkoxide from **3**.

Scheme II



This scheme can also be ruled out on the basis of experiments conducted in the presence of Me_3SiCl. If dialkoxy intermediate **3** is not trapped by Me_3SiCl, then **11** should be trapped because it also is a molecule that should have some stability. However, because trimethylsilanol is a stronger acid[18] than either methanol or ethanol (and trimethylsilyl oxide is therefore likely to be a better leaving group), at least some of the final product should have the structure shown in eq 3.



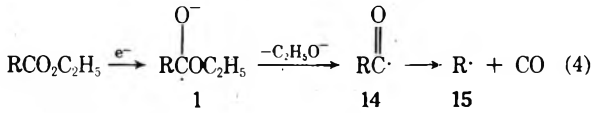
(3)

All data that have been found to date on reductions of esters point to the conclusion that the acyloin condensation mechanism does not involve the formation of dialkoxy derivative **3** and diketone **4** and therefore *must not involve the dimerization of two initially formed radical anions or the addition of an ester dianion to a second mole of ester.* Moreover, the schemes presented above do not account for reductions in liquid ammonia[7,19–22] and in hydrocarbon solvents[23–25] where acids, alcohols, and other anomalous products are found. (References 7 and 19–25 are only a few representative examples.)

Initial Radical Nature of the Reaction

That the initial step in the acyloin condensation involves the addition of one electron to the ester forming the radical anion **1** does not seem arguable. What subsequently occurs may still be open to considerable debate.

Evidence which supported the initial radical nature of the reaction was obtained from reductions in which an initially formed radical anion could decompose to carbon monoxide, alkoxide, and a resonance-stabilized tertiary radical.[26] Reduction of the esters $RCO_2C_2H_5$ [R = 1-phenylcyclopentyl, 1-phenylcyclohexyl, and 2,3,4-trimethyl-3-pentenyl] produced acyloin, RH, RR, and RCOR. The sequence of reactions suggested to account for these results was



(4)

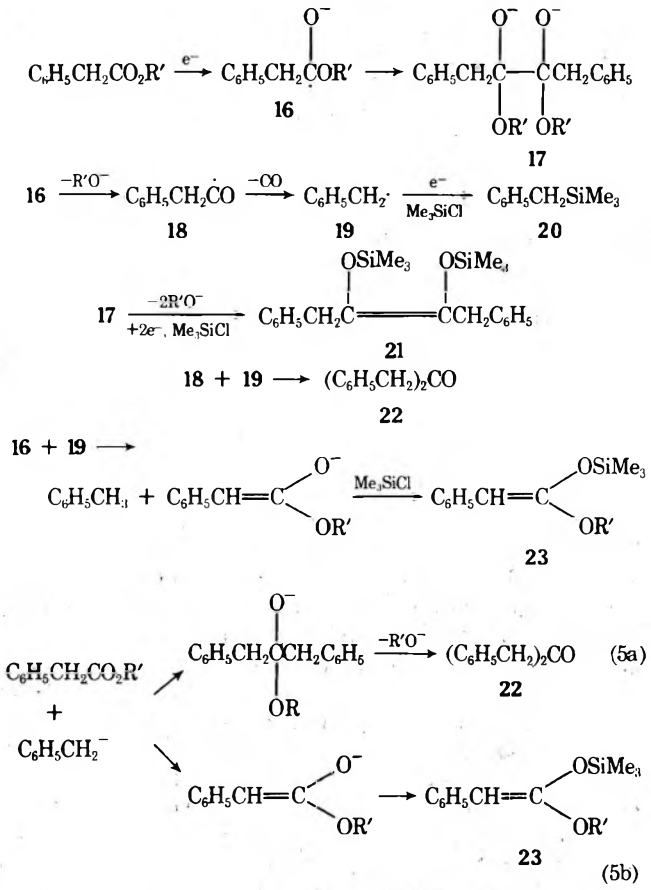
The radical **15** was presumed to dimerize to form R–R, react with **14** to produce ketone, or abstract a hydrogen atom from solvent to produce RH. The acyloin was supposed to be formed by dimerization of **1** or **14** followed by reduction.

Recently, the reduction of phenylacetic esters in the presence of Me_3SiCl was also explained in terms of free radical intermediates (Scheme III).[3] Bibenzyl, which is found in reactions involving benzyl radicals, is surprisingly absent from the reaction mixture. This suggests that the benzyl radical might not be present at all. This point is discussed in more detail below.

Compound **23**, the silylated derivative of the original ester was also isolated. It was suggested that this product was formed by hydrogen atom abstraction from **16** to give the enolate corresponding to **23** which was rapidly silylated.

An alternative explanation involving benzyl anions could explain all the results of Scheme III. Benzyl anion could attack starting ester at carbonyl to produce ketone, or it could abstract a proton to give enolate of starting ester (eq 5). A pathway by which benzyl anions can form is discussed below.

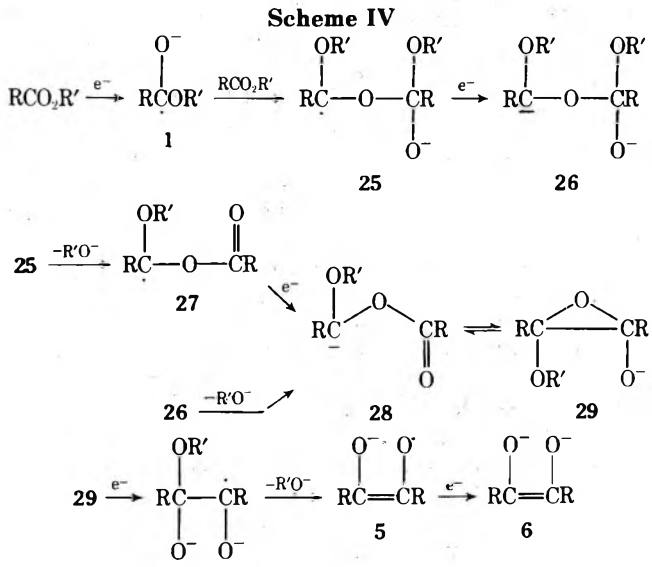
Scheme III



Unified Acyloin Condensation Mechanism

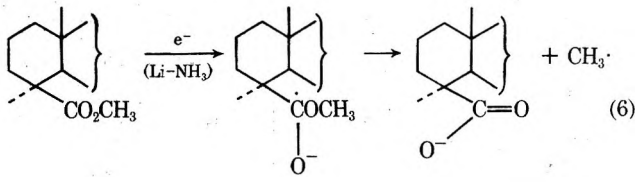
Scheme IV describes an alternative to the currently accepted acyloin condensation mechanism. This section will describe precedents for the formation and fate of each intermediate and will attempt to show how the sequence can be interrupted at many points to give the anomalous products which have been found. Next, the outlines of Scheme IV will be used to describe the products of the reduction of dimethyl dimethylmalonate[22] in which a large number of anomalous products are found. Finally, two cases will be described which are difficult to explain by any mechanism at all. Note that the proposed mechanism of Scheme IV involves no ketone (either mono- or di-) and involves discrete steps in which one electron is added at each juncture.

Scheme IV

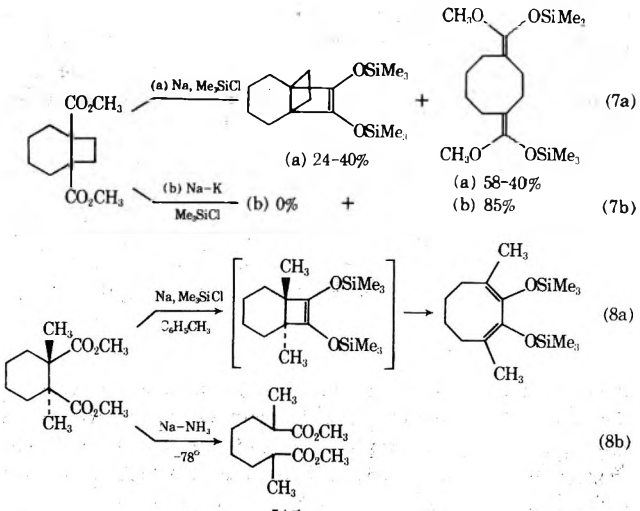


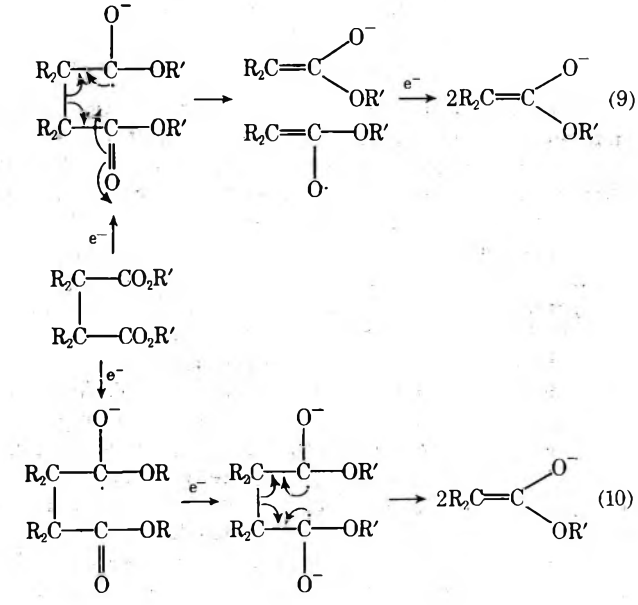
(I) The Initially Formed Radical Anion (1). The initially formed radical anion can have three possible fates: (1) addition to a second molecule of ester to give the first oxy-bridged intermediate **25** (see below), (2) β scission to produce a carboxylate anion and an alkyl radical, and (3) in the case of substituted succinic esters, fragmentation to produce (finally) two enolate anions.

The β scission reaction takes place with esters which are so hindered that they are not hydrolyzed by base. Thus, reaction 6 probably occurs.[19] Note that in this case, the ester is so highly hindered that approach of a second ester to form the oxy-bridged intermediate **25** cannot readily occur.



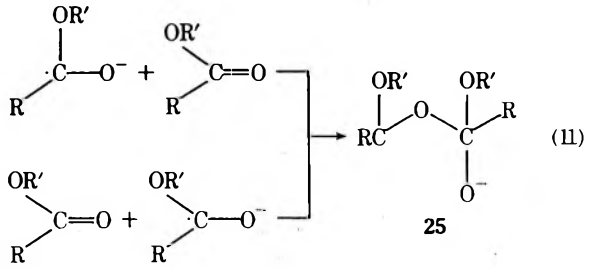
The fragmentation reaction of succinic esters is exemplified by two cases: eq 7[27] and 8.[28a] Three factors seem to facilitate fragmentation: (1) exceptional strain in the potential cyclic product, (2) increased reducing power of the metal–medium, and (3) in liquid ammonia, solvation of the initially formed radical anion. This means that there are at least two alternate pathways that can occur *before* closure





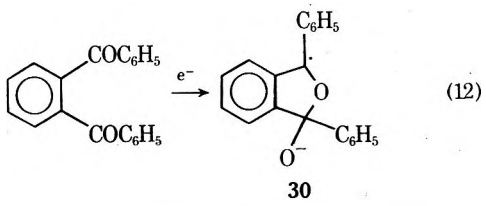
to the oxy-bridged radical anion **25** (eq 9, 10). It is quite possible that fragmentations of succinic esters in liquid ammonia[28] involve an apparent two-electron reduction of the diester by a very fast addition of a second electron to the initially formed radical anion (eq 10). The timing of the addition is the most important step in the acyloin condensation mechanism (*vide infra*).

(II) Oxy-Bridged Radical Anion 25. The oxy-bridged radical anion **25** can be formed either by attack of the oxygen of an ester radical anion on carbonyl carbon of an unreduced ester or by attack of the carbon of the radical anion on carbonyl oxygen of unreduced ester (eq 11). The first



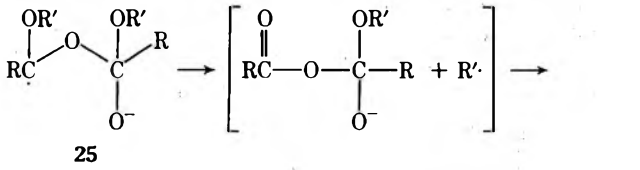
(11)

mode of attack needs no further comment while the second is found in trialkyltin hydride reductions of acid chlorides and ketones.[29] In addition, the esr spectrum of the oxy-bridged radical anion **30** has been recently observed (eq 12).[30]



(12)

Oxy-bridged radical anion **25** could have three fates: (1) β scission and decomposition to produce ester, carboxylate anion, and a radical (eq 13), (2) addition of a second electron to form dianion **26**, and (3) loss of alkoxide to form radical **27**. The β scission and fragmentation reaction may have been observed in the case of some benzoic esters of alcohols such as benzyl, allyl, cinnamyl, etc.[25] (*vide infra*).

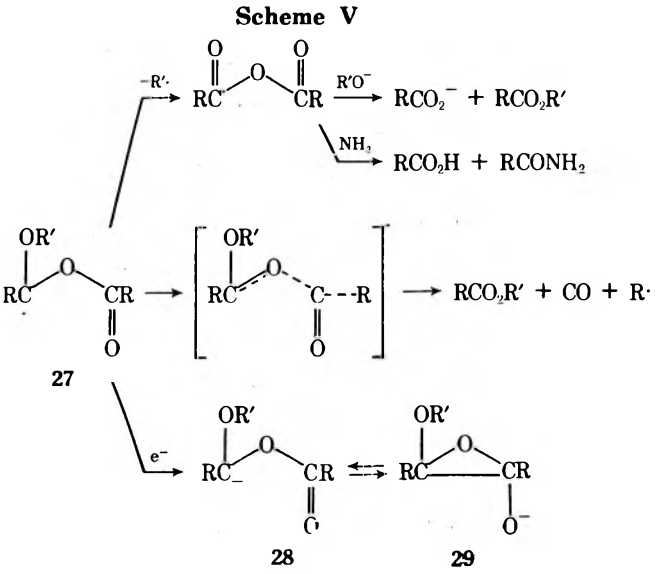


$$RCO_2^- + RCO_2R' + R'\cdot \quad (13)$$

(III) Radical 27. Discussion of the formation and fate of dianion **26** will be passed over for the moment and instead the fate of radical **27** will be discussed because it is here that an earlier point concerning the timing of the addition of the second electron becomes very important. The various fates of radical **27** are summarized in Scheme V.

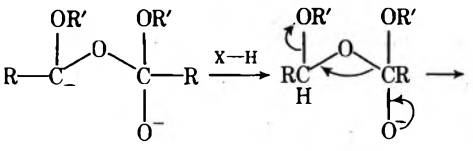
Scheme V offers another pathway for formation of acids in hydrocarbon solvents. Such a reaction was noted in the reduction of benzoic esters using large particle size sodium.[25] This result was quite puzzling until a simple calculation was carried out on surface area per unit volume for sodium particles of 1-mm and 1-μ particle size. Comparison of these two surfaces showed that the 1-μ particle size sodium had a surface area 10^3 times greater than that of the 1-mm particle size sodium. This means that in a given unit volume, the ratio of molecules of unreacted ester to available sodium atoms in the large particle size case is 10^3 times greater than in the small particle size case. This indicates that there is a greater chance of electron release to the ester (giving **25** or **27**) with the large particle size sodium. Once one electron is released to the ester, giving one molecule of **25** or **27**, the situation is now reversed, for the ratio of available sodium atoms to **25** or **27** molecules is now 10^3 times greater with the small particle size sodium than with the large particle size sodium. This means that the second one-electron reduction to **26** or **27** is more favorable in the small particle size case. These calculations suggest that *the most important step in the acyloin condensation mechanism is the timing of the transfer of the second electron to the substrate and that this step determines to a great extent what course the reaction will take.* This timing is a function of both the reducing power of the metal–medium and the various steric and electronic factors in the substrate.

Scheme V



For reactions conducted in liquid ammonia Scheme V offers one pathway for the formation of amides.[7] Scheme V also provides a pathway for the formation of radicals in the reduction of those esters where resonance-stabilized tertiary radicals can be formed.[26] We believe that Scheme V better accounts for the radical products (R–R and R–H) found than the α elimination previously proposed[26] (see eq 4).

(IV) Dianion 26. Dianion **26** has two possible pathways for decomposition: (1) loss of alkoxide to give oxy-bridged anion **28** and (2) in ammonia or at high concentrations of starting ester,[24] protonation and fragmentation to aldehyde and ester (eq 14). Further reduction of the aldehyde would

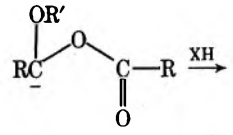


$$RCHO + RO^- + RCO_2R' \quad (14)$$

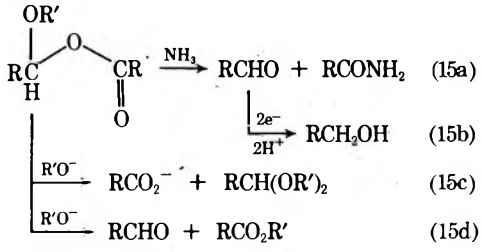
lead to alcohol if sufficient reducing agent were present. This reaction would take place in a situation where R is very sterically crowded and thus cannot go further to **28** $\rightleftarrows$ **29**, because the bonding distance cannot be attained. This is, in fact, the result obtained in the reduction of methyl mesitoate by lithium in liquid ammonia.[19]

(V) Oxy-Bridged Anion 28. The entire concept of an oxy-bridged anion is hoary. It was first suggested by Favorsky[31] as providing possible intermediates for the Cannizzaro reaction, benzilic acid rearrangement, and acyloin rearrangement, as well as the reaction that now bears his name.

In ammonia, protonation of **28** could occur, leading to amide, alcohol, and even aldehyde if insufficient reducing agent were present (eq 15).[7,20,22]

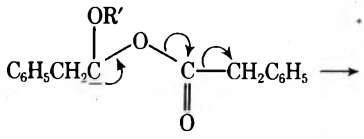


28

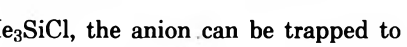


(15a) (15b) (15c) (15d)

Further examination of transformations of **28** shows that it can account for the reduction products of phenylacetic esters[3] in a way that explains the absence of bibenzyl but without invoking free radicals other than as transient radical-anion intermediates (eq 16). Thus, **28′** can fragment, producing a resonance-stabilized anion and starting ester.



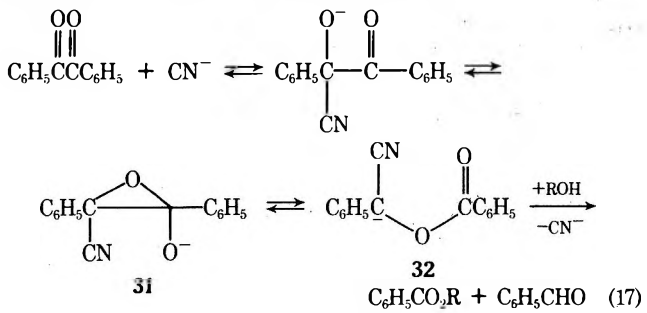
28′



(16)

In the presence of Me_3SiCl, the anion can be trapped to produce benzyltrimethylsilane (**20**) or it can attack the starting ester (perhaps in a "cage" reaction). Attack at carbonyl would produce dibenzyl ketone (**22**) while attack at the benzylic hydrogen would produce enolate of the starting ester which is subsequently silylated to give **23.** No bibenzyl is predicted by this scheme. A similar fragmentation pathway in the reactions involving tertiary benzylic or allylic compounds[26] also produces resonance-stabilized anions which account for all products except dimer hydrocarbons.

The steps involving the conversion of **28** to **29** parallel very closely, in reverse, the pathways suggested for cleavage of benzils by cyanide ion (eq 17)[32] or by methylsulfinyl carbanion.[33] The anion **31** is comparable to **29** while **32** is

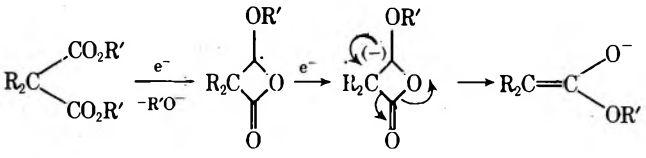


31 **32**

(17)

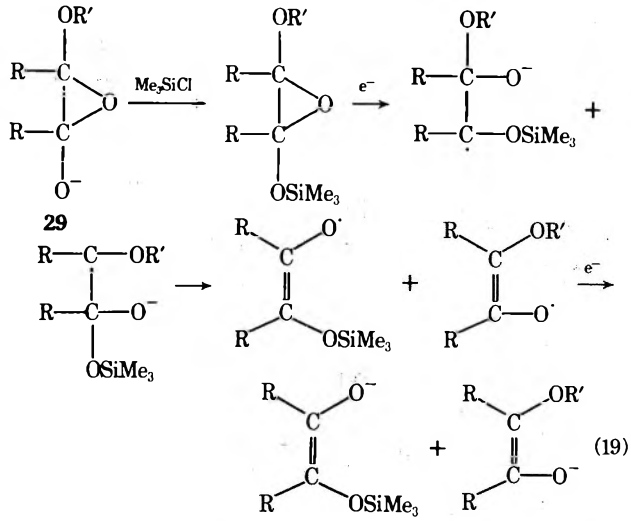
comparable to **28.** Furthermore, an intermediate very much like **29** was proposed to account for products from the peracid oxidation of β-diketones.[34] A very similar structure is also found in the hydrate of 1,2-cyclohexanedione which is formulated as a dihydroxyepoxycyclohexane.[35]

Malonic esters undergo a reaction in which the elements of carbon monoxide and alkoxide are lost to give the substituted acetic ester (eq 18).[22,36] Note that the closure of **28″** to the epoxide derivative would produce a 2-oxabicyclo[1.1.0]butane. An alternate pathway open to **28″** is expulsion of carbon monoxide and formation of ester enolate, which is the result observed in hydrocarbon solvents at room temperature and above. This result fits with the previously stated concept that most of the anomalous products of the acyloin condensation can be explained most readily as results of anionic reactions.



28″ (18)

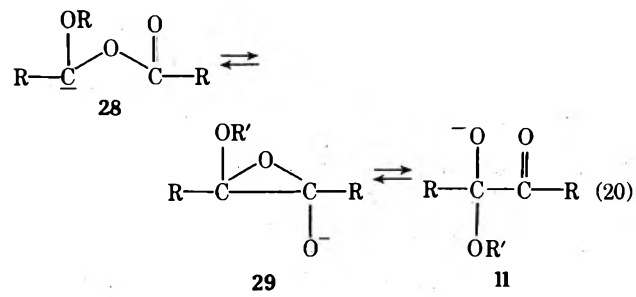
(VI) Epoxide 29. The formation of epoxy intermediate **29** was just discussed. The reduction of epoxides by alkali metals in both hydrocarbon solvents and liquid ammonia has been carefully investigated.[37] Thus conversion of **29** to semidione **5** and subsequent reduction to endiolate **6** is easily understood. However, if Me_3SiCl is present, **29** should have sufficient lifetime to be silylated before reduction to a silylated semidione. Silylated **29** is a nearly symmetrical intermediate and reduction could occur in either of two directions (eq 19). No mixed silylated–alkylated enediolates



29 (19)

are found. The ring opening of silylated **29** in one direction only may be rationalized in the following way. Comparison of *tert*-butyl methyl ether with trimethylsilyl methyl ether by nmr shows that the oxygen of the trimethylsilyl methyl ether is more electronegative than that in *tert*-butyl methyl ether.[38] The reason for this is participation of the vacant silicon d orbitals in delocalizing the lone pairs on oxygen to a certain extent. Thus, inductively, the carbon next to the silyloxy group in silylated **29** can more readily accept an electron than the carbon next to the alkoxy group.

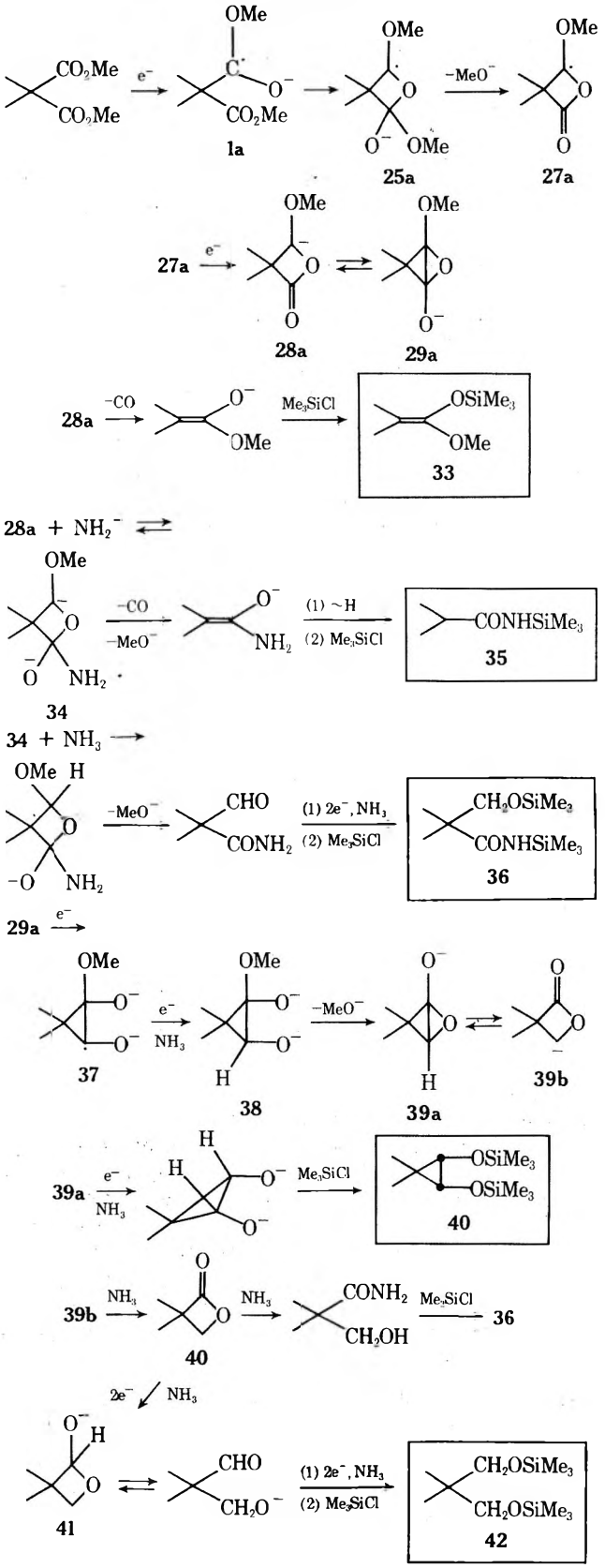
One other intermediate could be involved in the equilibrium **28** ⇌ **29** of Scheme IV. This is intermediate **11** of Scheme II (eq 20). For the reasons stated previously under Scheme II it is felt that **11** is not involved in the acyloin condensation mechanism because no mixed silyloxy-alkoxy alkenes are found when the reaction is conducted in the presence of Me_3SiCl.



28 **29** **11**

(20)

Scheme VI



One final piece of evidence is now offered which strongly implies that the mechanism for the acyloin condensation is not the "classical" one of Scheme I. Figure 1A is a plot of yield vs. ring size for the acyloin condensation, the Dieckmann condensation, and the Thorpe–Ziegler condensation.[39] Note that the rapid drop in yield for the acyloin condensation falls at the eight-membered ring while in both the Dieckmann and the Thorpe–Ziegler reactions, the drop is at the nine-membered ring. Entropy considerations should govern the formation of a given size ring, no matter how it was formed. Figure IB is a plot of the size of the first formed intermediate vs. yield for all three condensation reactions. Note that in the "unified" mechanism discussed above, the oxy-bridged intermediates are one member larger than the ring size of the final product. The plots of intermediate size vs. yield correspond well for all three cases.

Reduction of Dimethyl Dimethylmalonate

The variety of products issuing from the reduction of dimethyl dimethylmalonate by sodium in liquid ammonia[22] offers an example in which the generality of the "unified" acyloin mechanism can explain all products. Scheme VI gives pathways to these products in terms of intermediates **25**–**29** of Scheme IV. In these reactions, Me_3SiCl was added at the end of the reduction to facilitate isolation of the products.[22]

Table I is a compilation of the yields of the various products as the reaction conditions were changed. Examination of this table shows that there are probably two independent groups of products. The yields of **40** and **42** are nearly independent of all changes in conditions, while those of **33**, **35**, and **36** change as the temperature is lowered from −34 to −78°. Note also that at −34° the total yield of **33**, **35**, and **36** is 56% while at −78° the yield of **33** is 57% and **35** and **36** completely disappear. This suggests that **33**, **35**, and **36** arise from a common intermediate.

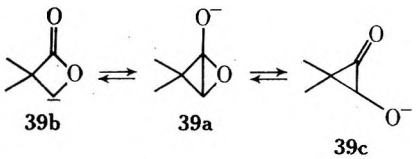
Scheme VI is consistent with this view. Compound **33** is formed by fragmentation of intermediate **28a**, as shown in eq 18. Compounds **35** and **36** are formed from **34**, an ammonolysis product of **28a**. If dianion **34** decomposes with loss of carbon monoxide and methoxide, the precursor to **35** is formed. On the other hand, if **34** is protonated before decomposition, then a pathway to **36** is now opened. The disappearance of **35** and **36** as the temperature is lowered suggests that the ammonolysis of **28a** (to **34**) is much slower at −78° and that at −78° **28a** can fragment or be reduced further. This is consistent with the expectation of a lower activation energy for fragmentation or reduction of **28a** than for its ammonolysis.

The independence of the yield of **40** and **42** from all changes in conditions also suggests a common precursor, intermediate **39**. Intermediate **39** is formed in preference to a cyclopropene semidione. Instead, **37** undergoes further reduction and protonation to give **39a** ⇄ **39b**. Reduction of **39a** to the *cis*-cyclopropanediolate precursor of **40** is easily explained in terms of the known metal–amine reduction of epoxides which proceeds with inversion of configuration at carbon.[37b,c]

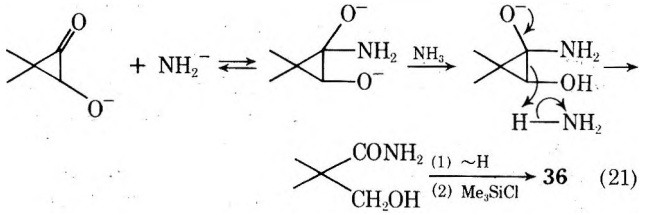
The pathway from **39b** to the silylated diol **42** involves the cyclic hemiacetal **41**, produced by reduction of 2,2-dimethylpropiolactone (**40**). The suggestion of the hemiacetal **41** is particularly plausible because a cyclic hemiacetal *has been* identified among the products of an acyloin condensation conducted in liquid ammonia.[20] Diols have also been found in other acyloin condensations.[23,24]

Ammonolysis of **40** could also produce the amide alcohol **36**. However, if this were the major pathway to **36**, then a concomitant rise in the yield of **42** should be noted as the temperature is lowered. Since **42** is found in such small yields (3–4%), any contribution by this pathway to the overall yield of **36** must be negligible.

A cyclopropanone derivative **39c** is also possible in the equilibria represented by **39a**–**c**. Because of the known propensity of cyclo-



propanones to react with nucleophiles,[40] **39c** would be rapidly trapped by the adjacent oxy anion to form hemiketal **39a**. Attack of ammonia (or amide) on **39c** could lead to **36** (eq 21), but again a



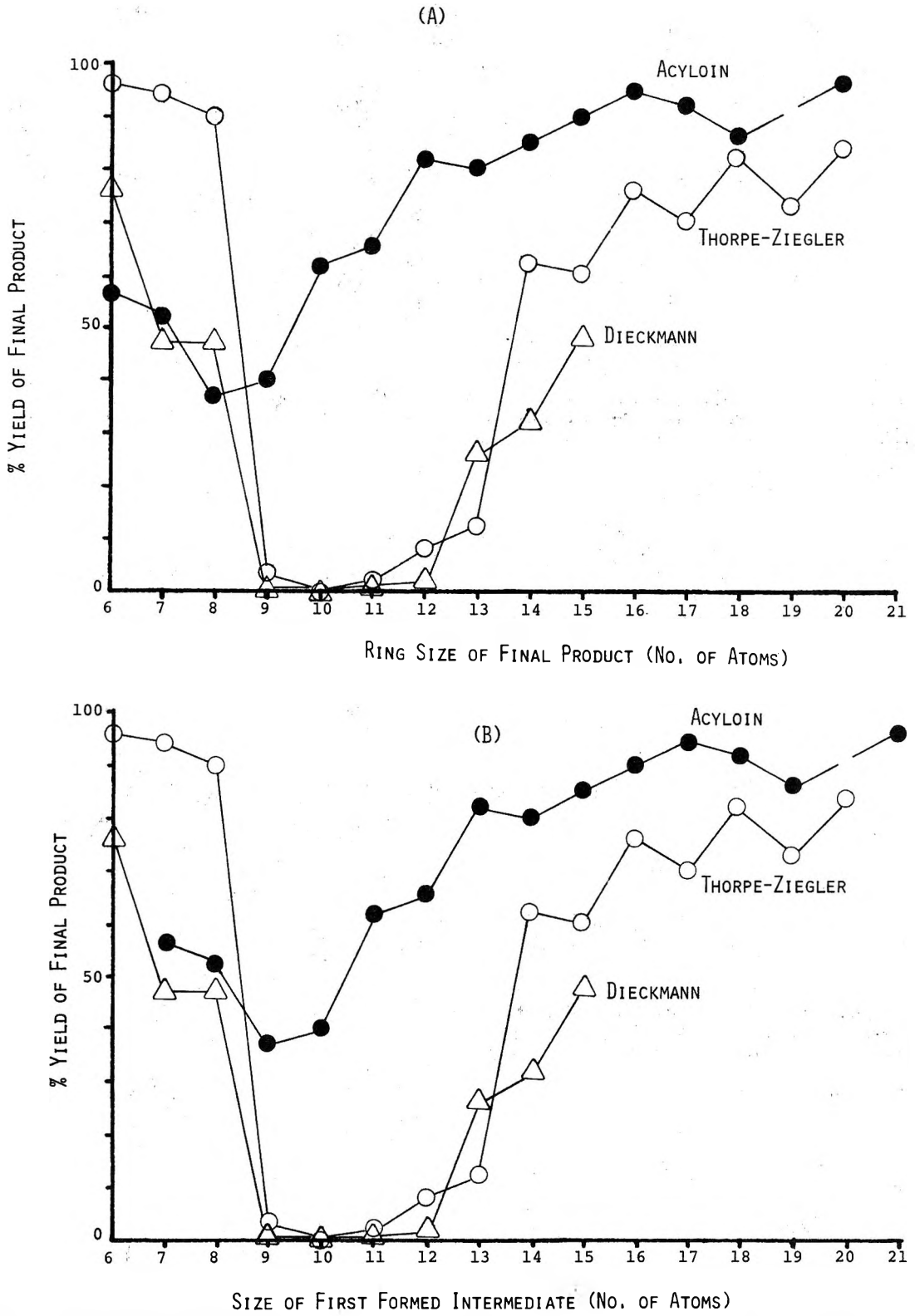
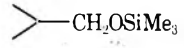


Figure 1. Dependence of yield of various cyclization processes on product ring size (A) and on the size of the hypothetical first formed cyclic intermediate (B) [adapted from J. Sicher, *Progr. Stereochem.*, **3**, 215 (1962)].

decrease in yield of **36** with decreasing temperature should produce a rise in the yield of **40** and **42** if eq 21 described the major pathway to **36**. Furthermore, reduction of **39c** should produce a *trans*-cyclopropanediolate on the grounds of greater charge separation in this molecule over that in the *cis*-cyclopropanediolate (eq 22). These complications make any substantial contribution of **39c** very unlikely as no products derived from it are found.

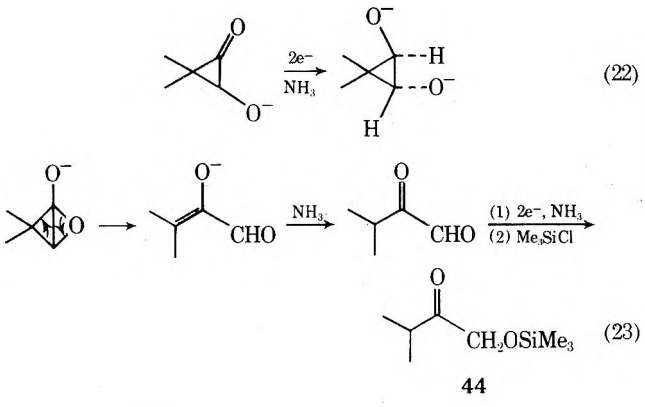
The proposed intermediacy of the 2-oxabicyclo[1.1.0]butane intermediates **29a** and **39a** leads to predictions of a variety of products *via* a combination of thermal rearrangements[41] and reductions. One such rearrangement is shown in eq 23. Compound **44** has been tentatively identified in these reactions.

When the reduction of dimethyl dimethylmalonate in liquid ammonia is conducted in the presence of methanol **43** is produced on subsequent treatment with Me_3SiCl. This is easily accounted for



43

by methanolysis of the enolate precursor of **33** and subsequent Bouveault–Blanc[41] reduction to the alcoholate of **43**. In fact, it is likely that the mechanism of the Bouveault–Blanc reduction is a variant of the acyloin condensation mechanism (see eq 15d).



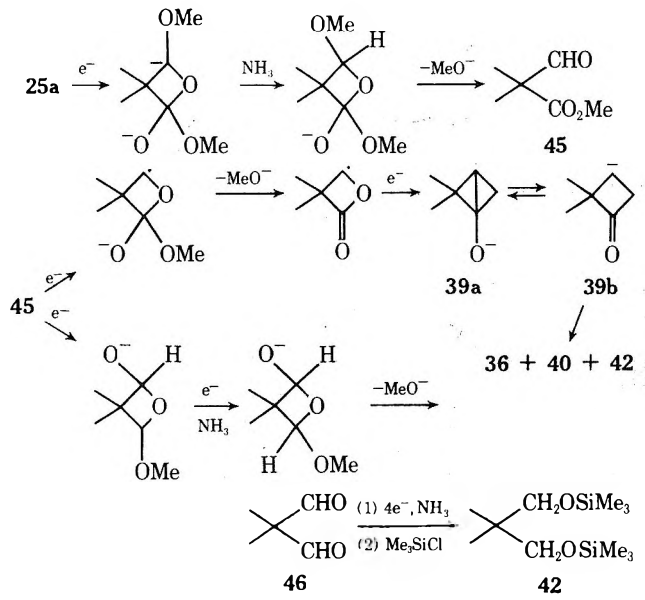
(22)

(23)

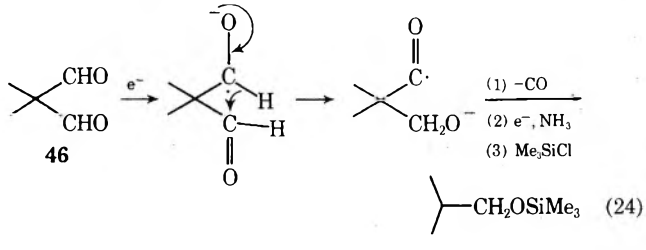
44

Scheme VI did not include an exposition of the fate of a possible dianion intermediate (**26a**) resulting from reduction of **25a**. It is not likely that **26a** is in the pathway for this reduction. Scheme VII summarizes the possible fates for **26a**, in which the intermediacy of aldehyde ester **45** is predicted. However, reduction of **45** under the

Scheme VII



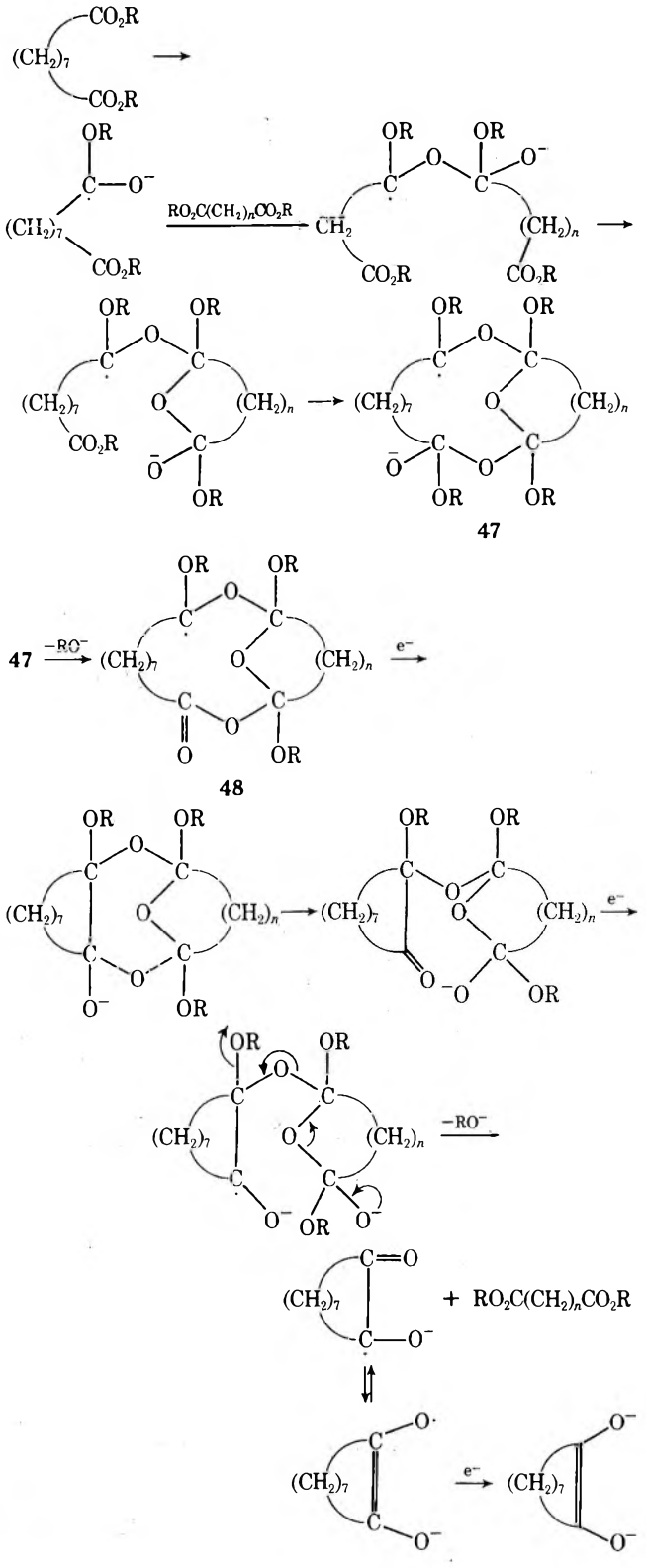
acyloin reaction conditions produced a mixture which consisted of **35** (6%), **40** (25%), **42** (25%), and **43** (45%).[22] These results suggest that any pathway for the reduction of the diester that goes through **26a** must be negligible. The production of **43** from **46** could involve a type of internal Cannizzaro reaction (eq 24).



(24)

43

Scheme VIII



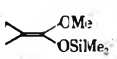
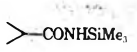
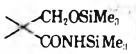
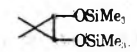
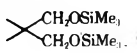
Results Difficult to Explain

The simultaneous reduction of a mixture of two different long-chain diesters gives very peculiar results.[43] When dimethyl nonanedioate is reduced alone, the yield of acyloin is 16%. In the presence of an equimolar amount of another long-chain diester, a yield of nine-membered acyloin of 52–62% is obtained![43]

Table II presents a comparison of some results obtained in both the Dieckmann and acyloin condensations. Note that the Dieckmann cyclization is worthless for monomer in the C_9–C_{12} range but that cyclic dimer is produced. In the acyloin condensation with added Me_3SiCl, the yield for all ring sizes ranges from fair to excellent.[4] Related data are plotted in Figure 1A and B.

Compare the two cases in Table II in which the acyloin condensation was carried out in the presence of Me_3SiCl under both normal and high-dilution conditions. Under normal conditions, the yield of dimer is considerable. The mixed-ester reactions[43] were carried out without added Me_3SiCl under normal conditions. Under high-dilution conditions, the reaction becomes monomolecular and the

Table I
Yields of Various Products from the Reduction of Dimethyl Dimethylmalonate by Sodium in Liquid Ammonia[22]

Conditions	 33	 35	 36	 40	 42
(1) $Na–NH_3$, ether, −34° (2) Me_3SiCl	6	25	25	25	3
(1) $Na–NH_3$, ether, −78° (2) Me_3SiCl	57			25	3
(1) $K–NH_3$, ether, −78° (2) Me_3SiCl	38		7	25	5
(1) $Na–NH_3$, CH_3OH, ether, −34° (2) Me_3SiCl		10		22	3

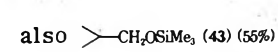
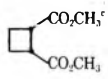
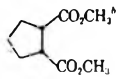
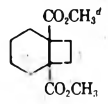
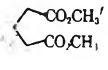
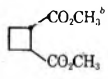
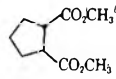
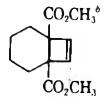
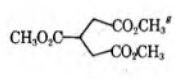
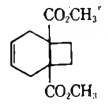
also  (43) (55%)

Table II
Comparison of Yields (%) for Cyclization of $RO_2C(CH_2)_nCO_2R$ under Various Conditions

N = final ring size	Dieckmann[a,b]	Acyloin			
		Ref 43[c]	Ref 43[d]	Me_3SiCl (A)[e]	Me_3SiCl (B)[f]
8	15 (dimer = 11)				72–85
9	0 (dimer = 28)	5	5 (16)	22 (dimer = 62)	68
10	0 (dimer = 12)	52	69 (52)	53 (dimer = 20) 22 (dimer = 73)	58–69
11	0.5 (dimer = 23)	60	62 (69)		48
12	0.5 (dimer = 16)	57	84 (72)		68
13	24 (dimer = 19)	62	52 (64)		84
14	32 (dimer = 2)	58	87 (84)		67

[a] Taken from Table II in J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15** (1967). [b] Note that for the Dieckmann reaction the value of n to obtain a given size ring must be 1 larger than in the acyloin condensation. [c] Yield of C_9 cycle when 0.01 mol of C_9 diester is cyclized with 0.01 mol of the diester for which $n = N - 2$. [d] Yield of C_N cycle when 0.01 mol of C_N is cyclized with 0.01 mol of C_9 diester. The number in parentheses is the yield when no other ester is present. [e] Reference 3, ester added fairly rapidly. [f] Reference 44, ester slowly added *via* high-dilution cycle.

Table III
Esters Which Are Not Reduced

Reduced ↑	$C_2H_5O_2CCO_2C_2H_5$[a]				
Not reduced ↓	$CH_3O_2CCO_2CH_3$[b]				
					

[a] Reference 36b. [b] Reference 44. [c] Reference 45. [d] Reference 27. [e] Reference 46. [f] Reference 47. [g] Reference 48.

yield of monomer goes up, although reaction rates are slow. [The relative rates in parentheses are C_9 (16), C_{10} (6), C_{11} (6.6), C_{12} (2), and C_{14} (1.7).[43]]

Study of Table II provides a clue to what might occur when two long-chain esters are reduced simultaneously.[43] The relative rate studies show that the C_9 diester is reduced at a much faster rate than the other esters studied. Therefore, could the initially formed radical anion from the C_9 diester be trapped by a higher carbon numbered diester to produce an intermediate bimolecular product which decomposes to two monomolecular products? Scheme VIII offers a very speculative suggestion. Note that in intermediates **47** and **48**, the ends of the C_9 diester are now held in a 14-membered ring, and the C_n diester is held in a C_{n+3} size ring (the size of the intermediate in the unimolecular acyloin condensation). If $n + 2 = 9$, then a 10-membered ring is formed which results in no net gain in ring size and dimer is formed. With $n + 2 > 9$, then going to such structures as **47** and **48** might be favored, opening a pathway to higher yields of the C_9 monomolecular acyloin.

In Table III are collected a number of other anomalies in the acyloin condensation. For these examples there can be no mechanism because the diesters are not reduced at all! For comparison some diesters are included which are reduced and have structures similar to those of the diesters which are not reduced. (Not all the known examples of nonreduction are recorded in Table III. For more complete listing see ref 4.)

This paper has presented a number of conclusions about the acyloin condensation mechanism which are at variance

with the generally accepted mechanism of the reaction. It is hoped that further discussion and experimentation will result which will either prove or disprove these conclusions. Furthermore, because of the importance of the acyloin reaction as a synthetic tool in organic chemistry, more work is needed to describe (1) adsorption and desorption of organic molecules on alkali metal surfaces and (2) steric, conformational, and electronic effects on the electron transfer to esters.

References and Notes

(1) See reviews: (a) V. Prelog, *J. Chem. Soc.*, 420 (1950); (b) M. Stoll, *Chimia*, **2**, 217 (1948); (c) K. Ziegler in Houben-Weyl, "Methoden der Organischen Chemie," Vol. 4/2, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1955, pp 739, 755; (d) L. I. Belen'kii, *Russ. Chem. Rev.*, **33**, 551 (1964); (e) D. J. Cram, *Record Chem. Progr.*, **20**, 71 (1959); (f) N. J. Leonard, *ibid.*, **17**, 243 (1956); (g) B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N.Y., 1964, pp 27–42; (h) J. A. Van Allan, *Amer. Perfum. Essent. Oil Rev.*, 33 (1949).

(2) K. T. Finley, *Chem. Rev.*, **64**, 573 (1964).

(3) K. Rühlmann, *Synthesis*, 236 (1971).

(4) J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, in press.

(5) S. M. McElvain, *Org. React.*, **4**, 256 (1948).

(6) F. F. Blicke, *J. Amer. Chem. Soc.*, **47**, 229 (1925).

(7) M. S. Kharasch, E. Sternfeld, and F. R. Mayo, *J. Org. Chem.*, **5**, 362 (1940).

(8) G. A. Russell and P. R. Whittle, *J. Amer. Chem. Soc.*, **89**, 6781 (1967), reported formation of semidiones under the conditions of the acyloin condensation.

(9) (a) J. C. Speck, Jr., and R. W. Bost, *J. Org. Chem.*, **11**, 788 (1946); (b) J. H. Van de Sande and K. R. Kopecky, *Can. J. Chem.*, **47**, 163 (1969); (c) J. Cologne and P. Brison, *Bull. Soc. Chim. Fr.*, 175 (1962); (d) F. Chen, R. E. Robertson, and C. Ainsworth, *J. Chem. Eng. Data*, **16**, 121 (1971).

(10) *Cf.* (a) H. Smith "Chemistry in Non Aqueous Ionizing Solvents," Vol. I, Interscience, New York, N.Y., 1963, Part II, p 174; (b) C. Walling, "Free Radicals in Solution," Wiley, New York, N.Y., 1957, p 585; (c) A. J. Birch, *Quart. Rev., Chem. Soc.*, **4**, 69 (1950).

(11) D. B. Sharp and E. L. Miller, *J. Amer. Chem. Soc.*, **74**, 5643 (1952).

(12) The second-order rate constant for the reaction of methanol with triisopropylchlorosilane is $\sim 1.5 \times 10^{-4}$ l. mol^{-1} sec^{-1}.[13] We estimate that the rate of the reaction of Me_3SiCl with methanol would be at least an order of magnitude greater. Furthermore, the reaction of triphenylfluorosilane with hydroxide is 10^6 times faster than with water.[14] Thus, we estimate that the reaction of methoxide with Me_3SiCl would be at least these orders of magnitude greater than that of methanol with Me_3SiCl.

(13) A. D. Allan, J. C. Charlton, C. E. Eaborn, and G. Modena, *J. Chem. Soc.*, 3688 (1957).

(14) C. G. Swain, R. M. Esteve, Jr., and R. H. Jones, *J. Amer. Chem. Soc.*, **71**, 965 (1949).

(15) K. Rühlmann, B. Fichte, T. Kiriakidis, C. Michael, G. Michael, and E. Gründemann, *J. Organometal. Chem.*, **34**, 41 (1972).

(16) (a) R. E. Robertson, M.S. Thesis, Colorado State University, 1971. (b) Control experiments in which Me_3SiCl either was present initially or was added at the end of the reduction gave essentially the same results.

(17) E. L. Totton, R. C. Freeman, H. Powell, and T. L. Yarboro, *J. Org. Chem.*, **26**, 343 (1961).

(18) (a) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **68**, 2282 (1946); (b) R. West and R. H. Baney, *ibid.*, **81**, 6145 (1959).

(19) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 217 (1958).

(20) J. J. Bloomfield and J. R. S. Irelan, *J. Org. Chem.*, **31**, 2017 (1966).

(21) T. Okubo and S. Tsutsumi, *Technol. Rep. Osaka Univ.*, **12**, 457 (1962) [*Chem. Abstr.*, **59**, 7422*g* (1963)].

(22) F. Chen and C. Ainsworth, *J. Amer. Chem. Soc.*, **94**, 4037 (1972).

(23) A. E. Kober and T. L. Westmann, *J. Org. Chem.*, **35**, 4161 (1970).

(24) D. Machtinger, *Bull. Soc. Chim. Fr.*, 1341 (1961).

(25) H. Stetter and K.-A. Lehmann, *Justus Liebigs Ann. Chem.*, 499 (1973).

(26) (a) E. Van Heyningen, *J. Amer. Chem. Soc.*, **74**, 4861 (1952); (b) E. Van Heyningen, *ibid.*, **77**, 4016 (1955).

(27) J. J. Bloomfield, R. A. Martin, and J. M. Nelke, *J. Chem. Soc., Chem. Commun.*, 96 (1972).

(28) (a) P. G. Gassman and X. Creary, *J. Chem. Soc., Chem. Commun.*, 1214 (1972); (b) E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem.*, **76**, 281 (1964).

(29) H. G. Kuivula, *Synthesis*, 499 (1970).

(30) J. A. Campbell, R. W. Koch, J. V. Hay, M. A. Ogliaruso, and J. F. Wolfe, *J. Org. Chem.*, **39**, 146 (1974).

(31) Al. Favorsky, *Bull. Soc. Chim. Fr.*, [4] **43**, 551 (1928).

(32) H. Kwart and M. M. Baevsky, *J. Amer. Chem. Soc., Soc.*, **80**, 580 (1958).

(33) J. C. Trisler, J. K. Doty, and J. M. Robinson, *J. Org. Chem.*, **34**, 3421 (1969).

(34) H. O. House and W. F. Gannon, *J. Org. Chem.*, **23**, 879 (1958).

(35) L. De Borger, M. Anteunis, H. Lammens, and M. Verzale, *Bull. Soc. Chim. Belg.*, **73**, 73 (1964).

(36) (a) F. Krollpfeiffer and A. Rosenberg, *Chem. Ber.*, **69**, 465 (1936); (b) Y. N. Kuo, F. Chen, C. Ainsworth, and J. J. Bloomfield, *Chem. Commun.*, 136 (1971).

(37) (a) M. Mousseron, R. Richard, R. Granger, F. Winternitz, G. Combes, E. Cavals, L. Souche, M. Cabanes, and P. Froger, *Bull. Soc. Chim. Fr.*, **51**, 629 (1946); (b) A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 4604 (1957); (c) G. Nomine, D. Bertin, and A. Pierdet, *Tetrahedron*, **8**, 217 (1960).

(38) (a) H. A. Brune, *Chem. Ber.*, **97**, 2829 (1964); (b) T. Ostdick and P. A. McKusker, *Inorg. Chem.*, **6**, 98 (1967).

(39) See reviews: (a) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," Interscience, New York, N.Y., 1970, Chapter 1; (b) J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15**, 28 (1964).

(40) N. J. Turro and W. B. Hammond, *Tetrahedron*, **24**, 6029 (1968).

(41) *Cf.* J. Ciabattoni, *J. Amer. Chem. Soc.*, **93**, 4902 (1971), and references therein.

(42) L. Bouvealt and G. Blanc, *C. R. Acad. Sci.*, **136**, 1676 (1903).

(43) K. T. Finley and N. A. Sasaki, *J. Amer. Chem. Soc.*, **88**, 4267 (1966).

(44) J. J. Bloomfield, unpublished work.

(45) J. J. Bloomfield, R. G. Todd, and L. T. Takahashi, *J. Org. Chem.*, **28**, 1474 (1963).

(46) D. Ginsburg, *Accounts Chem. Res.*, **7**, 249 (1972).

(47) U. Schräpler and K. Rühlmann, *Chem. Ber.*, **97**, 1383 (1964).

(48) P. E. Eaton, private communication.

A Suggestion for the Revision of Mechanistic Designations

Robert D. Guthrie

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Received July 18, 1974

A simple system for the designation of chemical reaction mechanisms is suggested. The new system represents each bond-making and bond-breaking step in symbolic form and requires only two symbols plus atomic symbols for the elements to represent all heterolytic and homolytic reactions including electron-transfer reactions. Minor modification of the system allows the designation of ion-paired intermediates and caged radical pairs. An approach to the designation of photochemical reaction mechanisms is also suggested. The new system can serve as a digital code which, when applied to a set of reagents, will generate both mechanism and products. Its application to information retrieval is anticipated.

In the past 30 years chemistry has become increasingly mechanistic. The term mechanism has many peripherally different definitions but basically means a description of the sequence of bond-making and bond-breaking steps occurring as a set of starting molecules, atoms, or ions is converted to a new set. When mechanisms are grouped for classification, extramechanistic information is included to indicate the outcome of the reaction, *i.e.*, substitution, elimination, or addition. This procedure gives more information than would be available from the purely mechanistic part of the classification symbols, but it still leaves important parts of the known details of the mechanism to be associated with the symbols by memorization.

As an example, consider the classification SN2. The most

descriptive part of the symbol gives the information that the eventual outcome of the reaction is substitution of one group for another but it does not convey the important fact that the reaction is concerted. To the uninformed beginner it might seem redundant that the attack of a nucleophile would have to be designated as bimolecular. The symbol SN1 would completely baffle a beginning student until he was told that this is a two-step reaction and the designations nucleophilic and unimolecular apply to different steps. Even the most mechanistically organized textbooks invariably group SN1 and SN2 reactions together, implying a nonexistent similarity in the events leading to products. Mechanistically, an SN2 reaction is more closely related to the attack of base on a carbon acid to form a carbanion than to an SN1 reaction and the factors which facilitate the first two reaction types are closely related. It is not uncommon to find other nucleophilic substitutions, such as those involving addition–elimination, which is still a third mechanistic type, incorporated in discussions of SN1 and SN2 reactions.

It is not the main purpose of this paper to support a mechanistic approach to teaching organic chemistry. Some chemical educators feel that students find the mechanistic approach more difficult than the functional-group or reaction-outcome approaches. We would, however, suggest that a completely mechanistic approach has never been given a chance. The nomenclature system we will suggest has the pedagogic advantage of having reaction-type symbols that directly describe molecular events. The new system also provides a number of more general benefits and directives.

Chemical Reactions as Bond-Making and Bond-Breaking Processes

Background. Almost all chemical reactions involve bond making and bond breaking. These processes are the lowest common denominators of all reaction mechanisms. A reasonable system of mechanistic nomenclature should therefore start with a system for labeling the distinguishable types of bond making and bond breaking and continue by indicating the sequence of such steps which occur as reactants are converted to products. The first section of this paper is essentially a description of the method previously suggested by Mathieu and coworkers.[1] We have altered the symbolism slightly and made a few extensions.

Association Processes. Association processes may be separated into three categories, *i.e.*, homolytic (A·), nucleophilic (AN), and electrophilic (AE), *i.e.*

$$X^{\cdot} + R^{\cdot} \longrightarrow R{:}X \quad (A^{\cdot})$$
$$X{:} + R \longrightarrow R{:}X \quad (A_N)$$
$$X + R{:} \longrightarrow R{:}X \quad (A_E)$$

These categories subdivide into various charge types when the substrate (R) and reagent (X) structures are specified. As in previous systems, ambiguity arises when it is not clear which reactant should be considered the reagent and which the substrate.[2] This difficulty can produce two descriptions of the same mechanism. However, the problem may be avoided in a manner to be described later in this paper.

Dissociation Reactions. The reverse of these associations will be called homolytic dissociation (D·), nucleophobic dissociation (DN), and electrophobic dissociation (DE) and are illustrated as

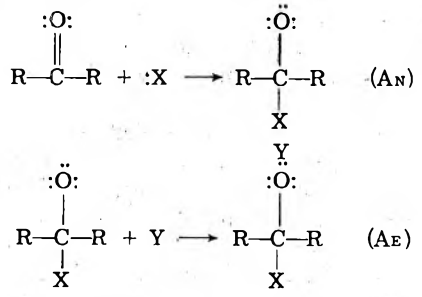
$$R{:}X \longrightarrow R^{\cdot} + X^{\cdot} \quad (D^{\cdot})$$
$$R{:}X \longrightarrow R + X{:} \quad (D_N)$$
$$R{:}X \longrightarrow R{:} + X \quad (D_E)$$

Use of the term nucleophobic to describe a process in which an electron pair is repelled by the nucleus has the advantage that both forward and reverse reactions are identically subscripted and are therefore easily remembered.[3]

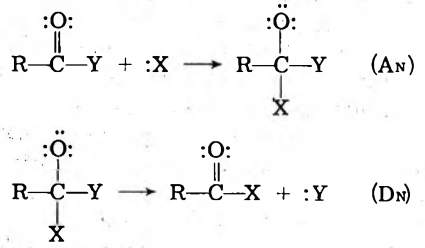
Nonconcerted Combinations of Two Processes. If two or more bond-forming or bond-breaking processes, or two sets thereof, are not synchronous, a plus sign will be introduced between the terms describing each separate step. For example, an SN1 reaction becomes DN + AN

$$RX \longrightarrow R + :X \quad (D_N)$$
$$R + :Y \longrightarrow R{:}Y \quad (A_N)$$

Nucleophilic addition to C=O could be AN + AE



or AE + AN for the corresponding electrophilic addition. With a leaving group attached to C=O, the reaction could be AN + DN



In all, there are 16 possible combinations. Of these, eight are unlikely because they usually increase or decrease charge by 2. These are either combinations of identically labeled A's or D's (AN + AN) or a sum of two different processes with different labels (AN + DE). Thus, for a two-term combination, the probable processes are those for which only two of the symbols are identical. Exceptions to this arise when the part of the molecule being designated as substrate changes between steps as in the abstraction of some group.

The four remaining probable processes not discussed above all involve DE terms. For uncharged molecules this denotes expulsion of a cation and there is fairly general agreement that, for most examples of this process, a base or nucleophile assists in removal of the cation, probably *via* a concerted process. An E1 reaction, for example, is probably never a DN + DE type because some base, however weak, is involved in removal of the proton, even though this often is omitted in textbook representations. Decarboxylation of a carboxylate anion more closely approximates a true DE process, but this representation simply reflects ignorance of the changes in solvation as the carbon dioxide is being formed. The same objection can be raised to all of the four single-term descriptions: AN, DN, AE, DE. This is not a weakness of the system but rather a lack of experimentally demonstrated facts. As will be seen below, a great strength of this scheme is a flexibility which allows a mechanism's designation to keep pace with increasing awareness of its complexity.

Concerted Combinations of Two Processes. If two or more bond-making or bond-breaking processes occur in a concerted, synchronous fashion, the plus sign will be removed. An SN2 reaction then becomes ANDN. Certain types of SE2 may be AEDE. Cycloadditions could be AEAN and their reverse DEDN. The order of the terms is obvious-

ly unimportant for a concerted reaction so that only eight combinations are possible. As in the nonconcerted cases, combinations with more or less than two different symbols indicate group abstraction.

Use of the System to Describe Common Reaction Types

Comparison of Systems. Before proceeding to a discussion of nomenclature for other common mechanistic types, a brief comparison of the information provided by the existing and proposed systems is in order. Consider, for example, the relative merits of SN2 *vs.* ANDN as a description of the reaction of CH_3I and ^-OH. The numerical part of the former symbol is unnecessary in the proposed system because every dissociation reaction is unimolecular and, with the exception of intramolecular reactions, for which we will later suggest distinguishing symbols, associations are always bimolecular. Thus, the molecularity of each step in a reaction is obvious from its symbol. The uninformed student might assume that ANDN meant nucleophilic displacement on iodine or on hydrogen. Both of these alternatives are more properly considered ANDE reactions. Although neither of these reactions compete when this particular substrate is treated with hydroxide ion, the origin of the classification difference is illustrative. In the association step, the hydrogen or iodine atom is considered part of the substrate, but in the dissociation step it is not. The arbitrary change in frame of reference results in a designation for which the number of different symbols is other than 2.

While the system discussed above is satisfactory for the designation of simple mechanistic types and is superior to the existing method, ambiguities develop in the description of more complex reactions. Moreover, while the system conveys some extramechanistic information, this feature is dependent on the availability of a consistent method for making the substrate–reagent assignment. We will now develop a different subscriptive procedure which not only avoids the substrate–reagent decision but which also describes the mechanistic events in sufficient detail to allow the determination of product structure.

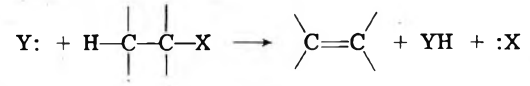
A Modification Which Avoids the Substrate–Reagent Decision. In order to give complete reaction-outcome information, the two atoms involved in each bond-making and bond-breaking process must be specified in the designation. This can be easily done by subscripting the atomic symbols of the two atoms after each A or D notation. Conveniently, it is not necessary to employ the designations N or E provided that a standard direction for electron flow is chosen. We will subscript the atomic symbols so that the *first subscripted atom is the one carrying the electron pair in a heterolytic process.* A homolytic process will be designated by placing a dot between the two atomic symbols.

Nucleophilic and Electrophilic Substitutions. The three processes referred to in the preceding section now become

$$HO: + CH_3I \longrightarrow CH_3OH + :I \qquad (A_{OC}D_{IC})$$
$$HO: + CH_3I \longrightarrow HOH + :CH_2I \qquad (A_{OH}D_{CH})$$
$$HO: + CH_3I \longrightarrow HOI + :CH_3 \qquad (A_{OI}D_{CI})$$

The designations are clearly distinguishable and completely specified. This modified system has the pedagogic drawback that mechanistic classes are not so easily identified, but with some practice the general categories can be recognized. In the foregoing set of reactions, for example, all of the designations have the form $A_{XZ}D_{YZ}$ where X and Y represent the entering and leaving groups, respectively, and Z is an atom on which concerted nucleophilic displacement is occurring. An electrophilic displacement would have the common atom subscripted first and have the general form $A_{ZX}D_{ZY}$. Nonconcerted nucleophilic and electrophilic substitutions will have the forms $D_{XZ} + A_{YZ}$ and $D_{ZX} + A_{ZY}$, respectively.

Elimination Reactions. The most commonly encountered elimination reaction is the loss of HX



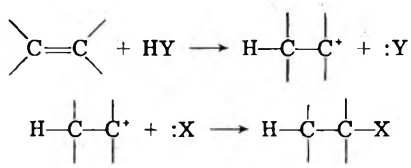
The accepted mechanistic alternatives are

$$E1 = D_{XC} + A_{YH}D_{CH}$$
$$E2 = A_{YH}D_{CH}D_{XC}$$
$$E1cB = A_{YH}D_{CH} + D_{XC}$$

The presence of identical terms indicates that the reaction outcome is the same for all three mechanistic variations. It should be noted that insofar as the "substrate" is concerned, it is possible to obtain the same reaction outcome with different symbols. In the case of elimination reactions, there is a set of possible mechanisms whose representations contain the terms A_{HY}, D_{CX}, and D_{HC}, which lead to the same products. It is generally true that, for any mechanistic representation, reversal of the subscript order for one term will require that all the others be either reversed or replaced. This has the effect of reversing the direction of electron flow and may or may not lead to a realistic mechanistic alternative. In the present example, the combination $A_{HY}D_{CX}D_{HC}$ is, in fact, observed as a component part of the mechanism for reduction of hindered ketones by isopropyl Grignard reagents (X = Mg, Y = C). A more complete representation of this mechanism would be $A_{HY}D_{CX}D_{HC}A_{OX}$. The absence of a balancing A term in our representation of the common elimination types simply ignores the fate of the departing nucleophobe.

Returning to the common elimination types, $D_{XC} + A_{YH}D_{CH}$, $A_{YH}D_{CH}D_{XC}$, and $A_{YH}D_{CH} + D_{XC}$, it will be noted that not all of the possible sequences are represented. An inquisitive student might ask, "Why not $A_{YH} + D_{CH}D_{XC}$ (hydrogen bonding followed by concerted elimination) or $D_{XC}A_{YH} + D_{CH}$ (hydrogen-bond formation concerted with loss of nucleophobe)?" We feel that, by systematizing thought, adoption of our scheme might stimulate the search for evidence of new mechanistic types. Some apparently complex mechanistic distinctions can be represented in simple terms by this system. The question of anchimeric assistance, for example, reduces to a consideration of the validity of a single plus sign in the mechanistic designation.

Addition Reactions. The general form of acid-catalyzed addition of HX to a double bond is



The addition is seen to be the reverse of an E1 reaction and this relationship is apparent from the symbolic representation $A_{CH}D_{YH} + A_{XC}$. The A's and D's are simply interchanged and the order of the terms reversed. Addition of HX, where HX itself serves as the proton source, is a special case of the reaction above (Y = X).

A similar relationship exists between nucleophilic addition to a multiple bond and the E1cB reaction and this is evident using the new terminology. The reverse of an E2 reaction would be designated $A_{XC}A_{CH}D_{YH}$. The combina-

tion $A_{XQ}A_{QY}$ is representative of a termolecular reaction unless X and Y are atoms in the same molecule. Reverse E2 reactions are highly improbable.

It is probably worth mentioning at this point that for reactions involving formation or destruction of multiple bonds, the π bond is not indicated in the designation. This means that for β-elimination reactions, the species generated is formally a zwitterion

$$H—C—C—X \longrightarrow {}^{+}C—C^{-} + HX$$

As this species is a very minor resonance contributor to most carbon–carbon double bonds, the double bond may be regarded as formed at this point and inclusion of an additional A_{CC} term seems superfluous. We would reserve this abbreviation of the system for cases in which the plus and minus charges are generated on adjacent carbons. All other cases should specifically designate bond formation if that is intended.

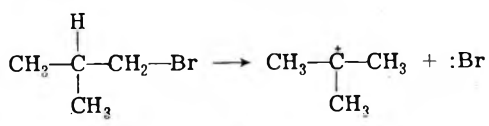
A related problem is that our system does not indicate the hybridization of the atom involved in a particular bond-making or -breaking process. Nucleophilic attack at carbon is A_{XC} regardless of whether C is present as tetrahedral carbon, C=Y, C≡Y, etc. We considered including a method for designating this in the system, but it seemed to open the door for inclusion of a variety of structural distinctions of increasing subtlety, the logical extension of which was a complete designation of the structures of all reagents. A reviewer has suggested $A_{OH^-,CH_3} + D_{I^-,CH_3}$ for the SN2 reaction of methyl iodide with hydroxide. We have no objection to this and feel that the capacity for such extension is a strength of the system. For simplicity in this paper, however, we will confine our subscripting to the two atoms directly involved. We would point out that a considerable amount of implicit structural information is contained in the mechanistic designation because of structural exclusion of certain mechanistic types. $A_{XC} + D_{YC}$ is not an observed mechanism for nucleophilic displacement at saturated carbon and the designation therefore implies trigonal or digonal carbon.

Free-Radical Reactions. As mentioned above, homolytic reactions require special notation. For simple association and dissociation of radicals, the order of subscripting is arbitrary, but if a free radical is bonding to or separating from a diamagnetic species, it is informative to *subscript the atom carrying the unpaired electron first.* The reaction

$$RS\cdot + H_2C{=}CH_2 \longrightarrow RSCH_2—CH_2\cdot$$
$$RSCH_2—CH_2\cdot + RSH \longrightarrow RSCH_2CH_3 + RS\cdot$$

will be designated $A_{S\cdot C} + A_{C\cdot H}D_{S\cdot H}$

Rearrangements. In rearrangement processes where bonds are broken and new bonds formed without separation of any parts of the molecule or ion, increased clarity is obtained if the intramolecular processes are placed within parentheses. For example, the reaction



would be designated $D_{BrC}(A_{HC}D_{HC'})$. The order of the terms is unimportant, provided that the intramolecular processes are adjacent for bracketing. We have chosen to indicate the bonds made or broken in the order of their increasing number of bond distances from one reaction terminus (arbitrarily taken as the C–Br bond). *If the same atomic symbol is used more than once in a designation, a prime notation will be affixed each time the symbol refers to a new atom.* In more elaborate cases, it might be desirable to number the different atoms of the same element but this is usually unnecessary.

Complex Reactions

General Considerations. For complex reactions these mechanistic designations can become quite lengthy. For example, acid-catalyzed ester hydrolysis can be represented as $A_{OH}D_{XH} + A_{O'C} + A_{XH'}D_{O'H'} + A_{O''H'}D_{XH'} + D_{O''C} + A_{XH}D_{OH}$. This is clearly too unwieldy for oral communication of mechanistic thought. Its value lies in the fact that the groups of terms present are readily related to the component parts of other mechanisms. To illustrate, the first two terms are of the same general form as all electrophilic additions to multiple bonds. The combination $A_{OH}D_{XH} + D_{OC}$ will be common to all acid-catalyzed dehydrations, ether cleavages, etc. The relationship to acid-catalyzed amide hydrolysis is evident in the replacement of $A_{OH}D_{XH} + D_{OC}$ by $A_{NH}D_{XH} + D_{NC}$, thus allowing ready recognition of the mechanistic similarity. In general, mechanisms which are too complex or unique to warrant a special designation in the system presently in use are easily named in the new system and their relationship to more common types becomes apparent.

Reactions Involving Electron-Transfer Steps. As an example, consider the "SRN1" mechanism recently studied by Bunnett[4]

$$M^n + ArX \longrightarrow [ArX]\cdot^- + M^{n+1} \quad (1)$$
$$[ArX]\cdot^- \longrightarrow Ar\cdot + X^- \quad (2)$$
$$Ar\cdot + R{:}^- \longrightarrow [ArR]\cdot^- \quad (3)$$
$$[ArR]\cdot^- + ArX \longrightarrow ArR + [ArX]\cdot^- \quad (4)$$

The first and fourth steps present a problem in that no bond-making or -breaking steps are required. Electron-transfer reactions are generally thought to proceed by complex formation prior to the electron-transfer step and can be treated as A + D processes within the framework of the proposed nomenclature system.

If the electron transfer were an inner-sphere process, such as

$$ArX + M^n \longrightarrow ArXM \longrightarrow [ArX]\cdot^- + M^{n+1}$$

the designation would be $A_{M\cdot X} + D_{XM}$ or $A_{MX} + D_{X\cdot M}$. We prefer the former representation if the donor (M) is paramagnetic and the latter when it is diamagnetic.

For an outer-sphere reaction, we suggest subscripting a symbol for the molecular orbital of the donor which carries the electron to be transferred followed by a symbol for the orbital in the acceptor which receives the electron. For the particular case of the SRN1 mechanism, the full designation will be $A_{M\cdot\pi} + D_{\pi M} + D_{XC} + A_{C'C} + A_{\pi\cdot\pi'} + D_{\pi'\pi}$. The symbol π is understood to represent a π molecular orbital. In the fifth and sixth terms of the representation, the electron is considered to be transferred to a new π system even though it is identical with the one involved in the first step. In other words, the reaction is considered to take place among a set of molecules which are all different even if the structures of some are identical.

The third and fourth terms present a new problem. Although the third term is D_{XC}, a valid alternative is $D_{C\cdot X}$. Both representations are correct because the reaction is both a nucleophobic and a homolytic dissociation. We have chosen to represent reactions involving attack or retreat of a nonbonded pair of electrons as heterolytic even if a free radical is formed or destroyed in the process. Thus the fourth term is $A_{C'C}$ rather than $A_{C\cdot C'}$.

Photochemical Reactions. These can be regarded as intramolecular electron-transfer reactions and treated

within the framework of our scheme. For example, the basic reaction

$$A \xrightarrow{h\nu} A^*$$

can be designated ($A_{\Psi\Psi^*}D_{\Psi^*.\Psi}$). The parentheses indicate the intramolecular nature of the process. Intersystem crossing could be termed $A_{st}D_{t\text{-}s}$ but this requires six symbols where two would suffice. We suggest that the combination ST be used for singlet to triplet interconversion. As an example, consider the photochemical preparation of benzpinacol

$$Ph_2C{=}O \xrightarrow{h\nu} {}^1[Ph_2C{=}O]^*$$
$${}^1[Ph_2C{=}O]^* \longrightarrow {}^3[Ph_2C{=}O]^*$$
$${}^3[Ph_2C{=}O]^* + XH \longrightarrow Ph_2\dot{C}OH$$
$$2Ph_2\dot{C}OH \longrightarrow Ph_2C(O{-}H)\text{—}CPh_2(O{-}H)$$

We suggest the designation $2[(A_{\Psi\Psi^*}D_{\Psi^*.\Psi}) + ST + A_{O\text{-}H}D_{X\text{-}H}] + A_{C\text{-}C}$. *When a series of steps occurs more than once in the formation of one molecule of product, the repeated series is enclosed in brackets and a coefficient indicating the number of occurrences placed in front of the brackets.* This bracketing technique can also be used for parallel sequences which generate intermediates that subsequently react with each other. For example, photochemical formation of mixed pinacol could be represented $[(A_{\Psi\Psi^*}D_{\Psi^*.\Psi}) + ST + A_{O\text{-}H}D_{X\text{-}H}] + [(A_{\Psi\Psi^*}D_{\Psi^*.\Psi}) + ST + A_{O\text{-}H}D_{X\text{-}H}]' + A_{C\text{-}C'}$. Note that the prime notation has been placed outside of the second bracketed sequence to avoid having to prime each atom and orbital in the second sequence. The use of brackets in this way should be regarded as an optional technique for increasing clarity. In the preceding mixed pinacol case, its use is convenient but not necessary.

Reactions Involving Ion Pairs. It is well established that ion pairing of intermediates can affect the outcome of chemical reactions. It is therefore useful to have a notation to distinguish these. For the sequence

$$RX \rightleftharpoons R^+X^- \rightleftharpoons R^+\,|\,|X^- \rightleftharpoons R^+ + X^-$$

where the first intermediate is an intimate ion pair and the second a solvent-separated ion pair, we suggest the designation $D_{((RX))} + D_{(RX)} + D_{RX}$. The subscript R represents the atom bonded to X in RX. The same technique can be used in free-radical reactions to indicate caged pairs. It will be noted that no attempt has been made to indicate reversibility of steps. The system proposed describes the fate of the minimum number of molecules required by the stoichiometry. If there was more than one path to the product, we would regard the reaction as proceeding by more than one mechanism.

Use of the New Systems

Pedagogical Use. For the purpose of teaching mechanistic organic chemistry to beginners, we suggest that the N and E labels be used to designate mechanistic categories such as ANDN for SN2 reactions but that the atomic symbol subscripts be introduced when individual cases are compared: $A_{OC}D_{FC}$, $A_{OC}D_{ClC}$, $A_{OC}D_{BrC}$, etc., are all ANDN reactions with different nucleophobes but a common oxygen nucleophile.

Information Retrieval. Once translated into this system, mechanisms could be easily indexed. The main categories would be the A–D sequences and these would be subdivided into atomic variations. Further subdivision could be based on structural units (functional groups, ring systems, etc.) and, finally, each subcategory could be indexed by complete reactant structures. It would be a simple matter to determine whether a particular complete mechanism had been previously proposed. Finding the component parts of mechanisms, on the other hand, presents a formidable cross-indexing problem.

Suppose, for example, the goal was to find examples of nucleophilic displacement of fluoride from aromatic systems by the $A_{XC} + D_{FC}$ mechanism. Subdivision of A + D mechanisms would probably start with the first subscripted atom, so that search for examples involving a particular nucleophile would be much easier than the search for a nucleophobe. It would be necessary to examine each nucleophile subdivision for fluoride in the second term. All of these data would then be screened to remove nonaromatic substrates (acyl fluorides, vinyl fluorides, etc.). The situation is analogous to the search of a formula index for all compounds containing five oxygens.

A related problem arises if the search demands information not present in the mechanistic symbols alone. It is the nature of this system that a complete mechanism is not generated until the designation is applied to a particular substrate. Supposing that the search was for examples of nucleophilic addition of sulfur to double bonds, the term A_{SC} does not include the bonding at carbon. A relatively simple screening of substrates could be used for mechanisms where A_{SC} appeared as the first term. It would be more difficult to find those cases for which the double bond was generated in steps preceding that designated by A_{SC}.

We suggest that such complexities can be handled using high-speed computers. A suitable format would have to be devised for storage of both structural and mechanistic information. Much effort has been devoted to computer coding of molecular structure. Our system provides a workable approach to coding mechanistic information. Programs to interpret and screen the data in accord with the search goals can be envisioned to solve problems of the type discussed above.

We anticipate that in addition to its value for information retrieval, the computerized system would have predictive capability. The frequent appearance of certain mechanistic types and the absence of others would allow the computer to formulate mechanistic generalities. Perhaps new and useful reactions could be predicted.

Because the computerized system would be capable of generating the structures of reaction products from those of reactants, it also provides a source of synthetic information. Existing programs for chemical syntheses could possibly be adapted to use information abstracted in this form.

Summary of Advantages of the Proposed System

We have proposed a new system for the designation of reaction mechanisms. We feel that it has the following important advantages.

(1) Any mechanism can be designated, using only two mechanistic symbols and atomic symbols.

(2) Molecularity decisions are unnecessary.

(3) The mechanism is related to the symbols by logical rules so that no memorization is required. A beginning student can express a mechanism symbolically after a brief introduction to the rules.

(4) The system can be used to organize reactions into truly mechanistic categories.

(5) The system is an aid to mental organization, both for the reaction mechanician who would like to consider all possibilities in a system under study and for the beginner who can recognize similarities between mechanisms.

(6) The pedagogic potential is considerable. A student who is asked to translate mechanisms into symbols and *vice versa* is forced to blend structural change with electron movement. Memorization is discouraged and logical deduction is required. The system also should adapt well to computer-assisted instructional programs and automated examination grading.

(7) The system should be adaptable to information retrieval and would be easily computer coded.

(8) The basic framework provides possibilities for modernization. If, for example, a simple coding system for molecular orbitals were to become available, the atom-designating subscripts could be replaced by molecular orbital designations and possibly allow the incorporation of stereochemical information.

Acknowledgment. The author would like to thank Dr. J. F. Bunnett and Dr. J. W. Wilson for helpful comments and constructive criticism.

References and Notes

(1) J. Mathieu, A. Allis, and J. Valls, *Angew. Chem.*, **72**, 71 (1960). We learned of this paper only after the first draft of our paper was completed. This is mentioned because it points out two important facts: (1) that a system based on the designation of each bond-making and bond-breaking step will be the logical outcome of any serious consideration of mechanistic nomenclature and (2) that chemists are extremely reluctant to accept new nomenclature systems regardless of their advantages.
(2) Common usage seems to be inorganic attacks organic and where both reagents are organic, charged attacks uncharged, but there are many exceptions and examples for which rules are not available.
(3) The terms nucleofugal and electrofugal have also been used: H. Zollinger, *Accounts Chem. Res.*, **6**, 335 (1973), and ref 1.
(4) (a) R. A. Rossi and J. F. Bunnett, *J. Amer. Chem. Soc.*, **94**, 683 (1972); (b) *ibid.*, **96**, 112 (1974).

The Nature of the Ortho Effect. XI. Reaction Rates of Carboxylic Acids with Diazodiphenylmethane

Marvin Charton

Department of Chemistry, Pratt Institute, School of Science, Brooklyn, New York, 11205

Received August 26, 1974

Rate constants for the reaction of diphenyldiazomethane with eight sets of ortho-substituted benzoic acids, six sets of phenylacetic acids, and seven sets of other acids were correlated with the equations

$$Q_X = \alpha\sigma_{IX} + \beta\sigma_{RX} + \psi\nu_X + h$$
$$Q_X = \alpha\sigma_{IX} + \beta\sigma_{RX} + h$$

to detect the presence of steric effects. All of the benzoic acids clearly showed the presence of a steric effect. This is the first time that a steric effect has been definitively demonstrated in sets of ortho-substituted benzene derivatives. The results obtained show that the electrical effect is definitely predominant, in good agreement with previous findings. Of the eight sets of benzoic acids studied, seven show steric acceleration of the rate; the eighth shows steric deceleration of the rate. Of the six phenylacetic acid sets studied, three showed steric effects. One these was rate accelerating; the other two were rate decelerating. Again, the electrical effect was predominant in these sets. Of the seven sets of other carboxylic acids studied, only the *cis*-α-phenylcinnamic acids showed a steric effect. Again, the electrical effect was predominant in this set. The composition of the electrical effect varied sufficiently to make impossible the use of a single set of ortho-substituent constants for the correlation of all sets studied. The values of α and β obtained in the correlations are linear in the $E_T(30)$ solvent parameters. New values of $E_T(30)$ have been calculated for *i*-BuOH and Me_2EtCOH. The possibility of hydrogen bonding in the case of hydroxyl substituents is evaluated. Hydrogen bonding definitely occurs in the case of salicylic acid; it may possibly occur in the case of 2-hydroxyphenylacetic acid.

In this paper we extend our previous work[1-5] on the nature of the ortho effect by a study of the rates of reaction of ortho-substituted carboxylic acids with diphenyldiazomethane by means of linear free energy relationships. The major objectives of this investigation are to detect the presence or absence of steric effects and to determine the composition of the electrical effect. The method which was employed in the study of steric effects is based on the correlation of the rate constants with linear free energy relationships. In order to carry out the analysis of the data it is necessary to examine four possible cases. 1. The steric effect may be represented by a steric parameter. Then the data will follow the equation

$$Q_X = \alpha\sigma_{IX} + \beta\sigma_{RX} + \psi\nu_X + h \quad (1)$$

where σ_I and σ_R represent the localized (field) and delocalized (resonance) electrical effects and υ is a steric parameter defined as[6]

$$\upsilon_X = r_{VX} - r_{VH} = r_{VX} - 1.20 \quad (2)$$

In eq 2, r_{VX} and r_{VH} are the van der Waals radii of the X group and the hydrogen atom, respectively. We have chosen υ as a steric parameter in preference to the Taft E_S steric parameters[7] because we have previously demonstrated a linear relationship between E_S and the van der Waals radii.[1] 2. The steric effect cannot be represented by some steric parameter, and therefore the data do not obey a linear free energy relationship. In this case, the electrical effect of the X substituent remains a function of σ_{IX} and σ_{RX}. Whatever part of the rate constant is not represented by the electrical effect is dependent on the steric effect S_X. Then for the rate constant of the compound bearing the X substituent we may write

$$Q_X = \alpha\sigma_{IX} + \beta\sigma_{RX} + S_X + h \quad (3)$$

3. The steric effect is constant. Then υ_X is constant, and therefore $\psi\upsilon_X$ is constant. From eq 1

$$Q_X = \alpha\sigma_{IX} + \beta\sigma_{RX} + h' \quad (4)$$

where

$$h' = h + \psi\nu_X \quad (5)$$

Table I: Results of Correlations[r]

Set	α	β	ψ	h	R[a]	F[b]	r_{12}[c]	r_{13}[c]	r_{23}[c]	s_{est}[d]	s_α[d]	s_β[d]	s_ψ[d]	s_h[d]	n[e]
1A	1.55	1.04	0.556	−0.467	0.988	66.38[f]	0.730[l]	0.183	0.086	0.0691	0.137[f]	0.277[i]	0.0723[f]	0.0595[f]	9
1B	1.37	0.888		−0.130	0.828	6.562[k]	0.730[k]			0.226	0.441[k]	0.901[o]		0.987[o]	9
2A	1.45	0.820	0.522	−0.0701	0.993	154.1[f]	0.323	0.171	0.302	0.0554	0.0776[f]	0.0836[f]	0.0567[f]	0.0461[n]	11
2B	1.39	1.02		0.277	0.897	16.49[g]	0.323			0.188	0.262[f]	0.273[h]		0.0900[i]	11
3A	2.68	2.58	0.752	0.360	0.998	168.2[h]	0.920[l]	0.414	0.073	0.0205	0.220[h]	0.294[i]	0.0468[h]	0.0203[h]	6
3B	−0.448	−1.49		0.316	0.698	1.424[m]	0.920[k]			0.191	0.948[p]	1.39[o]		0.187[n]	6
4A	2.10	1.18	0.564	−1.45	0.996	196.9[f]	0.730[l]	0.183	0.086	0.0535	0.106[f]	0.214[h]	0.0560[f]	0.0461[f]	9
4B	1.91	1.03		−1.11	0.906	13.77[h]	0.730[k]			0.225	0.440[h]	0.900[o]		0.131[f]	9
5A	2.48	1.85	0.498	−0.938	0.994	137.8[f]	0.730[l]	0.183	0.086	0.0702	0.139[f]	0.281[h]	0.0735[h]	0.0605[f]	9
5B	2.32	1.72		−0.635	0.937	21.63[g]	0.730[k]			0.205	0.400[h]	0.817[l]		0.119[h]	9
6A	1.67	1.25	0.394	−0.278	0.984	50.50[f]	0.730[l]	0.183	0.086	0.0787	0.156[f]	0.315[i]	0.0824[h]	0.0679[h]	9
6B	1.54	1.14		−0.387	0.907	13.86[h]	0.730[k]			0.170	0.331[h]	0.677[n]		0.0988[p]	9
7A	2.15	2.09	−0.118	−1.31	0.999	839.8[f]	0.730[l]	0.183	0.086	0.0239	0.0475[f]	0.0957[f]	0.0250[h]	0.0206[f]	9
7B	2.19	2.12		−1.38	0.995	276.9[f]	0.730[k]			0.0508	0.0992[h]	0.203[h]		0.0296[h]	9
8A	1.94	1.50	0.222	−1.26	0.996	190.2[f]	0.730[l]	0.183	0.086	0.0460	0.0913[f]	0.184[f]	0.0481[h]	0.0396[f]	9
8B	1.87	1.44		−1.13	0.977	62.55[f]	0.730[k]			0.0964	0.188[f]	0.385[h]		0.0561[f]	9
9A	0.377	0.308	0.0384	0.414	0.992	122.3[f]	0.203	0.273	0.062	0.0170	0.0204[f]	0.0391[f]	0.0178[l]	0.0136[f]	10
9B	0.364	0.297		0.437	0.986	118.6[f]	0.203			0.0210	0.0241[f]	0.0480[f]		0.0103[f]	10
10A	0.437	0.347	0.00969	0.0605	0.993	147.4[f]	0.203	0.273	0.062	0.0183	0.0220[f]	0.0422[f]	0.0191[p]	0.0147[h]	10
10B	0.434	0.344		0.0664	0.993	247.2[f]	0.203			0.0173	0.0199[f]	0.0396[f]		0.00847[f]	10
11A	0.520	0.436	0.0190	0.287	0.996	230.6[f]	0.203	0.273	0.062	0.0174	0.0209[f]	0.0401[f]	0.0182[o]	0.0139[f]	10
11B	0.514	0.431		0.299	0.995	341.1[f]	0.203			0.0175	0.0202[f]	0.0401[f]		0.00857[f]	10
12A	0.509	0.422	−0.230	−0.0776	0.994	153.4[f]	0.203	0.273	0.062	0.0214	0.0258[f]	0.0494[f]	0.0224[o]	0.0172[h]	10
12B	0.517	0.428		−0.0916	0.992	227.9[f]	0.203			0.0215	0.0248[f]	0.0492[f]		0.0105[f]	10
13A	0.603	0.514	−0.101	−0.448	0.997	290.1[f]	0.203	0.273	0.062	0.0195	0.0235[f]	0.0450[f]	0.0204[h]	0.0157[f]	10
13B	0.637	0.542		−0.510	0.982	96.56[f]	0.203			0.0408	0.0471[f]	0.0935[h]		0.0200[f]	10
14A	0.672	0.601	−0.0996	−0.703	0.997	343.4[f]	0.203	0.273	0.062	0.0199	0.0240[f]	0.0459[f]	0.0208[h]	0.0159[f]	10
14B	0.705	0.628		−0.764	0.986	121.9[f]	0.203			0.0404	0.0466[f]	0.0925[f]		0.0198[f]	10
15A	0.228	0.270	0.0253	−0.143	0.940	7.567[l]	0.062	0.285	0.130	0.0440	0.0683[k]	0.0801[k]	0.0870[p]	0.0399[k]	7
15B	0.234	0.267		−0.136	0.938	14.66[j]	0.062			0.0387	0.0576[i]	0.0698[i]		0.0275[h]	7
16A	0.330	0.184	−0.0237	0.775	0.994	86.31[g]	0.062	0.285	0.130	0.0147	0.0228[f]	0.0267[h]	0.0290[o]	0.0133[f]	7
16B	0.325	0.186		0.768	0.993	140.9[f]	0.062			0.0141	0.0209[f]	0.0254[h]		0.00999[f]	7
17A	0.257	0.314	0.0726	0.0109	0.925	5.920[l]	0.062	0.285	0.130	0.0582	0.0903[l]	0.106[l]	0.115[p]	0.0528[q]	7
17B	0.273	0.306		0.0316	0.914	10.22[k]	0.062			0.0536	0.0799[k]	0.0969[k]		0.0381[o]	7
18A	0.325	0.311	0.177	0.00577	0.916	5.186[m]	0.062	0.285	0.130	0.0757	0.118[l]	0.138[n]	0.150[o]	0.0687[q]	7
18B	0.364	0.292		0.0561	0.874	6.446[l]	0.062			0.0794	0.118[k]	0.143[n]		0.0564[o]	7
$19A_1$	0.153	0.0987	−0.00955	0.940	0.606	0.579[m]	0.062	0.285	0.130	0.0853	0.132[o]	0.155[p]	0.169[q]	0.0774[h]	7
$19A_2$	0.429	0.420	−0.0988	0.994	0.993	44.39[j]	0.601	0.386	0.116	0.0159	0.0389[h]	0.0454[i]	0.0329[l]	0.0156[f]	6
$19B_1$	0.151	0.0997		0.937	0.605	1.155[m]	0.062			0.0739	0.110[o]	0.134[o]		0.0526[f]	7
$19B_2$	0.383	0.399		0.963	0.958	16.93[j]	0.601			0.0305	0.0684[i]	0.0859[i]		0.0224[f]	6
20A	0.220	0.112	0.0820	1.29	0.958	3.468[m]	0.131	0.435	0.260	0.0480	0.110[o]	0.104[o]	0.0839[p]	0.0480[k]	5
20B	0.272	0.148		1.30	0.910	4.838[m]	0.131			0.0474	0.0944[n]	0.0961[o]		0.0447[h]	5
21A	0.742	0.281	−0.0463	0.505	0.9994	284.3[k]	0.131	0.435	0.260	0.0126	0.0288[k]	0.0273[l]	0.0221[o]	0.0126[i]	5
21B	0.713	0.260		0.496	0.997	157.1[h]	0.131			0.0207	0.0413[h]	0.0420[k]		0.0195[h]	5

[a] Multiple correlation coefficient. [b] *F* test for significance of regression. Superscripts indicate confidence levels. [c] Partial correlation coef ficients of σ_I on σ_R, σ_I on v, σ_R on v. [d] Standard errors of the estimate, α, β, ψ, and *h*. Superscripts indicate confidence level of "Student *t*" test. [e] Number of points in the set. [f] 99.9% confidence level (CL). [g] 99.5% CL. [h] 99.0% CL. [i] 98.0% CL. [j] 97.5% CL. [k] 95.0% CL. [l] 90.0% CL. [m] <90.0% CL. [n] 80.0% CL. [o] 50.0% CL. [p] 20.0% CL. [q] <20.0% CL. [r] The confidence level of the partial correlation coefficients is less than 90% unless otherwise indicated.

4. The steric effect is negligible or nonexistent. Then $\psi = 0$, and from eq 1

$$Q_X = \alpha\sigma_{IX} + \beta\sigma_{RX} + h \quad (6)$$

which is simply the entended Hammett equation. Equations 4 and 6 are equivalent.

There is a fifth case which may also be considered. It is possible that in some sets[8] no steric effect occurs until a certain limiting substituent size is reached, while substituents whose size is greater than the limiting value will show a steric effect. Such a set consists of the combination of two subsets, one of which obeys eq 6 (shows no steric effect) whereas the other obeys eq 1 or 3.

The analysis of the data may now be carried out as follows.

I. The set to be studied is correlated with eq 1. The correlation is tested for significance by means of the F test, for which a confidence level greater than or equal to 90% is considered meaningful. If the correlation is significant then, the set may belong to case 1, case 3, or case 4. Case 1 is distinguished from cases 3 and 4 by a "student t" test of ψ. A confidence level greater than or equal to 90.0% indicates that the set is an example of case 1. If the confidence level of the t test is less than 90.0% then the set belongs to case 3 or case 4. If the correlation with eq 1 is not meaningful (that is, if the confidence level of the F test is less than 90.0%), then the set may be an example of case 2, case 3, or case 4, or it may be an example of case 1 with the wrong choice of steric parameter. It is also necessary to consider the confidence levels of the partial correlation coefficients r_{13} and r_{23} which measure the extent of correlation between σ_I and υ and between σ_R and υ, respectively. If either of these partial correlation coefficients has a confidence level greater than or equal 90.0% then it is impossible to separate the steric and electrical effects in the set being studied.

II. The data set being studied is correlated with eq 6. The measure of a successful correlation is again the confidence level of the F test. If the correlation is meaningful, then the set is an example of case 3 or case 4. That this must be true is shown by the following argument. If the set belongs to case 1 or case 2 then a steric effect is present. Since eq 6 does not account for this steric effect it cannot successfully correlate a set which belongs to case 1 or case 2. Case 3 may be distinguished from case 4 by a "student t" test for the significance of the difference between the experimentally observed value for h (this is the data point for the unsubstituted member of the set) and the value of h obtained from the correlation. If $h_{obsd} \neq h$, then the set belongs to case 3. If $h_{obsd} = h$, then the set is an example of case 4. Should the correlations with both eq 1 and 6 be unsuccessful, the set is either an example of case 2, or it belongs to case 1 and the choice of a steric parameter and incorrect. Unfortunately, it is not possible at the present time to distinguish between these possibilities. It might be argued that case 5 is also a possibility. Case 5 can be discerned by plotting the data against appropriate substituent constants. Those members of the set which do not shown a steric effect will give a linear plot, from which the larger groups will deviate.

Twenty sets of reaction rates of ortho-substituted carboxylic acids with diphenyldiazomethane have been subjected to the analysis described above. For the data used in these correlations, see the paragraph at the end of this paper regarding supplementary material. The σ_I constants required were taken from our compilation[9] when possible. The σ_R constants were obtained from the equation

$$\sigma_R = \sigma_p - \sigma_I \quad (7)$$

Table II
Values of ψ and P_S

Set	Solvent	T	ψ	P_S	Solvent parameter $[E_T(30)]^a$
1	EtOH	20	0.556	18	51.9
2	EtOH	30	0.522	19	51.9
3	EtOH	40	0.752	13	51.9
4	Dioxane	30	0.564	15	36.0
5	EtOAc	30	0.498	10	38.1
6	$MeOCH_2CH_2OH$	30	0.394	12	52.3
7	Me_2NCHO	30	−0.118	2.7	43.8
8	Me_2SO	30	0.222	6.0	45.0
9	MeOH	30	0.0384	5.3	55.5
13	t-BuOH	30	−0.101	8.3	43.9
14	Me_2EtCOH	30	−0.0996	7.3	(40.6)[b]
19	EtOH	30	−0.0988	10	51.9

[a] K. Dimroth, C. Reichardt, J. Siepmann, and F. Bohlmann, *Justus Liebigs Ann. Chem.*, 661, 1 (1963). [b] Calculated in this work.

using the σ_p constants of McDaniel and Brown[10] when available. In the case of the nitro group, the value of σ_I is taken from previous work.[11] Values of υ are generally taken from our collection.[6] Exceptions are the υ values for i-Pr and Et for which values of 0.76 and 0.56 respectively were used. These values were obtained by a method which will be described in a future publication. The value of the rate constant for the hydroxyl group was excluded from all sets in which it occurs (sets 2, 15, 16, and 17) due to the possibility of hydrogen bonding.

Results

Results of the correlations with eq 1 and 6 are set forth in Table I. Correlations labeled A and B are with eq 1 and 6, respectively. Results for correlation of set 19 with eq 1 and 6 were greatly improved by the exclusion of the value for the nitro group (sets $19A_2$ and $19B_2$).

Discussion

Steric Effect. Of the eight sets of benzoic acids in various solvents, three gave a confidence level of 99.9% and five a CL of 99.0% for the "student t" test for the significance of ψ. It is clear, then, that sets 1–8 belong to case 1. This is the most certain, clear-cut steric effect we have ever observed for any physical or chemical data for ortho-substituted benzenes.[1-5] To describe the magnitude of the steric effect we have defined the quantity P_S, the percent of steric effect, by means of the equation

$$P_S = \frac{|\psi|\,100}{|\alpha| + |\beta| + |\psi|} \quad (8)$$

Values of P_S are set forth in Table II. The values of P_S for the benzoic acid sets range from 2.7 to 19. Thus, although the steric effect is unquestionably present, in all sets it is subordinate to the electrical effect. This is in agreement with our previous results. We have so far observed no set of data, chemical or physical, in which the steric effect was predominant.[1-5] It is interesting to observe that seven of the eight benzoic acids gave positive values of ψ indicating steric acceleration of the rate while the set in dimethylformamide gave a negative value of ψ, indicating steric retardation of the rate. While the magnitude of the steric effect as measured by both ψ and P_S varies with solvent, inspection of Table II shows no relationship of either ψ or P_S with the $E_T(30)$ solvent parameters. As most solvent parameters are very approximately linearly related to each other we

Table III
"Student *t*" Tests for the Significance of the Difference between *h* and h_{obsd}

Set	h_{obsd}	h^a	b	$s_h{}^a$	t	n^c
10	0.0570	0.0664	0.0094	0.00847	1.110[d]	10
11	0.290	0.299	0.009	0.00857	1.050[d]	10
12	−0.0926	−0.0916	0.0010	0.0105	0.095[e]	10
15	−0.145	−0.136	0.009	0.0275	0.327[f]	7
16	0.780	0.768	0.012	0.00999	1.201[d]	7
17	0.0170	0.0316	0.0146	0.0381	0.383[f]	7
18	−0.00131	0.0561	0.0574	0.0564	1.018[d]	7
21	0.505	0.496	0.009	0.0195	0.462[f]	5

[a] From Table I. [b] $h_{obs} - h$. [c] Number of points in the set. [d] 50% CL. [e] 20% CL. [f] 20% CL.

may conclude that neither ψ nor P_S is related to any other solvent parameter.

Of the six sets of phenylacetic acids correlated with eq 1, two gave very good confidence levels for the "student *t*" test of 99.0%, one gave a poor confidence level of 90.0%, and the other three did not give significant confidence levels. Sets 10, 11, and 12 must belong to case 3 or case 4 as they all gave excellent correlations with eq 6. To differentiate between these possibilities, we must determine whether $h = h_{obsd}$. Values of the "student *t*" test for the significance of the difference between h and h_{obsd}, together with their confidence levels, are set forth in Table III. Inspection of these values for sets 10, 11 and 12 shows that there is no significant difference between h and h_{obsd} for these sets. It therefore follows that these sets are members of case 4 and are free of any steric effect.

Inspection of the ψ values for the sets which belong to case 1 shows that set 9 has a small accelerating steric effect on the rate whereas sets 13 and 14 show larger decelerating effects on the rate. It is perhaps significant that sets 13 and 14 were studied in *t*-BuOH and Me_2EtCOH, respectively. These are the largest and bulkiest of the solvents in which the phenylacetic acids were studied. It is of interest to note that the P_S values of sets 9, 13, and 14 again clearly show the predominance of the electrical effect, in agreement with our previous results.[1-5]

Of the seven sets of acids with side chains intervening between the carboxyl group and the ring which were correlated with eq 1, only one set gave a meaningful "student *t*" test for the significance of ψ, a confidence level of 90% was obtained indicating poor results. This is probably due to the small size of the set ($19A_2$) which had only six points. This set is probably an example of case 1. Of the remaining six sets, five (sets 15–18 and 21) gave significant correlations with eq 6. These sets belong to case 3 or case 4. The sixth set, set 20, did not give significant correlation with either eq 1 or 6. This is probably due to the small number of points in the set, five. Examination of the values of the "student *t*" test for the significance of the difference between h and h_{obsd} for sets 15–18 and 21 given in Table III shows that for all five of these sets h is equal to h_{obsd} and therefore these sets are examples of case 4; that is, they are free of steric interactions. The steric effect observed for sets $19A_2$ is one of rate deceleration. Again, the P_S value shows that electrical effects are predominant in this set.

Composition of the Electrical Effect. Previously[1] we have described the composition of the electrical effect by means of the parameter where

$$\epsilon = \beta/\alpha \qquad (9)$$

We believe that a better description of the composition of the electrical effect is the parameter P_R, given by

Table IV
Values of P_R

Set	Solvent	T	Side chain	$E_T(30)^a$	$P_R{}^b$
1	EtOH	20		51.9	40
2	EtOH	30		51.9	36
3	EtOH	40		51.9	49
4	Dioxane	30		36.0	36
5	EtOAc	30		38.1	43
6	$MeOCH_2CH_2OH$	30		52.3	43
7	Me_2NCHO	30		43.8	49
8	Me_2SO	30		45.0	44
9	MeOH	30	CH_2	55.5	45
10	EtOH	30	CH_2	51.9	44
11	*i*-BuOH	30	CH_2	(48.5)[c]	46
12	*i*-PrOH	30	CH_2	48.6	45
13	*t*-BuOH	30	CH_2	43.9	46
14	Me_2EtCOH	30	CH_2	(40.6)[c]	47
15	EtOH	30	CH_2CH_2	51.9	53
16	EtOH	30	CH_2O	51.9	36
17	EtOH	30	*T*-CH=CH	51.9	53
18	EtOH	30	*T*-CH=CPh	51.9	*d*
19	EtOH	30	*C*-CH=CPh	51.9	49
20	EtOH	30	C≡C	51.9	*e*
21	Dioxane	30	C≡C	36.0	27

[a] Footnote *a*, Table II. [b] P_R values for case 1 sets were calculated from correlations with eq 1; P_R values for case 4 sets were calculated from correlations with eq 6. [c] Calculated in this work. [d] β was not significant for this set. [e] Correlation was not significant for this set.

$$P_R = \beta 100/(\alpha + \beta) \qquad (10)$$

The P_R values have the advantage that their range is 0–100 while ϵ has a range from 0 to infinity. Values of P_R are reported in Table IV.

The P_R and ϵ values are related to each other by the expression

$$P_R = \epsilon 100/(\epsilon + 1) \qquad (11)$$

Values of P_R obtained range from 27 to 53. Obviously then no one ortho substituent constant will be applicable to all sets of data involving the reaction of carboxylic acids with diphenyldiazomethane. These results agree with our previous findings.[1-5]

The values of P_R for the benzoic acids seem somewhat dependent on solvent. Inspection of $E_T(30)$ values given in Table IV indicates no dependence of P_R on $E_T(30)$. There seems to be a dependence of P_R on temperature. Values of P_R for the benzoic acid sets range from 36 to 49. It should be noted that r_{12}, the partial correlation coefficient of σ_I on σ_R, was significant at the 90% CL for sets 1, and 3–8. This suggests that there may be some uncertainty in the P_R values for the benzoic acid sets. The values of P_R for the phenylacetic acids are essentially constant and are independent of the solvent. The sets show an average P_R value of 46.

We may now consider the variation of the P_R value with side chain. Considering only sets in EtOH at 30°, we may compare sets 2, 10, 15–17, and 19. In so doing, we observe that with the exception of set 16, there is an increase from $P_R = 36$ for no side chain to $P_R = 44$ for a CH_2 side chain to $P_R = 49$ to 53 for a two carbon-atom side chain. This result is in agreement with our previous observations on the variation of the composition of the electrical effect with side chain in proton transfer reactions.[5]

Variation of the Reaction Parameters with Solvents. Values of α and β for the phenylacetic acid sets (for sets 9,

Table V
Results of Correlations with Equations 12 and 13

Set	m	c	r[a]	F[b]	s_{est}[c]	s_m[c]	s_c[c]	n[d]
A_1	−0.0466	4.04	0.862	11.59[e]	0.207	0.0137[e]	0.615[f]	6
A_2	−0.0654	4.96	0.969	46.34[f]	0.115	0.00960[f]	0.447[f]	5
B_1	−0.0301	2.79	0.438	0.952[g]	0.467	0.0209[h]	1.39[i]	6
B_2	−0.0677	4.63	0.810	5.739[j]	0.338	0.0283[j]	1.32[e]	5
C	−0.0199	1.48	0.997	332.7[k]	0.00934	0.00109[f]	0.0548[f]	4
D	−0.0184	1.32	0.990	95.60[l]	0.0161	0.00189[m]	0.0946[f]	4

[a] Correlation coefficient. [b] F test for significance of regression. [c] Standard errors of the estimate, m, and c. [d] Number of points in the set. [e] 95.0% CL. [f] 99.0% CL. [g] <90% CL. [h] 50% CL. [i] 80% CL. [j] 90% CL. [k] 99.95% CL. [l] 97.5% CL. [m] 98.0% CL.

Table VI
Variation of the Reaction Parameter with Side Chain

Set	Side chain	α	β	Set	Side chain	α	β
2		1.45	0.820	17	*trans*-CH=CH	0.273	0.306
10	CH_2	0.434	0.344	18	*trans*-CH=CPh	0.364	*a*
15	CH_2CH_2	0.234	0.267	19	*cis*-CH=CPh	0.429	0.420
16	CH_2O	0.325	0.186				

[a] β was not significant for this set.

13, and 14 values of α and β are from correlations with eq 1; for sets 10, 11, and 12 values of α and β are taken from correlations with eq 6) were correlated with the $E_T(30)$ solvent parameters[12] by the equations

$$\alpha = mE_T + c \quad (12)$$

$$\beta = mE_T + c \quad (13)$$

Results of the correlations are given in Table V. Best results for the correlation of α and β of substituted benzoic acids are obtained on exclusion of the values for dioxane (sets A_2 and B_2, respectively). Set A_2 gave very good correlation and set B_2 gave poor but significant correlation. Correlation of α (set C) and β (set D) for phenylacetic acids gave excellent and good results, respectively. The correlation of α values seems to be superior to that of β values.

The results obtained for the correlation of α for phenylacetic acids (set 6) are good enough to permit their use in the calculation of new E_T values. Values of $E_T(30)$ were calculated for *i*-BuOH and Me_2EtCOH and the values obtained are 48.5 and 40.6, respectively.

Variation of Reaction Parameters with Side Chain. We may now consider the effect of the side chain on values of α and β. Appropriate values of α and β are reported in Table VI. All data are in EtOH at 30°.

Values of α and β for sets 2, 10, and 19 are from correlations with eq 1; values of α and β for sets 15–18 are from correlations with eq 6. With the exception of the α and β values for the *cis*-CH=CPh side chain, the magnitude of α and β falls off with increasing size of the side chain as is expected. The values obtained for the methylene side chain seem too small, however.

Hydrogen Bonding in the Case of Hydroxyl Substituent. The rate constants for X=OH were excluded from the correlations of sets 2, 15, 16, and 17 due to the possibility of hydrogen bonding. To determine whether hydrogen bonding occurs, values of the rate constant for the hydroxyl group were calculated as were values of the quantity $K_{OH,obsd}/k_{OH,calcd}$. These values are set forth in Table VII. The $k_{OH,calcd}$ values were calculated from the correlations with eq 1 in the case of set 2, the $k_{OH,calcd}$ values for sets 15, 16, 17 were calculated from correlations with eq 6. The value of $k_{OH,obsd}/k_{OH,calcd}$ for set 2 suggests a large hydrogen-bonding effect. The value of this ratio for set 16 indicates the possibility of a very small hydrogen bonding effect, if any exists at all. The values of $k_{OH,obsd}/k_{OH,calcd}$ for sets 15 and 17 show no hydrogen-bonding effect.

Table VII
Values of $k_{OH,calcd}$, $k_{CH,obsd}$, and $k_{OH,obsd}/k_{OH,calcd}$

Set	$k_{OH,calcd}$	$k_{OH,obsd}$	$k_{OH,obsd}/k_{OH,calcd}$
2	0.209	7.55	36
15	0.571	0.670	1.2
16	5.42	12.1	2.2
17	0.813	0.594	0.73

Registry No.—Diazodiphenylmethane, 883-40-9.

Supplementary Material Available. The data used in the correlations carried out in this paper will appear following this article in the microfilm edition of this journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-407.

References and Notes

(1) M. Charton, *Prog. Phys. Org. Chem.*, **8**, 235 (1971).
(2) M. Charton, *J. Amer. Chem. Soc.*, **91**, 6649 (1969).
(3) M. Charton and B. I. Charton, *J. Org. Chem.*, **36**, 260 (1971).
(4) M. Charton, *J. Org. Chem.*, **36**, 266 (1971).
(5) M. Charton, *J. Org. Chem.*, **36**, 882 (1971).
(6) M. Charton, *Progr. Phys. Org. Chem.*, **10**, 81 (1973).
(7) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 565.
(8) A data set, usually simply referred to as a set, consists of chemical (rate constants, equilibrium constants) or physical (spectral parameters, dipole moments, ionization potentials) properties for a group of compounds XGY in which X, the substituent, is varied; Y, the reaction site, and G, the skeletal group to which X and Y are bonded, are held constant. Also held constant are the reaction conditions such as medium and temperature.
(9) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(10) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(11) M. Charton and B. I. Charton, *J. Chem. Soc. B.*, 43 (1967).
(12) K. Dimroth, C. Reichardt, T. Siepmann, and F. Bohlmann, *Justus Liebigs Ann. Chem.*, **661**, 1 (1963).

β-Deuterium Isotope Effects for the Solvolysis of 2-Methyl-d_3-*exo*-2-norbornyl *p*-Nitrobenzoate and 2-Methyl-d_3-*endo*-2-norbornyl *p*-Nitrobenzoate

René J. Muller, Charles Winternitz, and B. L. Murr*

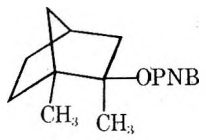
Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Received September 26, 1974

Kinetic isotope effects for the solvolysis of 2-methyl-d_3-*exo*-2-norbornyl *p*-nitrobenzoate and 2-methyl-d_3-*endo*-2-norbornyl *p*-nitrobenzoate were determined in 70% aqueous ethanol. Within experimental error, k_H/k_D for both epimers are similar—exo *p*-nitrobenzoate (1.22 ± 0.02 at 75.0°), endo *p*-nitrobenzoate (1.26 ± 0.04 at 130.0°; 1.31 ± 0.05 corrected to 75.0°)—where k_H/k_D is calculated for three deuteriums for fully deuterated substrate. The similarity of the kinetic isotope effects for the exo and endo epimers argues against the supposition of extensive bridging in the intermediate for the solvolysis of the exo *p*-nitrobenzoate. These results are in good agreement with kinetic isotope effect measurements for other deuterated tertiary norbornyl substrates already in the literature.

There is extensive experimental evidence that carbonium ions derived from solvolysis of esters of exo tertiary norbornanols are classical and do not involve significant bridging.

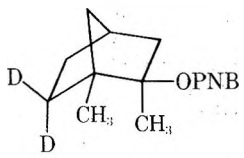
Goering and Humski, on observing that most of the activity remained in the products of solvolysis (alcohol + olefin) of optically active 1,2-dimethyl-*exo*-2-norbornyl *p*-nitrobenzoate (1) in 90% aqueous acetone, concluded that ionization proceeded predominantly through the asymmetric classical ion **2**.[1]



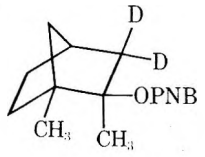
1

2

The same workers,[2] in trying to establish experimentally that the large γ-deuterium isotope effect (1.10) reported for the solvolysis of the secondary 6,6-dideuterio-*exo*-2-norbornyl brosylate[3] was a manifestation of assisted ionization, measured the rate of solvolysis of the tertiary 6,6-dideuterio-1,2-dimethyl-*exo*-2-norbornyl *p*-nitrobenzoate (**3**) in 90% aqueous acetone (78.47°). They observed a negligible kinetic isotope effect (k_H/k_D was 1.02 ± 0.01), a result consistent with the expectation of a classical intermediate.



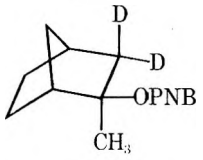
3



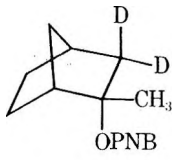
4

Humski[4] measured k_H/k_D for 1,2-dimethyl-*exo*-2-norbornyl-3,3-d_2 *p*-nitrobenzoate (**4**) in mixtures of 50–70% dioxane–water (69.30°). Although the observed kinetic isotope effects varied from 1.278 ± 0.010 for 50% dioxane–water to 1.351 ± 0.079 for 70% dioxane–water, the k_H/k_D calculated for ionization after correction for elimination was remarkably constant (1.22) over the entire range of solvent composition.[5a] Humski concluded that a k_H/k_D of 1.22 indicated that solvolysis proceeded through a classical intermediate.

Borčić and Sunko[6] measured k_H/k_D for both 2-methyl-*exo*-2-norbornyl-3,3-d_2 *p*-nitrobenzoate (**5**) and its endo epimer (**6**) in 70% aqueous acetone.[7] They observed a k_H/k_D of 1.334 ± 0.018 (95.0°) for **5** and 1.306 ± 0.060 (120.7°) for **6**. Even with the larger uncertainty in the value for **6**,



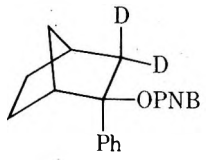
5



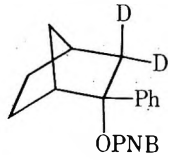
6

there does not seem to be a significant difference in kinetic isotope effects between the exo and endo *p*-nitrobenzoates. It should also be noted that the k_H/k_D for **5** falls within the range of the *observed* k_H/k_D for **4** measured by Humski in 70% dioxane–water (1.351 ± 0.079).[4]

Schaefer[8] examined 2-phenyl-*exo*-2-norbornyl-3,3-d_2 *p*-nitrobenzoate (**7**) and the endo epimer (**8**) in 60% aqueous dioxane. The observed k_H/k_D for **7** was 1.18 ± 0.02 (39.50°) and that for **8** was 1.15 ± 0.02 (62.50°). After correction to full deuteration[5b] (the *p*-nitrobenzoates contained 1.87 atoms of deuterium per molecule), k_H/k_D per D was 1.09 ± 0.01 for **7** and 1.08 ± 0.01 for **8**. Within the certainty of the measurements, the kinetic isotope effects for the exo and endo *p*-nitrobenzoates are indistinguishable and it was concluded that in both cases solvolysis involved a classical intermediate.

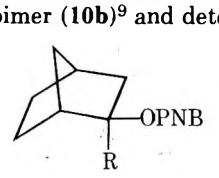


7

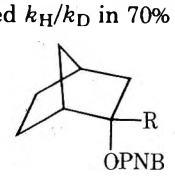


8

To complete the series of kinetic isotope effect measurements on tertiary norbornyl substrates, we prepared 2-methyl-d_3-*exo*-2-norbornyl *p*-nitrobenzoate (**9b**) and the endo epimer (**10b**)[9] and determined k_H/k_D in 70% aqueous ethanol at 75.0 and 130.0°, respectively. Rate constants for the solvolyses and the kinetic isotope effects (observed, corrected for full deuteration per D, corrected for full deuteration for three deuteriums, and, for **10**, corrected to 75.0°) are given in Table I. Within experimental error, $k_H/$



9



10

a, R = CH_3
b, R = CD_3

Table I
Rate Constants and Kinetic Isotope Effects for the Solvolysis of 9a, 9b, 10a, and 10b in 70% Aqueous Ethanol[a]

Compd[b]	Temp, °C	$10k$, hr^{-1}	$(k_H/k_D)_{obsd}$	$(k_H/k_D)_{corr/D}$[c]	$(k_H/k_D)_{corr/3D}$[d]
9a	75.0	2.51 ± 0.03	1.19 ± 0.02	1.07 ± 0.01	1.22 ± 0.02
9b		2.11 ± 0.03			
10a	130.0	2.63 ± 0.05	1.25 ± 0.04	1.08 ± 0.01 (correction to 75.0° negligible)	1.26 ± 0.04 (1.31 ± 0.05 corrected to 75.0°)[e]
10b		2.11 ± 0.05			

[a] Rate constants and standard deviations were calculated by computer as described in the Experimental Section and are the averages of two determinations. Errors for k_H/k_D were calculated from the formula given in W. J. Blaedel and V. W. Meloche, "Elementary Quantitative Analysis," 2nd ed, Harper and Row, New York, N.Y., 1963, p 642. [b] Deuterium analysis showed 2.59 atoms of D/molecule (86.3%) for **9b** and 2.74 atoms of D/molecule (91.3%) for **10b**.[12] [c] Isotope effect per D for fully deuterated substrate.[5b] [d] $[(k_H/k_D)_{corr/D}]^3$. [e] $(k_H/k_D)_{T_2} = (k_H/k_D)_{T_1}{}^{T_1/T_2}$.

k_D for the exo and endo deuterated *p*-nitrobenzoates are virtually the same. For closer comparison, since neither ester was fully deuterated, the observed kinetic isotope effects were corrected for full deuteration for three deuteriums, giving 1.22 ± 0.02 for **9b** and, after further correction to 75.0°, 1.31 ± 0.05 for **10b**.[10]

It is interesting to compare these results with those of Humski and Schaefer cited earlier. (Because our *p*-nitrobenzoates are trideuterated and the others dideuterated, k_H/k_D values corrected per D for full deuteration[5b] will be used for this comparison.) The k_H/k_D for **9b** (1.07 ± 0.01) is in fair agreement with Humski's number (1.11) for the solvolysis of **4** in aqueous dioxane; the k_H/k_D values for Schaefer's exo and endo *p*-nitrobenzoates **7** (1.09 ± 0.01) and **8** (1.08 ± 0.01) are, within experimental error, identical with k_H/k_D for **9b** (1.07 ± 0.01) and **10b** (1.08 ± 0.01).[11] The near identity of k_H/k_D for **9** and **10** argues against significant participation for the solvolysis of **9b**, as the results quoted earlier argued against it for the solvolyses of the exo tertiary substrates in **1**–**8**.

Experimental Section[12]

Synthesis. Methyl iodide-d_3 was prepared according to the procedure of Kuhn and Trischmann.[13]

2-Methyl-d_3-*endo*-2-norbornanol was prepared by adaptation of the procedure of Sauers.[14] A solution of Grignard reagent prepared from 51.64 g (0.3636 mol) of methyl iodide-d_3 and 8.8 g (0.36 mol) of magnesium in 110 ml of anhydrous ether was added to 20.0 g (0.182 mol) of norcamphor (Aldrich) in 150 ml of anhydrous ether. The reaction mixture was stirred at room temperature for 16 hr, allowed to stand overnight, and hydrolyzed by addition to a mixture of 200 g of ice, 26 g of ammonium chloride, and 50 ml of water. The layers were separated and the aqueous layer was extracted with ether (2 × 100 ml). The combined ether extracts were dried over magnesium sulfate and most of the solvent was removed by distillation through a Vigreux column. The crude product was distilled under aspirator pressure (~15 mm) to give 16 g (70%) of the deuterated norbornanol, bp 73.5–74.5°. The product solidified on standing, mp 30–31° (lit.[15] mp 31–32°).

2-Methyl-d_3-*endo*-2-norbornyl *p*-nitrobenzoate (10b) was prepared from the alcohol by the method of Brown.[15] To a stirred solution of 1 g (0.0079 mol) of the deuterated norbornanol in 30 ml of hexane, 2.72 ml (0.0079 mol) of *n*-butyllithium in hexane (Alfa Inorganics) was added with a syringe. Under nitrogen, 1.466 g (0.0079 mol) of *p*-nitrobenzoyl chloride (Aldrich, recrystallized from ligroin, mp 71–72°) was added to the stirred solution through a 15-cm tube attached to the flask. A fine, white precipitate appeared almost immediately and the suspension was stirred overnight.

The solid was removed by filtration and the hexane was removed on a rotary evaporator. Two recrystallizations from hot pentane afforded 0.5 g of **10b** mp 100–101° (lit.[15] mp 100.5°) after vacuum pumping. Deuterium analysis indicated the presence of 2.74 deuterium atoms/molecule (91.3%).

2-Methyl-d_3-*exo*-2-chlorononorbornane was prepared by adaptation of the procedure of Bartlett and Sargent.[16] A mixture of 12.6 g of 2-methyl-d_3-*endo*-2-norbornanol and 75 ml of concentrated hydrochloric acid was stirred vigorously at room temperature for 2 hr. Petroleum ether was added and the organic layer was separated, washed with saturated calcium chloride, and dried over calcium chloride. The solvent was removed on a rotary evaporator, affording about 14 g of a colorless oil. The ir spectrum showed no hydroxyl absorption.

2-Methyl-d_3-*exo*-2-norbornanol was prepared by adaptation of a procedure of Bartlett and Sargent.[16] Ice-cold aqueous 1 *N* sodium hydroxide (175 ml) was added to the flask containing the crude norbornyl chloride from the preparation above. The mixture was heated at 95° for 45 min and then stirred vigorously at room temperature for 16 hr. Ether was added and the organic layer was separated, washed with water, and dried over magnesium sulfate. The solvent was removed by careful evaporation, yielding a white, fluffy solid. The alcohol was recrystallized four times from pentane and sublimed, affording 6 g (57%) of fine, needle-like crystals, mp 84.8–85.4° (lit.[16] mp 84–85°).

2-Methyl-d_3-*exo*-2-norbornyl *p*-nitrobenzoate (9b) was prepared from the alcohol by the method of Brown[15] as described previously for the endo epimer. The ester crystallized as white, shimmering plates, mp 113.5–114.5° (lit.[15] mp 114.5°). Deuterium analysis indicated the presence of 2.59 deuterium atoms/molecule (86.3%).

2-Methyl-*endo*-2-norbornyl *p*-nitrobenzoate (10a) and **2-methyl-*exo*-2-norbornyl *p*-nitrobenzoate (9a)** were prepared by the same procedures described above except that methyl iodide was used instead of methyl iodide-d_3.

Kinetic Procedure. The rates of solvolysis in 70% aqueous ethanol for **9a, 9b, 10a,** and **10b** were measured with a Cary 14 ultraviolet spectrophotometer equipped with a thermostated cell holder, by following the absorbance [λ_{max} 2610 Å (ϵ 9330)] as a function of time. Because *p*-nitrobenzoic acid [λ_{max} 2710 Å (ϵ 10,037)] had a component of absorption at the λ_{max} of the ester, it was necessary to subtract the A_∞ value of the ester from each A_t value in the kinetic plot. In all cases, plots of $A_t - A_\infty$ *vs.* time were linear. As a check on the sampling technique, the undeuterated ester was solvolyzed at the same time as the deuterated ester for each determination of k_H/k_D.

The solvolyses were carried out in 10-ml Pyrex break seal ampoules. About 3 ml of approximately 1.3×10^{-4} *M* ester solution was dispensed into the ampoule, which was then fitted with a drying tube, cooled in Dry Ice–acetone, and sealed. Typically, seven or eight ampoules of both deuterated and undeuterated ester were prepared for each run. Solvolyses of the exo *p*-nitrobenzoate esters were carried out at 75.0° and those of the endo *p*-nitrobenzoates were carried out at 130.0°. After equilibration for about 1 hr, tubes were withdrawn every 0.5 hr, cooled in Dry Ice–acetone, and stored in the freezer (−20°) until analysis. The infinity samples were solvolyzed for at least 10 half-lives.

To check the analytical method, a run with **9a** was made where the unconverted **9a** and the liberated acid (as the anion) were separated by extraction and analyzed separately. Plots of ln $(A_t - A_\infty)$ *vs.* time for the disappearance of the ester and ln $(A_\infty - A_t)$ for the appearance of the acid were both linear and gave, within experimental error, the same rate constants as observed for solvolysis of **9a** measured by analyzing the ester–acid mixture.

The extraction procedure was carried out as follows. The aliquot to be analyzed (2 ml) was pipetted into a 50-ml separatory funnel (Teflon stopcock) containing 10 ml of spectral grade hexane and 1 ml of 5% sodium hydroxide. The separatory funnel was shaken vigorously for about 1 min. After the layers had separated, approxi-

mately 3 ml of the hexane solution was withdrawn with a Pasteur pipet and stored in a vial. The first few drops of the aqueous layer were discarded and the remainder of the solution was stored in a vial until analysis.

To prepare samples for the reference beam for the spectrophotometric analysis of both the hexane and the aqueous layers, an extraction was carried out exactly as described above except that 2 ml of 70% aqueous ethanol was used in place of the ester solution.

The 70% aqueous ethanol solution was prepared by weight, employing the appropriate corrections for buoyancy.[17] Reagent absolute ethanol (Pharmco) and distilled water were used without further purification. The solvent was stored in a sealed 2-l. erlenmeyer flask, equipped with a siphoning device.

Kinetic runs were carried out in 3-ml quartz uv cells (Pyrocell Manufacturing Company) which had a 1-cm path length. The cells had ground-glass stoppers, which were tightly sealed during the kinetic runs to minimize evaporation.

Beers' law plots of absorbance at 2610 Å *vs.* concentration were linear for both the exo and endo *p*-nitrobenzoate esters over the range of concentration through which the solvolysis kinetics were followed. Similar plots for *p*-nitrobenzoic acid both at 2710 Å (λ_{max} of the acid) and at 2610 Å (λ_{max} of the ester) were linear.

Rate constants were calculated from a sub-routine for plotting ln $(A_t - A_\infty)$ *vs.* time of a computer program devised by York,[18] modified by Dr. Michael Marron and used previously by Dr. John Conkling for calculating the rates of solvolysis of deuterated norbornyl brosylates.[19] An IBM 7094 computer was used for the calculations, giving the first-order rate constant and standard deviation for each run.

Acknowledgment. We wish to thank the National Science Foundation for the financial support of this work. We are grateful to Professor Alex Nickon and Dr. Raymond Weglein for commenting on the manuscript.

Registry No.—**9a,** 22467-58-9; **9a** free alcohol, 3212-15-5; **9b,** 53432-35-2; **9b** free alcohol, 53432-36-3; **10a,** 13351-30-9; **10a** free alcohol, 3212-16-6; **10b,** 53432-37-4; **10b** free alcohol, 53466-51-6; norcamphor, 497-38-1; methyl iodide-d_3, 865-50-9; *p*-nitrobenzoyl chloride, 122-04-3; methyl iodide, 74-88-4.

References and Notes

(1) H. L. Goering and K. Humski, *J. Amer. Chem. Soc.*, **90,** 6213 (1968).
(2) H. L. Goering and K. Humski, *J. Amer. Chem. Soc.*, **91,** 4594 (1969).
(3) B. L. Murr, A. Nickon, T. D. Schwartz, and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **89,** 1730 (1967); J. M. Jerkunica, S. Borčić, and D. E. Sunko, *ibid.*, 1732 (1967).
(4) K. Humski, *Croat. Chem. Acta*, **42,** 501 (1970).
(5) (a) When the correction is made for full deuteration, k_H/k_D per D is 1.11. (b) For full deuteration, k_H/k_D per D is given by $[k_H/k_D]_{obsd}^{1/X}$, where X = the number of atoms of deuterium per molecule [J. P. Schaefer, M. J. Dagani, and D. S. Weinberg, *J. Amer. Chem. Soc.*, **89,** 6938 (1967)].
(6) J. M. Jerkunica, B. Borčić, and D. E. Sunko, *Chem. Commun.*, 1488 (1968).
(7) No deuterium analysis was reported in this study.
(8) J. P. Schaefer, J. P. Foster, M. J. Dagani, and L. M. Honig, *J. Amer. Chem. Soc.*, **90,** 4497 (1968).
(9) The synthesis of the alcohol precursors of **10b** and **9b** was modeled after undeuterated analogs. See the Experimental Section.
(10) For the solvolysis of 1,2-dimethyl-*exo*-2-norbornyl *p*-nitrobenzoate (**4**) cited previously,[4] Humski observed that the k_H/k_D varied somewhat with the amount of elimination products as the solvent was changed from 50 to 70% dioxane–water. It should be pointed out that different amounts of elimination into the methyl groups of the undeuterated and deuterated *p*-nitrobenzoate esters could influence the k_H/k_D for **9** and **10.**
(11) Correction to 75° does not effect these numbers significantly.
(12) Melting points were determined in glass capillary tubes with a Thomas-Hoover apparatus and are corrected. Deuterium analyses (combustion-falling drop method) were performed by Mr. Joseph Nemeth, Urbana, Ill.
(13) R. Kuhn and H. Trischmann, *Justus Liebigs Ann. Chem.*, **611,** 117 (1958).
(14) R. R. Sauers, *J. Amer. Chem. Soc.*, **81,** 4873 (1959).
(15) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Amer. Chem. Soc.*, **86,** 1248 (1964).
(16) P. D. Bartlett and G. D. Sargent, *J. Amer. Chem. Soc.*, **87,** 1297 (1965).
(17) C. M. V. Santiago, Ph.D. Thesis, The Johns Hopkins University, 1969, p 113.
(18) D. York, *Can. J. Phys.* **44,** 1079 (1966).
(19) J. A. Conkling, Ph.D. Thesis, The Johns Hopkins University, 1969; B. L. Murr and J. A. Conkling, *J. Amer. Chem. Soc.*, **92,** 3462, 3464 (1970).

Bicyclo[3.2.0]hept-6-en-2-yl Carbonium Ion. 2-Methyl Substituent Effects[1]

Kazuyuki Yano

Department of Chemistry, Saitama Medical School, Moroyama-cho, Iruma-gun, Saitama 350-04, Japan

Received July 19, 1974

The methyl substituent effects on the rates and products of the solvolysis reactions of *exo*- and *endo*-2-methylbicyclo[3.2.0]hept-6-en-2-yl *p*-nitrobenzoates (**6**-OPNB and **5**-OPNB, respectively) were investigated by comparing those of the demethylated analogs (**7**-OTs and **2**-OTs, respectively) to elucidate the nature of the bicyclo[3.2.0]hept-6-en-2-yl carbonium ion **3.** The acetolysis rate of **7**-OTs indicates a rate enhancement of 3500 (25°) when compared to that of **2**-OTs, while **6**-OPNB undergoes solvolysis at a rate only 2.8 times as fast as **5**-OPNB at 25°. The acetolysis of **7**-OTs gives exclusively *anti*-7-norbornenyl acetate **14,** while **2**-OTs undergoes acetolysis to a 35:65 mixture of **7**-OAc and **14.** On the other hand, **5**-OPNB and **6**-OPNB yield exclusively **6**-OH through one common classical carbonium ion **15.** The above results suggest that **3** is mainly stabilized by a homoallylic interaction to lead to the initial carbonium ion **12,** which rearranges to the stable bishomocyclopropenyl carbonium ion **13.**

Although there is no straightforward demonstration of the existence of homoallylic carbonium ion intermediates, the unusual reactivities and stereospecific products of the solvolysis reactions of some rigid polycyclic ring compounds have been interpreted by homoallylic interactions between electron-deficient carbinyl carbon and electron-rich double bond.[2] In our recent study of *anti*-tricyclo[5.2.0.$0^{2,5}$]nona-3,8-dien-6-yl tosylate (**1**-OTs)[3] we observed that the rate of acetolysis of **1**-OTs is enhanced by a factor of 7.3×10^4 when compared to that of *endo*-bicyclo[3.2.0]hept-6-en-2-yl tosylate (**2**-OTs) which is in the partially similar ring system. In connection with this result, it

1-OTs **2**-OTs **3**

seems to be of some interest to further investigate the nature of the bicyclo[3.2.0]hept-6-en-2-yl carbonium ion **3.**[2-4] Thus, *exo*- and *endo*-2-methylbicyclo[3.2.0]hept-6-en-2-yl *p*-nitrobenzoates (**6**-OPNB and **5**-OPNB, respectively) and

Table I
Kinetic Data for Solvolysis of *exo*- and *endo*-2-Methylbicyclo[3.2.0]hept-6-en-2-yl *p*-Nitrobenzoates (6-OPNB and 5-OPNB), *exo*-Bicyclo[3.2.0]hept-6-en-2-yl Tosylate (7-OTs), and Related Compounds

Substrate	Temp, °C	k, sec^{-1}	ΔH^*, kcal/mol	ΔS^*, eu	k rel
6-OPNB[a]	125	$(1.71 \pm 0.02) \times 10^{-5}$ [b]	29.8 ± 0.3	−6.1 ± 0.8	
	150	$(1.68 \pm 0.02) \times 10^{-4}$ [b]			
	25	3.80×10^{-11} [c]			2.8
5-OPNB[a]	125	$(3.45 \pm 0.07) \times 10^{-6}$ [b]	28.2 ± 0.2	−13.2 ± 0.5	
	150	$(3.06 \pm 0.03) \times 10^{-5}$ [b]			
	25	1.38×10^{-11} [c]			(1.0)
7-OTs[d]	25	$(9.59 \pm 0.11) \times 10^{-6}$ [b]	23.9 ± 0.2	−1.5 ± 0.7	3.5×10^3
	50	$(2.35 \pm 0.04) \times 10^{-4}$ [b]			
2-OTs	25	2.70×10^{-9} [e]	28.1 ± 0.6[e]	−3.6 ± 1.5[e]	(1.0)
1-OTs	25	1.97×10^{-4} [e]	25.2 ± 1.4[e]	+9.0 ± 4.8[e]	7.3×10^4

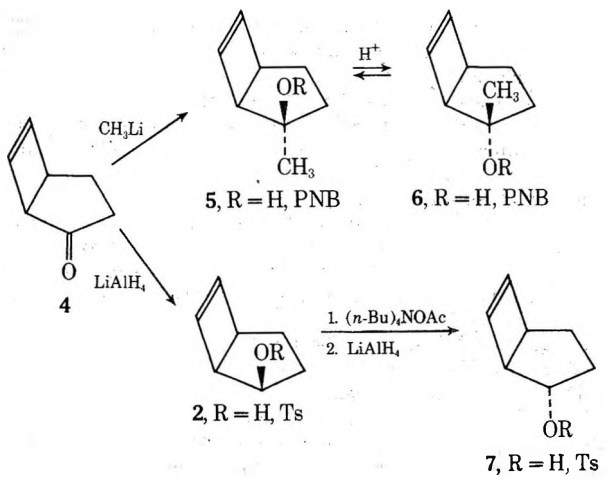
[a] *Ca.* 0.006 *M* in 50% acetone–50% water by volume. [b] The errors are deviation from the average of two runs. [c] Value extrapolated from data at higher temperature. [d] *Ca.* 0.02 *M* in acetic acid buffered with 0.045 *M* sodium acetate. [e] Reference 3.

the demethylated analogous tosylates (7-OTs and 2-OTs, respectively) have been synthesized and studied to obtain a quantitative assay of the methyl substituent effects on **3** formed in the solvolysis reactions. These results would provide some evidence for the existence of the homoallylic interaction in the transition state of the solvolysis reactions.

Results and Discussion

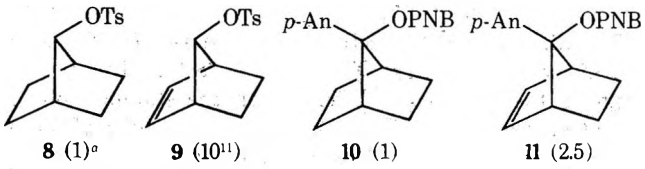
The known ketone **4**[5] was treated with freshly prepared methyllithium to produce exclusively **5**-OH in 83% yield, which was converted to **5**-OPNB in the usual fashion. The exo epimer (**6**-OH) was obtained by an acid-catalyzed isomerization of **5**-OH in low yield (17%) and converted to **6**-OPNB. The stereochemical assignments for the exo and endo epimers were based upon the methyllithium reaction of **4** and their nmr spectral data. Since attack of methyllithium on ketones would usually occur from the less hindered side of carbonyl groups, the only one product obtained here might be the endo epimer (**5**-OH). The nmr spectra of **5**-OPNB and **6**-OPNB show that the methyl group of **6**-OPNB absorbs at δ 1.20 which is shielded by 0.13 ppm more than of **5**-OPNB as expected by a result of diamagnetic anisotropic shielding effect. The exo alcohol (**4**-OH)[4b] was obtained by inversion of **2**-OTs[3] with tetra-*n*-butylammonium acetate in dry acetone[6] followed by lithium aluminum hydride reduction and was converted to **7**-OTs (23% based on **2**-OTs) (Scheme I).

Scheme I



The solvolytic reactivity of **7**-OTs was measured in buffered acetic acid by the uv absorbance method,[3] and the reactivities of **5**-OPNB and **6**-OPNB were measured in 50% aqueous acetone by the titrimetric method.[3] The kinetic data are summarized in Table I where literature values for related compounds are involved for comparison.

Generally, it has been known that the introduction of electron-releasing substituents at a cationic center leads to diminution in participation by double bonds resulting in a classical carbonium ion.[2a,7] For example, the acetolysis rate of *anti*-7-norbornenyl tosylate (**9**) is enhanced by a factor of 10^{11} over that of 7-norbornyl tosylate (**8**),[8] while 7-*p*-anisyl-*anti*-7-norbornenyl *p*-nitrobenzoate (**11**) undergoes solvolysis at a rate only 2.5 times greater than 7-*p*-anisyl-7-norbornyl *p*-nitrobenzoate (**10**).[9] Thus, a comparison of the exo/endo rate ratio for **5**-OPNB and **6**-OPNB to that for **2**-OTs and **7**-OTs will account for the natures of the initial intermediates formed on ionization of these isomeric compounds.



8 (1)[a] **9** (10^{11}) **10** (1) **11** (2.5)

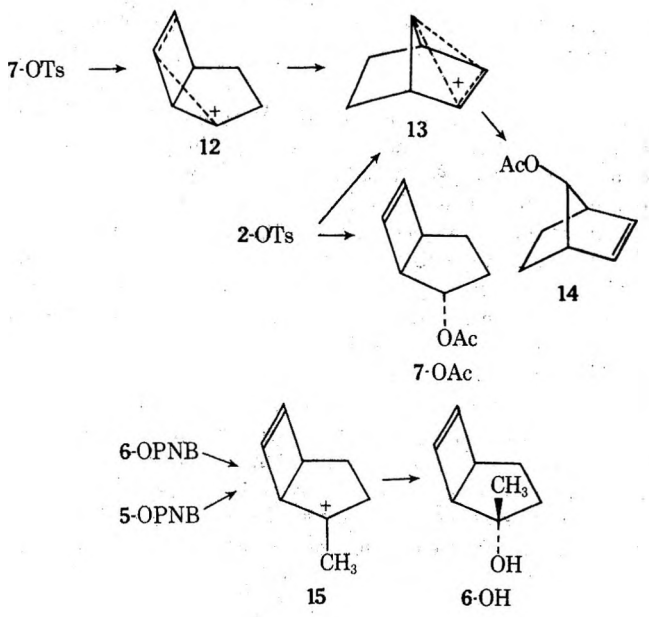
[a] k rel in parentheses.

It is clear from Table I that **7**-OTs is 3.5×10^3 times more reactive than **2**-OTs while **6**-OPNB undergoes solvolysis at a rate 2.8 times as fast as **5**-OPNB at 25°. This result suggests that the high reactivity of **7**-OTs might be mainly due to participation of the double bond in the ionization at the reaction site to produce the homoallylic carbonium ion **12**. Here, it is interesting to note that even **7**-OTs is less reactive than **1**-OTs in spite of the fact that the similar homoallylic interaction should be expected in their transition states. The difference in the reactivity of **1**-OTs and **7**-OTs (*ca.* 20) appears to result from a combination of two factors. First, an increase in reactivity of **1**-OTs probably results from a ground-state interaction[10] with the *anti*-cyclobutene ring providing relief of strain at the transition state. Second, there is likely a more favorable geometry for the homoallylic interaction by the double bond in **1**-OTs than in **7**-OTs; since the nmr spectral study of **7**-OTs suggests **7**-OTs in a "boat" conformation,[11] this conformation would provide decrease in the homoallylic interaction because of the prolonged distance between the reaction center and the double bond, compared to the rigid tricyclic tosylate (**1**-OTs).

The acetolysis of **7**-OTs gives exclusively *anti*-7-norbornenyl acetate **14**, while **2**-OTs undergoes acetolysis to a 35:

65 mixture of 7-OAc and 14 in accord with Story's result.[2a] From the kinetic data and the solvolysis studies, it is suggested that the incipient positive center of 7-OTs is stabilized first by the homoallylic interaction to produce the initial carbonium ion intermediate 12,[12] which rapidly rearranges to the bridged carbonium ion 13. On the other hand, 2-OTs leads predominantly to 13 and, at the same time, partially to 7-OAc by attack of solvent. Both epimeric *p*-nitrobenzoates, 5-OPNB and 6-OPNB, however, yield exclusively 6-OH as only the monomeric alcohol, suggesting one common classical carbonium ion intermediate 15 which is captured by solvent from the less hindered side. The observations are summarized in Scheme II.

Scheme II



The difference in the activation energies of 7-OTs (ΔH^* = 23.9 kcal/mol) and 2-OTs (ΔH^* = 28.1 kcal/mol) also suggests the significant difference in the stabilization of their transition states. The conformational studies of these bicyclic ring systems by X-ray analysis are under investigation.

Experimental Section

Melting points were taken on a Yamato MP-21 melting point apparatus and uncorrected. Infrared spectra were recorded on a Shimadzu IR-400 spectrophotometer and ultraviolet spectra were determined with a Shimadzu UV-200 spectrophotometer. Nuclear magnetic resonance spectra were recorded using a Hitachi R-24 instrument with the chemical shift (δ) given in parts per million down from TMS. Gas–liquid chromatography was performed on a Shimadzu GC-4B instrument. Mass spectra were determined with a JEOL-Q10 mass spectrometer. Microanalyses were determined in the microanalytical laboratory of Institute of Physical and Chemical Research, Wako-shi, Saitama, Japan.

***endo*-2-Methylbicyclo[3.2.0]hept-6-en-2-ol (5-OH).** To freshly prepared methyllithium in ether (*ca.* 0.05 mol) was added dropwise a solution of 4[3] (4.0 g, 0.037 mol) in 20 ml of ether at room temperature under nitrogen atmosphere. The resulting solution was stirred for 30 min. The excess methyllithium was destroyed by addition of ammonium chloride, and water was carefully added to the flask. After separation of the organic layer, the aqueous layer was extracted with ether. The ethereal solution was combined with the organic layer, and the combined solution was washed with water and dried ($MgSO_4$). After removal of ether distillation gave the endo alcohol 5-OH as a clear oil [3.8 g, 83%, bp 60–61.0° (9 mm)]: ir (film) 3350 (OH), 3050, 2930, 1290, 1150, and 1120 cm^{-1}; nmr (CCl_4) δ 6.15 and 6.03 (2 d, AB, 2 H, vinyl, J = 2.6 Hz), 3.50 (s, 1 H, –OH), 3.05 (m, 1 H, H_5), 2.75 (d, 1 H, H_1, J = 3.6 Hz), 2.20–1.70 (m, 1 H), 1.60–1.20 (m, 3 H), and 1.10 (s, 3 H, $-CH_3$); mass spectrum *m/e* 124 (M^+), 109, and 106.

***endo*-2-Methylbicyclo[3.2.0]hept-6-en-2-yl *p*-Nitrobenzoate (5-OPNB).** To a solution of 5-OH (500 mg, 4.04 mmol) in 15 ml of dry pyridine was added *p*-nitrobenzoyl chloride (760 mg, 4.10 mmol) in small portions at 0°. After completion of the addition, the resulting solution was allowed to stand in a refrigerator for 5 days and then poured into ice–water (100 g) containing 5 ml of concentrated hydrochloric acid. The product was extracted into chloroform, which was washed with dilute hydrochloric acid, water, 5% sodium bicarbonate solution, and water and dried ($MgSO_4$). Removal of the solvent gave a precipitate which was recrystallized from hexane to yield 810 mg (74%) of 5-OPNB: mp 109.5–110.5°; ir (Nujol) 1720 (C=O), 1610, 1525, 1350, 1310, 1290, 1120, 1110, and 720 cm^{-1}; nmr (CD_3COCD_3) δ 8.20 (A_2B_2, 4 H, aromatic, J = 9.0 Hz), 6.08 and 5.99 (2 d, AB, 2 H, vinyl, J = 2.6 Hz), 3.40 (d, 1 H, H_1, J = 3.2 Hz), 3.21 (m, 1 H, H_5), 2.70–1.90 (m, 3 H), 1.70–1.40 (m, 1 H), and 1.51 (s, 3 H, $-CH_3$).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53. Found: C, 66.05; H, 5.46.

***exo*-2-Methylbicyclo[3.2.0]hept-6-en-2-ol (6-OH).** To a solution of 5-OH (3.4 g, 0.0275 mol) in 100 ml of pentane at 0° was added a solution of 50% sulfuric acid (50 ml). The resulting mixture was allowed to stir for 10 hr at 0° and 40 hr at water-bath temperature, following the progress of the reaction by glpc (FFAP 15%, 3 m × 3 Φ column). After separation of the organic layer the aqueous layer was extracted with ether. The ethereal solution was combined with the organic layer, and the resulting solution was washed with water, 5% sodium bicarbonate solution, and water and then dried ($MgSO_4$). Evaporation of the solvent gave a mixture of 5-OH, 6-OH, and an unidentified ketone (<3%). The mixture was purified by chromatography on a silica gel column, eluting with 25% ether in benzene to give 567 mg (16.6%) of 6-OH as a clear liquid, which is crystallized on standing: mp 42–43.5°; ir (CCl_4) 3620 (free OH), 3320 (OH), 3040, 2930, 1060, and 1040 cm^{-1}; nmr (CCl_4) δ 6.00–5.70 (m, 2 H, vinyl), 3.07 (s, 1 H, H_1), 2.43 (br s, 1 H, H_5), 2.13–1.23 (m, 2 H), 1.40 (s, 1 H, –OH), 1.21–0.75 (m, 2 H), and 1.11 (s, 3 H, $-CH_3$): mass spectrum *m/e* 124 (M^+), 109, and 106.

***exo*-2-Methylbicyclo[3.2.0]hept-6-en-2-yl *p*-Nitrobenzoate (6-OPNB).** The exo alcohol 6-OH (100 mg) was converted to the *p*-nitrobenzoate (6-OPNB) as described above for 5-OH: yield 170 mg (78%); mp 78.0–79.5°; ir (Nujol) 1720 (C=O), 1610, 1530, 1350, 1270, 1110, and 720 cm^{-1}; nmr (CD_3COCD_3) δ 8.15 (A_2B_2, 4 H, aromatic, J = 10.0 Hz), 6.11–5.76 (m, 2 H, vinyl), 4.30 (s, 1 H, H_1), 2.78 (br s, 1 H, H_5), 2.10–1.59 (m, 3 H), 1.40–1.03 (m, 1 H), and 1.20 (s, 3 H, $-CH_3$).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53. Found: C, 65.63; H, 5.39.

Kinetic Measurements. The ratio of acetone to water was 50:50 by volume. For each run, approximately 80 mg of each 5-OPNB and 6-OPNB was weighed into a 50-ml volumetric flask and then filled with the 50% aqueous acetone. Eight tubes, containing 6 ml of the above solution, were sealed under nitrogen and heated in a constant temperature controlled oil bath (±0.3°). After the completion of the run, 5 ml of the solution was removed for titration. To the solution, 15 ml of water was added with a few drops of 0.1% Bromothymol Blue indicator in 50% ethyl alcohol. This mixture was titrated with 0.003 *M* sodium hydroxide in methanol under nitrogen.[3]

The exo-tosylate (7-OTs) was solvolyzed in acetic acid containing sodium acetate, and the rates were measured as previously described.[3] The kinetic data are shown in Table I.

Preparative Solvolyses of 5-OPNB and 6-OPNB. The *endo*-*p*-nitrobenzoate (5-OPNB, 200 mg) in 100 ml of 50% aqueous acetone containing 154 mg of 2,6-lutidine was sealed in six test tubes under nitrogen and heated for 47 hr at 150°. The cooled tubes were opened, and the acetone was removed by a rotary evaporation. The product mixture was isolated by ether extraction. After removal of the solvent, the product was purified by chromatography on a silica gel column, eluting with 20% ether in benzene to give 31 mg (34%) of a product which was identified as 6-OH by nmr comparison.

The exo-*p*-nitrobenzoate (6-OPNB) was solvolyzed as mentioned above except for being heated for 10 hr at 150°. The exo alcohol was obtained in 30% yield.

The low isolated yields of these reactions are attributed to sublimation during drying and an unidentified hydrocarbon which has a very short retention time in glpc. The absolute yields by glpc (FFAP 15%, 3 m × 3 Φ) analyses were shown to be 45% for 5-OPNB and 51% for 6-OPNB.

Preparative Acetolyses of 2-OTs and 7-OTs. The *endo*-tosylate (2-OTs, 200 mg) in 25 ml of acetic acid containing 84.5 mg of

sodium acetate was sealed in four test tubes under nitrogen and heated for 48 hr at 100°. The cooled tubes were opened, and the solution was neutralized with sodium bicarbonate and extracted with ether. The ethereal solution was washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated. The product was purified by chromatography on silica gel column, eluting with 20% ether in petroleum ether affording 82 mg (64%) of a mixture of 14[13] (65%) and 7-OAc (35%). The *exo*-tosylate (7-OTs, 67.8 mg) was solvolyzed at 50° to give 25 mg (58%) of 14.

Acknowledgment. I thank Dr. R. M. Coates at the University of Illinois for his suggestions and Dr. K. Kinoshita at S. M. S. for his discussion. I also wish to thank Moroyama-Kai for partial financial support of this research.

Registry No.—1-OTs, 41326-96-9; 2-OTs, 41326-98-1; 4, 1072-77-1; 5-OH, 53555-56-9; 5-OPNB, 53555-57-0; 6-OH, 53585-67-4; 6-OPNB, 53585-68-5; 7-OTs, 53585-69-6; *p*-nitrobenzoyl chloride, 122-04-3.

References and Notes

(1) A preliminary report has been presented at the 30th Anniversary Meeting of the Chemical Society of Japan, Osaka, April 1–4, 1974, preprints III, p 1094.
(2) (a) For recent reviews, see P. R. Story and B. C. Clark, Jr., in "Carbonium Ions," Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1972, pp 1007–1073; (b) H. Hanack and H. J. Schneider, *Angew. Chem., Int. Ed. Engl.*, 6, 666 (1967).
(3) R. M. Coates and K. Yano, *J. Amer. Chem. Soc.*, 95, 2203 (1973).
(4) (a) S. C. Lewis and G. H. Whitham, *J. Chem. Soc.* C, 274 (1967); (b) B. J. A. Cooke and P. R. Story, *Tetrahedron Lett.*, 1705 (1974).
(5) C. G. Scouten, F. E. Barton, Jr., J. R. Burgess, P. R. Story, and J. F. Garst, *Chem. Commun.*, 78 (1969).
(6) S. Winstein, E. C. Friedrich, R. Baker, and Y. I. Lin, *Tetrahedron, Suppl.*, 8, 621 (1966).
(7) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, N.Y., 1965.
(8) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Amer. Chem. Soc.*, 77, 4183 (1955).
(9) P. G. Gassman, J. Zeller, and J. T. Lumb, *Chem. Commun.*, 69 (1968).
(10) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, 86, 1854 (1964).
(11) The nmr spectra of 7-OTs and 2-OTs show that the C-2 proton in 7-OTs absorbs at δ 4.71 with a doublet (J = 2.4 Hz) and that the C-2 proton in 2-OTs does so at δ 4.72 with a quartet (J = 8.0 Hz), suggesting 7-OTs to be in a "bcat" and 2-OTs in a "chair" conformation.[4a] However, the nmr studies of 7-OH and 2-OH which have similar coupling constants with those of the corresponding tosylates show that the chemical shifts and coupling constants of these alcohols are not temperature dependent between 35 to 95° in CCl_4. The author wishes to thank Dr. K. Sato and Mrs. S. Yoshida for measurement of the temperature-dependent nmr spectra of these alcohols.
(12) In our study of 1-OTs, we suggested the possible existence of an initial carbonium ion intermediate, which rearranges to the stable norbornenyl-type carbonium ion.[3] This intermediate may be similar to the carbonium ion 12, which was also reported by Cook and Story.[4b]
(13) E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, 86, 1166 (1964).

Aromatic *N*-Oxides. VII. The Reaction of Diphenyl-2-pyridylmethane *N*-Oxide with Acetic Anhydride[1]

J. Hodge Markgraf,* Stuart R. Berryhill,[2] Lewis R. Groden, W. Michael Hensley, and Gavin G. Spence[2]

Department of Chemistry, Williams College, Williamstown, Massachusettes 01267

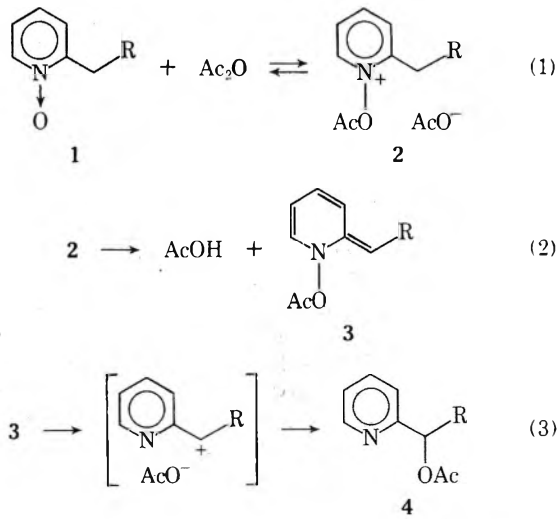
Walter J. McMurray

Section of Physical Sciences, Yale University School of Medicine, New Haven, Connecticut 06510

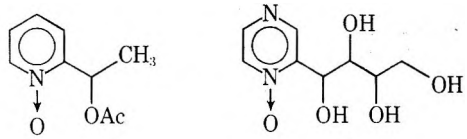
Received July 29, 1974

The rearrangement of diphenyl-2-pyridylmethane *N*-oxide (8) with acetic anhydride in acetonitrile was investigated. The product was identified as diphenyl-2-pyridylmethyl acetate (10). An intramolecular pathway was elucidated by a combination of oxygen-18 labeling studies and the conversion of 1-acetoxy-2-benzhydrylpyridinium perchlorate (14) to product by a base (Dabco) other than added acetate ion.

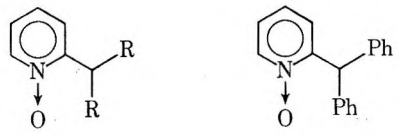
The reactions of aromatic *N*-oxides with acid anhydrides have been studied extensively since the first report in 1947 that pyridine *N*-oxide was converted to 2-pyridyl acetate when heated in acetic anhydride.[3] Twenty years ago several groups observed that alkyl substituents at C-2 of pyridine *N*-oxide altered the pathway to afford 2-pyridylmethyl acetates.[4-6] Since that time mechanistic aspects of these reactions have been thoroughly investigated and excellent reviews are available.[7,8] The generally accepted mechanism for side chain rearrangement is represented in eq 1–3, the key feature of which is the generation of an anhydrobase intermediate (3), which rearranges intramolecularly *via* an ion pair to product (4).[9]



The present work stemmed from our observation that nearly all reported examples of this rearrangement with 2-alkylpyridine *N*-oxides (1) involved structures with an α-methylene group. At the time this work was commenced we were aware of only two cases in which disubstitution at the α position of the side chain was involved; both compounds, 5[5] and 6,[10] were reported to undergo no rearrangement in acetic anhydride. Since the failure to observe the anticipated reaction with 5 and 6 could be attributed to an intramolecular interaction between the *N*-oxide moiety and the α-acetoxy group, it seemed desirable to test a simpler case of disubstitution such as 7. The choice of diphenyl-2-pyridylmethane *N*-oxide (8) was based on product considerations. Side chain rearrangement of 7 (R = alkyl) to a tertiary acetate would, upon acid hydrolysis, afford an alcohol capable of undergoing an undesirable dehydration. Subse-

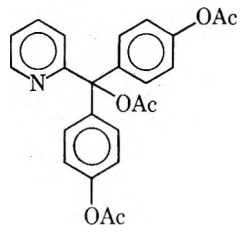


5 6



7 8

quent to the completion of this study Schnekenburger reported that 7 (R = *p*-acetoxyphenyl) rearranged in acetic anhydride to give 93% of **9**. Although no mechanistic stud-

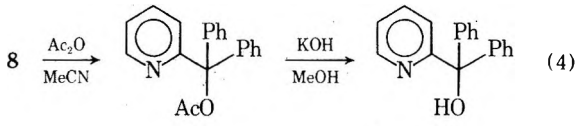


9

ies were carried out, it was assumed that the pathway involved a "concerted" rearrangement of the anhydrobase.

Results and Discussion

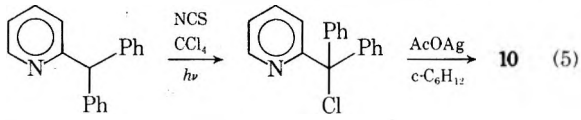
The reaction of 8 with excess acetic anhydride in refluxing acetonitrile yielded 94% of diphenyl-2-pyridylmethyl acetate (**10**) under optimum conditions. The initial struc-



(4)

10 11

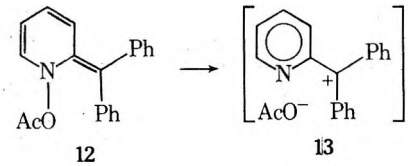
tural assignment was based on spectroscopic evidence: the presence of an acetate ester (ir, nmr), the presence of H-6, and the absence of the benzylic proton (nmr). If ring substitution had occurred, hydrolysis during work-up would have afforded an α-pyridone compound.[12] The identity of the previously unreported **10** was confirmed by hydrolysis to the known carbinol **11** and by comparison with an authentic sample of **10** prepared independently (eq 5).



(5)

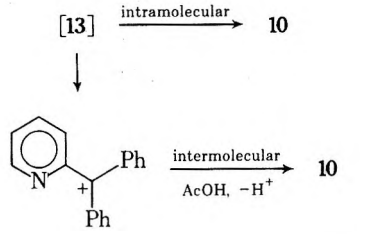
With the product structure established, our attention was focused on the mechanism for this rearrangement. Although the anhydrobase route (eq 1–3) was assumed to be applicable, the details of the final step were not secure. Ion pair **13**, derived from anhydrobase **12** (eq 6), could afford **10** either intramolecularly (eq 7) or intermolecularly (eq 8). The latter step would involve diffusion from the solvent cage and reaction of the diphenyl-2-pyridylmethyl cation with acetic acid. Our attempts to resolve this ambiguity were patterned after the elegant studies of Oae,[13] Traynelis,[14] and Muth.[15]

The reaction of 8 (no oxygen isotope enrichment) was carried out with uniformly labeled (>90 atom %) oxygen-18 acetic anhydride. Mass spectral analysis of the crude tertiary acetate showed the presence of three species of product **10** with molecular ions of *m/e* 303, 305, and 307 in relative



(6)

12 13



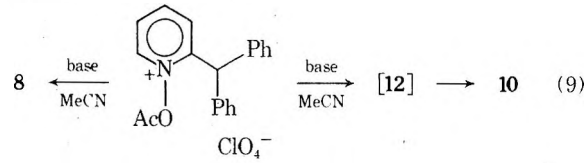
(7)

(8)

proportions of 12, 51, and 37, respectively.[16] Since the *m/e* values corresponded to an isotopic composition for **10** of zero, one, and two atoms of ^{18}O, the anticipated distinction between eq 7 and eq 8 could not be based on these data alone. The most abundant of the three species (*m/e* 305) was clearly produced by an intramolecular process, while the doubly labeled product (*m/e* 307) appeared consistent with an intermolecular pathway. An alternate interpretation, however, was possible for the latter species. The reaction of 8 with labeled acetic anhydride produced 1 equiv of acetic acid uniformly labeled with oxygen-18, and it was therefore possible that trityl ester **10** had undergone dissociation and exchange in the reaction medium. That this process could occur was demonstrated by a control experiment in which unlabeled **10** was refluxed in acetonitrile with labeled acetic acid. The mass spectrum of the recovered ester exhibited molecular ions only at *m/e* 303 and 307. Thus the isotopic labeling studies indicated that the major, if not the exclusive, pathway was the intramolecular process (eq 8).

Additional mechanistic inferences were drawn from the ^{18}O experiments. Mild alkaline hydrolysis of labeled **10** (from 8 and labeled acetic anhydride) afforded diphenyl-2-pyridylcarbinol (**11**) whose mass spectrum contained molecular ions at *m/e* 261 and 263 in relative proportions of 51 and 49, respectively.[16] The *m/e* values corresponded to species of **11** unlabeled and labeled with one ^{18}O atom. When adjustments were made for the generation of **11** from unlabeled and doubly labeled **10**, it was estimated that singly labeled **10** produced the species at *m/e* 261 and 263 in a ratio of *ca.* 3:1. This result indicated that complete equilibration of the oxygen atoms did not occur for the acetate ion within the ion pair. Such a preference for ^{16}O bond formation at the side chain may be caused by steric effects within the anhydrobase **12**; similar interpretations have been proposed by Oae.[13] Supporting evidence for this assignment of the ^{18}O distribution was obtained from the infrared spectra of the esters. The carbonyl stretching frequency of unlabeled **10** occurred at 1742 cm^{-1}, whereas labeled **10** exhibited a medium shoulder at 1748 and a strong doublet at 1727 and 1709 cm^{-1}. The greater intensity of the lower frequency doublet was consistent with ^{18}O as the predominant oxygen isotope of the carbonyl group.[17]

The intramolecular nature of the rearrangement was corroborated by studies with 1-acetoxy-2-benzhydrylpyridinium perchlorate (**14**). Thus, treatment of **14** with base



(9)

14

yielded a product mixture composed of **8** and **10**. A variety of bases was investigated and 1,4-diazabicyclo[2.2.2]octane (Dabco) proved to be the reagent of choice. The reaction (eq 9) was monitored by nmr spectroscopy, and the product composition was deduced from ir analysis. The conversion of analogous 1-acetoxypyridinium ions to mixtures of starting *N*-oxides and rearranged acetates has been observed primarily with added triethylamine or acetate ion,[14,15,18] although Dabco has effected a similar "back reaction."[19] High-pressure liquid chromatography of the reaction mixture confirmed the presence of **8** and **10**. This analytical procedure also showed that trace amounts of diphenyl-2-pyridylmethane (**15**) were produced. Similar deoxygenations have been observed with picoline *N*-oxides.[20] The process, which is always a minor pathway, involves free radical intermediates.

Experimental Section

Melting points, uncorrected, were determined on a modified Hershberg apparatus with total-immersion Anschutz thermometers. Spectra were recorded on the following instruments: Perkin-Elmer 237B ir spectrophotometer (polystyrene film calibration); Beckman DB-G uv spectrophotometer; Perkin-Elmer R12B nmr spectrometer at 60 MHz, chemical shifts in ppm from an internal TMS reference; AEI MS-9 mass spectrometer at an ionizing voltage of 70 eV. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Materials. Triethylamine was refluxed over acetic anhydride and distilled, and a middle cut was stored over solid potassium hydroxide and then redistilled from barium oxide: middle cut bp 87.5–88° (736 mm). Dabco from Houdry Process and Chemical Co. was recrystallized from methanol–diethyl ether and vacuum sublimed: mp 156–157° (sealed tube).

The following reagents were used without further purification: acetic anhydride (99.2%) from J. T. Baker; acetonitrile (<0.01% water, stored over molecular sieves) from Eastman Kodak; uniformly labeled oxygen-18 acetic anhydride and acetic acid (min 90 atom %) from Bio-Rad Laboratories; **15** from Aldrich.

Diphenyl-2-pyridylmethane *N*-Oxide (8). To a solution of diphenyl-2-pyridylmethane (10 g, 0.041 mol) in acetic acid (75 ml) was added 30% hydrogen peroxide (5.5 ml) and the solution was heated at 70–80°. After 3 hr additional 30% H_2O_2 (4.0 ml; total 9.5 ml, 0.12 mol) was added, and the solution was heated an additional 9 hr. The reaction solution was concentrated at reduced pressure to 15 ml and the yellow residue, which solidified upon cooling, was triturated with diethyl ether to give 8.9 g (83%) of white crystals, mp 161.0–161.8°. The product was recrystallized from benzene to give 8.5 g (80%) of **8**: mp 161.6–162.1° (lit.[21] mp 164–166°); ir ($HCCl_3$) 1245 and 835 cm^{-1} (*N*-oxide); uv (CH_3CN) max 276 nm (ϵ 10,500); nmr (CD_3CN) δ 6.18 (s, 1, benzylic H), 8.15 (m, 1, H-6).

Diphenyl-2-pyridylmethyl Chloride. A magnetically stirred solution of diphenyl-2-pyridylmethane (2.2 g, 9.0 mmol) and *N*-chlorosuccinimide (2.7 g, 20 mmol) in 90 ml of CCl_4 was heated and irradiated 4.5 hr with a 275-W sunlamp. Insoluble succinimide was removed by gravity filtration from the cooled reaction mixture, and the filtrate was concentrated on a rotary evaporator at reduced pressure to give 2.4 g of a viscous residue which crystallized, mp 60–65°. The crude product was recrystallized twice from ligroin (charcoal decolorization) to give 0.44 g (17%) of diphenyl-2-pyridylmethyl chloride, mp 72.2–73.2°.

Anal. Calcd for $C_{18}H_{14}NCl$: C, 77.28; H, 5.04; N, 5.01; Cl, 12.67. Found: C, 77.12; H, 5.04; N, 4.96; Cl, 12.74.

Diphenyl-2-pyridylmethyl Acetate (10). A magnetically stirred mixture of diphenyl-2-pyridylmethyl chloride (2.0 g, 7.2 mmol) and silver acetate (1.5 g, 9.3 mmol) in 30 ml of cyclohexane was refluxed 3 hr under a nitrogen atmosphere, cooled, and filtered by suction. The filtrate was concentrated on a rotary evaporator under reduced pressure to give 2.0 g (92%) of a crystalline residue, mp 78–82°. The crude product was recrystallized from isooctane (charcoal decolorization) to give 1.3 g (60%) of **10**: mp 84.2–85.6°; ir ($HCCl_3$) 1742 cm^{-1} (C=O); uv (CH_3CN) max 259 nm (ϵ 4070); nmr (CD_3CN) δ 2.12 (s, 3 H, acetate), 8.47 (m, 1, H-6).

Anal. Calcd for $C_{20}H_{17}O_2N$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.07; H, 5.61; N, 4.57.

Rearrangement of 8. A solution of **8** (1.3 g, 5.0 mmol) and acetic anhydride (5.1 g, 50 mmol) in 100 ml of acetonitrile was refluxed 24 hr, concentrated on a rotary evaporator under reduced pressure, neutralized with 0.1 *N* NaOH, and extracted four times with 30-ml portions of diethyl ether. The combined ethereal extract was washed three times with 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated as above to yield 1.4 g (94%) of a semicrystalline yellow oil whose ir and nmr spectra were identical with those of authentic **10**. The crude product was recrystallized from isooctane (charcoal decolorization) to give 0.56 (37%) of **10**, mp 83.6–85.0°, mixture melting point undepressed. Variations over the following ranges defined the above optimal conditions: temperature, ambient or reflux; time, 3–120 hr; molar ratio of Ac_2O:**8**, 2:1 to 10:1.

Similarly, the rearrangement of **8** (0.072 g, 0.28 mmol) was carried out with uniformly labeled (>90 atom % ^{18}O) acetic anhydride (0.28 g, 2.6 mmol) in 6 ml of acetonitrile to afford 0.086 g (100%) of a viscous yellow oil, whose identity as uncontaminated **10** was confirmed by ir and nmr spectra. The isotopic composition of the crude product was determined by mass spectral analysis.

Diphenyl-2-pyridylcarbinol (11). A solution of rearrangement product **10** (1.4 g, 4.6 mmol) and KOH (0.42 g, 7.5 mmol) in 5 ml of methanol was refluxed 4 hr, diluted with 60 ml of water, neutralized with 2 *N* HCl, extracted with three 30-ml portions of diethyl ether, dried ($MgSO_4$), and concentrated under reduced pressure to give 0.99 g (83%) of a semicrystalline residue. A portion of the crude product was recrystallized from 95% ethanol (charcoal decolorization) to afford **11**, mp 102.8–103.5° (lit.[21] mp 105°), mixture melting point was undepressed with an authentic sample prepared by the reaction of 2-benzoylpyridine with phenylmagnesium bromide.[22]

Similarly, the hydrolysis of ^{18}O-labeled **10** (70 mg, 0.023 mmol) was carried out with KOH (20 mg, 0.3 mmol) in 2 ml of 50% aqueous methanol at reflux for 20 min. Work-up as above gave 34 mg (57%) of semicrystalline product; the isotopic composition of the crude product was determined by mass spectral analysis.

Acetolysis of 10. A solution of **10** (51 mg, 0.17 mmol) and uniformly labeled (>90 atom % ^{18}O) acetic acid (0.11 g, 1.7 mmol) in 4 ml of acetonitrile was refluxed 24 hr and worked-up as above to give quantitative recovery of **10**, whose identity was confirmed by ir and nmr spectra. The isotopic composition of the crude product was determined by mass spectral analysis.

1-Acetoxy-2-benzhydrylpyridinium Perchlorate (14). A solution of **8** (2.5 g, 9.6 mmol) and acetic anhydride (10 ml) in 125 ml of 0.1 *N* perchloric acid in acetic acid was refrigerated overnight. The crystalline product was collected, washed twice with cold Ac_2O–AcOH solution (12:1), and three times with cold diethyl ether, and dried *in vacuo* over P_2O_5 to give 3.4 g (88%) of **14**: mp 184.5–185.2° dec; ir (CH_3CN) 1842 cm^{-1} (C=O); nmr (CD_3CN) δ 2.20 (s, 3, acetate), 6.18 (s, 1, benzylic).

Anal. Calcd for $C_{20}H_{18}ClNO_6$: C, 59.49; H, 4.49; N, 3.47; Cl, 8.78. Found: C, 59.42; H, 4.52; N, 3.33; Cl, 8.94.

Reaction of 14 with Base. A solution of **14** (133 mg, 0.33 mmol) and 1,4-diazabicyclo[2.2.2]octane (37 mg, 0.33 mmol) in 10 ml of acetonitrile was refluxed for 24 hr, concentrated on a rotary evaporator at reduced pressure, diluted with 10 ml of water, made slightly alkaline with $NaHCO_3$, and extracted with three 10-ml portions of CH_2Cl_2. The combined extract was washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to dryness as above to give 87 mg of residual oil whose composition as a mixture containing **8** and **10** was deduced from ir and nmr spectra.

The mixture was analyzed by high-pressure liquid chromatography on a Waters Associates ALC 202/401 instrument fitted with a 2 mm × 4 ft Bondapak C_{18}/Corasil column and with acetonitrile:water (1:1) as the mobile phase. Compared to authentic samples of **8**, **10**, **15**, and **11**, the product mixture was shown to contain the first three of these compounds, but not the fourth.

The reaction of **14** with various bases in acetonitrile was analyzed by ir ($\nu_{C=O}$ 1742 cm^{-1} for **10**) and nmr (appearance of 8.47 for H-6 of **10** and disappearance of δ 6.18 for benzylic proton of **14**) spectra. The generation of **10** was not observed with the following bases: sodium acetate, pyridine, triethylamine, 1,5-diazabicyclo[4.3.0]nonene-5, 1,5-diazabicyclo[5.4.0]undecene-5, and 1,8-bis(dimethylamino)naphthalene. In some cases product mixtures were obtained which exhibited frequencies at 1718 or 1661 cm^{-1}, but these structures were not investigated further. Control experiments established that **10** was stable to Dabco under the reaction conditions.

Acknowledgments. The authors are indebted to Lewis Kurtzman and William A. Dark of Waters Associates for performing the high-pressure liquid chromatographic analysis. We thank Peter M. Wege for summer stipends to

L.R.G. and W.M.H. Valuable suggestions by Professor Vincent J. Traynelis (West Virginia University) regarding this manuscript are gratefully acknowledged. This work was supported by a grant from the Alfred P. Sloan Foundation to Williams College. A portion of this work (W.J.M.) was supported by Grant RR 00356 from the Biotechnology Resources Branch of the National Institutes of Health.

Registry No.—8, 21883-34-1; 10, 53608-48-3; 11, 19490-90-5; 14, 53608-50-7; diphenyl-2-pyridylmethane, 3678-72-6; diphenyl-2-pyridylmethyl chloride, 53608-51-8; *N*-chlorosuccinimide, 128-09-6; acetic anhydride, 108-24-7; 1,4-diazabicyclo[2.2.2]octane, 280-57-9.

References and Notes

(1) (a) Presented at the 6th Northeast Regional Meeting of the American Chemical Society in Burlington, Vt., Aug 1974. (b) Part VI: C. W. Koch, R. M. Milberg, R. J. Katt, J. H. Markgraf, and P. M. Wege, *J. Heterocycl. Chem.*, **11**, 475 (1974).
(2) Based in part on the Honors theses of S.R.B., 1973, and G.G.S., 1964, Williams College.
(3) M. Katada, *J. Pharm. Soc. Jap.*, **67**, 51 (1947); *Chem Abstr.*, **45**, 9536*d* (1951).
(4) G. Kobayashi and S. Furukawa, *Pharm. Bull.*, **1**, 347 (1953); *Chem. Abstr.*, **49**, 10948e (1955).
(5) V. Boeckelheide and W. J. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954).
(6) O. H. Bullitt and J. T. Maynard, *J. Amer. Chem. Soc.*, **76**, 1370 (1954).
(7) V. J. Traynelis, "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1969, pp 1–42.
(8) E. Ochiai, "Aromatic Amine Oxides," Elsevier, Amsterdam, 1967, pp 290–302, 310–325.
(9) See ref 7 (pp 23–31) for a detailed discussion of this pathway.
(10) S. Fujii and H. Kobatake, *J. Org. Chem.*, **37**, 2635 (1972).
(11) J. Schnekenburger, *Arch. Pharm. (Weinheim)*, **306**, 360 (1973).
(12) J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr, and R. G. Peterson, *J. Amer. Chem. Soc.*, **85**, 958 (1963).
(13) S. Oae, S. Tamagaki, T. Negoro, and S. Kozuka, *Tetrahedron*, **26**, 4051 (1970).
(14) V. J. Traynelis and P. L. Pacini, *J. Amer. Chem. Soc.*, **86**, 4917 (1964).
(15) C. W. Muth and R. S. Darlak, *J. Org. Chem.*, **30**, 1909 (1965).
(16) These values are percentages of the isotopic species representing the total molecular ion. For unlabeled **10** the relative abundance of M^+ was 3%; the base peak was *m/e* 259. For unlabeled **11** the molecular ion was the base peak.
(17) G. Aksnes, D. Aksnes, and P. Albriktsen, *Acta Chem. Scand.*, **20**, 1325 (1966).
(18) C. W. Muth, R. S. Darlak, M. L. DeMatte, and G. F. Chovanec, *J. Org. Chem.*, **33**, 2762 (1968).
(19) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).
(20) (a) V. J. Traynelis and R. F. Martello, *J. Amer. Chem. Soc.*, **80**, 6590 (1958); (b) *ibid.*, **82**, 2744 (1960); (c) V. J. Traynelis and A. I. Gallagher, *ibid.*, **87**, 5710 (1965).
(21) A. Deegan and F. L. Rose, *J. Chem. Soc. C*, 2756 (1971).
(22) A. E. Tschitschibabin and S. W. Benewolenskaja, *Ber.*, **61**, 547 (1928).

Acetylenedicarbonyl Fluoride. I. Its Physical Properties and Reaction with Nucleophilic Reagents

F. E. Herkes* and H. E. Simmons

Central Research Department,[1] E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Received September 18, 1974

Acetylenedicarbonyl fluoride (3) has been prepared by (a) reaction of SF_4 with the monopotassium salt of acetylenedicarboxylic acid and (b) by reaction of phenylsulfur trifluoride with acetylenedicarboxylic acid. The physical and spectral properties including a mass spectral analysis of 3 have been determined. The diacyl fluoride reacts with alcohols, phenols, and aliphatic primary and secondary amines to give the respective esters and diamides in good yield. With ethanethiol and 3, a mixture of α-ethylthiofumaroyl and maleoyl fluorides, is produced.

The properties and reactions of acetylenedicarbonyl halides have not been reported. Only two disclosures on their synthesis have been documented. The synthesis in low yield of acetylenedicarbonyl chloride (1) by a Diels–Alder displacement reaction involving maleic anhydride was reported in 1938.[2] Attempts to prepare 1 from acetylenedicarboxylic acid (2) or its salts by more direct routes[4a] give only addition products and tars.[3a,4b,c] Acetylenedicarbonyl fluoride (3) has been prepared by the controlled fluorination of 2 with SF_4.[5] Its properties and experimental details, however, were not reported.

$$\underset{2}{HO_2CC{\equiv}CCO_2H} + 2SF_4 \longrightarrow \underset{3}{FCC{\equiv}CCF} + 2HF + 2SOF_2$$

The diacyl halides of 2 are potentially reactive intermediates for the preparation of acetylenic compounds which cannot be conventionally prepared from 2 or its diesters. Acetylenedicarbonyl fluoride has been prepared by two additional routes[6] in moderate to good yields. We report here on these modified routes as well as a survey of its physical properties and reactions with alcohols, phenols, a thiol, and amines.

Synthesis

The fluorination of the monopotassium salt of 2 (4) in dimethylcyclohexane with SF_4 at 60° for 15 hr produced 3 in yields ranging from 48 to 70%, depending upon the purity of the SF_4 employed. The substitution of 2 by 4 alleviated the problem of having excess HF which is always a potential source of side reactions in the product mixture. The HF

$$\underset{4}{HO_2CC{\equiv}CCO_2K} + SF_4 \longrightarrow 3 + KHF_2 + 2SOF_2$$

produced in the fluorination is thus scavenged by the KF generated. Alternatively, 3 could be prepared in the laboratory and in glass equipment from 2 and phenylsulfur trifluoride[7] in 1,2-dibromoethane[8] at 10°. The latter preparation required a catalytic amount of HF to initiate the fluorination as evidenced by a short induction period at the onset of the phenylsulfur trifluoride addition. The yield of 3 using this route was *ca.* 50%.

$$2 + 2C_6H_5SF_3 \longrightarrow 3 + 2C_6H_5SOF + 2HF$$

Physical Properties of 3

Acetylenedicarbonyl fluoride has a bp of 46° and a fp of −51° (DTA). From −15 to 41° the vapor pressure obeyed the relation $\log P_{Torr} = -(1688 \pm 41)/T°\ K + 8.19 \pm 0.16$

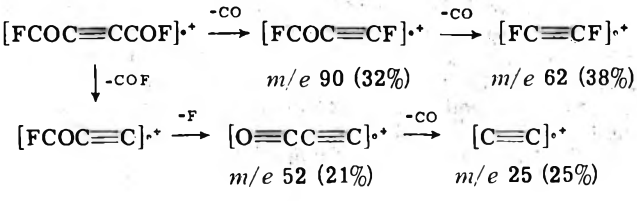
Table I
Mass Spectrum of Acetylenedicarbonyl Fluoride (70 eV)

m/e	Assigned ion+	Intensity
118	FCOC≡CCOF	52.1
99	FCOC≡CCO	6.0
90	FCOC≡CF	32.8
71	FCOC≡C	100.0
62	FC≡CF	38.4
52	COC≡C	20.7
47	COF	22.7
43	C≡CF	15.4
31	CF	19.9
28	CO	13.9
24	C_2	24.8
19	F	1.4
12	C	17.5

which gave $\Delta H_v = 7.72 \pm 0.27$ kcal mol^{-1} and $\Delta S_v = 22.5$ cal mol^{-1} deg^{-1}.

The mass spectrum of **3** has not been reported and is given in Table I. The base peak ion is FCOC≡C$^+$ ⇌ $^+$O=C=CF (*m/e* 71) resulting from the facile loss of COF$^+$. Fragment ions of FCOC≡CF·$^+$ (*m/e* 90) and FC CF·$^+$ (*m/e* 62) appear to be generated by carbon–carbon bond cleavage with elimination of CO followed by a skeletal migration of a fluorine atom. The ease to which this occurs is associated with the presence of the acetylenic linkage which may be ionized by electron removal followed by migration of the fluorine atom to the electron deficient site.[9] An additional striking feature of the fragmentation pattern of **3** is the large relative abundance of the C_2 ion (*m/e* 24) compared to that produced in the mass spectral fragmentation pattern of acetylenic esters and diesters.[9] The large intensity of the C_2 ion suggested that thermolysis or photolysis of **3** might generate the ion in the gas phase. Our attempts to generate the C_2 ion using flash photolysis, however, were unsuccessful. Scheme I summarizes the mass spectral fragmentation and rearrangement mode of **3**.

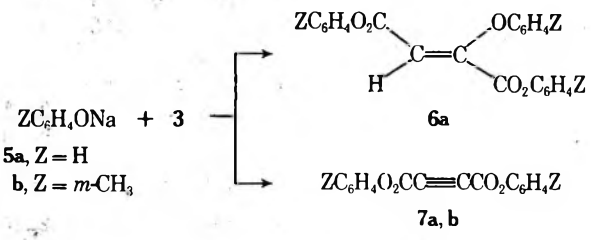
Scheme I



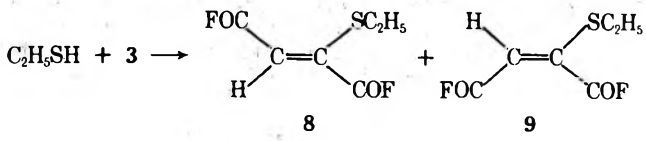
Having a center of symmetry about the acetylenic bond, **3** exhibits little absorption in the infrared spectrum. Raman analysis of **3** displayed strong absorptions for the acyl carbonyl and triple bond at 1824 and 2262 cm^{-1}, respectively. The ^{19}F nmr spectrum of **3** in methylene chloride displayed a sharp singlet at δ 49.4 and was shifted only to δ 50.5 when cooled to −90°. The ^{13}C satellite spectrum (see Experimental Section) yielded a fluorine–fluorine coupling of 1.8 Hz similar to an analogous four-bond coupling in perfluoro-2-butyne of 2.2 Hz.[10]

Reactions of 3

With Alcohols and Phenols. Acetylenedicarbonyl fluoride acylates alcohols under neutral conditions with negligible addition to the acetylenic bond to yield the corresponding diesters. For example, the diallyl[11] and dipropargyl[12] esters were obtained in 81 and 80% yield, respectively. Attempts to acylate phenols under similar conditions were unsuccessful, but addition of **3** to sodium phenoxide in dioxane at 15° produced a 3:1 adduct, diphenyl phenoxyfumarate (**6a**). The undesired addition of phenoxide ion to the triple bond was minimized by carrying out the addition of **3** to a suspension of **5** in fluorotrichloromethane at 0°. The insoluble diphenyl acetylenedicarboxylate (**7a**) could then be filtered and purified.



With Thiols. Treatment of a neat mixture of ethanethiol and NaF at 10° with **3** gave an exclusive mixture of only α-ethylthiofumaroyl (**8**) and maleoyl fluorides (**9**). The in-

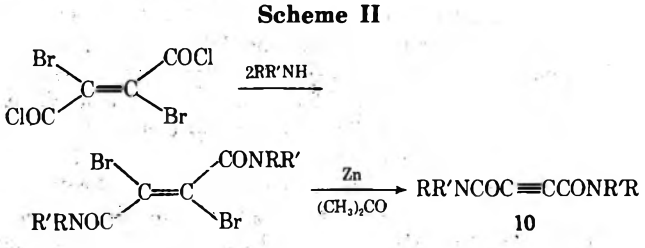


frared spectrum of the mixture exhibited strong absorptions at 1842 and 1802 cm^{-1} (COF). The ^{1}H nmr spectrum of the mixture displayed two nonequivalent ethyl groups. The vinyl proton in **9** appeared as a doublet of doublets resulting from geminal ($J_{H-F} = 4.5$ Hz) and trans ($J_{H-F} = 1.3$ Hz) coupling with the acyl fluorides.[13] The olefinic proton in **8** appeared as a doublet.

With Amines. In general, activated acetylenic derivatives add primary and secondary amines exothermically to yield imino or enamino derived products.[14] Attempts to prepare di- or tetrasubstituted acetylenedicarboxylic amides from dimethyl acetylenedicarboxylate and aliphatic amines have met with little success. An earlier report[15] described the synthesis of *N,N,N',N'*-tetraethylacetylenedicarboxamide (**10a**) from dimethyl acetylenedicarboxylate and diethylamine. Later work[16] established the compound to be the addition product, dimethyl α-diethylaminomaleate, rather than **10a**. Acetylenedicarboxamide[17] has been prepared from dimethyl acetylenedicarboxylate and aqueous ammonia at −10°.

Recently, a novel synthesis of new disubstituted and tetrasubstituted acetylenic diamides (**10**) was reported[18] starting from dibromofumaryl chloride followed by amination and dehalogenation (Scheme II). Similar acetylenic di-

Scheme II



amides (**10**) can also be prepared by controlled addition of primary and secondary amines to **3** in methylene chloride at 0°. The yields of these alicyclic and cyclic diamides **10** (Table II) ranged from 40 to 70%. Addition products appear also to be formed, but their isolation has not been attempted. The diamides are easily separated from these colored side products by column chromatography. Their properties are summarized in Table II. The infrared spectra of **10** showed the characteristic amide carbonyl at 1630–1650

Table II
Properties of Acetylenic Diamides (10)[a,b]

Compd	R	R'	Yield[c]	Mp, °C	ν(C=O), ν(C≡C), cm⁻¹ [d]	cm⁻¹ [e]
a	C_2H_5	C_2H_5	40	65	1642	
b	H	n-C_3H_7	67	151–153	1637	2238
c	H	i-C_3H_7	48	189–190	1642	2244
d	H	Allyl	45	103–104	1637	2246
e	n-C_4H_9	n-C_4H_9		Oil	1645	
f	H	C_6H_{11}	72	244–245	1634	2234
g	H	$CH_2C_6H_5$	45	204–205	1631	2245
h	H	1-Adamantyl	67	263–274	1645	2246
i	R,R' = N⟨ ⟩		43	98–99	1664	2237
j	R,R' = N⟨ ⟩O		64	145–147	1656	2230
k	R,R' = N⟨ ⟩		40	118–119	1626	2232

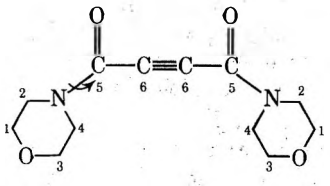
[a] Satisfactory analytical data were reported for all new compounds listed in the table. Compounds **10k** and **10f** had a ±0.7 deviation in the carbon analysis. [b] The ^1H nmr spectra of **10a–k** were measured in either $CDCl_3$ or DMSO-d_6 and displayed absorptions, coupling constants, and multiplicities consistent with the assigned structures. [c] Isolated yield. [d] Nujol mull. [e] Neat powder

Table III
^{13}C Nmr Spectrum of 10j in Methylene Chloride

δ, ppm	Assignment
−171.9	C_5
−101.4	C_6
−87.6	C_1 or C_3
−87.2	C_3 or C_1
−68.2	C_4
−63.0	C_2

cm^{-1} and Raman analysis displayed a strong absorption for the symmetric triple bond at 2232–2246 cm^{-1} (Table II). The pnmr spectra (Table II, footnote *b*) of the *N,N'*-disubstituted derivatives exhibited proton coupling through nitrogen with the adjacent methylene or methine proton. In **10b** the proton absorption of the α-methylene group appeared as a quartet arising from coupling through nitrogen in addition to the β-methylene hydrogens (*i.e.*, $J_{HN-H} \sim J_{H-H}$). In **10d** the amido hydrogen appeared as a triplet with J = 5.5 Hz resulting from α-methylene coupling. The tetrasubstituted derivatives of **10** displayed nonequivalence of the *N,N*-dialkyl group typical of disubstituted amides.

The cyclic diamides displayed complex pnmr spectra with the exception of **10j**. The pnmr of **10j** displayed two singlets of 1:1 intensity at δ 3.82 and 3.90 for the α- and β-methylene protons. No additional splitting was observed down to −64°, and the doublet coalesced in DMSO-d_6 at 90° to a singlet at δ 3.88. The ^{13}C nmr spectrum of **10j** exhibited six peaks. Their assignments and chemical shifts are summarized in Table III. Because of hindered rotation around the C–N bond, C_1 and C_3, and C_2 and C_4, are nonequivalent. In the other rotational isomer, because of the



symmetry of the ring system, the spectrum is exactly reproduced with C_1 and C_3 exchanged as well as C_2 and C_4. Since the ring is symmetric along the C–N bond, only one type of carbonyl carbon and acetylenic carbon is observed. The two singlets observed arise by accidental degeneracy of the C_1 and C_2 hydrogens. The chemical shifts of the C_1 and C_3 hydrogens, which are chemically equivalent, will have different chemical shifts because of restricted rotation around the C–N bond. Similarly, the chemical shifts and the C_2 and C_4 hydrogens are different. This coupled with the accidental degeneracy of the chemical shifts of hydrogen in C_1 and C_2 and also on C_3 and C_4 result in the observed two-line pattern in the proton spectrum.

Experimental Section

All melting points are uncorrected. Chemical shifts are expressed in δ, parts per million, downfield from an internal standard of TMS. The ^{13}C nmr spectrum of **10j** was recorded on a Bruker Scientific, In HFX-90 multinuclear magnetic resonance spectrometer operating at 22.6 MHz using CH_3I as an external reference.

Materials. All solvents including methylene chloride, dioxane, fluorotrichloromethane, 1,2-dibromoethane, and dimethylcyclohexane (isomeric mixture) were dried over molecular sieves (Type 4A). SilicAR CC7, 100–200 mesh, was obtained from Mallinckrodt Co. The amines used in the preparation of the acetylenic diamides were all commercially available and used without further purification.

The preparation of acetylenedicarbonyl fluoride (**3**) has already been described.[6] Analysis of the ^{13}C satellite coupling in the ^{19}F spectrum of **3** in carbon tetrachloride showed a set of doublets with $J_{^{13}C-F}$ = 324 Hz and a second set of doublets with $J_{^{13}C-F}$ = 115 Hz. Analysis of these couplings gave J_{F-F} = 1.8 Hz.

Diallyl Acetylenedicarboxylate. A mixture of 4.9 g (0.085 mol) of allyl alcohol and 4 g of NaF in 40 ml of dry benzene was treated dropwise with 2.0 g (0.017 mol) of **3** in 10 ml of dry benzene at 15°. After stirring for 20 hr, the mixture was filtered and benzene removed under vacuum. Residual benzene and allyl alcohol were removed at 25° at 0.001 Torr yielding 2.7 g (81%) of diallyl acetylenedicarboxylate:[11] bp 77–79° (0.4 Torr); ir (neat) 1754^{-1} (C=O), 1647 (C≡C), and 1250 cm^{-1} (CO).

Dipropargyl Acetylenedicarboxylate. A mixture of 4.8 g (0.085 mol) of propargyl alcohol and 4 g of NaF in 40 ml of dry benzene was treated dropwise with a solution of 2 g (0.017 mol) of **3** in 10 ml of dry benzene at 15°. After stirring 18 hr at 25°, the solids were filtered and the solvent and propargyl alcohol removed under vacuum. Fractional distillation yielded 2.2 g (80%) of dipropargyl acetylenedicarboxylate:[12] bp 95° (0.4 Torr); ir (neat) 3322 (HC≡C), 2155 (C≡C), 1742 (C=O), and 1250 cm^{-1} (CO).

Diphenyl Phenoxyfumarate (6a). A solution of 2 g (17 mmol) of **3** in 20 ml of dioxane was added dropwise to a mixture of 3.9 g (34 mmol) of sodium phenoxide[19] in 100 ml of dioxane at 15°. The mixture was stirred 2 hr and filtered. After removal of solvent *in vacuo*, the residue was chromatographed on 90 g of silica gel with 1:1 benzene–carbon tetrachloride to yield 1.7 g (28%) of pure **6b**: mp 137–138°; ir (Nujol) 1770 and 1727 cm^{-1} (C=O); nmr (DMSO) δ 5.69 (s, CH=C, 1 H), and singlet multiplet for aromatic protons.

Anal. Calcd for $C_{22}H_{16}O_5$: C, 73.39; H, 4.44. Found: C, 72.82; H, 4.38.

Diphenyl Acetylenedicarboxylate (7a). A suspension of 4.0 g (3.4 mmol) of sodium phenoxide[19] in 50 ml of fluorotrichloromethane was treated dropwise at −15° with a solution of 2.0 g (17 mmol) of **3** in 15 ml of fluorotrichloromethane. After 2 hr, the mixture was warmed to 25° and filtered. The solids were stirred 3 hr at 25° with 50 ml of fluorotrichloromethane followed by filtration. Removal of solvent from the filtrate yielded an oil whose infrared spectrum indicated a mixture of phenol and the 3:1 adduct **6**. The fluorotrichloromethane insolubles were extracted with benzene producing a tan solid on removal of the benzene. Recrystallization from ethanol yielded 2.2 g (50%) of pure (**7a**): mp 149–150°; ir (KBr) 1733 (C=C), 1587 cm^{-1} (C=C); nmr ($CDCl_3$), multiplet for the aromatic protons.

Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 72.08; H, 3.88.

Di-*m*-tolyl Acetylenedicarboxylate (7b). A solution of 1.0 g (8.5 mmol) of **3** in 15 ml of 1,1,2-trichlorotrifluoroethane was added dropwise to a stirred suspension of 2.2 g (17 mmol) of sodium *m*-cresoxide[19] in 50 ml of 1,1,2-trichlorotrifluoroethane at 0°. After 4 hr, the mixture was warmed to 25° and filtered. The solid was extracted with benzene (200 ml) to yield 1.3 g (52%) of **7b**: mp

85–86° (ethanol); ir (Nujol), 1727 (C=O), 1220 cm^{-1} (CO); uv (isooctane) sh 245 (ϵ 5320) and sh 225 nm (ϵ 6880); nmr ($CDCl_3$) δ 2.38 (s, CH_3, 6 H), 7.2–7.4 (m, phenyl, 8 H).

Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 480. Found: C, 73.22; H, 5.07.

Ethanethiol with 3. A solution of 2.0 g (17 mmol) of **3** in 10 ml of dry benzene was added dropwise to a stirred mixture of 3.1 g (50 mmol) of ethanethiol and 4 g of NaF in 40 ml of benzene at 10°. After 18 hr at 10°, the mixture was filtered followed by removal of benzene and excess thiol under vacuum. Distillation of the orange residue yielded a light yellow liquid: bp 49–56° (0.9 Torr). The infrared spectrum of the distillate indicated a mixture of α-ethylthiofumaroyl and -maleoyl fluorides: ir (neat) 1842 and 1802 (COF), 1572 cm^{-1} (C=C); nmr ($CDCl_3$), α-ethylthiofumaroyl fluoride, δ 1.37 (t, CH_3, 3 H), 3.08 (q, $-CH_2S-$, 2 H), 6.52 (doublet, J_{H-F} = 4.5 Hz, HC=C, 1 H), and α-ethylthiomaleoyl fluoride, δ 1.45 (t, CH_3, 3 H), 3.17 (q, $-CH_2-$, 2 H) (doublet of doublets, J_{H-F} = 4.5 Hz; J_{H-H} (trans) = 1.3 Hz, HC=C, 1 H).

General Method for the Preparation of Acetylenic Diamides 10. A mixture of 26 mmol of **3** and 6 g of NaF in 75 ml of dry methylene chloride was treated dropwise at 0° with 102 mmol of the primary or secondary alkyl amine in 30 ml of dry methylene chloride. After 0.5 hr, the mixture was warmed to 25° and filtered. The volatiles were removed on a rotary evaporator to yield dark semisolid residues. These residues were chromatographed on SiliCAR CC-7 employing a chloroform–carbon tetrachloride mixture as the eluent. The products, which eluted first, were then recrystallized from either chloroform, acetone, or a chloroform–hexane mixture and vacuum dried over P_2O_5 at 25° to yield analytically pure samples. In the case of **10f,g** the products precipitated from solution during the addition. In these cases the filter cake was washed with water (400 ml) and air dried prior to recystallization.

***N,N'*-Dicyclohexylacetylenedicarboxamide. Aqueous Method.** An Osterizer blender was charged with 3.64 g (33.4 mmol) of cyclohexylamine, 250 ml of distilled water, and 13.3 ml of 10% NaOH (33.4 mmol). The blender was started, and a solution of 3.0 g (16.7 mmol) of **3** in 125 ml of dry carbon tetrachloride was added in one portion. The mixture was stirred vigorously for 10 min and filtered. The yield of **10f** by this method was 2.3 g (50%) after recrystallization.

Registry No.—**3**, 675-75-2; **5a**, 139-02-6; **5b**, 4549-72-8; **6a**, 53683-88-8; **7a**, 53683-89-9; **7b**, 53683-90-2; **8**, 53683-91-3; **9**, 53683-92-4; **10a**, 25883-23-2; **10b**, 29453-12-1; **10c**, 53683-93-5; **10d**, 53683-94-6; **10e**, 29606-11-9; **10f**, 53683-95-7; **10g**, 53683-96-8; **10h**, 53683-97-9; **10i**, 29453-10-9; **10j**, 53683-98-0; **10k**, 25883-25-4; diallyl acetylenedicarboxylate, 14447-07-5; allyl alcohol, 107-18-6; dipropargyl acetylenedicarboxylate 3154-91-4; propargyl alcohol, 107-19-7; ethanethiol, 75-08-1; diethylamine, 109-89-7; propylamine, 107-10-8; isopropylamine, 75-31-0; allylamine, 107-11-9; dibutylamine, 111-92-2; cyclohexylamine, 108-91-8; benzylamine, 100-46-9; 1-adamantylamine, 768-94-5; piperidine, 110-89-4; morpholine, 110-91-8; pyrrolidine, 123-75-1.

References and Notes

(1) Contribution No. 2187.
(2) O. Diek and W. E. Thiele, *Chem. Ber.*, **71B**, 1175 (1938); attempts to repeat this reaction sequence have not been successful.[3]
(3) (a) R. N. McDonald and R. A. Kruegler, *J. Org. Chem.*, **28**, 254 (1963); (b) F. D. Marsh, Central Research Department, E. I. du Pont de Nemours and Co., Inc., private communication.
(4) (a) S. Patai, Ed., "The Chemistry of Acyl Halides," Interscience, New York, N.Y., 1972; (b) O. Diels and W. E. Thiele, *Chem. Ber.*, **71B**, 1173 (1938); (c) F. E. Herkes, private communication.
(5) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960).
(6) F. E. Herkes and H. E. Simmons, *Synthesis*, **3**, 166 (1973).
(7) W. A. Sheppard, *Org. Syn.*, **44**, 82 (1964).
(8) 1,2-Dibromoethane (bp 131°) was employed as the solvent to provide a large boiling point differential. Any inert solvent of comparable boiling point would also be suitable.
(9) J. H. Bowie, D. H. Williams, P. Madsen, G. Schroll, and S. O. Lawesson, *Tetrahedron*, **23**, 305 (1967).
(10) N. Muller and D. T. Carr, *J. Phys. Chem.*, **67**, 112 (1963).
(11) C. D. Heaton and C. R. Nollar, *J. Amer. Chem. Soc.*, **71**, 2948 (1949); authors report 70% esterification yield with H_2SO_4 catalyst.
(12) J. Randell, B. W. Brodman, A. Hirshfeld, and E. D. Bergmann, *J. Phys. Chem.*, **69**, 928 (1969); authors report 4% esterification yield without catalyst.
(13) T. P. Vasileff and D. F. Koster, *J. Org. Chem.*, **35**, 246 (1970).
(14) H. G. Viehe, Ed., "The Chemistry of Acetylenes," Marcel Dekker, New York, N.Y., 1969, pp 286–299.
(15) C. Vassiliades and H. Capatos, *C. R. Acad. Sci.*, **194**, 1830 (1932).
(16) R. J. Alaimo and D. G. Farnum, *Can. J. Chem.*, **43**, 700 (1965).
(17) A. J. Saggiomo, *J. Org. Chem.*, **22**, 1171 (1957).
(18) K. E. Schulte, J. Ruisch, and K. Coen, *Chim. Ther.*, **5**, 72 (1970); K. Coen, H. Moellmann, J. Reisch, and K. E. Schulte, *Arzneim.-Forsch.*, **19**, 1761 (1969).
(19) W. R. Boehme, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 492.

Acetylenedicarbonyl Fluoride. II. Its Reaction with Arylamines to Yield Isomaleimides, Maleimides, and α-Phenylimino- and α-Phenylaminofuramides

F. E. Herkes

Central Research Department,[1] E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

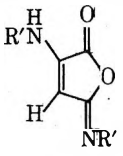
Received September 18, 1974

Contrary to expectation, acetylenedicarbonyl fluoride, **2**, had been found to react with aniline and substituted anilines under strict nonacid conditions to yield 1-arylamino-4-arylimino-α-crotonolactones (*i.e.*, isomaleimides), **3**. Under acidic conditions, the isomeric 1-arylaminomaleimides, **4**, are formed. The configuration of **3** was deduced chemically by mild reduction of **3a** (R = H) with sodium borohydride to give 2-anilino-1-hydroxy-4-phenylimino-2,5-dihydrofuran, **9**, which in turn could be reoxidized back to **3a** with MnO_2. Similarly, the reduction of **4a** (R = H) yielded 4-anilino-5-hydroxy-2-pyrrolin-2-one, **10**. With excess aniline and **2**, the only product isolated was the 3:1 adduct, *N,N*-diphenyl-*N*-phenyliminofuramide, **13**. The imino isomer, **13**, was found to tautomerize slowly in DMSO at 50° producing the isolatable enamino derivative, **16**. The isomerization was observed to be irreversible and catalyzed by acid. The physical and spectral properties of **3** and **4** are summarized as well as the pnmr data for all the compounds described.

Several reports on the synthesis of *N,N'*-diphenylacetylenedicarboxamide (**1**) have recently appeared. Schulte,[2a] *et al.*, obtained **1** by addition of phenyl isocyanate to acetylenedimagnesium iodide. A later report by Dehmlow[2b] described the formation of **1**, based on infrared data, by photolysis of diethoxycyclobutenedione in an aniline–ether mixture. With the reported[3,4] synthesis of acetylenedicarbonyl fluoride (**2**) there appeared to be an additional and more general route to **1** and other acetylenic dianilids.

The condensation of primary and secondary aliphatic and alicyclic amines with **2** was observed[3] to yield the corresponding acetylenic diamides with minimal addition of

Table I
Physical Properties of
1-Arylamino-4-arylimino-α-crotonolactones[a]

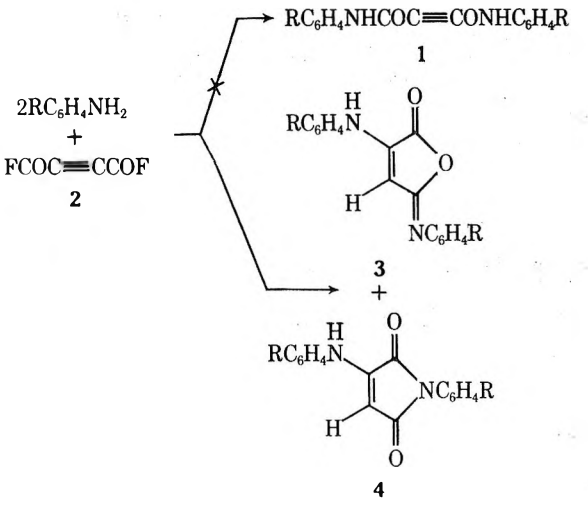


3

Compd	R′	% yield[b]	Mp, °C	νC=O, cm⁻¹	νC=N, cm⁻¹	νC=C, cm⁻¹
a	C_6H_5	65	329	1786	1706	1629
b	4-FC_6H_4	37	198	1779	1730	1629
c	2-FC_6H_4	34	155	1805	1715	1647
d	4-$CH_3C_6H_4$	31	160–162	1786	1701	1634
e	4-ClC_6H_4	50	190	1783	1704	1637
f	4-$NO_2C_6H_4$	45	284–285	1812	1706	1650
g	2-$NO_2C_6H_4$	16	179–181	1786	1712	1647

[a] Satisfactory analytical data were reported for all new compounds. [b] Isolated yield.

the amine to the triple bond. Extension of this reaction with aniline or ring-substituted anilines, however, failed to produce the expected acetylenic dianilids. Instead, isomeric products were isolated which involved the addition of 2 equiv of aniline with **2**. Under a variety of reaction conditions, these products were the new isomaleimides (**3**) and maleimides (**4**). With excess aniline, only a 3:1 adduct was isolated.



In this paper are reported the results of a study of the synthesis, structure proof, configurational assignment, and reactions of 1-arylamino-4-arylimino-α-crotonolactones (**3**). The preparation and chemistry of 1-arylamino-*N*-arylmaleimides (**4**) are also described.

Results and Discussion

Addition of aniline to a methylene chloride solution of freshly distilled **2** containing NaF at 5° produced a 65% yield of 1-anilino-4-phenylimino-α-crotonolactone (**3a**). Under strict nonacid conditions none of the isomeric maleimide, **4a**, was observed. Similar results were obtained using other substituted anilines. With crude (*i.e.*, once distilled) **2** a mixture of both the isomaleimide (**3**) and maleimide (**4**) was produced and could be separated and purified by column chromatography. For example, with aniline and **2**, the major product is α-anilino-*N*-phenylmaleimide (**4a**)[5] formed by acid-catalyzed rearrangement of **3a** during the course of the reaction. Pure **3a** could also be isomerized to

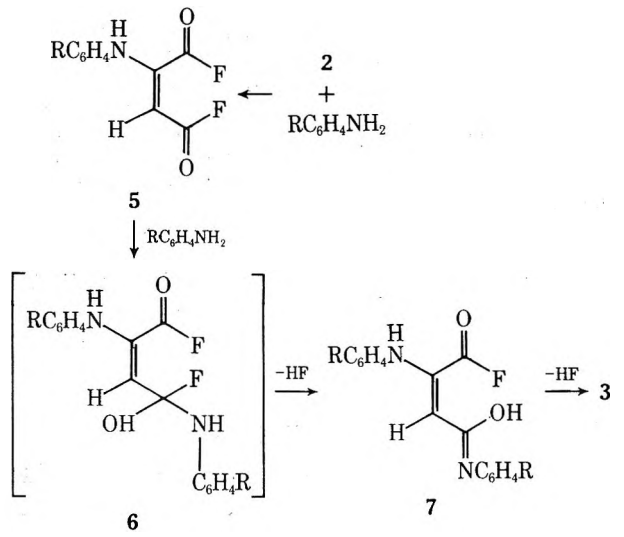
Table II
^{1}H Nmr[a] and Uv[b] Data for
1-Arylamino-4-arylamino-α-crotonolactones (3)

Compd	δNH	δvinyl	λ, nm (ε)	λ, nm (ε)
3a	9.95	5.82	233 (20,300)	335 (15,800)
3b	9.93	5.83	232 (17,300)	328 (15,400)
3c	9.86	5.41[c]	231 (19,900)	332 (10,500)
3d	9.76	5.72	240 (25,500)	365 (10,200)
3e	10.0	5.93	240 (24,800)	337 (20,100)
3f	*d*	6.59	250 sh (12,000)	365 (25,500)
3g	*d*	6.33	231 (27,900)	323sh (11,500)

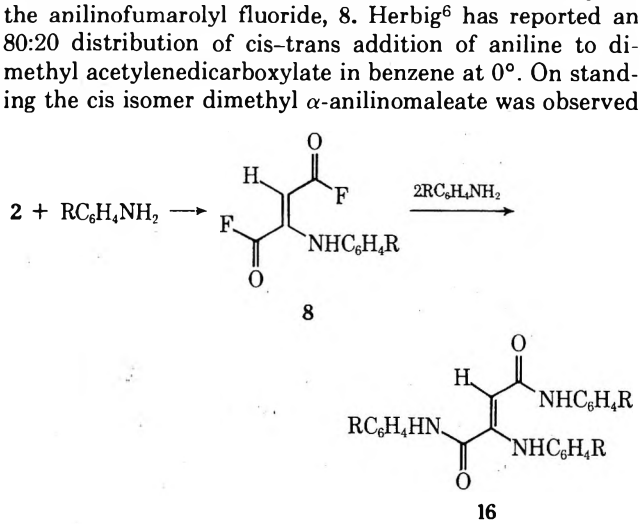
[a] Recorded in DMSO-d_6 and expressed in ppm downfield from internal TMS. [b] Measured in acetonitrile. [c] Doublet. [d] Not observed.

4a with anhydrous HCl, BF_3–etherate, and methanolic sodium methoxide. Use of an acidic solvent such as hexafluoro-2-propanol and pure **2** with 4-fluoroaniline gave the maleimide **4b**. The physical properties of **3** are summarized in Table I.

Isomaleimides 3. The formation of **3** involves an initial cis addition of the arylamine to **2** yielding the anilinomaleoyl fluoride, **5**, followed by addition of a second equivalent of arylamine to yield the intermediate **6**. Loss of HF



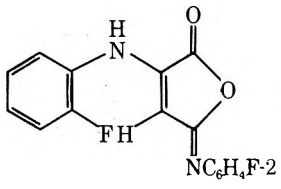
can then occur to form the hydroxy imino intermediate **7** which in turn cyclizes with loss of a second mole of HF to yield **3**. In all cases **3** was the only product isolated when freshly distilled **2** was used. It is possible that some trans addition occurred or isomerization of **5** took place to yield the anilinofumarolyl fluoride, **8**. Herbig[6] has reported an 80:20 distribution of cis–trans addition of aniline to dimethyl acetylenedicarboxylate in benzene at 0°. On standing the cis isomer dimethyl α-anilinomaleate was observed



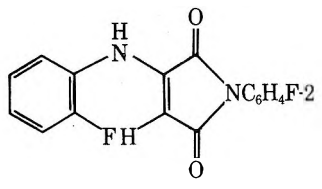
to isomerize to the thermodynamically more stable[7] dimethyl α-anilinofumarate. In the case of **2** with aniline, the initial kinetic product **5** reacts quickly with aniline to produce **3**. The trans addition isomer **8**, if produced, could react further with additional arylamine to yield the 3:1 adduct **16**. Alternatively, **16** could also be produced by addition of the arylamine to **3**. Inspection of the ir and pnmr spectra of the crude products before chromatography did not reveal the presence of **16**.

The structure and identification of **3** and **4** were based on elemental, infrared, pnmr, and mass spectral analyses. The infrared spectra of **3** exhibited intense characteristic[8] carbonyl absorption peaks in the 1783–1805-cm^{-1} region, absorption in the C=N region at 1704–1730 cm^{-1}, and N–H absorption of 3268–3378 cm^{-1} for the anilino hydrogen. The pnmr in DMSO-d_6 (Table II) displayed singlet absorptions at δ 9.8–10.0 and 5.4–6.6 for the respective anilino and vinyl protons in both **3** and **4**. In **3c** and **4c** the vinyl proton was split into a AX doublet with J_{H-F} = 2.5 Hz. The AX doublet of **3c** and **4c** is attributed to a through space coupling of the vinyl hydrogen with the ortho fluorine atom of the anilino group.

With both rings lying in the same plane, their internuclear distance would predict a large coupling. The observed H–F coupling of 2.5 Hz suggests, based on Myrhre's work,[9] that the H–F distance is in fact *ca.* 2.7 Å indicating a perpendicular or skewed conformation of the two rings. Direct H–F coupling through six bonds including a nitrogen atom would appear remote in **3c** and **4c**.



3c



4c

The mass spectrum of **3a** is essentially indistinguishable from **4a**. A comparison of their spectra under similar conditions is shown in Table III. The major fragment loss of phenyl isocyanate is observed in both compounds, and only a small loss of CO_2, characteristic of isoimides, from **3a** is observed.

Maleimides 4. The infrared spectra of the known and new maleimides displayed an unsymmetric doublet in the carbonyl region at 1757–1779 and 1704–1721 cm^{-1} characteristic of imides[6] and absorptions of 1626–1645 and 3257–3333 cm^{-1} for the vinyl and anilino N–H absorptions, respectively. The maleimides were yellow to yellow-orange in color and exhibited fluorescence in the solid form with ultraviolet light. In direct contrast, the isoimides **3** were not colored. The structure of **4a** was further confirmed by hydrogenation over PtO_2 to α-anilino-*N*-phenylaspartimide[4b] and comparison of the properties of **4a** with an authentic sample prepared from aniline and dimethyl acetylenedicarboxylate.[5] The pathway for the formation of **4** from crude **2** is envisioned as an acid-catalyzed ring opening of the initially formed **3**, rearrangement, and subsequent ring closure through nitrogen (Scheme I). Similarly, **3** could be isomerized quantitatively to **4** in methylene chloride at 25° using anhydrous HCl or BF_3–etherate. With longer reaction times using crude **2**, there was also observed some of the arylamine addition product. For example, with aniline **16** was detected. In these cases attack by the arylamine on the isoimidium salt can yield the ring-opened furamide product.[10]

Scheme I

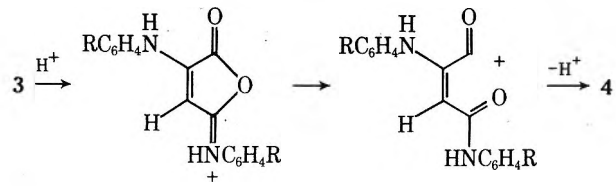
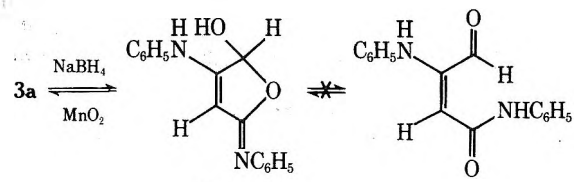


Table III
Mass Spectrum of 3a and 4a (70 eV)[a]

m/e	Ion+	Rel intensity 3a	Rel intensity 4a
265	M + 1	41.6	18.4
264	M	100	100
263	M − 1	29.0	10.0
220	M − CO_2	1.3	0
171	M − $C_6H_5NH_2$	3.6	1.3
145	M − C_6H_5NCO	61.5	12.7
144	M − C_6H_5NHCO	100	62.7
117	$C_6H_5NHC{\equiv}CH$	26.5	9.0
116	$C_6H_5NHC{\equiv}C$	17.8	5.1
93	$C_6H_5NH_2$	51.0	3.1
77	C_6H_5	9.0	9.3

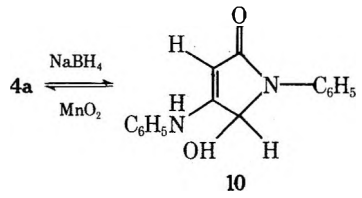
[a] Direct injection at 150°.

Configuration of Isomaleimides. In the case of **4** there is only one configurational isomer due to its inherent symmetry. However, in **3** there are two possible isomeric structures differing only by the substitution of the arylamino group relative to the carbonyl or arylimino carbon. Infrared, pnmr, ultraviolet (Table II), and mass spectroscopy were of little help in assigning the position of the arylamino substituent. Conventional attempts to hydrogenate **3a** failed. By chance, a mild chemical reduction of **3a** was found employing sodium borohydride in ethanol to yield 2-anilino-1-hydroxy-4-phenylimino-2,5-dihydrofuran (**9**).

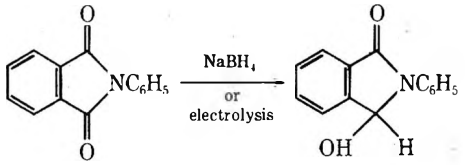


9

The infrared spectrum of **9** showed only the imino and olefinic absorptions at 1678 and 1684 cm^{-1} and the absence of the original carbonyl peak at 1786 cm^{-1}. Analysis of the 220-MHz pnmr spectrum of **9** in DMSO-d_6 exhibited a doublet of doublets for the 1-hydroxy and 1-methine protons at δ 6.25 and 5.93, respectively, with J = 10 Hz. A singlet peak at δ 6.04 was observed for the vinyl proton. Addition of D_2O collapsed the doublet at δ 5.93 to a singlet and completely exchanged the doublet at δ 6.25 and the singlet for the anilino hydrogen at δ 8.10. The chemical shifts for the vinyl, hydroxyl, and methine protons and their coupling constants are similar to those reported for hydroxyfurans formed either by photooxidation of pyrroles[11–13] or by ammonolysis of 2,5-dihydrofuran-2-ones.[14] The absence of coupling between the vinyl and methine protons supports the configuration shown for **9**. The mass spectrum of **9** displayed the parent ion at *m/e* 266 and peaks at *m/e* 248, 220, and 218 for the loss of H_2O, HCO_2H, and HCO_2H^+, respectively. Mild oxidation of **9** with activated MnO_2 in methylene chloride re-formed **3a**. The use of *excess* sodium borohydride for the reduction of **3a** repeatedly caused isomerization to **4a** followed by a similar reduction of the carbonyl in **4a** to yield 4-anilino-5-hydroxy-3-pyrrolin-2-



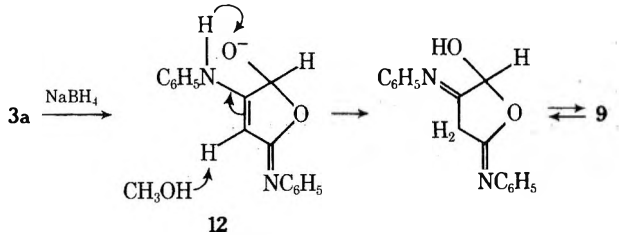
one (**10**) in almost quantitative yield. Its infrared spectrum displayed absorptions for the anilino group and a peak at 1664 cm^{-1} for the carbonyl function. The 220-MHz pnmr in DMSO-d_6 displayed singlet absorptions at δ 9.33 and 5.35 for the anilino and vinyl protons, and a doublet of doublets at δ 5.94 and 6.77 for the respective methine and hydroxyl protons with J = 10 Hz. Addition of D_2O exchanged the anilino and hydroxyl proton leaving only a singlet absorption for the methine and vinyl protons, supporting the configuration shown in **10**. Mild reoxidation of **10** to **4a** could also be effected using activated MnO_2 in methylene chloride. The reaction of sodium borohydride with **3a** and **4a** represents the first case of maleimide and isomaleimide reduction to yield stable cyclic products. No tautomerism to the open ring structure was observed by solution pnmr for **9** and **10**. Similar reductions of phthalimide either electrolytically[15] or with sodium borohydride[16] have been reported to yield the corresponding hydroxyphthalimidines



(**11**). *N*-Phenylmaleimide failed to react with methanolic sodium borohydride under the reaction conditions used for **3a** and **4a**.

The presence and proximity of the anilino group adjacent to the carbonyl appear to provide activation and/or stabilization for the carbonyl as well as a potential source for an intramolecular proton abstraction in the case of the primary adduct, **12** (Scheme II). Proton abstraction of **12**

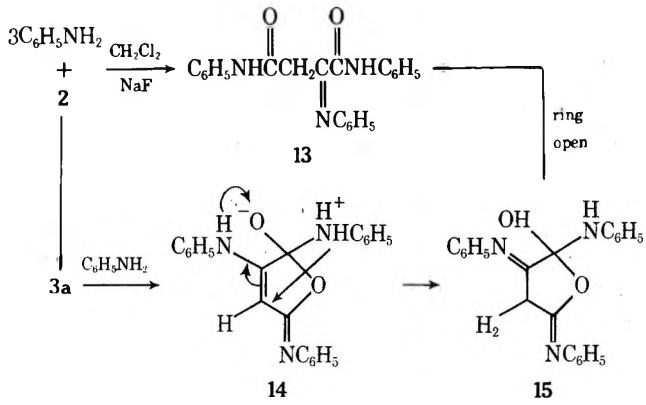
Scheme II



12

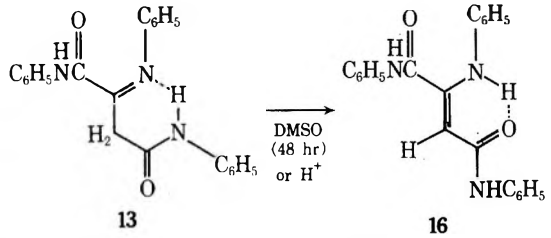
can also occur from the decomposition of the initial borohydride complex similar to that described by Horii, *et al.*[16]

3:1 Adduct of Aniline and 2. When excess aniline was employed with purified **2** under similar conditions described for **3a**, the 3:1 adduct, *N,N*-diphenyl-*N*-phenyliminofuramide (**13**) was the only product isolated. The furamide **13** appears to be formed by addition of a third mole of aniline to **3a** since the reaction could be carried out in a stepwise fashion employing **3a** and aniline. The pnmr of **13** in DMSO-d_6 indicated that the imino form was the only tautomer present. The spectrum displayed a singlet at δ 3.67 for the methylene hydrogens and singlets at δ 10.05 and 10.30 for the amide protons. The lower field amide absorption at δ 10.05 is less deshielded than the higher field amide proton because of intramolecular hydrogen bonding between the amide hydrogen and the amino nitrogen. The

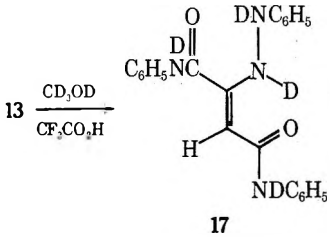


infrared spectrum exhibited a peak with shoulder at 1661 cm^{-1} for the carbonyl group and an intense absorption at 1704 cm^{-1} for the C=N stretch.

The isolation of **13** suggests that aniline can attack **3a** in either the imino or enamino tautomeric form. The absence of the imino isomer in the pnmr of **3a** suggests that it is not the reacting species with aniline. Rather, it appears that aniline adds to the enamino form to yield the intermediate **14** which could by a series of proton transfers produce **15** followed by ring opening yielding **13**. When a DMSO-d_6 solution of **13** was allowed to stand 48 hr at 25°, a quantitative conversion to the enamino tautomer, *N,N*-diphenyl-α-anilinofuramide (**16**), was observed. The pnmr in



DMSO-d_6 displayed only a vinyl singlet at δ 5.65 and the appearance of a third amino proton at δ 10.00. Singlet absorptions for the amide protons were also observed at δ 10.60 and 10.65. Addition of trifluoroacetic acid failed to alter the pnmr spectrum of **16**. Addition of trifluoroacetic acid–perdeuteriomethanol to a freshly prepared solution of **13** in DMSO-d_6 converted it to the deuterated enamine **17**.



17

No methylene, vinyl, or N–H absorptions were observed after 1 min at 35° indicating a fast acid-catalyzed equilibration of the enamine and imino forms. Similar observations on the independent isolation of primary enamine and its tautomeric imine have been reported for the anilino and phenyliminoethyl butenonates[17] and crotonates[18] as well as other amine[19] derivatives. The formation of **13** in methylene chloride, a nonpolar solvent, thus allows for the isolation of an imino derivative which when dissolved in a polar–aprotic solvent such as DMSO produces the isolable thermodynamically more stable enamine derivative.

Experimental Section

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. Proton nmr spectra were recorded on a Varian Associates A-60 nmr spectrophotometer

using DMSO-d_6 as the solvent. Chemical shifts are expressed in δ (parts per million) downfield from an internal standard of TMS. The 220-MHz nmr spectra of **9** and **10** were recorded on a Varian Associates High Resolution 220-MHz nmr spectrometer. Infrared spectra were recorded on a Perkin-Elmer 21 and mass spectra on a Du Pont CEC 21-103C mass spectrometer. Ultraviolet spectral analyses were obtained usinga Cary 17 ultraviolet spectrometer. Elemental analyses were performed by the Analytical Laboratories of the Central Research Department.

Materials. All solvents including methylene chloride, chloroform, carbon tetrachloride, and hexane were dried over molecular sieves (Type 4A). Silica gel (SilicAR CC7) having 100–200 mesh was obtained from Mallinckrodt Co. The anilines used in the preparation of **3** and **4** were all commercially available and were used without further purification. Acetylenedicarbonyl fluoride (**2**) was prepared from acetylenedicarboxylic acid monopotassium salt and SF_4 in dimethylcyclohexane.[4] The diacid fluoride was distilled directly from the filtrate after removal of KF, KHF_2, and unreacted starting acid. This distillate represented once distilled **2**.

General Preparation of α-Arylamino-4-arylimino-α-crotonolactones (3). A solution of 53 mmol of the appropriate arylamine in 200 ml of methylene chloride was added dropwise to a slurry of 12 g of NaF and 26 mmol of **2** (freshly distilled from NaF directly into the reaction vessel) in 600 ml of methylene chloride at 5°. After stirring 1 hr, the mixture was warmed to 25° and filtered. Removal of the solvent under vacuum left a residue which was chromatographed on 90 g of neutral silica gel with 2:1 v/v carbon tetrachloride–chloroform to yield the isomaleimides, **3**. Mixed solvent recrystallization using chloroform and hexane yielded analytically pure samples. Their yields and physical and spectral properties are summarized in Tables I, II, and III.

α-Anilino-*N*-phenylmaleimide (4a).[5] A solution of 6.4 g (0.070 mol) of aniline in 50 ml methylene chloride was added dropwise to a slurry of 4.0 g (0.034 mol) of crude **2** (once distilled) and 4 g of NaF in 100 ml of methylene chloride at −5°. The mixture was stirred 1.5 hr, warmed to 25°, and filtered. The solvent was removed under vacuum, and the residue was chromatographed on 90 g of neutral silica gel with 4:1 v/v chloroform–carbon tetrachloride to yield 3.0 g (43%) of **4a**: mp 238–239° (chloroform); dipole moment (dioxane) 5.393 D; ir (KBr) 3257 (NH), 1767, 1704 (C=O), 1626 cm^{-1} (C=C); uv (CH_3CN) 239 (ϵ 23,300), 280 (ϵ 7330), and 376 nm (ϵ 8030).

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.69; H, 4.79; N, 10.84.

α-(4-Fluoroanilino)-*N*-(4-fluorophenyl)maleimide (4b). A mixture of 2.0 g (0.017 mol) of purified **2** and 20 g of NaF in 125 ml of hexafluoro-2-propanol was treated dropwise with a solution of 3.8 g (0.034 mol) of 4-fluoroaniline in 20 ml of hexafluoro-2-propanol at 5°. After stirring 15 min, the mixture was warmed to 25° and filtered and the solvent was removed from the filtrate. Chromatography of the residue on 90 g of neutral silica gel with 1:1 v/v chloroform–carbon tetrachloride yielded 2.1 g (41%) of **4b**. Recrystallization from chloroform gave mp 256° dec; ir (KBr) 3311 (NH), 1757, 1709 (C=O), and 1642 cm^{-1} (C=C); uv (CH_3CN) 237 (ϵ 16,700), 288 (ϵ 11,500), and 375 nm (ϵ 4740); mass spectrum, *m/e* 300 (M^+).

α-(2-Fluoroanilino)-*N*-(2-fluorophenyl)maleimide (4c). A mixture of 2 g (0.017 mol) of crude **2** and 8 g of NaF in 50 ml of methylene chloride was treated dropwise with a solution of 3.8 g (0.034 mol) of 2-fluoroaniline in 20 ml of methylene chloride at 25°. After stirring 1 hr, the mixture was filtered and filtrate was concentrated under vacuum. The residue was chromatographed on 90 g of neutral silica gel with 1:1 v/v carbon tetrachloride–chloroform to yield 2.8 g (55%) of product. The first eluted compound was the isomaleimide, **3c** (1.0 g, 20%). The second eluted product was **4c** (1.8 g, 35%): mp 119–121° (chloroform–hexane); ir (KBr) 3322 (NH), 1779, 1727 (C=O), and 1642 cm^{-1} (C=C); uv (CH_3CN) 231 (ϵ 20,800), 262 (ϵ 8940), and 307 nm (ϵ 8850).

Anal. Calcd for $C_{16}H_{10}N_2O_2F_2$: C, 64.00; H, 3.33; N, 9.33. Found: C, 63.33; H, 3.31; N, 9.15.

α-(4-Methylanilino)-*N*-(4-methylphenyl)maleimide (4d). A mixture of 3.0 g (0.026 mol) of crude **2** and 12 g of NaF in 200 ml of methylene chloride at 10° was treated dropwise with a solution of 5.4 g (0.051 mol) of 4-toludine in 30 ml of methylene chloride at 10° and allowed to react at 25° for 18 hr. The solids were filtered and the solvent was removed from the filtrate. Recrystallization of the residue from chloroform gave 3.4 g (46%) of **4d**: mp 228–229°; ir (KBr) 3300 (NH), 1757, 1706 (C=O), and 1637 cm^{-1} (C=C); uv (CH_3CH) 240 (ϵ 18,150), 288 (ϵ 13,000), and 382 nm (ϵ 5140); mass spectrum *m/e* 292 (M^+).

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.59; H, 5.83; N, 9.85.

α-(4-Chloroanilino)-*N*-(4-Chlorophenyl)maleimide (4e). A slurry of 8 g of NaF and 2.0 g (0.017 mol) of crude **2** in 50 ml of methylene chloride was treated dropwise with a solution of 4.3 g (0.034 mol) of 4-chloroaniline in 25 ml of dioxane at 5°. After stirring for 1.5 hr, the mixture was warmed to 25° and filtered, and the solvent was removed from the filtrate. Methylene chloride (25 ml) was added to the residue and the yellow maleimide was filtered to yield 2.2 g (39%) of **4e**: mp 244–245° (chloroform–hexane); ir (KBr) 3333 (NH), 1773, 1724 (C=O), and 1645 cm^{-1} (C=C); uv (CH_3CN) 246 (ϵ 24,700), 290 (ϵ 11,100), and 377 nm (ϵ 7490).

Anal. Calcd for $C_{16}H_{10}N_2O_2Cl_2$: C, 57.41; H, 3.01; N, 8.41. Found: C, 56.65; H, 2.98; N, 8.10.

The second filtrate was chromatographed on 90 g of neutral silica gel with 1:1 carbon tetrachloride–chloroform to yield 2 g (35%) of the isomaleimide, **3e**.

***N,N'*-Diphenyl-α-*N*-phenyliminofuramide (13).** A solution of 0.8 g (0.102 mol) of aniline in 300 ml of methylene chloride was treated dropwise with 3 g (0.025 mol) of purified **2** in 50 ml of methylene chloride at 5°. After 15 min, the mixture was filtered and the solvent was removed. Recrystallization of the tan residue from chloroform gave 4 g (60%); mp 207–208°; ir (KBr) 3333 (NH), 1661 (C=O), 1704 cm^{-1} (C=N); uv (C_2H_5OH) 224 (ϵ 22,800), 240 (ϵ 19,700), and 325 nm (ϵ 8560); mass spectrum, *m/e* 357 $(M)^+$, 264 $(M - C_6H_5NH_2)^+$, 237 $(M - CONHC_6H_5)^+$, 144 $(237 - C_6H_5NH_2)^+$, 118 $(C_6H_5NCO)^+$, 93 $(C_6H_5NH_2)^+$, 77 $(C_6H_5)^+$; ^1H nmr (DMSO-d_6) δ 3.31 (s, HOD or H_2O), 3.67 (s, CH_2), 10.05 (s, NH), and 10.30 (s, NH). Ratio of NH:NH:CH_2 was 1:1:2. A complex multiplet for the aromatic protons was observed.

Anal. Calcd for $C_{22}H_{19}N_3O_2 \cdot \frac{1}{2}H_2O$: C, 72.19; H, 5.51; N, 11.48. Found: C, 72.36; N, 5.07; N, 11.72.

The furamide **13** could also be prepared by allowing a solution of 200 mg of **3a** and 5 ml of aniline in 25 ml of methylene chloride to stir for 2 hr at 0° and then 1 hr at 25°. Removal of solvent and recrystallization from chloroform–hexane gave **13**, mp 206–207°.

***N,N'*-Diphenyl-α-anilinofuramide (16).** A solution of **13** in dimethyl sulfoxide was allowed to stand 48 hr. The solution was added to ice water and the mixture was filtered. The solid filtered was dried under vacuum over P_2O_5: mp 197–198°; ir (KBr) 3484 (NH) and 1639 cm^{-1} (C=O); uv (C_2H_5OH) sh 227 (ϵ 17,100) and 338 nm (ϵ 26,100); ^1H nmr (DMSO-d_6) δ 5.65 (s, vinyl H), 10.00 (s, enamine NH), 10.60 and 10.65 (s, amide NH), complex multiplet for aromatic protons.

3-Anilino-2-hydroxy-5-phenylimino-2,5-dihydrofuran (9). A mixture of 1.0 g (3.8 mmol) of **3a** in 15 ml of dry dimethoxyethane was treated in one portion at 5° with 0.20 g (3.9 mmol) of sodium borohydride. After stirring 1 hr at 5° and 4 hr at 25°, the mixture was filtered. The solvent was removed under vacuum and the residue was hydrolyzed with 5 ml of an aqueous saturated ammonium chloride solution. The product was filtered, dried, and recrystallized from acetonitrile: mp 209–210° dec; ir (KBr) 3289 (wide, NH and OH), 1684 (C=N), 1664 cm^{-1} (C=C); uv (C_2H_5OH) 253 (ϵ 20,900) and sh 315 nm (ϵ 5690); ^1H nmr (DMSO-d_6) (220 MHz) δ 8.10 (s, NH), 6.04 (s, vinyl H), 5.93 (d, >CH), 6.25 (d, >C—OH), with J = 10 Hz). Addition of D_2O collapsed the doublet at δ 5.93 to a singlet and completely exchanged the doublet at δ 6.25 and singlet at δ 8.10. Mass spectrum: *m/e* 266 $(M)^+$, 248 $(M - H_2O)^+$, 219 $(M - H_2CO_2H)^+$, 220 $(M - HCO_2H)^+$, 117 $(C_6H_5NHC{\equiv}CH)^+$.

Anal. Calcd for $C_{16}H_{14}N_2O_2 \cdot \frac{3}{2}H_2O$: C, 65.58; H, 4.82; N, 9.56. Found: C, 65.00; H, 5.02; N, 9.68.

A mixture of **6** and activated MnO_2 in 25 ml of methylene chloride was stirred 2 hr at 25°. The mixture was filtered and the solvent was removed from the filtrate to yield a product whose infrared spectrum was identical with the isomaleimide, **3a**.

4-Anilino-5-hydroxy-Δ³-pyrrolin-2-one (10). A solution of 0.40 g (1.6 mmol) of **4a** in a mixture of 35 ml of dioxane–25 ml of ethanol was treated in one portion with 0.11 g (3.0 mmol) of sodium borohydride and mixture was stirred for 3 hr at 25°. The excess hydride was decomposed with acetic acid (*ca.* 1 ml) and the solvents were removed under vacuum. Water (5 ml) was added to the residue and the product was filtered and dried to yield 0.39 g. Recrystallization from the methanol–chloroform mixture gave mp 218–220°; ir (KBr) 3289 (broad, NH and OH), 1664 (C=O), and 1629 cm^{-1} (C=C); uv (C_2H_5OH) 232 (ϵ 12,500) and 315 nm (ϵ 23,500); 220-MHz ^1H nmr (DMSO-d_6) δ 9.33 (s, NH), 5.35 (s, vinyl H), 5.94 (d, CH), 6.77 (d, C—OH) with J = 10 Hz. Addition of D_2O completely exchanged the doublet at δ 6.77 and the singlet at δ 9.33 and collapsed the doublet at δ 5.94 to a singlet. Mass spectrum:

m/e 266 (M^+), 338 (monosilylated product)$^+$, 410 (disilylated product)$^+$, 248 [monosilylated − $(CH_3)_3SiOH]^+$.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.24; H, 5.31; N, 10.53. Found: C, 71.15; H, 5.26; N, 10.34.

A mixture of 100 mg of **10** and 500 mg of activated MnO_2 in 10 ml of methylene chloride was stirred at 25° for 1 hr. Removal of MnO_2 and solvent yielded the yellow fluorescent maleimide, whose infrared spectrum was identical with an authentic sample of **4a**.

Registry No.—**2**, 675-75-2; **3a**, 53683-74-2; **3b**, 53683-75-3; **3c**, 53683-76-4; **3d**, 53683-77-5; **3e**, 53683-78-6; **3f**, 53683-79-7; **3g**, 53683-80-0; **4a**, 13797-26-7; **4b**, 24978-25-4; **4c**, 53683-81-1; **4d**, 53683-82-2; **4e**, 53683-83-3; **9**, 53683-84-4; **10**, 53683-85-5; **13**, 53683-86-6; **16**, 53683-87-7; aniline, 62-53-3; 4-fluoroaniline, 371-40-4; 2-fluoroaniline, 348-54-9; 4-methylaniline, 106-49-0; 4-chloroaniline, 106-47-8; 4-nitroaniline, 100-01-6; 2-nitroaniline, 88-74-4.

References and Notes

(1) Contribution No. 2188.
(2) (a) K. E. Schulte, J. Reisch, and K. Coen, *Chim. Ther.*, **5**, 72 (1970); (b) E. V. Dehmlow, *Tetrahedron Lett.*, 1271 (1972).
(3) F. E. Herkes and H. E. Simmons, *J. Org. Chem.*, **40**, 420 (1975).
(4) F. E. Herkes and H. E. Simmons, *Synthesis*, **3**, 166 (1973).
(5) (a) N. D. Heindel, *J. Org. Chem.*, **35**, 3138 (1970); (b) S. K. Khetan, J. G. Hiriyakkanovar, and M. V. George, *Tetrahedron*, **24**, 1567 (1968); (c) W. I. Awad, S. M. A. R. Omran, and F. Nagreb, *ibid.*, **19**, 1591 (1963); (d) M. Hashimoto and M. Ohta, *Nippon Kagaku Zasshi*, **78**, 181 (1957); (e) J. F. Grove, *Ann. Appl. Biol.*, **35**, 25 (1948); (f) E. Hayada and S. Theodoropulos, *Tetrahedron*, **24**, 2241 (1968); (g) J. Reisch, *Pharmazie*, **26**, 420 (1967).
(6) K. Herbig, R. Huisgen, and H. Huber, *Chem. Ber.*, **99**, 2546 (1966).
(7) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).
(8) M. K. Hargreaves, J. G. Prichard, and H. R. Save, *Chem. Rev.*, **70**, 439 (1970).
(9) P. C. Myrhre, J. W. Edmonds, and J. D. Kruger, *J. Amer. Chem. Soc.*, **88**, 2459 (1966).
(10) G. V. Boyd, *Chem. Commun.*, 1147 (1969).
(11) P. de Mayo and S. T. Reid, *Chem. Ind. (London)*, 1576 (1962).
(12) G. P. Quistad and D. A. Lightner, *Chem. Commun.*, 1099 (1971).
(13) H. Suhr and A. Szabo, *Justus Liebigs Ann. Chem.*, **757**, 37 (1971).
(14) F. Farina, M. V. Martin, and M. C. Parades, *Synthesis*, **3**, 167 (1973).
(15) D. W. Weedy and D. L. Muck, *J. Amer. Chem. Soc.*, **93**, 4264 (1971).
(16) Z.-I. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, **26**, 2273 (1961).
(17) C.-g. Shin, M. Musaki, and M. Ohta, *Bull. Chem. Soc. Jap.* **44**, 1657 (1971).
(18) M. Masaki, C. Shin, H. Kurita, and M. Ohta, *Chem. Commun.*, 1447 (1968).
(19) Y. Iwanami, *Bull. Chem. Soc. Jap.*, **44**, 1311 (1971).

Bromination and Chlorination of 1,1,1-Trifluoro-*N*-phenylmethanesulfonamides

R. D. Trepka* and J. W. McConville

Contribution No. 720 from the Central Research Laboratories, 3M Company, Saint Paul, Minnesota 55101

Received July 18, 1974

Bromination of aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides in ethanol–water usually gave only one product when an extra equivalent of bromine was used to react with the acidic sulfonamide. Chlorination was much less selective and mixtures were always obtained. The (1,1,1-trifluoromethanesulfonyl)amino moiety was ortho–para directing in both cases. A number of halogen aryl substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides were prepared by bromination and chlorination in higher overall yields than with prior syntheses which consisted of sulfonylation of the previously prepared halogenated aniline with trifluoromethanesulfonyl fluoride or anhydride. The chlorination of unsubstituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamide was surveyed in various solvent–catalyst systems to prepare *N*-(2,4-dichlorophenyl)-1,1,1-trifluoromethanesulfonamide. The CH_3COOH–$AlCl_3$ and nitrobenzene–$AlCl_3$ systems gave the best selectivity with up to 70% 2,4-dichloro product produced in the latter system. Incremental addition of $AlCl_3$ to nitrobenzene during chlorination increased the rate of reaction and resulted in a mixture containing 81% 2,4-dichloro-, 10.4% 4-chloro-, and 8.6% 2,4,6-trichlorosulfonamide. Pure *N*-(2,4-dichlorophenyl)-1,1,1-trifluoromethanesulfonamide was then obtained by fractional crystallization in a yield of ~60%.

We have recently reported that halogen substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides possess interesting and unique biological activity as herbicides and plant growth regulators.[1,2] The preparation of these compounds was generally by reaction of the substituted aniline with trifluoromethanesulfonyl fluoride or the corresponding anhydride. However, sulfonylations of di- and trihalogenated anilines were usually low yield reactions and often required usage of the more reactive and more expensive trifluoromethanesulfonic acid anhydride. In extreme cases, such as the preparation of *N*-(2,4,6-trichlorophenyl)-1,1,1-trifluoromethanesulfonamide, the sodium salt of the substituted aniline had to be preformed before sulfonylation could be effected.[2]

It has now been found that sulfonylation of mono- or unsubstituted anilines with trifluoromethanesulfonyl fluoride is generally a facile reaction (yields greater than 75%) and suitable starting materials are therefore readily available for subsequent halogenation. For this reason, halogenation of the parent and monosubstituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides was investigated as a possible alternate, higher yield route to the di- and trihalogenated compounds reported in this paper. Additionally, to the best of our knowledge, a careful study of the mixture of products resulting from halogenation of any alkanesulfonanilide previously had not been undertaken with presently available gas–liquid partition chromatography techniques.

The (methanesulfonyl)amino group has been shown to be an ortho–para director in electrophilic aromatic substitution. Shriner[3] in 1932 nitrated methanesulfonanilide with nitric acid in sulfuric acid and obtained only 2,4-dinitromethanesulfonanilide while Kostova[4] in 1959 treated ethanesulfonanilide in dichloroethane with chlorine and zinc oxide and obtained only 2,4-dichloroethanesulfonanilide. Low yields (5–10%) of other products probably would not have been detected because of the analytical procedures used by these authors. In addition, no attempt was made to moderate experimental conditions such that only monosubstitution would have occurred. More recently, the (1,1,1-trifluoromethanesulfonyl)amino moiety was shown to be an ortho–para director in the nitration of 1,1,1-trifluoro-*N*-phenylmethanesulfonamide.[5,6] However, the

Table I
Bromination of $XC_6H_4NHSO_2CF_3$ in 85% Ethanol–15% Water

X	Registry No.	Conditions[a]	Bromination Position	Registry No.	Mp (°C)	Yield (%)
H	456-64-4	30 min, 80°	4	23384-06-7	58–59	26.6
			2,4-di	23384-22-7	106–107	23.8
H		6 hr, reflux[b]	2,4-di		106–107	58.7
2-F	23383-98-4	30 min, 80°	4	53608-52-9	90.5–91.5	65.2
2-Cl	23384-02-3	30 min, 80°	4	53608-53-0	114.4–115.3	33.3
2-CH_3	53443-75-7	1 hr, reflux[c]	4	53608-54-1	88–90	88.7
4-F	23384-00-1	1 hr, 60°	2	53608-55-2	58–59	34.2
4-Cl	23384-04-5	45 min, 50°	2	53608-56-3	105–106	45.2
4-CF_3	23384-12-5	1.5 hr, reflux	2	53608-57-4	78–80	66.3

[a] Two moles of bromine per mole of sulfonamide unless specified otherwise. [b] Three moles of bromine per mole of sulfonamide. [c] Solvent, 63% ethanol–37% water.

Table II
Chlorination of $XC_6H_4NHSO_2CF_3$ with $AlCl_3$ as Catalyst

X	Solvent	Reaction Conditions	Chlorination Position	Registry No.	Mp or Bp (mm), °C	Approximate Composition (%)
2-F	Acetic acid	11 hr, 50°	4	53608-58-5	75–80 (0.05)	88
			4,6	53608-59-6	85–90 (0.05)	12
4-F	Acetic acid	56.5 hr, 50°	2	53608-60-9	75–78.5	75[a]
			2,6	53608-61-0	95–96	17
4-F	Acetic acid	8 hr, 100°	2,6		95–96	100
4-CF_3	Nitrobenzene	6 hr, 50°	2	27573-83-7	91.5–92.5	41[b]
			2,6	53608-62-1	109–111	57

[a] Includes 8% unreacted 1,1,1-trifluoro-*N*-(4-fluorophenyl)methanesulfonamide. [b] Includes 2% unreacted 1,1,1-trifluoro-*N*-(4-trifluoromethylphenyl)methanesulfonamide.

more electronegative di(1,1,1-trifluoromethanesulfonyl)amino group was shown to be predominately a meta directing group (89% meta–11% para nitration).[5]

Experimental Section

The preparations and physical properties of the aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamide starting materials and all of the mono-, di-, and trichlorinated 1,1,1-trifluoro-*N*-phenylmethanesulfonamides were reported previously as was the general procedure for sulfonylation of substituted anilines with trifluoromethanesulfonyl fluoride.[2] All new compounds had satisfactory carbon, hydrogen, and nitrogen microanalyses (±0.3%) and infrared spectra. All melting points are uncorrected.

General Bromination Procedure. Bromine (3 mol) was added dropwise at room temperature to a solution of the 1,1,1-trifluoro-*N*-phenylmethanesulfonamide (1 mol) in 85% ethanol–15% water. The solution warmed to about 35° during the addition. The solution was refluxed until the bromine color was discharged (6 hr). The reaction mixture was cooled and poured into ice–water and the crystals were filtered. Recrystallization was from hexane–benzene.

General Chlorination Procedure. Chlorine, dried with concentrated sulfuric acid, was passed through a calibrated flowmeter into a nitrogen flushed, mechanically stirred, and electrically heated solution of the sulfonamide. The reaction was initially exothermic in acetic acid. With acetic acid solvent, the mixture was poured into ice–water and the resulting oil extracted twice with dichloromethane. With sodium hydroxide and water as solvent, the final acidic reaction mixture was extracted directly. Product recoveries were nearly quantitative because of the high lipophilicity of the various sulfonamides. With nitrobenzene solvent, the acidic sulfonamides were extracted with sodium hydroxide solution after addition of petroleum ether to decrease the solubility of the sodium salt in the organic phase.

Gas–Liquid Partition Chromatography. Product analyses were by a Varian Aerograph 202B gas chromatograph. The 0.25 in. o.d. column was packed with 7 in. of 15% XE60 on ABS followed by 3 ft of 25% QF1 on Anakrom P. The helium pressure was 50 cm^3/min and the column temperature was 205°.

Results

Preparative Brominations. The bromination reactions are summarized in Table I. There was no indication of more than one product even when examined by glpc except as noted for the bromination of 1,1,1-trifluoro-*N*-phenylmethanesulfonamide (1). Bromination of 1 with 1 equiv of bromine gave an oil upon reaction work-up. This oil was an unseparable mixture of largely starting material and a small amount of the 4-brominated product (estimated from the infrared spectrum). However, bromination of 1 with 2 equiv of bromine gave an easily separable mixture of 4-bromo (oil) and 2,4-dibromo (crystalline) derivatives in the yields given in Table I. Bromination of 1 with 3 equiv of bromine resulted only in 2,4-dibromination.

Preparative Chlorinations. These reactions are summarized in Table II. The chlorination reactions were not as selective as were brominations since it was impossible to obtain only monochlorination. Product percentages are approximate since detector response factors were not determined. Pure products were obtained by preparative glpc utilizing a Beckman Megachrom^R chromatograph equipped with a 0.75 in. o.d. column packed with 12 ft of 25% SE-30 on Chromosorb P. The helium pressure was 1.5 psi and the column temperature was 200°.

Chlorination of 1,1,1-Trifluoro-*N*-phenylmethanesulfonamide (1). The chlorination of 1 was investigated in more detail as a preparative procedure for obtaining *N*-(2,4-dichlorophenyl)-1,1,1-trifluoromethanesulfonamide. This compound is a novel herbicide and plant growth regulator which had been prepared previously in low yields (3.4%) by the sulfonylation of 2,4-dichloroaniline.[2] The effect of solvent and catalyst was first surveyed and the results of the initial survey are shown in Table III. All of the possible chlorinated products had previously been prepared by other means and detector response factors were used to calculate exact product composition percentages.

The more active solvent–catalyst systems such as CCl_4–$AlCl_3$ and NaOH–water produced a more random mixture and a larger amount of the undesired 2,4,6-trichloro product. The NaOH–water system was also undesirable since evolved hydrochloric acid neutralized the sodium hydrox-

Table III
Survey of Effect of Catalyst (0.5 g) and Solvent (50 ml) on Chlorination of $C_6H_5NHSO_2CF_3$ (0.05 mol)

Catalyst	Solvent	Temp (°C)	Time (hr)	Total Chlorine (mol)	Composition (%) Starting Material	2-Cl	4-Cl	2,4-diCl	2,6-diCl	2,4,6-triCl
$CuCl_2$	CH_3COOH	60	2	0.20	0	19.0	65.2	14.7	0.1	0.7
$ZnCl_2$	CH_3COOH	50	2	*a*	1.1	18.9	73.7	4.7	0	1.6
$FeCl_3$	CH_3COOH	50	2	*a*	0	16.8	60.8	19.4	1.2	1.9
$AlCl_3$	$CHCl_3$	50	2	0.44	16.3	3.3	57.2	19.9	0.2	2.9
$AlCl_3$	CCl_4	50	2	0.44	0	22.0	62.0	5.8	0	10.2
$AlCl_3$	CH_3COOH	70	1.5	0.33	0	10.5	57.0	29.9	0.1	2.5
$AlCl_3$	Nitrobenzene	50	3	*a*	0	5.7	44.0	44.2	0.8	5.3
	$NaOH/H_2O$[b]	40	1	0.17	0	15.0	15.3	50.3	11.2	8.2
S_2Cl_2	CH_3COOH	50	2	0.44	0	10.0	79.0	7.0	4.0	Trace

[a] Not measured. [b] Used 0.0525 mol of NaOH.

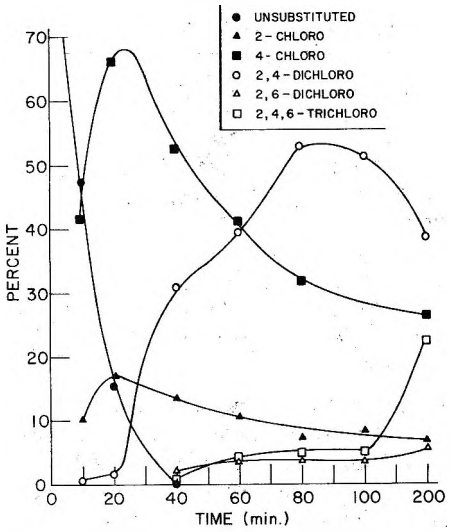


Figure 1. Chlorination of 1 (0.05 mol) in acetic acid (50 ml)–$AlCl_3$ (0.5 g) at 20° (0.22 mol of Cl_2/hr).

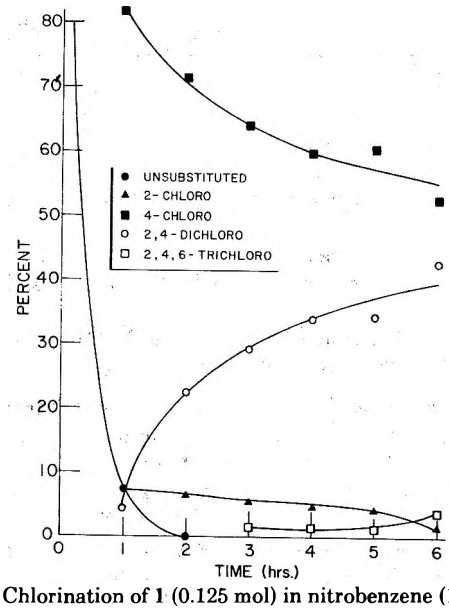


Figure 2. Chlorination of 1 (0.125 mol) in nitrobenzene (160 ml) at 50° (0.47 mol of Cl_2/hr).

ide resulting in precipitation of the sulfonamides making the reaction heterogeneous. Primarily 4-chloro and 2,4-dichloro products were produced in the less active systems such as CH_3COOH–$AlCl_3$ and nitrobenzene–$AlCl_3$ and these systems were investigated in more detail. In all these solvent–catalyst systems, pure 4-chloro-1,1,1-trifluoromethanesulfonamide could be isolated by fractional recrystallization in yields of greater than 50% if chlorination times were reduced.

The product ratios as a function of time were determined by glpc for the solvent–catalyst system CH_3COOH–$AlCl_3$. These results are plotted in Figure 1. In this system the concentration of the 2,4-dichloro product never exceeded 52.5% since the 2,4,6-trichloro concentration became large before all of the 2-chloro and 4-chloro products were consumed. The chlorination of 1 in nitrobenzene (no catalyst) at 50° was slow as shown in Figure 2. The addition of $AlCl_3$ (0.09 mol/mol of sulfonamide) resulted in only a slight rate increase at 50° and had a negligible effect upon product ratios. However, in nitrobenzene–$AlCl_3$ at 80° an increased reaction rate was observed, and results are shown in Figure 3.

A significant improvement of the nitrobenzene–$AlCl_3$ over the CH_3COOH–$AlCl_3$ system is that the concentration of 2,4,6-trichloro product did not increase significantly with time in the former system. In order to further increase the rate of chlorination in nitrobenzene, 0.15 mol of $AlCl_3$ for each mole of 1 was added at the beginning and after 3.5 hr of chlorination. At the end of 6.5 hr, the reaction mixture contained approximately 81% 2,4-dichloro, 10.4% 4-

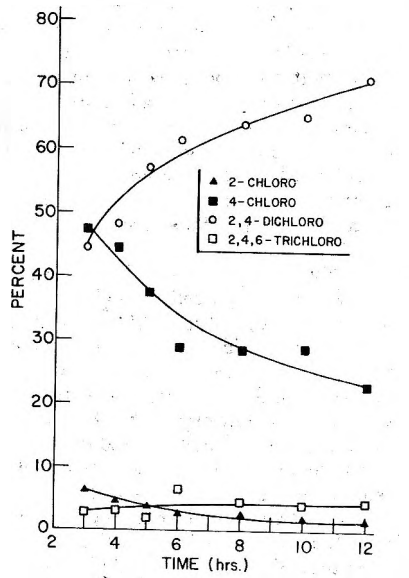
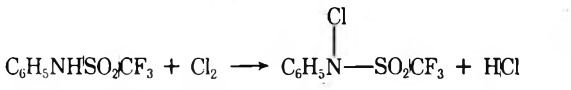


Figure 3. Chlorination of 1 (0.125 mol) in nitrobenzene (160 ml)–$AlCl_3$ (1.5 g) at 80° (0.30 mol of Cl_2/hr).

chloro, and 8.6% 2,4,6-trichloro products. Pure 2,4-dichloro product was then obtained by fractional recrystallization in yields of approximately 60%.

Discussion and Conclusions. In the halogenation of sulfonamides, the first equivalent of halogen probably

reacts at the acidic (1,1,1-trifluoromethanesulfonyl)amino site (pK_a = 4.45 for 1)[1] as illustrated for the chlorination of



1. Attempts to isolate such an intermediate in this study were unsuccessful. Such intermediates have been isolated from numerous aryl-substituted *N*-phenylbenzenesulfonamides[7] and *N,N*-dichloroalkanesulfonamides have also been prepared.[8] The former compounds rearrange in glacial acetic acid to give ortho–para ring chlorination. In addition, further chlorination of the *N*-chloro-*N*-phenylbenzenesulfonamides with sodium hypochlorite in glacial acetic acid results in the formation of *N*-chloro-*N*-(2,4,-dichlorophenyl)benzene sulfonamide.[7] Therefore the directing group in the present study is probably an *N*-halogen-(1,1,1-trifluoromethanesulfonyl)amino moiety which is clearly an ortho–para directing group as indicated by the results shown in Tables I and II.

In the present study bromination of 1,1,1-trifluoro-*N*-phenylmethanesulfonamides was found to be much more selective (only 2,4-dibromination with 3 equiv of bromine) than was chlorination. Both bromination and chlorination of aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides result in higher overall yields when compared with the previous syntheses[2] and require less expensive starting materials. The halogenation technique also allowed syntheses of sulfonamides in cases where the corresponding di- or trihalogenated anilines were not commercially available. These anilines could have been prepared by conventional techniques but the subsequent sulfonylations would then have been low yield reactions as previously described.

Acknowledgments. The authors are indebted to Mr. P. B. Olson and coworkers for the elemental analyses. We wish to thank Dr. T. S. Reid and Dr. J. E. Robertson for their interest and encouragement.

Registry No.—Bromine, 7726-95-6; chlorine, 7782-50-5.

References and Notes

(1) R. D. Trepka, J. K. Harrington, J. E. Robertson, and J. T. Waddington, *J. Agr. Food Chem.*, **18**, 1176 (1970).
(2) R. D. Trepka, J. K. Harrington, J. W. McConville, K. T. McGurran, A. Mendel, D. R. Pauly, J. E. Robertson, and J. T. Waddington, *J. Agr. Food Chem.*, **22**, 1111 (1974).
(3) R. L. Shriner, M. T. Goebel, and C. S. Marvel, *J. Amer. Chem. Soc.*, **54**, 2470 (1932).
(4) A. G. Kostova, R. Kh. Gershman, and V. T. Akin'shina, *Zh. Obshch. Khim.*, **29**, 2012 (1959).
(5) L. Z. Gandel'sman, M. I. Dronkina, V. P. Nazaretyan, and L. M. Yagupol'skii, *Zh. Org. Khim.*, **8**, 1659 (1972).
(6) Nomenclature of the fluorinated compounds is according to *Chem. Abstr.* **7**, Subject Index, Part 1, Section IV (1972).
(7) F. D. Chattaway, *J. Chem. Soc.*, **85**, 1181 (1904).
(8) N. N. Melnikov, I. D. Sukhareva, and F. Ya. Kavenoki, *Zh. Prikl. Khim.*, **18**, 568 (1945).

On The Alkylation of Multisite Aromatic Heterocycles. 1,2,3,4-Thiatriazoles

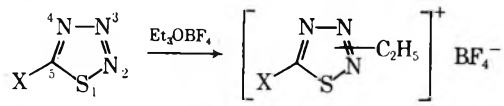
A. Holm,* K. Schaumburg, N. Dahlberg, C. Christophersen, and J. P. Snyder* [1]

Chemistry Laboratories II and V, H. C. Ørsted Institute, University of Copenhagen, DK-2100 Copenhagen, Denmark

Received February 21, 1974

5-Substituted 1,2,3,4-thiatriazoles are alkylated with triethyloxonium tetrafluoroborate to give a single product. The location of the ethyl group in the ring at position 3 has been accomplished by means of ^1H, ^{15}N, and ^{13}C nmr. CNDO calculations were performed to rationalize the exclusive alkylation of nitrogen β to sulfur. The theoretical and experimental results are in conflict, suggesting that the reaction is more complicated than it appears.

The 5-substituted 1,2,3,4-thiatriazole system 1 possesses five potential sites to which an alkylating agent may be delivered. Two quite different problems arise in an attempt to decide the course of the reaction. The first concerns substituent *vs.* ring attack. The second arises in the latter case and involves a decision as to which heteroatom of 1 has been alkylated. It is to these questions that we primarily address ourselves in the sequel.



1a, X = SCH_2CH_3 **2a**, X = SCH_2CH_3
b, X = SCH_3 **b**, X = SCH_3
c, X = C_6H_5 **c**, X = C_6H_5

Treatment of sodium 1,2,3,4-thiatriazole-5-thiolate (1, X = S^-) with diphenylmethyl, triphenylmethyl, and benzoyl chloride were formerly believed to yield 4-substituted 1,2,3,4-thiatriazoline-5-thiones.[2] In a recent paper these reactions were reexamined and evidence was presented that the products obtained in fact are all 5-substituted 1,2,3,4-thiatriazoles.[3] On the other hand it was reported by Neidlein and Tauber that alkylation of 5-arylamino-1,2,3,4-thiatriazoles (1, X = NHAr) with diazomethane leads to formation of 4-methyl-5-arylimino-1,2,3,4-thiatriazolines, while alkylation with dimethyl sulfate provides 5-*N*-aryl-*N*-methylamino-1,2,3,4-thiatriazoles.[4] These results prompted us to investigate the reaction of 5-mercapto-1,2,3,4,-thiatriazole (1, X = SH) with diazomethane and triethyloxonium tetrafluoroborate. Only the 5-alkylthio-1,2,3,4-thiatriazoles are formed.

By contrast the latter products, 1a and 1b, as well as 5-phenylthiatriazole (1c), can be alkylated with $Et_3O^+BF_4^-$ yielding crystalline salts. Under similar alkylating conditions, the alkoxy derivative (1, X = OC_2H_5) decomposes entirely to nitrogen, sulfur, and ethyl cyanate as previously described.[5] Apparently the electronegative ethoxy moiety reduces electron density in the ring sufficiently so that alkylation cannot compete with fragmentation.

The structures of the former salts are analyzed below on the basis of ^1H, ^{13}C, and ^{15}N nmr data.

S *vs.* N Alkylation. Upon treatment with triethyloxonium tetrafluoroborate the 5-ethyl- and 5-methylthio derivatives of 1 (**a, b**) lead to a single product salt in each case in 65 and 35% yields, respectively. The ^1H nmr values of starting thiatriazoles and the corresponding ethyl derivatives are given in Table I.

Ring alkylation is immediately suggested since the ethyl

Table I
^{1}H Nmr Values of Thiatriazoles and Thiatriazolium Salts

Compd	$-SCH_3$	$-SCH_2CH_3$	$-SCH_2CH_3$	$-NCH_2CH_3$	$-NCH_2CH_3$
1a		3.43[a]	1.57		
2a		3.57[b]	1.51	5.26	1.83
1b	2.88[a]				
2b	3.02[b]			5.38	1.86
2c				5.34[c]	1.94

[a] Solvent, CCl_4. [b] Solvent, d_6-acetone. [c] Solvent, $CD_3OD/CDCl_3$ (1:1).

groups delivered by the alkylating agent display δ values expected of *N*-ethyl salts[6] rather than *S*-ethyl salts.[7] Furthermore the new bands appearing in the nmr spectra of the alkylated alkylthio derivatives **2a** and **2b** are virtually superimposable with those of the phenyl system **2c**, a substance for which side-chain alkylation is not possible.

In all cases of alkylation, products are crystalline and stable up to 180–200° in the solid state. Although nothing has been reported regarding the cycloaddition behavior of *S*-alkyl thiephenium salts,[8] thiophene *S*-oxides dimerize spontaneously at ambient temperatures.[9] A cryoscopic molecular weight determination on the phenyl salt **2c** shows that the compound is monomeric. Solutions of the latter are stable (nmr) for periods of at least 1 year. Finally the ^{1}H nmr spectra of salts **2a–c** (Table I) do not accommodate the nonequivalence of alkyl substituents expected of dimers.

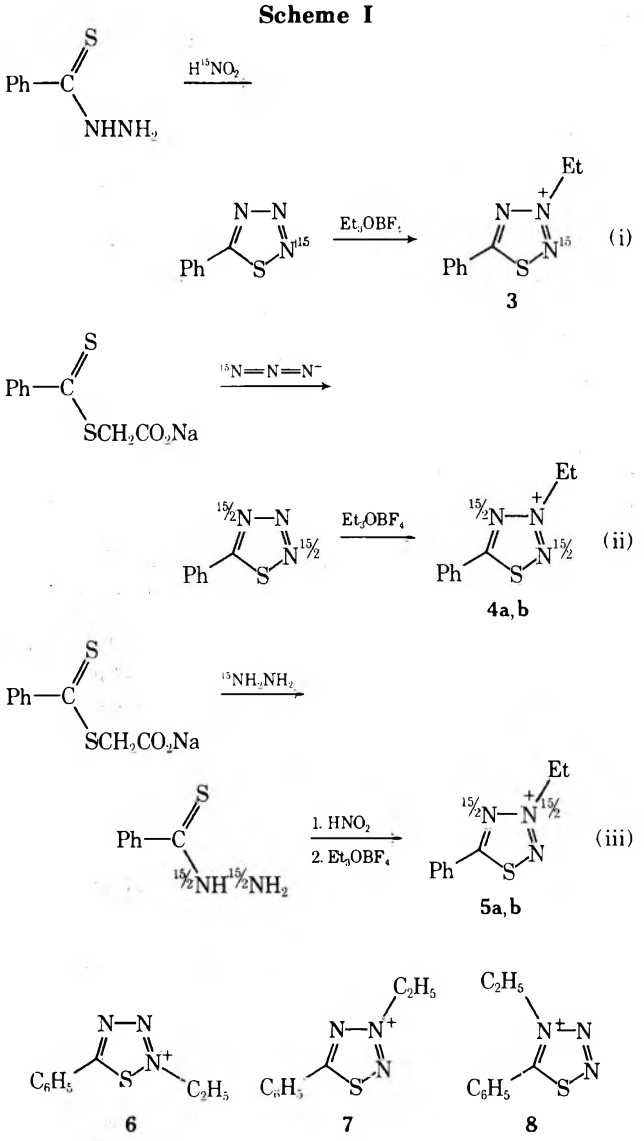
In sum, the proton nmr spectra, molecular weight measurement, and stability of thiatriazolium salts **2a, 2b,** and **2c** argue for N *vs.* S alkylation within the ring. In addition the near identity of chemical shifts and coupling constants for the ethyl groups suggests strongly that the position of alkylation is common to the three salts. In an attempt to define which of the three nitrogens has been ethylated, three isotopically distinct ^{15}N-labeled 5-phenyl-1,2,3,4-thiatriazoles have been prepared as outlined in the synthetic scheme (Scheme I). Each compound was subsequently alkylated with triethyloxonium tetrafluoroborate (**3, 4,** and **5**) and analyzed by ^{15}N and ^{13}C nmr spectroscopic data.

The three possible N-alkylation products are illustrated by structures **6, 7,** and **8** (*i.e.*, N-2, N-3, and N-4 alkylation, respectively). Both nitrogen chemical shifts and coupling constants (J_{NH}, J_{NC}) derived from the labeled substances **3, 4,** and **5** have been used to locate the alkylated nitrogen as N-3.

Alkylation Product 3 (^{15}N-2). In the ^{1}H nmr spectrum of salt **3** the methylene signal at δ 5.34 ppm is observed as a double quartet with $^3J_{HH}$ = 7.25 Hz and an additional splitting of 2.4 Hz. The methyl signal at δ 1.94 ppm is a clean triplet ($^3J_{HH}$ = 7.25 Hz) exhibiting a line width at half height of 0.2 Hz. The 2.4-Hz splitting of the methylene signal can be assigned to ^{15}N–H interaction by means of heterodecoupling. The corresponding ^{15}N-2 chemical shift is found to be -31 ± 2 ppm. No change in line width of the methyl signal was observed during the decoupling experiment.

Alkylation Product 4 (^{15}N-2 and ^{15}N-4). The ^{1}H nmr spectrum of **4a** and **4b** is very similar to that of **3** described above. The methyl signal is a sharp triplet with a line width of ~0.2 Hz, while the methylene signal again appears as a double quartet. The latter, however, evidences a line width somewhat larger than that found for compound **3.** Decoupling at the nitrogen frequency determined above for N-2 results in a quartet of triplets (see Figure 1). The outer lines are separated by 1.64 Hz. This spacing represents the coupling of the methylene protons to ^{15}N at position 4. Thus altering the nitrogen decoupling frequency produces another triplet structure in which the spacing of the outer lines is 2.4 Hz. The shift position of ^{15}N-4 is accordingly -73 ± 2 ppm.

Scheme I



Alkylation Product 5 (^{15}N-3 and ^{15}N-4). The low abundance of ^{15}N in sample **5** (30% total, 15% in **5a** and **5b,** respectively) limits the accuracy of the nmr measurement. Nonetheless, although the methylene signal is dominated by the methyl-induced quartet, satellites with a spacing of 1.7 Hz can be observed. The satellites disappear when the material is irradiated at -73 ppm, the shift frequency determined for ^{15}N-4. In the decoupled spectrum no evidence for an additional set of satellites was found. An upper limit of about 1.2 Hz is therefore placed on the magnitude of the coupling between CH_2 and ^{15}N at position 3. In contrast to the isotopic substitutions **3** and **4,** the methyl signal of **5** displays ^{15}N satellites with a spacing of 3.7 Hz. To erase the latter, irradiation at yet a third nitrogen frequency was necessary. The chemical shift of ^{15}N-3 is consequently established as -91 ± 2 ppm. Structure **7′** and Table II summarize the three nitrogen shift values for salt **2c** derived from the isotopic species **3, 4,** and **5.**

Further General Discussion of the Nmr Spectra of the Alkylation Products. Recently, nitrogen chemical shift data have been reported for a large number of five-membered heterocycles.[10] Among the molecules cited are

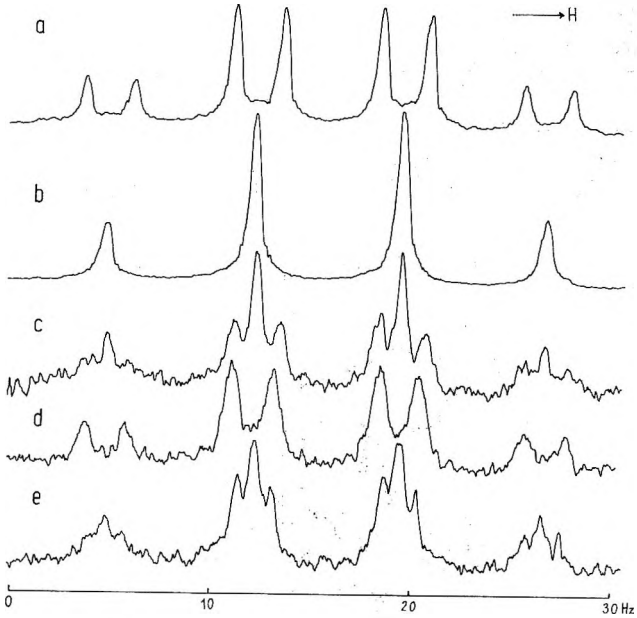
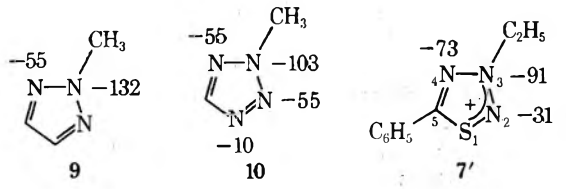


Figure 1. ^1H nmr spectra displaying the CH_2 group in the thiatriazolium salts 3 and 4 (a and b and c, d, and e, respectively) under ^{15}N selective decoupling. Spectra a and d show the undecoupled bands of 3 and 4 respectively. The decoupling rf field is present but offset sufficiently (15 kHz) so as not to influence the spectra. Curve b depicts the decoupling of ^{15}N-2 in compound 3 at a frequency of 10,137,040 ± 3 Hz. Spectrum c illustrates the result of irradiating salt 4 at 10,136,620 ± 5 Hz. At the latter frequency ^{15}N-4 is decoupled. The resulting spectrum is a superposition of equally intense spectra a and b. In e ^{15}N-2 (4) was irradiated at 10,137,040 ± 3 Hz leading to a combination pattern containing b and type a [J (^{15}N(4)–CH_2) = 1.64 Hz; *cf.* Table II].

2-methyl-1,2,3-triazole (**9**) and 2-methyl-1,2,3,4-tetrazole (**10**) (Chart I). No thiatriazoles were included in the work,

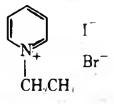
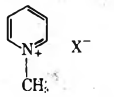
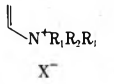
Chart I
^{14}N Chemical Shift for Triazole 9 (CH_3OH) and Tetrazole 10 (CH_3OH) and ^{15}N Shifts for Salt 7′ (3, 4, 5) ($CDCl_3/CD_3OD$ 1:1) in Parts per Million Upfield from CH_3NO_2



but based on a few selected examples the authors suggest that ring substitution of CH with S ought to have a minor influence on chemical shifts in the nitrogen nmr spectrum. In the present case the ring carries a positive charge which may well be located largely on sulfur.[11] Consequently a deshielding of N-2 relative to N-4 can be expected. Given these considerations the ^{14}N chemical shifts observed for compounds **9** and **10** may be seen as expectation values for salt **2c** to within 10–20 ppm. Furthermore it appears to be general that nitrogen atoms in five-ring aromatic heterocycles lacking σ lone-pair electrons are shielded to a greater extent than nitrogens bearing them. The former give rise to signals in the range −100 to −190 ppm while the latter are observed from 0 to −25 ppm for N–**N**–N and from −20 to −70 ppm for the N–**N**–C combination.[10] In view of this correlation, the ^{15}N chemical shift values determined for **2c** (*cf.* **7′** and Table II) can be consistently interpreted as an indication of alkylation at N-3.

The assignment is strengthened by evaluation of the heteronuclear coupling constants. Thus the ^{15}NH coupling constants for thiatriazolium salts can be profitably compared to literature data (Table II). These and other measurements[14] permit the generalization that $|^2J_{NH}| < |^3J_{NH}|$. Applied to compound **2c**, the latter suggests that a sizable nitrogen coupling to methyl should be observable when ^{15}N is bonded directly to CH_2CH_3. Table II illustrates that only ^{15}N-3 fulfills the necessary criterion. In agreement with previous work[15,16] the methylene group shows little or no nitrogen coupling (<1.2 Hz).

Table II
^{15}N Chemical Shifts and ^{15}NH Coupling Constants for Thiatriazolium Salt 7 and Related N-alkylated Heterocycles[a]

^{15}N position	$\delta(^{15}N)$,[b] ppm	$J(^{15}N–CH_2)$, Hz	$J(^{15}N–CH_3)$, Hz
2	−31 ± 2	2.43 ± 0.05	<0.2[c]
3	−91 ± 2	<1.20[c]	3.74 ± 0.1
4	−73 ± 2	1.64 ± 0.05	<0.2[c]
			3.4[a,d] 3.1[a,e]
			0.6–1.8[a,e]
		<Line width	2.8[a,f]

[a] Coupling constants for heterocycles other than 7 were measured as $J(^{14}NH)$ values and converted to $J(^{15}NH)$ by $J(^{14}NH) = 0.7129 \times J(^{15}NH)$; *cf.* M. Bose, N. Das, and N. Chatterje, *J. Mol. Spectros.*, 18, 32 (1965). [b] Position relative to CH_3NO_2; $\delta(NH_4^+) = -360$ ppm. [c] Coupling not observed. The values listed represent the observable half-width limit. [d] Reference 14. [e] Reference 15. [f] M. Ueyama and K. Tori, *Org. Magn. Resonance*, 4, 913 (1972).

Of importance in confirming the site of alkylation is the ^{13}C shift position of NCH_2, a doublet at 61 ppm (J = 5 Hz). Data given by Bucci[19] shows that for the neutral NCH_2CH_3 moiety a chemical shift value of 50 ppm can ordinarily be expected. The increased electronegativity of N-3 in **7′**, by virtue of ring-supported positive charge, leads to a downfield shift bringing the value close to what is observed for ethoxy derivatives. The ^{13}C data is in accord with pmr chemical shifts (Table I) in ruling out S alkylation.

The splitting of the methylene carbon resonance in **3** by ~5 Hz corresponds to a ^{15}N–^{13}C coupling constant. The quantity is in the range found by Lichter and Roberts[14] for heteronuclear splittings of this type.

The total evidence, proton and ^{15}N and ^{13}C chemical shift data as well as spin–spin splitting constants (J_{NH} and J_{NC}), effectively eliminates sulfur alkylation and simultaneously fixes the site of ethylation for **2c** to be N-3.

Attempts were made to unambiguously synthesize 5-phenyl-3-ethyl-1,2,3,4-thiatriazolium tetrafluoroborate (**7**)

Table III
^{13}C Chemical Shifts for Phenylthiatriazole 1c and Thiatriazolium Salt 7[a]

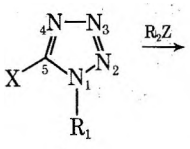
Compd	C_1	C_{ortho}	C_{meta}	C_{para}	C-5	CH_2	CH_3
1c	125.84	129.14	129.14	132.63	178.46		
2c	122.79	129.07	129.52	135.48	186.42	60.65	49.58
Δδ	−3.05	−0.07	0.38	2.85	7.96		

[a] Lines are measured relative to internal TMS. δ ($CDCl_3$) has been used as secondary standard. Positive δ values correspond to low field shifts.

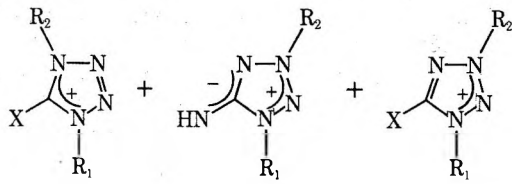
by a nonalkylation route. Thus 2-ethylthiobenzoylhydrazine was treated with nitric acid in tetrafluoroboric acid, but only an unidentified sulfur-free compound was obtained. Apparently redox processes dominate the cyclization reaction.

Thermal Properties of Thiatriazolium Tetrafluoroborates. The alkyl N-3 assignment is consistent with the pronounced thermal stability of the salts. All 5-substituted thiatriazoles decompose spontaneously either at room temperature or upon slight warming with evolution of N_2, whereas the salts are unchanged up to 180–200°. Evidently alkylation at the 3 position effectively blocks the ability of the system to eject nitrogen under mild conditions. It must be pointed out, however, that this observation permits no *a priori* prediction concerning the thermal properties of thiatriazolium salts bearing a substituent at the 2 or 4 position.

Reactivity Considerations. The finding that the alkyl moiety is located on N-3 of the phenyl salt **2c** was unexpected. There are several reasons for believing *a priori* that N-4 might be the preferred nucleophilic center. The literature records a single example of thiatriazole ring alkylation. Diazomethane is reported to deliver methyl to the 4 position.[4] Similar results are available for other multisite heterocycles. A variety of papers argue that tetrazoles **11** are alkylated exclusively on N-4 to give **12**.[20,21a] In the case of 5-aminotetrazole (**11**, X = NH_2; R_1 = alkyl) the major product was assigned structure **12**, while the mesoionic derivative **13** (N-3 alkylation) was isolated in low yield.[22] A recent careful study shows that in least one case (**11**, X = C_6H_5), alkylation at N-3 (*i.e.*, **14**) competes favorably with reaction at N-4.[23]

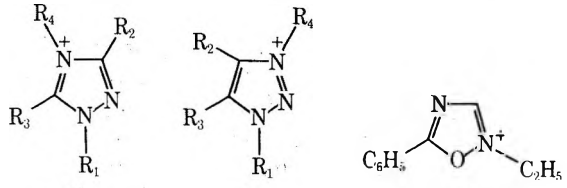


11

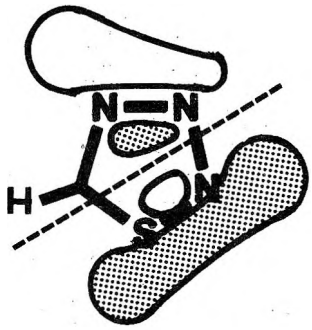


12 **13** **14**

1,2,4-Triazoles are reported to alkylate[21b] and protonate[24] at N-4 (*i.e.*, **15**), while the 1,2,3 isomers produce the



15 **16** **17**



18

X	Total charge distribution	Sigma framework charge distribution	Frontier orbital coefficients $\Sigma(C^f)^2$
S	+0.07	−0.15	0.27
N-2	−0.19	+0.05	0.29
N-3	+0.11	+0.03	0.14
N-4	−0.39	−0.02	0.30

Figure 2. CNDO calculated charge densities (total and σ) and highest occupied molecular orbital for thiatriazole. The relative areas correspond to the squares of the contributing atomic orbital coefficients.

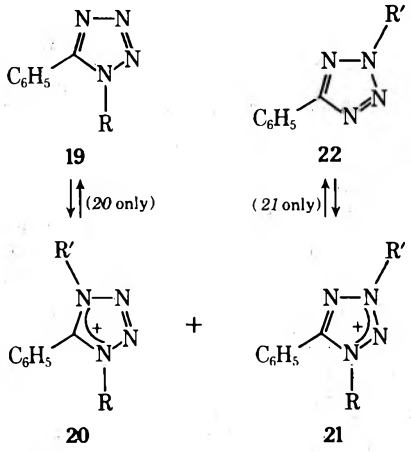
N-3 derivatives **16**.[25] A contrasting example is the N-2 alkylation product **17** from a 1,2,4-oxadiazole.[20b]

If the above examples were to be used as a guide to relative nitrogen nucleophilicity in five-membered heterocyclic rings of the type described, the following reactivity order is suggested: N-4 ≥ N-3 ≫ N-2.[26] This generalization should be regarded with caution. Only certain of the above citations provide definitive structural evidence as to the site of alkylation. Furthermore there is no uniformity with regard to ring substituents, the type of alkylating agent or the solvent employed. It is well known that these and other factors strongly influence the site of reactivity for related ambident systems.[27] An additional product controlling influence, kinetic *vs.* thermodynamic control, is discussed below.

In an attempt to derive a reactivity rationale for our assignment, SCF–MO–CNDO calculations[28] have been carried out for the unknown parent thiatriazole **18**. Total charge densities[29] and the frontier orbital electron distribution for the energy-geometry optimized heterocycle are given in Figure 2. These theoretical quantities have been used as indices of positional reactivity under conditions where the reaction is charge controlled or orbital controlled, respectively.[34,35] In the present case both criteria predict the reactivity order N-4 ≳ N-2 > N-3.

In sum general literature trends for poly nitrogen heterocycles suggest N-4 to be at least strongly competitive with N-3 as the favored nucleophilic center in thiatriazoles,

while our calculations indicate a clear preference for N-4 over N-3.[36] On the contrary the latter bears the alkyl moiety. There are several factors which permit partial reconciliation of the apparent disagreement. It is possible that the 4-ethyl salt **8** is generated in a kinetically controlled step followed by dealkylation and re-ethylation at N-3 to give the thermodynamically favored isomer **7**.[37] Similar heterocycles have been observed to undergo a thermodynamic equilibration of this type, but always in the presence of iodide ion, a powerful nucleophile.[23,33] In particular 1-alkyl-5-phenyltetrazoles **19** alkylate both at N-4 (**20**) and N-3 (**21**) under mild conditions. The system is ultimately converted through the less stable N-3 salt **20** to the energetically favored 1-alkyl-4-phenyltetrazole **22**.[23]



In the present case (**1c** → **7**) it seems unlikely that the tetrafluoroborate anion or possible traces of F^- have the capability to promote the required dealkylation. Furthermore the reaction has been monitored by nmr under ambient conditions during its early stages. The result does not support a multistep reaction scheme. The only new signals which appear in the spectrum of the freshly prepared solution are those arising from the 3-ethyl salt.[38]

A second explanation for the observed result may be steric in origin. Bulky substituents affect product distribution in the positional alkylation[40] and quaternization[33] of di-, tri-, and tetraaza heterocycles in a decided manner. Likewise 2-substituted 1,2,3-triazoles quaternize less readily than the 1-substituted isomer.[41]

It has not been demonstrated conclusively that the alkylthio derivatives **2a** and **2b** are ethylated at position 3. Based on the course of the reaction for phenylthiatriazole **1c** and the similar nmr spectra of salts **2** (Table I), it seems reasonable to assume that the side-chain sulfur cases possess structure **7**. If this hypothesis is valid and steric effects dominate electronic factors, both phenyl and *S*-alkyl are completely blocking reaction at position 4. Results reported for the phenyltetrazole **19** and the *s*-triazolo[4,3-*a*]pyridine[33] system make it unlikely that steric compression alone would direct the alkylating agent so specifically.

In conclusion, a conflict remains between the present result, literature precedent and the calculations. The general lack of reaction at N-2 for multisite heterocycles appears an even greater anomaly than the absence of observable competition between N-3 and N-4 for thiatriazoles **1**. The course of the thiatriazole alkylation clearly needs much closer attention.

Experimental Section

Nmr. ^1H spectra were obtained on a Varian HA-100 spectrometer by frequency sweep at 32°. The samples were prepared by dissolving 15 mg of the thiatriazolium compound in a 50:50 mixture of $CDCl_3$ and CD_3OD with TMS as internal reference. After several freeze–thaw cycles the degassed samples were sealed. ^{15}N decoupling was performed using a Schlumberger FSD 120 frequency synthesizer. The probe was modified for heterodecoupling according to McFarlane.[16] The chemical shift of ^{15}N was determined by comparison with the the decoupling frequency for ammonium nitrate.[42] The ^{13}C spectrum of compound **7** was obtained using the sample described above on a Varian XL-100 Fourier transform spectrometer: 100 *k* transients, pulse width 60 μsec over a range of 5000 Hz, aquisition time 0.4 sec, 4 K data points.

Alkylation of 1,2,3,4-Thiatriazole-5-thiol. A. Diazomethane (140 mmol, 2.5% ether solution) was added dropwise to 1,2,3,4-thiatriazole-5-thiol (11.9 g, 100 mmol) in dry diethyl ether (100 ml) at −20°. The resulting solution was stored overnight at 0° and then concentrated *in vacuo* without heating to ~50 ml. Concurrently 5-methylthio-1,2,3,4-thiatriazole, mp 32.0–34.0° (8.0 g, 60.1 mmol, 60%), precipitated from solution. The material was identified by comparison of its ir and nmr spectra with that of an authentic sample (mp 34.0–34.5°).[2a]

Evaporation of the mother liquor led to additional less pure product (mp 29.0–33.0°, 4.5 g, 33.8 mmol) corresponding to a total yield of 94%.

B. 1,2,3,4-Thiatriazole-5-thiol (1.00 g, 8.4 mmol) was neutralized with 0.6 ml of 50% aqueous sodium hydroxide (pH 9, phenolphthalein) and mixed with methylene chloride (10 ml) by stirring. Triethyloxonium tetrafluoroborate (1.60 g, 8.4 mmol) in methylene chloride (5 ml) was added at 0°. During addition sodium tetrafluoroborate precipitated. After filtration and drying ($MgSO_4$) the solution was evaporated to dryness and the remaining solid recrystallized from methanol (5 ml) (1.12 g, 8.4 mmol, 100%). The product was identified as above.

Alkylation of 5-Substituted 1,2,3,4-Thiatriazoles. The 5-substituted 1,2,3,4-thiatriazole (20 mmol) was dissolved in methylene chloride (10 ml) and a solution of triethyloxonium tetrafluoroborate (20 mmol) in methylene chloride (10 ml) was added dropwise over a short period of time. The system was surrounded with a water bath at ambient temperature. After standing overnight at room temperature the solvent was removed and the residue extracted several times with dry ether. The thiatriazolium salts thus obtained were recrystallized from absolute ethanol. Yields were from 50 to 70% after crystallization; for nmr shift values, see Table I.

With different 5 substituents the following analytical results were obtained: C_6H_5, mp 87.5–88.5° (Calcd for $C_9H_{10}N_3SBF_4$: C, 38.75; H, 3.87; N, 15.07. Found: C, 39.05; H, 3.69; N, 15.22.); CH_3S, mp 86.0–86.5° (Calcd for $C_4H_8N_3S_2BF_4$: C, 19.45; H, 3.47; N, 16.95. Found: C, 19.27; H, 3.28; N, 16.81.); C_2H_5S, mp 58.0–59.5° (Calcd for $C_5H_{10}N_3S_2BF_4$: C, 22.83; H, 3.83; N, 15.97. Found: C, 22.87; H, 3.83; N, 15.97.).

2-^{15}N-Labeled 5-Ethyl-3-phenyl-1,2,3,4-thiatriazolium Tetrafluoroborate (3). To 2-^{15}N-5-phenyl-1,2,3,4-thiatriazole (0.20 mmol) [prepared from thiobenzhydrazide and $Na^{15}NO_2$ (95% isotopically labeled) by the usual (see also below) procedure[43]] in methylene chloride (150 μl) was added triethyloxonium tetrafluoroborate (0.20 mmol) in methylene chloride (150 μl). After 24 hr at room temperature the solvent was removed *in vacuo* and the remaining solid or half-crystalline product washed a few times with dry ether. Recrystallization from absolute ethanol (300 μl) yielded ~25 mg of the crystalline title compound in 95% isotopic purity. Sometimes the material crystallized only after short boiling with ethanol. With the exception of J_{NH}, the ^1H nmr spectrum is identical with that of the unlabeled species.

Mixture of 3-^{15}N- and 4-^{15}N-Labeled 3-Ethyl-5-phenyl-1,2,3,4-thiatriazolium Tetrafluoroborate (5a,b). A. Preparation of the ^{15}N-Labeled Thiatriazole. To $^{15}NH_2NH_2$, H_2SO_4 (1.3 mmol) [prepared according to Bak, *et al.*,[44] from $^{15}NH_4Cl$ (30% isotopically labeled)] neutralized with 1 *N* NaOH (2.6 ml) and cooled in ice was slowly added a solution of carboxymethyl dithiobenzoate[45] (1.3 mmol) in 1 *N* NaOH (1.3 ml). After 1 hr at room temperature the mixture was extracted with a total of 15 ml of ether, washed with a small amount of water, dried over $MgSO_4$, and evaporated *in vacuo*. Thiobenzhydrazide thus formed was converted to the thiatriazole by the usual procedure.[43a]

B. The thiatriazole was alkylated with Et_3OBF_4 as described above for the 2-^{15}N-labeled product. The yield was ~20 mg of a crystalline mixture of the title compounds each 15% isotopically labeled. With the exception of J_{NH}, the ^1H nmr spectrum is identical with that of the unlabeled species.

Mixture of 2-^{15}N- and 4-^{15}N-Labeled 3-Ethyl-5-phenyl-1,2,3,4-thiatriazolium Tetrafluoroborate (4a,b). A. Preparation of $Na^{15}N_3$. The procedure used is a small-scale modification

of well-known methods.[46] A small test tube with a side arm containing solution A was closed by means of a rubber bulb and the side arm fitted with a plastic tube leading to solution C kept cooled in an ice bath. By means of a needle pierced through the rubber bulb, and reaching below the surface of solution A, nitrogen was swept through the system in a gentle stream during the whole procedure. From a syringe, fitted with a needle pierced through the rubber bulb, solution B was added slowly to solution A. After finishing addition the converted solution C was left covered overnight and the precipitate then isolated by means of centrifugation. The $Na^{15}N_3$ (95% isotopically pure at one nitrogen) thus formed was washed two times with small amounts of CH_3OH–Et_2O (1:1) and then with dry ether, yield 17 mg. Solutions: A, $Na^{15}NO_2$ (95% isotopically labeled) (60 mg), H_2O (200 μl), C_2H_5OH (25 μl); B, H_2O (200 μl), concentrated H_2SO_4 (25 μl), C_2H_5OH (25 μl); C, Na (25 mg) in CH_3OH (300 μl), NH_2NH_2, H_2O (50 μl), ether (500 μl).

B. Formation of the Thiatriazole. A solution of carboxymethyl dithiobenzoate[45] (5.0 mmol) in 1 *N* NaOH (5 ml) and water (1 ml) was prepared and washed with ether to remove impurities. Excess ether dissolved in the water phase was removed by bubbling a stream of nitrogen through the solution. To 0.6 ml of this solution was added the above prepared $Na^{15}N_3$ (17 mg). The resulting solution was left at room temperature for 4 hr. The thiatriazole was isolated by means of centrifugation and carefully washed with water, yield 15 mg.

C. The thiatriazole was alkylated with $Et_3OB_4^-$ as described above for the 2-^{15}N-labeled product. The yield was ~5 mg of a crystalline mixture of the title compounds each 47.5% isotopically labeled. With the exception of J_{NH}, the ^{1}H nmr spectrum is identical with that of the unlabeled species.

The Alkylation Process of 5-Phenyl-1,2,3,4-thiatriazole Followed by Means of Pmr Spectroscopy. Equivalent amounts of thiatriazole (32.0 mg) and $Et_3OB_4^-$ (37.6 mg) were dissolved in CD_2Cl_2 (0.5 ml) and the ^{1}H nmr signals recorded at given intervals during 22 hr, the time necessary for practical transformation. No signals besides those of the starting materials and the signals arising from 3-ethyl-5-phenyl-1,2,3,4-thiatriazolium tetrafluoroborate were observed.

Molecular Weight Determination. 3-Ethyl-5-phenyl-1,2,3,4-thiatriazolium tetrafluoroborate (1.427 g) was dissolved in water (86.3593 g) and the freezing point depression determined to 0.222° ± 0.005°. From these values a molecular weight of 277 ± 5 can be determined (calculated 279).

Acknowledgment. We are grateful to Professor S. Forsén (University of Lund, Sweden) for the ^{13}C spectrum and to Dr. M. Begtrup (Denmark's Technical University) for unpublished nmr data and several key literature citations.

Registry No.—**1a,** 52098-78-9; **1b,** 52098-77-8; **1c,** 34733-85-2; **2a,** 53336-74-6; **2b,** 53336-76-8; **2c,** 53336-78-0; triethyloxonium tetrafluoroborate 368-39-8.

References and Notes

(1) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient, 1971–1976.
(2) (a) E. Lieber, E. Oftedahl and C. N. R. Rao, *J. Org. Chem.*, **28,** 194 (1963); (b) E. Lieber, C. N. Pillai, J. Ramachandran, and R. D. Hites, *ibid.*, **22,** 1750 (1957).
(3) C. Christophersen and A. Holm, *Acta Chem. Scand.*, **25,** 2015 (1971).
(4) R. Neidlein and J. Tauber, *Arch. Pharm.*, **304,** 687 (1971).
(5) K. A. Jensen and A. Holm, *Acta Chem. Scand.*, **18,** 826 (1964).
(6) M. Begtrup, private communication.
(7) M. C. Caserio, R. E. Pratt, and R. J. Holland, *J. Amer. Chem. Soc.*, **88,** 5747 (1966).
(8) G. Brumlik, A. Kosak, and R. Pitcher, *J. Amer. Chem. Soc.*, **86,** 5360 (1964).
(9) J. L. Melles and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **72,** 491 (1953); W. Davies and F. C. James, *J. Chem. Soc.*, 15 (1954); W. J. Bailey and E. W. Cummins, *J. Amer. Chem. Soc.*, **76,** 1932 (1954); *cf.* C. D. Hurd, *Quart. Rep. Sulfur Chem.*, 4 (A), 90 (1969).
(10) M. Witanowski, L. Stefaniak, H. Januszewski, Z. Grabowski, and G. A. Webb, *Tetrahedron*, **28,** 637 (1972).
(11) CNDO calculations[12] have been performed on the three methyl salts of 1,2,3,4-thiatriazole corresponding to the isomeric species **6, 7,** and **8** (*i.e.*, NCH_3, **2, X** = H). In all cases the heteroatom bearing the burden of the charge is sulfur (+0.30 to +0.34). Nitrogen charges are either low and positive or negative (+0.23 to −0.33). Computed bond orders[13] likewise suggest salts of type **6–8** to possess a high degree of electron distribution of the type represented by structure **7′**.
(12) J. P. Snyder, unpublished results; *cf.* ref 28 for the parameterization.
(13) R. J. Boyd, *Can. J. Chem.*, **51,** 1151 (1973).
(14) R. L. Lichter and J. D. Roberts, *J. Amer. Chem. Soc.*, **93,** 5218 (1971).
(15) J. F. Biellmann and H. Callot, *Bull. Soc. Chim. Fr.*, 397 (1967).
(16) H. C. E. McFarlane and W. McFarlane, *Org. Magn. Resonance*, **4,** 161 (1972).
(17) G. J. Ray, R. J. Kurland, and A. K. Colter, *Tetrahedron*, **27,** 735 (1971).
(18) M. Begtrup, *Acta Chem. Scand.*, **27,** 3101 (1973); **B28,** 61 (1974).
(19) P. Bucci, *J. Amer. Chem. Soc.*, **90,** 252 (1968).
(20) (a) F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Amer. Chem. Soc.*, **73,** 4457 (1951); G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chem. Ind. (London)*, 1355 (1955); R. M. Herbst and C. F. Froberger, *J. Org. Chem.*, **22,** 1050 (1957); R. M. Herbst and K. G. Stone, *ibid.*, **22,** 1139 (1957). (b) D. M. Zimmerman and R. A. Olofson, *Tetrahedron Lett.*, 3452 (1970).
(21) (a) G. F. Duffin, *Advan. Heterocycl. Chem.*, **3,** 37 (1964); (b) 35 (1964).
(22) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Amer. Chem. Soc.*, **76,** 2894 (1954).
(23) T. Isida, S. Kozima, K. Nabika, and K. Sisido, *J. Org. Chem.*, **36,** 3807 (1971).
(24) G. B. Barlin and T. J. Batterham, *J. Chem. Soc., B,* 516 (1967).
(25) F. Krollpfeiffer, A. Rosenberg, and C. Mühlhausen, *Justus Liebigs Ann. Chem.*, **515,** 119 (1935); R. H. Wiley and J. Moffat, *J. Amer. Chem. Soc.*, **77,** 1703 (1955); C. S. Rondestvedt and P. K. Chang, *ibid.*, **77,** 6532 (1955).
(26) To our knowledge there are no recorded cases of N-2 alkylation for 1,2,3,4-tetrazoles (**11**) or the isomeric thiazoles where R_1 is other than a proton. The oxadiazole precursor of **17** appears to represent an exception to the overall trend.
(27) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland,, *J. Amer. Chem. Soc.*, **77,** 6269 (1955). D. C. Nonhebel and H. D. Murdoch, *J. Chem. Soc.*, 2153 (1962). S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, **86,** 1997 (1964); **87,** 3228 (1965). N. A. J. Rogers and A. Sattar, *Tetrahedron Lett.*, 1471 (1965). P. A. Chopard, R. F. Hudson, and G. Klopman, *J. Chem. Soc.*, 1379 (1965). J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N.Y., 1968, pp 298–302.
(28) R. J. Boyd and M. A. Whitehead, *J. Chem. Soc., Dalton Trans.*, 73 (1972); 78 (1972); 81 (1972).
(29) It is imperative to point out that the calculated total excess charges are due almost entirely to polarization of the π-electron framework, although the alkylation process surely engages primarily the σ-electron system. Preliminary calculations of the potential surface for protonation of thiatriazole **18** indicate that an electrophile prefers an in-plane attack.[12] This is in accord with the intuitive view of lone-pair N alkylation as well as *ab initio* calculations on related systems.[30] Calculated π-electron densities of polyaza heterocycles have been used previously to rationalize reactivity,[31] but predictions[32] have not always been rewarded by experimental verification.[33]
(30) R. Bonaccorsi, A. Pullman, E. Scrocco, and J. Tomasi, *Chem. Phys. Lett.*, **12,** 622 (1972); *Theoret. Chim. Acta (Berl.)*, **24,** 51 (1972).
(31) L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.*, **47,** 113 (1951); W. Woźnicki and B. Zurawski, *Acta Phys. Polonica.*, **31,** 95 (1967).
(32) K. T. Potts, H. R. Burton, and S. K. Roy, *J. Org. Chem.*, **31,** 265 (1966).
(33) W. W. Paudler and R. J. Brumbaugh, *J. Heterocycl. Chem.*, **5,** 29 (1968).
(34) G. Klopman and R. F. Hudsón, *Theoret. Chim. Acta*, **8,** 165 (1967); G. Klopman, *J. Amer. Chem. Soc.*, **90,** 223 (1968).
(35) R. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, **2,** 36 (1973).
(36) Similar calculations for substituted thiatriazoles in several conformations (*i.e.*, **1,** X = C_6H_5, SCH_3, NH_2) lead to the same qualitative partial and total electron distribution as for the parent system.[12]
(37) A referee has suggested a 1,5-sigmatropic shift as a possible alternative rearrangement pathway.
(38) This finding furthermore rules out the formation of considerable quantities of other alkylated isomers lost during work-up (crystallized yields of **2** are 50–70%; see Experimental Section). Thiatriazoles **1** are labile in the presence of mineral or Lewis acids giving rise to such products as nitriles and disulfides.[39] The moderate, crystallized yields of **2** are thus attributed to acid-catalyzed (HCl, HF, BF_3) decomposition of starting thiatriazoles.
(39) A. Holm, unpublished results.
(40) F. L. Pyman, *J. Chem. Soc.*, **97,** 1814 (1910); K. v. Auwers and H. Hollman, *Chem. Ber.*, **59,** 601 (1926); R. A. Henry, *J. Amer. Chem. Soc.*, **73,** 4470 (1951); C. Pedersen, *Acta Chem. Scand.*, **13,** 888 (1959); C. L. Habraken and J. A. Moore, *J. Org. Chem.*, **30,** 1892 (1965).
(41) R. Gompper, *Chem. Ber.*, **90,** 382 (1957). M. Begtrup and P. A. Kristensen, *Acta Chem. Scand.*, **23,** 2733 (1969). M. Begtrup, *ibid.*, **25,** 249 (1971); M. Begtrup and K. V. Poulsen, *ibid.*, **25,** 2087 (1971).
(42) B. M. Schmidt, L. C. Brown, and D. Williams, *J. Mol. Spectrosc.*, **3,** 30 (1959).
(43) (a) K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15,** 1104 (1961). (b) K. A. Jensen and A. Holm *Acta Chem. Scand.*, **23,** 2183 (1969).
(44) B. Bak, C. Hylling Christensen, D. Christensen, T. S. Hansen, E. J. Pedersen, and J. T. Nielsen, *Acta Chem. Scand.*, **19,** 2434 (1965).
(45) K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15,** 1087 (1961).
(46) J. Thiele, *Chem. Ber.*, **41,** 2681 (1908); W. L. Semon and V. R. Damerelle, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N.Y., 1961, p 204.

Azole Chemistry. X.[1] Silaazoles

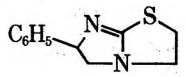
Howard Alper* [2] and Michael S. Wolin

Department of Chemistry, State University of New York at Binghamton, Binghamton, New York 13901

Received July 24, 1974

2-Mercaptoimidazoles and -benzimidazoles react with bromomethyldimethylchlorosilane in tetrahydrofuran to give the respective bromomethyldimethylchlorosilane derivates. Cyclodehydrohalogenation of the latter by 1,8-bis(dimethylamino)naphthalene affords 2-dimethylsila-3*H*-imidazo[2,1-*b*]thiazoles and 2-dimethylsila-3*H*-thiazolo[3,2-*a*]benzimidazoles in good yields. The spectral properties of the new heterocycles are discussed.

A number of fused azoles exhibit important pharmacological activity (*e.g.*, **1**, tetramisole, is a commercial, broad spectrum anthelmintic).[3-7]

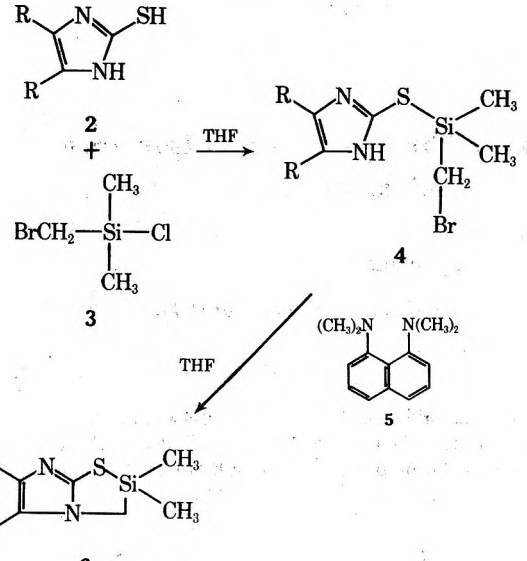


1

It was of considerable interest to learn what effect the replacement of a ring carbon by silicon would have on the activity of azoles of structural type **1**. The preparation of these heterocycles was required as a first step in attempting to answer this question. We now wish to report a simple and convenient synthesis of the 2-dimethylsila-3*H*-imidazo[2,1-*b*]thiazoles and 2-dimethylsila-3*H*-thiazolo[3,2-*a*]benzimidazoles.

Results and Discussion

Reaction of 2-mercaptoimidazole (**2a**, R = H) or 4,5-diphenyl-2-mercaptoimidazole (**2b**, R = C_6H_5) with bromomethyldimethylchlorosilane (**3**) in anhydrous tetrahydrofuran (THF) afforded the bromomethyl silylated imidazoles (**4a** (R = H), **4b** (R = C_6H_5)), characterized on the



basis of analytical data and spectral results (Table I). Previous studies using α-halo carbonyls[8] and epoxy bromides[9] showed that condensation occurs at the mercapto group of 2-mercaptoimidazoles or 2-mercaptobenzimidazoles.

The infrared (ir) spectra of **4** (KBr disk) were characterized by an NH stretching band at 3400 cm^{-1}; a weak absorption at 1427–1433 cm^{-1} due to asymmetric deformation of the methyl groups bound to silicon.[10] The nmr spectra (DMSO-d_6) of **4a** and **4b** showed singlets at δ 0.20 and 0.22, respectively, corresponding to the *gem*-dimethyl group, and singlets at δ 2.87 and 2.97, respectively, for the methylene group.

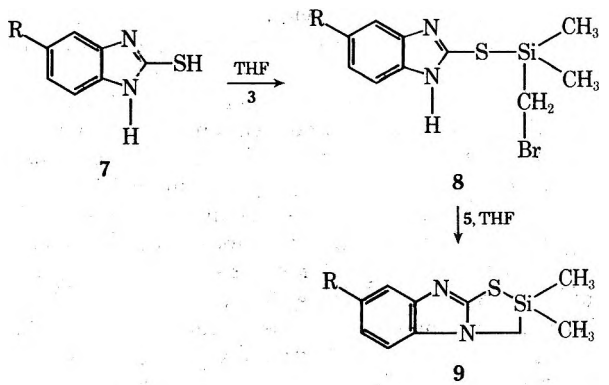
Table I
Yields and Melting Points for 4, 6, 8, and 9

Compd	Formula[a]	Mp, °C	Yield,[b] %
4a, R = H	$C_6H_{11}BrN_2SiS$	177–178	46
4b, R = C_6H_5	$C_{18}H_{19}BrN_2SiS$	205–206	50
6a, R = H	$C_6H_{10}N_2SiS$	128–133	80–85
6b, R = C_6H_5	$C_{18}H_{18}N_2SiS$	150 dec	80–90
8a, R = H	$C_{10}H_{13}BrN_2SiS$	218–219	47
8b, R = NO_2	$C_{10}H_{12}BrN_3O_2SiS$	>177 dec	31
9a, R = H	$C_{10}H_{12}N_2SiS$	181–182	>80
9b, R = NO_2	$C_{10}H_{11}N_3O_2SiS$	165 dec	65

[a] All compounds except **4a** (R = H) (*Anal.* Calcd: C, 28.69. Found: C, 29.42.) and **9a** (R = H) (*Anal.* Calcd: C, 54.50. Found: C, 53.93.) gave C, H, and N analysis within 0.4 of the calculated values. [b] No attempt was made to optimize yields.

Cyclodehydrohalogenation of **4** to **6** was effected in high yield by use of the powerful but nonnucleophilic base, 1,8-bis(dimethylamino)naphthalene (**5**, "proton sponge").[11] Nucleophiles, such as hydroxide or methoxide ion, cleaved the sulfur–silicon bond of **4**. The ir spectra of 2-dimethylsila-3*H*-imidazo[2,1-*b*]thiazole (**6**, R = H) and its 5,6-diphenyl derivative (**6**, R = C_6H_5) showed the expected asymmetric and symmetric deformation bands for the methyl groups attached to silicon, but lacked any absorption due to an NH group. In the nmr spectrum, the signal for the methyl groups of **6a** (R = H) and **6b** (R = C_6H_5) appeared at almost the same chemical shift as noted for **4**, while the methylene groups of **6** displayed a singlet at higher field than observed for the corresponding protons of **4** (*i.e.*, δ 2.56–2.59 for methylene protons of **6**).

Condensation of 2-mercaptobenzimidazole (**7a**, R = H) or 2-mercapto-5-nitrobenzimidazole (**7b**, R = NO_2) with **3** in THF gave **8a** (R = H) and **8b** (R = NO_2), which on exposure to 1,8-bis(dimethylamino)naphthalene afforded 2-dimethylsila-3*H*-thiazolo[3,2-*a*]benzimidazole (**9a**, R = H) and its 7-nitro derivative (**9b**, R = NO_2)[12] in good yields (Table I). The ir and nmr spectral properties for **8** and **9** were completely analogous to data discussed for the related



systems, **4** and **6**. In addition, a parent molecular ion peak was observed in the mass spectrum of **9a**, R = H, at *m/e* 220.

In summary, condensation of mercaptoazoles with bromomethyldimethylchlorosilane, followed by cyclodehydrohalogenation, constitutes a simple two-step entry into fused silaazoles. This synthetic pathway should be applicable to other azoles such as mercaptotriazoles and mercaptotetrazoles. Compounds **4**, **6**, **8**, and **9** are currently being screened for pharmacological activity.

Experimental Section

General. Elemental analyses were determined by Hoffmann-La Roche, Nutley, N. J., Pascher Microanalytical Laboratory, Bonn, Germany, and by Heterocyclic Chemical Corp., Harrisonville, Missouri. Infrared spectra were determined using a Perkin-Elmer 457 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. All mass spectra were obtained from an AEI MS-902 spectrometer.

Bromomethyldimethylchlorosilane and 1,8-bis(dimethylamino)-naphthalene were purchased from Pierce and Aldrich Chemical Co., respectively, and were used as received. The mercaptoazoles were commercially available and were recrystallized from aqueous ethanol and then oven dried, prior to use.

Solvents were purified by standard techniques. All reactions were run under a nitrogen atmosphere. All weighings and reaction work ups were carried out in a glove bag (N_2 atmosphere).

General Procedure for Reactions of Mercaptoazoles (2, 7) with Bromomethyldimethylchlorosilane (3). To a solution of the mercaptoazole in THF (40–70 ml) was added, by syringe techniques, an approximately equimolar amount (7–15 mmol) of bromomethyldimethylchlorosilane. The mixture was stirred at room temperature for 1 day and filtered, and the white solid was washed well with the THF and then dried *in vacuo*. The yields, melting points, and analytical data for **4** and **8** are listed in Table I.

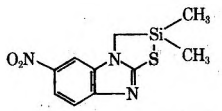
General Procedure for Cyclodehydrohalogenation of 4 and 8. A suspension of **4** or **8** (5–12 mmol) in THF (50–80 ml) containing 1,8-bis(dimethylamino)naphthalene (1.0–1.5:1.0 mol ratio of **5**:**4**,**8**) was stirred for 1 day at room temperature. The solution was filtered to remove protonated **5** and any unreacted **4** or **8**, and the filtrate was evaporated *in vacuo*. The residue obtained was treated with hexane and filtered, and the product (**6**, **9**) was washed well with hexane and dried. The hexane washings contained unreacted **5** (if present). The yields, melting points, and analytical data for **6** and **9** are given in Table I.

Acknowledgment. We are indebted to the National Institutes of Health for support of this research. We thank Mr. R. W. Stout for carrying out some preliminary experiments.

Registry No.—**2a**, 872-35-5; **2b**, 3718-54-5; **3**, 16532-02-8; **4a**, 53178-96-4; **4b**, 53279-97-5; **6a**, 53178-98-6; **6b**, 53178-99-7; **7a**, 583-39-1; **7b**, 6325-91-3; **8a**, 53179-00-3; **8b**, 53179-01-4; **9a**, 53179-02-5; **9b**, 53179-03-6; i, 53179-03-6.

References and Notes

(1) Azole Chemistry. IX: H. Alper and L. Pepper, *Can. J. Chem.*, in press.
(2) Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada KIN 6N5.
(3) C. J. Sharpe, R. S. Shadbolt, A. Ashford, and J. W. Ross, *J. Med. Chem.*, **14**, 977 (1971).
(4) J. P. Paolini and L. J. Lendway, *J. Med. Chem.*, **12**, 1031 (1969).
(5) P. G. Stecker, Ed., "The Merck Index," 8th Ed, Merck and Co., Rahway, N.J., 1968, p 1029.
(6) M. E. McMenim, German Patent 2,326,308 (Dec 6, 1973); *Chem. Abstr.*, **80**, 59943q (1974).
(7) J. Mohan, V. K. Chadha, H. S. Chaudhary, B. D. Sharma, H. K. Pujari, and L. N. Mohapata, *Indian J. Exp. Biol.*, **10**, 37 (1972).
(8) H. Ogura, T. Itoh, and K. Kikuchi, *J. Heterocycl. Chem.*, **6**, 797 (1969).
(9) H. Alper and E. C. H. Keung, *J. Org. Chem.*, **37**, 1464 (1972).
(10) R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectrometric Identification of Organic Compounds," 3rd ed, Wiley, New York, N.Y., 1974, p 141.
(11) R. W. Alder, P. S. Bowman, W. R. P. Steele, and D. R. Winterman, *Chem. Commun.*, 723 (1968).
(12) We cannot, at present, distinguish **9b**, R = NO_2, from i.



i

Benzimidazole Chemistry. I. Syntheses of the Three *N*-*n*-Propyl Isomers of 4-Amino-2,6-dimethylbenzimidazole

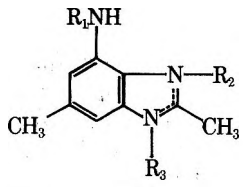
Robert E. Lyle* and John L. LaMattina

Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824

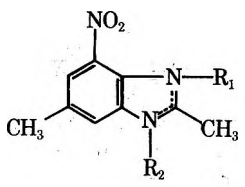
Received August 2, 1974

The specific preparations of 1-*n*-propyl-7-amino-2,5-dimethylbenzimidazole (**1**), 1-*n*-propyl-4-amino-2,6-dimethylbenzimidazole (**2**), and 4-*n*-propylamino-2,6-dimethylbenzimidazole (**3**) are described. These methods make use of the regiospecific or highly regioselective acylation and alkylation possible in the substrates. A correlation of isomeric structure with nmr spectra is also presented.

The regiospecificity of acylation and alkylation at multiple sites available in substituted fused imidazoles has received the greatest attention with purine derivatives because of their importance in living systems.[1] These data have received only limited application to the prediction of the reactivity of substitution of benzimidazoles.[2] For this reason the syntheses of 1-*n*-propyl-7-amino-2,5-dimethylbenzimidazole (**1**), 1-*n*-propyl-4-amino-2,6-dimethylbenzimidazole (**2**), and 4-*n*-propylamino-2,6-dimethylbenzimidazole (**3**) were attempted in order to obtain authentic examples of the three structures for comparison. Similarly 1-*n*-propyl-2,6-dimethyl-4-nitrobenzimidazole (**4**) was prepared and an unsuccessful attempt was made to synthesize 1-*n*-propyl-2,5-dimethyl-7-nitrobenzimidazole (**5**).



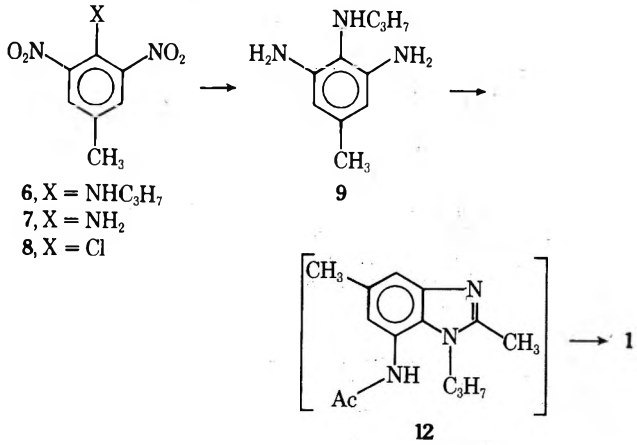
1, $R_1 = H$; $R_2 = n\text{-}C_3H_7$; $R_3 = CH_3$
2, $R_1 = H$; $R_3 = n\text{-}C_3H_7$; $R_2 = CH_3$
3, $R_1 = n\text{-}C_3H_7$; $R_2 = H$; $R_3 = CH_3$



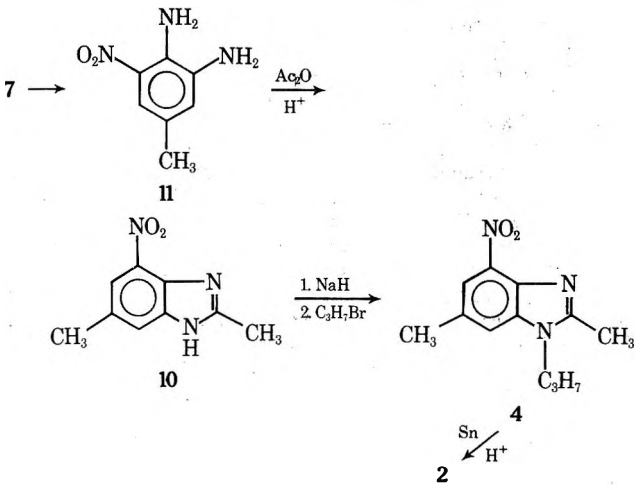
4, $R_2 = n\text{-}C_3H_7$; $R_1 = CH_3$
5, $R_1 = n\text{-}C_3H_7$; $R_2 = CH_3$

The synthesis of authentic **1** could be accomplished from the symmetrical *N*-*n*-propyl-2,6-dinitro-*p*-toluidine (**6**) obtained from 2,6-dinitro-*p*-toluidine (**7**)[3] by a Sandmeyer

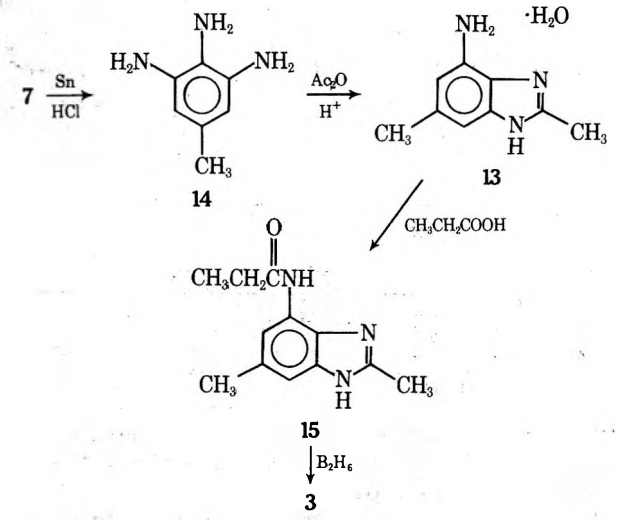
reaction[4] to 4-chloro-3,5-dinitrotoluene (8) followed by nucleophilic displacement of the halogen with *n*-propylamine. The structure of **6** was evident from the method of synthesis and the nmr spectrum which required a symmetrical structure. The reduction of the nitro groups with tin and hydrochloric acid gave the triamine **9**, which underwent cyclization with acetic anhydride to the intermediate acylated benzimidazole **12**. Hydrolysis of the acetamide gave authentic 1-*n*-propyl-7-amino-2,5-dimethylbenzimidazole (**1**) in 42% overall yield from **8**.



The synthesis of authentic 1-*n*-propyl-4-amino-2,6-dimethylbenzimidazole (**2**) was based on the selectivity of alkylation of adenine[5] and the anticipated steric interference to alkylation at a nucleophilic position adjacent to the large nitro group. Thus, 4-nitro-2,6-dimethylbenzimidazole (**10**), prepared from **7** by selective reduction of one nitro group to 3-nitro-5-methyl-*o*-phenylenediamine (**11**)[6] and ring closure, was converted to the anion with sodium hydride and alkylated with *n*-propyl bromide. The product was reduced with tin and hydrochloric acid to give a compound differing from **1** in melting point and spectral data. The only logical structure for this product is **2** based on the method of formation and spectral data, *vide infra*.



The synthesis of the third isomer, **3**, was also based on the selectivity observed on acylation of adenine which was shown to form an unstable diacyl derivative which was rapidly hydrolyzed to the 6-acyladenine.[7] Thus, 4-amino-2,6-dimethylbenzimidazole (**13**) was prepared by cyclization with acetic anhydride of the triamine **14** formed from the tin and hydrochloric acid reduction of **7**. Heating **13** with propionic acid gave a propionamide the infrared spectrum of which showed absorption bands at 1650 and 1538 cm^{-1} indicative of a secondary amide. These data are consistent with the structure **15**. Reduction of **15** with diborane[8] gave the desired 4-*n*-propylamino-2,6-dimethylbenzimidazole (**3**).



The alkylation of the anion of **15** was attempted, for this reaction should give substitution at the amide nitrogen at position 4, or the imidazole nitrogen farthest removed from the amide group, providing an alternate synthesis of **3** or **2**, depending on the site of alkylation. The alkylation product was hydrolyzed and the nmr clearly showed that alkylation had occurred on the imidazole ring, for the triplet for the NCH_2 was at about 4 ppm. Further study clearly showed the product to be 4-amino-2,6-dimethyl-1-propylbenzimidazole (**2**).

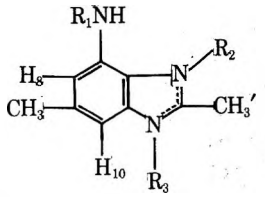
The alkylation of 2,6-dimethyl-4-nitrobenzimidazole (**10**) provided a synthetic method for 1-*n*-propyl derivative **4** and an alternate route was investigated for the preparation of 2,5-dimethyl-1-*n*-propyl-7-nitrobenzimidazole (**5**) from the corresponding amino derivative **1**. Attempted oxidation of the amino group with peracids[9] or the replacement of the diazonium salt with nitrite ion using a copper catalyst[10] failed to give an isolable product. Apparently extensive decomposition occurred in the former reaction and reduction and phenol formation resulted by the second method. These data suggest that severe steric interaction between a 1-alkyl group and a 7-substituent provides unfavorable interference in the transition state for the formation of **5**. No further attempt was made to prepare **5**.

Discussion of Nmr Spectra

The chemical shifts relative to TMS for the protons of the three isomers are listed in Table I. In comparing compounds **1** and **2**, it is worthwhile to compare the aromatic protons (H_8 and H_{10}) and the *N*-methylene group of each. When the propyl group is in the 3 position (R_2) both aromatic protons are relatively unaffected; thus, H_{10} appears at 7.01 ppm and H_8 at 6.37 ppm. When the propyl group is in the 1 position (R_3) in compound **2**, H_{10} should be shielded and, therefore, be shifted. H_8 has the exact same chemical shift in **1** and **2**. The chemical shift of the NCH_2 group has also changed. This is due presumably to the fact that this group in the 3 position (R_2) is deshielded by the 4-amino function. Thus, there is an upfield shift of 0.16 ppm for the NCH_2 in going from compound **1** to **2**.

As one might expect, there is a large difference in the chemical shifts of **3** relative to those of **1** and **2**. The electron-poor imidazole ring as well as the aromatic ring current deshield the methylene protons of the NCH_2 leading to an 0.8–1.0 ppm downfield shift in **1** and **2** as compared with **3**. The aromatic protons are shifted upfield due to the inductive effect of the propyl group.

Table I[11]
Nmr Spectra of *N*-*n*-Propylbenzimidazole



Compd	R_1	R_2	R_3	H_{10} (s)	H_8 (s)	CH_3' (s)	CH_3 (s)	n-C_3H_7 NCH_2 (t)	n-C_3H_7 CH_2 (h)	n-C_3H_7 CH_3 (t)
1	H	n-C_3H_7		7.01	6.37	2.52	2.36	4.12	1.84	0.96
2	H		n-C_3H_7	6.52	6.37	2.55	2.39	3.96	1.81	0.95
3	n-C_3H_7	(H)	(H)	6.41	6.12	2.41	2.34	3.12	1.58	0.91

It is evident from these data that within a series of substituted benzimidazoles the location of a substituent can be determined by nmr spectroscopy.

The position of alkylation and acylation of 4-amino-2,6-dimethylbenzimidazole can be compared with the corresponding reactions in purines. The primary amino group on the benzo ring is acylated more readily than the imidazole nitrogens and gives a more stable acyl derivative. Alkylation of the benzimidazole anion occurs at the less hindered nitrogen of the imidazole ring.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and were not corrected Elemental analyses were determined using an F&M Model 185, C, H, and N analyzer. Infrared spectra were determined using a Perkin-Elmer Model 337 spectrometer with samples prepared as KBr pellets. The nuclear magnetic resonance spectra were determined using a JEOL Model MH-100 spectrometer.

4-Chloro-3,5-dinitrotoluene (8). A solution of 5.6 g (0.081 mol) of sodium nitrite in 120 ml of concentrated sulfuric acid was cooled to 20° and a slurry of 14.7 g (0.075 mol) of 4-amino-3,5-dinitrotoluene (7) in 150 ml of warm glacial acetic acid was added at such a rate to keep the temperature below 40°. After stirring for 0.5 hr at 40°, the solution was added in portions to 15.8 g (0.16 mol) of cuprous chloride in 150 ml of concentrated hydrochloric acid. After the addition was finished, the reaction mixture was heated at 80° for 0.5 hr. The yellow solid which had separated was removed by filtration. The solid was boiled in 500 ml of benzene and the solution was decanted from the inorganic solids. Evaporation of the benzene gave 12.4 g (76.5%) of 4-chloro-2,5-dinitrotoluene (8) as a yellow solid: mp 112–114° (lit.[12] mp 113–114°).

4-*N*-Propylamino-3,5-dinitrotoluene (6). A solution of 5.0 g (0.023 mol) of 8 in 40 ml of benzene and 5 ml of triethylamine was placed in a 250-ml round-bottomed flask and 7.4 g (0.125 mol) of *n*-propylamine was added. The mixture was heated under reflux for 2 hr and the solvent was evaporated to give a mixture of solid and oil. This mixture was triturated with 70 ml of hot pentane and the insoluble material removed by filtration. The filtrate was evaporated in a hood, leaving behind 4-*N*-propylamino-3,5-dinitrotoluene (6) as orange solid. Recrystallization from hexane afforded 5.5 g (100%) of 6: mp 65–66° (lit.[13] 55°).

Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.57. Found: C, 49.90; H, 5.54; N, 17.33.

4-Amino-2,6-dimethyl-3-propylbenzimidazole (1). A three-necked 500-ml round-bottomed flask, fitted with a condenser and overhead stirrer, was charged with 120 ml of concentrated hydrochloric acid. Mossy tin (18.0 g) was carefully added, followed by 7.2 g (0.030 mol) of 6 and the mixture was heated for 1 hr. After cooling to 5° with an ice bath, 75 ml of $CHCl_3$ was added. The mixture was made basic with 140 g of 50% NaOH, then filtered to remove the insoluble inorganics. The $CHCl_3$ layer was separated from the filtrate and the aqueous layer was extracted four more times with 25-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were washed with 50 ml of H_2O, dried over Na_2SO_4, filtered, and evaporated to give 4.0 g (74.1%) of 9 as a light red oil: nmr ($CDCl_3$, in ppm) 6.03 (s, 2 H), 3.44 (br, 5 H), 2.84 (t, 2 H), 2.14 (s, 3 H), 1.58 (h, 2 H), 0.96 (t, 3 H).

This oil was immediately treated with 20 ml of acetic anhydride in a 250-ml round-bottomed flask and heated on a steam bath for 15 min. After cooling, the mixture was treated with 60 ml of 3 *N* hydrochloric acid, and then heated under reflux for 2.5 hr. The mixture was cooled, made basic with concentrated NH_4OH, and extracted four times with 25-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were evaporated, and the residue was added to 40 ml of 6 *N* HCl and heated under reflux for 2.5 hr. The mixture was made basic with concentrated NH_4OH and extracted three times with 30-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were dried over Na_2SO_4, filtered, and evaporated leaving behind a crude solid. Recrystallization of the solid from 25% aqueous ethanol afforded 2.3 g (51.5%) of 1 as light brown needles, mp 185–186°.

Anal. Calcd for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.87; H, 8.54; N, 20.73.

3,4-Diamino-5-nitrotoluene (11). A solution of 11.82 g (0.0600 mol) of 7 in 150 ml of dimethoxyethane and 15 ml of chloroform was hydrogenated over 600 mg of 10% Pd/C at ambient temperature and a pressure of 3 atm. The mixture was allowed to absorb the amount of hydrogen required to reduce one nitro group during 1.5 hr. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated by evaporation in a hood to give a dark solid residue. Recrystallization of the solid from 40% aqueous ethanol gave 8.1 g (81%) of 11 as a dark red crystalline solid: mp 152–154° (lit.[14] 152–154°).

2,6-Dimethyl-4-nitrobenzimidazole (10). A solution of 7.5 g (0.045 mol) of 11 and 25 ml of acetic anhydride was heated in a 500-ml round-bottomed flask on a steam bath for 0.5 hr. The flask was fitted with a condenser, and 80 ml of 3 *N* hydrochloric acid was added to the cooled reaction mixture. The mixture was heated under reflux 1 hr and diluted with 100 ml of H_2O. The solution was boiled with Norit briefly and then filtered through a Celite pad. The cooled filtrate was made basic by addition of concentrated NH_4OH. The precipitate which formed was removed by filtration and dried. Recrystallization of the solid from 35% aqueous EtOH gave 4.8 g (56%) of 10 as a tan solid, mp 238–240° (lit.[14] 238–240°).

2,6-Dimethyl-4-nitro-1-propylbenzimidazole (4). A mixture of 4.78 g (25.0 mmol) of 10, 1.06 g (25.0 mmol) of a 57% NaH–paraffin oil dispersion, and 100 ml of dry tetrahydrofuran was heated under reflux for 3 hr. To the cooled solution was added 12.3 g (0.100 mol) of *n*-propyl bromide, and the mixture was heated at reflux for 36 hr. The mixture was cooled and 200 ml of H_2O was added. The aqueous solution was extracted four times with 30-ml portions of $CHCl_3$, and the combined $CHCl_3$ layers were dried (K_2CO_3), filtered, and evaporated, leaving 3.8 g (66%) of a brown solid, the nmr of which showed the presence of only 4. Recrystallization from 40% aqueous EtOH afforded 4 as gold needles, mp 135.5–136°.

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.53; H, 6.48; N, 17.63.

4-Amino-2,6-dimethyl-1-propylbenzimidazole (2). A mixture of 1.00 g (4.30 mmol) of 4, 3.0 g of mossy tin, and 20 ml of concentrated hydrochloric acid was placed in a 100-ml round-bottomed flask and heated on a steam bath for 1.5 hr. The cooled mixture was made basic with 30 g of 50% NaOH, and then extracted four times with 25-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were dried over Na_2SO_4, filtered, and evaporated leaving an oil, which solidified when triturated with pentane. Recrystallization of the solid from hexane afforded 0.66 g (75.9%) of 2 as white needles, mp 94–95°.

Anal. Calcd for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.79; H, 8.58; N, 20.52.

3,4,5-Triaminotoluene (14). A mixture of 3.9 g (0.020 mol) of **7**, 9.0 g of mossy tin, and 60 ml of concentrated hydrochloric acid was placed in a three-necked 500-ml round-bottomed flask, fitted with a condenser and overhead stirrer, and heated on a steam bath for 1 hr. The cooled mixture was made basic with 80 g of 50% NaOH, then extracted four times with 50-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were dried over Na_2SO_4, filtered, and evaporated leaving behind a white solid. Recrystallization of the solid from benzene afforded 1.7 g (63%) of **14** as white needles, mp 100–102.5° (lit.[15] 105°).

4-Amino-2,6-dimethylbenzimidazole Monohydrate (13). A mixture of 3.7 g (0.027 mol) of **14** and 25 ml of acetic anhydride was heated in a 250-ml round-bottomed flask on a steam bath for 15 min. After cooling the mixture, 50 ml of 3 *N* hydrochloric acid was added, and the reaction was heated under reflux for 2 hr. The mixture was cooled, made basic with concentrated NH_4OH, and extracted four times with 40-ml portions of $CHCl_3$. Evaporation of the combined $CHCl_3$ layers yielded an oily residue, which was treated with 60 ml of 6 *N* hydrochloric acid and heated under reflux for 3 hr. The cooled mixture was made basic with concentrated NH_4OH, and allowed to sit in the refrigerator for 3 hr, resulting in the formation of 3.0 g (62.5%) of **13** as long light gold needles, mp 97–98.5° (lit.[16] 100°). This was used without further purification.

4-Propionamide-2,6-dimethylbenzimidazole (15). A mixture of 3.0 g (0.017 mol) of **13** and 50 ml of propionic acid was heated under reflux for 6 hr. The mixture was poured into 100 ml of ice water, and made basic with concentrated NH_4OH. The resulting precipitate was removed by filtration and washed liberally with water. After drying the solid it was recrystallized from tetrahydrofuran to yield 2.7 g (75.7%) of **15** as a white crystalline solid, mp 139° dec.

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 65.98; H, 6.98; N, 19.27.

2,6-Dimethyl-4-*N*-propylaminobenzimidazole (3). A three-necked 250-ml round-bottomed flask, fitted with a condenser, addition funnel, and septum, was charged with 20.5 ml (20.5 mmol) of a 1 *M* borane–THF solution. A solution of 1.77 g (8.20 mmol) of **15** in 80 ml of hot dry THF was added to the mixture over a 10-min period and the reaction was heated under reflux for 3.5 hr. To the cooled mixture 60 ml of 6 *N* hydrochloric acid was added slowly. The THF was removed by distillation at atmospheric pressure. Sodium hydroxide pellets were added to saturate the aqueous phase and the latter was extracted three times with a total of 60 ml of ether. The ether was evaporated leaving behind an oil which was treated with 60 ml of 6 *N* hydrochloric acid and heated at reflux for 2 hr. After cooling sodium hydroxide pellets were added until the mixture was basic and the latter was extracted a total of three times with 60 ml of ether. After drying with Na_2SO_4, the ether was evaporated leaving behind a solid. Recrystallization from 40% EtOH–H_2O afforded 1.0 g (60.2%) of **3** as a white amorphous solid, mp 87–88°.

Anal. Calcd for $C_{12}H_{17}N_3 \cdot 0.5H_2O$: C, 67.89; H, 8.55; N, 19.79. Found: C, 68.19; H, 8.86; N, 19.94.

Acknowledgment. The authors wish to express appreciation to Ciba-Geigy, Greensboro, N.C., for their encouragement and assistance during this investigation.

Registry No.—**1**, 53369-82-7; **2**, 53369-83-8; **3**, 53369-84-9; **4**, 53369-85-0; **6**, 2078-03-7; **7**, 6393-42-6; **8**, 5264-65-3; **9**, 53369-86-1; **10**, 53369-87-2; **11**, 53369-89-4; **13**, 19364-67-1; **14**, 27530-48-9; **15**, 53369-88-3; *n*-propylamine, 107-10-8; *n*-propyl bromide, 106-94-5; propionic acid, 79-09-4.

References and Notes

(1) J. H. Lister in "Fused Pyrimidines. Part II. Purines," D. J. Brown, Ed., Wiley-Interscience, New York, N.Y., 1971, pp 129, 192–194, 220–233, 280–281, 323–330, 342–348.
(2) J. B. Wright, *Chem. Rev.*, **48**, 397 (1951).
(3) H. Crocker and B. Jones, *J. Chem. Soc.*, 1808 (1959).
(4) F. Gunstone and S. Tucker, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 160.
(5) L. Townsend, R. Robins, R. Loepply, and N. Leonard, *J. Amer. Chem. Soc.*, **86**, 5320 (1964).
(6) R. E. Lyle and J. LaMattina, *Synthesis*, 726 (1974).
(7) A. Schein, *J. Med. Chem.*, **5**, 302 (1962).
(8) H. C. Brown and P. Hein, *J. Org. Chem.*, **38**, 912 (1973).
(9) W. Herz and D. Murty, *J. Org. Chem.*, **26**, 418 (1961).
(10) H. Hudson, A. Mahadevan, and E. Ward, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N.Y., 1955, p 341.
(11) All nmr spectra were determined in $CDCl_3$ and chemical shifts are reported in parts per million relative to TMS and represent the center of multiplets. Abbreviations used are s = singlet, t = triplet, h = hextet.
(12) G. Parkes and A. Farthing, *J. Chem. Soc.*, 1275 (1948).
(13) A. Hantsch, *Ber.*, **43**, 1673 (1910).
(14) H. Gillespie, F. Spano, and S. Graff, *J. Org. Chem.*, **25**, 942 (1960).
(15) R. Adams and E. DeYoung, *J. Amer. Chem. Soc.*, **79**, 417 (1957).
(16) H. Lindemann and H. Krause, *J. Prakt. Chem.*, **115**, 256 (1928).

Aril Azines. III.[1] Reaction of Benzil Benzal Monoazine with Sodium Methoxide

Peter Yates* and E. M. Levi

Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario, Canada M5S 1A1

Received September 26, 1974

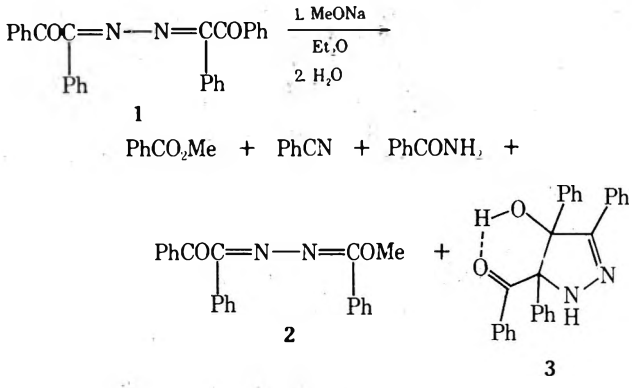
Reaction of benzil benzal monoazine (**5**) with sodium methoxide in ether gives as the major product benzil diazine (**9**). Several other products are formed, which include benzonitrile, benzamide, benzoic acid, 5-methoxy-1,2,5-triphenyl-3,4-diaza-2,4-pentadien-1-one (**2**), 3,4,5-triphenylpyrazole (**6**), *N*-benzylbenzamide (**7**), and a dihydro derivative of benzil diazine (**10**). It is suggested that the products are formed *via* two primary reaction pathways: (i) nucleophilic attack by methoxide ion on the benzal carbon atom of **5**, and (ii) abstraction of a proton from this carbon atom by methoxide ion.

The reaction of benzil monoazine (**1**) with sodium methoxide in ether has been shown to give the products depicted in Scheme I.[2] A possible pathway for the formation of the dihydro product **3** has been proposed to be that shown in Scheme II.[2] This postulate has led us to attempt to generate the anionic species **4** in an alternative fashion.

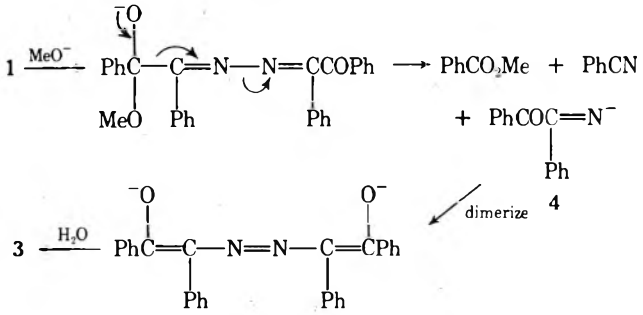
To this end the reaction of benzil benzal monoazine (**5**) with sodium methoxide was investigated in the hope that reaction might proceed, at least in part, by removal of the azomethine proton followed by fragmentation to benzonitrile and the anion **4**. In the event, treatment of **5** with sodium methoxide in boiling ether led to the rapid development of a blue coloration that later became dark red-brown; after 5 days aqueous work-up gave a plethora of products, which did not include **3**. These are shown in Scheme III; only **9** was isolated in major amount (35%).

Compounds **2** and **6** were identified by direct comparison with samples of those compounds that had been obtained previously in our work with benzil monoazine.[2] *N*-Benzylbenzamide (**7**) was identified by comparison with an au-

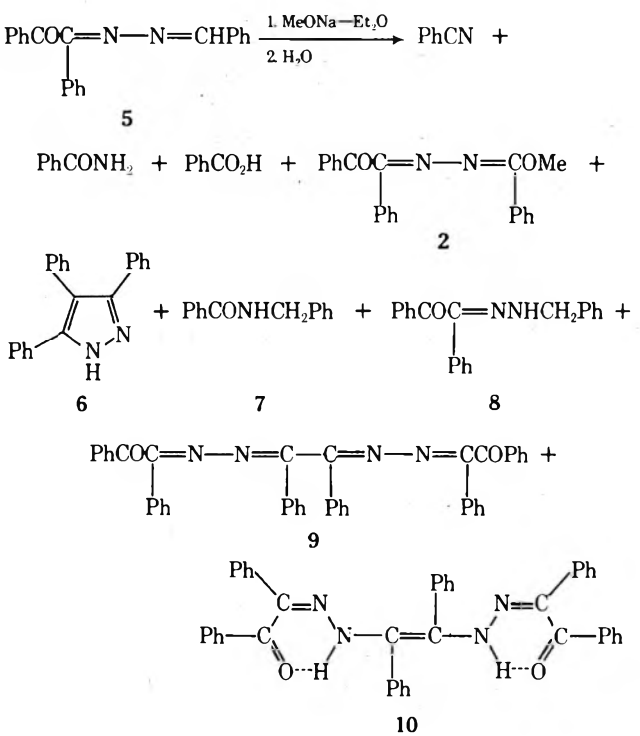
Scheme I



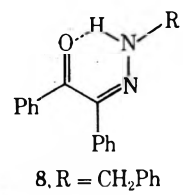
Scheme II



Scheme III



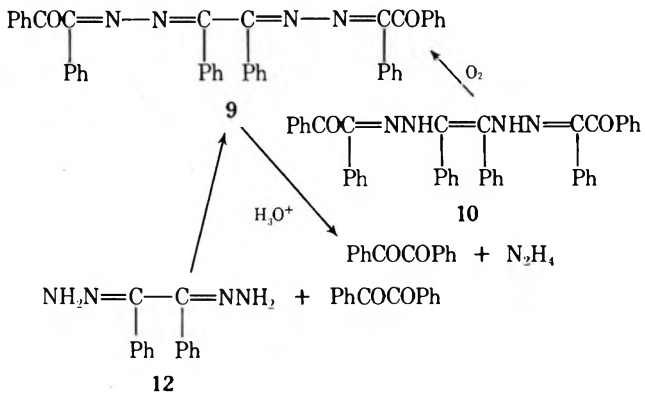
thentic sample prepared by treatment of benzoyl chloride with benzylamine.[3] The structural assignment 8 is tentative, since insufficient material was available for full characterization; it is made on the basis of the similarity of the ir spectrum of this product with that of benzil monohydrazone (11).



8, R = CH_2Ph
11, R = H

The structure of the yellow diazine 9 was assigned on the basis of the close similarity of its ir spectrum to that of benzil monoazine (1) and its hydrolysis to benzil and hydrazine. The assignment was confirmed by the independent preparation of 9 from benzil dihydrazone (12) and benzil (Scheme IV). Compound 10 separated from the original reaction mixture as an orange-red solid at the water–ether interface after treatment of the reaction mixture with water. It could not be purified by recrystallization since the red solutions formed in organic solvents rapidly turned yellow in air, giving the diazine 9.[4] A sample of the solid after thorough washing with ether and water gave elemental analytical data corresponding to the composition $C_{42}H_{32}N_4O_2 \cdot 0.5H_2O$; mass spectrometry corroborated the assignment of the formula $C_{42}H_{32}N_4O_2$. This formulation and its very facile oxidation to 9 suggested that it is a dihydro derivative of 9, and structure 10 (or the geometrical isomer at the ethylenic bond) is proposed on the basis of the relationship of its ir spectrum to the ir spectra of 8 and 11.

Scheme IV

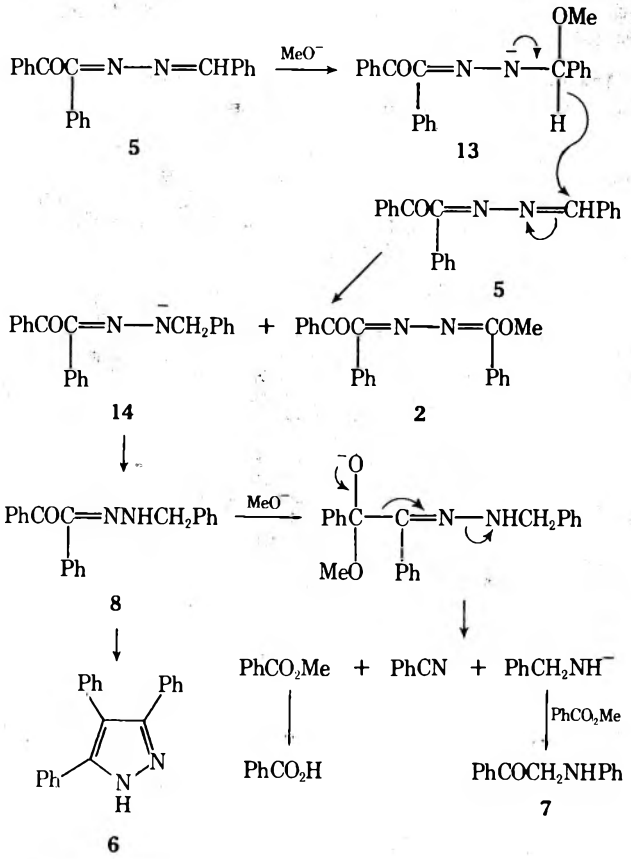


The formation of the products other than 9 and 10 from 5 and sodium methoxide can be envisaged as occurring *via* initial attack of methoxide ion to give the anion 13 (Scheme V). Hydride transfer from 13 to a second molecule of 5 would produce 2 and the anion 14, which could serve as the source of products 6, 7, and 8 and the smaller fragments observed (Scheme V). Alternatively, the anion 14 could arise *via* hydride or electron transfer from methoxide ion to 5. Scheme V involves the protonation of 14 before work-up; the proton source is considered to be methanol formed by proton abstraction from 5 (*vide infra*). The isolation of benzoic acid but not of methyl benzoate is attributed to hydrolysis of the latter by hydroxide ion formed in the conversion of 8 to 6.

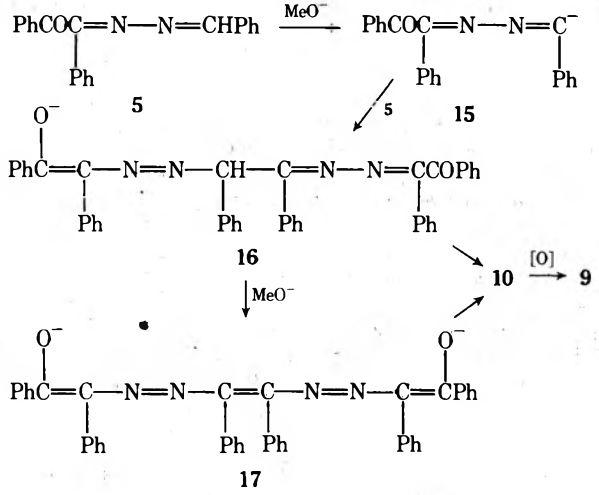
The formation of products 9 and 10 is postulated to involve a different primary reaction—proton abstraction by methoxide ion of the azomethine hydrogen of 5 to give the anion 15 (Scheme VI). Reaction of this with a second molecule of 5 would serve as a source of 10, *via* formation of its anion 16 or its dianion, 17; it is possible that the initial blue color of the reaction mixture is due to the latter species.[5] The azine 9 is considered to arise by oxidation of 10, either during the course of the reaction or during work-up.

The fact that compound 3 was not observed among the products from the reaction of 5 with sodium methoxide fails to provide evidence concerning the intermediacy of 4 in the formation of 3 from 1 and sodium methoxide. For,

Scheme V



Scheme VI



although the possibility exists that 4 might be formed from 5 *via* elimination of benzonitrile from **15**, there is no evidence that this occurs.

Experimental Section

Benzil Benzaldehyde Monoazine (5).[6] Benzil monohydrazone (17.0 g, 0.077 mol) was added to a solution of benzaldehyde (9.4 g, 0.088 mol) in absolute ethanol (550 ml) and the solution was refluxed for 3 hr. The solution was concentrated to *ca.* 100 ml and cooled to give yellow plates (15.25 g), mp 139–146°. Further concentration and cooling gave a second crop (5.30 g), mp 149–150.5°. The combined crops were dissolved in a mixture of benzene (50 ml) and ethanol (50 ml), and the solution was concentrated to 75 ml to give benzil benzaldehyde monoazine (20.2 g): mp 149–150° (lit.[6] mp 150°); λ_{max} ($CHCl_3$) 5.94 μ; λ_{max} (EtOH) 260 (log ϵ 4.23), 306 nm (log ϵ 4.46); δ ($CDCl_3$) 7.43 (m, 11 H), 7.92 (m, 4 H), 8.57 (s, 1 H).

Reaction of 5 with Sodium Methoxide. Benzil benzaldehyde monoazine (14.4 g) and dry sodium methoxide (9.06 g) in dry ether (1.2 l.) were stirred under a blanket of dry nitrogen. After 24 hr the solution was deep blue, and after 5 days red-brown. The red-brown reaction mixture was shaken with water (300 ml). The red-orange solid at the water–ether interface and suspended in the aqueous phase was filtered, washed with water and ether, and dried. This solid, compound **10** (0.52 g), had mp 184.5–185° dec; λ_{max} ($CHCl_3$) 3.01, 6.14 μ; *m/e* (%) 624 (4), 519 (6), 491 (5), 415 (28), 414 (58), 402 (5), 387 (6), 311 (10), 310 (24), 297 (10), 194 (5), 178 (10), 165 (10), 150 (10), 134 (14), 110 (7), 109 (55), 108 (17), 107 (13), 106 (27), 105 (100), 104 (65), 103 (29).

Anal. Calcd for $C_{42}H_{32}N_4O_2 \cdot 0.5H_2O$: C, 79.60; H, 5.25; N, 8.85. Found: C, 79.70; H, 5.40; N, 8.86.

The aqueous solution was extracted with ether, and the extracts were combined with the red ethereal solution, whose color rapidly changed to yellow. This process was not dependent on light. The aqueous solution was acidified to give benzoic acid (1.04 g, 7%); this was recrystallized to give material, mp 119–120°; mmp 120–121°.

The combined ethereal solutions were concentrated to *ca.* 150 ml and on standing for 5 days gave a mixture of crystals (4.11 g) from which a white crystalline solid, mp 165–173°, was separated manually. This was crystallized from ether to give material: mp 178–179° dec; λ_{max} ($CHCl_3$) 2.99, 3.04 (complex), 5.98 μ; solutions of this material in hot carbon tetrachloride or chloroform were red. Consistent elemental analytical and mass spectral data could not be obtained for this substance.

The residual yellow crystalline solid had mp 164–180°. Several recrystallizations from ethanol–benzene gave material, mp 184–186°. An analytical sample, mp 184.5–185.5°, was prepared by several recrystallizations of this material from acetic acid: λ_{max} ($CHCl_3$) 5.98 μ; λ_{max} (CH_2Cl_2) 258 (log ϵ 4.59), 318 nm (log ϵ 4.67); δ ($CDCl_3$) 7.15–7.55 (m, 26 H), 7.97 (m, 4 H).

Anal. Calcd for $C_{42}H_{30}N_4O_2$: C, 81.01; H, 4.86; N, 9.00. Found: C, 80.73; H, 4.85; N, 9.11.

This was identified as benzil diazine (**9**) by mmp 184–185° with an authentic sample (*vide infra*), mp 184–185°. Its mixture melting point with benzil monoazine was 169–175° and with benzil benzaldehyde monoazine, 141–144°.

The original ethereal solution was evaporated, and the residue was taken up in benzene–petroleum ether and chromatographed on alumina (B.D.H.; 480 g). Elution with benzene–petroleum ether (1:1) gave an oil (1.01 g) that contained mainly benzonitrile, identified by ir and nmr spectroscopy and by odor.

Further elution with benzene–petroleum ether (1:1) gave an oil (0.62 g), which was crystallized from ether to give crystalline material, mp 121–123°; this was recrystallized from ether to give needles, mp 124–125°. It was shown to be 1,2,5-triphenyl-5-methoxy-3,4-diaza-2,4-pentadien-1-one (**2**) by ir spectral comparison and by mixture melting point comparison with an authentic sample.[2]

Further elution with benzene–petroleum ether (1:1, 3:1, and 9:1) and benzene gave additional benzil diazine (2.56 g; total, 6.06 g), mp 184–185°.

Elution with ether–benzene (1:99) gave an orange oil (0.62 g) that crystallized from benzene to give *N*-benzylbenzamide (**7**): mp 104–105° and mmp 104–105° with an authentic sample (*vide infra*), mp 103.5–104°; λ_{max} (CCl_4) 3.05, 6.00 μ; δ ($CDCl_3$) 4.43 (d, J = 6 Hz, 2 H; s after D_2O treatment), 7.17 (m, 9 H; 8 H after D_2O treatment), 7.73 (m, 2 H).

Elution with ether–benzene (1:9) gave a green gum (0.78 g), which was rechromatographed under the same conditions to give material (0.54 g) that crystallized from ethanol as a solid, mp 125–135°; after recrystallization from ethanol this gave greenish needles, mp 147–148°; λ_{max} ($CHCl_3$) 3.01, 6.09 μ.

Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 79.89; H, 6.33; N, 8.95.

Elution with ether gave a white solid (0.57 g) from which 3,4,5-triphenylpyrazole (**6**), mp 265–266.5°, was obtained by crystallization from ethanol; it had mmp 265–266.5° with an authentic sample,[2] mp 265–266.5°.

Elution with methanol–chloroform (1:1) gave a black oil (0.57 g) that had an ir spectrum characteristic of benzamide and crystallized from water to give benzamide, mp 121–124°.

Hydrolysis of 9. Compound **9** (0.65 g) was heated in aqueous 66% sulfuric acid (75 ml) for 20 min. The mixture was poured into water (500 ml) and continuously extracted with ether for 2 days. The ethereal solution was dried and evaporated to give benzil (0.58 g, 88%), which after crystallization from ethanol had mp 90–93.5°. The aqueous acidic solution was treated with excess salicylaldehyde to detect hydrazine.[7] The solution became fluorescent and

on standing salicylalazine crystallized and was filtered to give fluorescent needles (0.42 g, 96%), mp 214–216° (lit.[8] mp 213°); mmp 214–216° with an authentic sample, mp 214–216°, prepared from salicylaldehyde and hydrazine dihydrochloride in water. The ir spectra of the two samples were indistinguishable.

Conversion of 10 to 9. Compound **10** (58 mg) was dissolved in dichloromethane and the red solution was allowed to stand in the air until the color had changed to yellow. The solution was evaporated, and the residue was crystallized from acetic acid to give yellow crystals (44 mg, 78%) of benzil diazine, mp 182–184°; mmp 182–184°.

***N*-Benzylbenzamide (7).** Benzoyl chloride (1.40 g, 0.0100 mol) in dry ether was added to a solution of benzylamine (2.14 g, 0.0200 mol) in dry ether (50 ml). White crystals formed, which were filtered and washed well with ether. The filtrate and washings were evaporated to give a white solid, which was crystallized from benzene to give *N*-benzylbenzamide (1.50 g, 50%), mp 103.5–104° (lit.[3] mp 105–106°).

Benzil Dihydrazone. (12). Benzil dihydrazone was prepared by boiling a solution of benzil and 2 equiv of hydrazine hydrate in 1-propanol under reflux for 60 hr: mp 151.5–152.5° (lit.[9] mp 152–153°); λ_{max} ($CHCl_3$) 2.90, 3.03; 6.19, 6.30 μ; δ ($CDCl_3$) 5.67 (br s, 4 H), 7.2–7.7 (m, 10 H).

Benzil Diazine (9). Benzil dihydrazone (2.38 g, 0.0100 mol) and benzil (4.20 g, 0.0200 mol) were heated under reflux in 1-propanol for 5 hr with a few drops of concentrated hydrochloric acid. A yellow crystalline mass, mp 171–180°, crystallized on cooling. Three crystallizations from glacial acetic acid gave benzil diazine, mp 184–185°.

Acknowledgment. We thank the National Research Council of Canada for support of this work.

Registry No.—**2**, 53555-48-9; **5**, 53555-49-0; **6**, 18076-30-7; **7**, 1485-70-7; **8**, 53555-51-4; **9**, 53555-50-3; **10**, 53555-52-5; **12**, 4702-78-7; sodium methoxide, 124-41-4; benzoyl chloride, 98-88-4; benzylamine, 100-46-9; benzil, 134-81-6; hydrazine, 302-01-2; benzil monohydrazone, 5344-88-7; benzaldehyde, 100-52-7.

References and Notes

(1) For paper II see P. Yates and E. M. Levi, *Can. J. Chem.*, in press.
(2) P. Yates, E. M. Levi, and B. L. Shapiro, *Can. J. Chem.*, **52**, 3343 (1974).
(3) E. Beckmann, *Chem. Ber.*, **23**, 3319 (1890).
(4) In contrast to the autoxidation of **3**,[2] this autoxidation does not appear to be photochemically induced; this is explicable in terms of the pathway proposed for the oxidation of **3**, wherein the photochemical step involves its conversion to an intermediate analogous to **10**.
(5) In the light of our considerations relating to the possible dimerization of **4**,[2] it is of interest to note that **17** could arise by dimerization of **15**.
(6) T. Curtius and K. Thun, *J. Prakt. Chem.*, **44**(2), 161 (1891).
(7) F. Feigl and V. Anger, "Spot Tests in Inorganic Analysis," 6th ed, Elsevier, Amsterdam, 1972, p 338.
(8) H. Cajar, *Chem. Ber.*, **31**, 2803 (1898).
(9) T. Curtius and A. Blumer, *J. Prakt. Chem.*, **52**(2), 117 (1895).

Diazotization of *endo*-7-Aminomethylbicyclo[3.3.1]nonan-3-ols and *endo*-7-Aminomethylbicyclo[3.3.1]non-2-ene[1]

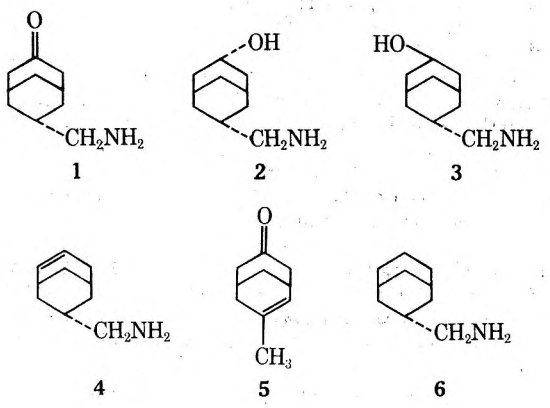
Thomas A. Wnuk,[2] John A. Tonnis,*[3] Michael J. Dolan,[3] Stanley J. Padegimas,[2,4] and Peter Kovacic*[2]

Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201, and Department of Chemistry, University of Wisconsin—La Crosse, La Crosse, Wisconsin 54601

Received August 21, 1974

Diazotization of *endo*-7-aminomethylbicyclo[3.3.1]nonan-*exo*-3-ol (**3**) with aqueous nitrous acid produced 3-methylbicyclo[3.3.1]non-2-en-*exo*-7-ol (**7**), *exo*-7-methylbicyclo[3.3.1]nonan-3-one (**8**), and presumably *exo*-8-hydroxybicyclo[4.3.1]dec-2-ene (**9**) as major products. Exposure of *endo*-7-aminomethylbicyclo[3.3.1]nonan-*endo*-3-ol (**2**) to both protic (acetic acid or water) and aprotic (benzene) deamination resulted mainly in formation of 1-methyl-2-oxaadamantane (**19**) and 4-oxahomoadamantane (**20**) in addition to a component tentatively identified as *endo*-8-hydroxybicyclo[4.3.1]dec-3-ene (**21**). Compound **2** yielded *endo*-7-aminomethylbicyclo[3.3.1]non-2-ene (**4**) with dilute sulfuric acid. Deamination of **4** under conditions used for **2** provided 2-adamantanol (**28**) and 2-adamantyl acetate (**29**) as principal products. Elimination, transannular interactions, and apparently ring expansion comprise the dominant reaction routes. **7** gave **8** with sulfuric acid. The preparations of the isomeric 7-methylenebicyclo[3.3.1]nonan-3-ols (**10**) and *endo*-7-methylbicyclo[3.3.1]nonan-3-one (**11**) from reduction of 7-methyleriebicyclo[3.3.1]nonan-3-one (**12**) are described. Endo alcohol **10b** provided **19** under acidic conditions. Mechanistic aspects of the investigation are treated.

Previous reports from this laboratory have described the preparation[5] of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (**1**) and its versatility as a precursor to various bicyclo[3.3.1]nonane derivatives.[6] Reduction of **1** with $NaBH_4$ in alcoholic solvents provided the corresponding alcohols,[7] **2** (endo) and **3** (exo). Keeping in mind the possibility for transannular interaction with the hydroxyl and alkenyl moieties, we intended to determine the response of **2** and **3**, as well as the aminoalkene **4**, toward various deaminating systems. Attention was devoted to mechanistic aspects.



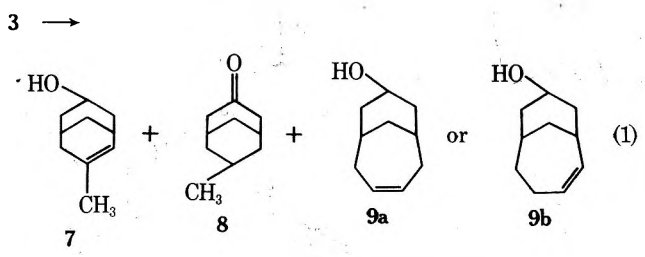
1 **2** **3** **4** **5** **6**

In related studies,[8] diazotization of **1** yielded 4-protoadamantanone and 3-methylbicyclo[3.3.1]non-2-en-7-one (**5**). *endo*-3-Aminomethylbicyclo[3.3.1]nonane (**6**) produced 3-methylbicyclo[3.3.1]non-2-ene, 3-methylenebicyclo[3.3.1]-nonane, *endo*-3-acetoxymethylbicyclo[3.3.1]nonane, and *endo*-3-hydroxymethylbicyclo[3.3.1]nonane.

Results and Discussion

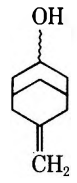
The isomeric amino alcohols **2** and **3** were subjected to deamination in three solvent systems. The major products resulted from elimination and transannular interactions. In addition, there was indication of ring expansion to the bicyclo[4.3.1]decene system.

***endo*-7-Aminomethylbicyclo[3.3.1]nonan-*exo*-3-ol.** When amino alcohol **3** was exposed to sodium nitrite and acetic acid in aqueous solution, the major products were 3-methylbicyclo[3.3.1]non-2-en-*exo*-7-ol (**7**) (50%), *exo*-7-methylbicyclo[3.3.1]nonan-3-one (**8**) (16%), and presumably *exo*-8-hydroxybicyclo[4.3.1]dec-2-ene (**9b**) (12%), eq 1.



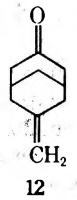
Several uncharacterized minor components (*ca.* 5% of the total) were also present. Structures for **7**, **8**, and **9** were assigned, in part, from spectral and microanalytical data. The nmr spectrum of **7** displayed an allylic methyl group, a multiplet for the alkene proton, and the characteristic seven-line multiplet indicating exo configuration[7] for the hydroxyl moiety.

The infrared spectrum of **8** showed strong carbonyl absorption, and the nmr data contained a doublet for the methyl protons, as well as broad absorption for the methylene protons adjacent to the carbonyl. The exo assignment for the methyl group is based on literature data[9-12] and independent synthesis. A simple preparative method for **8** consisted of exposing **7** to 75% sulfuric acid by analogy to work with lycopodine alkaloids.[13] Presumably, cation **15** (Scheme I) functions as an intermediate. Examples of the conversion of 7-methylenebicyclo[3.3.1]nonan-*exo*-3-ol[9,14] (**10a**) to **8** through the agency of sulfuric acid have been



10a, exo
b, endo

disclosed.[9,10] The stereochemistry was further corroborated by comparison with the endo isomer[11,15] (**11**) of **8** which was obtained by two routes. The first approach consisted of reduction of 7-methylenebicyclo[3.3.1]nonan-3-one[16] (**12**)



12

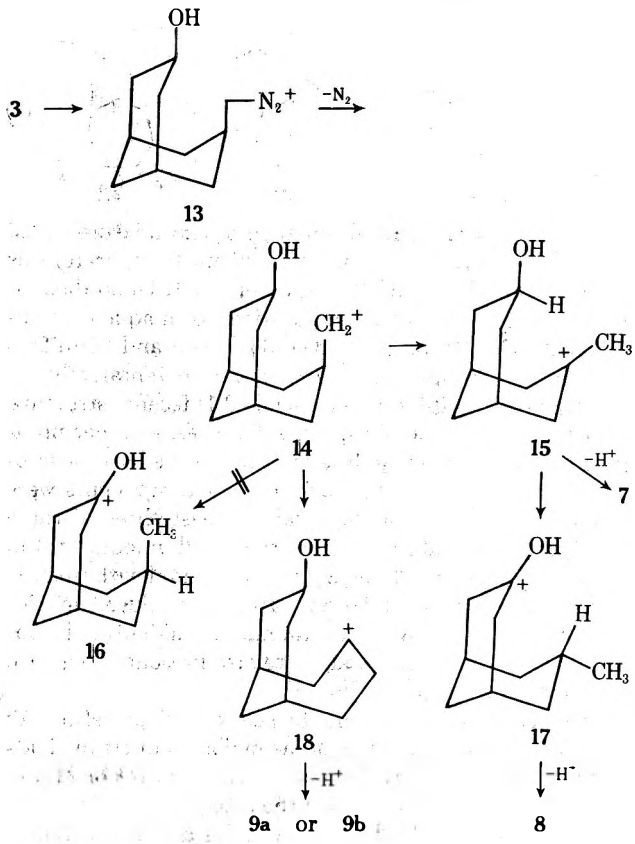
with $LiAlH_4$, followed by acetylation of the isomeric alcohols. After hydrogenation of the mixture of unsaturated acetates, the esters were saponified. Finally, chromic anhydride oxidation provided the desired ketone. A less complex route made use of direct hydrogenation[11,15] of **12** in the presence of platinum oxide. Ketone **11** exhibited spectral (ir and nmr) and physical properties different from those of its isomer **8**. An attempt to use **5**[8] as a precursor for **11** under reducing conditions (H_2–PtO_2) provided unchanged starting material. The reluctance to react can be attributed to the slow rate at which highly alkylated alkenes undergo hydrogenation.[17]

The unsaturated alcohol **9** had informative nmr features consisting of two alkene protons, as well as the seven-line multiplet for the proton α to the exo OH. A multiplet at δ 2.60, assigned to the allylic bridgehead proton, and the relative complexity of the spectrum support the unsymmetrical structure **9b**. The hydroxyl and alkene absorptions in the infrared region were also diagnostic, as was the molecular ion at *m/e* 152 in the mass spectrum. The isomeric alkenol **10a** was ruled out by comparison of the materials. Compound **10a** was prepared by $LiAlH_4$ reduction of **12**.

When isoamyl nitrite in acetic acid or isoamyl nitrite in acetic acid–benzene was used for deamination of **3**, mixtures arose which were difficult to separate by glpc. It appeared, however, that the yield of **8** was greater in these cases.

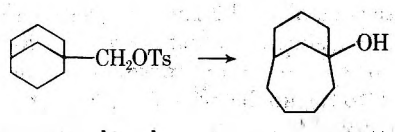
Scheme I outlines reasonable mechanistic pathways for formation of **7**, **8**, and **9** from **3**.

Scheme I



Rearrangement to **15** appears to be the predominant mode of reaction of the initially formed cation **14** (see below). Elimination from **15** comprises the major type of reaction, leading to **7**. Intermediate **15** can undergo further rearrangement by transannular hydride abstraction[10,13] with eventual production of **8** *via* **17**. Transannular hydride abstractions involving bicyclo[3.3.1]nonyl cations have been documented. For example, solvolysis[10] of the tosylate of *exo*-7-methylbicyclo[3.3.1]nonan-*exo*-3-ol provided more than 50% of 3-methylbicyclo[3.3.1]non-2-ene, in addition to exo-7-methylbicyclo[3.3.1]non-2-ene from 1,2 elimination. Additional examples are presented in a recent review.[18]

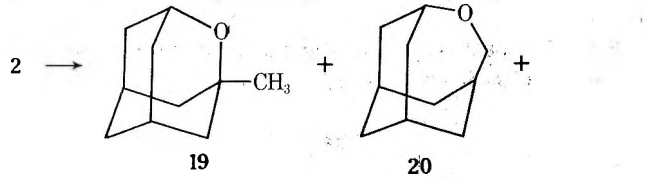
The Demyanov type rearrangement of **14** to **18** provides a rare example of ring expansion from a bicyclo[3.3.1]nonane to a bicyclo[4.3.1]decane. Subsequent elimination of a proton can occur with formation of **9**. A related ring enlargement *via* the (1-bicyclo[3.3.1]nonyl)methyl cation has been reported,[19] eq 2.

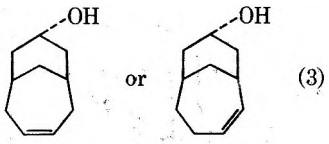


(2)

Prior literature that has come to our attention concerning diazotization of amino alcohols generally involved the 1-hydroxy-2-amino types. These compounds undergo ring expansion *via* Tiffeneu–Demyanov rearrangement.[20]

endo-7-**Aminomethylbicyclo[3.3.1]nonan-*endo*-3-ol.** In the case of the endo alcohol **2**, the major products were 1-methyl-2-oxaadamantane (**19**) and 4-oxahomoadamantane (**20**) in all three systems, eq 3. Identification of **19** and **20** was based on spectral and literature data.[8,21,22]





(3)

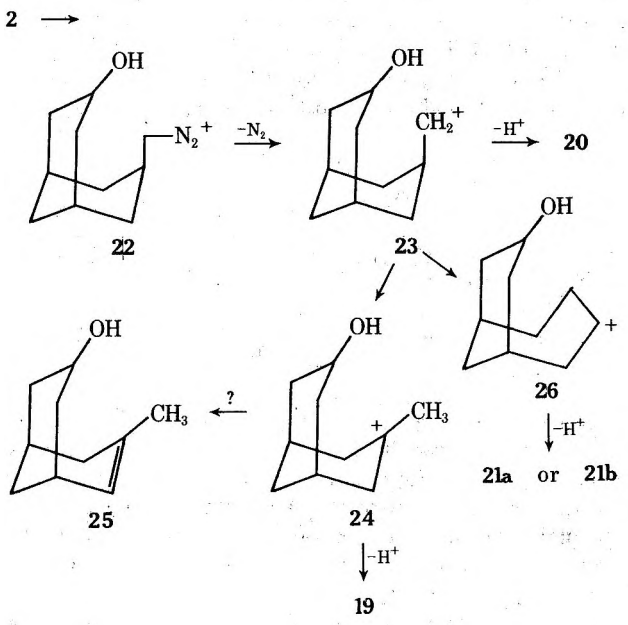
Our studies were carried out with a 95:5 mixture of **2**:**3** since alcohol of this composition (difficult to separate) was readily obtained by $NaBH_4$ reduction[7] of **1**. Upon diazotization with sodium nitrite and acetic acid in aqueous solution at 80–90°, **19** was formed in 36% yield and **20** in 26% yield. A third component (17%) has been tentatively assigned the *endo*-8-hydroxybicyclo[4.3.1]decene structure (most likely **21a**) from its spectral features. Another product (about 7%) appears to be a mixture on the basis of scrutiny by glpc and nmr. About four other components were present, each ~2–3% of the total. At least three of these minor products could arise from the small amount of **3** in the starting material. When **2** was deaminated with isoamyl nitrite in acetic acid at 80–85°, **19** was produced in 55% yield and **20** in 27% yield. Several minor, unidentified components (*ca.* 10% of the total) were also present along with less than 5% of **21**.

With benzene–isoamyl nitrite–acetic acid at reflux, **19** and **20** were again generated as the major products in yields of 23 and 60%, respectively, along with about 5% of **21** and minor components (about 8% of the total).

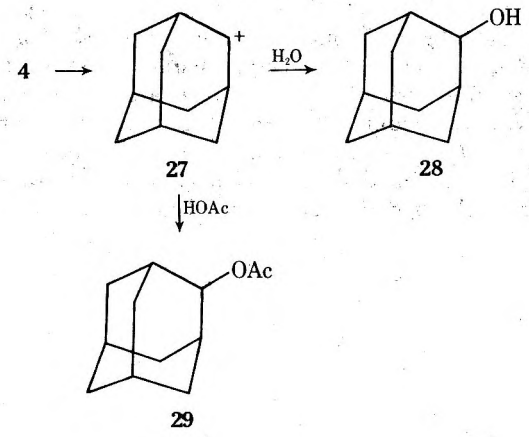
Since elimination leading to olefins is a common occurrence in deamination, it is noteworthy that this type of product was not observed as a major component. In an attempt to synthesize one of the possible hydroxyalkenes, 3-methylenebicyclo[3.3.1]nonan-*endo*-3-ol (**10b**), which might be formed during deamination, compound **12** was reduced with $LiAlH_4$ or $NaBH_4$. Only **19** was detected during glpc analysis of the product. Evidence (nmr) indicated that ring closure did not occur during reduction. Hence, conversion by acidic sites on the solid support may be responsible for some of the **19** isolated by glpc from the diazotization. When a base impregnated column was employed for glpc analysis, it was possible to separate and collect both **10a** and **10b** with very little **19** being formed. When the product mixture from the diazotization of **2** was examined with this column, substantial amounts of **19** were present, providing assurance that **19** is generated during diazotization. The conversion of **10b** to **19** during chromatography on silica gel has been reported,[9] as well as by acid catalysis.[21]

Formation of **19**, **20**, and **21** from **2** can be rationalized according to Scheme II.

Scheme II



Scheme III



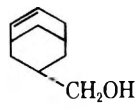
Attack of oxygen by the cation in **23** (see below) would yield **20**. Alternatively, **22** may serve directly as precursor to **20** *via* displacement of molecular nitrogen by the nucleophilic hydroxyl group. Rearrangement of **23** by a 1,2-hydride shift generates the more stable tertiary ion **24**. It is significant that a higher ratio of **20**:**19** is realized when nonpolar benzene serves as the medium. Presumably, the more polar acetic acid and water favor the conversion of **23** to **24**. Cation **23** may also rearrange by a second pathway (see above) to provide the ring-expanded, unsaturated alcohol **21** by way of elimination from **26**.

Transannular reactions in the bicyclo[3.3.1]nonane series are not uncommon. For example, both **5** and **12** produced 1-adamantanol on exposure to H_2/Pd.[8] Reductive cyclization was observed when **1** was hydrogenated in ethanol in the presence of Raney nickel.[7] Other examples are discussed elsewhere.[8,23]

endo-7-**Aminomethylbicyclo[3.3.1]non-2-ene.** Exposure of amino alcohol **2** to refluxing dilute sulfuric acid resulted in formation of **4** in moderate to good yields. The proposed structure for the aminoalkene is consistent with spectral and microanalytical data. Catalytic hydrogenation produced **6** which was identical with the compound obtained from Wolff–Kishner reduction[6] of **1**. Further characterization of **4** was effected through its benzoyl derivative. Dehydration of alcohols by dilute sulfuric acid is com-

monly employed.[24a] Indeed, too highly concentrated sulfuric acid favors hydration of olefins.[24b]

Amino olefin **4** was subjected to diazotization in the three systems. In all cases, the predominant product resulted from the intermediate 2-adamantyl cation **27**. Deamination of **4** with sodium nitrite and acetic acid in aqueous solution afforded a mixture of three products (Scheme III), the major component being 2-adamantanol (**28**). One of the minor products was 2-adamantyl acetate (**29**), prepared independently by acetylation of **28** with acetyl chloride. The second minor substance, not completely characterized, appears to be an unsaturated alcohol, per-



30

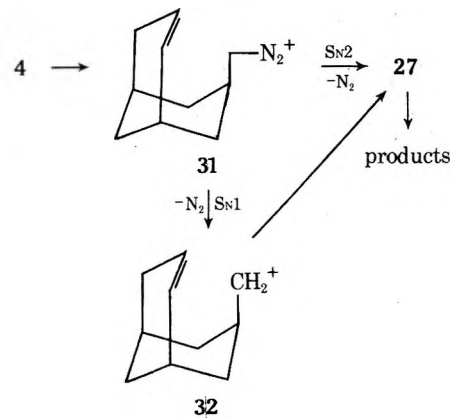
haps **30**[22,38] (or ring expanded product, see above) on the basis of ir and nmr data. Several contaminants were also present in trace amounts in the product mixture. Glpc analysis, in conjunction with authentic materials, pointed to the absence of 1-adamantanol and 4-protoadamantanols.

When diazotization of **4** was carried out in glacial acetic acid containing a small amount of acetic anhydride to ensure anhydrous conditions, the major product was 2-adamantyl acetate (**29**) (75%). Only one principal minor component (*ca.* 10%) was present. Although not identified, it most likely is the acetate of the alcohol which was tentatively assigned structure **30**.

Deamination of **4** was also carried out in benzene solution with isoamyl nitrite and acetic acid. Unlike previous runs in which reaction was immediate and rapid as indicated by nitrogen evolution at room temperature, there was no evidence of diazotization under these conditions. However, heating at reflux produced a mixture of products with **29** representing a major component. The other, unidentified products displayed relatively short retention times in glpc.

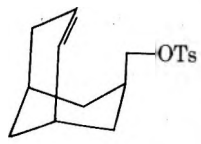
Formation of cation **27** from deamination of **4** might result from either of two paths (Scheme IV). The initially

Scheme IV



formed diazonium ion **31** might lose nitrogen *via* an SN1 type reaction to form the primary cation **32**. Ion **32** then attacks the π system generating the more stable ion **27**. However, it has been reported that diazonium ions do not undergo unimolecular fission to primary carbocations, but rather rearrange by a concerted process[25] (also see Schemes I and II). Alternatively, the π electrons in **31** could assist in the displacement of molecular nitrogen, *via* an SN2 mechanism, to yield **27** directly. The distinction between SN1 and SN2 routes in deamination reactions has been a topic of interest in recent years.[26]

Participation of π electrons in substitution reactions has literature precedent.[27] In a system closely related to our own, the tosylate of *endo*-7-hydroxymethylbicyclo[3.3.1]non-2-ene (**33**) provided mostly **28** in 80% acetone at

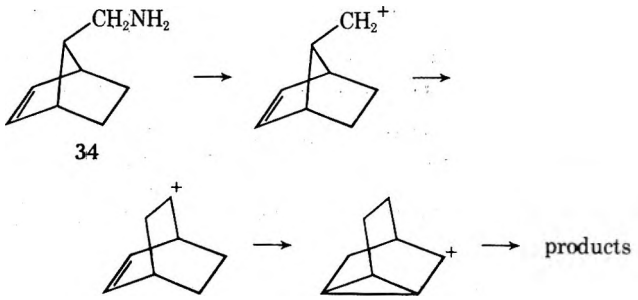


33

25°, along with about 5% of the internal return product, 2-adamantyl tosylate.[28] The rate ratio at 25° for **33** *vs.* its saturated counterpart was 2×20^4. In addition, **30** provided **28** with sulfuric acid.[22]

In deamination of a related compound **34**, involvement of the π electrons with the electrophilic site is not feasible at the initial stage[29] (Scheme V). With the isomeric amine,

Scheme V



the alkene function is unfavorably situated stereochemically for assisting in displacement.[29] Although the type of π participation illustrated in Scheme IV has been proposed in the case of certain diazonium ketones (enol forms), these hypotheses should be regarded as quite speculative.[8,30] Finally, diazotization of *endo*-3-aminobicyclo[3.3.1]nonane gave the 3-endo OH and bicyclonon-2-ene.[31]

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained with Beckman IR-8 and IR-20A and Perkin-Elmer 137 instruments, calibrated with the 1601- cm^{-1} band of polystyrene. Varian T-60 and HA-100 instruments were used to obtain nmr data which are reported in parts per million relative to tetramethylsilane as internal standard. Gas chromatography was carried out with a Varian Aerograph instrument (A-90-P, 1700, or 1800) with the following columns: (A) 15 ft × 0.25 in., 15% Carbowax 20M and 10% NaOH on Chromosorb P (30–60 mesh); (B) 10 ft × 0.25 in., 15% Ucon 50HB2000 and 5% NaOH on Chromosorb W (45–60 mesh); (C) 10 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W (45–60 mesh). Solutions were dried over Na_2SO_4. Microanalyses were performed by the Baron Consulting Co., Orange, Conn. Mass spectral data were obtained with a Hitachi Perkin-Elmer RMU-6E instrument.

The preparations of **2** and **3** have been described[7] previously. The sample of **2** used in diazotization was obtained from **1** and $NaBH_4$ in methanol, and contained 5–7% of **3** by glpc (column A at 225°).

Diazotization of 3. In Water. A mixture of **3** (1.7 g, 10 mmol), water (40 ml), sodium nitrite (0.85 g, 12 mmol), and acetic acid (0.8 ml, 13.5 mmol) was heated at 80–90° for 3 hr. After the cooled solution was extracted with methylene chloride, the organic layer was washed first with 5% sodium bicarbonate, next with water, and then dried. Glpc analysis (column C), with camphor as internal standard, indicated the presence of three major components: **7** (16%), **8** (50%), and **9** (12%). Pure samples were obtained by preparative glpc followed by sublimation.

8: mp 51.5–53.5° (see below); ir (CCl_4) 1695 cm^{-1} (C=O); nmr

(CCl_4) δ 0.84 (d, 2, CH_3, J = 4–5 Hz); mass spectrum m/e 152 (M^+).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.62; H, 10.31.

2,4-Dinitrophenylhydrazone, mp 178.5–180°, from 95% ethanol (see below).

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.07; H, 5.81; N, 17.02.

7: mp 46–49°; ir (CCl_4) 3350 (OH), 1670 (C—C), 1438, 1377 (CH_3), and 1050 cm^{-1} (C—O); nmr (CCl_4) δ 5.45 (m, 1, HC=C), 3.88 (m, 1, C*H*OH, J_{Ax} = 3–4 Hz, J_{Bx} = 13–14 Hz), 1.60 (s, 3, allylic CH_3); mass spectrum m/e 152 (M^+).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.76; H, 10.49.

9: mp 41.5–45.5°; ir (CCl_4) 3570, 3330 (OH), 1650 (C=C), 1040 (C—O), and 714 and 680 cm^{-1}; nmr (CCl_4) δ 5.55 (m, 2, alkene), 3.80 (m, 1, C*H*OH), 3.33 (s, 1, OH), 2.60 (m, 1); mass spectrum m/e 152 (M^+).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.63; H, 10.47.

In Acetic Acid. A solution of **3** (2 g, 12 mmol), acetic acid (30 ml), and isoamyl nitrite (2 ml, 15 mmol) was warmed at 60–65° for 3 hr. A greenish color and gas evolution were evident upon mixing. Water (30 ml) was added, and the cooled mixture was extracted with pentane and with benzene. The combined organic extract was washed successively with water, 5% sodium bicarbonate, and water, and then dried. Solvent removal yielded 2.5 g of a yellow oil. Glpc (column C) showed three principal products at least two of which were mixtures and not characterized further. The presence of an acetate was indicated by ir analysis. A positive test with 2,4-dinitrophenylhydrazine pointed to the presence of a ketone, most probably **8**.

***exo*-7-Methylbicyclo[3.3.1]nonan-3-one (8 from 7).** Compound **7** (122 mg) was stirred with 4 ml of 75% sulfuric acid for 6 hr at room temperature. The reaction mixture was diluted with water, and then extracted with pentane. Solvent removal afforded the crude product. Glpc analysis (column C) indicated that the conversion of **7** to **8** was essentially quantitative with no by-products. A pure sample was obtained by preparative glpc and subsequent sublimation, mp 54.5–56.5° [lit.[9] mp 57–58°]. The nmr and infrared spectra were identical with those of the ketone isolated from diazotization of **3**; 2,4-dinitrophenylhydrazone, mp 183.5–184.5°, mixture melting point with same derivative of **8** from diazotization of **3**, 182–186°.

***endo*-7-Methylbicyclo[3.3.1]nonan-3-one (11 from 12). (1).** Compound **12** (1.33 g) was shaken with 326 mg of PtO_2 in 120 ml of ethyl acetate under 40 psi of hydrogen for 48 hr. The catalyst was removed by filtration, and the solvent was evaporated under reduced pressure to give crude **11** as a yellow solid in greater than 95% yield. Glpc analysis (column C) showed the presence of one very minor impurity as well as the absence of **5**. Preparative glpc and sublimation provided pure **11**, mp 40–42° [lit.[11] mp 42.5–43.5°]; ir (CCl_4) 1706 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.81 (d, 3, CH_3, J = 6 Hz); mass spectrum m/e (rel intensity) 152 (35), 109 (65), 95 (100); 2,4-dinitrophenylhydrazone, mp 170.5–172°, from 95% ethanol.

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.89; H, 5.95; N, 16.86.

(2). Compound **12** (2.0 g, 13.3 mmol) was reduced with (0.25 g, 6.6 mmol) $LiAlH_4$ in refluxing ether. The crude alcohol mixture was acetylated with acetic anhydride (5 ml)–sodium acetate (3 g)–water (25 ml) by warming on a steam cone for 45 min. Methylene chloride extraction provided 3.3 g of a light yellow liquid. Glpc analysis indicated only partial acetylation. An alternate process was carried out by stirring the crude product with acetyl chloride (7.5 ml)–triethylamine (30–35 ml)–benzene (75 ml) for 1.5 hr at room temperature. Samples of the endo and exo acetates were isolated by glpc. The infrared spectra (CCl_4) confirmed the presence of ester and exocyclic methylene functionalities.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: (exo) C, 73.96; H, 9.61; (endo) C, 73.99; H, 9.15.

The crude mixture of acetates was hydrogenated at low pressure over 1 g of Pd/C catalyst in 50 ml of methanol. After the catalyst was removed by filtration, the saturated esters in the methanol solution were saponified by heating for 2–3 hr with 40 ml of 5% NaOH. The methanol was evaporated, and the basic solution was extracted with CH_2Cl_2. Drying and solvent removal provided the crude saturated alcohols.

The crude alcohol mixture was oxidized[32] as follows. An oxidizing solution of chromium trioxide (4 g), water (5 ml), acetic acid (12 ml), and concentrated sulfuric acid (3.6 ml) was added dropwise to a solution of the crude alcohols (*ca.* 200 mg) in 10 ml of CH_2Cl_2 and 5 ml of acetic acid until the orange color of the oxidant persisted at room temperature. After 15 ml of water was added, the layers were separated. The aqueous layer was extracted with CH_2Cl_2; the combined CH_2Cl_2 solution was washed with water and then dried. Solvent removal left a yellow oil. Preparative glpc (column C) provided a sample of **11** which proved identical (ir, nmr) with that obtained from the direct catalytic reduction of **12**.

1,3-Dibromoadamantane. A literature procedure[33] was followed with 1-bromoadamantane (100 g), bromine (200 ml), boron tribromide (25 g), and aluminum bromide (0.5 g). The progress of the reaction was monitored by periodic analysis of small aliquots by glpc. Work-up provided 125 g (90%) of the desired product, mp 108–111°, from Skelly B [lit.[34] mp 106–108° (sealed tube)].

12 from 1,3-Dibromoadamantane. A literature method[35] was used with 125 g of 1,3-dibromoadamantane (diglyme as solvent). Work-up led to 41 g (65%) of **12**, mp 159–164° [lit.[35] mp 160–164°]. The product contained traces of diglyme which did not interfere with subsequent reactions.

Attempted Preparation of 11 from 5. A 70-mg sample of **5** was shaken with 108 mg of PtO_2 in 21 ml of ethyl acetate under 40 psi of H_2 for 48 hr. Catalyst and solvent removal left a green colored oil. Glpc analysis (column C) in conjunction with the infrared spectrum indicated the oil to be mainly unreacted **5**.

Diazotization of 2. In Water. A mixture of **2** (2 g, 12 mmol), acetic acid (0.8 ml, 13.5 mmol), water (40 ml), and sodium nitrite (0.85 g, 12 mmol) was heated at 80–90° for 2 hr. The cooled solution was extracted with methylene chloride, and the extract was washed with 10% sodium carbonate and water, and then dried. Solvent removal afforded a yellow oil, 1.8 g. Glpc analysis (column C), 1-adamantanol as internal standard, showed the presence of **19** (36%) and **20** (26%). A minor component (7%) proved to be a mixture upon closer examination. A second component (17%) was tentatively identified as **21**: nmr ($CDCl_3$) δ 5.78 (m, 2, alkene), 3.80 (m, 1, C*H*OH), 2.75 (s, 1, OH, exchangeable with D_2O), 2.4–1.3 (rest of H); ir (CCl_4) 3450, 2995, 1647, 1047, and 707 cm^{-1}; mass spectrum, m/e 152 (M^+).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.54; H, 10.27.

Identification of **19** and **20** was accomplished by spectral comparison (ir and nmr) with authentic[36] samples. Several minor contaminants (each 2–3% of the total) were also present.

In Acetic Acid. A solution of **2** (2 g, 12 mmol) and isoamyl nitrite (2 ml, 15 mmol) in acetic acid (30 ml) was kept at 85° for 3 hr. Water (30 ml) was then added, and the cooled solution was extracted with pentane and with benzene. The combined extract was washed with 5% sodium bicarbonate and water, and then dried. Solvent removal afforded 4.2 g of light yellow oil. The product mixture contained appreciable quantities of isoamyl alcohol, isoamyl acetate, and isoamyl nitrite. Glpc analysis (column C), 1-adamantanol as standard, revealed the presence of **19** (55%) and **20** (27%) in addition to four–five minor components (*ca.* 10% of total).

In Benzene. A mixture of **2** (2 g, 12 mmol), acetic acid (0.8 ml, 13.5 mmol), and isoamyl nitrite (2 ml, 15 mmol) in 40 ml of benzene was heated at reflux for 3 hr. The cooled benzene solution was washed with 5% sodium bicarbonate and water, and then dried. Solvent removal afforded 4.4 g of light yellow oil. Isoamyl alcohol, isoamyl acetate, and isoamyl nitrite were present in appreciable quantity. Glpc analysis (column C, 1-adamantanol as internal standard) showed the presence of **19** (23–24%), **20** (60%), and **21** (4–5%) and four–five minor components (*ca.* 10% of total).

Reduction of 12 with $NaBH_4$. A mixture of compound **12** (2.5 g, 16.7 mmol), $NaBH_4$ (0.64 g, 17 mmol), and absolute ethanol (40 ml) was stirred at room temperature for 12 hr. Saline (20%, 5 ml) was added, and the reaction mixture was stirred a few minutes more. The volatile solvents were removed under reduced pressure, and the residue was extracted with CH_2Cl_2. Evaporation of the dried solution gave a crude product, 2.5 g. Glpc analysis (column C, 190°) indicated the presence of **19** and unreacted **12**, identified by their ir and nmr spectra. Glpc analysis (column A) provided **10a** and **10b** which were further purified by sublimation: **10a**, mp 89–90° [lit.[9] mp 93–94°]; **10b**, mp 79–81° [lit.[21] mp 88°]. The infrared and nmr spectral characteristics of the isomeric alcohols were in accord with prior observations.[14]

Compound **12** (0.5 g) was reduced by refluxing with 0.63 g of $LiAlH_4$ in 30 ml of ether for several hours. The reaction mixture was quenched with D_2O and then worked up as described above. The white solid which remained was examined by nmr. None of **19** was contained in the crude product mixture as evidenced by the

lack of the characteristic singlet for the methyl group in **19**. A sample of crude **10b** was subjected to gas chromatography (column C). The nmr spectrum of **19** obtained in this way indicated no incorporation of deuterium into the methyl group during rearrangement on the column, indicating that acidic sites on the solid support are responsible for the conversion of **10b** to **19** during glpc.

***endo*-7-Aminomethylbicyclo[3.3.1]non-2-ene (4 from 2 and 3).** A 75:25 mixture[7] of **2** and **3** (503 mg, 2.9 mmol) was refluxed for 24 hr in 40 ml of 0.1 *M* sulfuric acid. After the solution was made strongly alkaline with 20% sodium hydroxide, the resulting oil was taken up in ether. Solvent removal from the dried solution gave 350 mg, 80% of a light yellow oil which was 95% pure by glpc (column B). An analytical sample of **4** was obtained by preparative glpc: ir (neat) 3345, 3260 (NH_2), 2990 (vinyl CH), 1640 (C=C), and 1600 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 5.68 (m, 2, CH=CH), 2.62 (d, 2, CH_2NH_2), and 1.67 (m, 13, CH, CH_2, and NH_2 exchangeable with D_2O).

Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.62; H, 11.10; N, 9.01.

Benzamide, mp 135–136°, from cyclohexane: ir (KBr) 3220 (NH), 3050 (aromatic CH), 2990 (vinyl CH), 1635, 1550 (CONH); nmr ($CDCl_3$) δ 7.56 (m, 5, aromatic), 6.77 (m, 1, NH), 5.72 (m, 2, vinyl H), 3.40 (m, 2, CH_2NHCO), and 1.70 (m, 11, CH and CH_2).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.48. Found: C, 79.77; H, 8.26; N, 5.25.

When the above procedure was carried out with 12 g of the mixture of **2** and **3**, 500 ml of 0.1 *M* sulfuric acid, and methylene chloride as extracting solvent, **4** was isolated in 55% yield, bp 64–65° (0.24 mm), bp 42–43° (0.05 mm). Essentially all of the unreacted starting material was recovered by the extraction procedure, and then was separated from **4** by distillation.

6 from 4. A 20-mg sample of **4** in 15 ml of methanol was hydrogenated under 45 psi of hydrogen with 10% palladium on charcoal at room temperature for 2 hr. The catalyst was removed by filtration, and the solvent was evaporated to afford an essentially quantitative yield of **6**. The exact yield could not be determined because of rapid absorption of atomspheric carbon dioxide. Spectral analysis showed the absence of **4**; benzamide, mp 93–95° [lit.[6] mp 93.5–94.5°].

Diazotization of 4. In Water. A solution of sodium nitrite (593 mg, 8.6 mmol) in 2 ml of water was slowly added to a solution of **4** (651 mg, 4.3 mmol) in 10 ml of water containing acetic acid (0.6 ml, 10 mmol). The mixture was then stirred at room temperature for 20 min followed by heating on a steam bath for 30 min. The solid which had separated was taken up in ether. The ether solution was washed with 5% sodium bicarbonate and water, and then dried. Solvent removal gave 632 mg of a yellow solid. Glpc (column C) showed the solid to be 2-adamantanol **28** (90% pure, 87% yield) with minor amounts of 2-adamantyl acetate (**29**) (~5%) and an unsaturated alcohol, perhaps **30** (~5%). Products **28**[37] and **29** were identified by comparison of their infrared spectra to those of authentic samples.

In Acetic Acid. To a solution of 757 mg (5 mmol) of **4** in 10 ml of glacial acetic acid and 2 ml of acetic anhydride was added 690 mg (10 mmol) of sodium nitrite in small portions. The mixture was then stirred at room temperature for 30 min, followed by heating on a steam bath for 30 min. The mixture was diluted with 150 ml of water, and extracted with ether. The ether solution was washed with 5% sodium hydroxide and water, and then dried. Solvent removal afforded 803 mg of a light yellow oil. Glpc analysis (column C) showed the oil to be principally 2-adamantyl acetate **29** (75% yield), along with one unidentified contaminant.

In Benzene. A solution of **4** (765 mg, 5.1 mmol), isoamyl nitrite (610 mg, 5.2 mmol), and acetic acid (0.3 ml, 5.2 mmol) in 20 ml of benzene was refluxed for 1 hr. The solution was then treated with anhydrous potassium carbonate, filtered, and then evaporated to yield 870 mg of a yellow oil. Glpc analysis (column C) showed the oil to be composed of 2-adamantyl acetate **29** (44% yield) and a mixture of low boiling components.

29 from 28. A small sample of **28** and a large excess of acetyl chloride in benzene were warmed on a steam bath for 1 hr. The solution was then washed with water, 5% sodium hydroxide, and again with water. Solvent removal from the dried solution yielded **29**, ~98% pure by glpc. A pure sample of **29** was obtained by preparative glpc: ir (CCl_4) 1710 (C=O), 1235 ($OCOCH_3$), 1040 and 1025 cm^{-1}; nmr (CCl_4) δ 4.84 (br, 1, CHOCO) and 2.2–1.2 (m, 17, CH, CH_2, and $OCOCH_3$).

Acknowledgment. For support of this work, we are grateful to the National Science Foundation for a research grant, and to the Undergraduate–Graduate Research Collaboration Program sponsored by the National Science Foundation. We are indebted to Dr. Irwin Klundt, Aldrich Chemical Co., for assistance in the preparation of 7-methylenebicyclo[3.3.1]nonan-3-one. We also thank Dr. J.-H. Liu for preliminary work on the diazotization of **3**, and Mr. Paul Karges and Dr. Michael Kurz for aid in obtaining the mass spectral data.

Registry No.—**2**, 50361-66-5; **3**, 50361-68-7; **4**, 53516-37-3; **4** benzamide, 53516-38-4; **7**, 52927-60-3; **8**, 37741-56-3; **8** dinitrophenylhydrazone, 53516-39-5; **9b**, 53516-40-8; **10a** acetate, 53516-41-9; **10b** acetate, 53516-42-0; **11**, 40727-31-9; **11** dinitrophenylhydrazone, 53516-43-1; **12**, 17933-29-8; **21a**, 53516-44-2; **28**, 700-57-2; **29**, 19066-22-9.

References and Notes

(1) Paper XII of the series Adamantanes and Related Compounds.
(2) University of Wisconsin—Milwaukee.
(3) University of Wisconsin—La Crosse.
(4) Postdoctoral Associate, 1970–1971.
(5) P. Kovacic, J.-H. Liu, P. D. Roskos, and E. M. Levi, *J. Amer. Chem. Soc.*, **93**, 5801 (1971).
(6) J.-H. Liu, G. A. Gauger, and P. Kovacic, *J. Org. Chem.*, **38**, 543 (1973).
(7) J. A. Tonnis, T. A. Wnuk, M. J. Dolan, and P. Kovacic, *J. Org. Chem.*, **39**, 766 (1974).
(8) J.-H. Liu and P. Kovacic, *J. Org. Chem.*, **38**, 3462 (1973).
(9) L. Stéhelin, L. Kanellias, and G. Ourisson, *J. Org. Chem.*, **38**, 851 (1973).
(10) M. A. Eakin, J. Martin, W. Parker, C. Egan, and S. H. Graham, *Chem. Commun.*, 337 (1968).
(11) K. Kimoto, T. Imagawa, and M. Kawanisi, *Bull. Chem. Soc. Jap.*, **45**, 3698 (1972).
(12) R. M. Black and G. B. Gill, *Chem. Commun.*, 972 (1970); W. H. W. Lunn, *J. Chem. Soc. C*, 2124 (1970). The absence of a triplet at δ 0.9 in the nmr spectrum of **8** indicates that the ring containing the methyl group is not in the boat form. For a discussion of the conformational nature of the bicyclo[3.3.1]nonane ring system, see S. J. Padegimas and P. Kovacic, *J. Org. Chem.*, **37**, 2672 (1972), and references cited therein.
(13) W. A. Ayer and K. Piers, *Chem. Commun.*, 541 (1965).
(14) W. Parker, private communication, 1970.
(15) F. N. Stepanov, E. N. Martynova, L. A. Zosim, A. G. Yurchenko, and A. P. Krasnoshchek, *J. Org. Chem. USSR*, **7**, 2615 (1971); the melting point indicates the endo isomer, rather than the exo assignment of the authors. Isomerization may be occurring in the subsequent hydrogenation with Raney nickel.
(16) H. Stetter and P. Tacke, *Chem. Ber.*, **96**, 694 (1963).
(17) M. Freifelder, "Practical Catalytic Hydrogenation," Wiley, New York, N.Y., 1971, p 128.
(18) H. Kato, *J. Synthetic Org. Chem. Jap.*, **28**, 682 (1970).
(19) S. H. Graham and D. A. Jones, *J. Chem. Soc. C*, 188 (1969).
(20) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N.Y., 1968, pp 291, 800.
(21) H. Stetter, J. Gärtner, and P. Tacke, *Chem. Ber.*, **99**, 1435 (1966).
(22) A. C. Udding, H. Wynberg, and J. Strating, *Tetrahedron Lett.*, 5719 (1968).
(23) G. L. Buchanan, "Topics in Carbocyclic Chemistry," Vol. 1, D. Lloyd, Ed., Plenum Press, New York, N.Y., 1969, Chapter 3.
(24) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," Wiley, New York, N.Y., 1953, (a) p 32; (b) p 174.
(25) L. Friedman, "Carbonium Ions," Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1970, p 664.
(26) For references to reviews on aliphatic deamination, see ref 8.
(27) R. G. Lawton, *J. Amer. Chem. Soc.*, **83**, 2399 (1961); P. D. Bartlett and S. Bank, *ibid.*, **83**, 2591 (1961); S. Winstein and P. Carter, *ibid.*, **83**, 4485 (1961).
(28) D. J. Raber, G. J. Kane, and P. v. R. Schleyer, *Tetrahedron Lett.*, 4117 (1970).
(29) J. A. Berson and J. J. Gajewski, *J. Amer. Chem. Soc.*, **86**, 5020 (1964).
(30) M. Miyano and C. R. Dorn, *J. Org. Chem.*, **37**, 268 (1972).
(31) R. A. Appleton, C. Egan, J. M. Evans, S. H. Graham, and J. R. Dixon, *J. Chem. Soc. C*, 1110 (1968).
(32) L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Vol. 1, Wiley, New York, N.Y., 1968, p 145, procedure (d).
(33) G. L. Baughman, *J. Org. Chem.*, **29**, 238 (1964).
(34) T. M. Gorrie and P. v. R. Schleyer, *Org. Prep. Proced.*, **3**, 159 (1971).
(35) A. R. Gagneux and R. Meier, *Tetrahedron Lett.*, 1365 (1969).
(36) J.-H. Liu, Ph.D. Thesis, University of Wisconsin—Milwaukee, 1973.
(37) C. J. Pouchert, The Aldrich Library of Infrared Spectra, Aldrich Chemical Co., Milwaukee, Wis., 86G.
(38) Note added in Proof. Comparison with nmr spectra of authentic material indicates that the compound is not **30**. We are grateful to Professor P. v. R. Schleyer and Professor H. Wynberg for supplying the spectra.

Conformational Analysis of 1,3-Dioxacyclohept-5-enes. Proton and Carbon-13 Magnetic Resonance. Evidence for a Twist–Boat Conformation

Michael H. Gianni* and Michael Adams

Chemistry Department, St. Michael's College, Winooski Park, Vermont 05404

Henry G. Kuivila and Karl Wursthorn

Chemistry Department, New York State University at Albany, Albany, New York 12222

Received August 9, 1974

Twist–boat conformations have been assigned to *cis*- and *trans*-4,7-dimethyl-1,3-dioxacyclohept-5-ene and to *r*-2-*tert*-butyl-*cis*-4,*trans*-7-dimethyl-1,3-dioxacyclohept-5-ene on the basis of carbon-13 substituent effects. These assignments are consistent with pmr spectra. The data also suggest that 2,2-dimethyl-1,3-dioxacyclohept-5-ene is in a twist–boat conformation but *r*-2-*tert*-butyl-*cis*-4,*cis*-7-dimethyl-1,3-dioxacyclohept-5-ene is in a chair conformation.

Conformational analysis of the 1,3-dioxacycloalkanes has received considerable recent attention.[1-4] The 1,3-dioxacyclopentanes[2] and 1,3-dioxacycloheptanes have numerous low-energy conformations available to each of an equilibrating pair of diastereoisomers. In contrast 1,3-dioxacyclohexane has only one favorable low-energy chair conformation for each isomer of a cis–trans pair.[1]

An analogous situation is found for simple cycloalkanes. Five-[5] and seven-membered[6] cycloalkanes pseudorotate among several low-energy conformations whereas cyclohexane has only one low energy conformation.

Nmr studies indicate that 1,2-benzocycloheptene, 5,5-dimethyl-1,2-benzocycloheptene, cycloheptene, and 5,5-difluorocycloheptene exist in chair conformations. Low-temperature nmr studies on 1,3-dioxacyclohept-5-ene, 2,2-dimethyl-1,3-dioxacyclohept-5-ene, and 1,3-dioxa-5,6-benzocycloheptene failed to define a specific conformation for these compounds but did reveal that 2,2-dimethyl-1,3-dioxa-5,6-benzocycloheptene exists in a twist–boat conformation.[7c] It has been shown that 3,5-dioxabicyclo[5.1.0]-octane exists in a twist–boat conformation.[9a] In contrast cycloheptene oxide exists in an equilibrium of two chair conformations.[9b] Encouraged by the discovery of these twist–boat conformations and by data on the carbon-13 hydrogen coupling constants of C2 in some 1,3-dioxacycloalkanes[7d] a search was initiated for twist–boat conformations among the 1,3-dioxacyclohept-5-enes. We now report the results of that search and also a correlation of carbon-13 substituent effects.

Configurational Assignments. The cis and trans isomers of 4,7-dimethyl-1,3-dioxacyclohept-5-ene were separated by gas chromatography. Configurational assignments were made on the basis of proton magnetic resonance spectral data. Examination of models indicates that the C2 protons for the cis isomer are diastereotopic in all conformations. The cis configuration was therefore assigned to that isomer whose C2 protons gave an AB nmr spectrum with chemical shifts of 302 and 283 Hz. These values compare favorably with those reported for the C2 protons of *cis*-4,7-dimethyl-1,3-dioxacycloheptane, 290 and 272 Hz.[3]

The trans configuration was assigned to the remaining isomer which had a single C2 proton signal at 287 Hz. This value compares favorably with a reported value of 282 Hz for the C2 protons in *trans*-4,7-dimethyl-1,3-dioxacycloheptane.[3,10]

Configurational assignments for *r*-2-*tert*-butyl-*cis*-4,*cis*-7-dimethyl-1,3-dioxacyclohept-5-ene and *r*-2-*tert*-butyl-*cis*-4,*trans*-7-dimethyl-1,3-dioxacyclohept-5-ene were made on the basis of the meso–*d*,*l* isomer ratio found for the 3-hexene-2,5-diol[10] starting material. The 4,7-dimethyl-1,3-dioxacyclohept-5-enes prepared from the 3-hexene-2,5-diol gave products with a cis–trans ratio of 4:1 as indicated by the areas for the C2 protons in the nmr spectrum. It follows that the meso–*d*,*l* ratio is 4:1. The cis,-cis–cis,trans isomer ratio for the *r*-2-*tert*-butyl-4,7-dimethyl-1,3-dioxacyclohept-5-enes prepared from the same 3-hexene-2,5-diol paralleled the 4:1 distribution.

The pmr spectra are consistent with these assignments. The C2 proton for the *r*-2-*tert*-butyl-*cis*-4,*cis*-7-dimethyl isomer absorbs at higher field, 248 Hz, than the C2 proton for the *cis*-4,*trans*-7 isomer, 261 Hz. This parallels the data for *cis*- and *trans*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane which gave signals for the C2 protons at 246 and 250 Hz, respectively. It is also accordant with C2 proton signals for cis,cis and cis,trans isomers of *r*-2-*tert*-butyl-4,7-dimethyl-1,3-dioxacycloheptane.[4]

Carbon-13 Chemical Shifts. All the carbon-13 spectra were recorded at ambient temperatures at which the rates of interconversions of the conformations were fast. Therefore the chemical shifts are average values to which each of the conformations contributes according to its population.

The carbon-13 chemical shifts for a series of 1,3-dioxacyclohept-5-enes are summarized in Table I. The assignments of the carbon resonances were made on the basis of relative intensities and comparison with chemical shifts for 1,3-dioxacycloheptanes.

Assignments were made in a straightforward way. The *tert*-butyl methyl signals were readily distinguished from the methyl groups substituted directly on the ring by signal intensity. That for the quaternary carbon of the *tert*-butyl group was distinguished by reduced intensity and the chemical shifts for C5 and C6 were readily assigned because of the magnitude of the downfield shift expected for vinyl carbons. The signals assigned to C2, C4, and C7 correspond to chemical shifts in 1,3-dioxacycloheptanes and to the chemical shifts for C2, C4, and C6 in 1,3-dioxacyclohexanes.

Some important observations can be made from the data in Table I. The difference in geometry between the 1,3-dioxacycloheptanes and the 1,3-dioxacyclohept-5-enes has little effect on the saturated carbon-13 chemical shifts. The signals for C2 are within 4 ppm of the corresponding signals for the dioxacyclohexanes and dioxacycloheptanes. The C4 and C7 methyl signals fall within a very narrow range and suggest that these methyl groups experience very similar surroundings. It was this observation which first indicated that *cis*- and *trans*-4,7-dimethyl-1,3-dioxacyclohept-5-ene exist in twist–boat conformations.

The signals for the methyl carbons of the *tert*-butyl groups fall within a narrow range and are not affected by

Table I
Chemical Shifts for Some 1,3-Dioxacyclohept-5-enes[a]

Entry	Compd	Registry no.	C2	C4,7	C5,6	Me	*t*-BuMe-	C_q[b]
			Carbon-13 Chemical Shifts					
1	1,3-Dioxacyclohept-5-ene	5417-32-3	96.38	66.95	130.58			
2	2-*tert*-Butyl-	53586-63-3	110.81	68.10	128.99		24.96	36.21
3	2,2-Dimethyl	1003-83-4	101.73	61.23	129.74	24.02		
4	*cis*-4,7-Dimethyl-	53643-36-0	93.26	74.16	134.39	21.29		
5	*trans*-4,7-Dimethyl-	53586-64-4	93.77	71.23	134.71	21.58		
6	*r*-2-*tert*-Butyl-*cis*-4,*cis*-7-dimethyl-	53586-65-5	109.88	74.60	134.06	22.21	24.92	36.44
7	*r*-2-*tert*-Butyl-*cis*-4,*trans*-7-dimethyl-	53626-27-0	109.88	74.60	134.06	22.15	25.02	36.96
			Proton Chemical Shifts[c]					
1			286	251	340			
2			248	261,254	340		53	
3				248	336	80		
4			302,283	268	331	77		
5			287	267	328	74		
6			248	257	329	75	54	
7			261	257	323	68	54	

[a] All chemical shifts are in ppm downfield from internal TMS. [b] The quaternary carbon of the *tert*-butyl group. [c] All chemical shifts are in Hz downfield from internal TMS.

Table II
Carbon-13 Chemical Shift Substituent Effects for Some 1,3-Dioxacyclohept-5-enes[a,b]

Entry	Compd	C2	C4,7	C5,6
1	2-*tert*-Butyl-	−14.43 (−15.27)	−1.15 (−1.46)	+1.59 (+0.34)
2	2,2-Dimethyl-	−5.35	+5.72	+0.84
3	*cis*-4,7-Dimethyl-	+3.12 (0.60)	−7.21 (−8.65)	−3.81 (−3.71)
4	*trans*-4,7-Dimethyl-	+2.61 (+2.72)	−4.28 (−5.15)	−4.13 (−6.46)
5	*r*-2-*tert*-Butyl-*cis*-4,*cis*-7-dimethyl[c]	−13.50 (−14.21) [0.93]	−7.65 (−7.88) [−6.50]	−3.48 (−3.74) [−5.07]
6	*r*-2-*tert*-Butyl-*cis*-4,*trans*-7-dimethyl-[c]	−13.50 (−10.93) [0.93]	−7.65 (−3.30, −10.66) [−6.50]	−3.48 (−6.59) [−5.07]

[a] All values are in ppm calculated from 1,3-dioxacyclohept-5-ene. A negative value indicates a signal downfield from the reference compound. [b] Values in parentheses are for corresponding 1,3-dioxacycloheptanes taken from ref 4. [c] Values in brackets are referenced to 2-*tert*-butyl-1,3-dioxacyclohept-5-ene.

Table III
Carbon-13 Chemical Shift Substituent Effects Produced by Substitution on 1,3-Dioxacyclohept-5-ene and 2-*tert*-Butyl-1,3-dioxacyclohept-5-ene[a]

Entry	Compd	α	β	γ	δ
1	2-*tert*-Butyl	−14.43 (−15.27)[b]		−1.15 (−1.46)	+1.59 (+0.34)
2	2,2-Dimethyl-	−5.35		+5.72	+0.84
3	*cis*-4,7-Dimethyl-	−7.21 (−8.65)	−3.81 (−4.47)	+3.12 (+3.17, −0.57)	
4	*trans*-4,7-Dimethyl-	−4.28 (−5.15)	−4.13 (−7.22)	+2.16 (+0.42, 1.55)	
5	*r*-2-*tert*-Butyl-*cis*-4,*cis*-7-dimethyl-[a]	−6.50 (−6.42)	−5.07 (−4.08)	+0.93 (+1.06)	
6	*r*-2-*tert*-Butyl-*cis*-4,*trans*-7-dimethyl-[a]	−6.50 (−1.84, −9.20)	−5.07 (−6.93)	+0.93 (+4.34)	

[a] Values compared to 2-*tert*-butyl-1,3-dioxacyclohept-5-ene. [b] Values in parentheses are from the corresponding 1,3-dioxacycloheptanes, ref 4.

substitution on the ring. There is no indication of an axial *tert*-butyl group.[4] Substituents at C4 and C7 do affect the signals at C5 and C6 but a substituent at C2 does not.

Carbon-13 Substituent Effects. Table II lists the carbon-13 chemical shift substituent effects produced on each carbon of unsubstituted 1,3-dioxacyclohept-5-ene by introduction of alkyl groups at several positions. Table III summarizes these same effects but lists them as to origin, *i.e.*, α, β, γ, and δ. This table also lists sbstituent effects produced by substitution on 2-*tert*-butyl-1,3-dioxacyclohept-5-ene. The values in parentheses are for corresponding 1,3-dioxacycloheptanes.

The α and β effects are generally consistent with those for cyclohexane, 1,3-dioxacyclohexane, and 1,3-dioxacycloheptane. A *tert*-butyl substituent at C2 gives α values of −14.43 and −13.50 ppm. These values compare with −11.06 and −15.25 ppm for 1,3-dioxacyclohexane and 1,3-dioxacycloheptane, respectively. A *gem*-dimethyl substitution at C2 gives an α shift of −5.35 ppm which compares with −3.21 ppm for 2,2-dimethyl-2,3-dioxacyclohexane.

The relation of the γ effect to conformation is probably the best understood of the chemical shift substituent parameters.[1,5,11] It reflects a paramagnetic shift due to a 1,3-diaxial steric compression. The δ effect reflects the same kind of compression for a 4,7-diaxial interaction.

The γ effect for the 2,2-dimethyl derivative (+5.72 ppm) is smaller than that for 2,2-dimethyl-1,3-dioxacyclohexane (7.51 ppm).[1,12] This was unexpected because models indicate that the distance between the 1,3-diaxial methyl and hydrogen atoms is smaller for 2,2-dimethyl-1,3-dioxacyclohept-5-ene than for the dioxacyclohexane homolog. Thus for a chair conformation a bigger γ shift for the 1,3-dioxacyclohept-5-ene was expected. In a twist–boat conformation the distance between the axial C2 methyl group and the axial C4 hydrogen is considerably larger than it is for the chair conformation. The small γ shift is consistent with a twist–boat conformation but an unequivocal assignment cannot be made.

The 3.12 ppm γ shift at C2 for *cis*-4,7-dimethyl-1,3-dioxacyclohept-5-ene, **1**, is consistent with a twist–boat conformation. A chair conformation would require a very small or no γ shift. For example the γ shift at C2 for *cis*-4,6-dimethyl-1,3-dioxacyclohexane is +0.7 ppm. In contrast the γ shift at C2 for the trans isomer is +7.6 ppm.[12a]

The twist–boat conformation has a 1,3-methyl–hydrogen interaction but models indicate that the distance between the C4 methyl group and the C2 hydrogen is greater than in the corresponding chair conformation. This accounts for the small γ shift compared to +7.6 ppm for *trans*-4,6-dimethyl-1,3-dioxacyclohexane. Therefore the evidence indicates that the twist–boat conformation is more favorable than the chair conformation for which both methyl groups are equatorial.[12b] The angle strain imposed by the C5,6 double bond and the generalized anomeric effect may well account for this rather surprising conclusion. A twist–boat should relieve the angle strain and the dipolar repulsions due to the generalized anomeric effect.

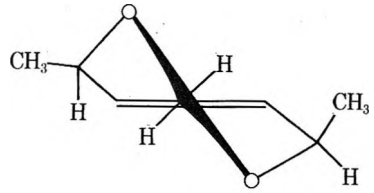
A boat conformation is not a reasonable alternative since it does not account for the γ shift at C2. The situation here is analogous to that for cycloheptene,[13] in which the boat conformation is estimated to be least stable by 3.37 kcal/mol. It is reasonable to expect the boat conformation for 1,3-dioxacyclohept-5-ene to be of even higher energy, when compared to its chair conformation, than boat cycloheptene, compared to its chair, because of the shorter COC bonds. This shorter distance makes the interaction between the prow of the boat and the double bond even more severe than in cycloheptene.[15] Therefore it is reasonable to exclude the boat conformation from consideration.

A twist–boat conformation has also been assigned to the trans isomer, **2**. This assignment is consistent with the 2.61 ppm γ shift at C2. This value is considerably smaller than the +7.6 ppm found for *trans*-4,6-dimethyl-1,3-dioxacyclohexane.

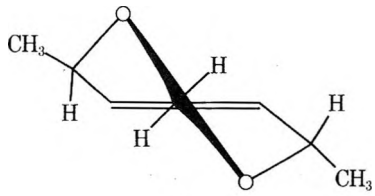
A rapid equilibrium between two chair conformations would account for the A_2 spectrum of the C2 protons. However, the chair conformation has a 1,3-diaxial methyl–hydrogen interaction across COC bonds and a 4,7-methyl–hydrogen interaction. It is known that the sum of the energies of these interactions is sufficiently high that such conformations must be excluded from the conformational array of 4,7-dimethyl-1,3-dioxacycloheptanes. These interactions are at least as severe as those found in the 1,3-dioxacyclohexanes which are estimated at 2.9 kcal/mol.[14] Therefore it is reasonable to exclude the chair conformation from consideration.

The γ shift (+0.93 ppm) for *r*-2-*tert*-butyl-*cis*-4,*cis*-7-dimethyl-1,3-dioxacyclohept-5-ene is consistent with a chair conformation. This value is in accord with +0.7 ppm for *cis*-4,6-dimethyl-1,3-dioxacyclohexane and −0.1 ppm for *r*-2-*cis*-4,*cis*-6-trimethyl-1,3-dioxacyclohexane. Examination of models indicates that the twist–boat conformation has a severe 1,3-*tert*-butyl–methyl interaction. This interaction should manifest a γ shift at both the methyl carbon and the *tert*-butyl group.[4] This is not in accordance with the carbon-13 data.

A twist–boat conformation is assigned to *r*-2-*tert*-butyl-*cis*-4,*trans*-7-dimethyl-1,3-dioxacyclohept-5-ene. This conformation has neither a 1,3-diaxial nor a 4,7-diaxial methyl–hydrogen interaction. It is consistent with the small value of the γ shift at C2 and the absence of a paramagnetic shift at the C7 methyl carbon. The C2 γ shift for



1



2

r-2-*cis*-4,*trans*-6-trimethyl-1,3-dioxacyclohexane is +2 ppm. This compound is known to have an axial methyl group. It is reasonable to conclude that there is no axial methyl group and therefore no chair conformation for the corresponding 1,3-dioxacyclohept-5-ene.[16]

Experimental Section

Proton nmr spectra were recorded on a Varian A-60A nmr spectrometer. Samples were run as 10% solutions in carbon tetrachloride. All chemical shifts are reported in hertz downfield from internal TMS. The carbon-13 spectra were recorded at 25.15 MHz on a Varian HA 100D nmr spectrometer interfaced with a Digilab NMR-FTS-3 pulse and data system. The number of data points was 8K or 16K as required to obtain satisfactory resolution. Spectra were recorded with broad-band proton decoupling. All chemical shifts were referenced to internal TMS and reported in ppm. All mass spectra were determined on a AEI-9 high resolution mass spectrometer. The infrared spectra were recorded on a Beckman IR-8 instrument and the absorption values are reported in microns.

1,3-Dioxacyclohept-5-ene was prepared as described in the literature.[17]

2-*tert*-Butyl-1,3-Dioxacyclohept-5-ene. The general procedure for the preparation of these compounds is that of Brannock and Lappin.[17] The preparation of 2-*tert*-butyl-1,3-dioxacyclohept-5-ene is described as a general example. A mixture of 8.8 g (0.1 mol) of *cis*-2-butene-1,4-diol, 8.6 g (0.1 mol) of pivaldehyde, 50 ml of benzene, and 50 mg of *p*-toluenesulfonic acid was refluxed under a Dean-Stark distillation trap until 1.8 ml of water was collected. The mixture was fractionally distilled at reduced pressure to give a 75% yield of the desired product: bp 38–40° (2 Torr); ir 3.4, 3.65 6.1, 6.7, 7.2, 9.5, and 10.0; *m/e* 156 (parent peak).

4,7-Dimethyl-1,3-dioxacyclohept-5-ene. The mixture of isomers had bp 25° (0.3 Torr) and the yield was 40%. The isomers were separated by glpc (12 ft 5% 1,2,3-tris(cyanoethoxy)propane on Chromosorb). The cis–trans ratio was 4:1 and the trans isomer was the first peak: ir (mixture) 3.3, 3.6, 6.9, 7.3, 9.0, 9.7, 10.8, 11.3; *m/e* 128 (parent peak).

2-*tert*-Butyl-4,7-Dimethyl-1,3-Dioxacyclohept-5-ene.[18] The mixture of isomers had a bp 36–40° (1 Torr) and the yield was 70%. The cis–trans ratio was 4:1 and the first peak was *r*-2-*tert*-butyl-*cis*-4,*cis*-7-dimethyl-1,3-dioxacyclohept-5-ene: ir (neat) 3.4,

6.9, 7.3, 7.8, 8.2, 8.9, 9.7, and 10.8; *m/e* 184 (parent peak). The isomers were best separated by glpc (8 ft Carbowax 20 *M* 10% on Chromosorb).

2,2-Dimethyl-1,3-dioxacyclohept-5-ene. A mixture of 8.8 g (0.1 mol) of 2-butene-1,4-diol, 20.0 g of anhydrous copper sulfate, 50 mg of *p*-toluenesulfonic acid, and 50 ml of anhydrous acetone was placed in a pressure bottle which was sealed and heated to 50° for a period of 2 weeks. Fractional distillation gave a 50% yield of the desired product: bp 18–20° (1 Torr); ir (neat) 3.3, 3.5, 6.9, 9.9, 11.6, 13.1; *m/e* 128 (parent peak).

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Acknowledgment is also made to the National Science Foundation for Grant GP 20861 for purchase of equipment with ^{13}C and F.T. capabilities.

References and Notes

(1) A. J. Jones, E. L. Eliel, D. M. Grant, M. C. Knoeber, and W. F. Bailey, *J. Amer. Chem. Soc.*, **93**, 4772 (1971).
(2) W. E. Willy, G. Binsch, and E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 5394 (1970).
(3) M. H. Gianni, J. Saavedra, and J. Savoy, *J. Org. Chem.*, **38**, 3971 (1973).
(4) M. H. Gianni, J. Saavedra, J. Savoy, and H. G. Kuivila, *J. Org. Chem.*, **39**, 804 (1974).
(5) M. Christl, H. J. Reich, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 3462 (1971).
(6) M. Christl and J. D. Roberts, *J. Org. Chem.*, **37**, 3443 (1972).
(7) E. F. Mooney, Ed., "Annual Reports on NMR Spectroscopy," Vol. 4, Academic Press, New York, N. Y., p 129; (b) B. Pesce, Ed., "Nuclear Magnetic Resonance in Chemistry," Academic Press, New York, N. Y., 1965, p 128; (c) S. Kabuss, H. Friebolin, and H. Schmid, *Tetrahedron Lett.*, 469, (1965). (d) The C2 carbon-13 hydrogen coupling constants for a series of 1,3-dioxacycloalkanes are recorded here because they provided the original indication that twist-boat conformations might be more common in these compounds than was previously believed. It was expected that the double bond in 1,3-dioxacyclohept-5-ene would spread the dioxamethylene (OCO) bond angle with respect to 1,3-dioxacycloheptane. In so far as these coupling constants relate to the dioxamethylene bond angle the data suggest that the angle is not larger but smaller. This observation is not inconsistent with a twist-boat conformation for 1,3-dioxacyclohept-5-ene. The coupling constants have an accuracy of 0.5 Hz at best and the change in values is small and therefore not conclusive. The values for diethoxymethane, which is assumed to be strain free, and 1,3-dioxacyclooctane, which was expected to be strain free, give testimony to the idea that the coupling constants are sensitive to bond angle. The ^{13}C–H coupling constants are as follows: 1,3-dioxacyclopentane, 164; 1,3-dioxacyclohexane, 163; 1,3-dioxacycloheptane, 164; 1,3-dioxacyclooctane, 161; 1,3-dioxacyclohept-5-ene, 164.5; and diethoxymethane, 161 Hz.
(8) R. Knoor, C. Ganter, and J. D. Roberts, *Angew. Chem.*, **79**, 577 (1967); *Angew. Chem., Int. Ed. Engl.*, **6**, 556 (1967).
(9) (a) M. H. Giann and R. Mohan, unpublished data; (b) K. L. Servis, E. A. Noe, N. R. Easton, and F. A. Anet, *J. Amer. Chem. Soc.*, **96**, 4185 (1974).
(10) M. H. Gianni, J. Saaverdra, R. Myhalyk, and K. Wursthorn, *J. Phys. Chem.*, **74**, 210 (1970).
(11) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **94**, 5318 (1972).
(12) (a) G. M. Kellie and F. G. Riddell, *J. Chem. Soc. B*, 1030 (1971). (b) These values do not exclude a twist–diequatorial chair equilibrium.
(13) N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, **94**, 5734 (1972).
(14) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **88**, 5347 (1966); (b) F. G. Riddell, *Quart. Rev., Chem. Soc.*, 3646 (1967).
(15) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 209.
(16) The difference between the chemical shift for an axial and equatorial methyl carbon is greater than 1 ppm for 1,3-dioxacyclohexanes and 3 ppm for cyclohexanes: ref 1 and 11.
(17) K. C. Brannock and G. R. Lappin, *J. Org. Chem.*, **21**, 1366 (1956).
(18) We use the Beilstein system of nomenclature (see also IUPAC Bulletin 35, June 1969) for cis–trans isomers with rings with more than two substituents whose stereochemistry must be indicated. The lowest number substituent of specified stereochemistry (equatorial 2-*tert*-butyl) is used as a reference point and given the prefix *r*. See also *J. Org. Chem.*, **35**, 2849 (1970).

Synthesis and Enol Determinations of 2,2-Disubstituted 6-Cyanocyclohexanones

Stuart S. Kulp,* Ronald W. Schmoyer, David E. Freeze, and Jerome Buzas

Department of Chemistry, Moravian College, Bethlehem, Pennsylvania 18018

Received August 7, 1974

A series of 14 new 2-R-2-R′-6-cyanocyclohexanones was synthesized. The enol–keto contents of 19 compounds of this type were determined by quantitative ir study of conjugated CN (enol) and unconjugated (keto) absorbances. Application of the concept that steric inhibition of enolization was important in this system seemed appropriate. The per cent enol found for the R, R′ compounds were 37 (H, H), 24 (Ph, Ph), 20 (Me, Me), 18 (Et, Et), 19 (Me, Ph), 13 (CH_2CH_2Ph, Ph), 10 (Et, Ph), 10 (Pr, Ph), 10 (Am, Ph), 6 (*i*-Bu, Ph), 6 (c-Hex, Ph), 5 (*i*-Pr, Ph), 4 (CH_2Ph, Ph), and 5 (*n*-Bu, Ph). The series can be classified in four categories by percentage: A, only parent compound, ~37; B, four compounds, ~20; C, four compounds, ~10; and D, five compounds, ~5. The equivalency or extent of dissimilarity (branching) of substituents, number of conformations, and the 2-alkyl ketone effect rationalize the data with one exception and support the view that steric interference decreases enolization in these β-keto nitriles.

Large differences in the relative rates of hydrolysis of a series of α,α-disubstituted α′-cyanocycloalkanone imines (1) to their corresponding cyano ketones (2) have been observed.[2-4] The results were qualitative and the availability of a number of these β-keto nitriles or extension of the series by their ready synthesis suggested that quantitative date on the enolization of the latter might be useful.

The imines were more difficult to hydrolyze as their steric requirements increased. The isoelectronic imine (>C=N) and carbonyl bonds (>C=O) are not only chemically similar[5] but are also subject to similar steric limitations on the degree of enolization.[6,7] Whereas steric hindrance afforded a satisfactory explanation for the conversion of >C=N to >C=O in our previous work, this is an irreversible reaction. The enolization process, however, is an equilibrium condition. The concept that there can be steric inhibition of enolization has been employed to account for decreased enol contents in a series of compounds with increasing steric requirements[8a] but exceptions are also known.[8b] Steric requirements can have a profound effect.[8c] Studying our compounds seemed to offer an opportunity to contribute to the developing knowledge of enol–keto equilibria.[8d] Therefore, the percentage enol in a series of 2,2-disubstituted 6-cyanocyclohexanones (2_K) was obtained.

The compounds listed in Table I were either on hand from earlier work or were synthesized from the appropriate disubstituted acetonitriles by alkylation with 5-chloropentanenitrile and cyclization in one reaction to the cyanocyclohexanone imines[3] (eq 1) which were subsequently hydrolyzed to keto nitriles. The effectiveness of the two-step,

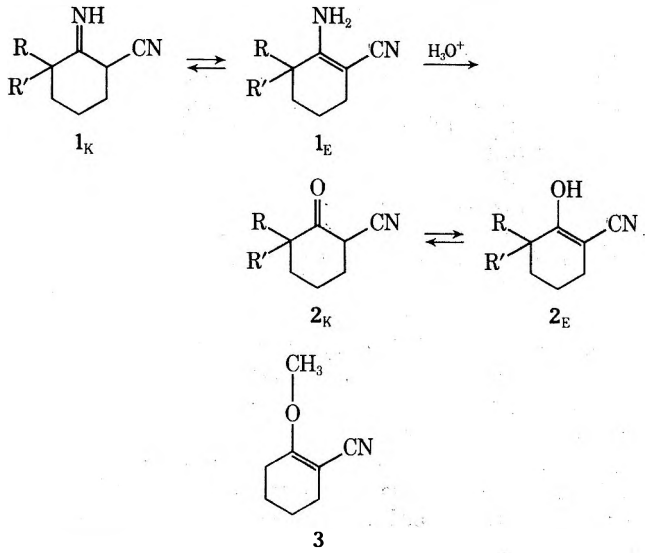
Table I
Enol Contents of 2,2-Disubstituted 6-Cyanocyclohexanones (2)

Compd	R	R'	% enol (2210 cm^{-1} CN conj)	% keto (2250 cm^{-1} CN unconj)	Total % (E + K)	% enol nmr
2a	H	H	37	60	97	30
2b	Me	Me	20	74	94	19
2c	Ph	Ph	24	77	101	
2d	CH_3	Ph	19	79	98	
2e	Et	Et	18	79	97	23
2f	CH_2CH_2Ph	Ph	13	90	103	15
2g	Et	Ph	10	86	96	10
2h	n-C_3H_7	Ph	10	96	106	
2i	n-C_5H_{11}	Ph	10	94	104	
2j	c-C_6H_{11}	Ph	6	106	112	6
2k	i-C_4H_9	Ph	6	98	104	
2l	i-C_3H_7	Ph	5	95	100	4
2m	n-C_4H_9	Ph	5	102	107	
2n	CH_2Ph	Ph	4	103	107	

$$RR'CHCN + Cl(CH_2)_4CN \longrightarrow RR'C(CN)[CH_2]_4CN \longrightarrow \mathbf{1} \quad (1)$$

one-batch, alkylation–cyclization was readily monitored by running the infrared spectrum. The presence of any uncyclized substituted adiponitrile was indicated by unconjugated nitrile absorption at ~2250 cm^{-1} whereas the cyclic cyanoimine (mainly existing as its tautomeric β-amino vinyl cyanide, H_2N—C=C—CN)[2,9] showed a strong, sharp peak at ~2210 cm^{-1} for conjugated nitrile.

The classical Kurt Meyer titration method and modification[10] for determining enol contents of these alicyclic compounds were found to be nonreproducible. Others have reported similar unreliability.[11] Ultraviolet spectroscopic determinations of enol content[12] did not correlate with ir and nmr values due to solvent and concentration differences and this technique is not the method of choice.



Quantitative infrared spectroscopy was examined next. Preliminary attempts to use either the C=C or C—OH region were inconclusive.

The nitrile region of the infrared spectrum of these compounds in dioxane solution offers an excellent method for determining their enol contents. There are two sharp peaks for the keto and enol structures appearing at ~2250 cm^{-1} for the nonconjugated keto nitrile (2_K) and ~2210 cm^{-1} for the conjugated enol nitrile (2_E). These peaks occur in a region of the spectrum where there is virtually no interference from other absorptions. Thus, there are two independent means of checking the equilibrium values. The per cent keto is obtained by comparing the nitrile absorbance at ~2250 cm^{-1} to a calibrated related standard, *e.g.*, $2a_E$ to 4-cyanocyclohexene (**5**). The complementary per cent enol isomer is obtained by comparing the nitrile absorbance at ~2210 cm^{-1} to a different calibrated related standard, *e.g.*, $2a_K$ to 1-cyano-2-methoxycyclohexene (**3**). The total of enol and keto isomers should account for 100% composition of the equilibrium system. The E + K column in Table I shows that the results generally strike total material balance. It was found that at least two sets of standards were necessary. For hydrogen or alkyl substituents, the reference compounds were 1-cyano-2-methoxycyclohexene (**3**) and 4-cyanocyclohexene (**5**). For compounds containing at least one aryl substituent, the reference compounds were 1-cyano-2-methoxy-3,3-diphenylcyclohexene (**4**) and 2-cyano-2-methyl-6,6-diphenylcyclohexanone (**6**). Obviously an enol and a keto standard for *each* compound would be preferable. The per cent enol, keto, and total for the 14 compounds studied are listed in Table I.

An alternative keto–enol analysis procedure was employed: high resolution nuclear magnetic resonance spectrometry.[13] The compound selected for initial intensive study was 6-cyano-2,2-diethylcyclohexanone (**2c**). The carbon-bound enolizable proton (δ 3.71 ppm) appeared as a distinct and deshielded multiplet well separated from the complex envelope of cyclohexyl ring and ethyl group methylene hydrogens (δ 1.2 to 2.7 ppm). The oxygen-bound enolizable proton (in the enol tautomer) could not be located in the spectrum even at very low field. There is ample precedent for similar enol OH's to be difficult to locate or apparently absent.[14] The only other clearly distinguishable resonances were the two overlapping methyl triplets at δ 0.78 ppm.

The keto–enol sample, prepared in $CDCl_3$, was allowed to obtain equilibrium distribution of isomers at probe temperature (34°) but there was essentially no further change in the spectrum after 5 min. Integration of the 3.71 ppm multiplet with reference to the two overlapping methyl resonances taken as six proton units was used to calculate the keto percentage as 77 ± 5%.

In order to firmly establish that the 3.71 downfield multiplet (which resembled two overlapping triplets of J = 4 Hz under high resolution scale expansion) was indeed due to the carbon-bound enolizable proton, two experiments were devised. A spectrum of a methyl enol ether (**3**) showed no such downfield proton. Furthermore, the $CDCl_3$ solution of the original 6-cyano-2,2-diethylcyclohexanone was treated with D_2O and with periodic shaking underwent slow diminution of the 3.71 ppm resonance until at the end of 16 days it had almost vanished.

The nmr method was then applied to six other compounds and gave the results found in Table I. The enolizable H was centered between 3.45 (*i*-Pr, Ph) and 3.9 (Me, Me) ppm in all cases. An attempt to use dioxane-d_8 as solvent failed due to impurity resonance at 3.56 ppm. The nonequivalence of methyls was clearly evidenced by two singlets at 2.23 and 2.31 for **2b** and two doublets at 0.49 and 0.88 for **2l**. The tabulated nmr data presented involve judicious choices in interpretation and calculation. Furthermore, at best these nmr data are ±5% reliable for quantitative work.

Alkylation experiments which were carried out to pre-

pare potential standards gave unanticipated results. Ethyl iodide was reacted with the sodium salt of 2,2-diphenyl-6-cyanocyclohexanone (2c) in an attempt to obtain the corresponding carbon ethylated product. However, the *O*-ethyl compound, 1-cyano-2-ethoxy-3,3-diphenylcyclohexene (6), was isolated. Others have shown that this type of alkylation is highly dependent upon reagents and conditions.[15] The reaction of the diphenyl keto nitrile (2c) under similar conditions with methyl iodide gave the *C*-alkylated product, 2-cyano-2-methyl-6,6-diphenylcyclohexanone (7). Repetition of the methylation on the phenyl isopropyl compound (2l) also gave *C*-alkylation. The nmr spectrum of 2-cyano-6-isopropyl-2-methyl-6-phenylcyclohexanone (8) showed two doublets of equal intensity and spacing at 0.45 ppm (3 H) and 0.94 ppm (3 H) due to the restricted rotation of the isopropyl group and its nonequivalent methyls.

The compounds appear to fall into four main categories: (A) **2a** (H, H) is clearly the most highly enolized at ~37%; (B) four compounds (**2b, 2c, 2d, 2e**) [(Me_2), (Ph_2), (Ph, CH_3), (Et_2)] are ~20% enolized; (C) four compounds (**2f, 2g, 2h, 2i**) [(Ph, $(CH_2)_2Ph$), (Ph, Et), (Ph, *n*-C_3H_7), (Ph, *n*-C_5H_{11})] are ~10% enolized and (D) five compounds (**2j, 2k, 2l, 2m, 2n**) [(Ph, c-C_6H_{11}), (Ph, *i*-C_4H_9), (Ph, *i*-C_3H_7), (Ph, *n*-C_4H_9), (Ph, CH_2Ph)] are ~5% enolized.

Among effects which influence keto–enol equilibrium are resonance, hydrogen bonding, solvation, induction, steric requirements, and entropy. The structures of the alicyclic β-keto nitriles included in this work are quite complex mainly due to conformational possibilities of the cyclohexane system. Compounds of type A and B, except **2d**, have equivalent substituents. The change from hydrogens (**2a**) to other groups involves a change in steric requirement. Thus, these compounds have one enol form of cyclohexene, since pseudo axial and pseudo equatorial are equivalent, and two keto forms, CN equatorial (eclipsed to carbonyl) and CN axial (hydrogen eclipsed to carbonyl). Type C and D compounds, with different substituents adjacent to the carbonyl, present a more complicated situation. There are now two enol forms (ethyl pseudo axial, phenyl pseudo equatorial, and *vice versa* which can interconvert) leading *via* ketonization by hydrogen attachment above or below the plane of the cyclohexene nitrile to four arrangements of the keto nitrile (CN eclipsed to carbonyl with either phenyl or ethyl cis and CN staggered to carbonyl with either phenyl or ethyl cis). Examination of molecular models shows a preference for carbonyl-CN staggered conformations. Furthermore, the distinctions between type C and D compounds on steric grounds are emphasized. Type C compounds are alkyls with *α and β* methylene carbons but type D compounds, with the exception of **2m**, are branched either on the *α* or *β* carbon. The enigma introduced by **2m** eludes definitive comment but models suggest the *n*-butyl has more freedom of rotation than *n*-amyl and encounters considerable 1,3-diaxial interference similar to other type D compounds.

The major factors influencing enol–keto equilibria in this series appear to be population of the number of possible configurations and conformations and the "2-alkyl ketone effect."[16] The latter indicates some stabilization difference in going from methyl to ethyl but a large difference in comparing 2-ethyl to 2-isopropylcyclohexanone.

In summary, for enol values in this series the ir method of comparing conjugated nitrile absorbance with the corresponding easily prepared methyl enol ether standard absorbance curve is recommended for ±1% reliability. Although the population and steric effects discussed offer a reasonable interpretation of the data, it is difficult to disentangle all contingencies.[8c,17]

Table II
Properties of 2,2-Disubstituted 6-Cyanocyclohexanones (2)

Compd	Mp,[a] deg	% yield	Formula[b]
2d	64–64.5	90	$C_{14}H_{15}NO$
2f	128–130	100	$C_{21}H_{21}NO$
2h	104–104.5	100	$C_{16}H_{19}NO$
2i	40.5–42	90	$C_{18}H_{23}NO$
2j	149–151	85	$C_{19}H_{23}NO$
2k	71–72	80	$C_{17}H_{21}NO$
2l	94–95	94	$C_{16}H_{19}NO$
2m	52–53	70	$C_{17}H_{21}NO$
2n	122.5–123	93	$C_{20}H_{19}NO$

[a] Recrystallized from Et_2O (**2n**), 50% MeOH (**2l**), petroleum ether (**2d, 2i, 2k, 2m**), MeOH (**2f, 2j**), and 80% MeOH (**2h**). [b] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table.

Experimental[13] Section

1-Cyano-2-methoxycyclohexene (3). To 0.086 mol of 2-cyanocyclohexanone in 30 ml of dry ether was added excess diazomethane in ether (HOOD). Evolution of nitrogen occurred slowly and the mixture was allowed to stand at room temperature overnight. The excess diazomethane was destroyed by cautiously adding hydrochloric acid. The ethereal solution was washed with water then aqueous sodium hydroxide. After drying ($MgSO_4$), filtration, and concentration, the residue distilled cleanly at 114–116° (9 mm), 83% yield.

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.90; H, 8.24; N, 10.15.

1-Cyano-2-methoxy-3,3-diphenylcyclohexene (4). This compound was prepared as described above from 2,2-diphenyl-6-cyanocyclohexanone (**2c**). Recrystallization from methanol gave mp 102–103.5°, 87% yield.

Anal. Calcd for $C_{29}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.03; H, 6.49; N, 4.87.

4-Cyanocyclohexene (5) was obtained from K & K Laboratories, Inc., and distilled, bp 70–72° (17 mm).

2-Amino-1-cyano-3,3-disubstituted Cyclohexenes (1_E). These compounds were available or prepared by the method previously described.[3] The crude reaction mixtures obtained by alkylation of the disubstituted acetonitriles were heated under vacuum only to remove unreacted starting materials and the remaining undistilled dinitriles (which contained some cyclic enamines) were then cyclized. The enamines were obtained in 75–100% yields and had the following melting points: **1d**, 95–97°; **1f**, 114–115°; **1h**, 113–113.5°; **1i**, 64.5–66°; **1j**, 100–102°; **1k**, 77–80°; **1l**, 121–123°; **1m**, 64–67°; **1n**, 143–144°. The infrared spectra of all these compounds showed two NH stretch peaks and one conjugated CN peak as found earlier.

2,2-Disubstituted 6-Cyanocyclohexanones (2_K). These compounds were available or prepared as previously described.[3] The properties of the new ketones are listed in Table II.

Calibration Data for Infrared Determinations. Compound 3 in solutions of 0.131–1.314 mmol/10 ml of dioxane was used to run a calibration curve for conjugated nitrile absorbances (2210 cm^{-1}) for aliphatic compounds. Similarly compound 4 in dioxane at 0.344–1.552 mmol/10 ml of dioxane was used for compounds which contained at least one aryl substituent. The unconjugated nitrile absorbances at 2240 cm^{-1} were obtained from 5 in 2.643–4.748 mmol/10 ml of dioxane for aliphatic compounds and similar data were obtained with compound 6 for compounds with aryl substituent(s).

Enol and Keto Contents in Dioxane. The enol contents of 14 compounds (**2a–n**) in concentrations of ~3.5 mmol/10 ml of dioxane (0.35 *M*) were determined by comparing the nitrile absorbances to 3 for aliphatic substituents or 4 for aryl substituent(s) in matched 0.189-mm cells with dioxane in the reference cell. Keto contents were obtained similarly but the reference compounds were 5 and 6. The percentages are listed in Table I. Most of the β-keto nitriles equilibrated almost instantaneously but **2l, 2m,** and **2n** required 10 days to equilibrate.

1-Cyano-2-ethoxy-3,3-diphenylcyclohexene (6). In a dry apparatus 4.8 g (0.0175 mol) of 2c was dissolved in 210 ml of absolute

ethanol at 65°. An ethanol solution of 0.0175 mol of sodium ethoxide was added and the mixture was cooled to room temperature. To this was added 13.70 g (0.0875 mol) of ethyl iodide and after refluxing 1.5 hr an additional 5.26 g of ethyl iodide was added and reflux was continued another 1.5 hr. By this time the solution was neutral and it was allowed to cool and stand overnight. About two-thirds of the ethanol was removed by distillation, then 80 ml of water and 40 ml of ether were added. The separated ethereal solution was washed repeatedly until a negative test for iodide was observed. Evaporation of the ether left 4.7 g (91%) of crude product. Recrystallization from absolute methanol then 70% ethanol gave 1.1 g (21%) of very pure product, mp 116–117°. The infrared spectrum had nitrile absorption at 2210 cm^{-1} characteristic of conjugated CN as in **4**. The nmr spectrum in $CDCl_3$ had a triplet (3 H) at 0.93 ppm and a quartet (2 H) at 4.14 ppm showing an ethyl bonded to an oxygen.

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.19; H, 7.05; N, 4.60.

2-Cyano-2-methyl-6,6-diphenylcyclohexanone (7). Repetition of the above reaction with methyl iodide gave 33% pure product after vacuum sublimation and recrystallization from ether, mp 134.5–135°. The infrared spectrum in dioxane showed unconjugated nitrile at 2240 cm^{-1} and a shoulder at 2250 cm^{-1}. The nmr spectrum in $CDCl_3$ had a singlet (3 H) at 1.42 ppm, an aromatic (10 H) at 7.23 ppm, and methylenes (6 H) at ~2.85 ppm.

Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.06; H, 6.68; N, 4.64, 4.77.

2-Cyano-6-isopropyl-2-methyl-6-phenylcyclohexanone (8). Similarly **2l** and methyl iodide gave an oil which was vacuum distilled and crystallized with difficulty. Recrystallization from 30–60 petroleum ether gave a 40% yield, mp 77.5–78.5°. The nmr spectrum ($CDCl_3$) had a doublet (3 H) at 0.45 ppm, a doublet (3 H) at 0.94 ppm, a singlet (3 H) at 1.12 ppm, a singlet (1 H) at 1.99 ppm, a septet (6 H) at 2.56 ppm, and an aromatic (5 H) at 7.32 ppm.

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.92; H, 8.29; N, 5.49. Found: C, 80.14; H, 8.12; N, 5.65.

Acknowledgment. We thank Lehigh University, Dr. Ned Heindel, and Mr. Richard Conley for running and assistance in interpreting the nmr spectra.

Registry No.—**1d**, 53586-66-6; **1f**, **53586-67-7**; **1h**, 18072-65-6; **1i**, 18072-67-8; **1j**, 53586-68-8; **1k**, 53586-69-9; **1l**, 53586-70-2; **1m**, 18072-66-7; **1n**, 18072-68-9; **2a** enol form, 53586-71-3; **2a** keto form, 4513-77-3; **2b** enol form, 53586-72-4; **2b** keto form, 10219-83-7; **2c** enol form, 53586-73-5; **2c** keto form, 15719-03-6; **2d** enol form, 53586-74-6; **2d** keto form, 53586-75-7; **2e** enol form, 53586-76-8; **2e** keto form, 15595-78-5; **2f** enol form, 53586-77-9; **2f** keto form, 53586-78-0; **2g** enol form, 53586-79-1; **2g** keto form, 15595-79-6; **2h** enol form, 53586-80-4; **2h** keto form, 53586-81-5; **2i** enol form, 53586-82-6; **2i** keto form, 53586-83-7; **2j** enol form, 53586-84-8; **2j** keto form, 53586-85-9; **2k** enol form, 53586-86-0; **2k** keto form, 53586-87-1; **2l** enol form, 53586-88-2; **2l** keto form, 53586-89-3; **2m** enol form, 53586-90-6; **2m** keto form, 53586-91-7; **2n** enol form, 53586-92-8; **2n** keto form, 53586-93-9; **3**, 53586-94-0; **4**, 53586-95-1; **6**, 53586-96-2; **7**, 53586-97-3; **8**, 53586-93-4.

References and Notes

(1) Taken in part from the Honors Papers of R.W.S. (1965), D.E.F. (1968), and J.B. (1970).
(2) S. S. Kulp, V. B. Fish, and N. R. Easton, *Can. J. Chem.*, **43**, 2512 (1965).
(3) S. S. Kulp, *Can. J. Chem.*, **45**, 1981 (1967).
(4) S. S. Kulp, J. Molnar, P. J. Miller, and S. T. Herman, *J. Org. Chem.*, **36**, 2203 (1971).
(5) M. M. Spring, *Chem. Rev.*, **26**, 297 (1940).
(6) G. K. Schweitzer and E. W. Benson, *J. Chem. Eng. Data*, **13**, 452 (1968).
(7) R. C. Fuson, J. Corse, and C. H. McKeever, *J. Amer. Chem. Soc.*, **62**, 3250 (1940).
(8) (a) M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, N.Y., 1956, p 237; (b) G. S. Hammond, W. G. Borduin, and G. A. Guter, *J. Amer. Chem. Soc.*, **81**, 4682 (1959); (c) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, N.J., 1963, p 376; (d) M. T. Rogers and J. L. Burdett, *Can. J. Chem.*, **43**, 1516 (1965).
(9) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles," Wiley, New York, N.Y., 1970, p 4.
(10) (a) A. Gero, *J. Org. Chem.*, **26**, 3156 (1961); *ibid.*, **19**, 1960 (1954); (b) O. Riobe and L. Gouin, *C. R. Acad. Sci.*, **234**, 1889 (1952).
(11) N. L. Allinger, L. W. Chow, and R. A. Ford, *J. Org. Chem.*, **32**, 1994 (1967).
(12) P. B. Russell and J. Mentha, *J. Amer. Chem. Soc.*, **77**, 4245 (1955).
(13) Ir spectra were run on a Perkin-Elmer Model 237-B. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were by Dr. George I. Robertson, Jr., Florham Park, N.J. Nmr spectra were obtained on a Perkin-Elmer Hitachi R20A calibrated against tetramethylsilane.
(14) N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Leplay, *J. Org. Chem.*, **32**, 2678 (1967).
(15) M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35**, 161 (1970).
(16) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N.Y., 1962, p 240.
(17) S. Forsén and M. Nilsson, "The Chemistry of the Carbonyl Group," Vol. 2, J. Zabicky, Ed., Interscience, New York, N.Y., 1970, p 198 and 203.

Aminocyclitols. 31. Synthesis of Dideoxystreptamines[1]

Tetsuo Suami,* Seiichiro Ogawa, Hayashi Uchino, and Yuji Funaki

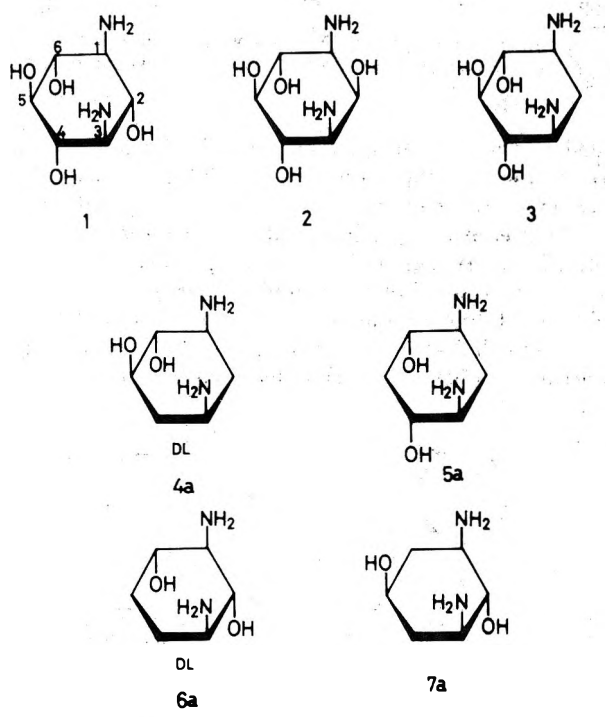
Department of Applied Chemistry, Faculty of Engineering, Keio University, Hiyoshi, Yokohama 223, Japan

Received June 17, 1974

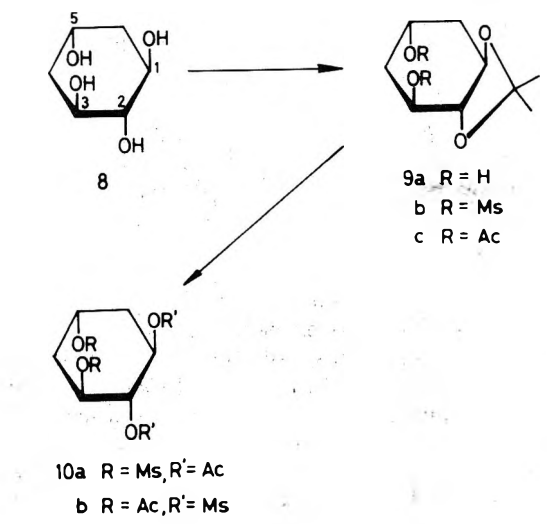
All four predicted positional isomers of dideoxystreptamine have been synthesized. From the two mesylates (**10a** and **10b**), 2,4-(**4a**) and 4,6-dideoxystreptamine (**7a**), together with the acetyl derivatives of two other diaminocyclohexanediols (**11** and **12**), were obtained. 2,5-Dideoxystreptamine (**5a**) was synthesized regioselectively in good yield *via* an intermediate 1,3-hydrazino compound (**15a**) obtained by hydrazinolysis of 1,4-*cis*-diepoxycyclohexane (**14**). 4,5-Dideoxystreptamine (**6a**) was prepared from the dimesylates **17** and **19**.

In 1969, Rinehart and his coworkers[2] described the first successful bioconversion of streptamine (**1**)[3] and 2-epistreptamine (**2**)[4] to semisynthetic neomycin A and B using mutants of *Streptomyces fradiae* in a fermentation media containing **1** and **2**. Very recently, two papers[5,6] on the bioconversion of aminocyclitols to antibiotics have been published. Rinehart and collaborators[5] have tested 29 analogs of 2-deoxystreptamine (**3**) as to whether they are incorporated into antibiotics and it has been found that only two compounds (**1** and **2**) undergo bioconversion to active antibiotics. Structural features of the aminocyclitols which allow the bioconversion were limited to a minor modification of 2-deoxystreptamine; their results suggested guidelines for subsequent synthesis of 2-deoxystreptamine analogs. Along this line, we have attempted to synthesize dideoxystreptamines. In the neomycins,[7] paromomycins,[8] and ribostamycin[9] an aminohexose and D-ribose are linked to the hydroxyl groups at C-4 and C-5 of 2-deoxystreptam-

ine. Therefore, 2,4-dideoxystreptamine (**4a**) might be incorporated into these antibiotics by a bioconversion technique. Since the kanamycins[10] have two amino sugars on the C-4 and C-6 positions of 2-deoxystreptamine in α-glycosidic linkages, 2,5-dideoxystreptamine (**5a**) is an attractive compound for the bioconversion. However, none of the four possible isomers of dideoxystreptamine has been described in the literature so far. In the present paper, we wish to report the synthesis of all the predicted dideoxystreptamine isomers: 2,4- (**4a**), 2,5- (**5a**), 4,5- (**6a**), and 4,6-dideoxystreptamine (**7a**).[11] Besides the possibility of the bioconversion, these dideoxystreptamines will be used for a total chemical synthesis of hybrimycin analogs by methods extensively exploited by three research groups[12] to investigate relationships between structural features of aminocyclitols and biological activities of synthetic antibiotics.



2,4- (4a) and 4,6-Dideoxystreptamines (7a). These compounds were synthesized starting from two dimesylates (**10a** and **10b**) of 1,3/2,5-cyclohexanetetrol (**8**), which was prepared by hydrogenolysis of 1,5-dibromo-1,5-dideoxy-*chiro*-inositol[13,14] in 32% yield. Treatment of **8** with 2,2-dimethoxypropane in dimethylformamide in the presence of a catalytic amount of *p*-toluenesulfonic acid gave the 1,2-*O*-isopropylidene derivative (**9a**) as a homogeneous syrup, which was treated with mesyl chloride in pyridine yielding the dimesylate (**9b**) in 62% yield based on **8**. On hydrolysis with 50% aqueous acetic acid followed by acetylation, **9b** was converted to 1,2-di-*O*-acetyl-3,5-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (**10a**) in 89% yield. Compound **9a** was also treated with acetic anhydride in pyridine to give an oily diacetyl derivative (**9c**). Compound **9c** was hydrolyzed under mild conditions and subsequently treated with mesyl chloride in pyridine yielding 1,5-di-*O*-acetyl-2,3-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (**10b**).



Azidolysis of **10a** with an excess amount of sodium azide in refluxing 2-methoxyethanol for 20 hr followed by acetylation gave a mixture of azido compounds. The mixture was catalytically hydrogenated and subsequently acetylated to give a mixture of tetraacetyl derivatives of three diaminocyclohexanediols which were separated by fractional crystallizations to afford **4b, 11,** and **12** in 13, 24, and 13% yields, respectively. Structural elucidations of the compounds were carried out on the basis of pmr spectroscopy and the proposed reaction mechanism. Three diazido compounds were produced from **10a** by nucleophilic substitution of its mesyloxy groups by azide ions. Thus, the axially located 5-mesyloxy group is initially replaced by an azido group by direct SN2 attack of the nucleophile with an inversion of the configuration at C-5. On the other hand, substitution of the 3-mesyloxy function is assumed to proceed either *via* neighboring-group participation or direct SN2 reaction. Therefore, the structures of the three diazido–diol acetates formed may be formulated as the acetates of (1,3,5/2)-3,5-diazido-1,2-, (1,2,5/3)-2,5-diazido-1,3-, and (1,5/2,3)-3,5-diazido-1,2-cyclohexanediols (precursors of **4b, 11,** and **12,** respectively). The pmr spectral data of the

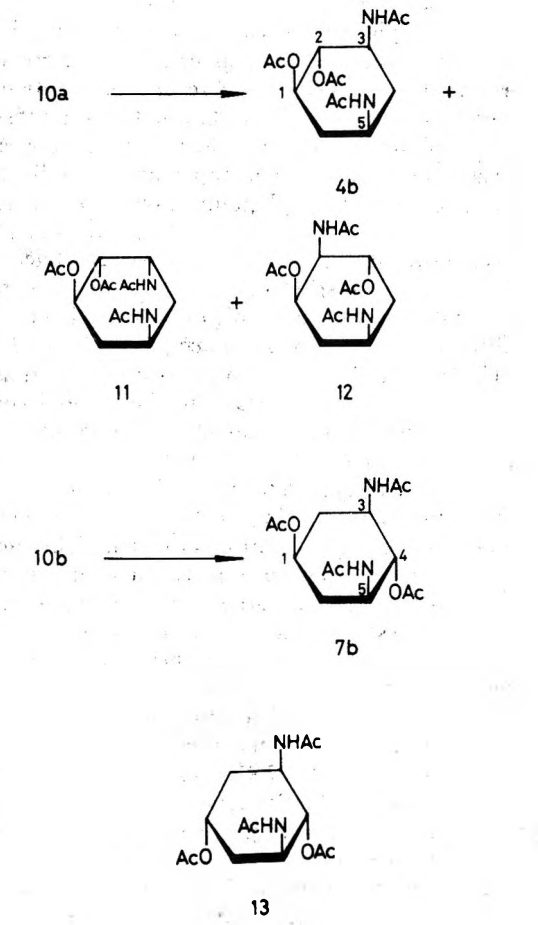


Table I
Characterization of Tetra-*N,O*-acetyldiaminocyclohexanediols

Compd	Mp,[a] °C	Chemical shifts of methyl protons[b] Acetamido Eq	Acetamido Ax	Acetoxy Eq	Acetoxy Ax	Microanalyses,[c] % C	H	N
4b	231.5–233	8.24 8.21		8.07 8.04		53.46	6.94	8.70
5b	292–293	8.22[d]		8.03[d]		53.35	6.94	8.84
6b	274–275.5	8.25[d]		8.12 8.04		53.01	6.89	8.60
7b	300–300.5	8.25[d]		8.10 8.01		53.51	7.03	8.77
11	269.5–270	8.20	8.12	8.07 8.00		53.34	7.09	8.76
12	190.5–191.5	8.17	8.10	8.02	7.95	53.52	7.03	8.63

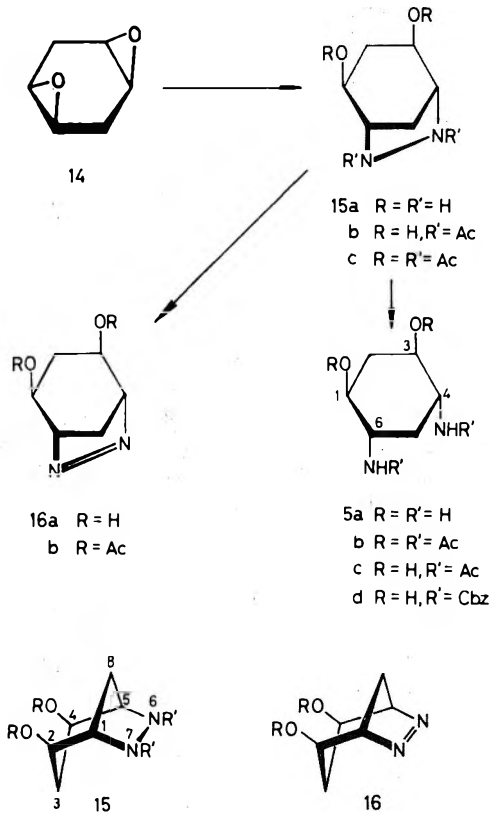
[a] Measured in a sealed capillary in a liquid bath and uncorrected. [b] Determined at 60 MHz in DMSO-d_6 with tetramethylsilane as an internal standard. Chemical shifts are given in τ values. [c] Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. [d] Singlet for two methyl groups.

tetra-*N,O*-acetyldiaminocyclohexanediols are listed in Table I. Assignments of the signals due to the acetyl methyl protons were based on the results of Lichtenthaler.[15] The pmr spectrum of **4b** indicated that all the substituents were in equatorial positions, and its unsymmetrical structure was demonstrated by an appearance of individual singlets due to the four acetyl groups. Consequently, structure **4b** was assigned to di-*O*-acetyl-(1,3/5/2)-3,5-diacetamido-1,2-cyclohexanediol (tetra-*N,O*-acetyl-2,4-dideoxystreptamine). The pmr spectrum of **12** showed the presence of two axial substituents, which established the structure as di-*O*-acetyl-(1,2,5/3)-2,5-diacetamido-1,3-cyclohexanediol. Compound **11** was shown by its pmr spectrum to possess one axial acetamido group in the favored conformation. Therefore, it was assigned to di-*O*-acetyl-(1,5/2,3)-3,5-diacetamido-1,2-cyclohexanediol.

On similar azidolysis followed by hydrogenation and acetylation, **10b** yielded a single crystalline tetra-*N,O*-acetyldiaminocyclohexanediol (**7b**) in 41% yield. The pmr spectral data indicated that **7b** possessed a symmetrical structure and that all the substituents were in equatorial positions, which established the structure as di-*O*-acetyl-(1,3,5/4)-3,5-diacetamido-1,4-cyclohexanediol (tetra-*N,O*-acetyl-4,6-dideoxystreptamine). The chemical shifts of the acetyl methyl protons of its epimer (**13**), (1,4/3,5)-isomer,[16] showed identical values compared with those of **7b** except for one signal of **13** at τ 7.91.[16] Mechanistically, substitutions of the two mesyloxy functions with azide ions may involve a neighboring-group participation reaction followed by direct SN2 reaction.

2,5-Dideoxystreptamine (5a). Introductions of 1,3-*cis*-diamino groups in cyclitols have been successfully carried out *via* 1,3-hydrazino derivatives by hydrazinolysis of suitable disulfonates or dideoxydihalogeno derivatives.[17] Therefore, the most promising synthetic route for **5a** was hydrazinolysis of *cis*-1,4-diepoxycyclohexane (**14**).[18] Compound **14** was prepared from 1,4-cyclohexadiene according to the directions of Craig, *et al.*[19] The separation of the stereoisomers of 1,4-diepoxycyclohexane formed was found to be most efficient by using silica gel column chromatography with 1:4 2-butanone–toluene as an eluent. The cis and trans isomers were thus obtained as pure crystals in 31 and 8% yields, respectively, based on 1,4-cyclohexadiene.

When **14** was treated with an excess amount of hydrazine in refluxing 2-methoxyethanol for 4.5 hr, the reaction proceeded smoothly to give a single crystalline 1,3-hydrazino compound (**15a**) in 85% yield, which was further characterized as the di-*N*-acetyl (**15b**) and the tetraacetyl derivatives (**15c**). Neither derivative exhibited an absorption in the amide II region in the ir spectra. Hydrogenation of **15a** in the presence of platinum catalyst or Raney nickel T-4[20] afforded a crystalline diaminocyclohexanediol (**5a**) in 88% yield, which was isolated and characterized as its dihydrochloride. Compound **5a** was converted into the tetraacetyl (**5b**), the di-*N*-acetyl (**5c**), and the di-*N*-carbobenzyloxy derivatives (**5d**) by the usual methods. On the basis of the



pmr spectral data, **5a** was assigned to di-*O*-acetyl-(1,3/4,6)-4,6-diacetamido-1,3-cyclohexanediol (tetra-*N,O*-acetyl-2,5-dideoxystreptamine). Thus, 2-proton double triplets having 4.5, 11, and 11 Hz splittings at τ 5.31 were ascribed to magnetically equivalent H-1 and H-3, indicating that all the substituents were in equatorial orientations.

Accordingly, **15a** was shown to be 6,7-diazabicyclo-[3.2.1]octane-(2*S*,4*R*)-diol ((1,3/4,6)-4,6-hydrazino-1,3-cy-

Table II
Chemical Shifts and Coupling Constants for 6,7-Diazabicyclo[3.2.1]octane-(2S,4R)-diol and -oct-6-ene-(2S,4R)-diol, and Their Derivatives[a]

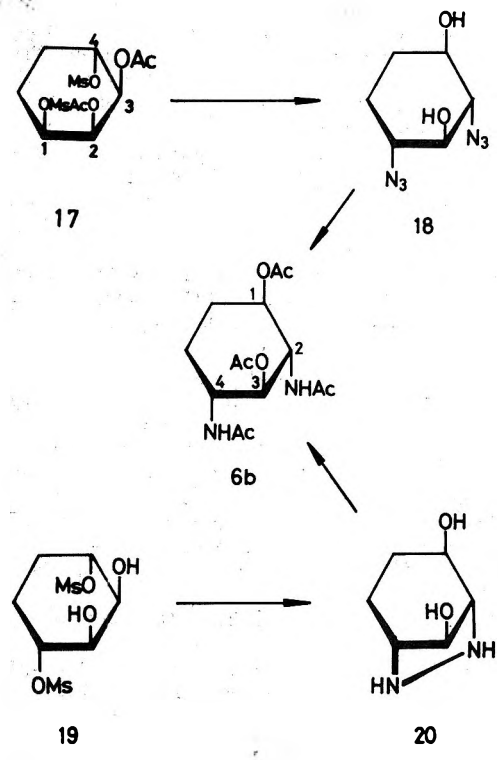
	15a (D_2O)	15b (D_2O)	15c ($CDCl_3$)	16a (D_2O)	16b ($CDCl_3$)
			Chemical Shifts[b]		
H-1,5	6.49	5.32	5.25	4.79	4.69
	d	t	t	dd	dd
H-2,4	6.13	5.73	4.78	6.04	4.96
	t	td	m	m	q
H-3a	7.93	8.21	8.01		8.29
	dt	t	t		t
H-3e	8.43	8.21	8.01		8.29
	d	t	t		t
H-8a	7.27	7.07	7.27	7.50	7.57
	d	d	d	d	d
H-8e	8.48				8.56
	td				td
			Coupling Constants[c]		
$J_{1,2}$ ($J_{4,5}$)	5.0	5.0	5.0	3.5	4.0
$J_{2,3a}$	5.0	3.5	3.5	6.0	4.0
$J_{2,3e}$	0	3.5	3.5	0	4.0
$J_{3a,3e}$	−17.0	0	0	−16.0	0
$J_{1,8a}$	0	0	0	0	0
$J_{1,8e}$	5.0	5.0	5.0	5.5	6.0
$J_{8a,8e}$	−12.0	−13.0	−12.5	−13.0	−12.5
$J_{2,8e}$ ($J_{4,8e}$)	1.0			1.0	1.5

[a] Measured at 60 MHz in $CDCl_3$ or D_2O with tetramethylsilane or sodium 3-(trimethylsilyl)-1-propanesulfonate as an internal standard, respectively. [b] Chemical shifts are given in τ values. Signals are denoted by s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), td (triplet of doublet), and m (multiplet). [c] Values are first order.

clohexanediol). The pmr spectra data (Table II) of **15a** and its derivatives well supported the proposed structures. In the pmr spectrum of **15a**, the C-8 transoid proton appeared as a doublet at lower field compared with the cisoid one, attributable to the deshielding effect of the syn-diaxial two hydroxyl groups on C-2 and C-4.[18,21] The C-3 axial proton appeared also to be deshielded by the hydrazino bridge. In the pmr spectra of **15b** and **15c**, no influence owing to a restricted rotation of the secondary amido groups was observed.

Compound **15a** was comparatively stable in the pure crystalline state; however, in solution or in an impure state, it decomposed gradually by oxidation to yield a crystalline azo compound (**16a**), which was further characterized by converting into the diacetate (**16b**). The presence of the azo group in **16a** and **16b** was clearly shown by characteristic uv absorptions of λ_{max} 336 nm in water and 344 nm in methanol, respectively.[22] Their pmr spectra also supported the proposed structures. Therefore, **16a** was assigned to 6,7-diazabicyclo[3.2.1]oct-6-ene-(2S,4R)-diol. Compound **16a** was obtained from **15a** by oxidation with hydrogen peroxide in 57% yield.

4,5-Dideoxystreptamine (6a). Compound **6a** was first obtained as its tetraacetyl derivative (**6b**) in 3% yield by azidolysis, followed by hydrogenation and acetylation, of 2,3-di-*O*-acetyl-1,4-di-*O*-mesyl-1,2,3/4-cyclohexanetetrol (**17**), which was prepared from 1,2:5,6-dianhydro-3,4-*O*-cyclohexylidene-*allo*-inositol[23] by lithium aluminum hydride reduction and successive mesylation.[24] Reaction of **17** with an azide ion is reasonably expected to proceed through initial formation of an intermediate 3,4-acetoxonium ion. Nucleophilic attack on C-3 results in formation of all-trans diazidodiol (**18**), but it seems preferable to attack on C-4.



All the substituents of **6b** were shown to be in equatorial orientations by pmr spectroscopy, and the 1-proton wide triplet at τ 5.25 and the 1-proton wide quartet at τ 6.08 were ascribed to H-2 and H-3, respectively, showing that they have trans-diaxial methine protons in the vicinal positions. Therefore, structure **6b** was assigned to di-*O*-acetyl-(1,3/2,4)-2,4-diacetamido-1,3-cyclohexanediol (tetra-*N,O*-acetyl-4,5-dideoxystreptamine).

In order to improve the yield of **6b**, an alternative route *via* a hydrazino compound was studied. As starting material 1,4-di-*O*-mesyl-1,4/2,3-cyclohexanetetrol (**19**) was used, which was readily available by lithium aluminum hydride reduction[24] of 1,2-anhydro-5,6-*O*-cyclohexylidene-3,4-di-*O*-mesyl-*chiro*-inositol[24] followed by mesylation. Treatment of **19** with an excess amount of hydrazine in refluxing 2-methoxyethanol for 6 hr, followed by hydrogenation and acetylation, afforded **6b** exclusively in 45% yield. This result was accounted for by assuming the selective formation of the 1,3-hydrazino compound (**20**).

Experimental Section[25]

1,3/2,5-Cyclohexanetetrol (8). This compound was prepared from 1,5-dibromo-1,5-dideoxy-*chiro*-inositol in 32% yield according to the directions of McCasland and Horswill,[13] mp 175–178°. Recrystallized sample melted at 178–180° (lit.[13] 179–180°). It was further characterized by preparation of the tetraacetate, mp 88–89° (lit.[14] 84–86°).

1,2-*O*-Isopropylidene-3,5-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (9b). To a solution of 8 (1.0 g) in dimethylformamide (20 ml) was added 2,2-dimethoxypropane (2.0 ml) and *p*-toluenesulfonic acid (20 mg), and the mixture was heated at 85–90° for 90 min. The mixture was cooled to 0°, neutralized with Amberlite IRA-410 (OH^-), and evaporated to yield the syrupy 1,2-*O*-isopropylidene derivative (**9a**). It was, without further purification, dissolved in pyridine (15 ml) and cooled below 0°. Mesyl chloride (2.5 ml) was added dropwise under agitation and the reaction mixture was allowed to stand in a refrigerator overnight. The mixture was then poured into ice–water (100 ml) and the resulting precipitate

was collected by filtration, giving 1.45 g (62.4%) of **9b** as needles: mp 127–132°; recrystallization from chloroform–ethanol raised its mp to 131–132°; pmr ($CDCl_3$) τ 4.73 (q, 1, H-5, J = 3 Hz), 5.08 (d of t, 1, H-3, $J_{2,3}$ = 9.5 Hz, $J_{3,4a} = J_{3,4e}$ = 5 Hz), 6.14 (d of t, 1, H-1, $J_{1,6a}$ = 11.7 Hz, $J_{1,6e}$ = 4.3 Hz), 6.51 (t, 1, H-2, $J_{1,2}$ = 9.5 Hz), 6.84 (s, 3, OMs), 6.91 (s, 3, OMs), and 8.52 (s, 6, $C(CH_3)_2$).

1,2-Di-*O*-acetyl-3,5-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (10a). A mixture of **9b** (0.97 g) and 50% aqueous acetic acid (25 ml) was heated at 75° for 80 min. The reaction mixture was then evaporated to dryness and the residue was treated with acetic anhydride (5 ml) and pyridine (7 ml) overnight at room temperature. The mixture was poured into ice–water to give 1.05 g (97%) of **10a**, mp 163–164°. Recrystallization from chloroform–ethanol gave 0.97 g (89%) of pure needles: mp 164–164.5°; pmr (DMSO-d_6) τ 6.70 (s, 3, OMs), 6.80 (s, 3, OMs), 7.96 (s, 3, OAc), and 8.01 (s, 3, OAc).

Anal. Calcd for $C_{12}H_{20}O_{10}S_2$: C, 37.11; H, 5.19; S, 16.51. Found: C, 37.02; H, 5.04; S, 16.46.

1,5-Di-*O*-acetyl-2,3-di-*O*-mesyl-1,3/2,5-cyclohexanetetrol (10b). The syrupy **9a** obtained from **8** (1.01 g) was treated with a 1:2 mixture (15 ml) of acetic anhydride and pyridine overnight at room temperature. The reaction mixture was poured into ice–water (100 ml) and extracted with ethyl acetate (30 ml), and the extract was washed successively with 10% aqueous potassium carbonate and water, dried over anhydrous sodium sulfate, and evaporated to give a syrup, which showed a single spot on tlc. The product was heated with 50% aqueous acetic acid at 70–75° for 30 min and evaporated to dryness. The resulting syrup was mesylated in the usual manner to give 1.76 g (66.5%) of **10b:** mp 168.5–171°. Recrystallization from chloroform–ethanol gave 1.52 g (57.7%) of pure needles: mp 172–173°; pmr (DMSO-d_6) τ 6.67 and 6.78 (s, 3, OMs), 7.92 and 7.95 (s, 3, OAc).

Anal. Calcd for $C_{12}H_{20}O_{10}S_2$: C, 37.11; H, 5.19; S, 16.51. Found: C, 37.12; H, 5.09; S, 16.74.

Di-*O*-acetyl-(1,3,5/2)-3,5-diacetamido-1,2-cyclohexanediol (Tetra-*N,O*-acetyl-2,4-dideoxystreptamine) (4b), -(1,5/2,3)-3,5-diacetamido-1,2-cyclohexanediol (11), and -(1,2,5/3)-2,5-diacetamido-1,3-cyclohexanediol (12). A mixture of **10a** (0.752 g), sodium azide (0.73 g), and 90% aqueous 2-methoxyethanol (30 ml) refluxed for 20 hr. The reaction mixture was then evaporated to dryness and the residue was treated with a 1:2 mixture (15 ml) of acetic anhydride and pyridine overnight at room temperature. An insoluble material was filtered and washed with acetic anhydride (5 ml) and toluene (5 ml), and the filtrate and washings were combined and evaporated to give a syrupy product, which was purified by passing through a short alumina column with ethyl acetate as an eluent. A solution of the product in ethanol (15 ml) was hydrogenated in Parr shaker apparatus in the presence of Raney nickel T-4[20] under pressure (3.4 kg/cm^2) overnight at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to give a syrupy product, which was treated with a 1:2 mixture (8 ml) of acetic anhydride and pyridine overnight at room temperature. The crystals deposited directly from the reaction mixture were collected by filtration and washed with toluene giving 139 mg (23.8%) of **11:** mp 255–260° dec. Recrystallization from ethanol–ether gave an analytically pure sample: mp 269.5–270°; pmr (DMSO-d_6) τ 1.96 (d, 1, J = 10 Hz, NHAc), 2.20 (d, 1, J = 8 Hz, NHAc).

The residual reaction mixture was concentrated to give a syrup which was dissolved in ethyl acetate (5 ml) and kept in a refrigerator overnight, affording 78 mg (13.4%) of **4b:** mp 223–225° (the slight turbidity of the melt disappeared at 240°). An analytical sample was obtained by two recrystallizations from ethyl acetate–ether: mp 231.5–233°; pmr (DMSO-d_6) τ 2.10 (d, 1, J = 8 Hz, NHAc), 2.16 (d, 1, J = 10 Hz, NHAc).

The mother liquor from **4b** was concentrated to give a syrup, which was dissolved in ether (3 ml) and kept in a refrigerator overnight to afford 74 mg (12.7%) of **12** as granular crystals: mp 126–129.5°. Recrystallization from ethanol–ether gave an analytical sample: mp 190.5–191.5°; pmr (DMSO-d_6) τ 2.17 (d, 1, J = 8.5 Hz, NHAc), 2.29 (d, 1, J = 8 Hz, NHAc), 5.79 (d of d, 1, H-2, J = 4 and 5 Hz, after deuteration).

Di-*O*-acetyl-(1,3,5/4)-3,5-diacetamido-1,4-cyclohexanediol (Tetra-*N,O*-acetyl-4,6-dideoxystreptamine) (7b). A mixture of **10b** (0.61 g), sodium azide (0.64 g), and 90% aqueous 2-methoxyethanol (30 ml) was heated at reflux for 20 hr. The reaction mixture was then evaporated to dryness and the residue was treated with acetic anhydride (5 ml) in pyridine (10 ml) overnight at room temperature, and filtered to remove an insoluble material. The filtrate was evaporated to give a syrup which was dissolved in ethanol (10 ml) and hydrogenated as described above. The product was acetylated in a similar way to give crystals, which were recrystallized from dimethyl sulfoxide–water to afford 200 mg (40.7%) of **7b** as thin needles: mp 300–300.5°; pmr (DMSO-d_6) τ 5.31 (t, 1, H-2, J = 11 Hz), 6.10 (t of d, 2, H-1 and H-3, J = 4.5, 11, and 11 Hz).

***cis*-1,4-Diepoxycyclohexane (14).** This compound was prepared from 1,4-cyclohexadiene according to the directions of Craig, *et al.*[19] Separation of a mixture of the two stereoisomers of 1,4-diepoxycyclohexane thus obtained was effected by use of a silica gel column chromatography with 1:4 2-butanone–toluene as an eluent, giving cis and trans isomers as chromatographically homogeneous crystals in 31.4 and 7.9% yields, respectively, based on 1,4-cyclohexadiene used. The cis diepoxide melted at 58–60° (lit.[19] 60–61°), and the trans one at 92–100° (lit.[19] 106–107°).

6,7-Diazabicyclo[3.2.1]octane-(2*S*,4*R*)-diol ((1,3/4,6)-4,6-Hydrazino-1,3-cyclohexanediol) (15a). A mixture of **14** (1.0 g), anhydrous hydrazine (2.5 ml), and 2-methoxyethanol (60 ml) was refluxed for 4.5 hr. The mixture was evaporated to give a crystalline residue, which was pulverized and washed with ethanol, affording 1.09 g (85%) of **15a** as granular crystals: mp 193–200°. This compound was shown to be pure enough for an elementary analysis. Attempted recrystallization from water–ethanol resulted in decomposition.

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.98; H, 8.39; N, 19.43. Found: C, 49.66; H, 8.23; N, 19.36.

Compound **15a** (0.50 g) was treated with acetic anhydride (5 ml) and pyridine (10 ml) overnight at room temperature. The mixture was evaporated to give a syrup which was crystallized from ethanol–ether affording 1.0 g (93%) of the tetraacetyl derivative **(15c)**: mp 131°; ir (KBr) 1740 (OAc) and 1650 cm^{-1} (NAc).

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.95; H, 6.42; N, 8.98.

Compound **15a** (0.40 g) was treated with acetic anhydride (5 ml) in methanol (40 ml) for 2 days at room temperature. The mixture was evaporated to give a crystalline residue which was pulverized with ethanol–*n*-hexane affording 0.50 g (79%) of the di-*N*-acetyl derivative (**15b**): mp 184–186°. Recrystallization from ethanol gave an analytical sample: mp 185–187°; ir (KBr) 1670 and 1620 cm^{-1} (NAc).

Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.92; H, 7.04; N, 12.22.

Compound **15c** could be transformed into **15b** in the usual way.

(1,3/4,6)-4,6-Diamino-1,3-cyclohexanediol (5a) Dihydrochloride (2,5-Dideoxystreptamine Dihydrochloride). A solution of **15a** (1.2 g) in a 1:1 mixture (40 ml) of ethanol and water containing 12*M* hydrochloric acid (1.2 ml) was hydrogenated in a Parr shaker apparatus in the presence of platinum catalyst (70 mg) under hydrogen stream (3.4 kg/cm^2) for 4.5 hr at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to give a crystalline product, which was pulverized with ethanol and filtered to give 1.6 g (88%) of **5a** dihydrochloride as needles: mp 290–295° dec. An analytical sample was obtained by recrystallization from aqueous ethanol, which showed the same melting behavior and a single spot (R_f 0.21) on paper chromatography (6:4:3:1 1-butanol–pyridine–water–acetic acid).

Anal. Calcd for $C_6H_{14}N_2O_2 \cdot 2HCl$: C, 32.89; H, 7.36; N, 12.79; Cl, 32.36. Found: C, 32.76; H, 7.15; N, 12.41; Cl, 32.04.

(1,3/4,6)-4,6-Diacetamido-1,3-cyclohexanediol (5c). To a suspension of **5a** dihydrochloride (51 mg) in methanol (5 ml) was added Amberlite IRA-410 (OH^-) (*ca.* 1 ml) and the mixture was stirred until it became a clear solution. Acetic anhydride (0.5 ml) was added dropwise to the solution and the reaction mixture was settled at room temperature overnight. The mixture was evaporated and the residue was washed with ethanol to give 28 mg (49%) of **5c**, mp 297.5–301°. Recrystallization from methanol gave an analytical sample, mp 301–302°.

Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.02; H, 7.73; N, 11.90.

Di-*O*-acetyl-(1,3/4,6)-4,6-diacetamido-1,3-cyclohexanediol (Tetra-*N,O*-acetyl-2,5-dideoxystreptamine) (5b). The crude **5c** derived from **5a** dihydrochloride (81 mg) was treated with acetic anhydride (4 ml) and pyridine (6 ml) overnight at room temperature. After being heated at 100° for 30 min, the reaction mixture was filtered to remove unreacted **5c** (20 mg), and the filtrate was evaporated to dryness. The crystalline residue was recrystallized from ethanol–ether to give 51 mg (44% based on consumed **5c**) of **5b** as needles: mp 292–293°; pmr ($CDCl_3$) τ 3.75 (d, 2, J = 9 Hz, 2NHAc), 5.13 (t of d, 2, H-1 and H-3, J = 10.5, 10.5, and 5 Hz), 7.95 (s, 6, 2 OAc), 8.07 (s, 6, 2 NHAc); (DMSO-d_6) τ 5.31 (t of d, 2, H-1 and H-3, J = 11, 11, and 4.5 Hz), 6.11 (broad q of d, 2, H-4 and H-6).

Di-*N*-Carbobenzyloxy-(1,3/4,6)-4,6-diamino-1,3-cyclohexanediol (5d). To a solution of **5a** dihydrochloride (1.7 g) in a 2:1 mixture (60 ml) of acetone and water was added sodium carbonate (3.2 g). Carbobezyloxy chloride (14.3 ml of a 35% toluene solution) was added dropwise to the stirred solution under ice cooling. Stirring was continued overnight in a refrigerator, and then the resulting precipitates were collected and washed with toluene to give 2.65 g (83%) of **5d:** mp 198–199°. Recrystallization from ethanol afforded an analytical sample: mp 201°.

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.75; H, 6.37; N, 6.76. Found: C, 63.46; H, 6.27; N, 6.74.

6,7-Diazabicyclo[3.2.1]oct-6-ene-(2*S*,4*R*)-diol (16a). To a solution of **15a** (0.30 g) in water (5 ml) was added 30% hydrogen peroxide solution (0.65 ml, 3 molar equiv) and the solution was kept for 3 days at room temperature, at which time **15a** was shown to be completely converted into the faster moving component by tlc (5:1 2-butanone–toluene). An excess amount of hydrogen peroxide was destroyed by adding a small amount of Raney nickel and the mixture was filtered and evaporated to give a crystalline residue, which was pulverized with ethanol–ether giving 0.17 g (57%) of **16a,** mp 133–138°. Recrystallization from ethanol–ether afforded an analytical sample: mp 140–145°; uv_{max} (H_2O) 336 nm (ϵ 178).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.30; H, 6.99; N, 20.06.

Compound **16a** (60 mg) was treated with acetic anhydride (1 ml) in pyridine (5 ml) overnight at room temperature, and then the mixture was evaporated to give a syrup which crystallized upon addition of ethanol to give 57 mg (60%) of the diacetyl derivative (**16b**) as needles: mp 103–104°; uv_{max} (CH_3OH) 344 nm (ϵ 238).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.39. Found: C, 52.97; H, 6.18; N, 12.96.

This compound was also obtained from the decomposed **15a** by the usual acetylation.

2,3-Di-*O*-acetyl-1,4-di-*O*-mesyl-1,2,3/4-cyclohexanetetrol (17). A mixture of 2,3-*O*-cyclohexylidene-1,4-di-*O*-mesyl-1,2,3/4-cyclohexanetetrol[24] (4.93 g) and 80% aqueous acetic acid (100 ml) refluxed for 30 min, and the mixture was then evaporated to dryness and the residue was treated with acetic anhydride (15 ml) and pyridine (25 ml) overnight at room temperature. The reaction mixture was poured into ice–water (400 ml) and the resulting precipitate was collected by filtration, giving 3.57 g (72%) of **17** as needles: mp 152–153.5°; pmr ($CDCl_3$) τ 4.33 (t, 1, H-2, J = 2.5 Hz), 6.97 (s, 6, 2 OMs), 7.83 and 7.95 (s, 3, OAc).

Anal. Calcd for $C_{12}H_{20}O_{10}S_2$: C, 37.10; H, 5.20; S, 16.51. Found: C, 37.43; H, 5.12; S, 16.21.

1,4-Di-*O*-mesyl-1,4/2,3-cyclohexanetetrol (19). A mixture of 2,3-*O*-cyclohexylidene-1,4-di-*O*-mesyl-1,4/2,3-cyclohexanetetrol[24] (2.5 g) and 80% aqueous acetic acid (50 ml) was refluxed for 20 min. The reaction mixture was then evaporated to dryness and the residue was crystallized from ethanol to give 0.99 g (50%) of **19** as needles: mp 129–130°. The recrystallized sample melted at 131–132°.

Anal. Calcd for $C_8H_{16}O_8S_2$: C, 31.78; H, 4.66; S, 21.21. Found: C, 31.79; H, 4.88; S, 21.00.

Di-*O*-acetyl-(1,3/2,4)-2,4-diacetamido-1,3-cyclohexanediol (Tetra-*N,O*-acetyl-4,5-dideoxystreptamine) (6b). (a) A mixture of **17** (1.0 g), sodium azide (1.0 g), and 90% aqueous 2-methoxyethanol (40 ml) refluxed for 19 hr. The reaction mixture was treated according to the procedure described before for azidolysis of **10a.** The syrupy product was crystallized from ethanol–ether to give 21 mg (2.9%) of **6b:** mp 240°. An analytical sample was obtained by recrystallization from chloroform: mp 274–275.5°.

(b) A mixture of **19** (0.40 g), anhydrous hydrazine (0.5 ml), and 2-methoxyethanol (30 ml) was refluxed for 90 min. The reaction mixture was evaporated to dryness, and the syrupy residue was dissolved in water (12 ml) and treated with Amberlite IRA-410 (OH^-). The solution was hydrogenated as described above for **15a** and the product was acetylated in the usual manner to afford 188 mg (46%) of **6b:** mp 274–275.5°; pmr (DMSO-d_6) τ 2.24 (d, 2, J = 9 Hz, 2 NHAc), 5.25 (t, 1, H-3, J = 10.5 Hz), 6.08 (q, 1, H-2, J 10.5 Hz).

Acknowledgment. The authors wish to thank Professor K. L. Rinehart, Jr., for his interest and suggestion during this work.

Registry No.—**4b,** 53534-82-0; **5a** 2HCl, 53534-83-1; **5b,** 53534-84-2; **5c,** 53534-85-3; **5d,** 53534-86-4; **6b,** 53534-87-5; **7b,** 53585-07-2; **8,** 53585-08-3; **9a,** 53534-88-6; **9b,** 53534-89-7; **10a,** 53586-53-1; **10b,** 53534-90-0; **11,** 53585-09-4; **12,** 53534-91-1; **14** (cis), 16063-08-4; **14** (trans), 16063-09-5; **15a,** 53534-92-2; **15b,** 53534-93-3; **15c,** 53534-94-4; **16a,** 53534-95-5; **16b,** 53534-96-6; **17,** 53534-97-7; **19,** 53534-98-8; 2,3-*O*-cyclohexylidene-1,4-di-*O*-mesyl-1,2,3/4-cyclohexanetetrol, 53534-99-9; 2,3-*O*-cyclohexylidene-1,4-di-*O*-mesyl-1,4/2,3-cyclohexanetetrol, 53585-10-7.

References and Notes

(1) For paper 30 of this series, see T. Suami, K. Tadano, S. Nishiyama, and F. W. Lichtenthaler, *J. Org. Chem.*, **38,** 3691 (1973). Presented in part at the 28th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1, 1973 (abstracts of papers of the meeting, Vol. III, p 1316). In this paper, all the compounds except for meso compounds are racemic. All the formulas depict only one enantiomer of the respective racemates.

(2) W. T. Shier, K. L. Rinehart, Jr., and D. Gottlieb, *Proc. Nat. Acad. Sci. U.S.*, **63,** 198 (1969); *J. Antibiot.*, **23,** 51 (1970).

(3) R. L. Peck, R. P. Graber, A. Walti, E. W. Peel, C. E. Hoffhine, Jr., and K. Folkers, *J. Amer. Chem. Soc.*, **68,** 29 (1946).

(4) T. Suami, S. Ogawa, S. Naito, and H. Sano, *J. Org. Chem.*, **33,** 2831 (1968).

(5) W. T. Shier, S. Ogawa, M. Hichens, and K. L. Rinehart, Jr., *J. Antibiot.*, **26,** 551 (1973).

(6) M. Kojima and A. Satoh, *J. Antibiot.*, **26,** 784 (1973).

(7) S. A. Waksman and H. A. Lechevalier, *Science*, **109,** 305 (1949); K. L. Rinehart, Jr., "The Neomycins and Related Antibiotics," Wiley, New York, N.Y., 1964.

(8) R. P. Frohardt, T. H. Haskell, J. Ehrlich, and M. P. Knudsen, Belgian Patent 547976 (1956); *Chem. Zbl.*, **129,** 14128 (1958).

(9) T. Shomura, N. Ezaki, and T. Niida, *J. Antibiot.*, **23,** 175 (1970).

(10) H. Umezawa, M. Ueda, K. Maeda, K. Yagishita, S. Kondo, Y. Okami, R. Utahara, Y. Osato, K. Nitta, and T. Takeuchi, *J. Antibiot., Ser. A,* **10,** 181 (1957).

(11) In this paper, according to IUPAC tentative rules for cyclitol nomenclature (*J. Biol. Chem.*, **243,** 5809 (1968)), the diaminodiols were named as the stereoisomers of diaminocyclohexanediol of which the relative configurations were described by means of fractions (positional numbers). For convenience, since they could be regarded as the dideoxy derivatives of streptamine, this generic name was also used retaining its original numbering.

(12) (a) Y. Nishimura, T. Tsuchiya, and S. Umezawa, *Bull. Chem. Soc. Jap.*, **46,** 1263 (1973), and references cited therein; (b) A. Hasegawa, D. Nishimura, T. Kurokawa, and M. Nakajima, *Agr. Biol. Chem.*, **36,** 1773 (1972); (c) R. U. Lemieux, T. L. Nagabhushan, K. J. Clemetson, and L. C. N. Tucker, *Can. J. Chem.*, **51,** 53 (1973).

(13) G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **76,** 2373 (1954).

(14) G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **29,** 2354 (1964).

(15) F. W. Lichtenthaler and P. Emig, *Carbohyd. Res.*, **7,** 121 (1968); F. W. Lichtenthaler, G. Bambach, and P. Emig, *Chem. Ber.*, **102,** 994 (1969).

(16) T. Suami, S. Ogawa, S. Yanagida, and K. Nojima, *Bull. Chem. Soc. Jap.*, **45,** 2593 (1972).

(17) T. Suami, S. Ogawa, H. Uchino, and M. Uchida, *Bull. Chem. Soc. Jap.*, **46,** 3840 (1973).

(18) Reaction of **14** with various mono functional nucleophiles such as alkyl and dialkyl amines, and sodium benzyl mercaptide, had been studied. However, disubstituted cyclohexanediol with 1,3/4,6-configuration has never been obtained previously; *cf.* G. E. McCasland, A. K. M. Anisuzzman, S. R. Naik, and L. J. Durham, *J. Org. Chem.*, **37,** 1201 (1973).

(19) T. W. Craig, G. R. Harvey, and G. A. Berchtold, *J. Org. Chem.*, **32,** 3745 (1967).

(20) S. Nishimura, *Bull. Chem. Soc. Jap.*, **32,** 61 (1959).

(21) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 183–191.

(22) S. G. Cohen, R. Zand, and C. Steel, *J. Amer. Chem. Soc.*, **83,** 2895 (1961).

(23) T. Suami, S. Ogawa, S. Oki, and K. Ohashi, *Bull. Chem. Soc. Jap.*, **45,** 2597 (1972).

(24) T. Suami, S. Ogawa, and Y. Funaki, submitted for publication in *Bull. Chem. Soc. Jap.*

(25) Unless otherwise noted, melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. Solutions were evaporated under diminished pressure at 40–50°. Ir spectra were determined for potassium bromide disks with a JASCO IR-E spectrophotometer. Pmr spectra were measured at 60 MHz on a Varian A-60D spectrometer in deuteriochloroform ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) with reference to tetramethylsilane as an internal standard and the peak positions are given in τ values. Values given for coupling constants are first order. Tlc was performed on silica gel plates (Wakogel B-10) with a mixture of 2-butanone and toluene as solvent system. Elemental analyses were performed by Mr. S. Nakada, to whom our thanks are due.

Syntheses of Methyl *dl*-Jasmonate and Methyl *dl*-2-Epijasmonate

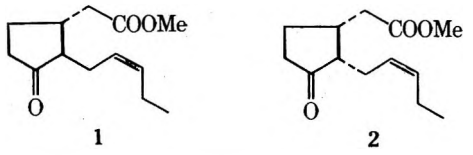
Hideo Tanaka and Sigeru Torii*

Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama, Japan 700

Received September 3, 1974

Syntheses of methyl *dl*-jasmonate (**1**) and methyl *dl*-2-epijasmonate (**2**) from 3a,7a-*cis*-3a,4,7,7a-tetrahydro-1-indanone (**3a**) are described. Efficient construction of the carbomethoxymethyl and *cis*-pentenyl moieties could be achieved by developing a successful method for a key step, the partial oxidation of aldehyde hemiacetal **6**, prepared from **3a**, to acid hemiacetal **7a**. The methyl ester of **7a** was converted to both **1** and **2** by different routes *via* the thioacetals **8b** and **11**, respectively.

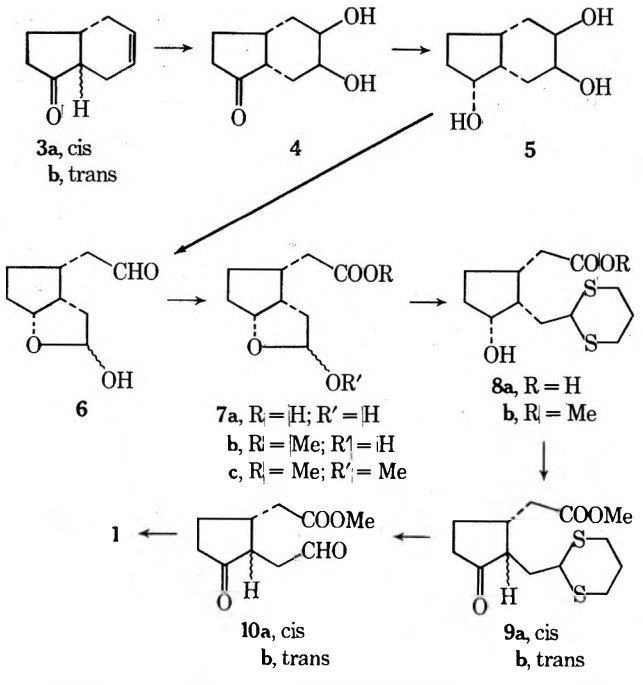
Methyl jasmonate[1] and related compounds[2] have been of interest as synthetic targets because of their use in the perfumery industry and as new members among the plant hormones. Indeed, much attention have been paid to the preparation of methyl *dl*-jasmonate (**1**) in recent years.[3] We now report syntheses of methyl *dl*-jasmonate (**1**) and methyl *dl*-2-epijasmonate (**2**), which involve efficient construction of the carbomethoxymethyl and *cis*-pentenyl moieties and include as a key step the partial oxidation of aldehyde hemiacetal **6**. In order to satisfy the stereochemical requirement for the formation of **6** we chose 1,7a-*cis*-3a,7a-*cis*-1,5,6-trihydroxyperhydroindan (**5**) as a starting material, which could be provided from 3a,7a-*cis*-3a,4,7,7a-tetrahydro-1-indanone (**3a**).[4]



1 **2**

The synthetic pathway leading to methyl *dl*-jasmonate is outlined in Scheme I. Interesting questions with regard to the scheme were whether oxidative fission of triol **5** would provide **6** and whether the formyl group of **6** could be oxidized selectively to the acid hemiacetal **7a**.

Scheme I



Oxidation of **3a** with $KMnO_4$–$MgSO_4$[5] in methanol at −40° afforded the diol **4** as white crystals in 69% yield. Stereoselective reduction of **4** was achieved by the treatment with sodium borohydride in ethanol to give **5** in good yield. The structure assignment could be established by conversion of **5** into the δ-lactone **11** and the γ-lactone **16**, respectively.

Treatment of **5** with sodium metaperiodate[6] at 2° gave the aldehyde **6** in 98% yield. The structure assignment of **6** was corroborated by the following spectral data.[7] The ir spectrum exhibited a broad band at 3320 (OH) and characteristic streching bands at 2723 (aldehyde, ν_{CH}) and 1724 cm^{-1} (C=O). The nmr spectrum in $CDCl_3$ showed δ 3.73 (1 H, OH), 4.82 (1 H, CHO), 5.51 (1 H, OCHO), and 9.75 (1 H, CHO).

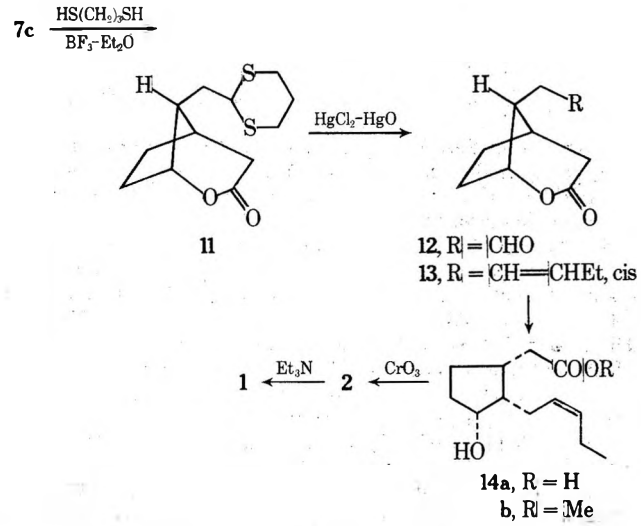
Under carefully controlled reaction conditions, oxidation of **6** with $KMnO_4$–$MgSO_4$ in aqueous acetone at 2° and subsequent esterification with diazomethane afforded the hemiacetal ester **7b** (60%) along with the dimer **17b** (10%)[8] and the lactone **16b** (10%). Without further purification the crude product was refluxed in dry methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid. Separation of the product by column chromatography over silica gel gave **7c** (65% yield based on **6**) and **16b** (10%). The nmr spectrum of **7c** showed the presence of two singlets due to a methoxy group at δ 3.27 (acetal) and 3.64 (ester), respectively. The acetal ester **7c** was converted in two steps, by thioacetalization to **8b** and by a slight modification of the Corey's oxidation method,[9] to the keto ester **9a** in 64% yield. Epimerization of **9a** was carried out by heating in triethylamine in a sealed tube at 130° to give **9b** in quantitative yield. Hydrolysis of **9b** with $HgCl_2$–HgO in aqueous acetonitrile[10] gave **10b** in 90% yield. The Wittig reaction of **10b** with salt-free *n*-propylidenetriphenylphosphorane[11] afforded **1** in 88% yield.

In the course of the thioacetalization of **7c** the presence of a catalytic amount of water facilitated formation of the thioacetal δ-lactone **11** (80% yield) rather than **8**. Hydrolysis of **11** with aqueous methanolic potassium hydroxide and subsequent esterification with diazomethane yielded **8** in 85% yield.

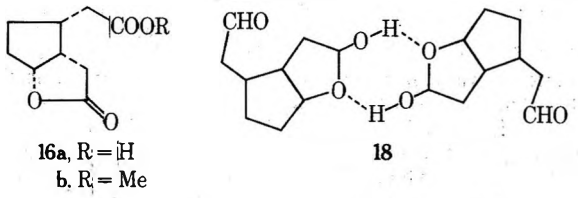
The second approach from **11** as shown in Scheme II also led to **1** *via* **2**. The conversion was accomplished as follows: hydrolysis of **11** to **12** and subsequent Wittig reaction afforded **13**, which on hydrolysis and esterification with diazomethane yielded **14b**.[12] Subsequent oxidation with chromic acid gave **2** in 61% overall yield. Epimerization of **2** to **1** proceeded smoothly on treatment with triethylamine in a sealed tube at 130°. Another route to methyl *dl*-2-epijasmonate (**2**) involved **10a**, prepared in 95% yield by hydrolysis of the thioacetal **9a** with $HgCl_2$–HgO in aqueous acetonitrile. Wittig reaction of **10a** with the salt-free phosphorane afforded **2** in good yield.

Normally one would expect that in the formation of **7a** from **6** the hemiacetal function should be protected from the action of oxidation reagents. Thus, oxidation of **6** with

Scheme II



chromic acid[13] followed by esterification gave the γ-lactone ester **16b** in quantitative yield. In contrast, runs using $KMnO_4$–$MgSO_4$ at 2° exhibit nearly exclusive selectivity for the oxidation of the formyl group. The reason for this behavior may be the presence of the dimeric form **18** and/



or hydrogen bonding to the acetone solvent *in situ*, which results in resistance to oxidation of the hemiacetal function.[14]

Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were determined with Hitachi R-24 and R-20 instruments. Ir spectra were recorded on a Hitachi EPI-S2, only major absorptions being cited. Mass spectral analyses were carried out on Hitachi RMS-4 and JEOL JMS-OISG mass spectrometers at 70 eV, with molecular and major fragment ions being cited: *m/e* (relative intensity). Column chromatography was carried out using Wako gel C-200 (silica gel) with benzene–AcOEt (20:1) as the developing solvent. Elemental analyses were performed by Mr. Tsutomu Okamoto of our laboratory. Anhydrous sodium sulfate was used for all drying operations.

3a,7a-*cis*-5,6-Dihydroxyperhydro-1-indanone (4). To a stirred EtOH solution (75 ml) of 3a,7a-*cis*-3a,4,7,7a-tetrahydro-1-indanone (**3a**)[4] (3.60 g, 26.5 mmol) a solution of $KMnO_4$ (3.98 g, 25.2 mmol) and $MgSO_4$ (2.98 g, 24.8 mmol) in water (95 ml) was added over 2 hr at −45 to −40°. After the addition was completed, the reaction mixture was stirred for 2 hr and for an additional 1 hr at room temperature and then filtered. The precipitate was washed several times with hot water. The combined filtrates were concentrated to *ca.* 10 ml using a rotary evaporator. The aqueous solution was extracted several times with AcOEt and the extracts were dried and concentrated. The residue was chromatographed (CH_2Cl_2–AcOEt, 1:1) to give 3.1 g (69%) of **4**: white crystals; mp 122–123°; ir (Nujol) 3375, 3280 (OH), and 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.90 (m, 1 H, HCO), 3.45 (m, 1 H, HCO), 3.20 (s, 2 H, OH), and 3.00–1.50 (m, 10 H); mass spectrum 170 (M^+).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.57; H, 8.22.

3a,7a-*cis*-1,7a-*cis*-1,5,6-Trihydroxyperhydroindan (5). A mixture of **4** (2.00 g, 11.75 mmol) and $NaBH_4$ (1.05 g, 27.85 mmol) in EtOH (200 ml) was stirred for 12 hr at room temperature. The reaction mixture was cooled with an ice–water bath and 34 ml of AcOH was added. After stirring for additional 0.5 hr, the mixture was evaporated to dryness and the residue was extracted ten times with hot AcOEt. Evaporation of the solvent afforded a white solid, whose recrystallization from AcOEt gave 1.72 g (84.9%) of **5**: white crystals; mp 160.5–161.0°; ir (neat) 3300 cm^{-1} (OH).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.83; H, 9.57.

1,5-*cis*-5,6-*cis*-6-Formylmethyl-3-hydroxy-2-oxabicyclo-[3.3.0]octane (6). A solution of **5** (300 mg, 1.74 mmol) and sodium metaperiodate (375 mg, 1.75 mmol) in water (90 ml) was stirred for 7 hr at 2° under nitrogen. The aqueous solution was extracted with $CHCl_3$, washed with water, dried, and concentrated to give 295 mg of **6**: ir (neat) 3320 (OH), 2723 (CHO), and 1724 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.21–3.37 (10 H), 3.73 (br s, 1 H, OH), 4.82 (m, 1 H, CHO), 5.51 (d, J = 3.6 Hz, OCHO), and 9.75 (m, 1 H, CHO). The product **6** was homogeneous in tlc [Merck PF 254, R_f 0.32 (benzene–acetone–*n*-hexane, 2:1:1)]; however, **6** is hygroscopic and was used in the following experiment without further purification. To a stirred acetone (60 ml) solution of **6** (300 mg, 1.76 mmol) a solution of $KMnO_4$ (279 mg, 1.75 mmol) and $MgSO_4$ (209 mg, 1.73 mmol) in water (6 ml) was added dropwise for 1 hr at 2–3°. After addition was completed, the mixture was stirred for 9 hr at 2–3°, and then 2-propanol (30 ml) was added. The mixture was stirred for 10 hr at 2–3° and for additional 5 hr at room temperature. The mixture was filtered and the precipitate was washed with hot water (3 ml). The combined filtrate and washings were concentrated to 3 ml and washed with $CHCl_3$. The aqueous solution was acidified with diluted HCl and extracted with $CHCl_3$. The extracts were dried. Removal of the solvent under reduced pressure gave 265 mg of an oil. Without further purification, the crude oil was treated with diazomethane to give 280 mg of products. Preparative tlc analysis of the liquid products indicated the following compounds to be present [R_f values, AcOEt–benzene (1:3); yields based on **6**]: **7b** (0.15, *ca.* 60%), **16b** (0.47, *ca.* 10%), and **17b** (0.55, *ca.* 10%). The physical and spectral data together with elemental analyses are as follows.

Compound **7b**: bp 65–68° (0.03 mm); ir (neat) 3425 (OH) and 1738 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.27–3.22 (10 H), 3.49 (br, 1H, OH), 3.67 (s, 3 H, CH_3O), 4.71 (m, 1 H, CHO), and 5.55 (d, J = 4.5 Hz, 1 H, OCHO).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.28; H, 8.18.

Compound **16b**: bp 82–85° (0.02 mm); ir (neat) 1775 (lactone C=O) and 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.60–3.20 (10 H), 3.69 (s, 3 H, CH_3O), and 5.05 (m, 1 H, CHO); mass spectrum 198 (M^+, 2), 180 (10), 166 (52), 152 (55), 149 (50), 138 (50), 125 (58), 96 (100), 81 (63), 74 (68), 67 (50), 55 (55), and 41 (63).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.80; H, 7.14.

Compound **17b**: mp 94.5–95.0°; ir (Nujol) 1739 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.13–3.20 (20 H), 3.67 (s, 6 H, CH_3O), 4.52 (m, 2 H, CHO), and 5.35 (d, J = 4.2 Hz, 2 H, OCHO); mass spectrum (15 eV) 199 [(M^+ + O)/2,2], 183 [(M^+ − O)/2, 99], 182 [(M^+ − O)/2 − H, 34], 151 (60), 150 (22), 139 (10), 123 (17), 122 (20), 109 (18), 108 (36), 95 (26), 94 (48), 82 (100), 81 (89), 68 (31), and 59 (25).

Anal. Calcd for $C_{20}H_{30}O_7$: C, 63.16; H, 8.10. Found: C, 63.42; H, 8.13.

1,5-*cis*-5,6-*cis*-6-Carbomethoxymethyl-3-methoxy-2-oxabicyclo[3.3.0]octane (7c). A solution of **7b** (170 mg, 0.85 mmol) and *p*-toluenesulfonic acid (3 mg) in MeOH (10 ml) was refluxed for 30 min. After distillation of most of the solvent fresh MeOH (30 ml) was added slowly during 2 hr under heating. When the addition was completed, the mixture was refluxed and then diluted cautiously with benzene (10 ml). The mixture was distilled slowly to a small volume (*ca.* 5–10 ml) under atomospheric pressure. The residue was taken up in ether (10 ml) and washed with aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed to give 173 mg (95%) of **7c**: ir (neat) 1739 cm^{-1}; nmr ($CDCl_3$) δ 1.30–2.50 (10 H), 3.27 (s, 3 H, CH_3O), 3.64 (s, 3 H, CH_3O), 4.53 (m, 1 H, CHO), and 4.55 (d, J = 4.2 Hz, 1 H, OCHO); mass spectrum 199 (M^+ − Me, 5), 181 (M^+ − MeO, 18), 182 (M^+ − MeOH, 48), 151 (51), 139 (11), 122 (46), 108 (58), 94 (83), 82 (90), 81 (100), 71 (60), 68 (59), 59 (58), 53 (49), and 41 (58).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.62; H, 8.42.

In the similar manner, the acetalization of **17b** with MeOH gave **7c** in almost quantitative yield.

Preparation of Thioacetals (8b and 11). To a stirred dry $CHCl_3$ solution (2 ml) of boron trifluoride etherate (251 mg, 1.80 mmol) a solution of **7c** (180 mg, 0.84 mmol) and 1,3-propanedithiol (92 mg, 0.85 mmol) in dry $CHCl_3$ (1 ml) was added dropwise at 2°. After stirring for 12 hr at room temperature the mixture was poured into ice–water and extracted with $CHCl_3$. The extracts were washed with aqueous $NaHCO_3$ and with water, dried, and

concentrated. The residue was chromatographed to give 187 mg (80%) of **8b** together with 15 mg (7%) of **11**.

In this reaction, when an excess amount of boron trifluoride etherate and commercial $CHCl_3$ (without drying operation) were employed, **11** was obtained in 80% yield together with a trace of **8b**.

Compound **8b** boiled at 112–114° (0.01 mm): ir (neat) 3485 and 1725 cm^{-1}; nmr ($CDCl_3$) δ 1.40–2.33 (10 H), 2.17 (s, 1 H, OH), 2.45 (br s, 2 H, CH_2CO), 2.87 (m, 4 H, CH_2S), 3.64 (s, 3 H, CH_3O), 4.10 (t, J = 6.6 Hz, SCHS), and 4.27 (m, 1 H, CHO); mass spectrum 290 (M^+, 8), 272 (1), 258 (3), 230 (1), 225 (1), 198 (4), 183 (19), 171 (2), 165 (4), 151 (43), 139 (10), 132 (74), 119 (100), 108 (33), 94 (20), 81 (56), 74 (39), 68 (21), 59 (26), and 41 (85).

Anal. Calcd for $C_{13}H_{22}O_3S_2$: C, 53.78: H, 7.64. Found: C, 53.64; H, 7.60.

Compound **11** melted at 105.2–105.5°: ir (Nujol) 1723 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.53–2.73 (12 H), 2.81 (m, 4 H, CH_2S), 4.10 (t, J = 8.4 Hz, 1 H, SCHS), and 4,63 (m, 1 H, CHO); mass spectrum 258 (M^+, 26), 230 (8), 211 (3), 198 (3), 186 (4), 156 (11), 132 (100), 119 (96), 106 (34), 74 (26), 67 (17), 55 (14), and 41 (44).

Anal. Calcd for $C_{12}H_{18}O_2S_2$: C, 55.78; H, 7.02. Found: C, 55.80; H, 6.88.

2,3-*cis*-3-Carbomethoxymethyl-2-(1′,3′-dithianyl-2′)methylcyclopentan-1-one (9a). To a stirred solution of *N*-chlorosuccinimide (100 mg, 0.74 mmol) in toluene (5 ml) was added at 0° methyl sulfide (1 ml) under nitrogen. The mixture was cooled to −25° and a solution of **8b** (60 mg, 0.21 mmol) in toluene (1 ml) was added dropwise. Stirring was continued for 3 hr at −25°, and then triethylamine (78 mg, 0.77 mmol) was added. The cooling bath was removed and after 5 min, ether was added. The organic layer was washed with 5% HCl and with water, dried, and concentrated. The residue was chromatographed to give 45 mg (76%) of **9a**: bp 107–110° (0.01 mm) (bath temperature); ir (neat) 1741 (shoulder) and 1734 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.36–2.96 (16 H), 3.71 (s, 3 H, CH_3O), and 4.16 (t, J = 7.2 Hz, 1 H, SCHS); mass spectrum 288 (M^+, 9), 257 (4), 215 (1), 182 (1), 134 (38), 133 (62), 132 (100), 119 (58), 106 (10), 97 (15), 85 (11), 83 (21), and 41 (31).

Anal. Calcd for $C_{13}H_{20}O_3S_2$: C, 54.16; H, 6.99. Found: C, 54.12; H, 7.00.

Epimerization of 9a. A solution of **9a** (24 mg, 0.08 mmol) in triethylamine (1 ml) was heated for 20 hr at 135–140° in a sealed tube. After removal of the solvent, distillation of the residue gave 23 mg (96%) of **9b**: bp 115–120° (0.02 mm) (bath temperature); ir (neat) 1737 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.48–2.95 (16 H), 3.70 (s, 3 H, CH_3O), and 4.28 (t, J = 7.2 Hz, 1 H, SCHS); mass spectrum 288 (M^+, 10), 257 (4), 215 (2), 182 (2), 134 (44), 133 (66), 132 (100), 119 (61), 106 (10), 97 (15), 86 (50), 84 (60), and 41 (38).

Anal. Calcd for $C_{13}H_{20}O_3S_2$: C, 54.16; H, 6.99. Found: C, 54.05; H, 7.06.

2,3-*trans*-3-Carbomethoxymethyl-2-formylmethyl-1-cyclopentanone (10b). To a stirred suspension of $HgCl_2$ (43 mg, 0.16 mmol) and HgO (17 mg, 0.08 mmol) in aqueous 80% MeCN (2 ml) a solution of **9b** (21 mg, 0.07 mmol) in aqueous 80% MeCN (2 ml) was added under nitrogen. The mixture was refluxed for 4 hr with stirring. After cooling the mixture was filtered and the precipitate was washed with CH_2Cl_2–*n*-hexane (1:1). The combined filtrates were washed with aqueous $AcONH_4$ and water, dried, and concentrated. The residue was chromatographed to give 13 mg (90%) of **10b**: bp 64–67° (0.04 mm) (bath temperature); ir (neat) 2775 (CHO), 1745, 1730, and 1722 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.35–2.90 (10 H), 3.67 (s, 3 H, CH_3O), and 9.71 (s, 1 H, CHO).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.62; H, 7.08.

Methyl *dl*-Jasmonate (1). To a stirred solution of **10** (8 mg, 0.04 mmol) a salt-free benzene solution (2 ml) of *n*-propylidenetriphenylphosphorane prepared from *n*-propyltriphenylphosphonium bromide (100 mg, 0.25 mmol) by the reported method[11] was added. After stirring for 10 hr at room temperature the reaction mixture was evaporated to a small volume and the residue was extracted several times with *n*-hexane. The extracts were concentrated and the residue was chromatographed to give 8 mg (88%) of **1**: bp 120–125° (7 mm) [lit.[3a] bp 81–84° (0.001 mm)]; ir (neat) 3000 (HC=C), 1741 (C=O), and 1650 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3 H, CH_3C), 1.45–2.90 (12 H), 3.69 (s, 3 H, CH_3O), 5.27 (d, J = 6 Hz, 1 H, HC=C), and 5.45 (d, J = 6 Hz, HC=C). Ir, nmr, and mass spectral data were identical with those of methyl *dl*-jasmonate reported in the literature.[3a,b]

8-*syn*-Formylmethyl-2-oxabicyclo[3.2.1]octan-3-one (12). To a stirred suspension of $HgCl_2$ (238 mg, 0.88 mmol) and HgO (95 mg, 0.44 mmol) in aqueous 80% MeCN (2 ml) a solution of **11** (100 mg, 0.39 mmol) in aqueous 80% MeCN (4 ml) was added. The mixture was refluxed for 4 hr. After work-up in the usual manner, there was obtained 62 mg (96%) of **12**: bp 115–125° (0.03 mm) (bath temperature); ir (neat) 2725 (CHO), 1747, 1735, and 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.60–3.06 (10 H), 4.68 (m, 1 H, CHO), and 9.88 (s, 1 H, CHO).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.47.

8-*syn*-(2-*cis*-Pentenyl)-2-oxabicyclo[3.2.1]octan-3-one (13). To a stirred solution of **12** (45 mg, 0.27 mmol) in benzene (0.5 ml) a salt-free benzene solution (2 ml) of *n*-propylidenetriphenylphosphorane prepared from *n*-propyltriphenylphosphonium bromide (200 mg, 0.52 mmol) was added under nitrogen and the mixture was stirred for 12 hr at room temperature. After work-up in the usual manner, there was obtained 44 mg (85%) of **13**: ir (neat 3000 (HC=C), 1738 (C=O), and 1651 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 3 H, CH_3C), 1.52–2.75 (12 H), 4.59 (m, 1 H, CHO), and 5.13–5.73 (m, 2 H, HC=C); mass spectrum (80 eV) 194 (M^+, 3), 176 (1), 162 (3), 151 (3), 134 (82), 125 (23), 119 (36), 105 (26), 93 (41), 81 (49), 79 (72), 68 (100), 67 (75), 55 (59), and 41 (89).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.38; H, 9.36.

1,2-*cis*-2,3-*cis*-3-Carbomethoxymethyl-2-(*cis*-2-pentenyl)-cyclopentan-1-ol (14b). A solution of 13 (45 mg, 0.27 mmol) and KOH (100 mg, 1.8 mmol) in MeOH (1 ml) containing a few drops of water was stirred for 12 hr at room temperature. The reaction solution was diluted with 3 ml of water and concentrated to a small volume with a rotary evaporator. The aqueous solution was acidified to pH 3–4 with diluted H_2SO_4, extracted with $CHCl_3$, washed with water, and dried. Evaporation of the solvent gave 34 mg of **14a**: ir (neat) 3700–2350 (COOH) and 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.98 (t, J = 7.2 Hz, 3 H, CH_3C), 1.50–2.72 (12 H), 4.22 (m, 1 H, CHO), 5.11–5.68 (m, 2 H, HC=C), and 6.33 (br s, 2 H, OH). Without further purification, the crude carboxylic acid **14a** was treated with diazomethane followed by column chromatography to give 35 mg (92%) of **14b**: bp 75–80° (0.01 mm) (bath temperature); ir (neat) 3500 (OH), 3000 (HC=C), 1734 (C=O), and 1654 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.97 (t, J = 7.2 Hz, CH_3C), 1.49–2.57 (12 H), 1.60 (s, 1 H, OH), 3.65 (s, 3 H, CH_3O), 4.20 (m, 1 H, CHO), and 5.09–5.70 (m, 2 H, HC=C); mass spectrum 208 ($M^+ - H_2O$, 19), 193 (2), 176 (9), 165 (30), 152 (64), 148 (27), 139 (64), 134 (100), 119 (85), 107 (74), 105 (80), 95 (67), 93 (81), 91 (63), 83 (56), 81 (57), 79 (88), 67 (73), 55 (84), and 41 (85).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.97; H, 9.70.

Methyl *dl*-2-Epijasmonate (2). To a stirred CH_2Cl_2 solution (3 ml) of **14b** (12.5 mg, 0.59 mmol) Jones reagent (0.2 ml) prepared from $Na_2Cr_2O_7$ (40 mg) and concentrated H_2SO_4 (50 mg) was added under cooling with an ice bath. After stirring for 10 min the ice bath was removed and the mixture was stirred for 5 hr at room temperature. The organic phase was separated, washed with aqueous $NaHCO_3$ followed with brine, dried, and concentrated. The residue was chromatographed to give 10 mg (81%) of **2**: bp 120–125° (7 mm) (bath temperature); ir (neat) 3000 (HC=C), 1742 (C=O), and 1654 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3 H, CH_3C), 1.60–2.99 (12 H), 3.69 (s, 3 H, CH_3O), and 5.07–5.71 (m, 2 H, HC=C); mass spectrum (80 eV) 224 (M^+, 26), 206 (10), 193 (9), 177 (7), 167 (3), 165 (2), 156 (20), 151 (46), 133 (15), 121 (13), 109 (32), 95 (64), 83 (100), 67 (50), 55 (52), and 41 (75).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.53; H, 9.05.

Epimerization of 2. A solution of **2** (10 mg, 0.045 mmol) in triethylamine (0.5 ml) was heated in a sealed tube for 6 hr at 130°. Evaporation of the solvent followed by distillation gave 9.5 mg of **1** (95%). Ir and nmr spectral data were identical with those of an authentic sample. The compound **1** boiled at 57–59° (0.025 mm).

2,3-*cis*-3-Carbomethoxymethyl-2-formylmethyl-1-cyclopentanone (10a). To a stirred suspension of $HgCl_2$ (65 mg, 0.24 mmol) and HgO (28 mg, 0.13 mmol) in aqueous 80% MeCN (1 ml) a solution of **9a** (32 mg, 0.11 mmol) in aqueous 80% MeCN was added. After refluxing for 3.5 hr the mixture was worked up in the usual manner to give 21 mg of **10a**: bp 67–69° (0.04 mm); ir (neat) 2720 (CHO) and 1738 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.42–3.25 (10 H), 3.68 (s, 3 H, CH_3O), and 9.77 (m, 1 H, CHO).

Anal. Calcd for $C_9H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.61; H, 7.03.

Wittig Reaction of 10a. To a stirred solution of **10a** (21 mg, 0.106 mmol) in benzene (0.5 ml) a benzene solution of salt-free *n*-propylidenetriphenylphosphorane prepared from *n*-propyltriphenylphosphonium bromide (200 mg, 0.52 mmol) was added under nitrogen and the mixture was stirred for 15 hr at room tem-

perature. The mixture was worked up in the usual manner to give 17 mg of **2** (72%), whose ir and nmr spectral data were identical with those of **2** obtained in the preceding experiment.

Hydrolysis of δ-Lactone 11. A solution of **11** (46 mg, 0.18 mmol) and KOH (100 mg) in MeOH (0.5 ml) containing a few drops of water was stirred for 6 hr at room temperature. The mixture was diluted with 5 ml of water and washed with $CHCl_3$. The aqueous solution was acidified with diluted HCl and extracted with $CHCl_3$. The extracts were washed with water and dried. Removal of the solvent gave 42 mg of **8a** as white crystals: mp 119.5–120.0°; ir (Nujol) 3525 (OH), 3350–2200 (COOH), and 1687 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{20}O_3S_2$: C, 52.17; H, 7.30. Found: C, 52.31; H, 7.10.

Treatment of **8a** with diazomethane followed by distillation gave 44 mg of **8b** (85%): bp 116–119° (0.02 mm). Ir and nmr spectra of **8b** were identical with those of an authentic sample.

1,5-*cis*-5,6-*cis*-6-(2′,2′-Dimethoxyethyl)-3-methoxy-2-oxabicyclo[3.3.0]octane (15). A solution of **6** (382 mg, 2.24 mmol) and *p*-toluenesulfonic acid (10 mg) in MeOH (35 ml) was refluxed for 2 hr. After processing as described in the preparation of **7c**, the residue was taken up in $CHCl_3$ (30 ml), washed with aqueous $NaHCO_3$, and dried. Removal of the solvent gave 465 mg (90%) of **15**: bp 50–52° (0.03 mm); ir (neat) 1126 and 1096 cm^{-1}; nmr ($CDCl_3$) δ 1.20–2.20 (10 H), 3.31 (s, 9 H, CH_3O), 6.38 (t, J = 5.7 Hz, 1 H, CHO), 6.56 (m, 1 H, CHO), and 6.98 (d, J = 4.2 Hz, 1 H, CHO).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 66.64; H, 9.15. Found: C, 66.98; H, 9.21.

1,5-*cis*-5,6-*cis*-6-Carbomethoxymethyl-3-oxo-2-oxabicyclo-[3.3.0]octane (16b). To a stirred solution of **6** (205 mg, 1.20 mmol) in ether (10 ml) was added an aqueous solution of 4 *N* chromic acid (1.3 ml) at 10° and the mixture was stirred for 10 hr at room temperature. The ether layer was separated and the aqueous solution was extracted with ether. The combined extracts were washed with water and dried. Removal of the solvent gave 191 mg (84%) of **16a**: ir (Nujol) 1767 (lactone) and 1698 cm^{-1} (COOH).

Without further purification, the acid **16a** was converted into the lactone ester **16b** by the action of diazomethane in quantitative yield: bp 82–85° (0.02 mm); ir (neat) 1775 (lactone C=O) and 1735 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.60–3.20 (10 H), 3.69 (s, 3 H, CH_3O), and 5.05 (m, 1 H, CHO); mass spectrum 198 (M^+, 2), 180 (10), 166 (52), 152 (55), 149 (50), 138 (50), 125 (58), 96 (100), 81 (63), 74 (68), 67 (50), 55 (55), and 41 (63).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.80; H, 7.14.

Chromic Acid Oxidation of 7b. To a stirred solution of **7b** (30 mg, 0.15 mmol) in ether (5 ml) a solution of 4 *N* chromic acid (0.3 ml) was added dropwise at room temperature. After processing as described above 27 mg (90%) of **16b** was obtained, whose ir and nmr spectra were identical with those of an authentic sample.

Registry No.—**1**, 20073-13-6; **2**, 53369-26-9; **3a**, 53320-14-2; **4**, 53320-15-3; **5**, 53320-16-4; **6**, 53320-17-5; **7b**, 53320-18-6; **7c**, 53320-19-7; **8a**, 53320-20-0; **8b**, 53320-21-1; **9a**, 53320-22-2; **9b**, 53320-23-3; **10a**, 53320-24-4; **10b**, 53320-25-5; **11**, 53320-26-6; **12**, 53320-27-7; **13**, 52403-88-6; **14a**, 53369-27-0; **14b**, 53369-28-1; **15**, 53320-28-9; **16a**, 53320-29-9; **16b**, 53320-30-2; **17b**, 53403-89-7; 1,3-propanedithiol, 109-80-8; *n*-propylidenetriphenylphosphorane, 16666-78-7.

References and Notes

(1) E. Demole, E. Lederer, and D. Mercier, *Helv. Chim. Acta*, **45**, 675 (1962).

(2) (a) D. C. Aldridge, S. Galt, D. Giles, and W. B. Turner, *J. Chem. Soc. C*, 1623 (1971); (b) H. Koshimizu, *Kagaku to Seibutsu*, **11**, 438 (1973).

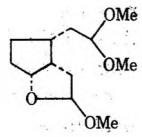
(3) (a) E. Demole and M. Stoll, *Helv. Chim. Acta*, **45**, 692 (1962); (b) K. Sisido, S. Kurozumi, and K. Utimoto, *J. Org. Chem.*, **34**, 2661 (1969); (c) G. Büchi and B. Egger, *ibid.*, **36**, 2021 (1971); (d) A. I. Meyers and N. Nazarenko, *Ibid.*, **38**, 175 (1973).

(4) Fractional distillation of cycloaddition products **3a** and **3b** prepared from cyclopentenone with butadiene by a 75-cm spinning column gave 48% of a higher boiling fraction, bp 99.5–100.0° (15 mm), which contains 98% of the cis isomer monitered by glpc: H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963).

(5) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4026 (1952).

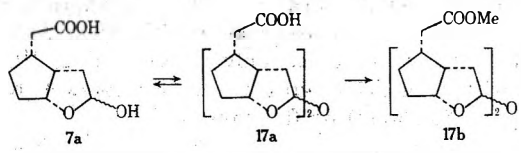
(6) W. A. Bonner, *J. Amer. Chem. Soc.*, **73**, 3126 (1951).

(7) Assignment of structure **6** was also based on its chemical nature, since conversion of **6** into the diacetal **15** was accomplished when it was refluxed in methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid.



15

(8) Independent treatment of the acid hemiacetal **7a** with slightly acidic $CHCl_3$ and then standing for several days at room temperature afforded **17a** in good yield, which on treatment with diazomethane gave **17b**.



7a 17a 17b

(9) E. J. Corey and C. U. Kim, *J. Amer. Chem. Soc.*, **94**, 7586 (1972).

(10) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971).

(11) L. Crombie, P. Hemesley, and G. Pattenden, *J. Chem. Soc. C*, 1016 (1969).

(12) In contrast, attempts to synthesis **14a** from the lithium salt of **7a** by the Wittig reaction according to the Corey's method failed: R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(13) H. C. Brown, C. P. Garg, and K-T. Liu, *J. Org. Chem.*, **36**, 387 (1971).

(14) A slightly different reactivity between aldehyde and hemiacetal functions attached to the cyclopentane ring has been used in a prostagiadin synthesis: D. Brewster, M. Myers, J. Ormerod, P. Otter, A. C. B. Smith, M. E. Spinner, and S. Turner, *J. Chem. Soc., Perkin Trans. 1*, 2796 (1973).

(15) Tic analysis using Merck silica gel 60 PF-254 precoated plates after treatment with 5% silver nitrate in EtOH–MeCN (1:1) before use revealed that the cis olefin (R_f 0.48) was contaminated with *ca.* 5% of the trans olefin (R_f 0.56) using benzene–AcOEt (10:1) as a developer.

Terpenoids. LXX.[1] The Structure of the Sea Cucumber Sapogenin Holotoxinogenin

Wai Lee Tan[2] and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

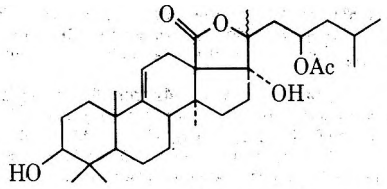
José Fayos and Jon Clardy[3]

Ames Laboratory-USAEC and Department of Chemistry, Iowa State University, Ames, Iowa 50010

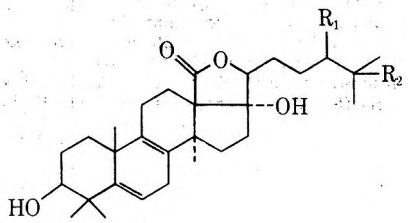
Received August 12, 1974

A new triterpenoid aglycone holotoxinogenin (**4a**) and its 25-methyl ether **5a** were isolated from the antifungal saponin holotoxin. The structure **4a** was shown to be 3β,20ξ,25-trihydroxy-16-oxolanost-9(11)-ene-18-carboxylic acid lactone (**18** → **20**). The ketonic functionality at C(16) is unprecedented in sapogenins from sea cucumbers. The full structure and stereochemistry was determined by X-ray analysis, thus establishing for the first time the absolute configuration of C(20) in the sea cucumber aglycones. Holotoxinogenin was found to be identical with stichopogenin A_4, whose earlier structure assignment is thus shown to be incorrect.

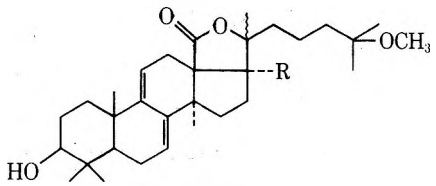
Sea cucumbers (Holothurians), members of the phylum Echinodermata, are known to possess toxic saponins in their body walls, as well as in the Cuvierian glands, for defensive and offensive purposes.[4] The toxicological and pharmacological aspects of these toxins have been studied extensively.[5] The chemical investigation of these saponins and their derived sapogenins began more than two decades ago and the tetracyclic triterpenoid structures of many of these compounds have since been established.[6,7] Recently, we reported the isolation and structure elucidation of a new sapogenin (**1**) from the dried skin of *Stichopus chloronotus* Brandt,[8] which contained only an isolated $\Delta^{9(11)}$-double bond without a C(12) substituent. Also noteworthy is the existence of a 23-acetoxy function.



1



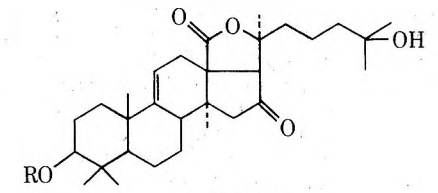
2a,
b, $R_1 = H$; $R_2 = OH$



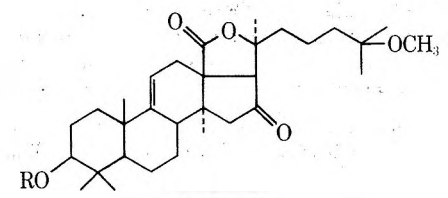
3a, R = H
b, R = OH

In 1969 Shimada reported the isolation of a new saponin, named holotoxin, from the body wall of the sea cucumber *Stichopus japonicus*,[9] the same species from which Elyakov, *et al.*,[10] isolated stichopogenins A_2 and A_4 and to which they assigned structures **2a** and **2b**. Crystalline holotoxin shows high activity against pathogenic fungi, a property that distinguishes it from the holothurins studied so far. The infrared spectrum of holotoxin is similar to that of holothurin but holotoxin lacks the sulfate group of the former. It is interesting to note that a considerable fraction of the biological potency of holothurin is linked to the possession of a negative charge center, and removal of this anionic character, *i.e.*, the sulfate group, causes a sharp decrease in its ability to destroy membrane excitability.[5a]

We report here the structures of two new sapogenins derived by acid hydrolysis of Shimada's holotoxin.[9] Due to the limited amount of material, the structures of holotoxinogenin (**4a**) and holotoxinogenin 25-methyl ether (**5a**)



4a, R = H
b, R = Ac



5a, R = H
b, R = Ac

were established predominantly by analysis of their spectral data and by X-ray analysis. Like **1**[8] these genins contain the unusual 9(11) double bond system; in addition they are unique in having a ketone function at C(16).

The mass spectrum of compound **5a** depicted a molecular ion at *m/e* 500. The composition of **5a** as $C_{31}H_{48}O_5$ was established by high resolution measurements on fragment ions corresponding to the loss of methyl and methanol. The nature of the oxygen functions was based on the following observations.

The infrared spectrum of sapogenin **5a** revealed the presence of a five-membered lactone ($\nu_{C=O}$ 1755 cm^{-1}) and one hydroxyl group (ν_{OH} 3440 cm^{-1}) which could be acetylated. The secondary nature of this hydroxyl group was established by the presence of only one H–C–O type proton in **5a** and its derivatives. The strongly negative Cotton effect, $[\theta]_{303}$ −16,500, in the CD spectrum of **5a** indicated the presence of a carbonyl chromophore. Since the ir spectrum did not have absorption corresponding to either an open-

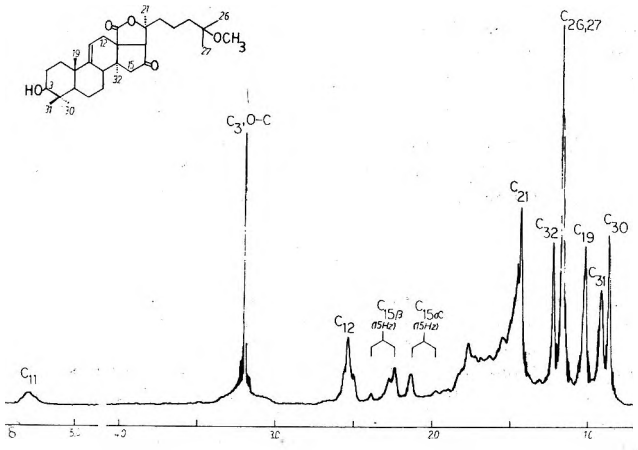


Figure 1. Nmr spectrum (100 Hz) of holotoxinogenin 25-methyl ether (**5a**) in deuteriochloroform.

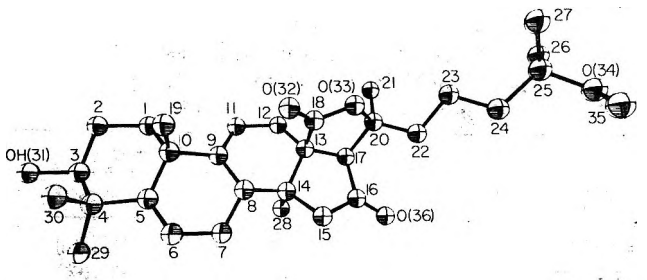


Figure 2. A computer generated perspective drawing of holotoxinogenin 25-methyl ether (**5a**). Atoms are carbons unless otherwise specified and hydrogens are not shown.

chain ketone or a six-membered ring ketone, but showed broad absorption at 1755 cm^{-1} the Cotton effect was presumably associated with a ketone contained in a five-membered ring. The negative Cotton effect would then require that it be either a 14α-16-ketone or a 14β-15-ketone.[11] This point was settled rigorously by the X-ray data discussed below.

The nmr spectrum (Figure 1) of **5a** showed the presence of seven methyl groups in addition to a methoxyl function. The general resemblance with previously reported spectra[6-8,12,13] strongly indicated the presence of the typical lanostane skeleton with a γ-lactone between C(18) and C(20).

The β configuration of the C(3) hydroxyl group was indicated by the position of a broad nmr absorption (δ 3.18) in the alcohol **5a**.[14] The β configuration of the C(3) alcohol is further substantiated by the well documented[15] larger lanthanide induced shift of the 4β-methyl as compared to the 4α-methyl group.[2]

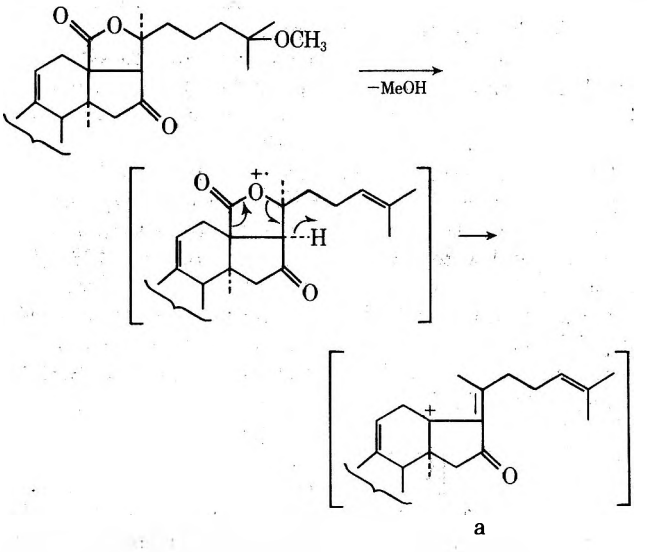
The position of the methoxyl group at C(25) was established by the fact that the nmr signal of the C(26) and C(27) protons at δ 1.16 was similar to that of ternaygenin (**3a**)[12] and praslinogenin (**3b**).[13] The presence of the mass spectral peak at *m/e* 73 [$(CH_3)_2C{=}O^+CH_3$] confirmed that like **3a** and **3b**, compound **5a** contained a methoxyl function at C(25).

The nmr spectrum (Figure 1) of **5a** showed simple geminal coupling (J = 15 Hz) at δ 2.05 and 2.31, which could be the result of the methylene protons α to a carbonyl group. This and the fact that the protons of the C(14) methyl group were more deshielded (δ 1.21) when compared with the C(14) methyl groups of praslinogenin (**3b**)[13] (δ 1.16) and ternaygenin (**3a**)[12] (δ 1.01) strongly suggest that the five-membered ring ketone function was at C(16).

The empirical formula of **5a** established by mass spectrometry required one more degree of unsaturation. There was only one olefinic proton (δ 5.3) in the nmr spectra (see Figure 1) of **5a** and **5b**. From spin decoupling data we concluded that the two-proton signal at 2.53 ppm was due to two allylic protons, which was consistent with three possible positions (Δ^5, Δ^7, or $\Delta^{9(11)}$, for the double bond. A definite conclusion was reached by X-ray crystallography.

The complete three-dimensional structure of holotoxinogenin 25-methyl ether (**5a**) was elucidated by a single crystal X-ray diffraction experiment. The results of this are shown in a drawing of the final X-ray model given in Figure 2. The X-ray work established firmly the 9–11 position of the double bond (1.35 Å distance) which could not be settled by the nmr studies; similarly it proved rigorously the presence of the 16-keto group whose infrared signal was masked by the lactone absorption. The negative Cotton effect, mentioned previously, thus settles the absolute configuration of the molecule. In general, the bond distances were normal, the only abnormally short intermolecular contact being a hydrogen bond between O(31) and O(34) of 2.93 Å.

The diagnostic peaks in the mass spectra of **5a** and **5b** are summarized in Table I. The fragmentations could be rationalized readily in terms of structure **5**. Both compounds possess an intense peak at *m/e* 73.065 (C_4H_9O) corresponding to $(CH_3)_2C{=}O^+CH_3$ which is a characteristic fragment ion for sapogenins with a C(25) methoxyl group.[10b,12,13] The ion of mass 381.244 ($C_{25}H_{33}O_3$) originates from cleavage between carbon atoms 1 and 2 and 4 and 5, respectively, of ring A. When **5a** is acetylated, the mass spectrum of the monoacetate **5b** also contains an *m/e* 381 peak, indicating that the fragmentation is indeed the result of cleavage of ring A. The spectra of **5a** and **5b** display peaks at *m/e* 423 and 465, respectively, which could be generated by the loss of methanol, carbon dioxide, and a hydrogen atom. A conceivable mechanism is the following.



a

In view of the fact that none of the previously known holothurinogenins exhibit such fragmentation, it seems reasonable to conclude that the presence of the C(16) keto group facilitates this fragmentation process by furnishing the α,β-unsaturated ketone moiety of ion a.

The structure of holotoxinogenin (**4a**) was established by a comparison of its spectra with those of **5a**. The mass spectrum of **4a** showed a molecular ion peak at *m/e* 486 ($C_{30}H_{46}O_5$). Like its methyl ether **5a**, **4a** contained a γ-lactone ring ($\nu_{C=O}$ 1755 cm^{-1}), one or more hydroxyl groups (ν_{OH} 3440 cm^{-1}), and essentially no uv absorption above 210 nm. It also had a negative Cotton effect curve that was identical in shape and sign with **5a**. Acetylation of **4a** at room temperature gave a monoacetate (**4a**) whose ir spec-

Table I
Diagnostic Peaks in the Mass Spectra of Holotoxinogenin 25-Methyl Ether (5a) and Its Acetate (5b)

	Relative intensity in %	
	5a	5b
M^+	500 (3)	542 (1%)
$M - CH_3$	485 (7%)	527 (6%)
$M - CH_3OH$	468 (100%)	510 (97%)
$M - CH_3OH + CH_3$	453 (15%)	495 (6%)
$M - CH_3OH + ROH^a$	450 (9%)	450 (6%)
$M - CH_3OH + ROH^a + CH_3$	435 (15%)	435 (26%)
$M - CH_3OH + CO_2 + H$	423 (12%)	465 (10%)
$M - CH_3OH$ + ring A	381 (4%)	381 (2%)
$M - ROH^a$ + side chain	367 (3%)	367 (2%)
$(CH_3)_2C{=}O^+CH_3$	73 (57%)	73 (100%)

[a] RO refer to the 3β-OH or 3β-OAc substituent.

with that of A_4 except that it lacks the 25-hydroxyl group and contains instead a $\Delta^{24(25)}$ double bond.

Roller, *et al.*,[12] suggested that the methoxyl function at C(25) of **3a** and **3b** might be an artifact produced from a hydroxyl precursor during the acid hydrolysis conditions. It is likely that this has also happened here and that the naturally derived aglycone is holotoxinogenin (**4a**).

Experimental Section

Melting points are uncorrected and were determined on a Kofler hot-stage microscope. All optical rotations were determined using chloroform as solvent. Infrared spectra were measured using a Perkin-Elmer Model 421 infrared spectrophotometer using polystyrene as external reference (1601 cm^{-1}). Ultraviolet spectra were measured in 95% ethanol on a Cary-14 recording spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian HA-100 or XL-100 spectrometer using deuteriochloroform as solvent. Tetramethylsilane was used as internal reference and line positions are given in the δ scale. Low-resolution mass spectra (70 eV) were obtained on AEI MS-9, Atlas CH-4, and Varian MAT-711 instruments with direct inlet systems. High-resolution spectra were determined on MS-9 and MAT-711 instruments.

Gas–liquid chromatography (glpc) was carried out on a Hewlett-Packard 402 high-efficiency instrument with glass columns packed with 3% of OV-25 on Gas-Chrom Q (100–200 mesh) from Applied Science Laboratories, Inc. Column chromatography was carried out using E. Merck neutral, activity grade II, aluminum oxide. Analytical scale thin layer chromatography was carried out on 5 × 20 cm, 250-μ silica get HF_{254} plates. Substances were visualized on these plates by spraying with ceric sulfate solution (2% in 1 *M* sulfuric acid) followed by heating on a hot plate.

We thank Dr. L. J. Durham for the nmr spectra, Mr. R. Ross, Mr. R. Conover, and Miss A. Wegmann for the mass spectra, and Mrs. R. Records for the CD measurements.

Hydrolysis of Holotoxin. Holotoxin[9,17] (1 g) was dissolved in 20 ml of 30% hydrochloric acid in methanol and heated under reflux for 3 hr. The mixture was diluted with methanol, the products precipitated by addition of water, and the aglycones extracted with dichloromethane. The dichloromethane layer was washed with water and sodium bicarbonate, dried (magnesium sulfate), and evaporated to give 340 mg of semisolid. Glpc demonstrated that it was a complex mixture of at least seven aglycones. The two major components holotoxinogenin (**4a**) and its 25-methyl ether (**5a**) were isolated in the following manner.

A 325-mg aliquot was dissolved in dichloromethane, absorbed on alumina activity II powder, and placed on an alumina II (50 g) column. Chromatography using gradient elution with benzene–ethyl acetate and several recrystallizations gave 39 mg of holotoxinogenin (**4a**) and 57 mg of holotoxinogenin 25-methyl ether (**5a**), both in about 90% purity (by glpc).

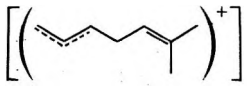
Holotoxinogenin (4a): mp 238–241° (from $CHCl_3$); $[\alpha]^{20}D$ −97.6° (c 0.25); CD (methanol) $[\theta]_{303}$ −14,274; ir (KBr) 3445 (broad, OH), 1750 (lactone C=O), 1460, 1440 (methylene adjacent to C=O), 1375, 1360, 1180, 1155, 1095, 1025, 940 cm^{-1}; essentially no uv absorption above 210 nm; nmr δ 0.86 (3, s, C(4α) CH_3), 0.91 (3, s, C(4β) CH_3), 1.01 (3, s, C(10) CH_3), 1.23 (9, s, C(14), C(25) CH_3), 1.42 (3, s, C(20) CH_3), 2.05 (1, one-half of AB quartet, J = 15 Hz, C(15) H), 2.31 (1, one-half of AB quartet, J = 15 Hz, C(15) H), 2.53 (1, broad, C(12) H_2), 3.19 (1, broad, C(3) H), 5.29 (1, broad, C(11) H); mass spectrum (relative intensity) 486 (4, M^+), 471,30811 (9, $M - CH_3$), 468.32153 (100, $M - H_2O$), 453.29980 (15, $M - H_2O + CH_3$), 450.31421 (9, $M - H_2O + H_2O$), 435.29053 (22, $M - H_2O + H_2O + CH_3$), 423.32397 (16, $M - H_2O + CO_2 + H$), 381.24268 (6, $M - H_2O$ + ring A), 367.22656 (5, $M - H_2O$ + side

Table II
Values for Methyl Group Signals in Holotoxinogenin Derivatives

Compd	C_4–CH_3	C_{10}–CH_3	C_{14}–CH_3	C_{20}–CH_3	C_{25}–CH_3	O–CH_3	O–C(O)CH_3
4a	0.86, 0.91	1.01	1.23	1.42	1.23, 1.23		
5a	0.85, 0.91	1.01	1.21	1.42	1.15, 1.15	3.18	
4b	0.91, 0.92	1.15	1.25	1.42	1.23, 1.23		2.08
5b	0.90, 0.92	1.15	1.23	1.42	1.15, 1.15	3.18	2.08

trum still indicated a hydroxyl absorption. Thus the five oxygen atoms of **4a** were contained in a γ-lactone, a ketone, and two hydroxyl groups, one of them being nonacetylable. Further confirmation was provided by comparing the nmr spectra of **4a** and **4b** with those of **5a** and **5b** (Table II), which clearly show that **4a** differs from **5a** only in the functionality at position C(25). Since **4a** contains one CH_2 unit less than **5a** and has no methoxyl singlet, the substituent at C(25) has to be a hydroxyl, which would result in larger deshielding of the C(26) and C(27) protons.

The mass spectrum of **4a** showed peaks at *m/e* 471.308 ($C_{29}H_{43}O_5$, $M - CH_3$) and a base peak at *m/e* 468.322 ($C_{30}H_{44}O_5$, $M - H_2O$) and also ions due to subsequent loss of methyl and water from the fragment of mass 468. Like **5a**, **4a** also had a peak at *m/e* 423.324 ($C_{29}H_{43}O_2$) presumably generated by the 16-ketone function. The peak at *m/e* 73 [$(CH_3)_2C{=}O^+CH_3$] was absent from the spectrum. Instead, intense ions at *m/e* 69,0704 [$(CH_3)_2C{=}CHCH_2^+$] and *m/e* 109.602



were encountered. These fragments have also been observed in other sapogenins (*e.g.*, koellikerigenin[14]) which contain a C(25) hydroxyl group. It follows that holotoxinogenin has structure **4a**.

The fact that Elyakov's stichopogenin A_4 (**2b**) was also isolated from *Stichopus japonicus*, and possessed the same empirical composition and melting point as **4a**, prompted us to question the correctness of the unprecedented diene formulation of ring B (**2**). A direct comparison[16] (mixture melting point, CD, ir, glpc, and mass spectrum) of the monoacetates of stichopogenin A_4 (**2b**) and holotoxinogenin (**4a**) showed that they were identical in all respects and that the diene system (*cf.* 2) was based on false assumptions. Examination of stichopogenin A_2 (**2a**) acetate indicated that it also contained a 16-keto group (from CD and mass spectral results) and hence its structure is identical

Table III
Fractional Coordinates for Nonhydrogen Atoms of Holotoxinogenin 25-Methyl Ether[a]

Atom	x	y	z
C(1)	1.0327 (3)	0.416 (1)	0.495 (1)
C(2)	0.9480 (3)	0.327 (1)	0.477 (1)
C(3)	0.9162 (3)	0.264 (1)	0.258 (1)
C(4)[b]	0.9626	0.070	0.9655
C(5)	1.0496 (3)	0.153 (1)	0.1245 (9)
C(6)	1.1023 (4)	−0.000 (1)	−0.032 (1)
C(7)	1.1785 (4)	0.121 (1)	−0.030 (1)
C(8)	1.2171 (3)	0.225 (1)	0.1707 (9)
C(9)	1.1661 (3)	0.350 (1)	0.3459 (9)
C(10)	1.0849 (3)	0.241 (1)	0.3456 (9)
C(11)	1.1945 (3)	0.531 (1)	0.512 (1)
C(12)	1.2751 (3)	0.628 (1)	0.5373 (9)
C(13)	1.3294 (3)	0.454 (1)	0.3926 (9)
C(14)	1.2931 (3)	0.353 (1)	0.1724 (9)
C(15)	1.3590 (4)	0.210 (1)	0.046 (1)
C(16)	1.4289 (4)	0.371 (1)	0.136 (1)
C(17)	1.4130 (3)	0.524 (1)	0.3612 (9)
C(18)	1.3438 (4)	0.274 (1)	0.4857 (9)
C(19)	1.0983 (4)	0.042 (1)	0.419 (1)
C(20)	1.4631 (3)	0.474 (1)	0.523 (1)
C(21)	1.4689 (4)	0.682 (1)	0.726 (1)
C(22)	1.5388 (4)	0.373 (1)	0.445 (1)
C(23)	1.5878 (4)	0.324 (1)	0.607 (1)
C(24)	1.6561 (4)	0.183 (1)	0.511 (1)
C(25)	1.7141 (4)	0.152 (1)	0.659 (1)
C(26)	1.7530 (4)	0.385 (1)	0.792 (1)
C(27)	1.6792 (4)	0.039 (2)	0.795 (1)
C(28)	1.2808 (4)	0.546 (1)	0.099 (1)
C(29)	0.9341 (4)	0.053 (2)	−0.114 (1)
C(30)	0.9469 (4)	−0.158 (1)	0.114 (1)
O(31)	0.8367 (2)	0.204 (1)	0.2460 (9)
O(32)	1.2987 (3)	0.1361 (9)	0.5069 (8)
O(33)	1.4164 (2)	0.2927 (9)	0.5562 (7)
O(34)	1.7772 (2)	0.0207 (9)	0.5456 (8)
C(35)	1.7610 (5)	−0.213 (2)	0.431 (2)
O(36)	1.4868 (2)	0.380 (1)	0.0474 (8)

[a] The estimated standard deviation of the least-significant figure is given in parentheses. [b] Atom is used to define origin and never varied.

chain, $C_6H_{13}O$), 328 (12), 274 (27), 259 (20), 241 (12), 109 (66), 69 (68), 55 (34), 43 (50).

Holotoxinogenin 3β-Acetate (4b). Holotoxinogenin (**4a**) (12 mg) was dissolved in 0.5 ml of (1:1) pyridine–acetic anhydride and stirred overnight. The usual work-up gave 13 mg of product. Recrystallization from methanol yielded 9 mg of **4b:** mp 221–223° (from MeOH); $[\alpha]^{20}D$ −84° (c 0.22); ir ($CHCl_3$) 3600 (OH), 1750 (lactone C=O), 1740 (five-membered ring C=O), 1720, 1240 (ester C=O), 1460, 1440 (methylene adjacent to C=O), 1360, 1150, 1125, 1090, 1025, 975. 940 cm^{-1}; nmr δ 0.91 (3, s, C(4α) CH_3), 0.92 (3, s, C(4β) CH_3), 1.15 (3, s, C(10) CH_3), 1.23 (6, s, C(25) CH_3), 1.25 (3, s, C(14) CH_3), 1.42 (2, s, C(20) CH_3), 2.08 (3, s, CH_3-C(O)-O), 2.05 (1, one-half of AB quartet, J = 15 Hz, C(15) H), 2.31 (1, one-half of AB quartet, J = 15 Hz, C(15) H), 2.53 (2, broad, C(12) H_2), 4.54 (1, broad, C(3) H), 5.19 (1, broad, C(11) H); mass spectrum m/e (relative intensity) 528 (2, M^+), 513 (4, M − CH_3), 510 (41, M − H_2O), 495 (4, M − H_2O + CH_3), 450 (5, M − H_2O + AcOH), 435 (21, M − H_2O + AcOH + CH_3), 381 (3, M − H_2O + ring A), 367 (3, M − AcOH + side chain), 465 (9, M − H_2O + CO_2 + H), 328 (3), 316 (18), 241 (13), 109 (49), 69 (62), 55 (31), 43 (100).

Holotoxinogenin 25-methyl ether (5a): mp 236–238° (from $CHCl_3$) $[\alpha]^{20}D$ −125° (c 0.32); $CD_{methanol}$ $[\theta]_{303}$ −16,500; ir (KBr) 3440 (broad, OH), 1755 (lactone C=O), 1460, 1440 (methylene adjacent to C=O in five-membered ring ketone), 1380, 1362, 1185, 1095, 1080, 1025, 940 cm^{-1}; essentially no uv absorption above 210 nm; nmr δ 0.85 (3, s, C(4α) CH_3), 0.91 (3, s, C(4β) CH_3), 1.01 (3, s, C(10) CH_3), 1.15 (6, s, C(25) CH_3), 1.21 (3, s, C(14) CH_3), 1.42 (3, s, C(20) CH_3), 2.05 (1, one-half of AB quartet, J = 15 Hz, C(15) H), 2.31 (1, one-half of AB quartet, J = 15 Hz, C(15) H), 2.53 (2, broad, C(12) H), 3.18 (1, broad, C(3) H), 3.18 (3, s, OCH_3), 5.3 (1, broad, C(11) H); mass spectrum m/e (relative intensity) 500 (3, M^+), 485.32690 (12, M − CH_3), 468.32251 (100, M − CH_3OH), 453.2998 (15, M − CH_3OH + CH_3), 450.31396 (9, M − CH_3OH + H_2O), 435.2915 (15, M − CH_3OH + H_2O + CH_3), 423.32495 (11, M − CH_3OH + CO_2 + H), 381.24390 (4, M − CH_3OH + ring A), 367.22827 (3, M − H_2O + side chain $C_7H_{15}O$), 328 (8), 274 (16), 259 (16), 241 (7), 231 (24), 109 (40), 73 (60), 55 (48), 43 (68).

Holotoxinogenin 25-Methyl Ether 3β-Acetate (5b). The holotoxinogenin 25-methyl ether (**5a**) (25.3 mg) was treated with 1:1 pyridine–acetic anhydride and set aside overnight at room temperature. The mixture was heated on a steam bath for half an hour and worked up in the usual way to yield 24 mg of product. Recrystallization from methanol gave 22 mg of **5b:** mp 230–233°; $[\alpha]^{20}D$ −71.5° (c 0.33); ir ($CHCl_3$) 1755 (lactone C=O), 1710, 1240 (ester -C(O) -O), 1740 (C=O in five-membered ring ketone), 1460, 1440 (methylene adjacent to C=O in five-membered ring ketone), 1376, 1362, 1095, 1085, 1025, 975, 940 cm^{-1}; nmr 0.90 (3, s, C(4α) CH_3), 0.92 (3, s, C(4β) CH_3), 1.15 (9, s, C(25) CH_3, C(10) CH_3), 1.23 (3, s, C(14) CH_3), 1.42 (3, s, C(20) CH_3), 2.05 (1, one-half of AB quartet, J = 15 Hz, C(15) H), 2.31 (1, one-half of AB quartet, J = 15 Hz, C(15) H), 2.08 (3, s, CH_3-C(O)-O), 2.53 (2, broad, C(12) H_2), 3.18 (3, s, OCH_3), 4.45 (1, m, C(3) H), 5.3 (1, broad, C(11) H); mass spectrum m/e (relative intensity) 542 (2, M^+), 527 (6, M − CH_3), 510 (97, M − CH_3OH), 495 (6, M − CH_3OH + CH_3), 465 (10, M − CH_3OH + CO_2 + H), 450 (5, M − CH_3OH + AcOH), 435 (27, M − CH_3OH + AcOH + CH_3), 381 (2, M − CH_3OH + ring A), 367 (2, M − AcOH + side chain $C_7H_{15}O$), 328 (3), 316 (17), 241 (10), 226 (10), 124 (13), 109 (37), 84 (35), 73 (100), 69 (34), 55 (27), 43 (62).

Table IV
Bond Distances in Holotoxinogenin 25-Methyl Ether[a]

Atom pairs	Distance	Atom pairs	Distance
C(1)–C(2)	1.54	C(14)–C(28)	1.52
C(1)–C(10)	1.53	C(14)–C(15)	1.54
C(2)–C(3)	1.53	C(15)–C(16)	1.52
C(3)–O(31)	1.41	C(16)–O(36)	1.20
C(3)–C(4)	1.56	C(16)–C(17)	1.53
C(4)–C(29)	1.51	C(17)–C(13)	1.54
C(4)–C(30)	1.53	C(18)–O(32)	1.20
C(4)–C(5)	1.57	C(18)–O(33)	1.34
C(5)–C(10)	1.55	O(33)–C(20)	1.46
C(5)–C(6)	1.50	C(20)–C(17)	1.57
C(6)–C(7)	1.51	C(20)–C(21)	1.52
C(7)–C(8)	1.47	C(20)–C(22)	1.49
C(8)–C(9)	1.49	C(22)–C(23)	1.56
C(8)–C(14)	1.51	C(23)–C(24)	1.51
C(9)–C(10)	1.54	C(24)–C(25)	1.53
C(9)–C(11)	1.35	C(25)–C(26)	1.53
C(11)–C(12)	1.49	C(25)–C(27)	1.52
C(12)–C(13)	1.53	C(25)–O(34)	1.44
C(13)–C(14)	1.55	O(34)–C(35)	1.43
C(13)–C(18)	1.53		

[a] The estimated standard deviation is 0.01 Å.

Crystallographic and X-Ray Data. Holotoxinogenin 25-methyl ether (**5a**) crystallizes in the triclinic crystal system and since it is optically active the space group must be P_1. The following unit cell was chosen: a = 17.367 (4), b = 6.277 (5), c = 7.034 (3) Å, α = 112.78 (2), β = 89.79 (2), and γ = 92.25 (2)°. The cell constants and their associated errors were obtained from a least-squares analysis of 15 reflections with θ values between 30.0 and 40.0°. The calculated density was 1.17 g/cm^3 for one molecule of $C_{31}H_{47}O_5$ in the unit cell.

A crystal of dimension 0.35 × 0.26 × 0.09 mm was used for data collection. All unique reflections with $\theta \leq 57°$ were collected on a fully automated four-circle Syntex $P2_1$ diffractometer. An ω scan of 2° was used because of the pronounced mosiac spread of the reflections. Backgrounds were collected on both sides of the scan for one-half of the scan time. A total of 1866 reflections were measured in this way. After correction for Lorentz polarization and

background effects 1601 reflections were judged observed, $|F_o| > 3\sigma(F_o)$. Three standard reflections were measured every hour and these showed no appreciable decline. The quantity $\sigma(F_o)$ was computed from $\{[l + \sigma(l)]/L_p\}^{1/2} - F_o$[18] and $\sigma(1)$ was computed from [total count + background count + 0.05(total count)^2 + 0.05(background)^2]$^{1/2}$.

Determination and Refinement of Structure. The observed structure factor amplitudes ($|F_o|^2$) were converted to normalized structure factors by removing the angular dependence of the reflections.[19] The solution of this 36 atom problem in the space group P_1 presented a severe challenge to direct methods. The largest 150 E's ($E \geq 1.6$) were assigned phases using the multisolution tangent formula approach.[19] Of the resultant 32 solutions the one with the lowest ψ_o residual was used to generate a Fourier map. The map was discouraging in that it resembled a continuous net of hexagons resembling chicken wire. The only encouraging aspect was the absence of outstandingly large peaks which meant that not much information had been destroyed by the squaring effect.[20] Nevertheless attempts to expand the model from various plausible fragments failed both through the use of the tangent formula[21] and through difference Fourier calculations using only those structure factors for which $F_c \geq 0.5F_o$. In both methods and for every fragment the model could not be forced to give additional atomic positions. Finally least-squares refinements with unit weights[22] did expand a 13-atom fragment into all 36 nonhydrogen atoms. Many cycles of least-squares refinements with anisotropic temperature factors for the nonhydrogen atoms and fixed-hydrogen atoms lowered the conventional discrepancy index to 0.048 for the 1601 observed reflections. Figure 2 is a computer generated perspective drawing of the final X-ray mode.[23] The absolute configuration is based on the negative Cotton effect CD measurement as only the relative configuration was determined by the diffraction experiment. (The estimated standard deviation in the bond lengths given in Table IV is 0.01 Å.) Table III is a listing of the fractional coordinates.

Acknowledgment. Financial assistance from the National Institutes of Health (Grants No. GM-06840 and RR-00612) is gratefully acknowledged.

Registry No.—**4a,** 53534-44-4; **4b,** 53534-45-5; **5a,** 53586-51-9; **5b,** 53534-46-6.

References and Notes

(1) For part LXIX, see M. Kaisin, Y. M. Sheikh, L. J. Durham, C. Djerassi, B. Tursch, D. Daloze, J. C. Braekman, D. Losman, and R. Karlsson, *Tetrahedron Lett.*, 2239 (1974).
(2) From part of the Ph.D. Thesis of W. L. Tan.
(3) Camille and Henry Dreyfus Foundation Teacher-Scholar Grand Awardee 1972–1977 and Fellow of the Alfred P. Sloan Foundation 1973–1975 at Iowa State University.
(4) B. W. Halstead, "Poisonous and Venomous Marine Animals of the World," Vol. 1, U. S. Government Printing Office, Washington, D.C., 1965, p 567.
(5) (a) S. L. Friess, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **31,** 1146 (1972). (b) M. M. Anisimov, E. B. Fronert, T. A. Kuznetsova and G. B. Elyakov, *Toxicon,* **11,** 109 (1973).
(6) J. S. Grossert, *Chem. Soc. Rev.*, **1,** 1 (1972).
(7) P. J. Scheuer, "Chemistry of Marine Natural Products," Academic Press, New York, N. Y., 1973, p 23–35.
(8) I. Rothberg, B. Tursch, and C. Djerassi, *J. Org. Chem.*, **38,** 209 (1973).
(9) S. Shimada, *Science,* **163,** 1462 (1969).
(10) (a) G. B. Elyakov, T. A. Kuznetsova, and V. E. Vaskovshy, *Khim. Prir. Soedin.*, **4,** 253 (1968), *Chem. Abstr.*, **70,** 45173v (1969); (b) G. B. Elyakov, T. A. Kuznetsova, A. K. Dzizenko, and Yu. N. Elkin, *Tetrahedron Lett.*, 1151 (1969).
(11) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, N. Y., 1960, p 73–114.
(12) P. Roller, C. Djerassi, R. Cloetens, and B. Tursch, *J. Amer. Chem. Soc.*, **91,** 4918 (1969).
(13) B. Tursch, R. Cloetens, and C. Djerassi, *Tetrahedron Lett.*, 467 (1970).
(14) (a) N. Entwistle and A. D. Pratt, *Tetrahedron,* **24,** 3949 (1968); (b) for a comparison of some 3α- and 3β-lanostane derivatives, see H. K. Adam, T. A. Bryce, I. M. Campbell, and N. J. McCorkindale, *Tetrahedron Lett.*, 1461 (1967).
(15) D. G. Buckley, G. H. Green, E. Ritchie, and W. C. Taylor, *Chem. Ind. (London),* 298 (1971).
(16) We are indebted to Professor G. B. Elyakov, Pacific Institute of Bio-organic Chemistry, USSR Academy of Sciences, Vladivostok, for samples.
(17) Kindly provided by Dr. R. I. Dorfman of Syntex Research, Palo Alto, Calif.
(18) D. E. Williams and R. E. Rundle, *J. Amer. Chem. Soc.*, **86,** 1660 (1964).
(19) P. Main, M. Woolfsor, and G. Germain, MULTAN, Department of Physics, University of York, York, England, 1971.
(20) J. Gassman and K. Zechmeister, *Acta Crystallogr., Sect. A,* **28,** 270 (1972).
(21) J. Karle, *Acta Crystallogr., Sect. B,* **24,** 182 (1968).
(22) W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program," USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, 1965.
(23) C. K. Johnson, "ORTEP, A Fortran Therman Ellipsoid Plot Program for Crystal Structure Illustrations," USAEC Report ORNL-3794, Oak Ridge National Laboratory, 1965.

Synthesis of Dipeptides of Aminophosphonic Acids[1]

M. Hariharan, R. J. Motekaitis, and A. E. Martell*

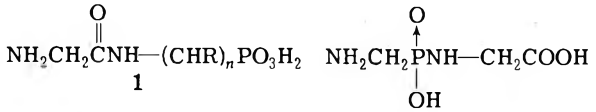
Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received June 26, 1974

Of the two classes of phosphono dipeptide derivatives, three new parent dipeptides were synthesized using a new method followed by the removal of the protective groups and were characterized by elemental and detailed nmr analyses. In addition, for two dipeptides containing amide linkages and terminal phosphonic acid groups the pK_a's and metal binding constants were determined. The peptides containing phosphonamide linkages could not be obtained in the free state because of their sensitivity toward acids and bases.

The recent isolation of 2-aminoethylphosphonic acid (2AEP) from several organisms[2a–e] and human beings[2f,g] has clearly shown that aminophosphonic acids are biologically an important class of compounds. Early publications of the natural occurrence of 2-aminoethylphosphonic acid suggested participation of the compound in lipid structures,[2a–e,3] but Quin[4] showed that occurrence in protein structures was also possible. Quin suggested[5] that the aminophosphonic acids could form part of polypeptide chains by amide formation through either one or both of their amino and phosphonic acid groups.

In a preliminary communication[6] we reported the preparation of the derivatives of several members of two classes (1 and 2) of phosphonic acid dipeptides. This note provides



R = H or CH_3
n = 1 or 2

complete details for the removal of the protective groups; describes the isolation of three new dipeptides, glycyl-1- and 2-aminoethylphosphonic acid and glycylaminomethylphosphonic acid; provides nmr characterization; and reports the proto- and metallophilicity of the dipeptides acting as ligands. Furthermore, a much simpler route was

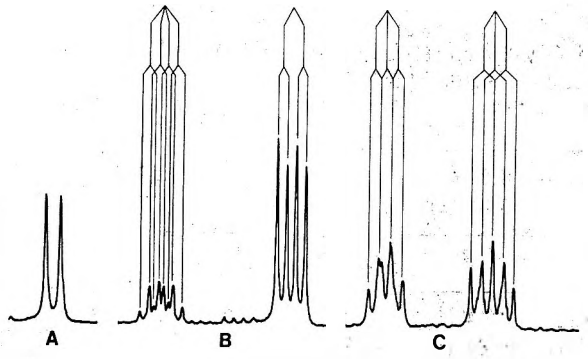


Figure 1. Nmr spectra of aminophosphonic acids in D_2O–NaOD solution; A, aminomethylphosphonic acid; B, 1-aminoethylphosphonic acid; C, 2-aminoethylphosphonic acid (assignments in text).

found for the synthesis of P-terminal phosphono dipeptides in the mixed carboxyliccarbonic anhydride method and was used to replace the acylated amino acid chloride method.

Results and Discussion

CON Peptides. The previously reported condensation of the acylated amino acid chloride with the aminophosphonic acid was abandoned as it proved to be rather tedious, resulted in low yields, and presented purification problems. A new, simpler mixed carboxylic–carbonic anhydride method was substituted for the preparation of class 1 peptides as shown in eq 1 and 2.

$$\underset{3}{\text{RNCHR'COOH}} + \underset{4}{\text{R''OCOCl}} \xrightarrow{Et_3N} \underset{5}{\text{RNCHR'CO—O—COR''}} \quad (1)$$

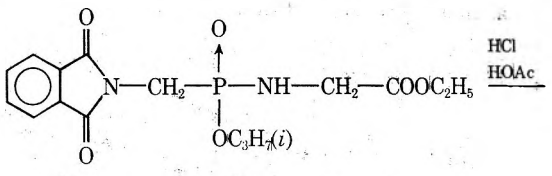
$$\underset{5}{\text{RNCHR'CO—O—COR''}} + \underset{6}{\text{NH}_2\text{CH}_2\text{P(O)(ONa)}_2} \longrightarrow \underset{7}{\text{RNCHR'CONHCH}_2\text{P(O)(ONa)}_2} \quad (2)$$

The method is similar to the preparation of normal peptides by the mixed anhydride method,[7] and essentially consists in treating a cold anhydrous dioxane solution of the acyl (R = phthaloyl or carbobenzoxy) aminocarboxylic acid with an equimolar quantity of ethyl chlorocarbonate (4, R'' = C_2H_5) in the presence of triethylamine and then adding an alkaline solution of the appropriate aminophosphonic acid (6). Since alcohol and carbon dioxide are the only by-products of the reaction, the dipeptides were obtained in fairly pure form by this method. An added advantage of the method is that when the phthalyl or carbobenzoxy[8] derivative of an optically active amino acid is used as one of the reactants, very little optical deactivation occurs in the formation of the mixed anhydride and hence the dipeptide. The removal of the protective phthalyl groups from the peptide derivatives was achieved using hydrazine under mild conditions.

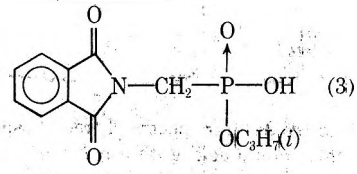
PON Peptides. In contrast to the two methods for the synthesis of peptides with free phosphonic acid groups as described above, the condensation of aminomethylphosphonic acid with *N*-acylated aminocarboxylic acids in the presence of dicyclohexylcarbodiimide (DCC) failed. Perhaps the aminophosphonic acids are too acidic for this reaction to occur. Evidence for this interpretation comes from the observation that aminophosphonic acid esters do condense with *N*-acylated aminocarboxylic acids in the presence of DCC.[9]

The peptide of the type represented by 2 was found to be more difficult to synthesize than are the peptides represented by 1. *N*-Acylated aminophosphonic acids were found not to condense with ethylglycinate in the presence of dicyclohexylcarbodiimide. Hence an alternate route for the synthesis of P–N peptides was developed as outlined earlier[6] by activating the phosphorus ester group with phosphorus pentachloride to form the phosphonochloridate intermediate, which in turn was reacted with the glycine ester.

The removal of the phthalyl group from the peptide 8 was found to be difficult because of the sensitivity of the P–N bond even to mild acids. Thus when 8 was allowed to stand in hydrochloric acid–acetic acid mixture for a short time (~30 min), the half-ester 9 separated out. The hydrolysis reaction is represented by eq 3.



8



9 (3)

Nmr Spectra. The nmr spectra of the two classes of peptides and their derivatives provided clear proof of their structures. A comparison of the spectra of the dipeptides with those of the corresponding amino and aminophosphonic acids is very useful in identifying the resonances and understanding the complex spin–spin interactions between the protons and the ^{31}P nucleus. All the nmr spectra were obtained in solvents consisting of D_2O with added sodium deuteroxide in order to avoid complications due to pH dependence. In the spectrum of aminoethylphosphonic acid the $-CH_2$ protons are split into a doublet, τ 7.33 and J_{P-H} = 11 Hz, by the ^{31}P nucleus. The spectrum of 1-aminoethylphosphonic acid is more complex. The –CH proton signals are split into an octet (τ 7.08 and J_{P-H} = 10.4 Hz); the quartet expected from the J_{H-H} spin–spin interaction with the $-CH_3$ protons is further split by the spin of one-half of the ^{31}P nucleus as shown in Figure 1. Similarly the $-CH_3$ proton signal is split into a quartet (τ 8.74 and J_{P-H} = 7 Hz) by long-range coupling with the ^{31}P nucleus. In the spectrum of 2-aminoethylphosphonic acid a quartet (τ 6.98 and J_{P-H} = 8 Hz) and quintet (τ 8.27 and J_{P-H} = 16 Hz) are observed for the N–CH_2 and the $-CH_2$–P protons, respectively. These multiplets for the methylene protons are separately a composite of six lines (as shown in Figure 1) with some of them overlapping one another. Here again these multiplets arise from the secondary splitting of the spin–spin interactions of the $-CH_2$ protons with the ^{31}P nucleus.

The spectra of the dipeptides contain the same features as those of the corresponding phosphonic acids in addition to the singlet due to the $-CH_2$ group of the amino acid moiety. In the nmr spectra of all the free dipeptides containing terminal phosphonic acid groups the signal for the $-CH_2$ group of the aminocarboxylic acid moiety overlaps the signals due the $-CH_n$–P (n = 1 or 2) protons. Thus the spectrum of glycylaminomethylphosphonic acid consists of only two lines (Figure 2; J_{P-CH} = 11 Hz). Similar features are seen in the spectra of the other two peptides. Thus in the case of the Gly-1-Aep peptide, J_{P-CH} = 10.2 Hz and

Table I[a]
Log Equilibrium Constants for Gly-Amp (H_2L), Gly-2-Aep (H_2L), Gly-Gly (HL), and Gly-β-Ala (HL) at 25.0 ± 0.05° and μ = 0.100 M KNO_3

Equilibrium quotient	Gly-Amp[b]			Gly-2-Aep[b]			Gly-Gly[c]			Gly-β-Ala[c]
$K_1^H = [HL]/[H][L]$	8.34 (2)			8.32 (1)			8.07			8.09
$K_2^H = [H_2L]/[H][HL]$	6.19 (1)			6.84 (1)			3.13			3.91
	Cu^{2+}	Ni^{2+}	Co^{2+}	Cu^{2+}	Ni^{2+}	Co^{2+}	Cu^{2+}	Ni^{2+}	Co^{2+}	Cu^{2+}
$K_{ML} = [ML]/[M][L]$	6.86 (1)	4.75 (1)	3.68 (1)	7.55 (1)	4.44 (1)	3.53 (1)	5.50	4.05	3.01	5.70
$K_{MHL} = [MHL]/[ML][H]$	5.19 (1)	5.79 (1)	6.29 (1)	5.21 (1)	6.64 (1)	6.87 (1)		6.29		
$K_A = [ML]/[MH_{-1}L][H]$	5.17 (1)			5.26 (1)			4.07			4.57

[a] Gly-Amp is glycylaminomethylphosphonic acid; Gly-2-Aep is glycyl-2-aminoethylphosphonic acid; Gly-Gly is glycylglycine; Gly-β-Ala is glycyl-β-alanine. [b] This work. [c] Reference 15.

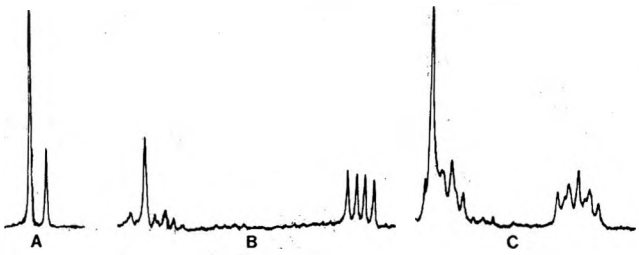


Figure 2. Nmr spectra of free phosphono dipeptides with terminal phosphonic acid group in NaOD solution; A, glycylaminomethylphosphonic acid; B, glycyl-1-aminoethylphosphonic acid; C, glycyl-2-aminoethylphosphonic acid (assignments in text).

J_{P-CH_3} = 7 Hz, and the Gly-2-Aep peptide, $J_{CH_2-CH_2}$ = 10 Hz and J_{P-CH_2} = 16 Hz. (More detailed nmr data on the compounds are given in the Experimental Section.)

pK_a's and Stability Constants. Due to the importance of the dipeptides synthesized in this work both the pK_a's and log stability constants with three representative metal ions were determined by potentiometric measurements at 25° and μ = 0.1. The results are indicated in Table I together with literature values of analogous compounds alongside for comparison purposes.

A comparison of each log K_1^H value for the phosphono dipeptides with the values of the ordinary dipeptides of Table I indicates its assignment to the protonation of the terminal amino group. Similarly, log K_2^H can be concluded to represent the protonation of the terminal P group.

The further comparison of the log K_{ML} data with the available data indicates that copper affinity increases one order of magnitude when a terminal phosphonate group is substituted for a carboxylate in a peptide. For Ni(II) and Co(II) the increase is less dramatic.

A comparison of log K_{MHL} values with the corresponding log K_2^H values strongly suggests that in the two CuHL chelates, Cu^{2+} is coordinated to the terminal amino group as well as to the peptide carbonyl. Likewise, in the NiHL and CoHL chelates the initial bonding must be to the PO_3^{2-} terminal and amido-O groupings explaining the approximately 2 log unit drop in the terminal N acidity constants. The case of glycylglycinenickel(II) corroborates this finding.[15]

Only copper(II) ion assists in the dissociation of the amidic proton present in each peptide (K_A), presumably because higher pH's result in M hydrolysis before this phenomenon could be observed.

Experimental Section

The reagents benzene, ether, tetrahydrofuran (THF), chloroform, and triethylamine used in the P–N peptide synthesis were completely dried before use. Triisopropyl phosphite was donated by Mobil Chemical, Richmond, Virginia, and was redistilled at 88° (33 mm) before use. The melting points given are uncorrected. The nmr spectra were recorded using a Varian T-60 nmr spectrometer. Elemental analyses were provided by Galbraith Laboratories, Knoxville, Tenn.

Phthalylglycine (Phtgly). Finely powdered phthalic anhydride (74 g, 0.5 M) and glycine (37.5 g, 0.5 M) were thoroughly mixed together and heated in an erlenmeyer flask to 145–150° for 0.5 hr over an oil bath. The fused mass was crystallized from methanol–water: mp 194 (lit.[10] 192–194); yield 90 g (90%).

Phthalylglycylaminomethylphosphonic Acid (Phtglyamp). A solution of 4.10 g (0.020 M) of phthalylglycine and 2.04 g (0.020 M) of anhydrous triethylamine in 40 ml of dry p-dioxane was cooled to −5° and treated with 2.17 g (0.020 M) of ethyl chloroformate. After 25 min of mixing a cold solution of 2.22 g (0.020 M) of aminomethylphosphonic acid and 1.06 g (0.020 M) of anhydrous sodium carbonate in 20 ml of water was added and the mixture was stirred for 3–4 hr allowing it to warm to room temperature. The mixture was acidified with concentrated hydrochloric acid and cooled, and the product that separated out as white crystalline material was filtered and dried. Any unreacted phthalylglycine was removed with hot ethylacetate and the product was recrystallized from alcohol–water: yield 4.5 g (75%); mp 195°; nmr (NaOD) 2.43 (s, 4, C_6H_4), 5.90 (s, 2, N–CH_2–CO), 7.70 (d, 2, –CH_2–P).

Phthalylglycyl-1-aminoethylphosphonic Acid (Phtgly-1-Aep). The procedure employed was similar to that described for phtglyamp. The carboxylic–carbonic anhydride formed by the reaction of 4.10 g (0.020 M) of phthalylglycine, 2.04 g (0.020 M) of triethylamine, and 2.17 g (0.020 M) of ethylchloroformate was treated with a neutral solution of 2.50 g (0.020 M) of 1-aminoethylphosphonic acid for 3 hr. The product was acidified and cooled, and the peptide was filtered off and was recrystallized: yield 4.1 g (66%); mp 225°; nmr (NaOD) 2.40 (s, 4, C_6H_4), 5.92 (s, 2, N–CH_2–CO), 6.01 (m, 1, CH–P), 8.75 (q, 3, –CH_3).

Phthalylglycyl-2-aminoethylphosphonic Acid (Phtgly-2-Aep). The procedure employed is similar to that employed for the preparation of Phtglyamp. The mixed anhydride formed by the reaction between 4.10 g (0.020 M) of phthalylglycine, 2.04 g (0.020 M) of triethylamine, and 2.17 g (0.020 M) of ethyl chloroformate was allowed to react with a neutral solution of 2-aminoethylphosphonic acid for 3 hr. The product was acidified and cooled, and the phthalyldipeptide obtained was filtered and recrystallized from alcohol–water: yield 4.2 g (67%); mp 236–238°; nmr (NaOD) 2.30 (s, 4, C_6H_4), 5.58 (s, 2, N–CH_2–CO), 6.33 → 6.73 (q, 2, CH_2–P), 7.82 → 8.40 (m, 2. NH–CH_2).

Dephthalylatin. The following procedure is representative of those employed for the dephthalylation of the phthalyated dipeptides.

Glycylaminomethylphosphonic Acid (Glyamp). Phthalylglycylaminomethylphosphonic acid (4.8 g, 0.016 mol), 1.0 g of sodium carbonate, and 1.0 ml of hydrazine were mixed with about 30 ml of distilled water and the clear mixture was stirred for 40 hr at room temperature. The precipitated phthalyl hydrazide was removed after acidifying with 15 ml of concentrated hydrochloric acid. On concentrating the filtrate, sodium chloride and hydrazine hydrochloride separated out. The addition of alcohol to the filtrate resulted in the separation of the free dipeptide. It was recrystallized from a water–alcohol mixture: yield 1.5 g (30%).

(1) **Glyamp:** mp 205° dec; nmr* (NaOD) 6.67 (s, 2, NH_2–CH_2), 6.71 (d, 2, CH_2–P). *Anal.* Calcd for $C_3H_9N_2O_4PH_2O$; C, 19.46; H, 6.00; N, 15.14; P, 16.73. Found: C, 19.28, H, 5.95; N, 14.94; P, 16.78.

(2) **Gly-1-Aep:** mp 235° dec; nmr (NaOD) 6.42 (s, 2, NH_2CH_2),

6.22 → 6.68 (m, 1, NH–CH–P), 8.30 → 8.80 (q, 3, $-CH_3$). *Anal.* Calcd for $C_4H_{11}N_2O_4P$: C, 26.37; H, 6.08; N, 15.38; P, 17.00. Found: C, 26.19; H, 5.92; N, 15.20; P, 17.10.

(3) **Gly-2-Aep:** mp 250° dec; nmr (NaOD) 6.37 (s, 2, NH_2–CH_2), 8.03 → 8.62 (m, 2, NH–CH_2), 6.30 → 6.82 (m, 2, CH_2–P). *Anal.* Calcd for $C_4H_{11}N_2O_4P$: C, 26.37; H, 6.08; N, 15.38; P, 17.00. Found: C, 26.46; H, 6.11; N, 15.33; P, 16.89.

Acknowledgment. The authors express their thanks to Dr. A. F. Isbell, Chemistry Department, Texas A&M University, for providing the aminophosphonic acids and for helpful discussions.

Registry No.—Glyamp, 30211-73-5; Gly-1-Aep, 53626-51-0; Gly-2-Aep, 53626-52-1; Phtglyamp, 38416-67-0; Phtgly, 4702-13-0; aminomethylphosphonic acid, 1066-51-9; Phtgly-1-Aep, 51814-60-9; 1-aminoethylphosphonic acid, 6323-97-3; Phtgly-2-Aep, 51814-61-0; 2-aminoethylphosphonic acid, 2041-14-7.

References and Notes

(1) This work was supported by a research grant, GM 20511, from The National Institute of General Medical Sciences.
(2) (a) M. Horiguch nd M. Kandatsu, *Nature (London)*, **184**, 901 (1959); (b) J. S. Kittredge, E. Roberts, and D. G. Simonsen, *Biochemistry*, **1**, 624 (1962); (c) L. D. Quin, *ibid.*, **4**, 324 (1965); (d) A. J. Koning, *Nature (London)*, **210**, 113 (1966); (e) T. Hori, O. Itasaka, H. Inoue, and K. Yamada, *J. Biochem. (Tokyo)*, **56**, 447 (1964); (f) J. A. Alhadeff and G. D. Davies, Jr., *Biochemistry*, **9**, 4866 (1970); (g) *Biochim. Biophys. Acta*, **244**, 211 (1971).
(3) (a) G. Rouser, G. Kritchevsky, D. Heller, and E. Lieber, *J. Amer. Oil Chem. Soc.*, **40**, 425 (1963); (b) E. Baer and N. Z. Stanacev, *J. Biol. Chem.*, **239**, 3209 (1964).
(4) L. D. Quin, *Science*, **144**, 1133 (1964).
(5) L. D. Quin, "Topics in Phosphorus Chemistry," Vol. 4, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N.Y., 1966.
(6) M. Hariharan and A. E. Martell, *Syn. Commun.*, **3**, 375 (1973).
(7) J. P. Greenstein and M. Winetz, "Chemistry of the Amino Acids," Wiley, New York, N.Y., 1961.
(8) M. Hariharan and A. E. Martell, unpublished results.
(9) K. Yamauchi, M. Kinoshita, and M. Imoto, *Bull. Chem. Soc. Jap.*, **45**, 2528 (1972).
(10) J. H. Billman and W. F. Harting, *J. Amer. Chem. Soc.*, **70**, 1473 (1948).
(11) F. E. King, J. W. Clark-Lewis, R. Wade, and W. A. Swindin, *J. Chem. Soc.*, 873 (1957).
(12) J. C. Sheehan and V. S. Frank, *J. Amer. Chem. Soc.*, **71**, 1856 (1949).
(13) S. R. Buck, *J. Amer. Chem. Soc.*, **69**, 254 (1947).
(14) S. Gabriel, *Ber.*, **41**, 242 (1908).
(15) A. E. Martell and R. M. Smith, "Critical Stability Constants," Vol. I, Plenum Press, New York, N.Y., 1974.

Mechanism and Stereochemistry of Oxetane Reactions. I. Stereospecific Synthesis of the Diastereoisomeric 2-Phenyl-3-methyloxetanes and Study of Their Configuration and Conformation by Nuclear Magnetic Resonance Spectroscopy

Aldo Balsamo, Giulio Ceccarelli, Paolo Crotti, and Franco Macchia*

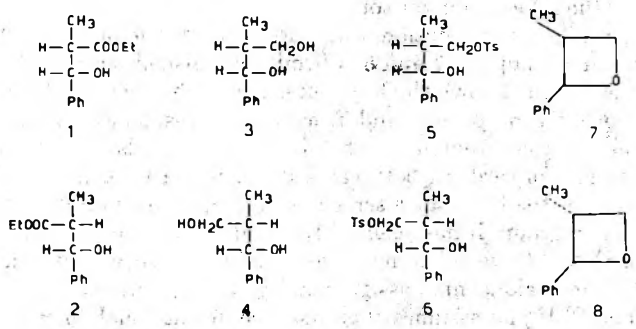
Istituti di Chimica Organica, Chimica Fisica e Chimica Farmaceutica, Università di Pisa, 56100 Pisa, Italy

Received March 5, 1974

The stereospecific synthesis of the diastereoisomeric 2-phenyl-3-methyloxetanes 7 and 8 has been achieved from the corresponding 1,3-diols through their monotosylates. The relative configurations of 7 and 8 have been unequivocally established by an extensive study of their nmr spectra. The assignment of the proton resonance signals has been effected on the basis of the shielding effects and of the coupling constants, and confirmed through additive shielding parameters. By using the J_{trans}/J_{cis} ratio it has been possible to obtain some informations on the conformational preference of the oxetane ring in the examined compounds.

The stereochemistry of the ring opening of small ring heterocycles such as oxiranes[1-3] and aziridine[4,5] in acid media is well known and documented. However, practically no information is available on the steric course of the analogous reactions of oxetanes.[6] Furthermore no "stereospecific" synthesis of diastereoisomeric couples of oxetane has been reported and only a few pairs of diastereoisomeric oxetanes have been prepared.[7] Since we are strongly interested in the study of mechanism and stereochemistry of the ring opening of small ring systems,[3,5] it was thought desirable to prepare and study diastereoisomerically pure oxetanes of unquestionable configuration. Oxetanes 7 and 8 appeared as promising substrates for this purpose and their synthesis and stereochemical characterization was the aim of this work.

The Reformatsky reaction of benzaldehyde and ethyl 2-bromopropionate gave a mixture of the diastereoisomeric esters *erythro*-1 and *threo*-2 whose relative configurations were deduced from their nmr spectra on the basis of the higher coupling constant of the benzylic proton for the threo isomer 2, as found for the corresponding methyl esters.[8] On the other hand reduction of 1 and 2 with $LiAlH_4$ afforded the known diols *erythro*-3 and *threo*-4.[8c,9] Reaction of 3 and 4 with *p*-toluenesulfonyl chloride in pyridine gave the respective monotosylates 5 and 6. The constitution of 5 and 6 could be inferred by the known fact that tosyl chloride should react preferentially with the primary rather than with the secondary hydroxyl group,[10] and confirmed from their nmr spectra. In fact whereas the chemical shift of the signals of the benzylic proton is almost the same for the diols 3 and 4 and the corresponding tosylates, the signals of the protons of the methylene group are shifted toward low field in the cases of tosylates. Treatment of 5 and 6 with potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature led to the diastereoisomerically pure oxetanes 7 and 8. The configurations of oxetanes 7 and 8 were



deduced from their method of synthesis. The complete stereospecificity of the formations of oxetanes 7 and 8 is in accordance with the mechanism of their formation from 5

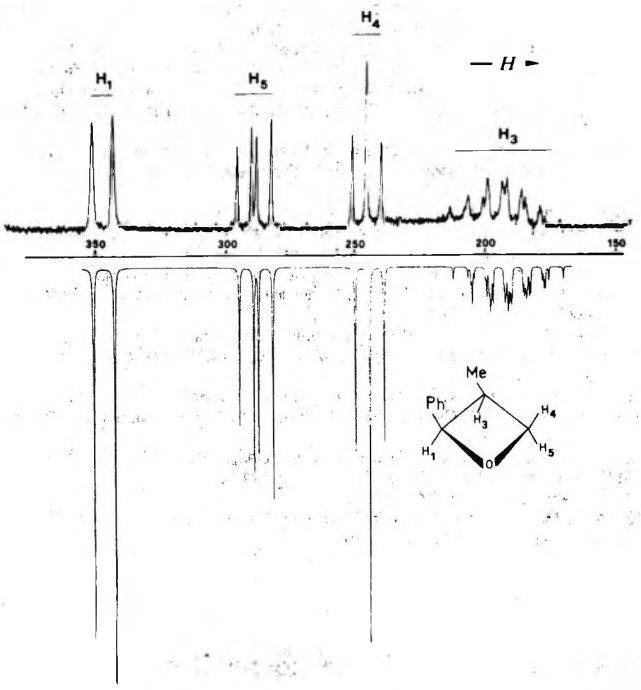


Figure 1. Observed and calculated spectrum of *cis*-2-phenyl-3-methyloxetane (7). Measured frequencies (in Hz) are relative to internal TMS.

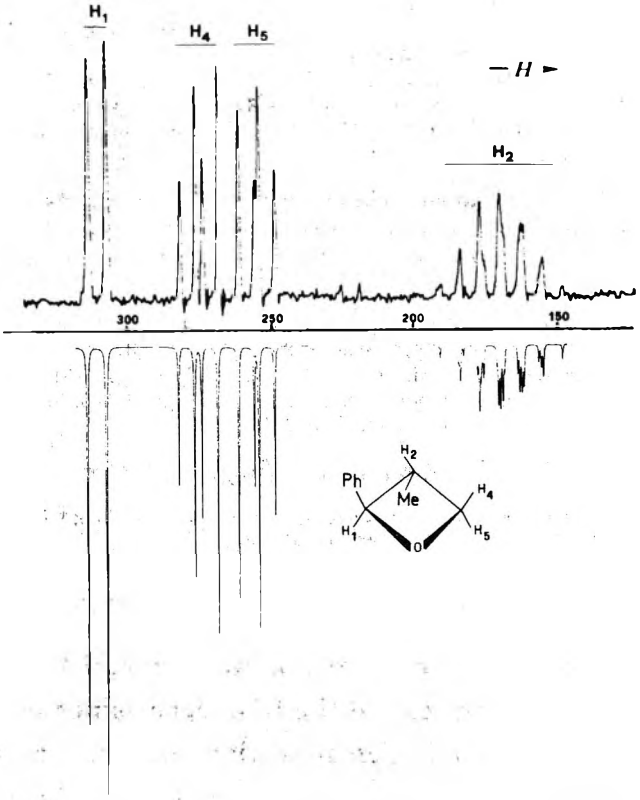


Figure 2. Observed and calculated spectrum of *trans*-2-phenyl-3-methyloxetane (8). Measured frequencies (in Hz) are relative to internal TMS.

and 6 which implies a SN2 type substitution. In this reaction the two chiral centers are not involved and oxetanes 7 and 8 should have the same relative configuration of the starting compounds. In any case the configurations of 7 and 8 have been unequivocally confirmed by an extensive study of their nmr spectra.

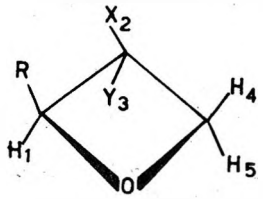
Relatively few nmr studies have been reported on the subject of oxetanes[11-17] in comparison with other four-membered ring compounds,[11,18] and just a few of those listed deal with conformational aspects.[13,14,17]

The complete analysis of the nmr spectra of *cis*-7 and *trans*-oxetane 8 should include, in addition to the oxetane ring and methyl group protons, the five protons of the phenyl ring; however, since the coupling constants between the protons of the phenyl and oxetane ring were not observable, the analyses have been performed as an $ABCDX_3$ spin system from the 60-MHz nmr spectra. The theoretical spectra were calculated using program LEQUOR, a seven-spin system modified from LAOCOON-3.[19] Figures 1 and 2 show the observed and calculated spectra of 7 and 8, respectively.

Table I gives the values of the spectral parameters of 7 and 8 obtained from the above mentioned analysis. Furthermore, the corresponding data for unsubstituted oxetane 9[16] and 2-phenyloxetane 10[12a] have also been reported for the sake of comparison.

While the attribution of the protons α to the phenyl and methyl groups of 7 and 8 is firmly established both on the basis of the known shielding effects of such substituents on the adjacent proton and from double resonance experiments, the assignment of H_4 and H_5 signals is not so straightforward. In both cases it is necessary to take into account the long-range screening effects of the methyl and phenyl group. It has been fairly well demonstrated that the use of additive shielding increments can often be a useful tool in making nmr assignments in configurational problems.[20] If one assumes that small conformational changes of the oxetane ring do not affect to a large extent the chemical shift of the oxetane protons and the substituent effects, then the evaluation of the chemical shifts through additive shielding parameters can be used with a sufficient accuracy in the present situation. The contribution to the chemical shift of the 2-phenyl group on the cis (H_4) and trans (H_5) protons can be computed by comparison of the suitable spectral parameters of 2-phenyloxetane (10) and of oxetane itself (9) ($\Delta\delta$(Ph cis) = +0.2 Hz; $\Delta\delta$(Ph trans) = +10.1 Hz). The shielding of the 3-methyl group on cis and trans vicinal protons can be, on the other hand, deduced by comparing the chemical shift of the H_1 proton of oxetanes 8 and 10 and 7 and 10, respectively ($\Delta\delta(CH_3$ cis) = −37.1 Hz; $\Delta\delta(CH_3$ trans) = −0.2 Hz). By adding the appropriate contribution to the chemical shift of the α protons of the unsubstituted oxetane 9, the theoretical chemical shift of H_4 and H_5 protons of 7 and 8 can be predicted (see Table I). The very good agreement between the calculated and observed chemical shifts provides unambiguous proof of the assignment of the relative proton resonance positions and clearly demonstrates the usefulness of the additivity principle also in these cyclic systems. The relative configurations of oxetanes 7 and 8 have been confirmed by the following considerations. Whereas the proton resonance position of the methyl group in the trans compound 8, when compared with the corresponding 3,3-dimethyloxetane (76.5 Hz),[12c] is practically unaffected by the presence of the phenyl group, in compound 7 it resonates at much higher field. This fact agrees with the shielding variation arising from the changes in the magnetic field caused by the ring current[21] keeping in mind that the phenyl ring should spend most of its time in a preferred conformation in which the plane of the phenyl ring lies very near the oxygen atom.[12a] Furthermore, the value of the J_{13} of 7 is higher than the J_{12} of 8 which agrees with the finding that in oxetanes vicinal cis coupling constants are of a higher value that the trans ones.[12,16] Furthermore, the values of the vicinal coupling constants of the H_4 and H_5 protons of 7 and 8 also confirm the assignment of their resonance positions made on the basis of the additive shielding increments.[22] A final confirmation came from the nuclear Overhauser effect

Table I
The Pmr Parameters for Oxetanes[a]



	Compd			
	7[b]	8[b]	9[16]	10[12a]
R	C_6H_5	C_6H_5	H	C_6H_5
X	CH_3	H	H	H
Y	H	CH_3	H	H
ν_1	347.43	310.47	277.25	347.61
ν_2	44.10	169.10	157.24	157.97
ν_3	191.97	77.90	157.24	178.73
ν_4	245.11 (240.4)	274.63 (277.3)	277.25	277.40
ν_5	288.71 (287.2)	254.89 (250.3)	277.25	287.36
J_{12}		6.67	6.60	7.31
J_{13}	8.10		8.70	7.79
J_{23}	7.10	6.80		−10.91
J_{24}		8.10	8.70	9.15
J_{25}		7.28	6.60	7.74
J_{34}	5.66		6.60	5.62
J_{35}	7.33		8.70	8.19
J_{45}	−5.59	−5.60		−5.75
J_{14}	0.0	0.0	0.14	−0.02
J_{15}	0.0	0.0	0.20	−0.03

[a] Chemical shifts (in Hz) are relative to TMS. [b] Values in parentheses have been calculated by the additive shielding parameters.

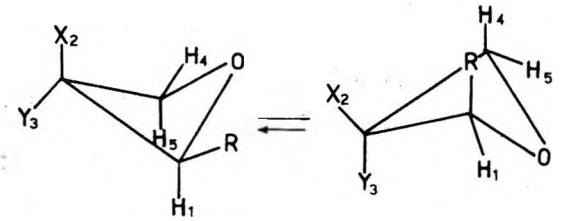
Table II
J_{trans}/J_{cis} Ratios for Oxetanes 7–10

J_{trans}/J_{cis}	7	8	9	10
J_{12}/J_{13}			0.76	0.94
J_{25}/J_{24}		0.90	0.76	0.85
J_{34}/J_{35}	0.77		0.76	0.69
J_{34}/J_{24}			0.76	0.61
J_{25}/J_{35}			0.76	0.95

(NOE); the intensities of the signals for H_4 in **7** and for H_1 and H_5 in **8** were increased respectively by 12, 18, and 11% on saturation of the methyl signal.

Even if oxetane is essentially planar,[23] it may be vibrating between two equivalent interconvertible ring-puckered conformations. However, the presence of one or more substituents on the ring can render one conformation more stable[14,24] and this could be made evident by nmr spectroscopy.

A comparison of the coupling constants of oxetanes **7**, **8**, and **10** with the corresponding ones of the unsubstituted oxetane **9** shows appreciable changes in the ring vicinal coupling constants; consequently, conformational modifications must occur with the substitution of the oxetane ring. However, the variation of the single coupling constants may not be the most reliable way to reveal small conformational changes because the coupling constants can be influenced by several factors other than dihedral angle modifications.[25] In a modification of the so-called "*R*-value" method,[26] the J_{trans}/J_{cis} ratio could provide a direct route for obtaining a qualitative picture of conformational preferences in these systems (factors other than conformational ones should be minimized by using this ratio[26a,b]). Table II reports the values obtained from oxetanes **7**, **8**, **9**, and **10**. Deviations from the J_{trans}/J_{cis} value 0.76 obtained from the parent oxetane **9** (in which there is absolutely no conformational preference between conformer a and b)



7a (R = Ph, X = CH_3, Y = H) 7b (R = Ph, X = CH_3, Y = H)
8a (R = Ph, X = H, Y = CH_3) 8b (R = Ph, X = H, Y = CH_3)
9a (R = X = Y = H) 9b (R = X = Y = H)
10a (R = Ph, X = Y = H) 10b (R = Ph, X = Y = H)

should be indicative of conformational modifications. When the oxetane ring assumes conformation a from an ideal planar structure the increase of dihedral angle between the 2 and 4 protons (φ_{24}) and 2 and 5 protons (φ_{25}) will decrease J_{24} and will increase J_{25};[27] evidently the effect on the value (J_{trans}/J_{cis}) will be an increase. The same situation will hold for the J_{12}/J_{13}, J_{25}/J_{35} ratios. On the contrary φ_{35} and φ_{34} will decrease, thus decreasing both J_{35} and J_{34}, but the over-all effect on the J_{34}/J_{35} will be a net decrease. The same is found for J_{34}/J_{24}. The exact opposite changes in the ratios will occur for conformation b.

The high value of the J_{25}/J_{24} for trans oxetane **8** indicates that it exists largely in the dipseudoequatorial puckered conformation a. Also for 2-phenyloxetane **10** (in the original paper[12a] the conformational aspect was not discussed by the authors) the J_{trans}/J_{cis} values are consistent with conformation a having the phenyl group pseudoequatorial.[14] Evidently the higher nonbonding repulsive interactions of the substituents in the more hindered pseudoaxial positions favor conformation a. The ratio found for the cis oxetane **7** does not differ significantly from the value obtained in the unsubstituted oxetane **9**; this means that **7** likely exists as an about 50:50 equilibrium of the two conformers a and b both with a pseudoequatorial and a pseudoaxial substituent.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer Infracord Model 137. Nmr spectra were determined on 10% solutions in carbon tetrachloride with a Varian DA-60 IL (operating at 60 MHz) spectrometer using tetramethylsilane as an internal standard. Peak positions were directly measured with a Marconi TF 2414 frequency meter and the mean values of five measurements were taken. Experimental line positions were determined to ±0.1 Hz. To compute the final chemical shifts, proton–proton couplings, and theoretical spectrum, an iterative program (LEQUOR) based on the method of Castellano and Bothner-By[19] was applied and solved with an IBM 370/155 computer equipped with a Calcomping plotting accessory. The parameters obtained should be correct to within ±0.1 Hz.

Glpc were run on a Carlo Erba Fractovap GV apparatus with a flame ionization detector, using a dual system with glass columns packed with 1% neopentylglycol succinate on 80–100 mesh silanized Chromosorb W. Preparative (2-mm layer) tlc were performed on silica gel F 254 plates containing a fluorescent indicator. Magnesium sulfate was used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator). Petroleum ether refers to the fraction boiling at 40–70°.

***erythro*-1 and *threo*-Ethyl-3-hydroxy-2-methyl-3-phenyl Propionate (2).** A mixture of 1 and 2 (106 g, bp 102–105° (0.2–0.3 mm) [lit.[28] 107–109° (0.3–0.4 mm)]) was obtained according to the procedure of Zimmermann and English[28] from benzaldehyde (63.6 g, 0.6 mol), ethyl bromopropionate (119.4 g, 0.66 mol) and zinc (43.9 g, 0.66 g-atom) in benzene (170 ml). The above mixture (30 g) was chromatographed through a 3.5 × 82 cm column of silica gel collecting 250-ml fractions. Elution was carried out, successively, with petroleum ether (9.0 l.) and 98:2 (9.0 l.), 97:3 (2.0 l.), 96:4 (63.0

l.), 95:5 (13.0 l.), 94:6 (9.0 l.) petroleum ether–ethyl acetate. The fractions were evaporated to dryness and checked by nmr and glpc. The fractions 104–190 were combinated as pure **1** (12.8 g): ir 2.86 (OH), 5.84 μ (CO): nmr δ 4.88 (1, H, d, J = 4.6 Hz, C_6H_5CH), 3.97 (2 H, q, CH_2), 2.60 (2 H, dq, CH_3CH), 1.11 (3 H, t, CH_3CH_2), 1.09 ppm (3 H, d, CH_3CH). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.12; H, 7.68.

The fractions 300–400 yielded pure **2** (5.5 g): ir 2.89 (OH), 5.82 μ (CO); nmr δ 4.56 (1 H, d, J = 8.55 Hz, C_6H_5CH), 4.02 (2 H, q, CH_2), 2.62 (2 H, dq, CH_3CH), 1.20 (3 H, t, CH_3CH_2), 0.91 ppm (3 H, d, CH_3CH). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.93; H, 7.56.

***erythro*-1-Phenyl-2-methyl-1,3-propanediol (3).** To a stirred suspension of $LiAlH_4$ (6.8 g, 0.18 mol) in dry ether (150 ml) was added dropwise a solution of **1** (12.5 g, 0.06 mol) in the same solvent (150 ml). The mixture was then refluxed for 7 hr and left at room temperature for 12 hr, after which excess $LiAlH_4$ was destroyed by adding water, followed by 2 M NaOH. The organic layer was separated, filtered, dried, and evaporated to give **3**[8c,9] (9.4 g) as a liquid: ir 2.97 μ (OH); nmr δ 4.76 (1 H, d, J = 3.1 Hz, C_6H_5CH), 3.41 (2 H, m, CH_2OH), 1.82 (1 H, m, CH_3CH), 0.67 ppm (3 H, d, J = 6.9 Hz, CH_3). The nmr data agree with the previously reported ones.[8c]

***threo*-1-Phenyl-2-methyl-1,3-propanediol (4).** Reduction of **2** (5.0 g, 0.024 mol) with $LiAlH_4$ (2.7 g, 0.072 mol) as described above yielded **4**[8c,9] (3.5 g) as an oil: ir 3.00 μ (OH); nmr δ 4.29 (1 H, d, J = 9.1 Hz, C_6H_5CH), 3.48 (2 H, m, C H_2OH), 1.81 (1 H, m, CH_3CH), 0.55 ppm (3 H, d, J = 6.9 Hz, CH_3). The nmr data agree with the previously reported ones.[8c]

***erythro*-1-Phenyl-2-methyl-3-tosyloxy-1-propanol (5).** A solution of tosyl chloride (3.81 g, 0.02 mol) in anhydrous pyridine (20 ml) was added to a solution of **3** (3.00 g, 0.018 mol) in the same solvent (30 ml), while keeping the temperature below 0°. After 4 days at 5°, the mixture was poured in ice and extracted with $CHCl_3$. Evaporation of the washed (1 M aqueous H_2SO_4, saturated aqueous $NaHCO_3$, and water) and filtered extracts gave pure **5** (3.9 g) as an oil: ir 2.80 (OH) 7.40, 8.41 and 8.51 μ (OSO_2-p-C_7H_7);[29] nmr δ 4.68 (1 H, d, J = 4.4 Hz, C_6H_5CH), 3.99, 3.71 (1 H each, q, CH_2O), 1.99 (1 H, m, CH_3CH), 0.74 ppm (3 H, d, J = 7.2 Hz, CH_3CH).

***threo*-1-Phenyl-2-methyl-3-tosyloxy-1-propanol (6).** **4** (3.0 g) was treated with tosyl chloride under the conditions used above to give pure **6** (4.3 g) as a liquid: ir 2.81 (OH), 7.40, 8.41, and 8.51 μ (OSO_2-p-C_7H_7);[29] nmr δ 4.20 (1 H, d, J = 8.2 Hz, C_6H_5CH), 4.07, 3.93 (1 H each, q, CH_2O), 1.97 (1 H, m, CH_3CH), 0.69 ppm (3 H, d, J = 7.2 Hz, CH_3CH).

***cis*-2-Phenyl-3-methyloxetane (7).** A solution of **5** (3.90 g, 12.2 mmol) in *tert*-butyl alcohol (40 ml) was treated with potassium *tert*-butoxide (1.8 g, 16.0 mmol) and left 24 hr at room temperature. Dilution with petroleum ether, filtration, and evaporation of the solvent gave a residue (1.50 g) consisting of crude **7**. Purification of this product through preparative tlc (a 8:2 mixture of petroleum ether–ethyl ether being used as eluent) yielded pure **7** (0.78 g): ir 10.15 μ (oxetane ring);[30] nmr (see Table I). *Anal.* Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.85; H, 8.05.

***trans*-2-Phenyl-3-methyloxetane (8).** Treatment of a solution of **6** (4.10 g, 12.8 mmol) in *tert*-butyl alcohol (40 ml) with potassium *tert*-butoxide (1.87 g, 16.7 mmol) as described above yielded **8** (1.70 g), which was purified through tlc to give pure product (0.95 g): ir 10.30 μ (oxetane ring);[30] nmr (see Table I). *Anal.* Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.83; H, 8.20.

Acknowledgment. This work was partly supported by a grant from the Consiglio Nazionale delle Ricerche (CNR).

Registry No.—**1**, 17226-82-3; **2**, 17226-81-2; **3**, 19774-62-0; **4**, 7087-77-6; **5**; 53432-97-6; **6**, 53432-98-7; **7**, 53432-99-8; **8**, 53433-00-4; **9**, 503-30-0; **10**, 4436-23-1; tosyl chloride, 98-59-9.

References and Notes

(1) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).
(2) A. Rosowsky, "Heterocyclic Compounds with Three- and Four-Membered Rings," A. Weissberger Ed., Part 1, Interscience, New York, N. Y., 1964, p 1.
(3) (a) G. Bellucci, B. Macchia, and F. Macchia, *Ann. Chim. (Rome)*, **59**, 1176 (1969); (b) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron*, **28**, 1299 (1972); (c) A. Balsamo, P. Crotti, B. Macchia, and F. Macchia, *Tetrahedron*, **29**, 199 (1973), and references cited therein.
(4) O. C. Dermer and G. E. Ham, "Ethylenimine and other Aziridines," Academic Press, New York, N. Y., 1969.
(5) G. Berti, G. Camici, B. Macchia, F. Macchia, and L. Monti, *Tetrahedron Lett.*, 2591 (1972).
(6) S. Searles, Jr., ref 2, Part 2, Interscience, New York, N. Y., 1964, p 983.
(7) A. V. Bogatskii, G. A. Filip, S. A. Petrash, L. S. Semerdzhi, Yu. Yu. Samitov, and G. V. P'Yankova, *Zh. Org. Khim.*, **7**, 577 (1971).
(8) (a) J. Canceill, J. Gabard, and J. Jacques, *Bull. Chem. Soc. Fr.*, 2653 (1966); (b) J. Canceill, J. J. Basselier, and J. Jacques, *ibid.*, 1024 (1967); (c) J. Canceill and J. Jacques, *ibid.*, 2180 (1970).
(9) K. Koga and S.-I. Yamada, *Chem. Pharm. Bull.*, **20**, 526 (1972).
(10) See, for example, R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **80**, 2726 (1958); W. S. Johnson, J. C. Collins, Jr., R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartmann, *ibid.*, **85**, 1409 (1963).
(11) R. F. M. White and H. Williams, "Physical Methods in Heterocyclic Chemistry," Vol. 4, A. R. Katritzky, Ed., Acedemic Press, New York, N. Y., 1971, p 121.
(12) (a) J. Jokisaari, E. Rahkamaa, and P. O. I. Virtanen, *Suom. Kemistilehti B*, **43**, 14 (1970); (b) J. Jokisaari and H. Ruotsalainen, *Z. Naturforsch. A*, **25**, 1655 (1970); (c) J. Jokisaari, *ibid.*, **26**, 136 (1971); (d) J. Jokisaari, E. Rahkamaa, and H. Maio, *ibid.*, **26**, 973 (1971).
(13) Yu. Yu. Samitov, A. V. Bogatskii, and G. A. Filip, *Dokl. Akad. Nauk SSSR*, **192**, 138 (1970); *Zh. Org. Khim.*, **7**, 585 (1971).
(14) A. A. Fomichev, R. G. Kostyanovsky, I. A. Zon, K. S. Zakharov, I. M. Gelia, and V. I. Markov, *Dokl. Akad. Nauk. SSSR*, **204**, 644 (1972).
(15) E. Lippert and H. Prigge, *Ber. Bunsenges. Phys. Chem.*, **67**, 415 (1963).
(16) R. Lozac'h and B. Braillon, *J. Chim. Phys. Physicochim. Biol.*, **67**, 340 (1970).
(17) A. A. Fomichev, I. A. Zon, I. M. Gella, R. G. Kostyanovsky, A. N. Saprin, and V. I. Markov, *Org. Magn. Resonance*, 5, 263 (1973).
(18) H. Booth, *Progr. Nucl. Magn. Resonance Spectrosc.*, **5**, 196 (1969).
(19) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).
(20) See, for example, S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969); U. E. Matter, C. Pasqual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691, 2023 (1969).
(21) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
(22) On the basis of the results obtained from the additive shielding increment calculations and the considerations of the coupling constants, it appears that the configuration assignment of the diastereoisomeric 2,3-dimethyloxetanes made by Samitov and coworkers[13] is in error and the acutal configuration is the inverse of that introduced by the Russian authors.[13]
(23) S. I. Chan, J. Zinn, and W. D. Gwinn, *J. Chem. Phys.*, **34**, 1319 (1961); A. Danti, W. J. Lafferty, and R. C. Lord, **ibid.**, **33**, 294 (1960); S. I. Chan, J. Zinn, and W. D. Gwinn, *ibid.*, **33**, 295 (1960); S. I. Chan, J. Zinn, J. Fernandez, and W. D. Gwinn, *ibid.*, **33**, 1643 (1960); S. I. Chan, T. R. Borgers, J. W. Russel, H. L. Strauss, and W. D. Gwinn, *ibid.*, **44**, 1103 (1966).
(24) G. Holan, C. Kowala, and J. A. Wunderlich, *J. Chem. Soc., Chem. Commun.*, 34 (1973).
(25) Reference 18, p 160.
(26) (a) J. B. Lambert, *J. Amer. Chem. Soc.*, **89**, 1836 (1967); (b) J. B. Lambert, R. G. Keske, and D. K. Weary, *J. Amer. Chem. Soc.*, **89**, 5921 (1967); H. R. Buys, *Recl. Trav. Chim., Pays-Bas*, **89**, 1253 (1970); (c) J. B. Lambert, *Accounts Chem. Res.*, **4**, 87 (1971).
(27) These and the other predictions follow directly from the use of the Karplus equation: M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).
(28) H. E. Zimmermann and J. English, Jr., *J. Amer. Chem. Soc.*, **76**, 2291 (1954).
(29) R. S. Tipson, *J. Amer. Chem. Soc.*, **74**, 1354 (1952).
(30) G. M. Barrow and S. Searles, *J. Amer. Chem. Soc.*, **75**, 1175 (1953).

Phenanthro[9,10-*c*]thiophene. Syntheses and Reactions[1]

Joan E. Shields*

Department of Chemistry, C. W. Post College, Brookville, New York 11548

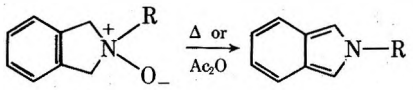
David E. Remy and Joseph Bornstein

Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167

Received September 5, 1974

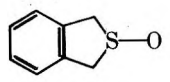
The reaction of 9-bromomethyl-10-chloromethylphenanthrene with alcoholic sodium sulfide has been found to yield not only 1,3-dihydrophenanthro[9,10-*c*]thiophene (**9**) as reported by earlier investigators, but also phenanthro[9,10-*c*]thiophene (**7**) in somewhat larger amount. Oxidation of **9** yielded the expected 1,3-dihydrophenanthro[9,10-*c*]thiophene 2-oxide (**8**) which, surprisingly, was also obtained from **7** by addition of the elements of water during attempted oxidation with *N*-bromosuccinimide in acetone–water solution. Sulfoxide **8** underwent facile elimination to afford **7** which gave a mixture of endo and exo Diels–Alder adducts on prolonged heating with *N*-phenylmaleimide in xylene.

Some time ago it was shown that isoindoline *N*-oxides (**1**, R = alkyl or aryl) lose the elements of water when pyrolyzed or treated with acetic anhydride to afford 2-substituted isoindoles (**2**) in good yield.[2] Subsequently, this

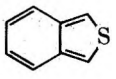


1 **2**

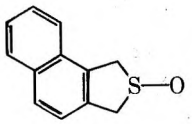
method was extended to the preparation of several polynuclear heterocyclic compounds where thiophene was annelated to benzene[3] and naphthalene.[4,5] For example, Cava and his coworkers[3,4] observed that 1,3-dihydrobenzo[*c*]thiophene 2-oxide (**3**) underwent dehydration to give benzo[*c*]thiophene (isothianaphthene) (**4**) and, in similar fashion, 1,3-dihydronaphtho[1,2-*c*]thiophene 2-oxide (**5**) afforded naphtho[1,2-*c*]thiophene (**6**). We now describe the first example of the reverse reaction: namely, the addition of the elements of water to phenanthro[9,10-*c*]thiophene (**7**) to form 1,3-dihydrophenanthro[9,10-*c*]thiophene 2-oxide (**8**). Furthermore, two new syntheses of **7** are reported together with a clarification of the results of the reaction used by earlier investigators[6] to prepare 1,3-dihydrophenanthro[9,10-*c*]thiophene (**9**).



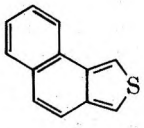
3



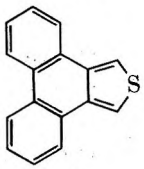
4



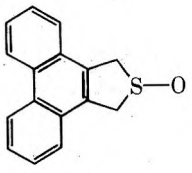
5



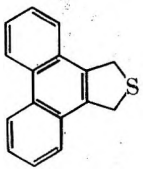
6



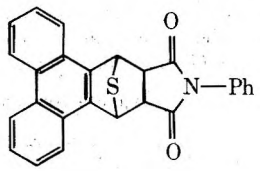
7



8



9



10, exo
11, endo

In connection with our general study of the chemistry of o-quinonoid heteroaromatic compounds and because of a specific interest in the effect of benzannelation[7] on the stability of these heterocycles, we had occasion recently to prepare 1,3-dihydrophenanthro[9,10-*c*]thiophene (**9**). Stille and Foster[6] had earlier described the synthesis of **9** by treatment of 9-bromomethyl-10-chloromethylphenanthrene with ethanolic sodium sulfide; they reported **9** to have mp 164–166°. Using their procedure we observed the formation of both phenanthro[9,10-*c*]thiophene (**7**) and the expected 1,3-dihydro derivative **9**. Similar results were obtained when the cyclization was subsequently repeated with 9,10-bis(bromomethyl)phenanthrene. Chromatographic separation of the reaction mixture afforded **7** (13%), mp 168–169°, and **9** (10%), mp 180–181°. The uv and nmr spectra of **7** and **9** served to distinguish these compounds. The uv spectrum of **9** was strikingly similar to that of 9,10-dimethylphenanthrene while **7**, as expected, exhibited absorption at longer wavelength due to the additional conjugation. Phenanthro[9,10-*c*]thiophene (**7**) showed only low-field absorption for aromatic protons in its nmr spectrum whereas the corresponding dihydro derivative **9** displayed typical benzylic signals in addition to peaks for aromatic protons.

To confirm further that the lower melting component of the product mixture is indeed phenanthro[9,10-*c*]thiophene (**7**), it was compared with an authentic sample (mp 168–169°) whose preparation was first reported by Hinsberg.[8] Both specimens were identical in all respects; hence, it is almost certain that the material melting at 164–166° and believed by Stille and Foster[6] to be 1,3-dihydrophenanthro[9,10-*c*]thiophene (**9**) was actually a mixture of **7** and **9**. The origin of **7** in the reaction of the 9,10-bis(halomethyl)phenanthrenes with sodium sulfide is obscure at this time, but it is possible that it is formed from **9** by oxidation during work-up of the reaction product. Compound **7**, like the previously reported nitrogen analog,[7,9] is an exceptionally stable o-quinonoid heterocycle and survives prolonged standing at room temperature. It will react slowly with *N*-phenylmaleimide (NPM), as noted below, suggesting that any difference in stability between **7** and **9** may be quite small. If this is the case, it would be reasonable to expect that oxidation of **9** to **7** should occur under relatively mild conditions. In this connection, it is interesting to note that the very reactive benzo[*c*]thiophene (**4**) was first synthesized by high-temperature catalytic dehydrogenation of its considerably more stable 1,3-dihydro derivative.[10]

Oxidation of sulfide **9** with sodium periodate in aqueous ethanol afforded the expected 1,3-dihydrophenanthro-

[9,10-*c*]thiophene 2-oxide (**8**) in 92% yield. When subjected to these same conditions, phenanthro[9,10-*c*]thiophene (**7**) was found to be inert, but quite surprisingly it underwent addition of the elements of water when treated with *N*-bromosuccinimide in aqueous acetone to give sulfoxide **8** in 77% yield. This material was shown by mixture melting point determination and spectral comparison to be identical with a specimen prepared from sulfide **9**. Using the procedures of Cava and coworkers[4] for effecting the dehydration of sulfoxides, we found that treatment of **8** with acetic anhydride or, more conveniently, pyrolysis of **8** in the presence of neutral alumina afforded phenanthro[9,10-*c*]thiophene (**7**) in 43% yield.

The high degree of stability possessed by **7** necessitated the use of rather drastic conditions to effect the Diels–Alder reaction; addition to NPM occurred only after a solution of the reactants in xylene was heated at reflux for 3 days. The reaction product was separated by column chromatography into two stereoisomeric adducts, exo isomer **10** (67%) and endo isomer **11** (9%). The assignment of structures **10** and **11** to the adducts was made on the basis of their nmr spectra which are similar in many respects to those of the related exo and endo NPM adducts of naphtho[1,2-*c*]thiophene.[4]

Experimental Section

Melting points were determined on a Mel-Temp melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord. Ultraviolet spectra were obtained on a Cary 17 spectrophotometer. Nuclear magnetic resonance spectra were taken on Varian Model T-60 and HA-100 spectrometers. Elemental analyses and molecular weight determinations were performed by Dornis and Kolbe Microanalytical Laboratory, Mülheim, Germany.

Reaction of 9-Bromomethyl-10-chloromethylphenanthrene with Sodium Sulfide. Phenanthro[9,10-*c*]thiophene (7) and 1,3-Dihydrophenanthro[9,10-*c*]thiophene (9). A solution of 19.0 g (0.08 mol) of sodium sulfide nonahydrate in 500 ml of ethanol was heated at reflux for 48 hr in an apparatus fitted with a Soxhlet extractor holding 5.0 g (0.015 mol) of 9-bromomethyl-10-chloromethylphenanthrene.[6] The reaction mixture was poured into 1 l. of water and the resulting suspension was collected by filtration. The crude solid was extracted with five 100-ml portions of boiling ethanol and the combined extracts were evaporated *in vacuo* to give 1.1 g of yellow solid. Chromatography on a column of silica gel with petroleum ether as eluent gave two fractions. The first fraction, on recrystallization from benzene–cyclohexane, afforded 450 mg (13%) of **7** as colorless, felted needles, mp 168.5–169°; uv λ_{max} (EtOH) (ϵ) 253 nm (58,800), 262 (58,000), 275 (7100), 290 (7900), 305 (7100), 320 (4700), and 334 (2000); nmr ($CDCl_3$) δ 7.20–8.40 (m).

Anal. Calcd for $C_{16}H_{10}S$: C, 82.01; H, 4.30; S, 13.68; mol wt, 234. Found: C, 82.06; H, 4.28; S, 13.60; mol wt, 232 (osmometry).

The second fraction from the column was recrystallized from benzene–petroleum ether to give 350 mg (10%) of **9** as colorless needles: mp 180–181°; uv λ_{max} (EtOH) (ϵ) 254 nm (55,000), 277 (11,000), 287 (8340), and 300 (9100); nmr ($CDCl_3$) δ 6.9–8.1 (m, 8, aromatic) and 4.0 (s, 4, benzylic).

Anal. Calcd for $C_{16}H_{12}S$: C, 81.31; H, 5.12; S, 13.57; mol wt, 236. Found: C, 81.22; H, 5.15; S, 13.57; mol wt, 239 (osmometry).

Phenanthro[9,10-*c*]thiophene (7) by the Hinsberg Condensation.[8] A solution of 6.0 g (0.029 mol) of phenanthrenequinone and 6.0 g (0.029 mol) of diethyl thiodiglycolate in 600 ml of benzene was prepared by warming the mixture to 70°. This solution was cooled to 40° and added to a solution of 6.0 g (0.11 mol) of sodium methoxide in 45 ml of methanol which was immersed in an ice bath. The resulting dark green solution was stirred under an atmosphere of dry nitrogen at room temperature for 5 days and then added to 1 l. of water. The reddish-orange two-phase mixture was concentrated at reduced pressure to a volume of 300 ml and filtered to remove 2.1 g (35%) of unreacted phenanthrenequinone. Acidification of the filtrate with hydrochloric acid afforded 2.5 g of an orange solid which was collected by filtration; recrystallization from aqueous ethanol gave 1.70 g of phenanthro[9,10-*c*]thiophene-1,3-dicarboxylic acid, mp 240° dec.[11] Decarboxylation of the diacid by sublimation at 160° (1.0 mm) or by heating at 260° until evolution of carbon dioxide ceased afforded 0.90 g of crude **7**. Chromatography of this material on silica gel with benzene as eluent and subsequent recrystallization from benzene gave a pure sample of **7**, mp 168–169°, identical with the specimen prepared above by the method of Stille and Foster.

1,3-Dihydrophenanthro[9,10-*c*]thiophene 2-Oxide (8). A. From Compound 9. To a boiling solution of 60 mg (0.26 mmol) of **9** in 15 ml of ethanol was added a solution of 64 mg (0.30 mmol) of sodium periodate in 2.5 ml of water. The resulting solution was heated at reflux for 20 hr, cooled, diluted by addition of 25 ml of water, and extracted with two 25-ml portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate and concentrated under reduced pressure to yield 80 mg of crude solid, mp 210–215°. Recrystallization from benzene–hexane of the material thus obtained gave 60 mg (92%) of pure **8**, mp 215–216°. This compound was shown by mixture melting point determination and ir and nmr spectral comparison to be identical with **8** prepared below from **7**.

B. From Compound 7. A solution of 1.10 g (4.7 mmol) of **7** in 175 ml of 85% aqueous acetone was warmed to 50° and maintained at this temperature while a solution of 0.91 g (5.1 mmol) of *N*-bromosuccinimide in 40 ml of 50% aqueous acetone was added with stirring over a 10-min period. The resulting yellow solution was stirred for 1 hr at room temperature and the acetone was then removed under reduced pressure. Filtration gave 1.1 g of light yellow needles, mp 197–202°. Recrystallization from benzene–hexane yielded 0.91 g (77%) of **8** as colorless needles: mp 215–216°; ir (mull) 1050 cm^{-1} (SO); uv λ_{max} (EtOH) (ϵ) 255 nm (53,500), 277 (8700), 287 (6300), 300 (7900); nmr ($CDCl_3$) δ 7.3–7.9 (m, 8, aromatic), 4.65 (s, 4, benzylic).

Anal. Calcd for $C_{16}H_{12}OS$: C, 76.16: H, 4.79; S, 12.71. Found: C, 76.10; H, 4.82; S, 12.76.

Pyrolysis of Sulfoxide 8. Formation of 7. An intimate mixture of 1.0 g (4.0 mmol) of **8** and 300 mg of neutral alumina (Merck, activity grade I) was heated in a sublimation apparatus at 180° (25 mm). The colorless crystals which collected on the cold finger were recrystallized from benzene to give 0.40 g (43%) of **7**, mp 167–168°. This material was shown to be identical with the samples of **7** prepared above.

Diels–Alder Reaction of 7 with *N*-Phenylmaleimide. Formation of Adducts 10 and 11. A solution of 900 mg (3.8 mmol) of **7** and 700 mg (4.0 mmol) of *N*-phenylmaleimide in 100 ml of dry xylene was heated under reflux for 72 hr. Evaporation of the resulting suspension *in vacuo* afforded 1.6 g of crude solid which was dissolved in benzene and chromatographed on silica gel using benzene as eluent. Three fractions were obtained. The first fraction gave 350 mg of a mixture consisting of unreacted **7** and *N*-phenylmaleimide. The second fraction yielded 1.03 g (67%) of exo adduct **10**, as a white solid, mp 253–255°, which on recrystallization from benzene–petroleum ether afforded an analytically pure sample: mp 254.5–255° dec; nmr (DMSO-d_6) δ 7.20–8.95 (m, 13, aromatic), 5.90 (s, 2, bridgehead), and 3.58 (s, 2, α to imide C=O).

Anal. Calcd for $C_{26}H_{17}NO_2S$: C, 76.64; H, 4.20; N, 3.44; S, 7.87; mol wt, 408. Found: C, 76.45; H, 4.15; N, 3.44; S, 7.86; mol wt, 410 (osmometry).

The third fraction gave 135 mg (9%) of endo adduct **11**. Recrystallization from benzene–petroleum ether yielded 110 mg of pure **11** as colorless plates: mp 225–226°; nmr (DMSO-d_6) δ 7.60–8.89 (m, 11, aromatic), 6.95 (m, 2, aromatic H ortho to N), 5.85 (m, 2, bridgehead), and 4.48 (m, 2, α to imide C=O).

Anal. Calcd for $C_{26}H_{17}NO_2S$: C, 76.64; H, 4.20; N, 3.44; S, 7.87; mol wt, 408. Found: C, 76.43; H, 4.42; N, 3.49; S, 7.85; mol wt, 410 (osmometry).

Acknowledgments. The authors are grateful to the U.S. Army Natick Laboratories for the award of a Predoctoral Fellowship to D.E.R.

Registry No.—**7**, 235-95-0; **8**, 53449-54-0; **9**, 53449-55-1; **10**, 53449-56-2; **11**, 53495-82-2; 9-bromomethyl-10-chloromethylphenanthrene, 35974-44-8; sodium sulfide, 16721-80-5; phenanthrenequinone, 84-11-7; diethyl thiodiglycolate, 925-47-3; phenanthro[9,10-*c*]thiophene-1,3-dicarboxylic acid, 19799-45-2; *N*-bromosuccinimide, 128-08-5; *N*-phenylmaleimide, 941-69-5.

References and Notes

(1) Presented in part at the Fifth Northeast Regional Meeting of the American Chemical Society, Rochester, N.Y., Oct 1973.
(2) For a review, see J. D. White and M. E. Mann, *Advan. Heterocycl. Chem.*, **10**, 119 (1969).
(3) M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.*, **88**, 4112 (1966).

(4) M. P. Cava, N. M. Pollack, O. A. Mamer, and M. J. Mitchell, *J. Org. Chem.*, **36**, 3932 (1971).
(5) D. W. H. MacDowell, A. T. Jeffries, and M. B. Meyers, *J. Org. Chem.*, **36**, 1416 (1971).
(6) J. K. Stille and R. T. Foster, *J. Org. Chem.*, **28**, 2708 (1963).
(7) J. Kopecký, J. E. Shields, and J. Bornstein, *Tetrahedron Lett.*, 3669 (1967); J. E. Shields and J. Bornstein, *J. Amer. Chem. Soc.*, **91**, 5192 (1969).
(8) O. Hinsberg, *Chem. Ber.*, **43**, 901 (1910). For a review of the Hinsberg thiophene ring synthesis, see D. E. Wolf and K. Folkers, *Org. React.*, **6**, 410 (1951).
(9) J. S. Dewar, A. J. Harget, N. Trinajstić, and S. D. Worley, *Tetrahedron*, **26**, 4505 (1970).
(10) R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.*, **20**, 244 (1963).
(11) Hinsberg, ref 8, p 903, reported the diacid decomposed at 270°, but noted this value depended on the purity of the compound and the method of heating.

Acid-Catalyzed Rearrangements of Humulene[1]

William G. Dauben,* James P. Hubbell, and Noel D. Vietmeyer

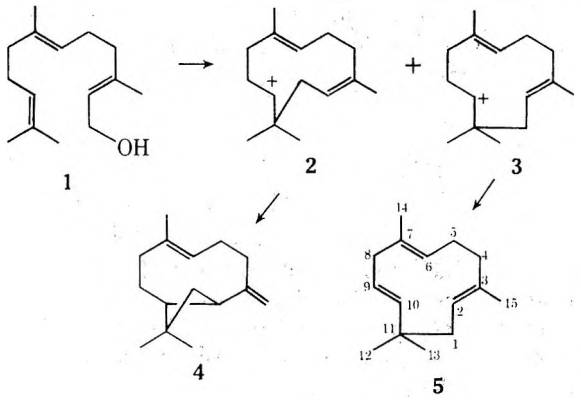
Department of Chemistry, University of California, Berkeley, California 94720

Received August 14, 1974

Upon extended treatment with acid, the sesquiterpene humulene yielded 20–25% α-caryophyllene alcohol and 70–75% mainly a new bicyclic sesquiterpene hydrocarbon. The structure of the material, as well as a series of its precursors, was established. The mechanism of the transformation was shown to proceed *via* a series of stepwise rearrangements.

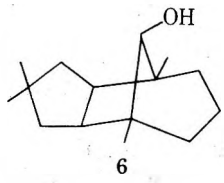
In recent years considerable interest has been directed toward the biogenesis, rearrangement, and synthesis of polyisoprenoid natural products. The finding of the enzymatically induced cyclization of squalene epoxide to lanosterol called attention to the high degree of specificity of a polycyclization initiated by formation of a carbonium ion. The *in vitro* equivalent of the process, *i.e.*, regiospecific carbonium ion generation, has been utilized by Johnson[2] to convert polyolefins to steroids, by Marshall[3] to convert bicyclo[4.3.1]decanes to hydroazulenes, and by studies in this laboratory[4] of the acid catalyzed rearrangement of the cyclopropyl–ene system in the sesquiterpene thujopsene to yield sesquiterpenes of the widdrene and chamigrene series.

In the Hendrickson biogenetic hypothesis for bicylic and tricyclic sesquiterpenes,[5] key intermediates were the eleven-membered ring carbonium ions **2** and **3**, respectively.



These ions were suggested to be the intermediates in the transformation of farnesol (**1**) to caryophyllene (**4**) and humulene (**5**). It was of particular interest that the ion **3** was related to humulene (**5**) by simple loss of a proton and such a relationship called attention to the possibility of the acid catalysis of the reverse process, **5** to **3**.

The acid-catalyzed rearrangement of α-humulene, itself, was first reported by Nickon[6] who reported that the hydrocarbon upon treatment with sulfuric acid in ether gave rise to alcohol **6** in 12–24% yield. The present studies were directed toward a more controlled reaction and investigation of all the products of the reaction. It was found that humulene (>97% pure) in refluxing dioxane–water containing 0.02 *M* perchoric acid yielded 20–25% of alcohol **6** (stable



6

under the reaction conditions) and that the 75–80% of the remaining material was more than 90% of one hydrocarbon. This major material was isolated and its structure established.

The product (**7**) was isomeric with humulene (mass spectrum) and possessed an s-trans conjugated diene chromophore (uv max 245 nm, ε 12,000). The nmr spectrum showed signals for one vinyl hydrogen atom, one vinyl methyl group, one quaternary methyl group, and an isopropyl group. The presence of the isopropyl group was further confirmed by double resonance studies and by an M − 43 peak (93% of base peak) in the mass spectrum. These data indicated the absence of any additional double bond in the structure and with the conjugated diene accounting for only two degrees of ursaturation, the hydrocarbon **7** must be bicyclic. Furthermore, the quaternary methyl group most likely was at an angular position.

The material was dihydrogenated and vpc analysis of the crude reduction product showed the presence of 79% of hydrocarbon **8**, 17% of hydrocarbon **9**, and 4% of starting material. If the reaction mixture was allowed to remain under hydrogenation conditions for an extended period (6–8 hr) practically no further uptake of hydrogen occurred but the only product obtained was **9**. The isomeric dihydro derivatives were isolated by preparative vpc. The nmr spectrum of **8** showed signals for one vinyl proton, an isopropyl group, an angular methyl group, and a new secondary methyl group but no vinyl methyl group. The final product **9** which was resistant to further hydrogenation showed no vinyl proton signals in the nmr spectrum but did show double bond absorption in the Raman spectrum. This unsaturated bond cannot be between two rings since there is an angular methyl group. Furthermore, since there is no vinyl methyl group, it follows that the isopropyl group must be on the tetrasubstituted double bond.

Treatment of hydrocarbon **8** with osmium tetroxide yielded diol **10** which was cleaved with lead tetraacetate to give a keto acid **11a**. The ir spectrum of the keto acid and its methyl ester indicated the presence of a five-membered

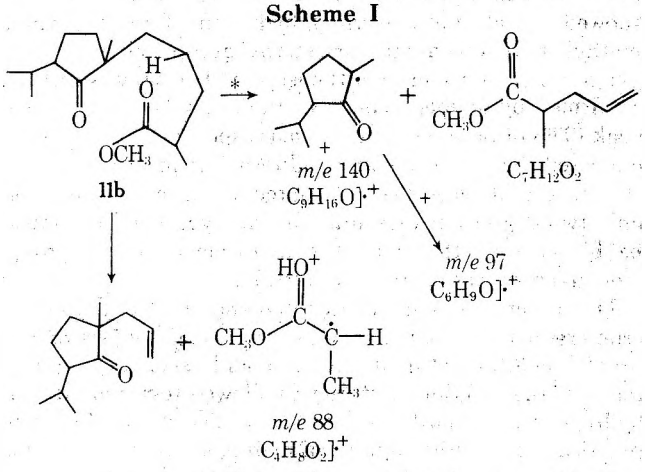
Table I
Acid-Catalyzed Rearrangement of Humulene[a]

	Relative %						
					Hydrocarbon		
Time, hr	α-Humulene	Alcohol 6	Alcohol 21	β-Humulene	7	19	20
0	100						
5	76			4.0			
8	57			4.6			
9	56						
13	46			5.7			
19	33	1.4	1.8	6.3			
35	20						
40	18	3.5	6.3	7.8	0.2	0.7	1.7
51	14.4	6.6	8.3	7.3	0.6	1.5	2.3
55	13.5	7.5	8.5		0.8	1.7	3.4
75	12	8.9	11.9	6.0	0.9	2.3	7.3
92				4.9			
134				4.4			
159	4.7	9.0	18.5	3.3	5.7	5.4	13.3
183	4	10.1	18.7		7.1	6.1	16.8
206	3.5	11.1	18.3	8.6	8.6	6.0	17.8
254	2.6	11.6	17.6		12.3	7.0	23.0
307	1.4	12.3	15.9		14.5	7.8	24.6
355		14.6	13.8		18.3	7.4	28.6
473		18.0	10.3		28.7	5.4	26.7

[a] A 0.105 *M* solution of humulene in a 20% aqueous dioxane, 0.02 *M* in $HClO_4$, was heated at 67°.

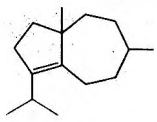
ring ketone (1739 cm^{-1}). Thus, the other ring of this bicyclic system must be seven membered. Further structural information was gained by high resolution mass spectrometry. The base peak for the keto ester **11b** had an *m/e* of 140 and by exact mass measure was $C_9H_{16}O$. The loss of mass 128 ($C_7H_{12}O_2$) most likely resulted from the McLafferty rearrangemert as shown in Scheme I and showed that this piece derived from the seven-membered ring portion of the

Scheme I



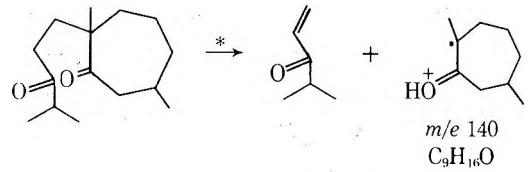
molecule could not contain the isopropyl group. Further evidence for the assignment of the isopropyl group on the cyclopentanone ring was the loss of 43 (C_3H_2) from the *m/e* 140 peak to form C_6H_9O (*m/e* 97). Some evidence suggesting the position of the tertiary methyl group in hydrocarbon 8 was derived from the appearance of *m/e* 88. This peak could result from a McLafferty rearrangement involving the ester function and would require a methyl group α to the ester function.

The isomeric monoolefin **9** with the tetrasubstituted double bond was also converted to a glycol and cleaved to yield the dione **12**. Since the earlier discussed nmr data showed the isopropyl group was on the double bond, the unsaturated linkage containing it must be exocyclic to a ring as it is the only arrangement possible for a tetrasubstituted double bond without involvement of the methyl group. The diketone possessed carbonyl frequencies in the infrared (1712, 1700 cm^{-1}) which were in agreement with those reported for the ozonization product of olefin **13** de-



13

rived from the sesquiterpene carotol.[7] Using high resolution mass spectral data, the peak of *m/e* 140 ($C_9H_{16}O$) was shown by a metastable ion study to have a parent of *m/e* 238 ($C_{15}H_{26}O_2$). The loss of $C_6H_{10}O$ would easily be ex-

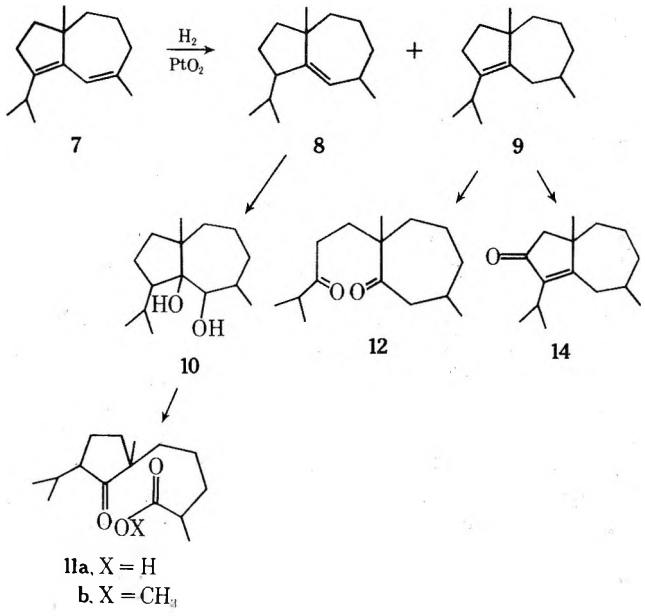


plained by a McLafferty rearrangement. This fragmentation pattern when coupled with the earlier discussed placement of the isopropyl group established that diketone **12** must contain a seven membered ring with two methyl groups (*m/e* **140**, $C_9H_{16}O$).

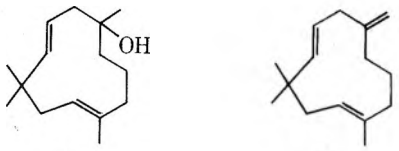
These degradational and spectral studies established the structure of the basic ring system of the rearrangement hydrocarbons. Further supporting evidence was obtained by allylic oxidation of olefin **9** to give the conjugated cyclopentenone **14**. The most characteristic change in the nmr spectrum of this product was the appearance of a sharp two-proton singlet corresponding to a methylene group between the carbonyl group and a quaternary center. This finding is direct evidence for the placement of an angular methyl group. The degradational studies are summarized in Scheme II.

To obtain additional information with regard to the reaction pathway, the rearrangement of humulene was run at a lower temperature and the course of the reaction was

Scheme II

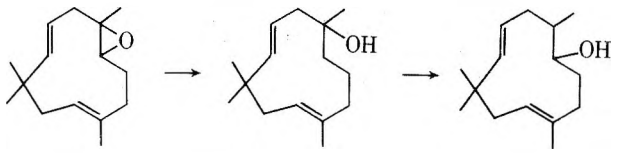


followed by vpc. The results (Table I, and Figure 1–3) showed that the initial products formed were humulol (**15**) and β-humulene (**16**).[8] The nmr spectrum of humulol was



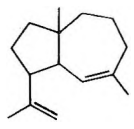
15 **16**

identical with a major alcohol isolated from hop oil by Buttery,[9] and later by Naya and Kotake.[10] To establish the correctness of structure **15** for the natural humulol, the material was synthesized in an unequivocal manner. Humulene was converted to the monoepoxide **17** (humulene epoxide II) by treatment with *m*-chloroperbenzoic acid and the resulting epoxide was allowed to react with lithium in ethylamine[11] to give humulol (**15**) in 9% yield and isohumulol (**18**) in 56% yield. The synthetic **15** possessed the same ir, nmr., and mass spectra as well as vpc retention time (500 ft × 0.02, PPE) as the natural humulol.



17 **15** **18**

Next, the major hydrocarbon intermediates formed during these controlled reactions were examined. The nmr spectrum of **19** showed signals for three vinyl protons, two



19

vinyl methyl groups, and one quaternary (angular) methyl group. The infrared spectrum showed bands at 890 and 1640 cm^{-1}, indicating the hydrocarbon possessed an unsymmetrical disubstituted methylene group. Specific hydrogenation of this double bond gave rise to a dihydro isomer which was shown to possess an isopropyl group by nmr analysis. The mass spectrum of this material showed a

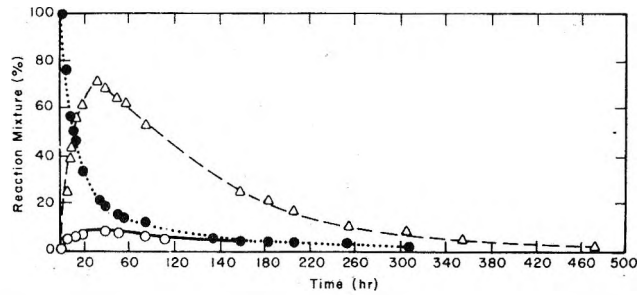


Figure 1. Relative composition *vs.* time: humulene (**5**), ●; humulol (**15**), △; β-humulene (**16**), ○.

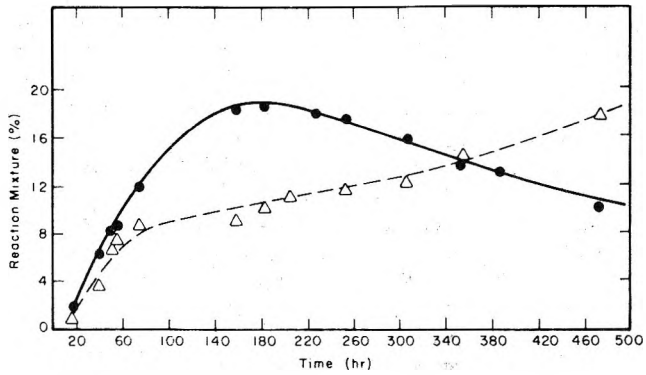


Figure 2. Relative composition *vs.* time: α-caryophyllene alcohol (**6**), △; alcohol **21**, ●.

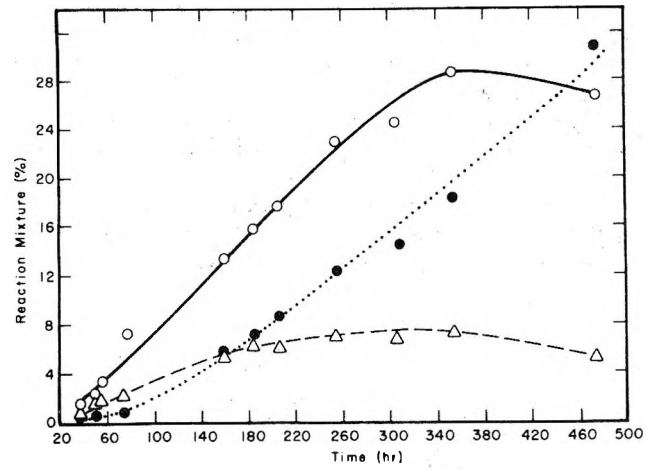
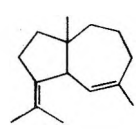


Figure 3. Relative composition *vs.* time: hydrocarbon **7**, ●; hydrocarbon **19**, ○; hydrocarbon **20**, △.

fragmentation pattern almost identical with that of hydrocarbon **7**, suggesting that both materials possessed the same carbon skeleton. This conclusion was verified by the finding that **19** upon treatment with acid was converted to **7**. Thus, the isopropenyl structure shown in **19** was established.

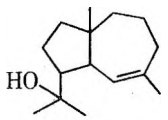
Hydrocarbon **20** also showed a mass spectral fragmentation pattern similar to that of **7**. The nmr spectrum showed



20

signals for one vinyl proton, three vinyl methyl group, and one quaternary (angular) methyl group. Also, the spectrum possessed a one-proton multiplet absorption at δ 3.20, characteristic of a doubly allylic hydrogen atom. Based upon these spectral features and its conversion to **7** upon acid treatment, the isopropylidene structure shown in **20** was established.

The alcohol **21** formed in the controlled studies was next studied. This material could only be obtained in 90% purity



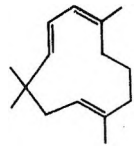
21

with α-caryophyllene alcohol being the only impurity. The nmr spectra of the material showed signals for one vinyl proton, two equivalent methyl groups α to a carbon atom holding a hydroxyl grouping, one vinyl methyl group, and one quaternary (angular) methyl group. The mass spectral fragmentation pattern, after loss of water, was similar to those of hydrocarbons **7**, **19**, and **20**. The alcohol was dehydrated *via* treatment of its mesylate with triethylamine and the hydrocarbon mixture obtained as shown, by vpc analysis, contained 16% of **7**, 30% of **19**, and 54% of **20**. All these results establish the structure **21** for the alcohol.

The structural assignments for the hydrocarbons **19** and **20** and for the alcohol **21** recently have been corroborated by Naya and Hirose[12] in an independent study, the gross carbon skeleton being based upon the present structural proof for the hydrocarbon **7**.

From the structures of the various intermediates formed in the controlled acid-catalyzed rearrangement of humulene and from the simple kinetic studies, it appears that humulol was first formed from humulene in a reversible reaction. Then, humulol *via* an intermediate(s) formed α-caryophylene alcohol (**6**) and alcohol **21**, the latter, in turn, being converted to hydrocarbons **19**, **20**, and **7**.

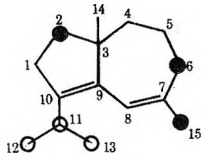
Attention was next directed to the details of the rearrangement pathway followed by humulene. Recent chemical studies by Nickon[6] and ^{13}C nmr studies by Nickon and Stothers[13] have elaborated the pathway leading to the formation of α-caryophyllene alcohol (**6**) and showed the requirement of the intermediate triene **22** in the rearrange-



22

ment process. To determine whether this same triene was a required intermediate in the formation of alcohol **21**, a time study was done for the conversion of humulene to **6** and **21** under reaction conditions of perchloric acid in refluxing dioxane–water. It was found that the ratio of their formation changed with time, the values for the ratio of **21** to **6** at 1, 2, and 4 hr being 0.6, 0.9, and 1.2, respectively. These data clearly indicate that triene **22** although a required intermediate for **6** is not so required for the formation of **21**. Also, if **21** came *via* triene **22**, a protonation of the isolated double bond would be required for the cyclization. Such a protonation should be reversible but Nickon and Stothers did not find a deuterium at this position in their study of the formation of **6** in D_2SO_4.

A sample of deuterated **7** was prepared from humulene under the same conditions used above for the preparation of deuterated **6**.[13] Under these conditions, the deuterium incorporation was extensive and the material contained 11% d_0, 15% d_1, 17% d_2, 17% d_3, 14% d_4, and 13% d_5, by mass spectral analysis. The nmr spectrum showed a significant loss (~30–40%) of absorption at the vinyl methyl group (C-15 humulene numbering) and a slight loss (~10–15%) of intensity at the isopropyl group (C-12 and C-13). There was no loss of absorption at the angular methyl group (C-14).

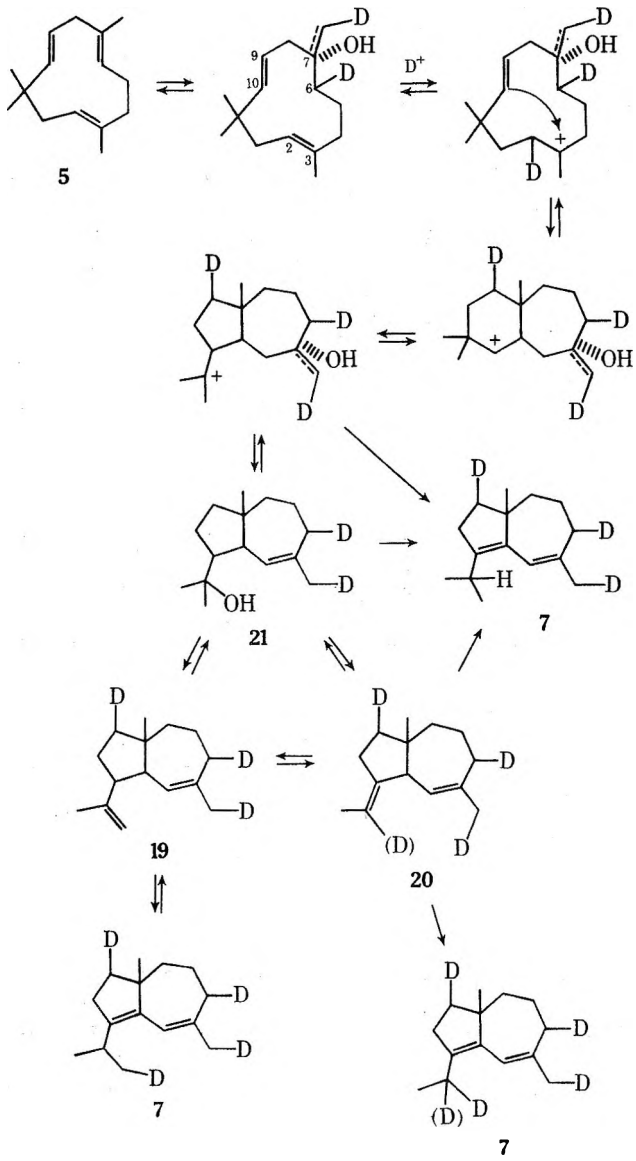


● = major deuterium location

○ = minor deuterium location

To obtain the placement of the other deuteria, hydrocarbon **7**, and its dihydro derivative **9** and deuterated **7** were submitted to ^{13}C nmr analysis. With the knowledge that α-humulene, β-humulene, and humulol are rapidly interconverted (see Figure 1) and by comparison of the absorptions of **7** with dihydro **9**, the assignment of the allylic methylene at C-6 was made. Also, in making some of the other assignments it was assumed that the absorpion bands of all carbons except 5, 6, 7, 8, 9, and 15 would not shift greatly upon dihydrogenation of **7** to **9**. The assumption was based upon the fact that the rigidity of the five-membered ring in **9** was retained. This analysis permitted assignment of C-2 in the spectrum. With deuterated **7**, major deuterium concentration was at carbons 2, 6, and 15; a

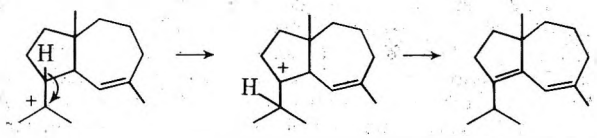
Scheme III



minor amount was located in the isopropyl carbons 11, 12, and 13.

With these data, the mechanism for the humulene interconversions can be accounted for as shown in Scheme III. First, the 6, 7 double bond of humulene is blocked by selective protonation either as humulol or β-humulene. This transformation directs the second protonation to occur at the 2,3 double bond, forming a tertiary carbonium ion which, in turn, cyclizes on the disubstituted double bond to yield the [5.4.0] bicycloundecane ring system. Finally, ring contraction with either concomitant dehydration (if humulol is the precursor) or double bond migration (if β-humulene is the precursor) leads to the products **7**, **19**, **20**, and **21**. Naya and Hirose[12,14a] have also studied the humulene isomerization and a similar mechanism to that first postulated by us was set forth on their minimal data.[14b]

Finally, it should be reemphasized that only a small amount of deuterium (<10%) was incorporated at C-11 of the isopropyl group. If, indeed, **21**, **19**, and **20** were required intermediates in the generation of **7**, then, as show, normal amounts of deuterium would have been found at C-11. Such not being the case indicates that under the conditions employed in this labeled experiment the majority of the final product **7** arose *via* a 1,2-hydride shift from C-10 to C-11, shown below.



Experimental Section

Microanalysis and mass spectra were obtained from the Microchemical and Mass Spectrometry Laboratories, College of Chemistry, University of California. Raman and some nmr (100 MHz) spectra were kindly provided by the U.S. Department of Agriculture Regional Laboratories, Albany, Calif. Unless noted, the infrared spectra were taken in carbon tetrachloride and the nmr spectra were taken in carbon tetrachloride with TMS as the internal standard. All carbon-13 nmr spectra were obtained at 25.2 MHz with a Varian XL100 spectrometer, with chloroform as a solvent and TMS as an internal reference, and were kindly provided by the Space Science Laboratory, University of Calif. Melting points were determined in open capillary tubes in a Buchi melting-point apparatus and are uncorrected.

In working up a reaction all solutions were dried by filtration through a small amount of anhydrous magnesium sulfate and were concentrated by rotary evaporation at reduced pressure with a water aspirator. Purification of compounds by column chromatography was carried out using Woelm neutral alumina or silica gel from E. M. Reagents.

All samples for analysis by vpc in kinetic studies of acid-catalyzed rearrangement reactions were neutralized by saturated sodium bicarbonate solution. The organic material was extracted with ether and the ether extract was dried and concentrated. If the samples were to be analyzed on capillary columns of OV101, OV225, or Apiezon, the alcohols were removed by chromatography on a short column of dry-packed activity III Woelm alumina.

Acid Treatment of Humulene. Into a 500-ml, three-necked flask fitted with a reflux condenser, stopper, serum cap, and a magnetic stirrer, under a nitrogen atmosphere, was added 180 ml of dioxane, 20 ml of water, 0.8 ml of 70% perchloric acid, and 4.2 g (20.6 mmol) of humulene. The solution was refluxed for 1 week at which time by vpc analysis (10 ft × ⅛ in. 5% KDH, 5% Carbowax 20M) it showed the presence of one major hydrocarbon. The reaction mixture was quenched with saturated sodium bicarbonate solution, the rearrangement products were extracted with hexane, and the extract was dried and concentrated. The residual oil was chromatographed on 80 g of dry-packed activity II alumina to give 2.1 g of hydrocarbons (hexane eluate) and 1.8 g of alcohols (ether eluate). Analysis of the hydrocarbon fraction by vpc (500 × 0.02″ OV101) showed one hydrocarbon was present to at least 90%. Collection of this hydrocarbon by vpc (10 ft × ⅜ in. 10% KOH, 10% Carbowax 20M) gave pure hydrocarbon **7**: ir (CCl_4, CS_2) 1380, 1372, 1369, 1360, 861 cm^{-1}; Raman 1650 cm^{-1}; uv (95% EtOH) 245 nm (ε 12,000); nmr δ 5.86 (s, 1), 2.70 (septet, 1, J = 7 Hz), 1.72 (s, 3), 0.94 (d, 3, J = 7 Hz), 0.92 (s, 3), 0.90, (d, 3, J = 7 Hz); cmr 143.2 (s), 139.1 (s), 137.2 (s), 119.3 (d, C-8), 50.1 (s, C-3), 42.4 (t, C-1), 40.4 (t, C-6), 37.0 (t, C-2), 27.6 (t and q, q = C-15), 27.1 (d, C-11), 24.8 (q, C-12 or C-13), 24.9 (t, C-4), 21.6 (q, C-12 or C-13), 20.7 ppm (q, C-14); mass spectrum (70 eV) *m/e* (rel intensity) 204 (100), 189 (100), 163 (93), 133 (25), 119 (21), 105 (26). The mass spectrum gave a parent peak at mass 204.1881 (called for $C_{15}H_{24}$, 204.1878).

Fractional crystallization of the alcoholic fraction gave 1.3 g of a pure alcohol whose ir, nmr, and mass spectrum were identical with those of α-caryophyllene alcohol (**6**).

Formation of Humulol (15). To a stirred solution of 3.3 g (16.2 mmol) of humulene, 120 ml of dioxane, and 30 ml of water heated in an oil bath at 47° (to 67°) was added 0.6 ml of 70% $HClO_4$. The reaction was followed by vpc (6 ft × ⅛ in., 10% SE-30) and stopped when 50 to 60% alcohol **15** was formed (less than 5% other products except starting humulene, at 47° approximately 2 weeks, at 67° approximately 6 hr). The crude product was chromatographed on neutral Woelm alumina (activity I) to give 1.3 g of humulene (hexane eluate) and 1.9 g of alcohol **15** (97% pure, ether eulate): ir 3570, 1385, 1377, 1364, 1111, 999 cm^{-1}; nmr δ 5.20 to 4.73 (m, 3), 1.58 (s, 3), 1.12 (s, 6), 1.06 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 222 (8), 204 (14), 125 (24), 122 (20), 103 (66), 82 (100).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.08; H, 11.71. Found: C, 80.83; H, 11.51.

Reaction of α-Caryophyllene Alcohol with Acid. Using the procedure and conditions for the rearrangement of humulene with perchloride acid, 136 mg (0.61 mmol) of α-caryophyllene alcohol was refluxed for 4 days. The product of the reaction was found from analysis by nmr and tlc to be the starting alcohol. No other products were found.

Hydrogenation of Hydrocarbon 7. To a shaking suspension of 200 mg of prehydrogenated PtO_2 in 80 ml of acetic acid (or ethyl acetate) at room temperature and atmospheric pressure was added 2.0 g (9.8 mmol) of hydrocarbon **7**. The volume of hydrogen uptake was followed until 9.8 mmol of hydrogen was absorbed (~1 hr). The reaction mixture was filtered, diluted with hexane, and washed several times with water and then saturated sodium bicarbonate solution to remove the acetic acid. The neutralized hexane solution was dried and concentrated to yield 1.95 g (9.5 mmol) of hydrocarbons. Analysis by vpc (500 ft × 0.02 in. OV225) showed 4% starting material, 17% of hydrocarbon **8**, and 79% of hydrocarbon **9**. Pure hydrocarbon **8** was obtained by preparative vpc (10 ft × ⅜ in. 10% KOH, 10% Carbowax 20M): nmr δ 5.18 (d of d, 1, J_1 = 2 Hz, J_2 = 2.5 Hz), 1.02 (d, 3, J = 7 Hz), 1.00 (d, 3, J = 7 Hz), 0.92 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 206 (19), 191 (25), 163 (100), 107 (19), 81 (22). The mass spectrum gave a parent peak at mass 206.2036 (calcd for $C_{15}H_{26}$: 206.2034).

To obtain pure hydrocarbon **9**, the mixture of hydrogenated hydrocarbons was placed under the hydrogenation conditions above for 6 to 8 hr. Analysis by vpc (500 ft × 0.02 in. OV225) showed hydrocarbon **9** was present in greater than 90% purity. Pure hydrocarbon **9** was obtained by preparative vpc (10 ft × ⅜ in. 90% KOH, 10% Carbowax 20M): ir (CCl_4, CS_2) 1381, 1375, 1370, 1360, 1182, 784, 762 cm^{-1}; Raman 1665 cm^{-1}; nmr δ 2.6 (septet, 1, J = 7 Hz), 0.96 (s, 3); cmr 140.89 ppm (s), 140.5 (s), 49.9 (s, C-3), 41.1 (q), 37.5 (t), 36.9 (d, C-8), 33.1 (t), 27.1 (t), 26.9 (d, C-11), 25.7 (q), 23.9 (q, C-12 or C-13), 22.9 (t), 21.9 (q, C-12 or C-13), 21.8 (q, C-14); mass spectrum (70 eV) *m/e* (rel intensity) 206 (32), 191 (65), 163 (100), 121 (36), 95 (37).

Anal. Calcd for $C_{15}H_{26}$: C, 87.38; H, 12.62. Found: C, 87.17; H, 12.63.

Osmylation of Hydrocarbon 8. A solution of 600 mg (2.9 mmol) of 79% pure hydrocarbon 8, 50 ml of dry ether, 2 ml of dry pyridine, and 800 mg (3.15 mmol) of OsO_4 was stirred at 25° in the dark for 1 week. To the reaction mixture was added 3 g of sodium bisulfite and 100 ml of 95% ethanol and the mixture refluxed for 6 hr. The solution was allowed to cool to room temperature and the inorganic material was removed by filtration. The organic filtrate was dried and rotary evaporated and the crude brownish diol was chromatographed on silica gel. The major product was fractionally crystallized from hexane to give 100 mn (0.42 mmol) of pure diol **10**: mp 82–83°; nmr δ 3.66 (d, 1, J = 7 Hz), 2.78 (d of septet, 1, J_{Ax} = 7 Hz, J_{Bx} = 2 Hz), 1.03 (d, 3, J = 7 Hz; 0.98 (s, 3), 0.94 (d, 3, J = 5 Hz), 0.92 (d, 3, J = 7 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 222 (12), 204 (54), 199 (100), 161 (58), 105 (50).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 75.00; H, 11.67. Found: C, 75.00; H, 11.74.

Cleavage of Diol 10. To a stirred solution of 4.5 ml of benzene

and 39 mg (0.17 mmol) of pure diol **10** under nitrogen atmosphere was added 85 mg (0.18 mmol) of $Pb(OAc)_4$. The reaction mixture was neutralized after 1 hr with 4.5 ml of 25% saturated sodium bicarbonate solution. The organic material was extracted with ether, and the extract was dried and concentrated to yield 32 mg (0.13 mmol) of keto acid **11a:** ir (crude) 1709, 1739 cm^{-1}. The acid was esterified with diazomethane to yield keto ester **11b:** ir 1736 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 268 (2), 237 (9), 140 (100), 97 (35), 88 (20). The mass spectrum gave a parent peak at mass 268.2047 (calcd for $C_{16}H_{28}O_3$: 268.2038).

Oxidation of Hydrocarbon 9. Following the procedure used for the osmylation and cleavage of hydrocarbon 8, 400 mg (1.65 mmol) of hydrocarbon **9** (90% pure) and 0.5 g (1.93 mmol) of osmium tetroxide gave, after work-up, 200 mg of a crude diol. The crude diol was cleaved with a 10% molar excess of $Pb(OAc)_4$ and the product was isolated by chromatography on silica gel. The pure diketone **12** (120 mg, 0.48 mmol) had the following properties: ir 1712, 1700 cm^{-1}; nmr δ 1.03 (d, 6, J = 7 Hz), 1.00 (s, 3), 0.97 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.63; M, 10.92. Found: C, 75.44; H, 10.89.

Allylic Oxidation of Hydrocarbon 9. Using the procedure of Mazur,[15] 100 mg (0.05 mmol) of hydrocarbon **9,** 0.175 g (0.05 mmol) of $HgBr_2$, and 120 ml of freshly distilled *tert*-butyl alcohol were placed in a quartz flask. The solution was irradiated in a Rayonet reactor at 254 nm with air bubbled through the solution for 1.75 hr. The mixture was diluted with hexane and the mixture was washed thoroughly with water. The organic material was dried and concentrated, and the residue was chromatographed on silica gel to give 60 mg (0.27 mmol) of pure enone **14:** ir 1698, 1634 cm^{-1}; uv max (95% EtOH) 241 nm (ϵ 9000); nmr δ 2.06 (s, 2), 1.16 (d, 3, J = 7 Hz), 1.14 (d, 3, J = 7 Hz), 1.08 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 220 (100), 205 (94), 191 (27), 178 (35), 177 (36).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.82; H, 10.91. Found: C, 81.61; H, 10.74.

Formation of Intermediate Hydrocarbons 19 and 20. Humulene was treated with acid in the usual manner and product formation followed closely by vpc (15 ft × ⅛ in. 1% OV1) until hydrocarbon **19** represented 6% of the reaction mixture and hydrocarbon **20** 18% of the mixture. The reaction mixture was worked up in the usual manner and collection by vpc (10 ft × 0.25 in. 2% SF96) gave pure hydrocarbons **19** and **20.** Hydrocarbon **19** had the following properties: ir (CCl_4, CS_2) 2178, 1642, 1374, 886, 860, 539 cm^{-1}; Raman 1642, 1669 cm^{-1}; nmr (100 MHz) δ 5.02 (s, 1), 4.62 (s, 3), 1.69 (s, 3), 1.63 (s, 3), 0.78 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 204 (92), 189 (100), 161 (60), 148 (30), 133 (35), 121 (67), 107 (39), 93 (36); mass spectrum (70 eV, high resolution) 204.1889 (calcd for $C_{15}H_{24}$: 204.1878). Hydrocarbon **20** had the following properties: ir 1374, 1182, 1147, 983, 864 cm^{-1}; Raman 1678, 1662 cm^{-1}; nmr (100 MHz) δ 5.51 (m, 1), 3.20 (broad s, 1), 1.73 (t, 3, J = 1.5 Hz), 1.57 (s, 6), 0.70 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 204 (72), 189 (100), 161 (80), 133 (24), 122 (22), 119 (30), 105 (30), 91 (27), 41 (30); mass spectrum (70 eV, high resolution) 204.1877 (calcd for $C_{15}H_{24}$: 204.1878).

Hydrogenation of Hydrocarbon 19. To a stirred suspension of 30 mg of prehydrogenated PtO_2 in 10 ml of ethyl acetate was added a solution of 19 mg (0.093 mmol) of hydrocarbon **19** in 1 ml of ethyl acetate. Stirring was continued until approximately 2.7 ml (0.12 mmol) of hydrogen was absorbed by the hydrocarbon. The solution was filtered and was concentrated to yield the crude hydrogenated hydrocarbon: nmr δ 5.16 (m, 1), 1.70 (s, 3), 0.88 (d, 3, J = 7 Hz), 0.83 (d, 3, J = 7 Hz), 0.75 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 206 (26), 191 (14), 162 (72), 135 (13), 123 (100), 109 (48), 93 (22), 81 (39).

Rearrangement of Hydrocarbon 19 with Acid. Using the procedure and conditions for the rearrangement of humulene with perchloric acid, 5 mg (0.024 mmol) of hydrocarbon **19** was refluxed for 1 day. The reaction mixture was worked up and analysis by vpc (500 ft × 0.02 in. OV101) showed greater than 90% hydrocarbon **7.**

Formation of Alcohol 21. Humulene was treated with perchloric acid in the usual manner and product formation followed closely by vpc (15 ft × ⅛ in. 1% OV1) until alcohol **21** represented about 15% of the reaction mixture (approximately 7.0 hr). The reaction was worked up in the usual manner and collection by vpc (10 ft × 0.25 in. 2% SF96) gave alcohol **21** with approximately 10% α-caryophyllene alcohol as an impurity. Alcohol **21** had the following properties: ir 3640, 3470, 1375, 1369, 938, 875 cm^{-1}; nmr δ 5.32 (m, 1), 1.73 (t, 3, J = 1 Hz), 1.12 (s, 6), 0.77 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 222 (8), 204 (80), 189 (100), 161 (63), 121 (16), 108 (21), 107 (19).

Dehydration of Alcohol 21. A stirred solution of 15 ml of dry ethyl ether, 6 ml of triethylamine, and 10 mg (0.045 mmol) of alcohol **21** in a 50-ml, round-bottomed flask with nitrogen atmosphere was cooled to −20° in a Dry Ice–carbon tetrachloride bath. To this solution was added 50 μl (0.64 mmol) of mesyl chloride and stirring was continued for 20 min. The solution was warmed to room temperature and poured into a solution of 20 ml of saturated sodium bicarbonate solution. The organic material was extracted with ether and the ether extract was washed with 5% hydrochloric acid, saturated with sodium bicarbonate, dried, and concentrated to yield the crude hydrocarbons. The crude hydrocarbon mixture on analysis by vpc (500 ft × 0.02 in. OV101) showed 16% of hydrocarbon **7,** 30% of hydrocarbon **19,** and 54% of hydrocarbon **20.**

Dehydration of Humulol. Humulol (100 μl) was injected on a 10 ft × 0.25 in. SF96 gas chromatographic column at 230° with a flow rate of 10 cm^3/min. The hydrocarbons were collected and analysis by vpc (500 ft × 0.03 in. Apiezon) showed 75% α-humulene and 25% β-humulene.

Epoxidation of Humulene. To a stirred solution of 3 g (14.7 mmol) of humulene and 20 ml of $CHCl_3$ at −20° was added 2.5 g (82.5% 14.5 mmol) of *m*-chloroperbenzoic acid dissolved in 100 ml of $CHCl_3$. The solution was stirred for 2 hr at the same temperature, washed twice with 20% potassium hydroxide and saturated sodium chloride, dried with $MgSO_4$, and concentrated. Analysis of the residue by vpc (6 ft × ⅛ in. 10% SE30) showed 63% epoxide and 37% humulene. The product mixture was chromatographed on neutral Woelm alumina (activity III) to give 1.8 g (8.18 mmol) of pure epoxide. The ir and nmr of the epoxide were identical with humulene epoxide **17.**[16]

Lithium, Ethylamine Opening of Epoxide 17. A dark blue solution of 1.9 g (8.6 mmol) of epoxide **17** and 3 g (0.43 mmol) of lithium in 100 ml of ethylamine, cooled in a Dry Ice-CCl_4 bath, was stirred for 3 hr at which time tlc showed complete disappearance of starting material. Saturated ammonium chloride solution was added and the ethylamine evaporated. The organic material was extracted with ether and the extract was dried and concentrated. Analysis of the reaction product by vpc (6 ft × ⅛ in. 10% SE-30) showed four major alcohols. The crude product was chromatographed on silica gel and the major fractions were purified by preparative vpc (10 ft × ¼ in. 2% SF96) to give compounds **18, 15,** and two other products. Compound **18** (56%) had the following properties: nmr δ 5.30–4.75 (m, 3), 3.63 (m, 1), 1.57 (s, 3), 1.07 (s, 3), 1.02 (s, 3), 0.83 (d, 3, J = 6 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 222 (64), 151 (29), 123 (26), 110 (100), 95 (50), 82 (98); mass spectrum (70 eV, high resolution) 222.1986 (calcd for $C_{15}H_{26}O$: 222.1983). Compound **15** (9%) spectral properties (ir, nmr, and mass spectrum) were identical with humulol.[9] Two compounds were isolated in 10 and 24% yields whose mass spectrum (70 eV) show parent peaks at mass 226 and 224, respectively.

Rearrangement of Humulene with D_2SO_4.[17] To a stirred solution of 10 ml of dry ether and 1 g (4.9 mmol) of humulene at 0° and under a nitrogen atmosphere was added 3 g of D_2SO_4. Stirring was continued for 18 hr. The reaction mixture was slowly poured into a solution of saturated sodium bicarbonate solution. The organic material was extracted with ether and the ether extract was washed with water, dried, and concentrated to yield the crude products. Column chromatography on a short column of alumina activity III gave the hydrocarbon products (hexane eluent). Collection by vpc (10 ft × ¼ in. 2% SF96) gave pure deuterated hydrocarbon **7.**

Acknowledgment. The authors are deeply indebted to Dr. Roy Teranishi for his assistance and to the Glidden Co. for their generous supply of humulene.

Registry No.—**5,** 6753-98-6; **7,** 41370-41-6; **8,** 53643-37-1; **9,** 43161-84-8; **10,** 53643-38-2; **11a,** 53643-39-3; **11b,** 53643-40-6; **12,** 53643-41-7; **14,** 43161-77-9; **15,** 24405-58-1; **17,** 19888-34-7; **18,** 53643-42-8; **19,** 41370-42-7; **20,** 41370-43-8; **21,** 41370-40-5.

References and Notes

(1) These results have been published in preliminary form in *J. Agr. Food Chem.*, **22,** 156 (1974), and were presented at the Ernest Guenther Award Symposium, 165th National Meeting of the American Chemical Society, Dallas, Texas, April, 1973. The work was supported by the National Science Foundation Grant No. G.P. 8700 and the Hoffmann-La Roche Foundation.
(2) W. S. Johnson, *Accounts Chem. Res.*, **1,** 1 (1968).
(3) J. A. Marshall and W. F. Huffman, *Syn. Commun.*, **1,** 221 (1971).
(4) W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, 2675 (1964); W. G. Dauben, L. E. Friedrich, P. Oberhansli, and E. L. Aoyagi, *J. Org. Chem.*, **37,** 9 (1972); W. G. Dauben and L. E. Friedrich, *ibid.*, **37,** 241 (1972); W. G. Dauben and E. I. Aoyagi, *ibid.*, **37,** 251 (1972).

(5) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).
(6) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961); A. Nickon, F. J. McGuire, J. R. Mahajan, B. Umezawa, and S. A. Narang, *J. Amer. Chem. Soc.*, **86**, 1437 (1964); A. Nickon, T. Iwadane, F. J. McGuire, J. R. Mahajan, A. Narang, and B. Umezawa, *ibid.*, **92**, 1688 (1970). This alcohol was originally called "α-caryophyllene alcohol" in that it was thought to be derived from caryophyllene. The studies reported in this reference showed such not to be the case and the investigators suggested the trivial name "apollanol." The Chemical Abstract's name for the alcohol is 1,2,3,3aα,4,5,6,7,8,8aα-decahydro-2,2,4a,8a-tetramethyl-*anti*-9-4,8-methanoazulen-9-ol. For the sake of simplicity, the material will be called alcohol **6** in the present discussion.
(7) V. Sykora, L. Novatny, M. Holut, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **26**, 788 (1961).
(8) V. Benesova, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **26**, 1832 (1961).
(9) R. G. Buttery, W. H. McFadden, R. E. Lundin, and M. P. Kealy, *J. Inst. Brew., London*, **70**, 396 (1964). These authors kindly supplied us with spectra of their authentic material.
(10) Y. Naya and M. Kotake, *Bull. Chem. Soc. Jap.*, **42**, 2405 (1969); *Nippon Kagura Zasshi*, **91**, 275 (1970). A sample was kindly supplied by these authors.
(11) A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 4604 (1957).
(12) Y. Naya and Y. Hirose, *Chem. Lett.*, 133 (1973).
(13) J. B. Stothers, C. T. Tan, A. Nickon, F. Huang, R. Snidhan, and R. Weglein, *J. Amer. Chem. Soc.*, **94**, 8581 (1972).
(14) (a) Y. Naya and Y. Hirose, *Chem. Lett.*, 727 (1973). (b) After submission of this manuscript, covering our earlier preliminary publication, D. Barnes, J. Forrester, and W. Parker (*J. Chem. Soc., Perkin Trans. 1*, 1598 (1974)) reported related studies on the humulene transformation.
(15) J. N. Friedman, M. Gorodetski, and Y. Mazur, *Chem. Commun.*, 874 (1971).
(16) N. P. Damodaran and S. Dev, *Tetrahedron*, **24**, 4123 (1968).
(17) A. W. Lutz and E. B. Reid, *J. Chem. Soc.*, 2765 (1954).

Photolysis of 2-Alkoxy-1,4-naphthoquinones

J. V. Ellis and J. E. Jones*

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

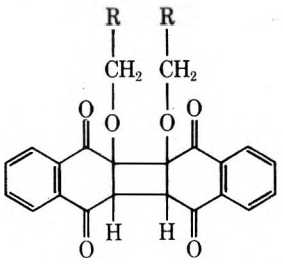
Received July 25, 1974

The photolysis of 2-methoxy- and 2-ethoxy-1,4-naphthoquinones in acetic anhydride solution caused dimerization and subsequent cyclization of the alkoxy group to spiro-3-oxetanols in high yield. Similar photolysis of the 2-isopropoxy derivative produced no dimer but a product in which ring closure *via* the keto group adjacent to the alkoxy group formed the acetate of 3,4-isopropylidenedioxy-1-naphthol. Photolyses of film coatings of various 2-alkoxy- and 2-aralkoxy-1,4-naphthoquinones produced reducing species that are believed to be the 3,4-alkylidenedioxy-1-naphthols.

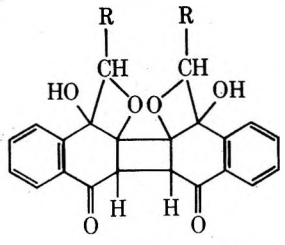
It is well known that certain alkoxy- and alkylamino-substituted quinones are photolyzed by intramolecular hydrogen abstraction and ring closure to produce substituted hydroquinones.[1-6] An interest in the photochemistry of quinones led us to investigate the photolysis of naphthoquinones containing alkoxy groups with more easily extractable H atoms, with the expectation that the cyclization reaction might occur more readily.

Results

Photolysis of 2-methoxy-1,4-naphthoquinone in acetic anhydride solution produced mainly two dimers (1 and 2),

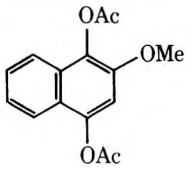


1, R = H
5, R = CH_3

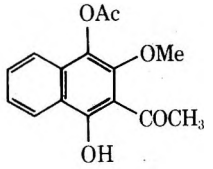


2, R = H
6, R = CH_3

neither of which was reported by Baldwin and Brown.[1] One (1) crystallized from the solvent in yellow prisms during photolysis, and the other (2) was recovered from the filtrate. Small quantities of the acetylated hydroquinone (3) and its rearrangement product (4) obtained by Baldwin and Brown may have been formed, but no attempt was made to isolate them.



3



4

Prolonged photolysis resulted in lower yields of 1 and larger quantities of 2, suggesting that the ring closure to the oxetanol structure occurred from irradiation of 1. The structure of 1 was assigned by analogy to the photooxidation of 2-methyl-[7] and 2-hydroxynaphthoquinone,[8] whose dimeric products are the result of head-to-head coupling. No attempt was made to determine the steric arrangement about the cyclobutane ring.

Upon being melted at a normal rate, the dimer (1) cleaved to the monomer, but when immersed in a preheated apparatus, the dimer melted rapidly only at temperatures above 210°. It was insoluble in all common solvents, and an nmr spectrum was unobtainable. It was cleaved when heated with solvents such as acetic anhydride or acetic acid during attempts at recrystallization. Although the dimer was detectable as a trace by mass spectrography, it was cleaved during analysis, giving relatively large quantities of the monomer; a fragmentation pattern characteristic of the monomer was observed. Its ir spectrum (KBr pressing) was different from that of the starting material.

The structure of 2 was assigned on the basis of its ir spectrum, which showed a very sharp OH band at 3500 cm^{-1} and a carbonyl band at 1680 cm^{-1}, its proton nmr spectrum, which showed two doublets characteristic of an AB system involving the $-CH_2-$group of a 3-aryl-substituted 3-oxetanol,[9,10] and its C^{13} nmr spectrum.

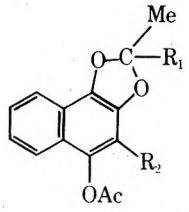
The compound lost two molecules of formaldehyde in the determination of the mass spectrum. The major component was mass 316 and the fragmentation pattern was nearly identical with that of the dimer of 1,4-naphthoquinone. The silated compound also lost formaldehyde thermally; the heaviest fragment observed was the tetrasilated dimer of 1,4-naphthoquinone.

Photolysis of an acetic anhydride solution of 2-ethoxy-1,4-naphthoquinone with narrow-band irradiation centered at 436 nm produced the simple dimer 5 in 90% yield. This dimer, whose absorption tailed out weakly to 400 nm, was converted to the spirooxetanol 6 upon being irradiated

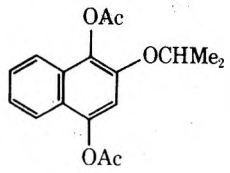
at 365 nm. Photolysis of the quinone with light of wavelengths longer than 370 nm produced **6** in 70% yield.

Other evidence consistent with structure **6** for the photolysis product of the quinone is its failure to be acetylated by acetic anhydride and its stability toward mild acid hydrolytic conditions. Both **2** and **6** were readily oxidized by air or oxidizing agents such as 2-*p*-iodophenyl)-3-(*p*-nitrophenyl)-5-phenyl-2*H*-tetrazolium chloride in alkaline solutions. Bubbling air through the alkaline solution of **6** caused its oxidative decomposition with liberation of acetaldehyde.

The 3-methyl derivative of 2-ethoxy-1,4-naphthoquinone produced no dimeric products. The major product was the ring-closed acetate **7a.** Other products isolated in



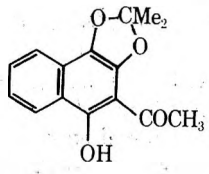
7a, R_1 = H; R_2 = Me
b, R_1 = Me; R_2 = H



8

much smaller yields were the 2-hydroxy-1,4-naphthoquinone and its acetate.

Photoreduction of 2-isopropoxy-1,4-naphthoquinone in acetic anhydride solution at room temperature produced no easily separable products. Gas chromatography of the residue remaining after removal of the acetic anhydride indicated the presence of small amounts of **7b** and **8** in about equal quantities, along with other products not easily identifiable. Only **7b** and its photo-Fries rearrangement product **9** were isolated in pure form. There was no evidence for the formation of dimeric products analogous to **1** or **2.**



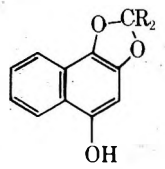
9

The structure of **7b** was established from ir, nmr, and mass spectra along with certain chemical evidence. The ir spectrum showed a maximum at 1645 cm^{-1}, consistent with the enediol ether,[11] as well as a maximum at 1755 cm^{-1}, associated with the acetoxycarbonyl group.

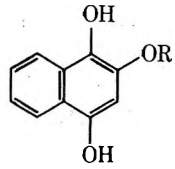
Saponification of **7b** in ethanol under N_2 by addition of NaOH occurred within a few seconds. Acidification by HCl produced the free hydroxy compound, which was extremely sensitive to aerial oxidation and was not isolated in a crystalline state. Bubbling air through the alkaline solution liberated acetone quantitatively and formed 2-hydroxy-1,4-naphthoquinone. The compound was not hydrolyzed by acid.[12]

Photolysis of film coatings of alkoxy or aralkoxy naphthoquinones for short times produced 2-hydroxy-1,4-naphthoquinone[7] and prolonged photolysis converted the hydroxyquinone into dimeric products.[13] Either solutions or film coatings of the alkoxyquinones were nonemissive at the onset of photolysis, but as irradiation proceeded an emission characteristic of **10** (R = Me) (maximum 420 nm in film or 440 nm in methanol solution) developed. The initial products were very labile in the presence of air and the intensity of emission decreased rapidly either in the dark or during prolonged irradiation.

Since oxidation of the hydroquinone **11** (R = isopropoxy) produced mainly the quinone and oxidation of **10** (R = Me) produced the 2-hydroxy compound, it is proposed that the initial products of the photolysis of 2-alkoxy or aralkoxy naphthoquinones under these conditions most likely have structures of the form of **10.**



10

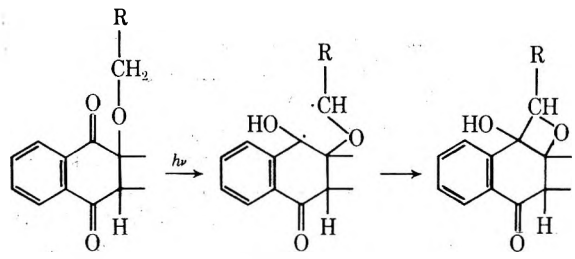


11

Discussion

Any discussion of mechanism to account for the different behavior of the isopropoxy derivative is admittedly speculative. The difference may lie in its failure to dimerize, the reason for which is not readily apparent.

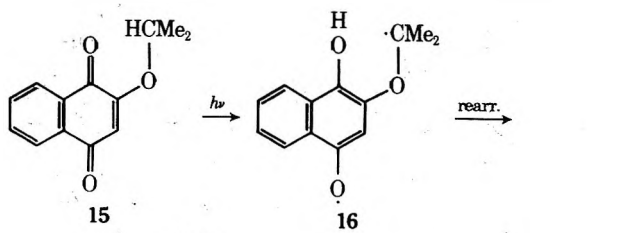
The methoxy and ethoxy derivatives most likely photodimerize to **12** as the first step. Excitation of the dimer, involving the carbonyl group adjacent to the alkoxy group (presumably $n\pi^*$), produces the diradical **13** following the H-transfer reaction. Ring closure of the diradical produces the oxetanol **14.**



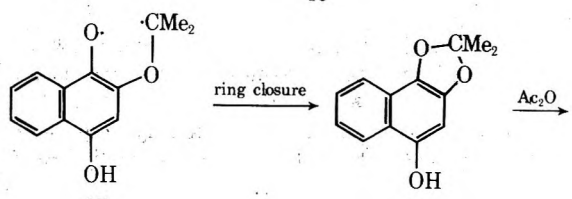
12 **13** **14**

Support for the stepwise process comes from the dimerization of the 2-ethoxy quinone and subsequent photolysis to produce the oxetanol. A similar cyclization and dimerization of a 3-methoxychromone reported by Gupta and Mukerjee most likely also involved two photolytic steps.[14]

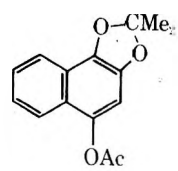
The failure of the isopropoxy compound **15** to dimerize allows the reaction from the excited state to proceed differently. The $n\pi^*$ excitation of the isopropoxy derivative and H abstraction might produce an intermediate shown as **16.**



15 **16**



17 **18**



19

Rearrangement and ring closure between the alkyl radical and the electron-deficient oxygen atom produces the substituted naphthol (18) which, by nucleophilic displacement on the acetic anhydride, produces the product (19). The aromatization following H transfer is impossible with the excited dimer (13).

Experimental Section

Photolysis of 2-Methoxy-1,4-naphthoquinone in Acetic Anhydride. A solution of 2.0 g of the quinone in 175 ml of acetic anhydride was photolyzed at room temperature in a Rayonet reactor equipped with mercury arc lamps rich in 365-nm radiation for 60 hr. During this time pale yellow prisms of **1** (0.88 g, 44%) separated from the solution: mp > 210° dec; uv max (CH_3CN) 205 (ϵ 5.3 × 10^4), 251 (ϵ 2.6 × 10^4), 278 nm (ϵ 2.8 × 10^3); ir (KBr) 1690 cm^{-1} (C=O) different from the monomer; mass spectrum (70 eV) *m/e* (major peaks underlined) 376, 346, 188, 173, 159, 158, 102, 89, 76.

Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.23; H, 4.26. Found: C, 69.9; H, 4.6.

Evaporation of the filtrate to dryness *in vacuo* and triturating the residue with acetonitrile produced 0.4 g (20%) of a yellow crystalline solid (**2**), which crystallized from acetic anhydride in pale yellow needles: mp 230–240° dec; ir (KBr) 3500 (OH), 1680 cm^{-1} (C=O) appreciably different from **1** at lower frequencies; nmr (DMSO) δ 3.12 (s, 1), AB pair 4.46, 5.06 (AB, 2, J = 7 Hz), 6.42 (s, 1, OH), 7.73 ppm (m, 4, aromatic); ^{13}C nmr (DMSO) δ 192.3 (s, 1, C=O), 146.4 (s, 1, aromatic), 136.2 (d, 1, aromatic), 129.7 (d, 1, aromatic), 128.6 (d, 1, aromatic), 127.3 (s, d, 2, aromatic), 84.5 (2t, 2, $-OCH_2$),[15] 91.1 (s, 1, -C-O-), 73.7 (s, 1, -C-O-), 46.5 ppm (d, 1, O=C—CH); mass spectrum (70 eV) *m/e* (major peaks underlined) 376, 346, 316, 299, 298, 288, 287, 271, 231, 215, 202, 130, 128, 104, 102, 76; mass spectrum after silation (70 eV) *m/e* (major peaks underlined) 604, 562, 561, 489, 462, 147, 75, 73.

Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.23; H, 4.26. Found: C, 70.1; H, 4.4.

1,4-Naphthoquinone dimer: mass spectrum (70 eV) *m/e* (major peaks underlined) 316, 299, 298, 288, 287, 271, 270, 231, 215, 202, 130, 128, 104, 102, 76.

A dilute alkaline methanol solution of **2** yellowed rapidly in air and reduced instantaneously a solution of 2-(*p*-iodophenyl)-3-nitrophenyl)-5-phenyl-2*H*-tetrazolium chloride.

Photolysis of 2-Ethoxy-1,4-naphthoquinone in Acetic Anhydride. 1. Dimerization. A solution of 0.15 g of the quinone in 10 ml of acetic anhydride was photolyzed using the 436 line of a mercury source. Removal of the acetic anhydride *in vacuo* produced the dimer (**5**), which crystallized from ethanol in colorless needles (0.135 g, 90%): mp 125–126°; uv max (CH_3CN) 233 (ϵ 5.25 × 10^4), 302 nm (ϵ 2.49 × 10^3); ir (KBr) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.04 (t, 3, J = 12 Hz, $CHCH_3$), 2.96 (q, 2, J = 11 Hz, CH_2CH_3), 3.56 (s, 1, CH), 7.45 (m, 2, aromatic), 7.75 ppm (m, 2, aromatic); mass spectrum (70 eV) *m/e* (major peaks underlined) 404, 387, 386, 360, 316, 314, 202, 158, 146, 105, 102, 89. The nmr quartet at 2.96 ppm showed a splitting of 3 Hz.

2. Spirooxetanol Formation. A solution of 2.0 g of the quinone in 175 ml of acetic anhydride was photolyzed using a high-pressure mercury arc filtered to pass only light of wavelengths longer than 370 nm. Removal of the acetic anhydride *in vacuo* gave a solid **6** (1.5 g), which crystallized from acetonitrile as nearly colorless prisms (1.4 g, 70%): mp 206–207°; uv max (CH_3OH) 255 (ϵ 2.18 × 10^4), 292 nm (ϵ 3050); ir (KBr) 3640 (OH), 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.74 (d, 3, J = 12 Hz, $CHCH_3$), 3.14 (s, 1, CH), 4.92 (q, 1, J = 10 Hz, $CHCH_3$), 5.34 (s, 1, OH), 7.62 (s, 1, aromatic), 8.23 ppm (m, 3, aromatic); ^{13}C nmr ($CDCl_3$ + DMSO) δ 191.2 (s, 1, C=O), 145.5 (s, 1, aromatic), 135.0 (d, 1, aromatic), 128.5 (d, 1, aromatic), 127.5 (s, d, 2, aromatic), 126.8 (d, 1, aromatic), 89.6 (d, 1, OCHR), 87.7 (s, 1, C-O), 73.6 (s, 1, -C-O-), 45.7 (d, 1, O=C—CH), 16.3 ppm (q, 1, CH_3); mass spectrum (70 eV) *m/e* (major peaks underlined) 202, 187, 173, 158, 146, 105, 102, 89.

Anal. Calcd for $C_{24}H_{20}O_6$: C, 71.28; H, 4.98. Found: C, 71.3; H, 5.0.

Photolysis in the Rayonet reactor produced the same results.

3. Spirooxetanol from Dimer. A solution of 0.1 g of the dimer **5** in 10 ml of acetic anhydride was photolyzed using the 365-nm line of a mercury source. Removal of the acetic anhydride *in vacuo* and trituration with ethanol gave nearly colorless needles of **6** (0.06 g, 60%). The product was identified by mp and nmr.

Upon acidification of an alkaline ethanolic solution of **6** which had been held under N_2, **6** was recovered unchanged. Bubbling air through the alkaline solution caused oxidative decomposition of **6** with 90% recovery of acetaldehyde as its dinitrophenylhydrazone. Alkaline solutions of the spirooxetanol reduced tetrazolium salts instantaneously.

Photolysis of 2-Ethoxy-3-methyl-1,4-naphthoquinone in Acetic Anhydride. A solution of 1.5 g of the quinone in 175 ml of acetic anhydride was photolyzed for 60 hr in the Rayonet reactor. Acetic anhydride was removed *in vacuo* and the residual oil was chromatographed on a silica column eluted with benzene.

Compound **7a** was obtained as a pale red oil: 0.5 g (33%): ir (KBr) 1660 (-OC=CO-), 1760 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.65 (d, 3, $CHCH_3$), 2.15 (s, 3, CH_3), 2.27 (s, 3, $COCH_3$), 6.26 (q, 1, J = 8 Hz, $CHCH_3$), 6.38 (m, 2, aromatic) 7.6 ppm (m, 2, aromatic); mass spectrum (70 eV) *m/e* (major peaks underlined) 258, 216, 201, 171, 115, 43.

Photolysis of 2-Isopropoxy-1,4-naphthoquinone in Acetic Anhydride. A solution of 5.0 g of the quinone in 175 ml of acetic anhydride was photolyzed for 60 hr in the Rayonet reactor. Acetic anhydride was removed *in vacuo* and the residual oil was triturated with 15 cm^3 of methanol. The solid that separated (1.7 g) was nearly pure starting material.

Alcoholic filtrates from three photolyses were evaporated to dryness and the residual oil was dissolved in benzene. Chromatography on a silica column eluted with benzene (or methylene chloride) produced two crystalline products.

Compound **7b** was obtained as pale yellow prisms from hexane (1.4 g, 11.7%): mp 84–86°; uv max (CH_3OH) 300 (ϵ 3800), 312 (ϵ 4300), 350 nm (ϵ 4100); ir (KBr) 1645 (-OC=CO-), 1755 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.72 (s, 6, $C(CH_3)_2$), 2.32 (s, 3, $COCH_3$), 6.92 (s, 1, =CH—), 7.32 (m, 2, aromatic), 7.72 ppm (m, 2, aromatic); mass spectrum (70 eV) *m/e* (major peaks underlined) 258, 216, 201, 176, 175, 102, 101, 43.

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.6; H, 5.6.

The Fries-rearranged product **9** crystallized from hexane as orange needles (1.1 g, 9.2%): mp 138–139°; uv (CH_3OH) 332 (ϵ 3150), 450 nm (ϵ 3640); uv (CH_3OH + NMe_3) 360 (ϵ 6200), 460 nm (ϵ 5100); ir (KBr) 1655 (-OC=CO-), 1640 cm^{-1} (acetyl C=O); nmr ($CDCl_3$) δ 1.76 (s, 6, $C(CH_3)_2$), 2.63 (s, 3, $COCH_3$), 7.30 (m, 3, aromatic), 8.18 ppm (m, 1, aromatic); mass spectrum (70 eV) *m/e* (major peaks underlined) 258, 240, 218, 217, 200, 199, 172, 144, 129, 115, 101, 43, 41.

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.9; H, 5.6.

C^{13} Nmr Spectra. The spectra were obtained by T. Regan on a Brucker HX-90 spectrometer equipped with a Digilab NMR-3 Pulse-Fourier transform system. Spectra under both broad-band and off-resonance continuous wave decoupling were obtained. The multiplicities were observed during partial decoupling. Chemical shifts are relative to tetramethylsilane.

Film Coatings. To 1 mmol of the compound was added 10 g of a 10% solution of Eastman cellulose acetate butyrate in acetone–methanol (10:7). The mixture was stirred until the solid dissolved. It was coated at a wet thickness of 200 μm on a film support and dried and cured at 40° to remove the solvents.

Acknowledgment. The authors are indebted to J. C. Fleming for supplies of quinones, to S. Farid for many helpful discussions, and to T. H. Regan for the ^{13}C nmr spectra and their interpretation.

Registry No.—**1**, 53626-42-9; **2**, 53626-43-0; **5**, 53626-44-1; **6**, 53626-45-2; **7a**, 53626-46-3; **7b**, 53626-47-4; **9**, 53626-48-5; **15**, 53626-49-6; 2-methoxy-1,4-naphthoquinone, 2348-82-5; 2-ethoxy-1,4-naphthoquinone, 7473-18-9; 2-ethoxy-3-methyl-1,4-naphthoquinone, 53626-50-9.

References and Notes

(1) J. E. Baldwin and J. E. Brown, *Chem. Commun.*, 167 (1969).
(2) D. W. Cameron and R. G. E. Giles, *J. Chem. Soc. C*, 1461 (1968).
(3) E. P. Fokin and E. P. Prudchenko, *Isv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk (2)*, 98 (1966); *Chem. Abstr.*, **66**, 37809j (1967).
(4) A. Juodvirsis and E. P. Fokin, *Isv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk (2)*, 124 (1970); *Chem. Abstr.*, **74**, 3540q (1970).
(5) T. G. Levine and M. C. Wani, *J. Org. Chem.*, **30**, 3185 (1965).
(6) M. C. Wani and T. G. Levine, *J. Org. Chem.*, **31**, 2564 (1966).
(7) Photolysis of 2-isopropoxy-1,4-naphthoquinone in film coatings produced the 2-hydroxyquinone in a quantum yield of 0.60 for measurements extrapolated to zero time.
(8) H. Werbin and E. T. Strom, *J. Amer. Chem. Soc.*, **90**, 7296 (1968).
(9) P. Yates and A. G. Szabo, *Tetrahedron Lett.*, 485 (1965).

(10) F. D. Lewis and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 311 (1970).
(11) J. B. Miller, *J. Org. Chem.*, **25**, 1279 (1960).
(12) The stability of the enediol ether to acid hydrolysis is not surprising. Cyclic ethers of aromatic diols are unusually stable toward acid cleavage, often requiring drastic conditions such as HI at elevated temperatures.
(13) S. C. Hooker, *J. Amer. Chem. Soc.*, **58**, 1212 (1936).
(14) S. C. Gupta and S. K. Mukerjee, *Tetrahedron Lett.*, 5073 (1973).
(15) The partially decoupled absorption at 84.5 ppm appeared as a triplet whose relative intensities were 1:5:1 instead of 1:2:1. The lower field member was actually a closely spaced doublet. This is consistent with the two H atoms on that carbon being anisochronous. Whether the unequal spacing for the two triplets is due to unequal partial decoupling or to unequal coupling of the carbon to the two anisochronous hydrogens was not resolved.

Substituent Effects on the Photochemical α Cleavage of Deoxybenzoin[1]

F. D. Lewis,*[2a] C. H. Hoyle,[2b] and J. G. Magyar[2b]

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

H.-G. Heine* and W. Hartmann

Zentralbereich Forschung, Wissenschaftliches Hauptlaboratorium der Bayer AG, 415 Krefeld-Uerdingen, Germany

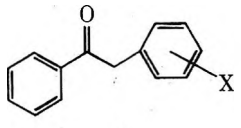
Received July 8, 1974

The effects of aromatic substituents which are not conjugated with the carbonyl on the photochemical behavior of deoxybenzoin have been investigated. Photochemical α cleavage is the exclusive primary photoprocess observed in benzene solution. Room temperature phosphorescence is observed for several deoxybenzoins and provides a convenient method of measuring triplet lifetimes. Substituents affect the rate constant for α cleavage without altering the triplet energy or radiative lifetime. The rate constants for α cleavage fit the Hammett equation with the use of σ^+ ($\rho = -1.1$). It is concluded that the transition state for α cleavage lies early on the reaction coordinate and has moderate ionic character.

Deoxybenzoin and several of its aryl-substituted derivatives undergo photochemical α cleavage (Norrish type I) to give a benzoyl–benzyl radical pair (eq 1).[3-6] The preceeding

$$Ar'\overset{O}{\overset{\|}{C}}CH_2Ar \xrightarrow{h\nu} [Ar'\overset{O}{\overset{\|}{C}}\cdot \cdot CH_2Ar] \longrightarrow \text{products} \quad (1)$$

paper in this series[5] describes the effects of α-methyl and α-phenyl substituents on the photochemical reactivity of deoxybenzoin. From a comparison of the rate constants for photochemical α cleavage of the deoxybenzoins studied and the rate constants for thermolysis of the corresponding peresters,[7] we concluded that the transition state for α cleavage resembles the excited ketone rather than the radical pair. This conclusion is contrary to the common assumption that the rate of α cleavage is determined by the stability of the radical pair or biradical intermediate.[8] In order to provide further information about the mechanism of photochemical α cleavage and the possible influence of polar effects in the transition state, we have investigated the photochemical and photophysical reactions of a number of substituted deoxybenzoins (1).[9] Polar effects, *e.g.*, partial



1

charge formation in the transition state, have often been used in interpreting the influence of substituents on free radical abstraction[11] and decomposition[12-14] reactions which result in the formation of benzyl radicals. For example, substituent effects on phenyl-substituted *tert*-butylperoxyphenylacetate thermolysis have been successfully explained in terms of different partial charge formation in the transition state.[12,13] In view of the previously observed similarity of the structure–reactivity relationships for photochemical α cleavage of deoxybenzoins and perester thermolysis,[5] we expected to observe polar contributions to the transition state for α cleavage.

Results

Quantum Yields and Kinetics. Irradiation of deoxybenzoin and a number of aryl-substituted deoxybenzoins in degassed benzene solution results in the formation of bibenzyls, toluenes, benzils, and benzaldehyde (eq 2). Quan-

$$\begin{aligned} &\overset{O}{\overset{\|}{PhCCH_2Ph}} \xrightarrow{h\nu} \overset{O}{\overset{\|}{PhC}}\cdot + \cdot CH_2Ph \longrightarrow \\ &\qquad PhCH_2CH_2Ph + PhCH_3 + \overset{O}{\overset{\|}{PhC}}\overset{O}{\overset{\|}{C}}Ph + \overset{O}{\overset{\|}{PhCH}} \quad (2) \\ &\Phi = \quad 0.056 \qquad 0.002 \qquad 0.006 \qquad 0.025 \end{aligned}$$

tum yields for product formation at 3% conversion from deoxybenzoin (0.03 *M*) are given in eq 2. The quantum yields for bibenzyl and benzil formation are corrected for the requirement of two benzyl or benzoyl radicals for the formation of one product molecule. Bibenzyls are the major products formed upon irradiation in degassed benzene solution for all of the deoxybenzoins in Table I. Toluene quantum yields are 2–5% of the bibenzyl quantum yields.

Irradiation of deoxybenzoin in the presence of either biphenyl (313-nm irradiation) or naphthalene (365 nm irradiation) gave linear Stern–Volmer plots for quenching of bibenzyl formation (Table I). The slope of the quenching plot ($k_q\tau$) for naphthalene quenching is twice as large as that for biphenyl quenching. Wagner[15] has previously reported that biphenyl quenches aryl ketone type II photoelimination with a rate constant ($\sim 2 \times 10^{-9}$ M^{-1} sec^{-1}) which is slightly less than the diffusion-controlled limit. Since the triplet energies of all the deoxybenzoins in Table I are similar (*vide infra*), it is assumed that the rate of triplet quenching by biphenyl will also be similar.

Quantum yields for benzaldehyde formation (Table II) were determined for degassed 0.03 *M* benzene solutions containing low concentrations of dodecanethiol. We have previously described the use of alkane thiols as efficient scavengers for benzoyl radicals.[5,16] Benzaldehyde quantum yields decrease rapidly with increasing conversion due to quenching by photoproduct.[5] The values given in Table II

Table I
Quantum Yields for Bibenzyl Formation and Kinetic Data for Biphenyl Quenching

$PhCOCH_2C_6H_4$-X, X	Φ^a	$k_q\tau$, M^{-1} [b]	$1/\tau \times 10^{-6}$, [d] sec^{-1}
H	0.056	1040	1.9
		2100[c]	2.4
p-OCH_3	0.13	294	6.8
p-CH_3	0.10	375	5.3
m-CH_3	0.048	412	4.9
p-F	0.070	842	2.4
p-Cl	0.052	1020	2.0
m-Cl	0.046	2160	0.93

[a] Quantum yields for bibenzyl formation in degassed benzene (~3% conversion). Corrected for requirement of two benzyl radicals per bibenzyl. [b] Least-squares slope of Stern-Volmer plot for quneching of bibenzyl formation by biphenyl. [c] Naphthalene quenching value from ref 5. [d] Calculated assuming $k_q = 2 \times 10^9$ M^{-1} sec^{-1} for biphenyl quenching and $k_q = 5 \times 10^9$ M^{-1} sec^{-1} for naphthalene quenching.

Table II
Quantum Yields for Benzaldehyde Formation and Kinetic Data for Naphthalene Quenching

$PhCOCH_2$-C_6H_4-X, X	Registry No.	Φ^a	$k_q\tau$, M^{-1} [c]	$1/\tau \times 10^{-6}$, sec^{-1} [d]
H	451-40-1	0.44[b]	3100	1.6
p-OCH_3	24845-40-7	0.23	270	19
p-CH_3	2430-99-1	0.18	1400	3.6
m-CH_3	34403-03-7	0.14	1100	4.5
p-F	347-91-1	0.17	1800	2.8
m-F	347-90-0	0.14	4900	1.0
p-Cl	6332-83-8	0.33	2700	1.9
m-Cl	27798-43-2	0.10[b]	3700	1.4
m-CF_3	30934-66-8	0.10[b]		

[a] Quantum yield for benzaldehyde formation in degassed 0.01 *M* dodecanethiol-benzene solution except as noted. Extrapolated to zero conversion. [b] Quantum yield in 3×10^{-3} *M* dodecanethiol-benzene. [c] Least-squares slope of Stern-Volmer plot for naphthalene quenching of benzaldehyde formation. [d] Calculated assuming $k_q = 5 \times 10^9$ M^{-1} sec^{-1}.

Table III
Absorption and Low-Temperature Emission Spectral Data for Deoxybenzoins

$PhCOCH_2C_6H_4$-X, X	λ_{max}, nm[a] (ϵ)	E_T, [b] kcal/mol	τ, msec
H	325 (129)	72.0	1.9
p-OCH_3	325 (256)	71.6	2.2
p-CH_3	325 (162)	71.0	1.9
m-CH_3	324 (156)		
p-F	325 (121)	72.2	2.5
m-F	323 (110)		
p-Cl	324 (128)	72.6	
m-Cl	323 (111)		
m-CF_3	323 (100)		

[a] Long wavelength absorption maximum in benzene solution at room temperature. [b] Estimated from the position of the highest energy emission maximum at 77°K in methylcyclohexane.

Table IV
Room-Temperature Phosphorescence Quantum Yield and Kinetic Data

$PhCOCH_2$-C_6H_4-X, X	Φ_P[a]	τ, μsec	τ_R, msec	$k_\alpha \times 10^{-6}$, sec^{-1}
H	0.0034	1.8[b]	0.53	0.56
		2.1[c]		
		0.83[d]		
p-OCH_3	<0.0001			
p-CH_3	0.0004	0.67[b]	1.6	1.5
p-F	0.0026	1.5[b]	0.59	0.67
		0.83[d]		
m-F	0.0028	3.6[b]	1.3	0.28
p-Cl	0.0035	2.6[b]	0.71	0.39
m-CF_3	0.0061	5.3[b]	0.86	0.19
$PhCOCH_3$	0.015	56[e]	3.7	
Ph_2CO	0.015	150[e]	10	

[a] Values in carbon tetrachloride, limits of error ± 0.0005. [b] Calculated from the slopes of linear Stern-Volmer plots for diene quenching in carbon tetrachloride. Limits of reproducibility ~20%. [c] Measured by single photon counting. [d] Diene quenching in benzene solution. [e] Measured by flash emission.

are extrapolated to zero conversion. Quenching of benzaldehyde formation by added naphthalene (365-nm irradiation) gave linear Stern–Volmer plots when maximum conversions were <1%. The estimated error in the kinetic data (±50%) is large due to the relatively long triplet lifetimes and the experimental difficulties associated with measuring quantum yields at very low conversion. The kinetic data in Tables I and II are in reasonable agreement except for the values for *p*-methoxydeoxybenzoin.

Spectroscopic Data. Ultraviolet absorption data for the n,π* absorption band in benzene solution are given in Table III. Neither the position nor the intensity of the n,π* absorption is significantly different in cyclohexane or carbon tetrachloride solution. Aryl substitution affects the intensity, but not the wavelength, of the n,π* absorption, as previously observed for benzyl ketones[17] and aldehydes.[18] The absorption intensities give a moderately good fit to a Hammett equation using σ^+ substituent constants (eq 3).

$$\epsilon = 143 \pm 6 + (-166 \pm 17)\sigma^+ \qquad (3)$$

$$r = 0.937$$

Emission spectra for several deoxybenzoins were recorded at 77°K in methylcyclohexane and EPA (ether–isopentane–ethanol). Structured emission similar to that for acetophenone was observed in both solvents. Triplet energies estimated from the position of the highest energy emission band in methylcyclohexane are given in Table III. Triplet lifetimes were determined by the flash emission method[5] at 77°K. Only short-lived (τ < 5 msec), single-component emission was observed in either methylcyclohexane or EPA.

Room temperature phosphorescence was observed for a number of deoxybenzoins, acetophenone, and benzophenone in highly degassed benzene or carbon tetrachloride solution (Table IV). The room-temperature spectra were broader than the 77°K spectra, but showed the same vibrational structure. The spectra disappeared completely upon exposing the solutions to air. The position of the highest energy emission maximum is 400 ± 2 nm (71.5 kcal/mol) for all the ketones in Table IV. Phosphorescence quantum yields were measured by comparing the integrated emission intensity to that of quinine sulfate.[19] The value obtained for benzophenone in carbon tetrachloride is identical with that reported by Saltiel and coworkers.[20]

Triplet lifetimes (τ) for the deoxybenzoins were determined by quenching of room temperature phosphorescence intensity by naphthalene or 2,5-dimethyl-2,4-hexadiene. Linear Stern–Volmer plots (eq 4) were obtained with both

$$\Phi_p^\circ/\Phi_p = 1 + k_q\tau[Q] \quad (4)$$

quenchers; however, the diene is the quencher of choice due to the absence of competitive absorption and emission. Assumption of diffusion-controlled quenching by diene in carbon tetrachloride ($k_q = 6.7 \times 10^9\ M^{-1}\ sec^{-1}$)[21a] and benzene ($k_q = 5.0 \times 10^9\ M^{-1}\ sec^{-1}$)[21b] leads to the estimated lifetimes given in Table IV. The lifetime of deoxybenzoin in carbon tetrachloride was also directly measured using time-correlated single photon counting. The value is similar to that obtained by phosphorescence quenching (Table IV). The lifetimes of acetophenone and benzophenone in degassed carbon tetrachloride are sufficiently long to allow measurement by a signal averaged flash emission technique (see Experimental Section). Larger phosphorescence quantum yields and longer lifetimes were observed in carbon tetrachloride than in benzene solution.[20,22] These parameters are highly dependent upon the purity of the solvent and ketone and the extent of degassing. A single batch of purified carbon tetrachloride[22] was used for all the measurements reported in Table IV.

Discussion

Photochemical α cleavage is the only primary photochemical process observed for the deoxybenzoins in Tables I and II. Weak room-temperature phosphorescence is observed for several deoxybenzoins (Table IV) and provides an invaluable probe of excited state behavior (*vide infra*).[5,23] Both α cleavage and phosphorescence occur from the lowest triplet excited state. The slopes of Stern–Volmer plots for naphthalene quenching of benzaldehyde formation (Table II) and the phosphorescence (Table IV) of deoxybenzoin in benzene are the same, within the experimental error. A simplified kinetic scheme which accounts for α cleavage and phosphorescence is given in eq 5–9.

$$PhCOCH_2Ar \xrightarrow[(2)\ ST]{(1)\ h\nu} T_1 \quad (5)$$

$$T_1 \xrightarrow{k_p} S_0 + h\nu \quad (6)$$

$$T_1 \xrightarrow{k_d} S_0 \quad (7)$$

$$T_1 \xrightarrow{k_\alpha} PhCO\cdot + \cdot CH_2Ar \quad (8)$$

$$T_1 + Q \xrightarrow{k_q} S_0 + Q^* \quad (9)$$

Since the triplet state of deoxybenzoin is formed with unit efficiency,[5] the quantum yields for phosphorescence and product formation (benzaldehyde or bibenzyl) in the absence of added quencher are as given in eq 10 and 11. The

$$\Phi_p^\circ = k_p/(k_p + k_d + k_\alpha) = k_p\tau \quad (10)$$

product quantum yields are determined by the efficiency of α cleavage ($k_\alpha\tau$) and the probability that the initially formed radical pair will give products (β). Assuming that added quencher does not alter β,[24] the same Stern–Volmer expression (eq 12) is obtained for quenching of phosphorescence or product formation.

$$\Phi_{BA}^\circ = \left(\frac{k_\alpha}{k_p + k_d + k_\alpha}\right)\beta = (k_\alpha\tau)\beta \quad (11)$$

$$\Phi_p^\circ/\Phi_p = \Phi_{BA}^\circ/\Phi_{BA} = 1 + k_q\tau[Q] \quad (12)$$

The results in Table I show that electron donating benzyl substituents give modest increases in the quantum yield for bibenzyl formation, whereas electron-withdrawing substituents have little or no effect. In view of the low bibenzyl quantum yields, the variation in triplet lifetime with aromatic substituents could be due to changes in the rates of α cleavage, radiative, and/or nonradiative decay. Since the

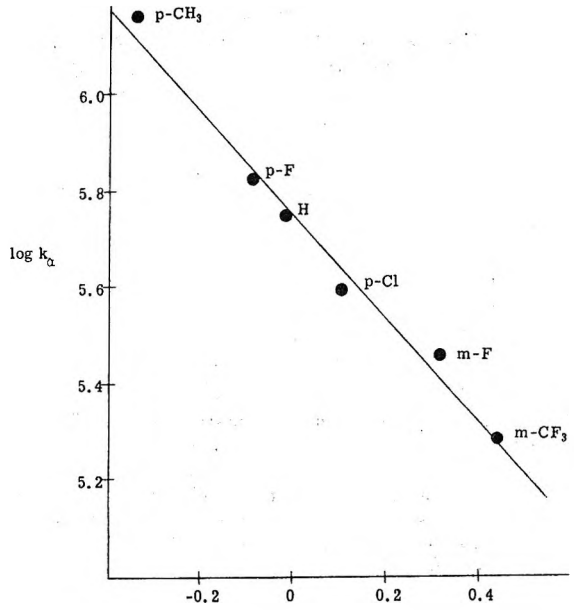


Figure 1. Hammett plot for photochemical α cleavage of deoxybenzoins.

values of $1/\tau$ are not significantly larger than rate constants for nonradiative decay of aryl ketones in benzene solution ($k_d \sim 3 \times 10^5\ sec^{-1}$),[10a,25] nonradiative decay may compete with α cleavage to a significant extent. The low quantum yields for bibenzyl formation (Table I) result in part from cage and noncage recombination of benzoyl and benzyl radicals as well as other free radical processes which compete with benzyl radical combination.[5,16] The quantum yields for benzaldehyde formation (Table II) are significantly larger due to the ability of alkane thiols to efficiently scavenge noncage benzoyl radicals.[5] The benzaldehyde quantum yields in Table II represent minimum values for the α cleavage quantum yield. Cage recombination of benzoyl and benzyl radicals can account for approximately one-half of the initially excited molecules.[16] For those deoxybenzoins with long triplet lifetimes, the alkane thiol scavenger decreases the quantum yield by quenching the $^3n,\pi^*$ excited state. Since the rate constant for thiol quenching of deoxybenzoin phosphorescence is $4.4 \times 10^7\ M^{-1}\ sec^{-1}$,[5] the rate of quenching by 0.01 M thiol is $0.44 \times 10^6\ sec^{-1}$. Thus quenching by thiol may influence the lifetimes and quantum yields in Table II.

The observation of weak room-temperature phosphorescence from deoxybenzoin and its benzyl-substituted derivatives (Table IV) provides a useful probe of photochemical reactivity. Room-temperature phosphorescence has previously been observed for several aromatic ketones in solution and phosphorescence quenching has been used to study the intermolecular reactions of aromatic ketones with a variety of solvents and other substrates.[19,21,25,26] The deoxybenzoins provide only the second example[27] of room-temperature phosphorescence from an aromatic ketone which undergoes an efficient intramolecular reaction. The triplet lifetimes in Table IV are determined by quenching of room-temperature phosphorescence with added diene. The value for deoxybenzoin has been confirmed by single photon counting. Not only is phosphorescence quenching far simpler than product quenching, but it eliminates the major sources of error in the product quenching studies, including quenching by products and by thiol scavenger. The triplet lifetimes for deoxybenzoin and *p*-fluorodeoxybenzoin determined by phosphorescence quenching are somewhat longer than those determined by product quenching and are considered to be more reliable. Triplet lifetimes are

also 2–3 times longer in carbon tetrachloride than in benzene. High apparent rate constants for nonradiative decay of aryl ketone triplets in benzene are due to quenching by benzene.[26c] A solvent effect on the rate constant for α cleavage seems much less likely.

Phosphorescence quantum yields for the deoxybenzoins decrease with decreasing triplet lifetime (Table IV). For *p*-methoxydeoxybenzoin the emission is too weak to allow accurate measurement with our spectrophotometer. Radiative lifetimes can be determined from the triplet lifetimes and phosphorescence quantum yields ($\tau_R = \tau/\Phi_p$). Values for acetophenone and benzophenone are in good accord with previous reports,[25,26a] The radiative lifetimes of the deoxybenzoins are somewhat shorter than that of acetophenone, perhaps as a result of a weak interaction of the carbonyl n,π* triplet with the α-aryl group. No significance should be attached to the variation in τ_R with substituent, in view of the substantial errors in Φ_p and τ.

The triplet lifetimes of the deoxybenzoins are all substantially shorter than those of acetophenone and benzophenone (Table IV). Photochemical α cleavage is responsible for at least part of the decrease in lifetime. The quantum yields for benzaldehyde formation (Table II) suggest that α cleavage is not the exclusive pathway for nonradiative decay of the deoxybenzoins in dodecanethiol–benzene solution. However, quenching by both thiol[5] and benzene[26c] results in triplet lifetimes 3 to 5 times shorter than those in carbon tetrachloride. Thus we assume that α cleavage is the predominant mode of deoxybenzoin nonradiative decay in carbon tetrachloride solution ($k_\alpha \sim 1/\tau$).

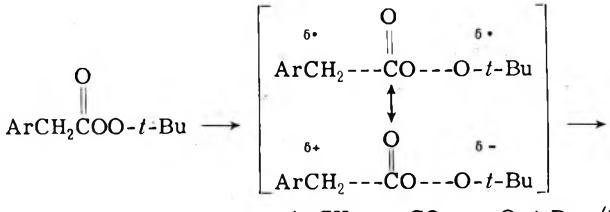
The rate constants for α cleavage in Table IV give a better fit to the Hammett equation[28] with the use of σ^+ (eq 13) than with σ (eq 14). The good fit of the k_α values to the

$$\log k_\alpha = 5.77 - (1.13 \pm 0.08)\sigma^+ \qquad r = 0.989 \quad (13)$$

$$\log k_\alpha = 5.88 - (1.35 \pm 0.15)\sigma \qquad r = 0.976 \quad (14)$$

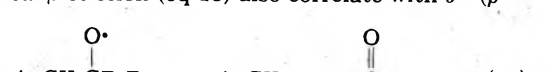
Hammett equation corroborates our assumption that the triplet lifetimes are largely determined by k_α. The Hammett relationships (eq 13 and 14) can be used to estimate values of k_α for *p*-methoxydeoxybenzoin; $k_\alpha = 4.5 \times 10^6(\sigma^+)$ and $k_\alpha = 9.9 \times 10^5(\sigma)$. The σ^+ value is in better agreement with both the kinetic data in Tables I and II and the low phosphorescence quantum yield (Table IV). It should be noted that neither the product quantum yields nor the triplet lifetimes in Tables I and II give satisfactory linear free energy relationships with any substituent parameters. This is a result of the fact that substituents affect both excited state reactivity and subsequent free radical reactions. There have been several previous attempts to correlate quantum yields or relative yields for photochemical abstraction[29] and cleavage[28,30] reactions with Hammett substituent constants. Since there is no necessary relationship between quantum yield and photochemical reactivity,[31] the results of these previous investigations must be interpreted with caution.

Correlations of free radical abstraction[11] and decomposition[12,13,32] reactions with σ^+ have frequently been interpreted as evidence for a transition state with ionic character. Bartlett and Rüchardt[12a] found that the rates of thermal decomposition of *tert*-butyl aryl peracetates (eq 15)



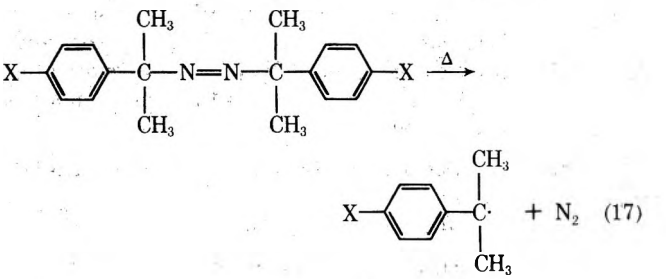
$$ArCH_2COO\text{-}t\text{-}Bu \longrightarrow [ArCH_2{-}{-}{-}CO{-}{-}{-}O\text{-}t\text{-}Bu \leftrightarrow ArCH_2{-}{-}{-}CO{-}{-}{-}O\text{-}t\text{-}Bu] \longrightarrow ArCH_2\cdot + CO_2 + \cdot O\text{-}t\text{-}Bu \quad (15)$$

correlate with σ^+ rather than σ ($\rho = -1.2$ at 65°). Walling and Clark[32] have recently reported that relative rates of alkoxy radical β scission (eq 16) also correlate with σ^+ ($\rho =$



$$ArCH_2CR_1R_2 \longrightarrow ArCH_2\cdot + R_1CR_2 \quad (16)$$

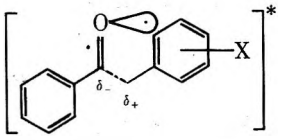
−1.04 at 30°). Thermolysis of azopropanes is cited as an example of a free radical reaction for which the transition state resembles the free radical.[7,14] The limited data for azocumene decomposition[14] (eq 17) show that substituent effects are substantially different than those for α cleavage.



$$k_{rel}\text{: Cl} > OCH_3 > CH_3 > F > H$$

The similar values of ρ for perester decomposition and photochemical α cleavage of deoxybenzoins illustrate once again[5] the remarkable similarity of the effects of substituents on the rates of these reactions and provide a possible insight into the nature of the transition state for α cleavage. Rüchardt[7] has conclusively demonstrated that the transition state for perester thermolysis lies early on the reaction coordinate and has little free radical character. Walling[32] appears to argue for radical character in the transition state for β scission (eq 16); however, he attributes benzyl substituent effects to the contribution of polar structures to the transition state and proposes similar transition states for β scission and perester thermolysis.

We conclude that the preponderance of evidence favors an early transition state with a moderate degree of ionic character for photochemical α cleavage[5] and perester thermolysis.[7] The transition state for α cleavage can be depicted as follows:



The partial negative charge can be stabilized by the electrophilic half-vacant nonbonding orbital on oxygen and the partial positive charge by electron-donating aromatic substituents. α substituents which are capable of stabilizing an adjacent positive charge should effectively accelerate photochemical α cleavage. The high photochemical reactivity of benzoin ethers indicates that this is indeed the case.[33]

Experimental Section

Materials. All deoxybenzoins were prepared by standard literature procedures and had physical and spectral properties in agreement with literature values.[34] Several deoxybenzoins were the gift of Dr. R. Scriven. All deoxybenzoins were extensively purified by recrystallization and vacuum sublimation to >99% purity by vpc. Naphthalene (Baker Photograde) and biphenyl (Aldrich zone refined) were used as received and 2,5-dimethyl-2,4-hexadiene was distilled prior to use. Benzene (spectrograde) was distilled from phosphorus pentoxide prior to use and carbon tetrachloride was purified by the method of Schuster and Weil.[22]

Quantum Yields and Lifetimes. Quantum yields for product formation, Stern–Volmer kinetic data, and 77°K triplet lifetimes were obtained as previously described.[5] Phosphorescence quantum

yields were determined for highly degassed samples sealed in Pyrex ampoules using a Perkin-Elmer MPF-2A spectrophotometer. Lifetimes for acetophenone and benzophenone were measured by pulsing the sample with the filtered output (Corning CS 7-60) of a Xenon Corp. 437A nanopulser and monitoring the transient emission at right angles with an RCA 1P28 photomultiplier through a Corning CS 3-74 filter. A Princeton Applied Research TDH-9 waveform eductor was used to average 100 or more decay transients and the output was recorded on an X–Y recorder. The single photon counting apparatus is similar to that described by Ware.[35]

Acknowledgment. The authors at Northwestern thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and PPG Industries for support of this research. We also thank Dr. D. R. Kory and J. K. McVey for measuring the 77°K phosphorescence lifetimes and W. L. Wallace for measuring the room-temperature phosphorescence lifetimes.

Registry No.—Acetophenone, 98-86-2; benzophenone, 119-61-9.

References and Notes

(1) Part VI: Photochemical α Cleavage of Ketones in Solution. Part V: ref 5.
(2) (a) Camille and Henry Dreyfus Teacher-Scholar, 1973–1978; (b) Northwestern University Fellow.
(3) J. Kenyon, A. R. A. A. Rassoul, and G. Soliman, *J. Chem. Soc.*, 1774 (1956).
(4) H.-G. Heine, *Tetrahedron Lett.*, 3411 (1972).
(5) H.-G. Heine, W. Hartmann, D. R. Kory, J. G. Magyar, C. E. Hoyle, J. K. McVey, and F. D. Lewis, *J. Org. Chem.*, **39**, 691 (1974).
(6) G. E. Robinson and J. M. Vernon, *J. Chem. Soc., Perkin Trans. 1*, 1277 (1972).
(7) (a) C. Rüchardt, *Angew. Chem., Int. Ed. Engl.*, **9**, 830 (1970); (b) C. Rüchardt, H.-D. Beckhaus, J. Bonnekessel, H. Bock, E. Dempewolf, F. A. Groeger, V. Golzke, G. Hamprecht, K. Herwig, J. Hinz, P. Lorenz, I. Mayer-Ruthardt, J. Müller, A. Oberlinner, and E. Schacht, "XXIII International Congress of Pure and Applied Chemistry," Special Lectures, Vol. 4, Butterworths, London, 1971, p 223.
(8) (a) J. C. Dalton and N. J. Turro, *Annu. Rev. Phys. Chem.*, **21**, 499 (1970); (b) P. J. Wagner and R. W. Spoerke, *J. Amer. Chem. Soc.*, **91**, 4437 (1969); (c) O. L. Chapman and D. S. Weiss, *Org. Photochem.*, **3**, 197 (1973); (d) H. Paul and H. Fischer, *Helv. Chim. Acta*, **56**, 1575 (1973).
(9) Aryl substituents conjugated with the carbonyl would be expected to effect photochemical reactivity by changing the energies of the triplet n,π^* and π,π^* states.[10]
(10) (a) F. D. Lewis and J. G. Magyar, *J. Org. Chem.*, **37**, 2102 (1972); (b) A. A. Baum, *J. Amer. Chem. Soc.*, **94**, 6866 (1972).
(11) W. A. Pryor, T. H. Lin, J. P. Stanley, and R. W. Henderson, *J. Amer. Chem. Soc.*, **95**, 6993 (1973), and references therein.
(12) (a) P. D. Bartlett and C. Rüchardt, *J. Amer. Chem. Soc.*, **82**, 1756 (1960); (b) R. C. Neuman, Jr., and J. V. Behar, *J. Org. Chem.*, **36**, 654 (1971); (c) W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, **92**, 5403 (1970).
(13) J. P. Engstrom and J. C. DuBose, *J. Org. Chem.*, **38**, 3817 (1973).
(14) (a) J. R. Shelton, C. K. Liang, and P. Kovacic, *J. Amer. Chem. Soc.*, **90**, 354 (1968); (b) J. W. Timberlake and M. L. Hodges, *Tetrahedron Lett.*, 4147 (1970).
(15) P. J. Wagner, *J. Amer. Chem. Soc.*, **89**, 2820 (1967).
(16) F. D. Lewis and J. G. Magyar, *J. Amer. Chem. Soc.*, **95**, 5973 (1973).
(17) R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962).
(18) H. Küntzel, H. Wolf, and K. Schaffner, *Helv. Chim. Acta*, **54**, 868 (1971).
(19) J. N. Demas and G. A. Crosby, *J. Phys. Chem.*, **75**, 991 (1971).
(20) J. Saltiel, H. C. Curtis, L. Metts, J. W. Miley, J. Winterle, and M. Wrighton, *J. Amer. Chem. Soc.*, **92**, 410 (1970).
(21) (a) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," Wiley, New York, N.Y., 1966, p 627; (b) P. J. Wagner and I. Kochevar, *J. Amer. Chem. Soc.*, **90**, 2232 (1968).
(22) D. I. Schuster and T. M. Weil, *Mol. Photochem.*, **4**, 447 (1972).
(23) F. D. Lewis and C. E. Hoyle, *Mol. Photochem.*, **6**, 235 (1974).
(24) Naphthalene and 2,5-dimethyl-2,4-hexadiene are poor radical traps: W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N.Y., 1966, Chapter 14.
(25) (a) W. D. K. Clark, A. D. Litt, and C. Steel, *Chem. Commun.*, 1087 (1969); (b) H. Lutz and L. Lindqvist, *ibid.*, 493 (1971).
(26) (a) C. A. Parker and T. A. Joyce, *Trans. Faraday Soc.*, **65**, 2823 (1968); (b) D. I. Schuster, T. M. Weil, and M. R. Topp, *Chem. Commun.*, 1212 (1971); (c) D. I. Schuster, T. M. Weil, and A. M. Halpern, *J. Amer. Chem. Soc.*, **94**, 8248 (1972); (d) I. E. Kochevar and P. J. Wagner, *J. Amer. Chem. Soc.*, **94**, 3859 (1972).
(27) P. J. Wagner, P. A. Kelso, A. E. Kemppainen, and R. G. Zepp, *J. Amer. Chem. Soc.*, **94**, 7500 (1972).
(28) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N.Y., 1970, p 335.
(29) (a) C. Walling and M. J. Gibian, *J. Amer. Chem. Soc.*, **87**, 3361 (1965); (b) D. A. Warwick and C. H. J. Wells, *Tetrahedron Lett.*, 4955 (1969); (c) S. Hashimoto and K. Kano, *ibid.*, 3509 (1970).
(30) (a) G. M. Coppinger and E. R. Bell, *J. Phys. Chem.*, **70**, 3479 (1966); (b) H. Kobsa, *J. Org. Chem.*, **27**, 2293 (1962); (c) Y. Ogata and K. Takagi, *Bull. Chem. Soc. Jap.*, **44**, 2186 (1971).
(31) P. J. Wagner and A. E. Kemppainen, *J. Amer. Chem. Soc.*, **94**, 7495 (1972).
(32) C. Walling and R. T. Clark, *J. Amer. Chem. Soc.*, **96**, 4530 (1974).
(33) (a) H.-G. Heine, *Tetrahedron Lett.*, 4755 (1972); (b) F. D. Lewis, R. T. Lauterbach, H.-G. Heine, W. Hartmann, and H. Rudolph, *J. Amer. Chem. Soc.*, in press.
(34) J. G. Magyar, Ph.D. Thesis, Northwestern University, 1974.
(35) W. R. Ware in "Creation and Detection of the Excited State," A. A. Lamola, Ed., Marcel Dekker, New York, N.Y., 1971.

Thermal Isomerizations of Dimethyl 3,4-Diphenylmuconates

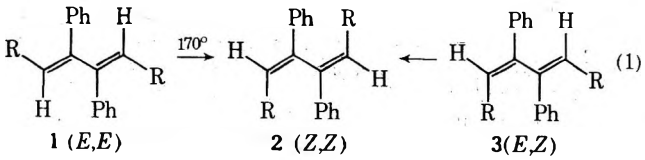
David L. Dalrymple* and William B. Russo

Department of Chemistry, University of Delaware, Newark, Delaware 19711

Received August 1, 1974

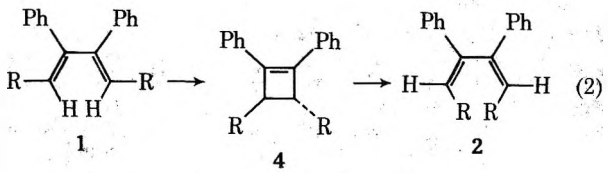
The isomerization of dimethyl (*E,E*)-3,4-diphenylmuconate to its *Z,Z* stereoisomer is shown to proceed through an isolable cyclobutene intermediate with the stereochemistry predicted by orbital symmetry rules. Rate constants and activation parameters have been obtained for the individual steps in the reversible isomerizations.

Several years ago one of us was led to a reinvestigation of the structure and reactivity of the diastereomeric dimethyl 1,3-diphenylbicyclobutane-2,4-dicarboxylates by the violations of orbital symmetry control suggested by the initial study of these compounds.[1] The major discrepancies have been resolved by subsequent work,[2,3] but the thermal interconversions of the dimethyl 3,4-diphenylmuconates **1**, **2**, and **3** which were reported[1,3] still invited explanation (eq 1, R = CO_2Me).



1 (*E,E*) 2 (*Z,Z*) 3(*E,Z*) (1)

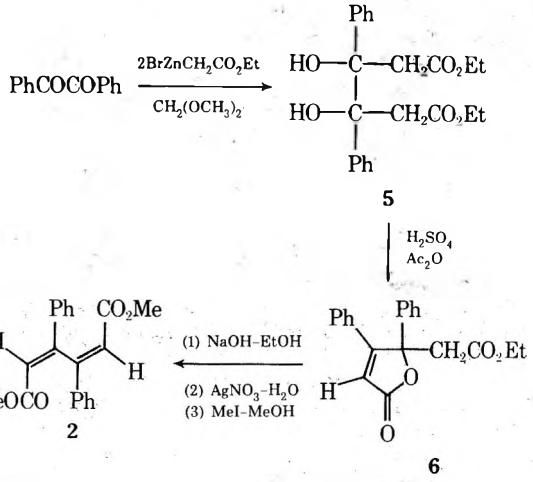
The thermal isomerization of **1** to **2** was originally observed by D'yakonov and coworkers,[1] and the conversion of **3** to **2** was postulated by them[3] to account for the observation that the thermolysis of the exo,exo- and endo,endo-substituted bicyclobutanes produced **2**, rather than **3** as predicted by orbital symmetry theory. The conversion of **1** to **2** could be accomplished by successive double-bond isomerizations involving **3** as an intermediate or by a conrotatory ring closure of **1** to cyclobutene **4** and subsequent conrotatory opening to **2** (eq 2, R = CO_2Me). The former pathway is consistent with the postulated conversion of **3** to **2**, while the latter has ample precedent in the work of Doorakian and Freedman.[4] The isomerization of **3** to **2** might proceed by a double-bond isomerization or by way of a disrotatory ("forbidden") opening of the cis isomer of **4**.



To elucidate the mechanisms of these interconversions a study of their kinetics was undertaken, and we are now able to report the results of this investigation.

As an alternative to the very inefficient synthesis *via* the bicyclobutanes,[1,2] the dimethyl 3,4-diphenylmuconates were prepared using the procedure of Beschke[5] (Scheme I).

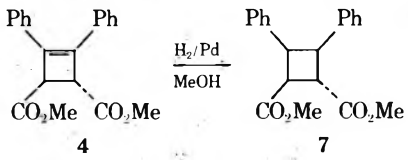
Scheme I



One significant modification of the original method was the use of dimethoxymethane as the solvent for the double Reformatsky reaction with preformed organozinc reagent.[6] This resulted in greatly improved yields and in the formation of *meso*-**5** as the only isolable product. The assignment of *Z,Z* stereochemistry to the muconate formed in this series of reactions is based on the fact that the nmr spectrum of the product indicates it is symmetric (*E,E* or *Z,Z*) and the assumption that the necessarily *Z* substitution of the double bond in lactone **6** is preserved.

The preparation of the *E,E* and *E,Z* stereoisomers, **1** and **3**, was accomplished by photochemical isomerization of **2**. Irradiation of a methanol solution of **2** at 254 nm produced a photostationary-state mixture of **1**, **2**, and **3** in a ratio of 24:30:46.[7] Separation by chromatography and fractional crystallization provided the (*E,E*)- and (*E,Z*)-muconates, **1** and **3**, needed for the study.

The thermal isomerization of **1** at 130–150° was followed by proton nmr in $CDCl_3$. It was immediately obvious that an intermediate was being formed prior to the appearance of the *Z,Z* stereoisomer, **2**. The appearance of the methine protons of the intermediate as a singlet at δ 4.18 suggested that it might be the proposed cyclobutene, **4**. That this was in fact the case was shown by its isolation and catalytic hydrogenation to the known dimethyl neotruxinate, **7**.[8]



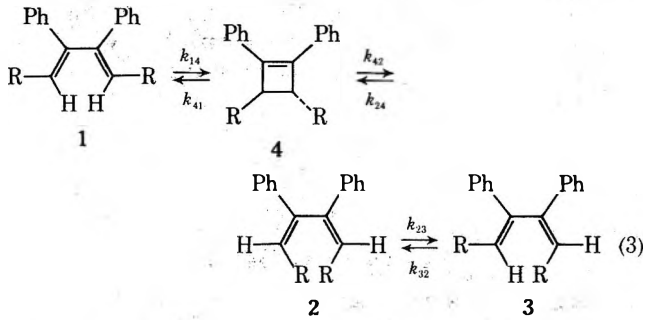
When the isomerization of **1** to **2** was followed to near equilibrium, small amounts of the *E,Z* isomer, **3**, were detectable. In order to ascertain the source of **3**, it was thermolyzed under identical conditions. The initial and only

Table I
Rate Constants for the Interconversions of 1, 2, 3, and 4[a]

Rate constant	130.1°	139.4°	149.8°
k_{14}	20.8 ± 0.1	42.7 ± 0.6	93 ± 4
k_{41}	49 ± 2	99 ± 5	204 ± 10
k_{42}	15.9 ± 0.4	37.6 ± 1.1	94 ± 3
k_{24}	0.5 ± 0.1	1.5 ± 0.3	3.5 ± 0.1
k_{23}	1.9 ± 0.2	2.4 ± 0.5[b]	3.2 ± 0.4[c]
k_{32}	6.4 ± 0.3	13.5 ± 0.6[b]	25.1 ± 0.7[c]

[a] Rate constants in $sec^{-1} \times 10^6$. [b] T = 138.9°. [c] T = 149.0°.

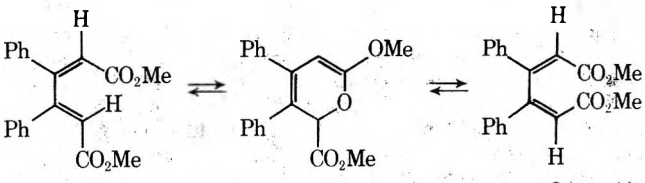
product detected for 4 half-lives of its disappearance was the *Z,Z* isomer, **2**, indicating the isomerizations can be described by eq 3 (R = CO_2Me). The equilibrium mixture at



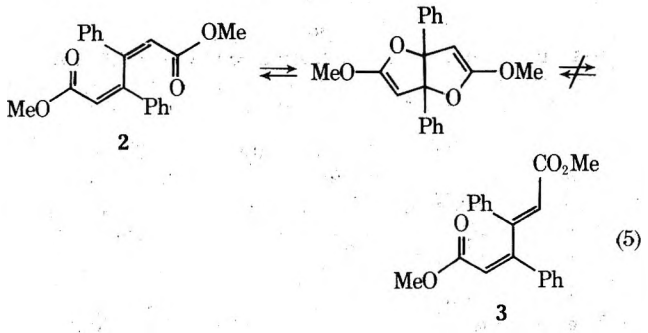
140° consisted of the compounds **1**, **4**, **2**, and **3** in a ratio of approximately 7:3:75:15.

In order to characterize further this series of reactions, the nmr data were analyzed to obtain the rate constants shown in Table I. Because of the large relative errors in k_{23} and k_{24}, it was possible to calculate accurate thermodynamic constants from differences in activation parameters only for the equilibrium between **1** and **4**: ΔH = 1.3 ± 0.5 kcal/mol, ΔS = 1.4 ± 1.2 eu, ΔG_{415} = 0.7 kcal/mol. It is apparent from these data that the strain between and the hindered rotation of the substituents on the butadiene skeleton in **1** nearly compensate for the strain and loss of diene rotation in cyclobutene **4**. The normally much greater stability of the butadiene tautomer is exemplified by the unsubstituted butadiene–cyclobutene system, where ΔH_{298} = 11.2 kcal/mol, ΔS_{298} = −3.6 eu, and ΔG_{298} = 12.3 kcal/mol.[9] Qualitative consideration of the data for the equilibrium between the cyclobutene, **4**, and the (*Z,Z*)-muconate, **2**, indicates that the latter's greater stability is due both to an increase in entropy and to a decrease in enthalpy of formation, *i.e.*, less strain and freer rotation of the substituents.

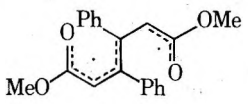
The kinetic parameters for the isomerization of the (*E,Z*)-muconate, **3**, to the (*Z,Z*)-muconate, **2**, are somewhat unusual for a double-bond isomerization: ΔH^* = 23.5 ± 3.6 kcal/mol, ΔS^* = −25 ± 9 eu. For comparison, the corresponding parameters for methyl *cis*-cinnamate are ΔH^* = 40.2 kcal/mol and ΔS^* = −14 eu.[10] The parameters are even less consistent with an alternative mechanism of isomerization through a pyran intermediate as shown in eq 4. Such intermediates have been reported in the isomeriza-



tions of 1,4-diacylbutadienes,[11] but even less negative entropies of activation are likely for this reaction.[12] A mecha-



nism involving a dihydrofurofuran[11] (eq 5) might account for the large negative entropy of activation, but a concerted raction to form this intermediate from the (*E,Z*)-muconate, **3**, seems sterically impossible. Thus the isomerization of **2** ⇄ **3** appears most likely to occur by simple twisting about one of the double bonds going through the intermediate or particularly well-stabilized transition state, **8**, in which the rotational freedom of several of the substituents is lost.



8

Experimental Section

Infrared spectra were measured on a Perkin-Elmer 137 spectrophotometer, ultraviolet spectra were recorded on a Bausch and Lomb Model 505, and nmr spectra were determined on Varian A-60A and Perkin-Elmer R-12B spectrometers. Melting points are uncorrected.

***meso*-Diethyl 3,4-Dihydroxy-3,4-diphenyladipate (5).** A mixture of 32.5 g (0.50 g-atom) of granular zinc and 150 ml of freshly purified dimethoxymethane was heated to reflux in a 1-l., three-necked flask fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel. To the stirred mixture 83.5 g (0.50 mol) of ethyl bromoacetate was added dropwise over 30 min. After the exothermic reaction which accompanies the addition subsided, the mixture was refluxed 1 additional hr. To the resulting solution 21.0 g (0.10 mole) of benzil in 200 ml of dimethoxymethane was added over a period of 1 hr, and the mixture was refluxed for 2 hr more. After addition of 200 ml of ice water, the mixture was transferred to a separatory funnel containing 200 ml of ether and 100 ml of 6 *N* sulfuric acid. After shaking of the mixture well, the aqueous layer was removed, and the organic layer was filtered to remove the product. The filtrate was concentrated to provide more product. The crude product was dissolved in hot benzene, which on trituration with ethanol and cooling gave 38.7 g (90%) of meso diester, **5**: mp 168–170° (lit.[5] mp 168°); ir (KBr) 3450, 1705, 1190, 1150, 752, 742, 700 cm^{-1}; nmr ($CDCl_3$, TMS) δ 7.1–8.1 (m, 10 H, Ar H), 4.55 (s, 2 H, –OH), 3.78 (q, J = 7 Hz, 4 H, $-OCH_2CH_3$), 3.35 (d, J = 16 Hz, 2 H), 2.27 (d, J = 16 Hz, 2 H), 0.92 ppm (t, J = 7 Hz, 6 H, $-OCH_2CH_3$).

Ethyl 2,3-Diphenylcrotonolactone-3-acetate (6). The lactone was prepared as described by Beschke[5] in 81% yield: mp 90–92° (lit.[5] mp 94°); nmr (CCl_4, TMS) δ 7.1–7.4 (m, 10 H), 6.24 (s, 1 H), 4.01 (q, J = 7.4 Hz, 2 H), 3.44 (d, J = 15.0 Hz, 1 H), 3.25 (d, J = 15.0 Hz, 1 H), 1.12 ppm (t, J = 7.4 Hz, 3 H).

Dimethyl (*Z,Z*)-3,4-Diphenylmuconate (2). The dimethyl ester was prepared *via* the sodium and silver salts of the diacid as described by Beschke for preparing the diethyl ester.[5] After recrystallization from methanol the ester (83% yield from **6**) had a melting point of 114–116°: lit.[1] mp 114°; uv (CH_3OH) λ_{max} 295 nm (ϵ 23,700); ir (KBr) 1710, 1630, 1610, 1185, 1160, 775, 682 cm^{-1}; nmr (CCl_4, TMS) δ 7.30 (m, 10 H), 6.44 (s, 2 H), 3.56 ppm (s, 6 H).

Dimethyl (*E,E*)-3,4-Diphenylmuconate (1). A 1% solution of **2** in spectral grade methanol was irradiated for 5 hr at 253.7 nm in a quartz tube in a photochemical reactor (New England Ultraviolet Co. Model RPR-100). Evaporation of the solvent provided a mixture of **1**, **2**, and **3** in a ratio (nmr) of 24:30:46, respectively. The mixture was separated into two fractions by dry column chromatography on silica gel (500 g of Waters Associates No. 27850/g), developing with chloroform. Elution of the band at R_f ~0.75 provided the *E,E* diester: mp 157–159° (lit.[1] mp 152°) after recrystallization from methanol; uv (CH_3OH) λ_{max} 262 nm (ϵ 14,000); ir (KBr) 1700, 1590, 1580, 1180, 1150, 750, 690 cm^{-1}; nmr (CCl_4, TMS) δ 7.32 (m, 10 H), 5.70 (s, 2 H), 3.42 (s, 6 H).

Dimethyl (*E,Z*)-3,4-Diphenylmuconate (3). The fraction at R_f 0.3–0.6 from the above chromatography was eluted with methanol. Evaporation of the solvent provided an oil consisting of **2** and **3**. After several fractional crystallizations from chloroform and methanol, the (*E,Z*)-muconate, **3**, was obtained: mp 96–98°; nmr (CCl_4, TMS) δ 7.2–7.6 (m, 10 H), 6.29 (s, 1 H), 6.04 (s, 1 H), 3.20 (s, 3 H), 3.15 ppm (s, 3 H). This material was contaminated with 5% of the (*Z,Z*)-muconate (by nmr) which could not be removed by further recrystallizations. This material was, however, sufficiently pure for thermolysis since the program used for analysis of the data could allow for its presence (see below).

Dimethyl 1,2-Diphenylcyclobutene-*trans*-3,4-dicarboxylate (4). A solution of 300 mg of **2** in 2 ml of chloroform was sealed in a thick-walled tube under nitrogen and heated at 140° in an oil bath for 6 hr. The resulting mixture of **1**, **2**, and **4** (65:15:20 by nmr) was separated by dry-column and preparative thin-layer chromatography (silica gel–chloroform) to provide 22.5 mg of **4**: mp 77–78° after recrystallization from methanol–water; uv (CH_3OH) λ_{max} (ϵ) 227 (20,700), 293 (14,600), 305 nm (sh) (13,500); ir (KBr) 1725, 1430, 1238, 1222, 754, 688 cm^{-1}; nmr ($CDCl_3$, TMS) δ 7.4–7.0 (m, 10 H), 4.18 (s, 2 H), 3.70 (s, 6 H); mass spectrum (70 eV) *m/e* (relative intensity) 322 (46), 290 (79), 263 (100), 262 (71), 231 (54), 203 (45), 202 (56), 129 (40), 102 (55).

Anal. Calcd for $C_{20}H_{18}O_4$: C, 72.49; H, 5.78. Found: C, 72.46; H, 5.51.

A sample of **4** in methanol was hydrogenated at atmospheric pressure using 10% palladium on charcoal as catalyst. Trituration of the filtered solution with water provided crystals which were recrystallized from methanol to provide dimethyl neotruxinate: mp 126–128° (lit.[8] mp 127°); nmr ($CDCl_3$, TMS) δ 7.10 (br, s, 10 H), 4.0–4.4 (m, 4 H), 3.78 (s, 3 H), 3.32 (s, 3 H).

Thermolyses of 1 and 3. Solutions of 40–60 mg of **1** or **3** in 0.4 ml of $CDCl_3$ were sealed in nmr tubes under nitrogen. The tubes were placed in a thermoregulated oil bath and withdrawn at regular intervals for analysis by proton nmr. The extent of reaction and product composition was determined from the relative areas of the respective methine proton signals (**1** at δ 5.85, **2** at 6.62, **3** at 6.10 and 6.25, and **4** at 4.18 ppm). Each peak was integrated ten times using a digital voltmeter connected to the spectrometer. The standard deviation of the average was typically 0.5% of the total integral. Three separate samples of **1** were thermolyzed at each of three temperatures, 130.1, 139.4, and 149.8 ± 0.2°. Twenty points were taken over periods of 24–120 hr, depending on the reaction temperature. The temperatures used for the thermolysis of **3** were 130.1, 138.9, and 149.0 ± 0.2°. As mentioned above, the samples of **3** used in the kinetic study contained 5–10% **2**.

Kinetic Analysis of Data. The data obtained from the thermolyses were analyzed for rate constants using the general curve-fitting program of Dye and Nicely.[13] The uncertainties quoted in Table I are standard deviations calculated by the program. The criterion of fit was a minimum weighted sum of squares of deviations of all dependent variables (concentrations). The differential equations used in the analysis of the thermolyses of **1** were

$$d[1]/dt = k_{31}[3] - k_{13}[1]$$

$$d[2]/dt = k_{32}[3] + k_{42}[4] - (k_{23} + k_{24})[2]$$

$$d[3]/dt = k_{13}[1] + k_{23}[2] - (k_{31} + k_{32})[3]$$

To simplify the calculations, k_{23} and k_{32} were set equal to the values determined independently from the thermolysis of **3**, and the concentration of **4** was set equal to 100 − ([1] + [2] + [3]). All concentrations were expressed as per cent of the total mixture.

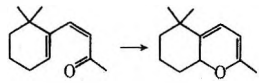
For analysis of the data from the thermolysis of **3**, the differential equation used was $d[3]/dt = k_{23}[2] - k_{32}[3]$.

Acknowledgments. The authors wish to express their appreciation to Messrs. Bruce Frye and Gifford Marzoni for their assistance. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. We also express our appreciation to the Michigan State University Computer Center for providing the program used in the kinetic analysis.

Registry No.—**1**, 7576-89-8; **2**, 7577-43-7; **3**, 53432-82-9; **4**, 53432-83-0; **5**, 53432-84-1; **6**, 36126-37-1; **7**, 52305-39-2; dimethoxymethane, 109-87-5; ethyl bromoacetate, 105-36-2; benzil, 134-81-6.

References and Notes

(1) I. A. D'yakonov, V. V. Razin, and M. I. Komendantov, *Tetrahedron Lett.*, 1127, 1135 (1966).
(2) R. B. Woodward and D. L. Dalrymple, *J. Amer. Chem. Soc.*, **91**, 4612 (1969).
(3) I. A. D'yakonov, V. V. Razin, and M. I. Komendantov, *Zh. Org. Khim.*, **5**, 386 (1969).
(4) G. A. Doorakian and H. H. Freedman, *J. Amer. Chem. Soc.*, **90**, 3582, 5310, 6896 (1968); G. A. Doorakian, H. H. Freedman, R. F. Bryan, and H. P. Weller, *ibid.*, **92**, 399 (1970).
(5) E. Beschke, *Justus Liebigs Ann. Chem.*, **384**, 143 (1911).
(6) J. Curé and M. Gaudemar, *Bull. Soc. Chim. Fr.*, 2471 (1969).
(7) The iodine-sensitized photoisomerization of **2** to **1** has been reported.[1]
(8) R. Stoermer and E. Asbrand, *Ber. Deut. Chem. Ges.*, **64**, 2796 (1931).
(9) S. W. Benson, *et al.*, *Chem. Rev.*, 69, 279 (1969), and references therein.
(10) G. B. Kistiakowsky and W. R. Smith, *J. Amer. Chem. Soc.*, **57**, 269 (1935).
(11) G. Maier and M. Wiessler, *Tetrahedron Lett.*, 4987 (1969).
(12) E. g., for the reaction of i → ii, $\Delta H^{\ddagger} = 20.6$ kcal/mol, $\Delta S^{\ddagger} = -4.8$ eu:



E. N. Marvel, G. Caple, T. A. Gosink, and G. Zimmer, *J. Amer. Chem. Soc.*, **88**, 619 (1966).
(13) J. L. Dye and V. A. Nicely, *J. Chem. Educ.*, **48**, 443 (1971).

Acylation of Vicinal Dianions. Formation of Products by Rearrangement and Proton Transfer

James G. Smith,* Isaac Ho, and George E. F. Simpson

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada

Received May 29, 1974

The acylation of the vicinal dianions **1** and **20**, respectively derived by reductive metalation of benzophenone anil and *N*-(*p*-cyanobenzal)aniline, was examined in detail with ethyl chloroformate as the acylating agent. In the case of **1**, dimethylcarbamoyl chloride was used as well. In addition to the expected acylation at the benzylic and amine anionic sites, additional products were formed by rearrangement of the acyl group and/or proton transfer. In the case of **1**, these reactions, under certain conditions, led to triacylated semibenzene derivatives as a major product. Reaction of **20** was more complicated since the reaction products consisted of mono-, di- and triacylated derivatives. The reaction was studied by generating the individual monoanions formed as intermediates in the reaction. Proton transfer was more dominant in this reaction although migration of a carbethoxy group again occurred.

Ethyl chloroformate is a useful reagent for characterizing and functionalizing anionic species. Recently, in studies of two vicinal dianions,[1,2] some interesting deviations from the anticipated acylation were noted. This report describes these reactions which involved acyl group migration and/or proton transfer and outlines some of the factors affecting the extent of the side reactions.

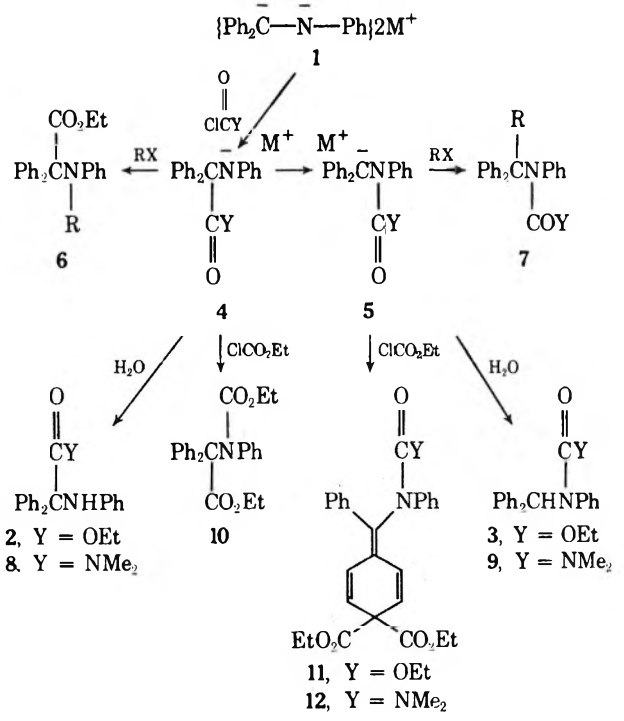
Scheme I summarizes our earlier observations with ethyl chloroformate and the vicinal dianion **1** derived from benzophenone anil. Thus rearrangement of the initially formed anion **4** (Y = OEt) to **5** (Y = OEt) occurred as clearly indicated by the characterizing reactions of **4** and **5** shown in Scheme I.

This rearrangement proceeded with even greater facility with dimethylcarbamoyl chloride[3] as acylating agent. Indeed, the unrearranged anion **4** (Y = NMe_2) could only be detected under reaction conditions unfavorable to rearrangement (*i.e.*, diethyl ether as solvent, lithium as counterion).

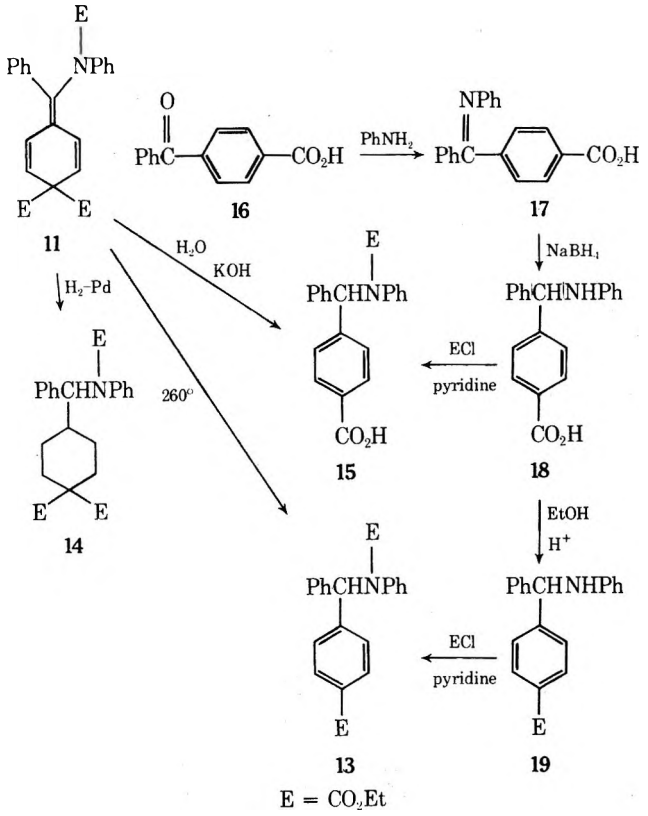
Proton transfer was observed[1] during further acylation of the rearranged monoacylated anion **5** to produce the semibenzene derivative **11**. Again this same reaction occurred with dimethylcarbamoyl chloride to give **12**. In the case of **11** both spectral and chemical evidence supported the proposed structure (see Scheme II and Experimental Section), while structure **12** was based on the presence of four vinyl protons in the 5.8–6.8 region of the nmr spectrum and on the strong absorption band in the 320–340-nm region of the uv spectrum.[4]

The availability of a second vicinal dianion **20** derived from *N*-(*p*-cyanobenzal)aniline[2] prompted a comparison of its behavior toward ethyl chloroformate with that of **1**. This reaction proved quite complex. With 1 equiv of acylating agent both mono- and diacylated products **21** and **23** were isolated (see Scheme III). With 2 equiv, the additional N-monoacylated product **22**, a second diacylated derivative **24** and a triacylated compound **25** were also formed. The relative amounts of these products varied somewhat with reaction temperature (see Table I).

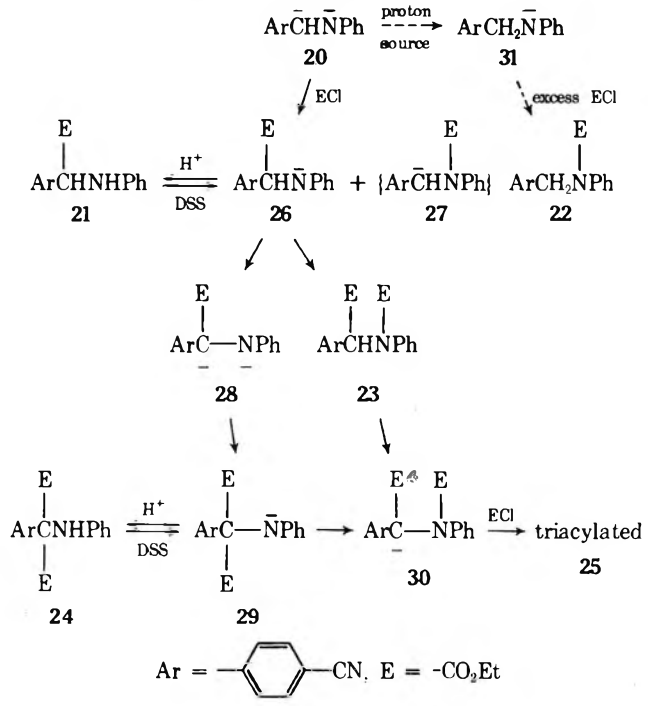
Scheme I
Acylation of the Benzophenone Anil Dianion



Scheme II
Proof of Structure for the Semibenzene Product



Scheme III
Acylation of Vicinal Dianion 20

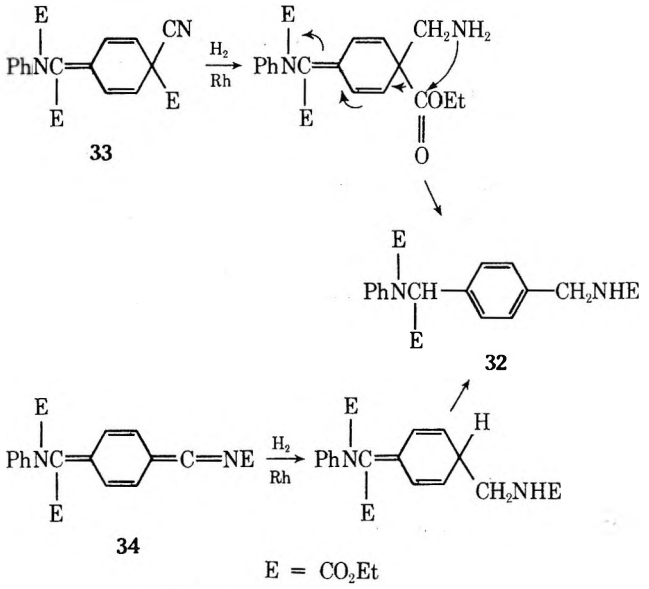


In order to analyze this behavior, the individual monoanionic species **26, 27, 29, 30,** presumed present in the reacting system, were generated by treating the corresponding protonated compounds with the disodium–stilbene (DSS) complex, followed by acylation with ethyl chloroformate of the anion in order to determine its behavior under the reaction conditions used in acylating dianion **20.** This approach failed to produce anion **27** from **22**—instead 4,4′-dicyanobibenzyl[6] was formed. The results are summarized in Table II and outlined below.

The anion **30** (from the C,N-diacylated compound **23** and DSS) produced the triacylated species **25** on acylation. Slow protonation of **30** by the solvent evidently occurred, since delaying the acylation for 16 hr produced only the starting material **23.** Rearrangement of the anion **29** (from the C,C-diacylated derivative **24** and DSS) occurred and only the C,N-diacylated product **23** was isolated after 16 hr. At shorter reaction times, acylation produced the triacylated species **25** indicating the intermediacy of anion **30** in the rearrangement.

Acylation of the anion **26** or **28** (from the C-acylated compound **21** and DSS) produced both the C,C-diacylated and the N-acylated compounds **24** and **22.** The latter product arose by acylation of the N-(*p*-cyanobenzyl)aniline which itself was formed by a reductive cleavage of **21** by DSS. Quenching of the anionic species showed this cleavage to account for about 30% of the reaction. Since no **23** was detected, the anion **29** was absent.

Isolation of the triacylated compound **25** was complicated by its thermal sensitivity[7] and column chromatography failed to give completely pure material. Thermal decomposition of **25** produced **24**; hydrogenation of **25** (2 mol of hydrogen reacted) gave a compound identified as **32** on the basis of its spectra and its synthesis (see Experimental Section). Two structures **33** and **34** are reasonable for the triacylated compound. Structure **33** is suggested by analogy



with the semibenzene product formed from the benzophenone anil dianion **1** and hydrogenation of the nitrile group followed by rearrangement provides **32.** In the case of **34,** hydrogenation followed by a proton shift produces **32.** Neither structure is completely satisfactory—**32** because a strained cyclic transition state must be proposed for the rearrangement and **34** because of the absence of a ketenimine band in the ir spectrum.

Discussion

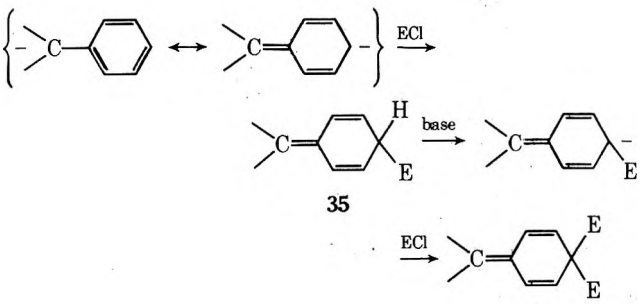
Of the two anionic centers in the vicinal dianions **1** and **20,** the carbanionic one is the more reactive. This is clearly evident in the acylation of **1** but is less obvious in the case of **20.** Here N-monoacylation (*i.e.*, **22**) is observed in significant quantities in reactions 3 and 4 (Table I). However, after acylation at the carbanionic center of **20,** the product **26** now contains a labile proton and can be transformed by a base to **28.** The base is, of course, the initial dianion **20**

and protonation of this produces **31** and/or the amine, *N*-(*p*-cyanobenzyl)aniline, which becomes the source of the *N*-monoacylated compound **22.** Note that the amount of **22** in reaction 3 closely approximates the amount of the *N*-(*p*-cyanobenzyl)aniline in reactions 1 and 2. The much lower temperature of reaction 4 retards proton transfer and the yield of **22** is less than in reaction 3.

Only in the presence of 2 equiv of ethyl chloroformate are reaction products observed which are clearly characteristic of proton transfer. Thus the anions **28** and **30,** formed by proton transfer, manifest themselves as the diacylated product **24** and the triacylated product **25.** In this regard, the amount of **24** in reaction 3 is of the same order of magnitude as the C-monoacylated product **21** of reaction 1. The difference between these values (9%) probably is due to rearrangement of **24** (through **29**) to **30.** Note that the sum of products **23** and **25** (both derived from **30**) in reaction 3 closely approximates the sum of the C,N-diacylated product **23** in reaction 1 plus the 9% difference.

A lower reaction temperature surpresses proton transfer but does not eliminate it. (Changing the counterion to lithium does not eliminate proton transfer insofar as the formation of **25** is concerned. Material balance was incomplete in these experiments; so the results are not discussed in detail.) Note the smaller amount of triacylated product **25** in reaction 4 compared to reaction 3 although the sum of **23** and **25** is equivalent in both reactions. The lower temperature also favors monoacylation over diacylation (reaction 2 *vs.* 1) and this larger amount of **21** (and its anion **28**) is reflected in the larger amount of **21** and **24** in reaction 4 compared to reaction 3. Again the combined amounts of **21** and **24** in reaction 4 approximates the amount of **21** in reaction 2.

In the case of the dianion **1,** proton transfer is observed only after acylation occurs in the ring as shown in the partial formulas. Rapid quenching of the reaction shortly after the addition of the second equivalent of ethyl chloroformate produced a complex mixture which included the *p*-carbethoxy derivative **13** arising by rearrangement of **35** during isolation.



E = CO_2Et

Delocalization of the anionic charge into the aromatic ringe[8] accounts for the ring acylation of monoanions **5** and **30.** In the case of **5,** it would appear that steric crowding at the benzhydrylic anionic site sufficiently inhibits acylation that ring acylation predominates. The C,N-diacylated compound **10** can be obtained by acylation of the unrearranged monoanion **4** (Y = OEt) but in this case the second acyl group is introduced at the less crowded amine anionic center. Similar considerations apply to the monoanions formed on acylation of the dianion **20.** Thus the steric crowding present in **30** causes acylation to occur at more remote locations producing **25.** However, the less crowded benzylic anion **28** yields the "normal" product **24** on further acylation.

Rearrangement of the acylated anions is slow relative to acylation or proton transfer. Although the C,C-diacylated compound **24** is observed to rearrange at room temperature *via* **29** to the C,N-diacylated species **23, 24** is a product of the acylation of **20** with 2 equiv of ethyl chloroformate. Thus neutralization of the reaction medium occurs faster than the rearrangement.

The driving force for the rearrangement is the formation of a more stable anion.[9] In the case of **4,** a benzhydrylic anion (*i.e.,* **5**) is generated while with **29** the rearrangement produces **30,** a benzylic anion additionally stabilized by the carbethoxy group. The rearrangement also appears dependent upon the degree of association of the ion pair with loose ion pairs favoring rearrangement. Thus the polarity of the solvent affects the reaction, rearrangement occurring much more rapidly in the more basic solvent THF.[10] Similarly, the lithium cation with its greater Lewis acidity than that of sodium[11] slows the rearrangement markedly because of its tight association with the amine anionic center.

Experimental Section

Melting points, measured in a Mel-Temp apparatus, are uncorrected. Infrared spectra were recorded on a Beckman IR-10 in KBr pellets unless otherwise indicated. Nmr spectra were recorded on a Varian T-60 spectrometer in $CDCl_3$; chemical shifts are reported in δ units downfield from internal tetramethylsilane.

Reaction products were isolated by diluting the reaction mixture with water, ether extracting, drying the extract with magnesium sulfate, and removing the solvent on a rotary evaporator. Column chromatography of the crude products was performed on 0.05–0.20-mm silica gel using hexane–25% benzene as solvent except where otherwise specified.

The preparation of dianion[12] **1** from benzophenone anil and dianion[2] **20** from *N*-(*p*-cyanobenzal)aniline has been described.

Acylation of Benzophenone Anil Dianion 1 without Rearrangement. Preparation of 2, 6, 8 and 10. The dianion **1** (M = Na, 0.01 mol) in THF was cooled to −75° and treated with 1.1 g (0.01 mol) of ethyl chloroformate. The color faded from deep red to pink over a 15-min period and was then quenched with methanol. Isolation of the reaction products (2.97 g) followed by chromatography gave 2.8 g (79% yield) of ethyl *N*,2,2-triphenylglycinate, **2.** Recrystallization from ethanol gave an analytical sample: mp 111–113°; nmr 0.97 (t, J = 8 Hz, 3, CH_3), 4.14 (q, J = 8 Hz, 2, CH_2), 5.2 (broad s, 1, NH), 6.3–7.7 (m, 15, aromatics); ir (KBr) 3420 (NH), 1735 (C=O), 1600, 1500, 750, 690 (aromatic), 1240, 1180 (ester C—O) cm^{-1}.

Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.54; H, 6.14; N, 4.23.

The above experiment was repeated except that the reaction mixture was treated with 1.4 g (0.01 mol) of methyl iodide prior to the methanol quench. The crude reaction product (3.3 g) was recrystallized from ethanol to give 2.48 g (72% yield) of ethyl *N*-methyl-*N*,2,2-triphenylglycine, **6** (R = Me): mp 84–85.5°; nmr 1.0 (t, J = 8 Hz, 3, CH_3), 2.88 (s, 3, NCH_3), 4.13 (q, J = 8 Hz, 2, CH_2), 6.5–7.6 (m, 15, aromatics); ir (film) 2830 (NCH_3), 1735 (C=O), 1600, 1500, 750 and 700 (aromatic CH), 1220 (ester C—O) cm^{-1}.

Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.19; H, 6.87; N, 4.10.

The dianion **1** (M = Li, 0.01 mol) in THF was treated with 1.2 g (0.01 mol) of dimethylcarbamoyl chloride at −78°, allowed to react for 1 hr, and quenched with ethanol, and the isolated crude product was recrystallized from ethanol to give 1.38 g (42% yield) of **8**: mp 219–220°; nmr 2.83 (s, 6, NMe_2), 5.0 (broad s, 1, NH), 6.5–7.6 (m, 15, aromatics); ir (KBr) 3400 (NH), 1640 (C=O), 750, 740, 690 (aromatic) cm^{-1}.

Anal. calcd for $C_{22}H_{22}N_2O$: C, 79.96; H, 6.71; N, 8.48. Found: C, 79.80; H, 6.67; N, 8.29.

In the case of **1** (M = Na) similar results were obtained provided quenching occurred after a 15-min reaction at −78°.

The dianion **1** (M = Li, 0.01 mol) in DEE was cooled to −78°, treated with 1.1 g (0.01 mol) of ethyl chloroformate, and allowed to warm to 20° for 15 hr. It was then recooled to −78° and treated with a second 1.1-g amount (0.01 mol) of ethyl chloroformate. After warming the mixture to 20° for 9 hr, the crude product (3.6 g) was isolated. Chromatography gave 2.4 g (60%) of ethyl *N*-carbethoxy-*N*,2,2-triphenylglycinate, **10,** mp 106–108°. Two recrystallizations from pentane gave an analytical sample: mp 109–111°;

nmr 1.08 (t, J = 7 Hz, 3, CH_3), 1.40 (t, J = 7 Hz, 3, CH_3), 4.12 (q, J = 7 Hz, 2, CH_2), 4.45 (q, J = 7 Hz, 2, CH_2), 7.0–7.4 (m, 15 aromatics); ir (KBr) 1730 and 1700 (C=O), 1600, 1500, 750, 700 (aromatics), 1230 (broad, ester C—O) cm^{-1}.

Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.65; H, 6.22: N, 3.46.

Acylation of the Benzophenone Anil Dianion, 1, with Ethyl Chloroformate and with Rearrangement. Preparation of 3, 7 (Y = OEt) and 11. The dianion 1 (M = Na, 0.01 mol) in THF was cooled to −75°, and ethyl chloroformate (1.1 g, 0.01 mol) was added. After 15 min the solution was allowed to warm to 20° (solution became dark red) and stand for 12 hr (solution A).

Quenching of solution A with methanol, isolation of the crude product (2.94 g), and chromatography with benzene–25% hexane gave 0.4 g of a benzhydrylaniline–benzophenone anil mixture followed by 2.0 g (61% yield) of crude *N*-carbethoxy-*N*-benzhydrylaniline, **3**, 57–60°. Recrystallization from pentane gave an analytical sample: mp 59–61°; nmr 1.1 (t, J = 7 Hz, 3, CH_3), 4.17 (q, J = 7 Hz, 2, CH_2), 6.71 (s, 1, CH), 6.9–7.3 (m, 15, aromatic H); ir (KBr) 1700 (C=O), 1300 (broad, C—O), 760, 720, 700, 680 (aromatic CH) cm^{-1}.

Anal. Calcd for $C_{22}H_{21}O_2N$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.88; H, 6.26; N, 4.06.

Solution A was treated with 1.4 g (0.01 mol) of methyl iodide at −78°. After warming and isolating the crude product (3.3 g), chromatography using benzene −25% hexane gave 2.6 g (75% yield) of crude **7** (R = CH_3, Y = OEt). Recrystallization from pentane gave an analytical sample: mp 88–91°; nmr 0.92 (t, J = 7 Hz, 3, CH_2CH_3), 1.73 (s, 3, CH_3), 3.91 (q, J = 7 Hz, 2, CH_2CH_3), 7.1–7.6 (m, 15, aromatic H); ir (KBr) 1710 (C=O), 1600, 1490, 760, 700 (aromatic CH) cm^{-1}.

Anal. Calcd for $C_{23}H_{23}O_2N$: C, 79.97; H, 6.71; N, 4.06. Found: C, 79.85; H, 6.69; N, 3.90.

Solution A was treated at −78° with 1.3 g (0.01 mol) of benzyl chloride and after 3 hr the reaction product (4.1 g) was isolated. Chromatography of 1 g using benzene 40% hexane gave 0.9 (88%) of **7** (R = $PhCH_2$, Y = OEt), mp 186–190°. An analytical sample was obtained by recrystallization from diethyl ether: mp 188–190°; nmr 0.87 (t, J = 7 Hz, 3, CH_2CH_3), 3.27 (s, 2, CH_2Ph), 3.86 (q, J = 7 Hz, 2, CH_2CH_3), 6.2–7.5 (m, 20, aromatic H).

Anal. Calcd for $C_{29}H_{27}NO_2$: C, 82.63; H, 6.46; N, 3.32. Found: C, 82.79; H, 6.50; N, 3.14.

Solution A was treated at −78° with 1.1 g (0.01 mol) of ethyl chloroformate and allowed to warm to 20°. The crude product (4.0 g) was chromatographed using benzene–25% hexane to give 1.4 g of **3** (42% yield). Continuing the elution with chloroform gave 2.4 g (50% yield) of **11** as a gum. The crude **11** was treated with activated charcoal in hot ethanol and the filtrate was cooled to 10°. After several days, **11** crystallized out (0.65 g): mp 83.5–85°; nmr 1.05 and 1.23 (overlapping t, J = 7 Hz, 9, CH_3), 4.16 and 4.20 (overlapping q, J = 7 Hz, 6, CH_2), 6.0–6.9 (m, 4, vinyl H), 7.0–7.5 (m, 10, aromatic H); ir (KBr) 1730, 1710 (C=O), 1500, 750, 690 (aromatic), 1240 (ester C—O) cm^{-1}; uv (EtOH) λ_{max} 230 (ϵ 1.5 × 10^4), 250 (sh, 1.3 × 10^4), 315 (2.0 × 10^4).

Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.71; H, 6.15; N, 2.95. Found: C, 70.93; H, 6.38; N, 2.89.

This experiment was repeated but the solution, after treatment with the second equivalent of ethyl chloroformate, was quenched with water after a 15-min reaction. Chromatography gave 2.16 g (65% yield) of **3** and 0.80 g (20% yield) of **13** identified on the basis of its spectral properties. No semibenzene **11** could be detected.

Reaction of the Benzophenone Anil Dianion, 1, with Dimethylcarbamoyl Chloride with Rearrangement. Preparation of 7 (R = Me, Y = NMe_2), 9 and 12. Reactions of the rearranged anion **5** (Y = NMe_2) proceeded in the same manner as that of **5** (Y = OEt). Thus, the reaction product of **1** (M = Na, 0.01 mol) in THF with 1.2 g (0.01 mol) of dimethylcarbamoyl chloride at −78° was allowed to warm to 20° to complete the rearrangement and then recooled to −78° (solution B).

Treatment of the solution B with methanol gave 3.15 g of crude product. Chromatography gave 1.63 g (50% yield) of **9**, mp 105–108°. A second fraction (1.13 g) eluted later which contained **9** and a second unidentified compound. Recrystallization of the crude **9** from hexane gave an analytical sample: mp 107–109°; ir (Nujol) 1670 (C=O, 1500, 1210, 1170, 750, 740, 690 cm^{-1}; nmr 2.73 (s, 6, NMe_2), 6.8–7.4 (m, 16, aromatic and benzylic H's).

Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.96; H, 6.71; N, 8.48. Found: C, 80.17; H, 6.48; N, 8.52.

Treatment of solution B with 1.4 g (0.01 mol) of methyl iodide and warming to 20° gave 3.2 g of isolated crude product. Chromatography gave 2.15 g (62% yield) of **7** (R = Me, Y = NMe_2), mp 130–145°. An analytical sample was obtained by column chromatography followed by two recrystallizations from hexane–25% benzene: mp 158–159°; ir (Nujol) 1660 (C=O), 1490, 770, 710, 700 (phenyl), 1180 cm^{-1}; nmr 2.30 (s, 3, CH_3),2.73 (s, 6, NMe_2), 6.5–7.6 (m, 15, aromatics).

Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.37; H, 7.18; N, 8.07.

Treatment of the rearranged anion **5** (Y = NMe_2) at −78° with 1.1 g (0.01 mol) of ethyl chloroformate followed by warming to 20° gave 3.66 g of isolated crude product. Chromatography using benzene gave 1.15 g (35% yield) of **9** followed by 0.9 g (19% yield) of **12.** Purification was effected by rechromatography and recrystallization from hexane–25% benzene: mp 113–115°; nmr 1.23 (t, J = 7 Hz, 6, CH_2CH_3), 2.77 (s, 6, NMe_2), 4.28 (q, J = 7 Hz, 4, CH_2CH_3), 5.9–6.3 (m, 2, vinyl H), 6.7–7.5 (m, 12, vinyl and aromatic H's); ir (Nujol) 1740, 1730 and 1670 (C=O's), 1500, 750, 700 (aromatics), 1250 (ester C—O) cm^{-1}; uv (EtOH) λ_{max} 264 (ϵ 1.74 × 10^4), 337 (1.94 × 10^4) nm.

Anal. Calcd for $C_{28}H_{30}N_2O_5$: C, 70.86; H, 6.37; N, 5.90. Found: C, 71.02; H, 6.51; N, 5.78.

Reactions of the Semibenzene 11. Pyrolysis of 11. The semibenzene **11** (0.75 g) was heated under nitrogen for 0.5 hr at 250°. The dark residue was chromatographed to give 0.5 g of product having nmr and ir spectra identical with thosof **13.**

Hydrolysis of 11. The semibenzene **11** (0.65 g) was dissolved in 50 ml of ethanol, 10 ml of 10% aqueous sodium hydroxide was added, and the mixture was refluxed 0.5 hr. Acidification (aqueous HCl) precipitated 0.4 g of product whose nmr and ir spectra were identical with those of **15.**

Hydrogenation of 11. The semibenzene **11** (0.8 g, 0.0017 mol) was hydrogenated in 20 ml of ethanol with 0.05 g of 5% Pd on charcoal as catalyst. Hydrogen uptake (119 cm^3 at NTP) corresponded to 3 mol/mol of **11.** The crude product, purified by short-path vacuum distillation using a sublimation apparatus, was a clear gum showing no absorption at 310 nm: nmr 1.0–1.4 (m, CH_3) and 1.4–2.6 (m, cyclohexyl H) (combined area 18), 3.9–4.4 (m, 6, CH_2), 5.04 (d, J = 10 Hz, 1, benzylic H), 6.5–7.4 (m, 10, aromatic H); ir (film) 1730 and 1700 (C=O), 1240 (broad, ester C—O, 750, 700 (aromatic) cm^{-1}.

Anal. Calcd for $C_{28}H_{35}NO_6$: C, 70.05; H, 7.38; N, 2.76. Found: C, 69.83; H, 7.33; N, 2.91.

Preparation of *N*-(*p*-Carboxybenzhydryl)aniline, 18. *p*-Benzoylbenzoic acid,[13] **16** (10 g, 0.044 mol), was converted to its corresponding anil **17** by the procedure previously described.[10] This product, mp 139–145°, hydrolyzed rapidly on attempted purification; consequently it was directly reduced. The crude anil, **17** (13 g), was dissolved in 50 ml of 0.2 *N* sodium hydroxide and 0.5 g (0.013 m) of sodium borohydride was added. After 24 hr of stirring, the solution was acidified to precipitate 8 g of crude **18.** Recrystallization from ethanol provided an analytical sample: mp 197–200°; nmr 4.94 (broad s, 2, NH and CO_2H), 5.62 (s, 1, CH), 6.5–7.4 (m, 10, C_6H_5's), 7.56 and 8.15 (AB q, J = 8 Hz, 4, *p*-C_6H_4); ir (KBr) 3360 (NH, OH), 1650 (C=O), 1600, 1530, 750, 700, 680 (aromatic), 1440, 1320, 920 (CO_2H).

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.31; H, 5.86; N, 4.37.

Preparation of *N*-Carbethoxy-*N*-(*p*-carboxybenhydryl)aniline, 15. A mixture of 2 g (0.005 mol) of **18** and ethyl chloroformate (1.1 g, 0.01 mol) in 20 ml of 1:1 benzene–pyridine was refluxed for 6 hr. After removal of the solvent, the product was dissolved in aqueous NaOH, the solution was filtered, and precipitation was done by acidification. Recrystallization from benzene–hexane gave 0.5 g of **15:** mp 149–151°; nmr 1.10 (t, J = 7 Hz, 3, CH_3), 4.21 (q, J = 7 Hz, 2, CH_2), 6.74 (s, 1, CH), 7.0–7.4 (m, 10, C_6H_5's), 7.46 and 8.11 (AB q, J = 8 Hz, 4, *p*-C_6H_4), 10.75 (s, 1, CO_2H); ir (KBr) 3200 (broad, OH), 1690 (C=O) 1600, 1500, 760, 700 (aromatics).

Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.60; H, 5.48; N, 3.50.

Preparation of *N*-(*p*-Carbethoxybenzhydryl)aniline, 19. Esterification of **18** was effected by refluxing in excess ethanol with sulfuric acid as catalyst. The crude product was purified by recrystallization from ethanol: mp 101–103°; nmr 1.35 (t, J = 7 Hz, 3, CH_3), 4.0 (broad s, 1, NH), 4.38 (q, J = 7 Hz, 2, CH_2), 5.56 (s, 1 CH), 6.5–7.4 (m, 10, C_6H_5's), 7.50 and 8.06 (AB q, J = 8 Hz, 4, *p*-C_6H_4); ir (KBr) 3380 (NH), 1700 (C=O), 1600, 1500, 750, 690 (aromatic), 1270 (broad, ester C—O) cm^{-1}.

Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.74; H, 6.48; N, 4.16.

Table I
Acylation of Dianion 20

Reaction	Temp, °C	Ethyl chloroformate[a]	Product compn[b] Amine[c]	Monoacylated 21	22	Diacylated 23	24	25
1	20	1	35	29	1	36		
2	−78	1	30	40	1	29		
3	20	2		1	29	22	20	28
4	−78	2		11	6	42	24	16

[a] Moles per mole of 20. [b] Area per cent by vpc. [c] *N*-(*p*-cyanobenzyl)aniline.

Preparation of *N*-Carbethoxy-*N*-(*p*-carbethoxybenzhydryl)aniline, 13. Acylation of 19 was effected in the same manner as used in the conversion of 18 to 15. The crude 13 was obtained as a gum by short-path distillation at 0.05 mm and 150° using a sublimation apparatus: nmr 1.12 (t, J = 7 Hz) and 1.38 (t, J = 7 Hz, 6, CH_3's), 4.17 and 4.41 (overlapping q, J = 7 Hz, 4, CH_2's), 6.71 (s, 1, CH), 6.9–7.3 (m, C_6H_5's), 7.39 and 8.05 (AB q, p-C_6H_4) (total 14); ir (film) 1720 (broad, C=O), 1270 (broad, ester C—O), 1600, 1500, 760, 690 (aromatics) cm^{-1}.

Anal. Calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.45; H, 6.46; N, 3.21.

General Procedure for the Acylation of Dianion 20. A THF solution of the dianion 20 (M = Na, 0.01 mol) was treated with ethyl chloroformate (0.01 or 0.02 mol) at −78° (or at room temperature). The adduct color changed from deep red to dark green. After stirring for 2 hr at −78°, the reaction mixture was warmed to room temperature overnight. The mixture was diluted with water, and the reaction product isolated by ether extraction.

The ether extracts were analyzed by vpc (flame ionization detectors) using a 5 ft × ⅛ in. column pack with 3% SE-52 on Varaport 30 and 5 ft × ⅛ in. column packed with 3% XE-60 on Varaport 30 at 195° with a helium flow rate of 30–40 cm^3/min, the latter column being necessary to obtain the ratio of the two diacylated products, 23 and 24. Peaks were identified by "spiking" with authentic samples. The results are summarized in Table I.

Reaction with 1 equiv of Ethyl Chloroformate. Isolation of Ethyl α-Anilino(*p*-cyanophenyl)acetate, 21, and Ethyl α-(*N*-carbethoxy anilino)-*p*-cyanophenylacetate, 23. The standard run was quenched with ethyl chloroformate (1.08 g, 0.01 mol) at −78°. The crude product (2.48 g) was chromatographed and three fractions were collected, the first two being eluted with benzene and the third with chloroform.

The first fraction was distilled to give 0.81 g (33%) of 21 as a pale yellow oil containing some *N*-(*p*-cyanobenzyl)aniline. Two additional distillations gave an analytical sample of 21, bp 189–192° (0.08 mm).[14]

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 10.00. Found: C, 72.63; H, 5.68; N, 9.85.

Reaction with 2 equiv of Ethyl Chloroformate at −78°. Isolation of Diethyl *p*-(Cyanophenyl)anilinomalonate, 24. The above reaction was repeated using 2 equiv of ethyl chloroformate (2.17 g, 0.02 mol) and the crude oil (3.53 g) was chromatographed. The first fraction (1.11 g) eluted with benzene was found to contain two components, 21 and 24. This fraction was rechromatographed on 60 g of silica gel with benzene as eluent to give as the first component 0.52 g (15%) of 24. Recrystallization from ethanol gave a white crystalline solid: mp 79–80°; ir (KBr) 3400 (NH), 2980, 1380, 1360 (aliphatic CH), 2220 (CN), 1760 (broad C=O), 1600, 1500 (aromatic C—C), 1020 (–C(=O)O–) cm^{-1}; nmr (D_2O washed) 1.11 (t, 6, J = 7 Hz, CH_3CH_2), 4.22 (q, 4, J = 7 Hz, CH_3CH_2), 6.3–7.4 (m, 5, NC_6H_5), 7.67 and 8.04 (AB q, 4, J_{AB} = 8 Hz, $-C_6H_4CN$).

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.05; H, 5.64; N, 7.70.

The second component which eluted (0.40 g, 11%) was distilled to give a pale yellow oil, bp 189–192° (0.09 mm). The ir and nmr spectra agreed in all respects with those of 21.

Continuing the elution of the original silica gel column with chloroform gave a second fraction, 2.10 g. Recrystallization from ethanol afforded 0.65 g (18%) of 23, mp and mmp 84–85°. Vpc analysis of the filtrate showed the presence of 23 and 25. Isolation of 25 is described below.

Isolation and Hydrogenation of 25. Preparation of Ethyl α-(*N*-Carbethoxyanilino)-*p*-(*N*-carbethoxyaminomethyl)phenylacetate, 32. The preceding reaction was repeated. A portion of the crude product (2.75 g) was chromatographed with diisopropyl ether as eluent. Two major fractions were collected. The first fraction (0.93 g) which contained a mixture of 21 and 24 was discarded. The second fraction (1.57 g) consisting of 23, 21, and 25 was rechromatographed with diisopropyl ether as eluent. A center fraction (1.05 g) was collected. Vpc analysis showed 30% of 23 and 70% of 25; the nmr showed multiplets at 1.0–1.6 (CH_3CH_2), 4.0–4.5 (CH_3CH_2), and 7.1–8.0 (vinyl and aromatic H's) and a singlet at 5.83 (CH of 23). Correcting the spectrum for the known content of 23 indicated three carbethoxy groups per mole of 25. This fraction was hydrogenated in ethanol (60 ml) at atmospheric pressure of H_2 at 22° with 5% of rhodium on carbon (0.5 g) for 24 hr, during which time a total of 135 cm^3 of hydrogen was taken up. The crude product was chromatographed with chloroform as eluent. One major fraction (0.6 g), a viscous pale yellow oil of 32, was collected which had a boiling point higher than 210° at 0.1 mm pressure: ir (film), 3370 (broad NH), 2990, 2950, 1380 (aliphatic CH), 1750, 1700 (broad C=O), 1600, 1500 (aromatic C—C), 1050 and 1030 (–C(=O)O–) cm^{-1}; nmr (D_2O washed) 1.1–1.4 (m, 9, CH_2CH_3), 4.0–4.5 (m, 8, CH_2CH_3 and $C_6H_4CH_2NH$), 5.90 (s, 1, benzylic H), 7.1–7.3 (m, 9, aromatic H).

Anal. Calcd for $C_{23}H_{28}N_2O_6$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.65; H, 6.45; N, 6.24.

Reaction with 2 equiv of Ethyl Chloroformate at Room Temperature. Isolation of Ethyl *N*-(*p*-Cyanobenzyl)-*N*-phenylcarbamate, 22. The above reaction was repeated at room temperature. The crude product (3.50 g) was chromatographed with benzene as eluent. The first fraction 0.6 g (17.1%) was recrystallized from ethanol to give 22, mp and mmp 80–81°. The ir and nmr spectra agreed with those of the authentic sample of 22 in all aspects.

Preparation of Ethyl *N*-(*p*-Cyanobenzyl)-*N*-phenylcarbamate, 22. Ethyl chloroformate (0.35 g, 0.0006 mol) was added in one portion to a stirred solution of *N*-(*p*-cyanobenzyl)aniline (0.67 g, 0.0003 mol) in ether (15 ml). The mixture was gently refluxed for 2 hr, washed with aqueous base, dried, and evaporated. The residue after recrystallization from ethanol gave 0.92 g (86% yield) of 22: mp 81–82.5°; ir (KBr) 2990, 1390, 1370 (aliphatic CH), 2220

Table II
Reactions of Model Anions

Substrate	Anion	Reaction conditions Time,[a] hr	Reagent	Product compn, % Monoacylated 21	22	Diacylated 23	24	25
23	30	0.5	ECl[b]			37		63
		16	ECl			100		
24	29	16	H_2O or ECl			100		
		0.5	ECl	3		32	44	21
21	26 (28)	0.5	ECl	2	18		80	
		16	H_2O	69	(31)[c]			

[a] Time of reaction with DSS. [b] Ethyl chloroformate. [c] *N*-(*p*-Cyanobenzyl)aniline.

(CN), 1700 (C=O), 1600, 1500, (aromatic C—C), 1010, and 1030 (–C(=O)O–) cm^{-1}; nmr 1.22 (t, 3, J = 7 Hz, CH_3CH_2), 4.22 (q, 2, J = 7 Hz, CH_3CH_2), 4.95 (s, 2, CH_2NPh), and 7.0–7.7 (m, 9, aromatic H).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 10.00. Found: C, 72.96; H, 5.85; N, 9.81.

General Procedure for the Reaction of *N*-(*p*-Cyanobenzyl)aniline Derivatives with the Disodium-Stilbene Complex and Ethyl Chloroformate. A THF solution of the disodium-stilbene complex was treated with a solution of an equivalent amount of the selected ester in THF (*ca.* 10 ml) at room temperature. The color changed from deep red of the stilbene complex to pale yellow or colorless immediately. The reaction was stirred and quenched with ethyl chloroformate. After 24 hr of additional stirring, this reaction mixture was diluted with water; the reaction product was isolated and analyzed by vpc using the same conditions as described earlier. The results are summarized in Table II.

Preparation of Ethyl α-(*N*-Carbethoxyanilino)-*p*-(*N*-carbethoxyaminomethyl)phenylacetate, 32. Ethyl α-(*N*-carbethoxyanilino)-*p*-cyanophenylacetate, **23** (0.704 g, 0.002 mol), was hydrogenated in ethanol (65 ml) with 5% rhodium on carbon (0.2 g) as a catalyst at atmospheric pressure of hydrogen for 24 hr, during which time 96 cm^3 of hydrogen was consumed. The crude hydrogenated product was then dissolved in anhydrous ether (20 ml) and ethyl chloroformate (0.216 g, 0.002 mol) was added. After being stirred for 24 hr, the mixture was treated with 3*N* sodium hydroxide (1.0 ml), and the organic product was isolated (0.69 g) and chromatographed with chloroform as eluent. Of the two fractions obtained, the first (0.21 g) contained incompletely hydrogenated material. The second fraction (0.26 g, 30% yield) was a pale yellow oil whose ir and nmr spectra were identical with those of **32** prepared by hydrogenation of the tricarbethoxy compound **25**.

Thermal Decomposition of 25. A small amount of **25** placed in a test tube under nitrogen was heated in a metal block at 260° for 6 hr. The product was analyzed by vpc and found to contain 90% of **23** and 10% of ethyl *N*-(*p*-cyanobenzyl)-*N*-phenylcarbamate, **22**. The latter compound was present in the initial **25** as an impurity.

Acknowledgment. This research was financially supported by the National Research Council of Canada.

Registry No.—**1** (M = Na), 53418-39-6; **1** (M = Li), 53418-40-9; **2**, 33672-87-6; **3**, 7714-87-6; **6** (R = Me), 33672-88-7; **7** (R = CH_3, Y = OEt), 53418-41-0; **7** (R = $PhCH_2$, Y = OEt), 53418-42-1; **7** (R = Me, Y = NMe_2), 53418-43-2; **8**, 53418-44-3; **9**, 53418-45-4; **10**, 42391-89-9; **11**, 42391-85-5; **12**, 53418-46-5; **13**, 42391-88-8; **14**, 42391-86-6; **15**, 42391-87-7; **17**, 53418-47-6; **18**, 53418-48-7; **19**, 42391-91-3; **20** (M = Na), 53418-49-8; **21**, 40577-15-9; **22**, 53418-50-1; **23**, 40577-09-1; **24**, 53418-51-2; **25**, 53418-52-3; **32**, 53418-53-4; ethyl chloroformate, 541-41-3; dimethylcarbamoyl chloride, 79-44-7; *N*-(*p*-cyanobenzyl)aniline, 37812-49-0.

References and Notes

(1) Preliminary reports on some aspects of this study have appeared: (a) J. G. Smith and G. E. F. Simpson, *Tetrahedron Lett.*, 3295 (1971); (b) *ibid.*, 1947 (1973).
(2) J. G. Smith and I. Ho, *J. Org. Chem.*, **38**, 2776 (1973).
(3) It was hoped to obtain evidence of an intramolecular nature for this rearrangement: T. A. Antkowiak, D. C. Sanders, G. B. Trimitsis, J. B. Press, and H. Shechter, *J. Amer. Chem. Soc.*, **94**, 5366 (1972).
(4) R. Heck, P. S. Magee, and S. Winstein, *Tetrahedron Lett.*, 2033 (1964).
(5) This synthesis is considerably more satisfactory than that reported in our preliminary communication.[1b]
(6) This interesting reaction is presently being investigated.
(7) In vpc analyses, the injection and detector temperatures were 210°; at 260°, **25** was not detected.
(8) See for example (a) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N.Y., 1965, pp 54–55; (b) V. R. Sandel and H. H. Freedman, *J. Amer. Chem. Soc.*, **85**, 2328 (1963); (c) R. Waack, L. D. McKeever, and M. A. Doran, *Chem. Commun.*, 117 (1969).
(9) R. M. Acheson, *Accounts Chem. Res.*, **4**, 177 (1971).
(10) J. Smid, "Ions and Ion Pairs in Organic Reactions," Vol. 1, M. Szwarc, Ed., Wiley-Interscience, New York, N.Y., 1972, pp 85–151.
(11) J. J. Eisch, "The Chemistry of Organometallic Compounds," Macmillan, New York, N.Y., 1962, pp 13–33.
(12) J. G. Smith and R. A. Turle, *J. Org. Chem.*, **37**, 126 (1972).
(13) E. Wertheim, *J. Amer. Chem. Soc.*, **55**, 2540 (1933).
(14) Spectral properties have been reported.[2]

Vinylogous Systems. III. Mass Spectra of Vinylogous Imides[1]

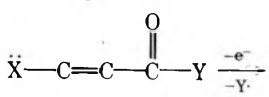
Daryl L. Ostercamp* and Richard G. Werth

Department of Chemistry, Concordia College, Moorhead, Minnesota 56560

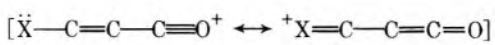
Received July 22, 1974

The mass spectra of sixteen acyclic, isocyclic, and heterocyclic vinylogous imides, –(O)CNC=CC(O)–, have been examined. Stereochemical and structural factors strongly influence the preferred fragmentation pathways, with oxazolium and/or isoxazolium fragment ions playing prominent roles in the decomposition of acyclic and isocyclic compounds.

Several reports have appeared concerning the mass spectral fragmentations of vinylogous amides (**1a**),[2-4] esters (**1b**),[3] urethanes (**1c**),[2] and *N*-acylurethanes (**1d**).[5] Loss of Y from the molecular ion of **1** to form the resonance stabilized α,β-unsaturated acylium ion **2** is the major initial fragmentation in many instances, and then **2** usually constitutes the base peak. Radical ions analogous to **2a** are also important intermediates in the fragmentation patterns of uracils.[6,7]



1a, X = R_2N; Y = R
b, X = RO; Y = R
c, X = R_2N; Y = OR
d, X = RC(O)NH; Y = OR



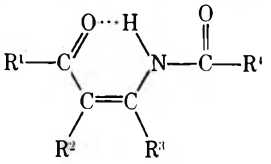
2a, X = R_2N
b, X = RO
c, X = RC(O)NH

The present study of vinylogous imides, β-amido α,β-unsaturated ketones, –(O)CNC=CC(O)–, had two main thrusts. First, we wanted to extend previous results by including compounds of greater stereochemical variety in our work.[8] Second, it seemed likely that the initial fragmentation of the imides would be unique, leading not to ion **2c**,[9] but, if stereochemically permissable, to highly stable oxazolium and/or isoxazolium daughter ions.[10] Earlier work in this laboratory[1,11] made available a number of acyclic, isocyclic, and heterocyclic vinylogous imides. We herewith report the mass spectral results for these compounds.

Experimental Section

Melting points are uncorrected. Mass spectra were obtained on an A.E.I. MS-9 mass spectrometer operating at 70 eV. Samples were introduced *via* a direct insertion probe. The inlet system tem-

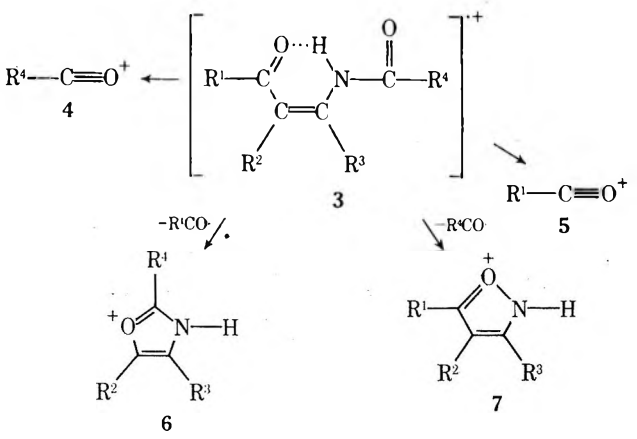
Table I
Relative Intensities of Principal Peaks in the Mass Spectra of Acyclic Cis-s-Cis Compounds



Compd	$[M]^{\cdot+}$	4	5	6	7	8	9	10	11
3a	15.2	55.4[a]	5.5[a]	59.0	2.1[b]	5.3[c]	100.0	13.7	11.6
3b	21.4	20.4	2.1[d]	100.0	3.6	10.5	96.2	12.4[d]	10.5
3c	12.8	9.8	45.8	100.0	7.1	3.8	90.0	24.8	3.3
3d	17.1	39.9	13.2[e]	84.1	100.0	2.6[c]	55.9	9.9[f]	0.9
3e	14.9	100.0[e]	4.7	28.5	0.8				
3f	8.7	100.0[e]	10.9	45.3	2.2				
3g[g]	17.8	100.0[e]	12.0	30.0	7.7				

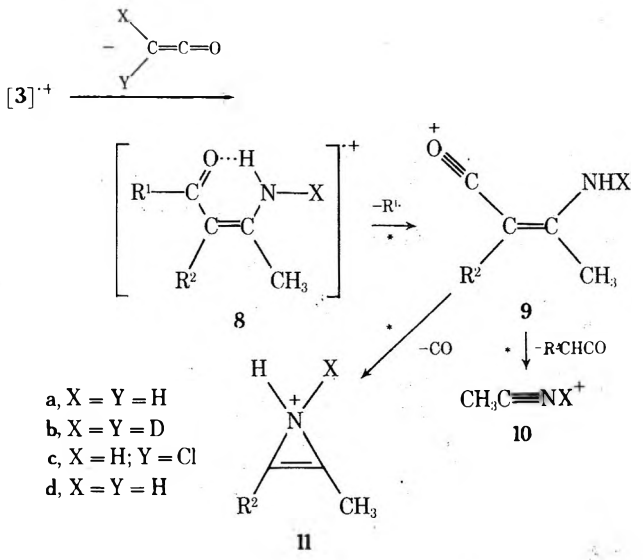
[a] Ions 4a and 5a are identical; relative importance of cleavage site is based upon results for compound 3b. [b] A single peak, m/e 112 (61.1%), is observed for ions 6a and 7a; values shown are based upon results for 3b. [c] Corrected for isotopic contribution from ion 6. [d] Ion 5b is CH_3CO^+ (m/e 43) and ion 10b is $CH_3C{\equiv}NH^+$ (m/e 42) plus $CH_3C{\equiv}ND^+$ (m/e 43). Experimental relative abundances of m/e 42 and 43 peaks are 4.3% and 10.2%, respectively. Assuming the fragmentation modes of ion 9 are of equal importance for compounds 3a and 3b, one can then assign the tabulated values of 12.4% for ion 10b and, indirectly, a value of 2.1% for ion 5b. [e] The characteristic stepwise fragmentation of $C_6H_5CO^+$ to $C_6H_5^+$ and $C_4H_3^+$ is observed along with the expected metastable transitions in every instance. [f] Based upon high-resolution results for 3c. [g] Although 3g does contain a cyclohexene ring, the compound is structurally very similar to 3f.

Scheme I



a, $R^1 = R^2 = R^3 = R^4 = CH_3$
b, $R^1 = R^2 = R^3 = CH_3$; $R^4 = CD_3$
c, $R^1 = R^3 = CH_3$; $R^2 = H$; $R^4 = ClCH_2$
d, $R^1 = C_6H_5$; $R^2 = H$; $R^3 = R^4 = CH_3$
e, $R^1 = R^3 = CH_3$; $R^2 = H$; $R^4 = C_6H_5$
f, $R^1 = R^2 = R^3 = CH_3$; $R^4 = C_6H_5$
g, $R^1 = CH_3$; $R^2 + R^3 = (CH_2)_4$; $R^4 = C_6H_5$

Scheme II



a, X = Y = H
b, X = Y = D
c, X = H; Y = Cl
d, X = Y = H

perature was maintained at 180–200°, except for deuterated compounds where it was 130–150°.[12] High-resolution mass spectra for 4-chloroacetylamino-3-penten-2-one (3c) and 3-acetylamino-5,5-dimethyl-2-cyclohexen-1-one (24b) were obtained on an A.E.I. MS-902 mass spectrometer. All values from exact mass measurement were accurate to within 15 ppm.

The preparation or source of each unlabeled compound utilized in the present work has been described earlier in this series.[1,11] Deuterated samples were prepared from acetic anhydride-d_6 and the appropriate vinylogous amide. Isotopically labeled compounds included 4-acetyl-d_3-amino-3-methyl-3-penten-2-one (3b), mp 47–48°, 2-(1-acetyl-d_3-aminoethylidene)cyclohexanone (12b), mp 33–35°, and 3-acetyl-d_3-amino-5,5-dimethyl-2-cyclohexen-1-one (24c), mp 157.5–158.5°.

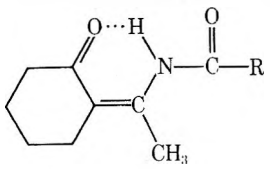
Results and Discussion

Spectral data are included in Tables I–V. The fragmentation pathways proposed below (Schemes I–VIII) are substantiated by (1) appropriate shifts in the spectra of labeled deuterium compounds 3b, 12b, and 24c; (2) appropriate metastable peaks (when present in all or most of the spectra this is indicated by an asterisk); and (3) selective high-resolution mass measurements.

Acyclic Compounds. Intensities of the major ions in the spectra of cis-s-cis[8] vinylogous imides 3a–g are collected in Table I. Inspection of this information supports the conclusion that the fragmentation pattern of the initially formed radical cation 3 (Schemes I and II) is directed by the location and nature of the particular acyl group involved.

Within Scheme I, a strong preference is noted for the formation of those ions, 4 and 6, which retain the *N*-acyl group. Assuming both acylium ions are formed directly from the molecular ion 3, it is not unreasonable that cation 4, a product of allylic cleavage, should be favored over 5, where the neutral fragment is a vinyl radical. High-resolution mass measurement (m/e 43 is greater than 99% C_2H_3O) plus the characteristic chlorine isotope pattern in the spectrum of 3c clearly indicate that acetyl cation 5c ($R^1 = CH_3$) prevails over ion 4c, $ClCH_2CO^+$. Although the latter ion's low abundance is presumably due to the inductive effect of the chlorine atom, a satisfactory rationalization of

Table II
Relative Intensities of Principal Peaks in the Mass Spectra of Isocyclic Cis-s-Cis Compounds



Peak	R = CH_3 (12a)	R = CD_3 (12b)	R = C_6H_5 (12c)
$[M]^{\cdot+}$	41.3	51.2	8.9
13	62.7	65.1	100.0[a]
14	61.9	56.3	20.0
15	64.7	40.5	16.5
16	31.8	26.0	20.0
17	15.8[b]	12.8	6.4
18	17.9[c]	20.9	
19	34.7[c]	36.7	
20	100.0	100.0	
21	19.7[b]	16.0	
22	17.1	14.9	
23	24.7	22.1	

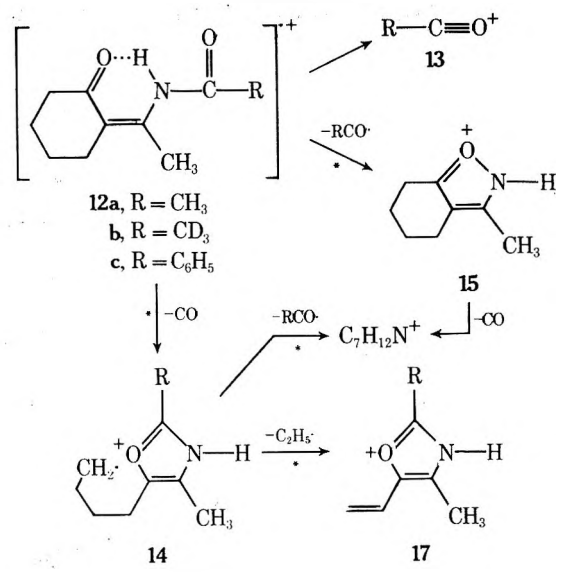
[a] See Table I, footnote *e*. [b] A single peak, *m/e* 124 (35.5%), is observed for ions **17a** and **21a**. Values shown are based upon results for **12b**. [c] Corrected for isotopic contribution from ion of next lower integral mass number.

the high intensity of ion **5c** is not apparent. The importance of the oxazolium[13] ion **6** compared to isoxazolium[13] ion **7** is consistent with the lower acidity of the former cation in aqueous solution.[14] Ring substituent effects are comparable or also favor **6** in all instances save that of **3d** (the only *C*-benzoyl compound), where the base peak is isoxazolium ion **7d** (*m/e* 160). Based upon high-resolution studies exact compositions were assigned to most of the important ions generated from compound **3g**: $[M]^{\cdot+}$, *m/e* 243, $C_{15}H_{17}NO_2$; **6g**, *m/e* 200, $C_{13}H_{14}NO$; **7g**, *m/e* 138, $C_8H_{12}NO$; **4g**, *m/e* 105, C_7H_5O; and *m/e* 77, C_6H_5.[15]

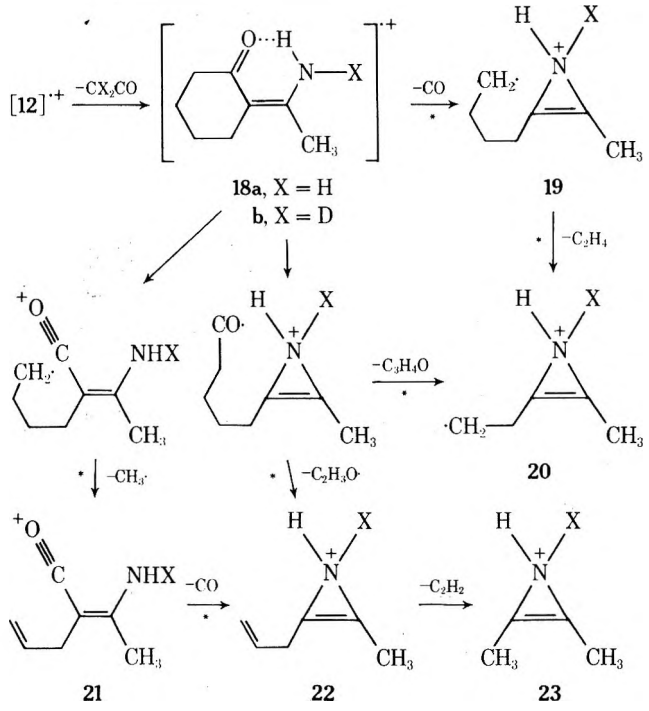
A very significant fragmentation pathway for acyclic *N*-alkanoyl imides **3a–d** is shown in Scheme II. Loss of the appropriate ketene with transfer of a hydrogen (or deuterium) atom to nitrogen (**3** → **8**) is followed by expulsion of methyl or phenyl radical (**8** → **9**), thereby affording resonance stabilized cation **9**.[16] Subsequent decomposition of even-electron ion **9** is unexceptional. The greater relative importance of azirinium cations **11a** and **11b** ($R^2 = CH_3$), compared to **11c** and **11d** ($R^2 = H$), is probably due to the electron-donating power of the additional methyl substituent. Exact mass measurement of all ions higher than *m/e* 39 in the spectrum of compound **3c** confirms the processes outlined in Scheme II, and in Scheme I as well. In particular the moderately intense peak (29.6%) at *m/e* 42 is primarily (84% C_2H_4N, 16% C_2H_2O) the even-electron nitrilium ion **10c** (X = H).

Isocyclic Compounds. Having established the basic behavior of representative acyclic compounds upon electron impact, it was of evident interest to determine what effect increasing stereochemical and/or structural restraint would have on the fragmentation pattern. We turn first to an examination of the principal ions in the mass spectra of 2-(1-acylaminoethylidene)cyclohexanones **12a–c** collected in Table II. Elemental compositions of all ions derived from **12a** and **12c** (see Schemes III and IV) are compatible with high-resolution data[15] and for **12a**, with the spectrum of labeled compound **12b** as well. Initial fragmentation of the

Scheme III

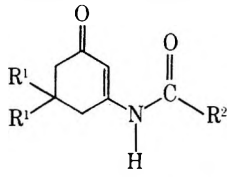


Scheme IV



molecular ion **12** is dominated by bond cleavage at carbonyl carbon, as was the case with acyclic compounds **3a–g**. Direct comparison of the relative intensities of related ions in Schemes I and III, *i.e.*, those from **3a** and **12a** and from **3f** and **12c**, reveals: (1) no dramatic difference between acylium ions **4** and **13**, (2) decreased abundance of oxazolium ion **14**, and (3) a large increase in importance of isoxazolium ion **15**. These results are reasonable, since incorporation of the *C*-acyl group into the six-membered ring of **12** not only means that formation of radical ion **14** requires an additional bond cleavage (compared to ion **6**), but also guarantees a more favorable entropy of activation for appearance of the isoxazolium ion **15** (compared to **7**). Ejection of the remaining carbonyl from **14** or **15** gives rise to a common product, even-electron ion **16**, as shown in Scheme III. Although high-resolution measurements confirm $C_7H_{12}N^+$ and compound **12a** exhibits a metastable peak at *m/e* 87.7 (**15** → **16**), what relatively stable structure corresponds to **16** is an open question for us.

Table III
Relative Intensities of Principal Peaks in the Mass Spectra of Isocyclic Trans-s-Trans Compounds



Peak	R^1, R^2 H, CH_3 (24a)	CH_3, CH_3 (24b)	CH_3, CD_3 (24c)	CH_3, C_6H_5 (24d)
$[M]^{\cdot+}$	34.9	27.0	28.2	7.8
25	25.5	13.8	13.5	4.8
26	0.3	14.1	15.2	2.2
27	46.8	100.0	100.0	10.6
28	79.7	66.9	70.9	100.0[a]
29	25.5	4.8	2.8	
30	100.0	89.9	77.8	
31	17.0	15.2	15.2	
32	1.8	37.2	34.3	8.2
33	4.1	37.2	36.0	

[a] See Table I, footnote *e*.

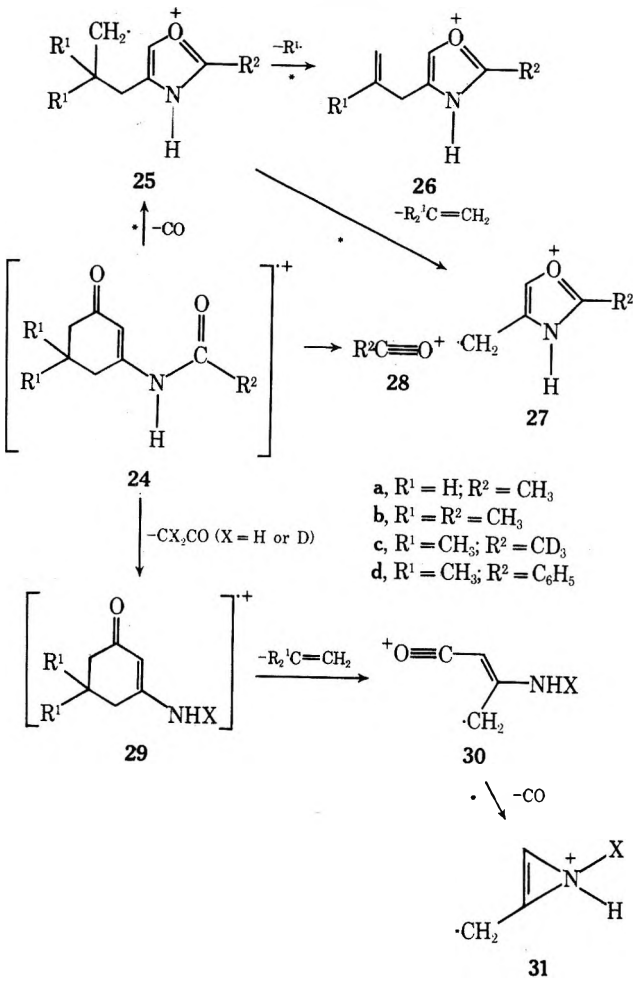
Scheme IV presents a competing fragmentation pattern open to molecular ions **12a** and **12b**, ordinary or labeled (X = D) ketene being eliminated in the first step to generate radical cation **18**. Further decomposition of **18** ultimately leads to azirinium radical ion **20** as the base peak, or to the less important even-electron azirinium ion **23**.

The mass spectra of trans-s-trans vinylogous imides **24a–d** were examined next (Table III), and the basic fragmentation pattern (see Scheme V) is clearly related to those of Schemes I–IV. Loss of an *N*-acyl radical ($R^2CO\cdot$) from molecular ion **24** is negligible,[17] for the resulting cation cannot attain the relatively stable isoxazolium structure (*cf.* ions **7** and **15**) unless ring cleavage[18] and subsequent trans → cis isomerization also occurs. On the other hand, no significant barrier to oxazolium ion formation (**24** → **25**) exists,[19] and indeed radical cation **27** constitutes the base peak in the mass spectra of compounds **24b** and **24c**.

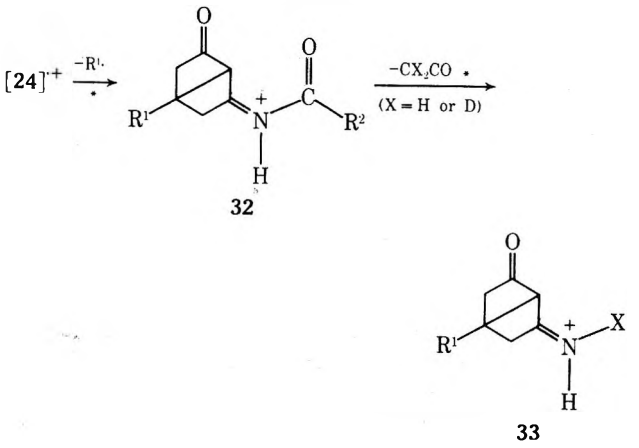
The most abundant ion produced upon electron impact of *N*-acetyl compound **24a** involves successive losses of ketene and ethylene, with appropriate metastable peaks being observed at *m/e* 80.6 (**24a** → **29a**) and *m/e* 62.1 (**29a** → **30a**). Highly conjugated radical cation **30** is also very important in the fragmentation of the two other *N*-acetyl compounds, **24b** and **24c**. Subsequent expulsion of carbon monoxide from **30** should give rise to azirinium[20] ion **31** as shown in Scheme V. In the case of compound **24a** exact mass measurements fully support the structures assigned to fragment ions **25**, **27**, **29**, and **30**.[15] Further substantiation of the pathways indicated in Schemes V and VI is provided by high-resolution data (ions of *m/e* greater than 39) for *gem*-dimethyl compound **24b** plus peak shifts in the spectrum of labeled compound **24c**. Examination of the *m/e* 55 peak (22.3%) in the high-resolution spectrum of **24b** showed it to be mainly (68% C_3H_5N, 32% C_4H_7) the azirinium radical cation **31b**.

Primary fission of a ring methyl group is significant in the mass spectra of compounds **24b–d**, the resulting tertiary carbocations **32b–d** possibly being stabilized *via* resonance involvement of the enamino system as envisioned in the bridged structures of Scheme VI. As expected, ejection of a hydrogen atom from molecular ion **24a** (R^1 = H) to form the secondary cation **32a** is not a favored process.

Scheme V



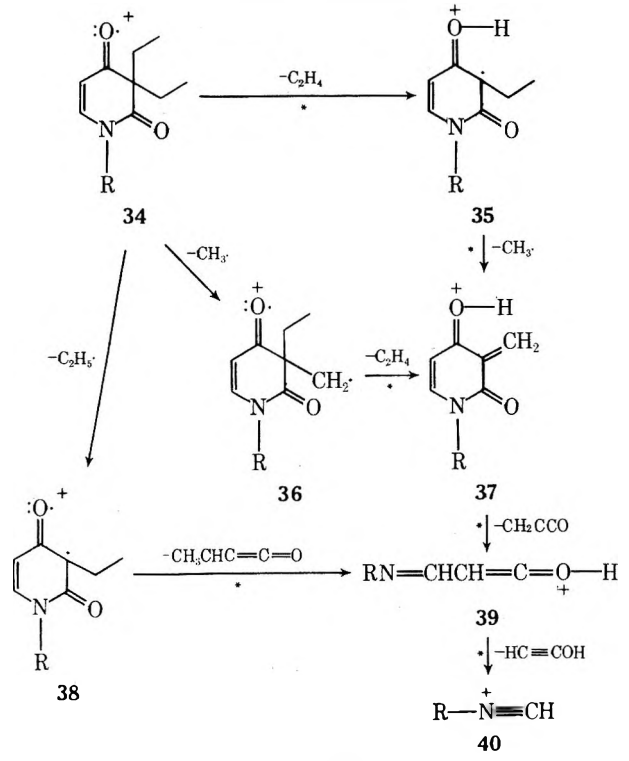
Scheme VI



Preferential loss of a methyl radical over a hydrogen radical is also evidenced in the low abundance of even-electron ion **26a**.

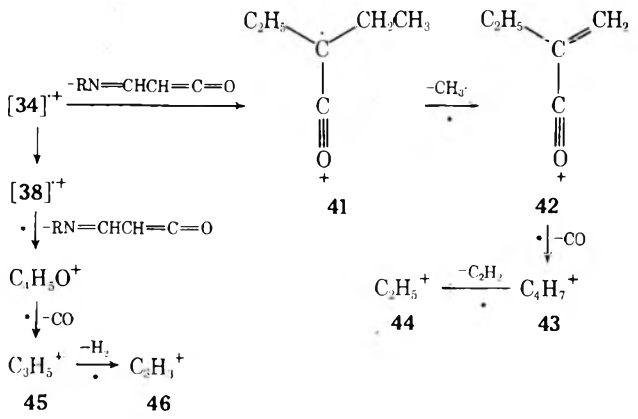
Heterocyclic Compounds. Finally, two groups of heterocyclic imides were studied, the stereochemistry of the conjugated system in each set being completely fixed. Schemes VII and VIII suggest decomposition mechanisms based upon mass spectral results for monocyclic cis-s-trans compounds **34a** and **34b** (Table IV). The abundance of metastable peaks plus elemental compositions for all charged species of *m/e* 69 or greater provide strong support for these fragmentation pathways. No oxazolium or isoxazolium fragment ions are observed, but rather the two most abundant high mass peaks in the spectra of **34** are due to

Scheme VII



a, R = H
b, R = CH_3

Scheme VIII



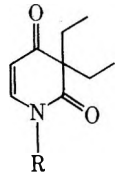
an initial McLafferty rearrangement (**34** → **35**, Scheme VII)[20] and an initial reverse Diels–Alder reaction (**34** → **41**, Scheme VIII), respectively.

Within Scheme VII all fragment ions retain the nitrogen atom, a relatively stable even-electron ion **39** being formed *via* ring cleavage (**37** → **39** or **38** → **39**). The structural relationship between cation **39** and cation **9** (Scheme II) is quite apparent.

Alternatively, the heterocyclic nitrogen atom can be ejected within a neutral vinylogous isocyanate molecule (RN=CHCH=C=O) in a first (**34** → **41**) or second (**38** → $C_4H_5O^+$) decomposition step (see Scheme VIII). Not surprisingly ion **42** dominates Scheme VIII, the ethacrylyl cation[22] being the base peak in the mass spectrum of compound **34a** and also very important in **34b**. Subsequent loss of carbon monoxide from **42** to yield a hydrocarbon fragment ion is as expected.[23]

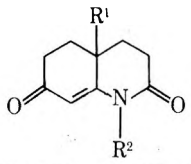
No consistent fragmentation pathway of high probability appears to exist for the three bicyclic compounds **47a–c**. Decomposition of the molecular ion to yield either an even-electron oxazolium or isoxazolium ion, or a highly resonance stabilized radical cation analogous to **35** (see Scheme VII), is incompatible with compound structure. Except for the high mass region of **47a**, the mass spectra of the three fixed trans-s-trans imides are characterized by ubiquitous ion clusters. In all cases the molecular ion peak is very abundant (see Table V) and either it or the [M − 28] radical ion constitutes the base peak. Ejection of an ethylene

Table IV
Relative Intensities of Principal Peaks in the Mass Spectra of Heterocyclic Cis-s-Trans Compounds



	R	
Peak	H· (34a)	CH_3 (34b)
$[M]^{\cdot+}$	8.2	7.4
35	92.9	100.0
36	31.0	3.5
37	9.4	15.0
38	12.7	15.7
39	57.4	71.4
40	13.6	23.3
41	86.8	73.6
42	100.0	85.7
43	45.9	30.8
44	13.0	9.5
45	25.4	17.2
46	15.0	7.9

Table V
Relative Intensities of Principal Peaks in the Mass Spectra of Heterocyclic Trans-s-Trans Compounds



	R^1, R^2		
Peak	H, CH_3 (47a)	C_6H_5, H (47b)	C_6H_5, CH_3 (47c)
$[M]^{\cdot+}$	54.4 ($C_{10}H_{13}NO_2$)[a]	93.2	100.0
M − 28	100.0 ($C_8H_9NO_2$)[a]	100.0	73.6
M − 29	12.6	31.2	17.4
M − 43	26.4 ($C_7H_6NO_2$)[a]	2.8	5.9
M − 56	8.1 (C_7H_9NO)[a]	21.8	15.6
M − 57	6.8 (C_7H_8NO)[a]	25.4	8.9
M − 69	4.6 (C_6H_8NO)[a]	6.1	3.2
M − 71	5.4 (C_6H_6NO)[a]	7.6	17.3
M − 84	18.2 (C_6H_9N)[a]	24.4	15.6
M − 85	7.6 (C_6H_8N)[a]	13.0	7.4
M − 97	16.2 (C_4H_4NO)[a]	7.0	2.8
M − 98	2.8 (C_5H_7N)[a]	17.0	4.9

[a] Fragment ion compositions for compound **47a** were determined by high-resolution measurement. The nominal masses are comprised of greater than 90% of ion of the indicated elemental composition with the exception of [M − 71] (greater than 75%) and [M − 98] (greater than 60%).

molecule from $[M]^{\cdot+}$ is followed by stepwise loss of two carbon monoxide molecules,[24] the resulting [M − 28], [M − 56], and [M − 84] peaks all being relatively unstable odd-electron species. Confirming metastable transitions for the first two steps are found in the spectra of all three compounds. Additional experiments to further elucidate the results of Table V do not seem to be a compelling objective at the present time.

Acknowledgment. The authors express their great appreciation to Professor F. W. McLafferty and Dr. J. W. Serum of Cornell University for furnishing the low-resolution and most of the high-resolution mass spectra. We also thank Mr. G. A. Cockayne, Mr. P. J. Taylor, and Dr. R. B. Webster of Imperial Chemical Industries Limited, Macclesfield, Cheshire, England for exact mass measurements of compounds **3c** and **24b**.

Registry No.—**3a,** 23652-94-0; **3b,** 53432-94-3; **3c,** 23754-49-6; **3d,** 23652-96-2; **3e,** 23112-27-8; **3f,** 23652-95-1; **3g,** 23674-49-9; **12a,** 23652-79-1; **12b,** 53432-95-4; **12c,** 23652-80-4; **24a,** 23674-56-8; **24b,** 23645-83-2; **24c,** 53432-96-5; **24d,** 23674-57-9; **34a,** 77-04-3; **34b,** 1130-18-3; **47a,** 1130-77-4; **47b,** 1216-47-3; **47c,** 1149-82-2.

References and Notes

(1) Part II, D. L. Ostercamp, *J. Org. Chem.*, **35,** 1632 (1970).
(2) J. J. Jakobsen, S.-O. Lawesson, J. T. B. Marshall, G. Schroll, and D. H. Williams, *J. Chem. Soc. B,* 940 (1966).
(3) M. Vandewalle, N. Schamp, and M. Francque, *Org. Mass Spectrom.*, **2,** 877 (1969).
(4) R. T. Aplin and R. Mestres, *Org. Mass Spectrom.*, **3,** 1067 (1970).
(5) A. M. Duffield, C. Djerassi, G. Schroll, and S.-O. Lawesson, *Acta Chem. Scand.*, **20,** 361, (1966).
(6) J. M. Rice, G. O. DudeK, and M. Barber, *J. Amer. Chem. Soc.*, **87,** 4569 (1965).
(7) T. Nishiwaki, *Tetrahedron*, **22,** 3117 (1966).
(8) See ref 1 for details concerning stereochemical classification of compounds used in this project. Intramolecular hydrogen bonding (where possible) would be strongly favored within the mass spectrometer vacuum.
(9) Presence of an electron-withdrawing *N*-acyl substituent would destabilize this fragment ion (as compared to **2a**). Apparently contradictory results have been obtained for three *N*-acyl vinylogous urethanes and one vinylogous imide.[5] However, all four are heterocyclic compounds, and alternative fragmentation would disrupt the ring.
(10) Sucn ions would result from direct loss of an acyl group. Cyclic azirinium ions have been postulated as minor fragment ions in the mass spectra of vinylogous amides.[3,4] The present expectation regarding stability is based on the twin factors of favorable ring size and aromatic character.
(11) D. L. Ostercamp, *J. Org. Chem.*, **30,** 1169 (1965).
(12) Representative starting compounds were shown to be thermally stable at 200°, thus precluding any thermal reaction in the inlet system.
(13) Ions analogous to **6** and/or **7** are essentially absent whenever the appropriate carbonyl group is stereochemically barred from participation (see discussion of cyclic compounds). Alternative structures, *i.e.*, acyclic or azirinium cations, would not enjoy aromatic stability. Oxazolium ion structures have been assigned to base peaks in the mass spectra of 5-methyl- and 4,5-dimethyl-2-hexyloxazole and 2,5-dimethyl-4-hexyloxazole: J. H. Bowie, P. F. Donaghue, H. J. Rodda, R. G. Cooks, and D. H. Williams, *Org. Mass Spectrom.*, **1,** 13 (1968).
(14) D. J. Brown and P. B. Ghosh, *J. Chem. Soc. B,* 270 (1969). We refrain from commenting on the relative resonance stabilization of ions **6** and **7,** as we are unable to find a reference to heats of hydrogenation and/or combustion of oxazole and isoxazole.
(15) The results are limited here to ions whose *m/e* is equal to or greater than 69.
(16) The second step, **8** → **9,** is equivalent to a prominent first step, **1a** → **2a,** in the fragmentation of the molecular ion of a vinylogous amide. As **9a** is here, so is **2a** often the base peak.[2-4]
(17) Relative intensities of $[M - R^2CO]$ cations for the following compounds are, for **24c,** 0.4% and, for **24d,** 0.2%.
(18) This would produce a diradicai, and so detract from product stability.
(19) Ring closure is accompanied by inversion of configuration at a vinyl carbon atom. The process may be viewed as an SNi reaction, carbon monoxide being the leaving group.
(20) Such fragmentation is also shown by analogous vinylogous esters and amides[3] and 5,5-dialkylbarbituric acids.[21]
(21) H.-F. Grutzmacher and W. Arnold, *Tetrahedron Lett.*, 1365 (1966).
(22) J. T. Watson and F. C. Falkner, *Org. Mass Spectrom.*, **7,** 1231 (1973).
(23) A. J. Bowles, E. F. H. Brittain, and W. O. George, *Org. Mass Spectrom.*, **2,** 809 (1969).
(24) See ion compositions for compound **47a** in Table V.

Site Selectivity on Hydrogenation of Bicyclo[4.2.1]nona-2,4,7-trien-9-one. A Possible Effect of Homoaromatic Delocalization

David I. Schuster*[1] and Chong W. Kim

Department of Chemistry, New York University, Washington Square, New York, New York 10003

Received September 5, 1974

The synthesis of bicyclo[4.2.1]nona-2,4-dien-9-one (**2**) by catalytic and diimide reduction of bicyclo[4.2.1]nona-2,4,7-trien-9-one (**1**) was investigated. It was found that direct reduction of **1** gave five reduced ketones, whose structures were determined spectroscopically, but none of **2**. An authentic sample of **2** was prepared in low yield by further reactions of two of the other reduced ketones. However, conversion of the ketone group of **1** to a dimethyl ketal, an ethylene ketal, or an alcohol prior to reduction, followed by treatment with diimide and then either hydrolysis or oxidation, respectively, gave high yields of **2**. The reduction *via* the dimethyl ketal has been developed into a useful preparative procedure for **2**. The reluctance of **1** to give **2** on direct reduction is attributed to homoaromatic interaction of the electrons on the isolated double bond at C_7–C_8 with the carbonyl at C_9 leading to sharply reduced electron density at C_7–C_8 compared to the diene moiety. The electron density in the diene may even be increased by bis(homocyclopentadienyl) interaction with the carbonyl. These effects are removed by conversion of C_9 to a tetrahedral configuration from the trigonal configuration in **1**. Steric effects in this system are analyzed and are concluded to be of less significance than the electronic effects.

We had need of bicyclo[4.2.1]nona-2,4-dien-9-one (**2**) for photochemical studies described elsewhere[2] and sought to prepare **2** by reduction of bicyclo[4.2.1]nona-2,4,7-trien-9-one (**1**). Compound **1** was recently synthesized through different routes by three groups.[3,4] We naively assumed that catalytic or diimide hydrogenation of **1** would preferentially reduce the isolated double bond (C_7–C_8) as opposed to the diene moiety.

Results

The synthesis of **1** utilized was essentially that of Antkowiak and Shechter.[3] The synthesis of **2** from **1** would seem to be simply accomplished by reduction of the C_7–C_8 double bond, since isolated double bonds are reduced preferentially to a conjugated diene grouping. However, **2** was not present in the complex product mixture derived from

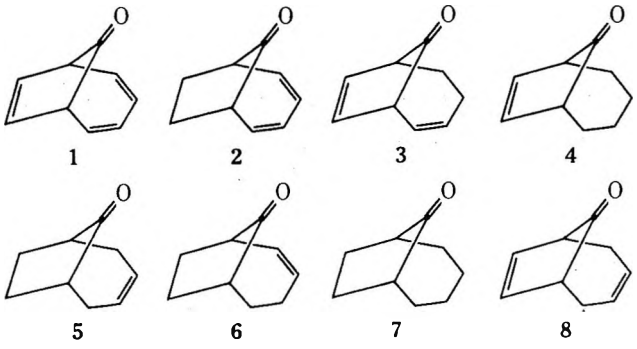
Table I
Product Distributions on Reduction of 1 and Derivatives

Reactant	Reducing agent	Mole ratio[a]	Products, % yield[b] 1	2	3	4	5	6	7
1	H_2[c]	0.5	50	0	40	2	4	4	Tr
1	H_2[c]	1.2	0	0	70	10	7	10	3
1	H_2[c]	1.6	0	0	41	17	16	18	8
1	H_2[c]	2.5	0	0	3	25	26	12	34
1	H_2[c]	2.0	0	0	15	35	20	20	10
1	Diimide[d]	1.5	70	0	20	5	0	5	Tr
1	Diimide[d,e]	2.0	45	0	35	10	0	10	Tr
1	Diimide[d]	2.0	33	0	42	10	0	13	3
1	Diimide[d]	2.0	40	0	40	10	0	5	5
1	Diimide[d]	4.0	Tr	0	Tr	40	0	Tr	60
9	Diimide[d]	1.0	0	67	2	0	0	30	1
10	Diimide[d]	1.0	0	62	15	0	0	19	3
11	Diimide[d]	2.0	0	39	25	1	0	30	5

[a] Ratio of reducing agent to reactant. [b] Products were analyzed by glpc on a 5-ft column of 30% Carbowax 20M on 80–100 Chromosorb W at 190°. Ketones 1 and 2, which are not separated on this column, were separated on a 6-ft column of 10% UCON 50 LB 550 X on Chromosorb P at 160°. Yields given are based on glpc peak areas measured by disk integration assuming equal response factors for all ketones and are percentages of the total measured area. Tr = trace peak in chromatogram. [c] Catalytic hydrogenation carried out in dioxane using a 10% Pd/C catalyst. [d] Diimide was generated from potassium azodicarboxylate *in situ*. Mole ratio based on quantity of PADA used. [e] Carried out in very dilute solution.

catalytic hydrogenation or from diimide reduction of **1**, which included virtually all of the other possible ketonic reduction products **3–8**.

Reduction of trienone **1** with up to 2 mol of hydrogen or potassium azodicarboxylate per mole of **1** using standard procedures led to a complex product mixture, from which ketones **3, 4, 5, 6,** and **7** could be isolated using preparative glpc. Dienone **2** was not present in detectable amount in any of the hydrogenation product mixtures. The distribution of products is given in Table I.

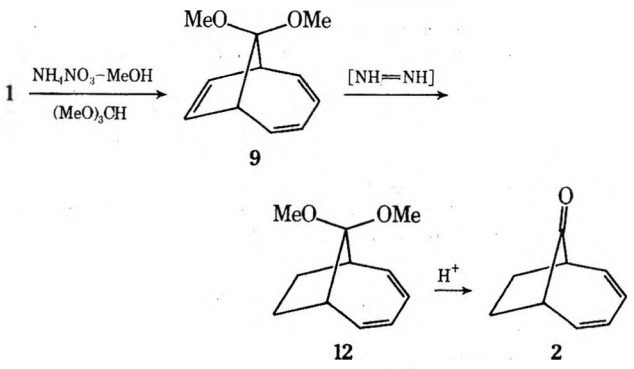


It should also be noted that the total yields of the possible products of further hydrogenation of **2**, namely, ketones **5, 6,** and **7**, always comprised a minor fraction of the total reaction mixture in the runs starting with trienone **1**. A synthesis of **2** was devised as follows. The catalytic hydrogenation of **1** was controlled to maximize the yield (39%) of **5** and **6**. The hydrogenated mixture without prior purification was brominated with a large excess of *N*-bromosuccinimide and then treated with zinc in acetic acid. The other three hydrogenated ketones **3, 4,** and **7** present in the original hydrogenation mixture do not interfere with the subsequent reactions. Either these ketones do not possess allylic positions which can be brominated or the brominated products give the starting material after treatment with zinc and acetic acid. Dienone **2** in 19% yield was isolated from the final mixture by preparative glpc (gas–liquid partition chromatography).

Mass spectroscopy distinguished between dihydro (**2, 3,** and **8**), tetrahydro (**4–6**), and hexahydro (**7**) reduction products of **1**. Dienone **3** was distinguished from **2** on the basis of nmr spectroscopy. In **3**, there are two different bridgehead protons at 2.92 and 3.19 ppm. Dienone **3** had two isolated olefinic protons at 5.76 and 6.16 ppm, whereas **2** had four protons of a butadiene group at 5.44 ppm, which collapsed on irradiation of the bridgehead protons (160 Hz) in a decoupling experiment. The decoupling of **3** was consistent with the structure and is described in the Experimental Section. Dienone **8** should have two different olefinic protons, probably different from those of **2** and **3**. Enone **4** showed two bridgehead protons (2.92 ppm), which are allylic and in the position α to the carbonyl. However, the bridgehead protons in enone **5** were not as deshielded as in **4** and, hence, did not appear as a separate peak. Enone **5** was detected only in the catalytic hydrogenation mixture, which is reasonable since the diimide molecule supplies two hydrogen atoms to the double bond through a six-membered cyclic transition state, and is thus unable to achieve 1,4 reduction. Enone **6** had an unsymmetrical pattern in its nmr spectrum, which could be distinguished from the symmetric spectrum of **4**.

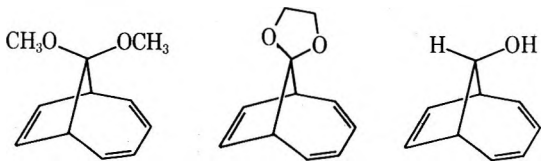
After preliminary rationalization of the lack of formation of **2** from the reduction of **1** (as discussed below), a new approach to **2** *via* ketal **9** was designed as shown in Scheme I.

Scheme I



Since trienone **1** isomerizes to indanone in the presence of Lewis acids (discussed below), a mild catalyst[5] and longer reaction time (5 days) were necessary for ketal formation in this case.

Reduction of **9** by diimide produced in about 70% yield the dimethyl ketal of **2** (see Table I), which was hydrolyzed to **2** without difficulty. The synthesis of **2** *via* **9** occurs in good overall yields and has been worked up into a useful preparative procedure for this elusive material. The synthesis of **2** could also be accomplished *via* the ethylene ketal **10**, which gave 62–67% yields of **2** on diimide reduction and acid hydrolysis. This route was much less useful preparatively because of difficulty in formation of ketal **10**.



9 **10** **11**

Alternatively, the carbonyl group of **1** could be reduced with sodium borohydride to alcohol **11**, reported previously,[6-8] which was then reduced with diimide. The crude reaction mixture was oxidized directly with magnesium dioxide to a mixture of ketones, which was analyzed by glpc by coinjection with the previously isolated ketones **2–7**. The major product produced in this way, as shown in Table I, was indeed **2**. A large decrease in the yields of **3** and **4** was also observed, further indicating that the primary site of reduction had shifted (relative to **1**) to C_7–C_8.

Discussion

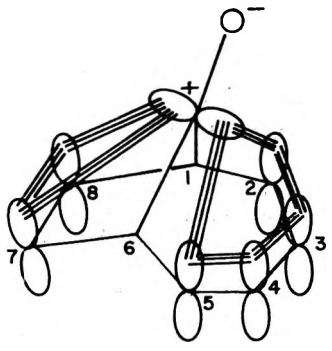
Earlier studies have established that the rates of reduction of olefins by diimide are sensitive to a variety of structural parameters, including torsional strain, bond angle bending strain, and substituent effects.[9] Electronic rather than steric effects of substituents appear to dominate in most systems,[9] although other workers[10] find that diimide reductions are sensitive to steric approach control. For example, only exo–cis addition to 2-norbornene-2,3-dicarboxylic acid is observed, and trans-substituted double bonds are reduced by diimide more rapidly than corresponding cis bonds in acyclic olefins. Special electronic effects can operate in certain systems, as demonstrated by the predominant reduction by diimide of the syn rather than the anti double bond in 7-hydroxy-, 7-acetoxy-, and 7-*tert*-butoxynorbornadiene.[11] The fact that the more sterically hindered (to exo–cis attack) double bond is the preferred site of reaction is rationalized by coordination of diimide with the oxygen atom attached to C_7, followed by delivery of hydrogen to the proximate double bond.

Thus, a variety of factors may be involved in catalytic and diimide reduction of the bicyclo[4.2.1]nonatrienes **1**, **9**, **10**, and **11** described in this paper. Models suggest that the diene moiety in **1** is highly strained, with the angle between the C_2–C_3 and C_4–C_5 double bonds perhaps as high as 135°. This would suggest that diimide reduction at the diene site in **1** ought to be particularly favored over reduction of the isolated double bond at C_7–C_8 because of greater relief of steric strain.[9] While this steric strain is undoubtedly relieved to some extent on conversion of the trigonal center at C_9 in **1** to a tetrahedral configuration at C_9 in **9**, **10**, and **11**, the residual strain would appear from models to be sufficient to expect preferential attack by diimide or hydrogen on the diene in **9**, **10**, and **11** on the basis of strain considerations alone. Furthermore, the orientation of the hydroxyl group in **11** should promote diimide attack on the diene moiety, by extrapolation of the earlier study[11] of substituted norbornadienes. This proximity effect[11] should be largely equalized in the ketals **9** and **10**.

Models also suggest that the five-membered ring in the bicyclo[4.2.1]nonatrienes is quite flat, although attempts at deuterium exchange of the bridgehead protons in **1** and **2** by extended treatment with D_2O and KOH in acetonitrile were unsuccessful. The reaction was monitored by nmr for a period of 2 months.[12] In any event, saturation of the carbonyl group of **1** should result in increased steric hindrance to exo–cis attack at the diene moiety relative to attack at the isolated double bond at C_7–C_8. On this basis, some decrease in the amount of products arising from initial attack on the diene in **9**, **10**, and **11** is anticipated purely on steric grounds. However, the extent of steric shielding of the diene in ketals **9** and **10** ought to be different, because of the freely rotating methyl in **9** which can assume conformations severely shielding the diene, while in **10** the methylene groups are rigidly held back from the reaction site. It is therefore striking that the course of hydrogenation of these two ketals is in fact very similar, suggesting that steric factors are probably not important in these systems.

The hydrogenation data demonstrate that none of **2** is formed on either direct hydrogenation or diimide treatment of trienone **1**, although **2** is the major product of the three-step sequence involving protection of the carbonyl at C_9, hydrogenation, and regeneration of the carbonyl. Thus, the isolated double bond which is totally unreactive relative to the diene **1** is the most reactive hydrogenation site in **9**, **10**, and **11**. This striking change in site reactivities is not readily rationalized on the basis of the various effects cited above. It seems that some special factors(s) are involved which operate so as to selectively reduce the reactivity of the isolated double bond in trienone **1**.

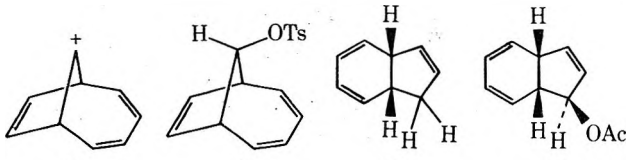
The results seem to us to be best understood on the basis of the operation of homoaromatic (and perhaps also antihomoaromatic) delocalization of π electrons in **1**.[13] Interaction of the C_7–C_8 π bond with the carbonyl p orbital at C_9 should remove electron density from C_7–C_8, by analogy with bis(homocyclopropenyl) interaction in the 7-norbornadienyl cation.[13,14] However, overlap in a similar manner of the p orbital at C_9 with the C_2–C_5 diene moiety on the other side of the molecule should be energetically unfavorable, since it would create an antiaromatic bis(homocyclopentadienyl) cation,[15] as shown in structure **I**. It is even



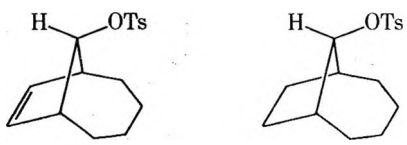
I

possible that electron density at the diene moiety may be increased in **1** if the (empty) p orbital at C_9 acts as a conductor of electron density from the potentially aromatic bis(homocyclopropenyl) cation on one side of the molecule to a potentially antiaromatic bis(homocyclopentadienyl) anion on the other side. On this basis, exclusive hydrogenation of **1** at the diene moiety is understandable. Reduction at C_9 would cancel these electronic effects and restore the "normal" reactivity pattern of a bicyclo[4.2.1]nonatriene, *i.e.*, preferred reduction at C_7–C_8.[16]

These considerations have obvious relevance to the discussion in recent literature of bicycloaromaticity[17] in the bicyclo[4.2.1]nonatrienyl cation **13** and related molecules. The first report relating to **13** showed that solvolysis of tosylate **14** is accompanied by deep-seated rearrangement.[7] Thus, reaction of **14** in tetrahydrofuran in the presence of lithium aluminum hydride gives *cis*-8,9-dihydroindene (**15**). This is consistent with results of later studies,[18,19] *e.g.*, the formation of acetate **16** on acetolysis of **14**. The rate of acetolysis of **14** is enhanced by a factor of 10^4 over that of the more saturated analogs **17** and **18**, despite the rate-retarding inductive effect of the butadiene moiety in **14**. This

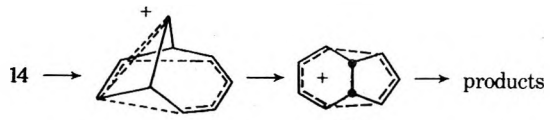


13 **14** **15** **16**



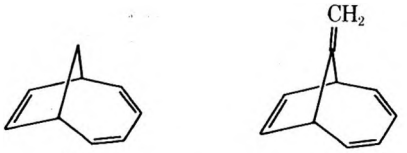
17 **18**

suggests that there is a stabilizing interaction of the bis(homocyclopropenyl) type between the C_7–C_8 π electrons and the developing p orbital at C_9 in **13**. There seems to be agreement that the observation of rearrangement coupled with rate acceleration on solvolysis of **14** seems best understood in terms of initial formation of a bicycloaromatic ion **19** in which stabilization by homoaromatic [*i.e.*, bis(homocyclopropenyl)] interaction[20] provides only a small portion (estimated as 20%)[19b] of the total stabilization. The interaction of the butadiene and homocyclopropenyl moieties is not sufficient, however, to prevent rearrangement of **19** to the bis(homotropylium) ion **20** which is the source of the observed products.[18,19]



19 **20**

Photoelectron spectroscopy provides some additional information about π-electron interaction in these systems. Data for the triene **21** indicate no appreciable interaction of this type,[21] although extensive π interaction is indicated for tetraene **22**.[22] Nonetheless, the authors in the latter



21 **22**

study[22] do not feel that the evidence at present *demands* the operation of bicycloaromatic delocalization in **22**. Similarly, we do not claim that our results *prove* that π delocalization of either the homoaromatic[20] or bicycloaromatic[17] variety is occurring to a significant extent in **1** and/or the hydrogenation transition states and that the data can be rationalized *only* on the basis of such effects. However, we do believe that such interactions and their mechanistic implications provide a consistent as well as compelling explanation of the experimental observations.[24]

Experimental Section

All melting points are uncorrected. Proton magnetic resonance spectra were obtained with a Varian Model A-60 spectrometer. Abbreviations used in reporting data are s = singlet, d = doublet, q = quartet, m = multiplet, br = broad, and sh = sharp. Mass spectra were obtained with a Varian M-66 double focusing cycloidal path mass spectrometer. Infrared spectra were taken on a Perkin-Elmer Model 137 Infracord spectrophotometer and ultraviolet spectra on a Cary Model 15 spectrophotometer.

Gas–Liquid Partition Chromatography. Analytical studies were carried out on a Hewlett-Packard Model 5750 research chromatograph using flame ionization detection. Preparative separations were made on an Aerograph preparative gas chromatograph, Model A-90-P. The column used for most of the ketone analyses was a 6 ft × ⅛ in. stainless steel column containing 20% Carbowax 20M on 80–100 mesh Chromosorb W, operating at a column temperature of 160° and the injection port set at 280°. The flow rates were helium 40–60 ml/min, hydrogen 40–60 ml/min, and air 300–400 ml/min. Under these conditions the retention times (min) of the ketones were as follows: **1** and **2** (not separated), 13.2; **3**, 8.6; **4**, 6.2; **5**, 10.4; **6**, 11.2; and **7**, 8.4. Where other columns and conditions are used, they are specifically indicated.

Bicyclo[4.2.1]nona-2,4,7-trien-9-one. The synthesis of **1** was essentially the same as that of Antowiak and Shechter[2] except that hydroquinone was added to the reaction mixture to lessen tar formation. After the reported work-up procedure, the crude reaction product was distilled quickly at 0.5 mm and was then redistilled through a short Vigreux column to give **1**, bp 80–90° (0.9 mm), as a colorless liquid: ν_{max}^{neat} 3025, 2945, 1760, 1580, 1260, 1150, 920, and 865 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 267 nm (ϵ 3000), 276 (2800), and 320 (630); $\delta_{TMS}^{CDCl_3}$ 5.46 (m, 6 H, olefinic) and 2.73 (br s, 2 H, bridgehead); *m/e* 132, 131, 116, 104, 103, 91, 78, and 72.

A by-product from the above reaction is the assumed dimer of bicyclo[4.2.1]nona-2,4,7-trien-9-one (**1**): ν_{max}^{KBr} 3000, 2950, 1675 (split), 1205, 880, 865, 695, and 660 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.2 (br s, 4 H), 3.2 (br s, 1 H), 3.6 (d, 1 H), 4.0 (br s, 1 H), and 5.9 (m, 8 H).

Bicyclo[4.2.1]nona-2,4-dien-9-one (2). Bromination–Debromination Route. Trienone **1** (2.11 g, 0.016 mol) in 40 ml of dioxane was catalytically hydrogenated over 10% Pd/C. A total reaction time of 13 hr was required to consume 920 ml of hydrogen at room temperature. The relative yields of the five reduced products at this point (glpc) were as follows: **1** (none), **2** (none), **3** (3.0%), **4** (24.7%), **5** (26.4%), **6** (12.4%), and **7** (33.7%).

To the above crude mixture in 30 ml of carbon tetrachloride were added 5.70 g (0.032 mol) of *N*-bromosuccinimide and 0.03 g of benzoyl peroxide. The mixture was heated at reflux for 50 min under a nitrogen atmosphere. The solid was removed by filtration, and the solvent was removed. The crude product was dissolved in 100 ml of ethyl ether and to it were added 1.64 g (0.025 g-atom) of zinc dust and 1.1 g (0.018 mol) of acetic acid. The mixture was stirred for 1.5 hr at room temperature and then heated at reflux for 30 min. After the mixture was cooled, 4.0 ml of pyridine was added. The salt formed was filtered off, and the ether layer was washed, dried, and concentrated. Dienone **2** was collected (18.8% overall yield) by preparative glpc using an 8-ft 10% Carbowax 20M column: ν_{max}^{neat} 3025, 2950, 2865, 1750, 1450, 1180, 865, 745, 700, and 650 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 264 nm (ϵ 3300) and 313 (500); $\delta_{TMS}^{CDCl_3}$ 5.44 (m, 4 H, butadienyl), 2.42 (br s, 2 H, bridgehead), and 2.00 (m, 4 H, ethanyl); *m/e* 134, 119, 106, 91, 85, 83, and 78.

Bicyclo[4.2.1]nona-2,4-dien-9-one (2). Dimethyl Ketal Route. In a typical run, ammonium nitrate (0.6 g) dissolved in 20 ml of methyl alcohol was added to a mixture of 2.11 g (0.016 mol) of trienone (**1**) and 2.12 g (0.020 mol) of trimethyl orthoformate.[5] The reaction mixture was stirred at room temperature for 5 days. Sodium carbonate (1.0 g) followed by 200 ml of ethyl ether was added. The ether layer was filtered and concentrated and the crude mixture was separated by column chromatography on silica gel, eluting with ether–hexane mixtures. Pure 9,9-dimethoxybicyclo[4.2.1]nona-2,4,7-triene (**9**, 400 mg) was obtained from the fourth, fifth, and sixth fractions (700 ml each), eluted with 20% ether–80% hexane: ν_{max}^{neat} 3025, 2930, 2825, 1450, 1295, 1205, 1130, 1055, and 710 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.86 (m, 4 H), 5.19 (d, J = 1.5 Hz, 2 H), 3.10 (sh s), 3.05 (sh s), and 3.10 (br) (total 8 H); *m/e* 178, 177, 147, 131, 121, 105, and 91.

Into a slurry of 194 mg (1.0 mmol) of potassium azodicarboxylate in 10 ml of dioxane under a nitrogen atmosphere was introduced 178 mg (1.0 mmol) of dimethyl ketal **9**. To this was added half of a solution of 120 mg (2.0 mmol) of glacial acetic acid in 3 ml of dioxane at the start of the reaction and the other half after 20

hr. After a total reaction time of 44 hr, the yellow color of the mixture was totally bleached. The solid was separated by filtration, and 100 ml of ethyl ether was added to the filtrate. The ether layer was washed with 5% carbonate solution and then with saturated sodium chloride solutions. The ethereal solution was dried over anhydrous magnesium sulfate and then concentrated. Analysis of the crude product by glpc and nmr indicated 67% conversion to ketal **12**. The mixture was chromatographed on a column of aluminum oxide of pH 7.8 (J. T. Baker) which was eluted with ether–hexane mixtures. In addition to ketal **12**, some dienone **2** was eluted directly from the column. However, the overall material balance was very poor. Attempts at separation of **12** from the crude mixture by fractional distillation and liquid–liquid partition chromatography were also unsuccessful. The ketal **12** was eventually separated in a pure state most efficiently by preparative glpc using a 15-ft column of 30% Carbowax 20M on Chromosorb W at 215° with the injection port set at 310°. The ketal **12** was identified primarily by its nmr spectrum: $\delta_{TMS}^{CDCl_3}$ 6.87 (m, 4 H), 3.34 (s, 6 H), 2.70 (br s, 2 H), and 2.08 ppm (m, 4 H).

In a typical run, 17.0 g of a sample which was about 70% of the ketal **12** was hydrolyzed by stirring with 3 *N* HCl for 15 min at room temperature. After the conventional work-up, a total of 2.09 g of bicyclo[4.2.1]nona-2,4-dien-9-one **2** was collected by preparative glpc on the 15-ft 30% Carbowax 20M column.

The material obtained was identical with that obtained earlier according to glpc analysis on two different columns: 6 ft × ⅛ in. column of 15% Carbowax 20M on 80–100 mesh Chromosorb W at 175° with the injection port at 265° (retention time 5.8 min); 15 ft × 0.25 in. column of 15% Carbowax 20M on 80–100 mesh Chromosorb W at 190° with injection port at 275° (retention time 20.2 min).

Bicyclo[4.2.1]nona-2,4-dien-9-one. Ethylene Ketal Route. Trienone **1** (1.4 g, 0.01 mol), 25 ml of ethylene glycol, a small amount of ammonium nitrate, and a trace of hydroquinone were mixed and stirred for 15 days at room temperature. Analysis by glpc indicated approximately 70% conversion to ketal **13**. The reaction was stopped after 17 days, 100 ml of water was added, and the mixture was extracted with 500 ml of pentane. The pentane layer was washed once with carbonate solution and three times with saturated salt solutions. The aqueous layer was extracted once with 300 ml of ether, and then the ether layer was washed as above with carbonate and saturated salt solutions. The pentane and ether layers were combined, dried over anhydrous sodium sulfate, and concentrated. The ketal **10** was obtained by preparative glpc on a 6 ft × ⅛ in. column of 25% Carbowax 20M on 80–100 mesh Chromosorb W. Spectral data for ethylene ketal **10** are as follows: ν_{max}^{neat} 3020, 2950, 2900, 1600, 1480, 1350, and 1275 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.83 (m, 4 H), 5.28 (d, 2 H), 3.81 (s, 4 H), and 2.82 ppm (m, 2 H); *m/e* 176, 175, 104, 86, and 84 (base peak).

The ketal **10** (80 mg, 0.46 mmol), 88 mg (0.46 mmol) of potassium azodicarboxylate, and 60 mg (1.0 mmol) of glacial acetic acid in 10 ml of dioxane were allowed to react as described for ketal **9**. The reduction was stopped after 9 hr of stirring at room temperature. After work-up, as above, the crude product was hydrolyzed with 3 *N* HCl for 15 min at room temperature. The ketonic mixture was analyzed by glpc as previously described and showed 62.0% **2**, 14.5% **3**, 19.4% **6**, and 2.6% **7**.

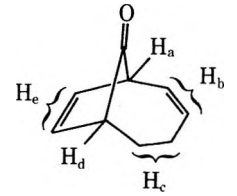
Bicyclo[4.2.1]nona-2,4-dien-9-one. Route *via* 9-Hydroxybicyclo[4.2.1]nona-2,4,7-triene. A solution of 1.06 g (0.008 mol) of trienone **1** and a trace of hydroquinone in 10 ml of methyl alcohol was slowly added to a stirred solution of 0.296 g (0.008 mol) of sodium borohydride and a drop of 50% aqueous KOH in 5 ml of water. The mixture was stirred for 20 hr, keeping the temperature below 25°. Hydrochloric acid (20 ml of a 2% solution) was added to destroy excess hydride, and the organic material was extracted with 300 ml of ether. The ether layer was washed with saturated salt solution, dried, and concentrated. A white solid was obtained with mp 47–51° (lit.[6] mp 52.0–52.5°; lit.[7] mp 51.0–52.5°) which showed only one peak by glpc analysis. The spectral data, in substantial agreement with previous reports,[6,7] are consistent with the assignment of structure **11**, 9-hydroxybicyclo[4.2.1]nona-2,4,7-triene, to this material: ν_{max}^{neat} 3560, 3020, 2950, 1405, 1220, 1105, 1060, 980, 910, and 690 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.85 (m, 4 H), 5.08 (d, J = 1.5 Hz, 2 H), 4.20 (br s, 1 H), 2.89 (m, 2 H), and 2.03 ppm (br s, 1 H); *m/e* 134, 133, 115, 105, 92, 91, and 78. The nmr spectrum agrees well with that reported by Shechter, *et al.*,[7] under somewhat better resolution: δ 5.89 (m, 4 H, diene), 5.03 (m, 2 H, olefinic), 4.26 (triplet of doublets, 1 H, C_9), 2.92 (br tr, J = 6 Hz, 2 H, bridgehead), and 1.64 (d, J = 12 Hz, OH).

Into a magnetically stirred slurry of 1.83 g (9.4 mmol) of potassium azodicarboxylate in 20 ml of dioxane under a nitrogen atmosphere was dissolved 630 mg (4.7 mmol) of alcohol **11**, above. A solution of 0.6 g (9.4 mmol) of glacial acetic acid in 2.5 ml of dioxane was added dropwise. After 12 hr of stirring at room temperature, a second portion of 0.6 g of acetic acid in 2.5 ml of dioxane was added. The yellow color of the mixture was completely bleached after a total reaction time of 24 hr. After 100 ml of ether was added, the mixture was filtered and the solvent was then removed on a Rotovap. The crude product (120 mg) was chromatographed on an aluminum oxide column. A liquid product, 94 mg, was isolated from a 300-ml fraction eluted with 15% ethyl acetate–85% ethyl ether. This material was dissolved in 20 ml of distilled hexane and activated manganese dioxide (1.0 g) was added. The reaction mixture was stirred for 2 days at room temperature. The solid was removed on a Rotovap. The crude mixture was analyzed by glpc on a 6-ft column of 10% UCON 50 LB 550 X on Chromosorb P by coinjection with authentic samples of ketones **2**–**7**. The relative amounts of products were 38.7% **2**, 24.9% **3**, 0.8% **4**, 30.2% **6**, and 5.4% **7**.

Diimide Reduction of Trienone 1. Into a magnetically stirred slurry of potassium azodicarboxylate (76.5 g, 0.394 mol) in 2.5 l. of distilled dioxane under a nitrogen atmosphere was added trienone **1** (26.0 g, 0.197 mol). A solution of distilled acetic acid (23.8 g) in 50 ml of dioxane was added dropwise into the reactor at room temperature over a period of 1 hr. After 10 hr of stirring, a second portion of acetic acid (23.8 g, total 0.788 mol) in 50 ml of dioxane was added. The reaction mixture was stirred for a total of 36 hr until the yellow color had almost disappeared. The remaining solid was removed by filtration, and the dioxane was removed. The residue was dissolved in 500 ml of ethyl ether. The ether solution was washed, dried, and concentrated. The crude product was distilled through a short Vigreux column. A portion boiling between 46 and 49° (0.1–0.06 mm) was collected, weighing 10.5 g. The glpc analysis of the distillate showed four components in addition to the starting material. The first three compounds were separated by preparative glpc on a 3-ft 20% Carbowax 20M column. The fourth peak overlapped with other components and was separated by a 15-ft 30% Carbowax 20M column. These four compounds were spectroscopically identified as **3**, **4**, **6**, and **7**.

Bicyclo[4.2.1]nona-2,7-dien-9-one (3): ν_{max}^{neat} 3030, 2950, 1765, 1430, 1155, and 745 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 255 nm (ε 330) and 295 (160); $\delta_{TMS}^{CDCl_3}$ 6.16 (doublet of quartets, J = 4, 7 Hz, 2 H), 5.76 (m, 2 H), 3.19 (m, 1 H), 2.92 (m, 1 H), and 2.12 (m, 4 H); *m/e* 134, 106, 91, 78 (base peak), and 28.

An nmr decoupling experiment on dienone **3** was carried out. On irradiation at H_a (196 Hz), the resonances of H_b and H_e were broadened, whereas only H_e peaks were broadened on irradiation at H_d (172 Hz). On irradiation at H_c (146 Hz), the H_b peaks were again broadened.



Bicyclo[4.2.1]nonan-7-en-9-one (4): ν_{max}^{neat} 2925, 2850, 1750, 1440, 1175, 850, 790, and 730 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 270 and shoulder extending to 310 nm; $\delta_{TMS}^{CDCl_3}$ 6.06 (d, 2 H), 2.92 (br s, 2 H), and 1.52 (br s, 8 H).

Bicyclo[4.2.1]nonan-2-en-9-one (6): ν_{max}^{neat} 3025, 2950, 1745, 1640, 1450, 1150, 715, and 660 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 295 and shoulder extending to 310 nm; $\delta_{TMS}^{CDCl_3}$ 5.77 (m, 2 H), 1.5–2.8 (10 H).

Bicyclo[4.2.1]nonan-9-one (7): ν_{max}^{neat} 3000, 2930, 2850, 1725, 1450, 1220, 1190, 1105, and 740 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.1–2.5 (14 H).

Catalytic Hydrogenation of 1. Trienone **1** (0.264 g, 2 × 10^{-3} mol) was hydrogenated in 10 ml of dioxane using 10% Pd/C as catalyst. During 3 hr of reaction at room temperature, 65 ml of hydrogen gas (118% based on one double bond) was absorbed. After removal of the catalyst and the solvent, a glpc analysis of the crude reaction mixture indicated none of the starting material and five reduced products: **3** (70%), **4** (3%), **5** (7%), **6** (10%), and **7** (3%). The new component (**5**) was isolated by preparative glpc and identified as bicyclo[4.2.1]nonan-3-en-9-one (**5**): ν_{max}^{neat} 3010, 2950, 2880, 1740, 1425, 1175, and 650 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.86 (br s, 2 H) and 2.9–1.2 (10 H).

Modified Synthesis of Potassium Azodicarboxylate. The

procedure described below is a modification of the reaction originally reported by Thiele.[23] Azodicarbonamide, 20 g (Aldrich Chemical Co.), was dumped into a 2-l. beaker at 0° containing 50 ml of 50% potassium hydroxide solution. The mixture was vigorously agitated while the ammonia evolved caused foam. The yellow paste was then agitated for 10 min, filtered quickly, and dissolved in 100 g of ice–water maintained at 1–2°. If the water temperature rises to about 5°, the compound decomposes rapidly. The aqueous solution was filtered very quickly into 500 ml of 95% ethyl alcohol at −20°. The yellow crystals precipitated in the alcohol were again filtered quickly. The recrystallization process was repeated once more with 100 g of ice–water and 500 ml of 95% ethyl alcohol. The potassium azodicarboxylate was washed with methanol by swirling for a few minutes. The material was dried overnight at high vacuum at room temperature and kept under vacuum in the refrigerator.

Acknowledgments. The authors are grateful to the National Science Foundation for support of this work under Grant GP-10828. They also thank Professor Harold Shechter of The Ohio State University for details of the synthesis of trienone 1 prior to publication. This work would not have been possible without this information. We also wish to thank Professor Shechter for providing helpful comments after reading the original draft of this manuscript. Finally, Professor Don Clarke of Fordham University is thanked for his cooperation in spin-decoupling experiments.

Registry No.—**1**, 34733-74-9; **1** dimer, 53535-25-4; **2**, 52902-51-9; **3**, 42948-89-0; **4**, 42948-91-4; **5**, 40863-57-8; **6**, 52089-56-2; **7**, 14252-11-0; **9**, 53555-53-6; **10**, 53555-54-7; **11**, 34712-67-9; **12**, 53555-55-8; trimethyl orthoformate, 149-73-5; potassium azodicarboxylate, 4910-62-7; azodicarbonamide, 123-77-3; potassium hydroxide, 1310-58-3.

References and Notes

(1) Work done at Nichols Laboratory, New York University, University Heights, Bronx, N.Y. 10453.
(2) D. I. Schuster and C. W. Kim, *J. Amer. Chem. Soc.*, **96**, 7437 (1974).
(3) T. A. Antkowiak and H. Shechter, *J. Amer. Chem. Soc.*, **94**, 5361 (1972).
(4) (a) E. Vedejs, R. A. Gabel, and P. D. Weeks, *J. Amer. Chem. Soc.*, **94**, 5842 (1972); (b) L. A. Paquette, R. H. Meisinger, and R. E. Wingard, Jr., *ibid.*, **95**, 2230 (1973).
(5) J. A. Van Allan, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 21.
(6) Compound **11** was cited in a communication by M. Sakai, A. Diaz, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 4452 (1970), but no properties of the material were reported. Subsequently, data for **11** were obtained in 1972 privately from Dr. M. Sakai, University of Alberta, which agree in general with those obtained in this work and also by Shechter, *et al.*,[7] and Diaz and Fulcher.[19b]
(7) T. A. Antkowiak, D. C. Saunders, G. B. Timitsis, J. B. Press, and H. Shechter, *J. Amer. Chem. Soc.*, **94**, 5366 (1972).
(8) The nmr spectrum of the crude reduction product indicated that only one epimer of **11** was formed, as also found in the parallel studies cited above.[6,7] The epimer with the hydroxyl syn to the diene moiety would be the expected product, on the basis of attack by hydride on the less hindered face of the carbonyl group.
(9) E. W. Garbisch, Jr., S. M. Schildcrout, D. B. Patterson, and C. M. Sprecher, *J. Amer. Chem. Soc.*, **87**, 2932 (1965), and references cited therein.
(10) E. E. van Tamelen and R. J. Timmons, *J. Amer. Chem. Soc.*, **84**, 1067 (1962).
(11) W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *J. Amer. Chem. Soc.*, **89**, 410 (1967).
(12) For the isolation and characterization of the strained bridgehead alkenes, bicyclo[4.2.1]non-1(8)-ene and bicyclo[4.2.1]non-1(2)-ene, see J. R. Wiseman, H. Chan, and C. J. Ahola, *J. Amer. Chem. Soc.*, **91**, 2812 (1969).
(13) For a review of homoaromaticity, see S. Winstein, *Quart. Rev., Chem. Soc.*, **23**, 141 (1969).
(14) P. R. Story and M. Saunders, *J. Amer. Chem. Soc.*, **84**, 4876 (1962).
(15) R. Breslow and J. M. Hoffman, Jr., *J. Amer. Chem. Soc.*, **94**, 2110 (1972), and references cited therein.
(16) Selective hydrogenation of a dimethyl derivative of **1** at the diene moiety has been reported,[4b] although no rationalization of this selectivity was given.
(17) J. B. Grutzner and S. Winstein, *J. Amer. Chem. soc.*, **94**, 2200 (1972); M. J. Goldstein and R. Hoffmann, *ibid.*, **93**, 6193 (1971).
(18) D. C. Sanders and H. Shechter, *J. Amer. Chem. Soc.*, **95**, 6858 (1973).
(19) (a) A. F. Diaz, J. Fulcher, M. Sakai, and S. Winstein, *J. Amer. Chem. Soc.*, **96**, 1264 (1974). (b) A. Diaz and J. Fulcher, *ibid.*, **96**, 7954 (1974).
(20) See S. Winstein, *Quart Rev., Chem. Soc.*, **22**, 141 (1969), and references cited therein.
(21) P. Bischof, R. Gleiter, and E. Heilbronner, *Helv. Chim. Acta*, **53**, 1425 (1970).
(22) M. T. Reetz, R. W. Hoffmann, W. Schaefer, and A. Schweig, *Angew. Chem.*, **85**, 45 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 81 (1973).
(23) J. Thiele, *Justus Liebigs Ann. Chem.*, **270**, 42 (1892).
(24) Note Added in Proof. Photoelectron spectroscopic data for trienone **1** have now been reported.[25] These are interpreted as showing the *absence* of homoconjugation and bicycloconjugation among the π systems of **1**, although interaction of the nonbonding orbital on oxygen and the HOMO of the butadiene moiety is indicated. These results argue against the interpretation presented above. However, it must be kept in mind that the PE data reflect interaction in the ground state of **1** while our discussion pertains to possible transition states for reaction of **1**.
(25) W. Schäfer, H. Schmidt, A. Schweig, R. W. Hoffmann, and H. Kurz, *Tetrahedron Lett.*, 1953 (1974).

Notes

Stereochemical Assignment by Mass Spectrometry. Metastable Ion Characteristics for Dehydrohalogenation

Kym C. Kim and R. Graham Cooks*

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received August 7, 1974

Mass spectrometry has not found wide application to problems in stereochemistry although some elegant demonstrations of its potential exist.[1] The usual but not the only approach[1c] is to measure fragment ion abundances for an elimination reaction; the spacial relationship between the groups involved in the elimination determines the activation energy for the reaction and hence the product ion abundance. We now show that the translational energy release associated with the fragmentation of metastable ions can serve to characterize the mechanism of a particular elementary reaction and so to distinguish stereoisomers. Thus, instead of relying only on a comparison of the relative extents to which different stereoisomers undergo a specific reaction, the reaction is further characterized in terms of its thermochemistry which might be unique to each stereoisomer. We also show that by employing two successive fragmentations it is sometimes possible to amplify stereochemical differences and so to facilitate the analysis. In particular, diastereometic ions can yield structurally isomeric fragment ions in the first step of the reaction. These products fragment as metastable ions and the relative abundances of the further products, in conjunction with the kinetic energies released, serve to characterize the primary product ions and so the neutral molecules.

Experimental Section

Measurements were made using a modified Hitachi RMH-2 mass spectrometer operated at an accelerating voltage of 8 KV, an ionizing electron energy of 70 eV, and an electron emission current of 1 mA. In some experiments a mass-analyzed ion kinetic energy spectrometer (MIKES) was also used under similar conditions. Reactions were followed in the first field-free region of the RMH-2 by the accelerating-voltage scan technique and in the preelectric sector region of the MIKES by electric sector scans. Kinetic energy releases were determined from the width of the metastable peak measured at half-maximum. A kinetic energy resolution of approximately 4000 (full width at half-maximum) was employed. Full details regarding instrumentation and methodology have been presented elsewhere.[2]

2,3-Difluorobutane was prepared by reaction of the *p*-toluenesulfonyl ester of the diol with KF in diethylene glycol.[3] The meso and *d,l* isomers were formed in approximately equal amounts and separated by preparative gas chromatography on an SF-96 column. The meso isomer is eluted first on a boiling point column.[4] **1-Fluoro-3-butene** was prepared from 1-hydroxy-3-butene by the same method. **2-Chloro-2-butene** was obtained commercially and the cis and trans isomers were separated by gc and their structures confirmed by nmr. The lower boiling isomer (trans, bp 63°) was eluted before the cis (bp 67°). **2-Chloro-1-butene** was obtained commercially and purified by gc. **2,3-Dichlorobutane** was obtained commercially and the meso and *d,l* isomers were separated by gc (SF-96).

Results

The 70-eV mass spectra of *d,l*- and *meso*-2,3-difluorobutane are identical. Both isomers show metastable peaks for the elimination of HF from both the molecular ion and the $(M - HF) \cdot^+$ fragment ion. The primary HF elimination is associated with a kinetic energy release of 15 ± 3 meV in both cases. However, the abundance of the metastable peak is about 15 times greater for the *d,l* than for the meso isomer. (The more intense peak height was 0.25% relative to that of the corresponding molecular ion.) The secondary HF elimination is associated with similar metastable ion abundances in the *d,l* and meso isomers; however, detailed analysis of the metastable peak at high kinetic energy resolution revealed a striking difference. Thus both isomers give composite metastable peaks[5] for this reaction, indicating that two processes occur for each isomer. The kinetic energy release for the broad component was 854 ± 30 meV for both isomers and approximately 32 meV for the narrow component in both cases. However (Figure 1), in one of the isomers the ratio of narrow to broad components was 3 times greater than in the other.

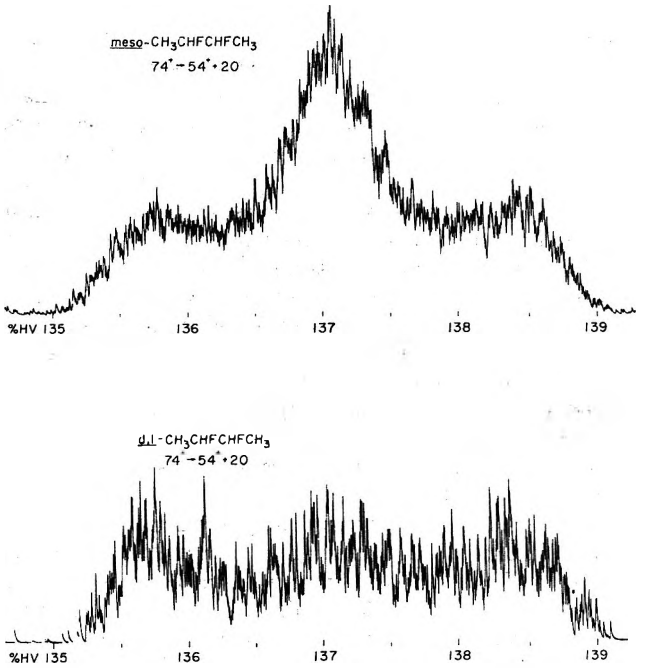


Figure 1. Overlapping broad and narrow metastable peaks for HF loss from the $(M - HF) \cdot^+$ fragment ion in *d,l*- and *meso*-2,3-difluorobutane. The spectra were obtained by scanning the accelerating voltage (HV) on the RMH-2 mass spectrometer.

The 2,3-dichlorobutanes could also be distinguished by ion kinetic energy spectrometry. Dehydrohalogenation of the molecular ions gave composite metastable peaks for both isomers with the relative contribution of the narrow peak being some 50% more intense in the meso compound.[6] Composite peaks were also observed for the secondary dehydrochlorination from the $C_4H_7Cl \cdot^+$ ion, the meso compound giving slightly more of the narrower component than the *d,l* isomer.

2-Chloro-1-butene and *cis*- and *trans*-2-chloro-2-butene all gave identical mass spectra. Moreover, the metastable peaks for HCl elimination from the respective molecular ions ($C_4H_7Cl \cdot^+$) were in each case similar to those observed for the further reaction of the primary products of dehydrochlorination of the 2,3-dichlorobutanes. The cis and trans isomers were indistinguishable in this regard but

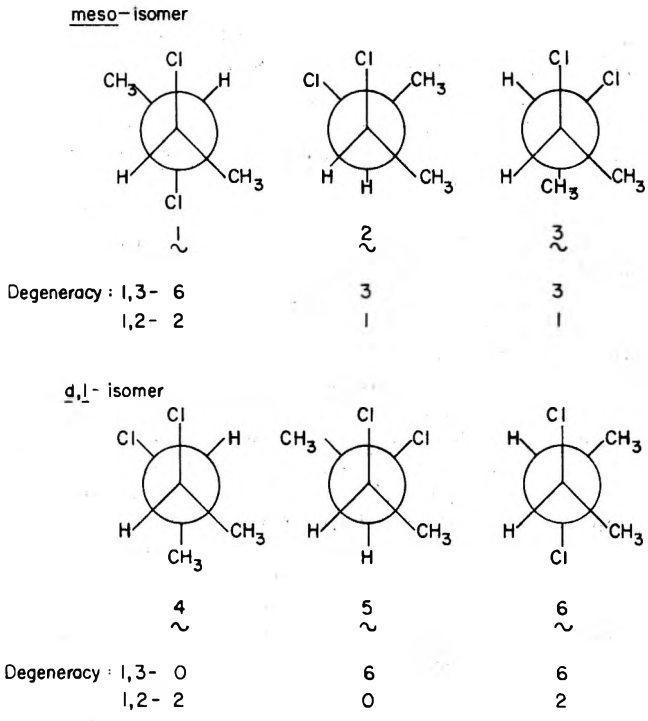
2-chloro-1-butene gave relatively more of the narrow component in this metastable ion reaction.

Discussion

The results presented show that it is possible to distinguish the stereoisomers under consideration by ion kinetic energy spectrometry. They also show that the fluoro and chloro compounds do not behave analogously.

In accounting for these observations note must be made of the fact that the kinetic energy release accompanying a metastable ion fragmentation can serve as a characteristic of ion structure and reaction mechanism.[7] This is facilitated by the results of previous studies on dehydrohalogenation by ion kinetic energy spectrometry.[6,8] A general conclusion possible from these studies is that dehydrohalogenation of haloalkanes will be associated with a large kinetic energy release when it occurs by 1,2 elimination and by a small release when it occurs by 1,3 elimination. Dependence of the relative abundances of metastable peaks associated with large and small energy releases upon the stereo isomer involved is the basic observation made in this study. Association of reaction mechanism with stereochemistry can hence be made.

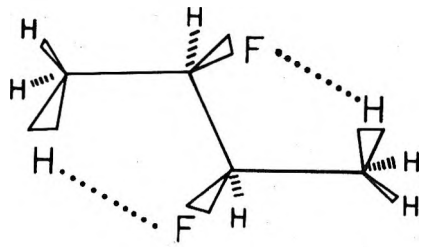
Consider, first, the primary dehydrochlorination of 2,3-dichlorobutane. Both isomers give both the broad and the narrow peaks which is interpreted as a result of competitive 1,2 and 1,3 eliminations.[5] The fact that 1,3 elimination is more favored relative to 1,2 elimination in the meso than in the *d,l* isomer follows from a consideration of literature data on rotamer stabilities.[9] In using these data it is assumed that the conformational preferences of the molecular ion will parallel those of the corresponding neutral molecules and that the potential energy minima reflect associated rotational barrier heights. Thus, *meso*-2,3-dichlorobutane can exist in three low-energy rotamers: one trans form (**1**) and two gauche forms (**2** and **3**) which are enantiomers.



The enthalpy of the trans configuration in the vapor phase is approximately 1.3 kcal/mol lower than that of the two gauche forms.[10] For the *d,l* isomer there are three separate rotamers of which one (**4**) is 1.5–1.6 kcal/mol more stable than the others.[10] The degeneracies for 1,2 and 1,3 eliminations are shown below the structures. Secondary hydrogen abstraction is assumed[6] to be favored over primary where competition is possible, *viz.* for the 1,2 elimination mechanism. It is apparent that in each isomer two of the total of four modes of 1,2 elimination are associated with the stable rotamer. Hence little, if any, difference in the abundance of the broad metastable peak is expected when the isomers are compared. However, for 1,3 elimination the reaction path degeneracy associated with the most stable *d,l* configuration is zero and hence its contribution to the metastable ion abundance should be negligible. Hence, the greater metastable ion abundance for the narrow peak is predicted to be associated with the meso isomer since for this isomer the population distribution of rotational isomers and the reaction path degeneracies favor the 1,3 elimination. The observed behavior confirms this prediction.

Since a conformational analysis of 2,3-difluorobutane has apparently not been reported, the experimental results cannot be compared with literature data in this case. Moreover, differences in steric size and electronegativity distinguish the fluoro and chloro compounds.

To account for the observed behavior we suggest that, at least in the molecular ion, rotamer **5** is specially stabilized in the fluorine case. Models show that in this species *two* H–F interactions involving quasi-five-membered rings (**7**)



7

could form such that one H–F bond locks the molecule into a configuration from which 1,3 elimination will occur from the other bond. This proposal is based upon the fact that electrostatic attractive forces between the polarizable methyl group and a halogen atom have significant effects upon conformational enthalpies.[11] The result, in terms of conformation preferences, is analogous to that when the halogen group is suitably oriented relative to a hydroxyl group—*viz.*, to that when the halogen hydrogen bonds to this group.[12] In the case of the strongly electronegative fluorine atom it seems to us appropriate to refer to the interaction as hydrogen bonding. It may be noted that the importance of strong hydrogen bonding in bimolecular mass spectrometry has recently been emphasized.[13]

The postulate of stronger hydrogen bonding in the fluoro than in the chloro compounds accounts for the suppression of the 1,2-elimination channel in both the meso and the *d,l* isomers. Moreover, since the *double* hydrogen bonding suggested above is applicable to only one of the six rotamers, hydrogen bonding also accounts for the much greater metastable ion abundance in the *d,l* as compared to the meso isomer. Another factor which probably contributes to the difference between the behavior of the fluorine and chlorine compounds is the steric size of halogen; it has been shown[1a] that HF elimination tends to occur *via* a cyclic activated complex of larger ring size than that for HCl elimination.

Turning to the secondary dehydrohalogenation, we again consider first the chloro compounds. The ion of interest is $C_4H_7Cl \cdot^+$ and the apposite observation concerns a difference of some 20% in relative peak heights for the broad and narrow components of the composite metastable peak in

the two isomers. A previous study[6] suggested that while the broad peak must be associated with 1,2 elimination across a saturated bond, the narrow peak could here be due either to 1,3 elimination or vinylic 1,2 elimination. It was also shown explicitly that the ratio of the broad and narrow components varied with the origin and, hence, the initial structure and internal energy distribution of the $C_4H_7Cl \cdot^+$ ion. These observations are supported by the new results obtained here on 2-chloro-2-butene and 2-chloro-1-butene. The conclusion must be that isomerization between the various $C_4H_7Cl \cdot^+$ structures is largely complete prior to metastable ion fragmentation, the small abundance differences associated with different methods of preparation reflecting differences in internal energy distributions.[14] Stereochemical distinctions can, therefore, not be made on the basis of the secondary dehydrochlorination.

In striking contrast, the secondary HF elimination gives the disparate metastable peaks illustrated in Figure 1. These differences must be due to *structural* differences in the reacting $(M - HF) \cdot^+$ ions since differences in the internal energy distributions, which for stereoisomers are expected to be very small in the molecular ions, should be even further reduced when the $(M - HF) \cdot^+$ product ions are compared.[15] (Compare also the preceding chlorine results.) Hence, we are apparently observing the amplification of stereochemical differences in the molecular ions into structural isomerism in the $(M - HF) \cdot^+$ fragment ions.

In accounting for this remarkable behavior the broad and narrow components are assigned, by analogy with dehydrochlorination,[6,8] as 1,2 elimination from saturated carbons on the one hand and 1,3 and/or vinylic 1,2 elimination on the other. The available data on HF loss also fit this picture, including that for 1-fluoro-3-butene which only shows a broad component (T = 0.80 eV) in the metastable peak for HF loss. Further evidence comes from the thermochemistry of the typical reactions 1 and 2. The heats of formation of the neutral C_4H_7F isomers are not well-known but it was sufficient for the comparison involved here to compare the analogous methyl-substituted butenes to account for the difference in the double-bond position. From the measured appearance potential[16] of the $(C_4H_7F - HF) \cdot^+$ ion, 11.9 ± 0.2 eV (AP − IP = 2.4eV), $\Delta H_f°(CH_3C{\equiv}CCH_3 \cdot^+)$ = 263 kcal/mol, $\Delta H_f°(CH_2{=}CHCH{=}CH_2 \cdot^+)$ = 236 kcal/mol, and $\Delta H_f°$ (HF) = −64.9 kcal/mol, it is estimated that the difference in the total energy available for partitioning in reactions 1 and 2 is ~41 kcal/mol. Hence the broad metastable peak is associated with reaction 2, which has a much greater energy available for partitioning.

$$CH_3CH{=}CFCH_3^{\bullet} \longrightarrow CH_3C{\equiv}CCH_3^{\bullet} + HF \quad (1)$$

$$CH_2{=}CHCHFCH_3^{\bullet} \longrightarrow CH_2{=}CHCH{=}CH_2^{\bullet} + HF \quad (2)$$

The stereochemical differences between the meso and *d,l* molecular ions translate into geometrical isomerism in the dehydrohalogenation products, whether formed by 1,2 or by 1,3 elimination. Thus, 1,2 elimination from the meso molecular ion yields exclusively the trans olefin, while the *d,l* isomer yields exclusively the cis olefin. A corresponding stereospecificity exists in formation of the ionized cyclopropane which is the intial product of 1,3 elimination from the molecular ion. The presence of the broad component in Figure 1 requires that the intially formed butene isomerize in part to a structure such as the reactant shown in (2) from which 1,2 elimination can occur from saturated carbons. The *trans*-2-fluoro-2-butene, perhaps because of hydrogen bonding,[17] may undergo 1,3 elimination of HF more readily than the cis isomer undergoes either 1,3 or 1,2 elimination. Hence, given a primary 1,2 elimination, the narrow component is expected to be more pronounced for the meso compound as is indeed observed. It is not possible to tell whether the metastable $(M - HF) \cdot^+$ ions are formed from the molecular ion by the 1,2 or the 1,3 elimination mechanism. However, both reactions are stereospecific and the observed behavior is accounted for in either event if the isomerization of the intital $(M - HF) \cdot^+$ product ion is stereochemically controlled.

Thus the overall effect is that optical isomerism in the molecular ions is translated into geometrical isomerism in the $(M - HF) \cdot^+$ ions and, hence, into differences in the relative proportions of structural isomers for those $(M - HF) \cdot^+$ ions which react further.

Conclusion

The marked differences observed in this study between metastable peaks for stereoisomers, even when a secondary ion fragmentation is considered, emphasize the delicacy of mass spectrometry as a stereochemical probe. The unique contribution of kinetic energy measurements is that they make it possible to dissect individual reaction mechanisms on the basis of their dynamics and so to assign stereochemistry. Both the effect seen in the primary fragmentation, which is due to conformation preferences in the molecular ion, and that seen in the secondary fragmentation, which depends on the translation of optical isomerism into geometrical isomerism in the initial step, can be expected to occur in other classes of compound.

Acknowledgment. We thank the National Science Foundation for support of this work and Dr. J. B. Grutzner and Dr. M. M. Green for helpful discussions.

Registry No.—KF, 7789-23-3; 2,3-butanediol-*p*-toluenesulfonyl ester, 49662-27-3; *meso*-2,3-difluorobutane, 53586-61-1; *d,l*-2,3-difluorobutane, 53586-62-2; 1-fluoro-3-butane, 675-56-9; 1-hydroxy-3-butene, 627-27-0; *cis*-2-chloro-2-butene, 2211-69-0; *trans*-2-chloro-2-butene, 2211-68-9; 2-chloro-1-butene, 2211-70-3; *meso*-2,3-dichlorobutane, 4028-56-2; *d,l*-2,3-dichlorobutane, 2211-67-8.

References and Notes

(1) See for example (a) M. M. Green, R. J. Cook, J. M. Schwab, and R. B. Roy, *J. Amer. Chem. Soc.*, **92**, 3076 (1970), and other papers in this series; (b) S. Meyerson and A. W. Weitkamp, *Org. Mass Spectrom.*, **1**, 659 (1968); (c) K. Pihlaja and J. Jalonen, *ibid.*, **5**, 1363 (1971), and other references therein; (d) J. K. MacLeod and R. J. Wells, *J. Amer. Chem. Soc.*, **95**, 2387 (1973).
(2) R. G. Cooks, J. H. Beynon, R. M. Caprioli, and G. R. Lester, "Metastable Ions," Elsevier, Amsterdam, 1973.
(3) Compare W. F. Edgell and L. Parts, *J. Amer. Chem. Soc.*, **77**, 4899 (1955).
(4) P. S. Fredericks and J. M. Tedder, *J. Chem. Soc.*, 3520 (1961).
(5) R. G. Cooks, M. Bertrand, J. H. Beynon, M. E. Rennekamp, and D. W. Setser, *J. Amer. Chem. Soc.*, **95**, 1732 (1973).
(6) K. C. Kim, J. H. Beynon, and R. G. Cooks, *J. Chem. Phys.*, **61**, 1305 (1974).
(7) (a) E. G. Jones, L. E. Bauman, R. G. Cooks, and J. H. Beynon, *Org. Mass Spectrom.*, **7**, 185 (1973); (b) J. H. Beynon and R. G. Cooks, *Advan. Mass Spectrom.*, **6**, 835 (1974).
(8) R. G. Cooks, K. C. Kim, and J. H. Beynon, *Int. J. Mass Spectrom. Ion Phys.*, in press.
(9) For previous observations on rotational isomers and their effects on mass spectra see M. E. Munk, C. C. Kulkarni, C. L. Lee, and P. Brown, *Tetrahedron Lett.*, 1377 (1970).
(10) P. J. D. Park and E. Wyn-Jones, *J. Chem. Soc. A*, 422 (1969).
(11) (a) G. Szasz, *J. Chem. Phys.*, **23**, 2449 (1955); (b) N. Sheppard, *Advan. Spectrosc.*, **1**, 288 (1959).
(12) Reference 11b, p 300.
(13) D. P. Ridge and J. L. Beauchamp, *J. Amer. Chem. Soc.*, **96**, 637 (1974).
(14) Compare M. L. Gross and P.-H. Lin, *Org. Mass Spectrom.*, **7**, 795 (1973), and references therein.
(15) D. J. McAdoo, P. F. Bente III, M. L. Gross, and F. W. McLafferty, *Org. Mass Spectrom.*, **9**, 525 (1974).
(16) The broad and narrow components must have very similar appearance potentials for both to give metastable peaks.
(17) *Chem. Eng. News*, 39 (Oct. 7, 1963).

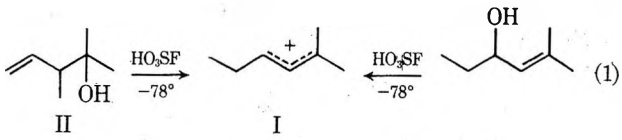
Carbonium Ions. XXIII. Chain Elongation in the Rearrangement of 2,3-Dimethyl-4-penten-2-ol to 2-Methyl-3-hexen-2-yl Cation

N. C. Deno* and Robert R. Lastomirsky

Chemistry Department, The Pennsylvania State University, University Park, Pennsylvania 16802

Received September 25, 1974

The 2-methyl-3-hexen-2-yl cation (I) is formed on addition of 2,3-dimethyl-4-penten-2-ol (II) to HO_3SF at −78°, eq 1. Ion I is the dominant product as evidenced by 90% of



II I (1)

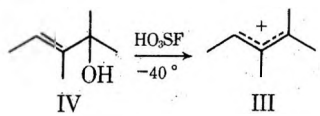
the nmr band areas being attributable to I. A novel feature of eq 1 is the elongation of the five-carbon chain of II to the six-carbon chain of I. This type of elongation does not seem to have been observed heretofore in allyl cation rearrangements[1] and will probably be uncommon because it would involve going from more branched to less branched carbonium ions.

The rearrangement cannot have taken place by H migration alone and paths involving H migration and 1,2-alkyl shifts are unlikely. The only attractive paths are those involving cyclopropylcarbonium ions and rearrangements of these ions of the type exemplified by the scrambling of methylene groups in the cyclopropylmethyl cation.[2] At least two paths involving this type of rearrangement can be constructed.

Structure I was assigned on the basis of its nmr spectrum: triplet at 1.29 (J = 6.5 Hz, ~3 H on C-6), unresolved quartet at 2.96 (2.0 H on C-5), singlet at 3.06 (6.0 H on *gem*-dimethyl), doublet at 7.74 (J = 14.5 Hz, 1.0 H on C-2), doublet at 9.60 (J = 14.5 Hz, 1.0 H on C-3). The band at 9.60 was broadened by coupling with the H on C-4. The band positions are in accord with precedent.[1]

The identification of I was confirmed by its independent synthesis by addition of 5-methyl-4-hexen-3-ol to HO_3SF at −78°, eq 1. This formation was quantitative.

It had been anticipated that II would form the 2,3-dimethyl-3-penten-2-yl cation, III, as the first stable observable cation. The question thus arose as to whether III was an intermediate in the formation of I. This was not the case. Addition of 2,3-dimethyl-3-penten-2-ol (IV) to HO_3SF at −40° produced III, eq 2. Ion III was stable at



IV III (2)

−40°. On warming to 25° it formed a mixture of cyclopentenyl cations (as did I) without the nmr bands of I ever appearing. This formation of cyclopentenyl cation mixtures is a common fate of carbonium ions.[3]

The identification of III rested on its mode of formation and nmr spectrum: singlet at 2.23 (3.0 H on C-3), a broad unresolved pair of bands at 2.75 (6.0 H of the *gem*-dimethyl), doublet at 3.11 (J = 6 Hz, 3.1 H on C-5), quartet at 9.55 (J = 6 Hz, 1.0 H on C-4). These are typical for allyl cations[1] and are in agreement with structure III.

It is remarkable that the two alcohols II and IV, which differ only in the position of the double bond, produce entirely different stable allyl cations, I AND III, on addition to HO_3SF at −78°.

Experimental Section

Nmr Spectra. Spectra were recorded on a Varian A-60 instrument. Spectra of ions I and III were recorded at −40°. Tetramethylammonium chloride (δ 3.10) was used as the internal standard in HO_3SF. Band positions are expressed in δ.

Carbonium Ion Precursors. 2,3-Dimethyl-4-penten-2-ol (II) was commercially available from Aldrich Chemical Co., Milwaukee, Wis. 2,3-Dimethyl-3-penten-2-ol[4] (IV) was prepared from CH_3Li and 3-methyl-3-penten-2-one. The nmr spectrum in CCl_4 consisted of a singlet (6 H, *gem*-dimethyl) at 1.22, an overlapping singlet and doublet (6 H, remaining two methyl groups) at 1.45–1.77, a singlet (H on OH) at 2.47, and a multiplet (H on C-4) from 5.20 to 5.77. The J coupling constants between hydrogens on C-4 and C-5 could not be accurately determined but both were in the same 6–7-Hz range. The boiling point (82–83° at 72 Torr) was in agreement with that reported (84–86° at 85 Torr[4]).

5-Methyl-4-hexen-3-ol[5] was prepared by $LiAlH_4$ reduction of 5-methyl-4-hexen-3-one. The nmr spectrum in CCl_4 consisted of a triplet (J = 6.5 Hz, 3 H on C-6) at 0.83, a multiplet (2 H on C-5) from 1.06 to 1.62, a pair of doublets (J = 1.5 Hz, 6 H on *gem*-dimethyl) at 1.65 and 1.70, a singlet (H on OH) at 3.07, a multiplet (H on C-4) from 3.93 to 4.35, and a multiplet (H on C-3) from 4.95 to 5.27. The boiling point (58° at 13 Torr) was in agreement with that reported (63–65° at 22 Torr[5]).

Acknowledgments. Support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Science Foundation is gratefully acknowledged.

Registry No.—I, 53567-43-4; II, 19781-52-3; IV, 53555-58-1; 3-methyl-3-penten-2-one, 565-62-8; 5-methyl-4-hexen-3-ol, 53555-59-2; 5-methyl-4-hexen-3-one, 13905-10-7.

References and Notes

(1) N. Deno in "Carbonium Ions," Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N.Y., 1970, pp 783–806.
(2) H. G. Richey, Jr., in "Carbonium Ions," Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N.Y., 1972, pp 1243 and 1279.
(3) N. Deno, D. B. Boyd, J. D. Hodge, C. U. Pittman, Jr., and J. O. Turner, *J. Amer. Chem. Soc.*, **86**, 1745 (1964).
(4) J. Colonge, *Bull. Soc. Chim. Fr.*, **2**, 754 (1935).
(5) J. Colonge and M. Reymermier, *Bull. Soc. Chim. Fr.*, 188 (1956).

A New Method for the Preparation of 4-Acylpyrazoles. The Reaction of C(α),N Dianions of Phenylhydrazones with Acid Chlorides

Charles F. Beam,* David C. Reames, Charles E. Harris, Luther W. Dasher, Wayne M. Hollinger, Neal L. Shealy, and Ronda M. Sandifer

Department of Chemistry, Newberry College, Newberry, South Carolina 29108

Matilda Perkins and Charles R. Hauser

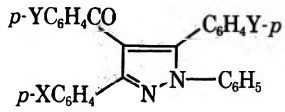
Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received September 6, 1974

The 1,4 dianions of phenylhydrazones having an α-hydrogen atom, such as dilithioacetophenone phenylhydrazone, have been condensed with esters[1] and nitriles[2] to give, after acid cyclization, numerous pyrazoles, especially 3,5-disubstituted pyrazoles.

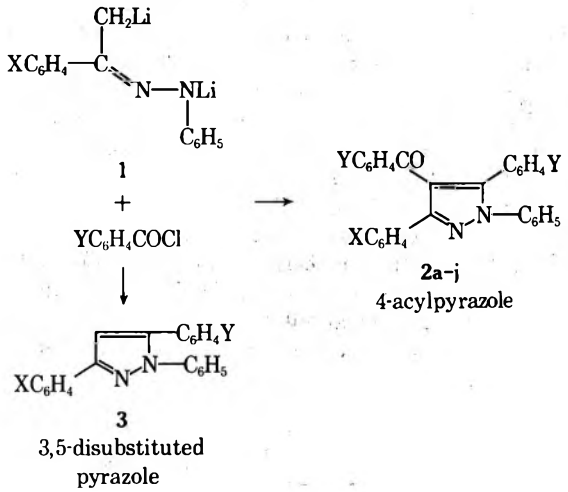
It was of interest to treat these dianions with aroyl chlorides in order to determine the effect of these more reactive electrophilic reagents and to compare the results with those already obtained for esters and nitriles. When the dilithiophenylhydrazones 1 were treated with benzoyl, *p*-chlorobenzoyl, and *p*-toluoyl chlorides, followed by acid cyclization, 4-acylpyrazoles **2a–j** were obtained instead of 3,5-disubstituted pyrazoles **3**.

Table I
4-Acylpyrazoles



Compd no.[a]	X	Y	Name (-pyrazole)	Yield, %	Mp, °C	Ir (C=O),[b] cm⁻¹
2a	H	H	4-Benzoyl-1,3,5-triphenyl-	100	174–176[c]	1650–1655
2b	H	Cl	4-(*p*-Chlorobenzoyl)-5-(*p*-chlorophenyl)-1,3-diphenyl-	38	169–170	1640–1650
2c	H	CH_3	1,3-Diphenyl-4-(*p*-toluoyl)-5-(*p*-tolyl)-	62	166–167	1640–1650
2d	F	Cl	4-(*p*-Chlorobenzoyl)-5-(*p*-chlorophenyl)-3-(*p*-fluorophenyl)-1-phenyl-	32	177–179	1640–1650
2e	F	H	4-(Benzoyl)-1,5-diphenyl-3-(*p*-fluorophenyl)-	68	143–144	1640–1650
2f	CH_3	H	4-(Benzoyl)-1,5-diphenyl-3-(*p*-tolyl)-	72	170–172	1640–1650
2g	Cl	H	4-Benzoyl-1,5-diphenyl-3-(*p*-chlorophenyl)-	43	153–156	1645–1655
2h	Cl	CH_3	3-(*p*-Chlorophenyl)-1-phenyl-4-(*p*-toluoyl)-5-(*p*-tolyl)-	30	184–186	1640
2i	CH_3	CH_3	1-Phenyl-4-(*p*-toluoyl)-3,5-di(*p*-tolyl)-	61	158–160	1640
2j	CH_3O	Cl	3-(*p*-Anisyl)-4-(*p*-chlorobenzoyl)-5-(*p*-chlorophenyl)-1-phenyl-	47	162–164	1650

[a] C, H, N analysis for 2b–j ± 0.30%. [b] The C=O absorption for 4-acylisoxazoles was reported at 1653 cm⁻¹ (KBr pellets); see ref 5. [c] Lit. mp 174°; N analysis, ±0.30%; see ref 4.

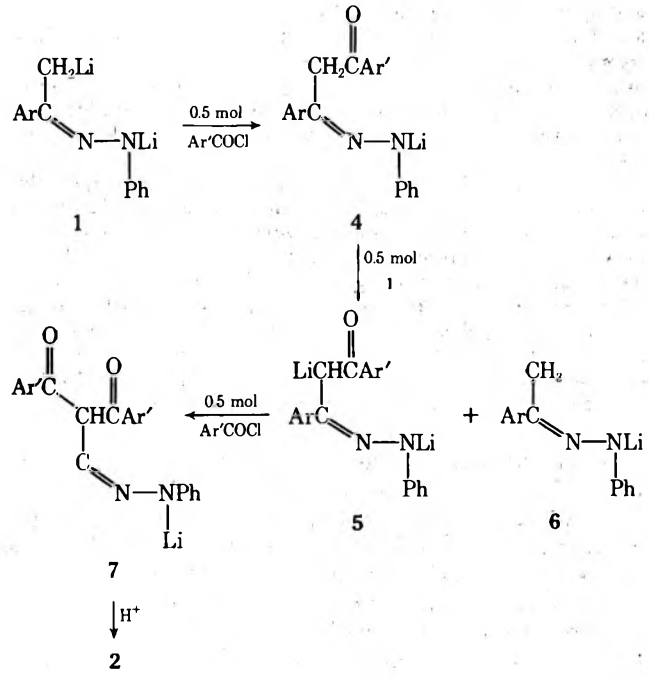


In a typical reaction, a freshly prepared phenylhydrazone was dissolved in tetrahydrofuran and treated with 2 molar equiv of *n*-butyllithium in hexane, and this was followed by condensation with 1 molar equiv of aroyl chloride, acid cyclization with 3 *N* hydrochloric acid, and recrystallization of the product. Optimum yields of products were obtained when the ratio of phenylhydrazone:base:acid chloride was 1:2:1; this is consistent with the proposed mechanism. The yield is based on one-half of the amount of acid chloride used, since two molecules of this reactant are needed for each molecule of 4-acylpyrazole prepared.

The sequence in Scheme I would account for the results obtained. Reaction of the phenylhydrazone with 2 equiv of *n*-butyllithium gives *C*(α),*N*-dilithiophenylhydrazone **1**. Prior to the addition of the full amount of the base, the reaction mixture was red in color, and it turned dark red to red-black in color after addition was complete, indicating complete conversion to dianion **1**. Treatment of **1** with 0.5 equiv of acid chloride leads to intermediate **4**, which with 0.5 molar equiv of dianion **1** gives **5** and **6**. Reaction of **5** with another 0.5 equiv of acid chloride, which was slowly being added to the reaction mixture, would lead to intermediate **7** and thence to **2**.

It was of interest to treat a phenylhydrazone with 1 molar equiv of base followed by 1 molar equiv of acid chloride. When acetophenone phenylhydrazone monoanion was

Scheme I



treated with benzoyl chloride, and was followed by acid cyclization, **2a** was isolated in 16% yield. This suggests formation of some C(α) ion in addition to the resonance stabilized N anion;[3] however, other monolithiophenylhydrazones treated with acid chlorides gave side products (unidentified, but definitely not pyrazoles), which supports the importance of the *C*(α),*N*-dilithiophenylhydrazone intermediate.

Only 5-(*p*-anisyl)-3-(*p*-tolyl)pyrazole resulted from the treatment of the dianion with *p*-anisoyl chloride followed by cyclization. The failure to form the 4-acylpyrazole evidently reflects the diminished reactivity of the acid chloride, which does not react further with intermediate **5** to give **7**.

Of the 4-acylpyrazoles, only **2a** has been reported, and it was prepared by the reaction of benzoyl chloride with 1,3,5-triphenylpyrazole.[4] The melting point of **2a** prepared in this work agreed with that reported (see Table I). The

carbonyl absorption for all of the 4-acylpyrazoles prepared was in the range of 1640–1655 cm^{-1}, comparing well with the values reported for 4-acylisoxazoles.[5]

This new route to 4-acylpyrazoles requires readily available starting materials, is easily and readily carried out, and products are easily purified.

Experimental Section

All combustion analyses were performed by Robertson Laboratory, Florham Park, N.J., and by M-H-W Laboratories, Garden City, Mich. Infrared spectra were obtained from a Perkin-Elmer 700 infrared spectrometer (0.1 mm, chloroform solvent). Melting points were taken in a Thomas-Hoover melting point apparatus in open tubes and are uncorrected. The *n*-butyllithium was obtained from the Lithium Corporation of America, Bessemer City, N.C. The tetrahydrofuran was obtained from Matheson Coleman and Bell and was used as supplied. The phenylhydrazones were prepared by a standard method,[6] recrystallized from ethanol, and used immediately.

General Procedure for the Preparation of 4-Acylpyrazoles. To a stirred solution of 0.02 mol of phenylhydrazone dissolved in 100 ml of dry THF, which was blanketed by nitrogen and cooled to 0°, was added 0.042 mol of *n*-butyllithium during 5 min. After stirring the resulting mixture for 30 min, 0.022 mol of acid chloride dissolved in 100 ml of THF was added during 5–10 min. The resulting mixture was stirred for 30 min and neutralized with 100 ml of 3 *N* HCl. The entire mixture was stirred and heated under reflux for 1 hr and cooled. The mixture was placed in a large flask and approximately 100 ml of ether was added, and this was followed by careful neutralization with sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with two 50-ml portions of ether. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated, and the resulting oil or residue was immediately crystallized and/or recrystallized from hot 95% ethanol.

Preparation of 3-(*p*-Methoxyphenyl)-5-(*p*-tolyl)pyrazole. Dianion (0.025 mol) was prepared by the treatment of 0.025 mol of 4-methylacetophenone phenylhydrazone with 0.055 mol of *n*-butyllithium (see above). This dianion was condensed with 0.05 mol (twofold excess) of *p*-anisoyl chloride dissolved in 100 ml of THF. After acid cyclization and isolation of product, 5.00 g (59%) of 3-(*p*-methoxyphenyl)-5-(*p*-tolyl)pyrazole was obtained: nmr ($CDCl_3$) δ 2.38 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3O), 6.72 (s, 1 H, C_4H), and 6.88–7.88 (m, 13 H, ArH). *Anal.* Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 80.98; H, 5.92; N, 8.09.

Acknowledgment. This work was supported at Newberry College by grants from the Petroleum Research Fund, which is administered by the American Chemical Society, and the South Carolina Heart Association, Inc. The Public Health Service, Research Grant CA-04455, supported the work at Duke University. The use of the A-60 nmr spectrometer and the cooperation of Dr. R. Cargill, at the University of South Carolina, are gratefully acknowledged.

Registry No.—**1a** dianion, 13636-57-2; **1d** dianion, 53608-33-6; **1f** dianion, 53608-34-7; **1g** dianion, 53608-35-8; **1j** dianion, 53608-36-9; **2a**, 53608-37-0; **2b**, 53608-38-1; **2c**, 53608-39-2; **2d**, 53608-40-5; **2e**, 53608-41-6; **2f**, 53608-42-7; **2g**, 53608-43-8; **2h**, 53608-44-9; **2i**, 53608-45-0; **2j**, 53608-46-1; benzoyl chloride, 98-88-4; *p*-chlorobenzoyl chloride, 122-01-0; *p*-toluoyl chloride, 874-60-2; *p*-anisoyl chloride, 100-07-2; 5-(*p*-anisyl)-3-(*p*-tolyl)pyrazole, 53608-47-2.

References and Notes

(1) R. S. Foote, C. F. Beam, and C. R. Hauser, *J. Heterocycl. Chem.*, **7**, 589 (1970).
(2) C. F. Beam, R. S. Foote, and C. R. Hauser, *J. Heterocycl. Chem.*, **9**, 183 (1972).
(3) D. W. Slocum, C. A. Jennings, T. R. Engelmann, B. W. Rockett, and C. R. Hauser, *J. Org. Chem.*, **36**, 377 (1971); R. E. Ludt, G. P. Crowther, and C. R. Hauser, *ibid.*, **35**, 1288 (1970).
(4) R. Rusco, *Gazz. Chim. Ital.*, **69**, 344 (1939); I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.*, **30**, 203 (1960).
(5) W. B. Renfrow, J. F. Witte, R. A. Wolf, and R. Bohl, *J. Org. Chem.*, **33**, 150 (1968).
(6) P. Mirone and M. Vampiri, *Atti Accad. Naz. Lincei, Rend., Cl. Sci. Fis. Mat. Nat.*, **12**, 583 (1952); *Chem. Abstr.*, **46**, 9423 (1952).

Acid-Catalyzed Rearrangement of 20-Vinylpregn-5-ene-3β,20-diol 3-Acetate[1]

Yves Letourneux, Milly Mee Lee Lo, Nabakrishna Chaudhuri, and Marcel Gut*

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

Received September 6, 1974

There are many reports that C-20 tertiary carbinol steroids may undergo dehydration,[2] rearrangement,[3] or both[4] under certain conditions.

A recent report by Narwid, Cooney, and Uskoković[5] on the Carroll rearrangement of (20*S*)-20-vinylpregn-5-ene-3β,20-diol 3-acetate (**2a**) prompts us to publish our results on the acid-catalyzed rearrangement of that compound. This work was undertaken in order to compare the behavior of the 20-vinyl- with the behavior of the 2-methyl-[3] and 20-ethynylcarbinols[4] under similar conditions.

The synthesis of 20-vinylpregn-5-ene-3β,20-diol 3-acetate (20-isomeric mixture) (**2a,b**) was achieved by treating 3β-hydroxypregn-5-en-20-one acetate (**1**) with vinylmagnesium bromide, followed by reacetylation[6] of the 3β-hydroxyl. The epimers **2a** and **2b** were isolated in an 11:1 ratio. The 20*S* configuration was assigned to the major product **2a** (77%) for the following reasons. (1) In a recent publication,[7] we have shown that the stereochemistries of nucleophilic additions of 20-keto steroids are in agreement with Cram's rule. (2) The (20*S*)-20-ethynylpregn-5-ene-3β,20-diol 3-acetate (**5**),[4,8] when selectively reduced with Lindlar catalyst,[9] gave a product identical in all respects with the vinylcarbinol **2a**.

The present study is concerned solely with acid-catalyzed reactions of the vinylcarbinol **2a**. The compounds isolated were those arising from dehydration and allylic rearrangement; no D-homoannulation was observed (Scheme I). Table I summarizes the results of this investigation.

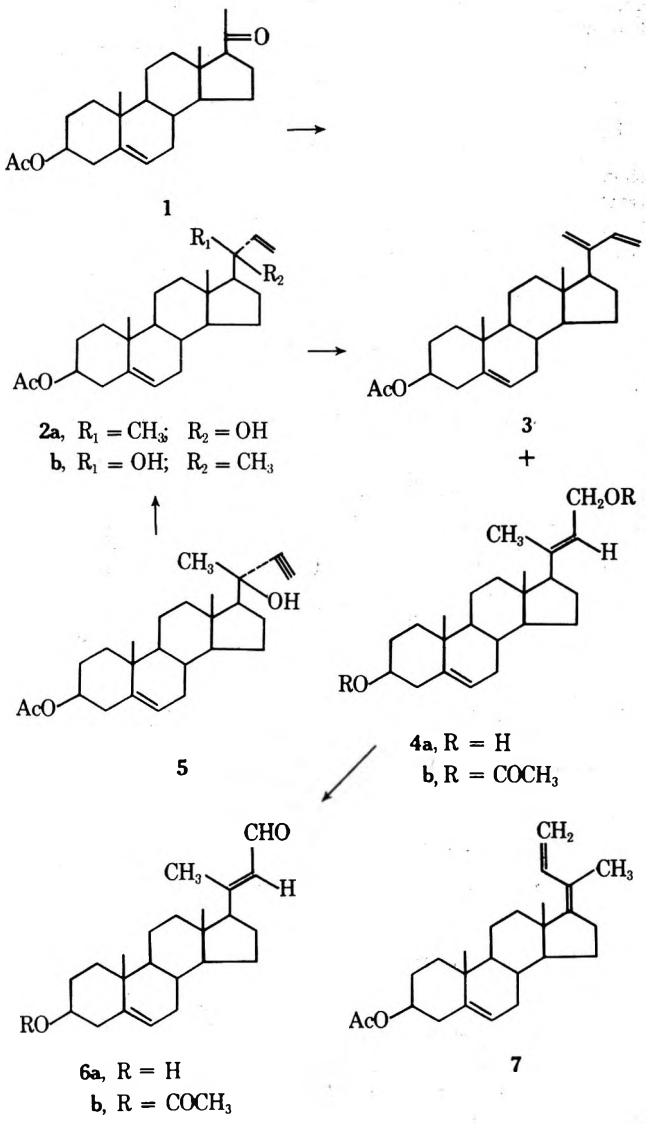
Table I
Reaction of Carbinol 2a

Reagents, conditions	Products in % yield 3	4b	7
AcOH–*p*-TsOH, 25°, 72 hr	20	50	
AcOH–I_2, 100°, 0.5 hr	10	50	
$POCl_3$–Py, 100°, 3 hr	30		
H_2SO_4–dioxane, 100°, 1 hr	80		
AcOH–*p*-TsOH, 100°, 0.25 hr		30	60
Benzene–PBr_3, 25°, 20 hr		70	

Structure of Triene 3. The elemental analysis of **3** showed that the compound was derived by loss of one molecule of water from the vinylcarbinol **2a** and the infrared spectrum showed the absence of any hydroxyl group. The ultraviolet absorption maximum was at 228 nm (ε 11,500), characteristic of a monosubstituted conjugated diene,[10,11] although higher than predicted according to Woodward's[12] rules. The proton magnetic resonance spectrum showed the presence of six vinylic protons and the absence of a methyl group on an unsaturated carbon, consistent with the structure **3**.

Structure of Diacetate 4b. The elemental analysis of **4b** indicated a formula derived from the starting material **2a** by acetylation of the alcoholic function. This was confirmed by the absence of any hydroxyl band in its infrared

Scheme I

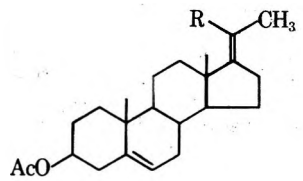


spectrum and the presence of two acetate peaks at δ 2.08 and 2.06 in its nmr spectrum. The absence of a terminal vinylic band in the infrared spectrum ruled out the possibility of the 20-acetate of compound **2a**. Furthermore, the nmr spectrum showed a peak at 1.74, assignable to a methyl group on an unsaturated carbon, which would fit the C-21 methyl in formula **4b**.

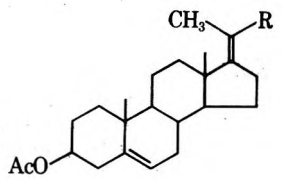
Stereochemistry of 4b. In order to determine the stereochemistry of the 20(22) double bond of **4b**, this compound was first hydrolyzed to the diol **4a** which was then oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone. The C-23 aldehyde **6a** was characterized by a strong infrared band at 1642 cm^{-1}, a uv absorption maximum at 247 nm, and a nmr peak at δ 10.1. The nmr signal of the C-21 methyl protons of **6a** appeared at δ 2.2. This indicated a cis configuration (with respect to the CH_3 and CHO groups) of the 20(22) double bond of **6a** and hence of **4b**. Faulkner[13] has shown that the average position of the nmr signals of the methyl protons of *E* olefins is at δ 2.15, and that of the *Z* olefins at δ 1.96. Recently we[14] have confirmed this stereochemical assignment of **6a** by converting it to the known (*E*)-cholesta-5,20(22)-dien-3β-ol.[5,15]

Structure of Triene 7. The infrared spectrum of norchola-5,17(20),22-trien-3β-ol acetate (**7**) displayed a conjugated diene band at 1580 cm^{-1} and a tetrasubstituted double bond at 1670 cm^{-1}. The uv absorption spectrum of **7** showed a maximum at 240 nm (ϵ 13,000) in agreement with the calculated value of 238 nm.[16]

The *Z* configuration about the 17(20)-double bond was determined by the position of the C-21 methyl peak in the nmr spectrum, as already described[8] for the following pairs:



7a, R = C≡N
b, R = C≡CH
c, R = $COOCH_3$



8a, R = C≡N
b, R = C≡CH
c, R = $COOCH_3$

7a and **8a**, **7b** and **8b**, and **7c** and **8c**. Table II gives the positions of the nmr peaks for the above-mentioned pairs.

Table II

	(*Z*)-7	(*Z*)-7a	(*Z*)-7b	(*Z*)-7c	(*E*)-8a	(*E*)-8b	(*E*)-8c
21-CH_3	1.76[a]	1.8[a]	1.76[a]	1.75[a]	1.92[b]	1.98[b]	1.90[b]

[a] Broad. [b] Triplet, J = 1.5–1.6 Hz.

Experimental Section

Melting points are not corrected. The rotations were measured in chloroform solution and the ultraviolet spectra were recorded on a methanol solution with a Cary spectrophotometer Model 11 MS. Nmr spectra were obtained in deuteriochloroform solution on a 60-MHz Varian Associates DA-60 spectrometer using tetramethylsilane as an internal reference and the positions of the proton signals are expressed in parts per million downfield from tetramethylsilane signals. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

(20*S*)-20-Vinylpregn-5-ene-3β,20-diol 3β-Acetate (2a) from 1. To a cooled and stirred Grignard solution, prepared from 5 g of magnesium turnings and 15 ml of vinyl bromide in 60 ml of tetrahydrofuran, was added dropwise a solution of 15 g of **1** in 100 ml of tetrahydrofuran. The reaction mixture was refluxed overnight, then hydrolyzed with a saturated solution of ammonium chloride. The organic material was extracted with ethyl acetate, which was washed with water, dried over sodium sulfate, and evaporated to yield 13.4 g (89%) of crystalline residue. The infrared spectrum showed an intense hydroxyl peak (3,20-diol) at 3333 cm^{-1} and no absorption in the carbonyl region. The crude reaction product was acetylated with 40 ml of acetic anhydride and 80 ml of pyridine at 23° for 24 hr. The reaction mixture was then poured into a large excess of water. The crystalline precipitate was filtered off, washed with water until all pyridine was removed, and finally dried at 45°. Recrystallization from methanol gave **2a**: mp 163–164°; $[\alpha]^{22}D$ −67° (c 1.10). The ir spectrum showed bands at 3500 (hydroxyl), 1712 and 1250 (acetate), and 916 cm^{-1} (vinyl group); nmr δ 0.86 (18-CH_3), 1.04 (19-CH_3), 1.40 (21-CH_3), 6.05 (22-H) d of d (J_{cis} = 10.5 Hz and J_{trans} = 17.5 Hz), multiplet between 5.5 and 4.8 Hz (3 H, 2 H_{23} + 1 H_6).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.87; H, 10.12.

(20*R*)-20-Vinylpregn-5-ene-3β,20-diol 3β-Acetate (2b) from 1. The mother liquors of **2a** were combined and after chromatography on thick layer plates and several recrystallizations from benzene there was obtained 1.03 g (7%) of **2b**: mp 200–202°; $[\alpha]^{22}D$ −23° (c 0.70). The ir spectrum was very similar to the spectrum of its 20 epimer; nmr δ 0.80 (18-CH_3), 1.04 (19-CH_3), 1.24 (21-CH_3), 6.07 d of d (22-H).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.37; H, 9.99.

Reduction of (20*S*)-20-Ethynylpregn-5-ene-3β,20-diol 3β-Acetate (5) to (20*S*)-20-Vinylpregn-5-ene-3β,20-diol 3β-Acetate (2a). A solution of 500 mg of **5** in 40 ml of ethyl acetate was added to 100 mg of Lindlar catalyst. The mixture was hydrogenat-

ed under 40 psi for 1 hr. The reduction mixture was filtered through Celite and the filtrate concentrated to give **2a**. After recrystallization from methanol the product melted at 163–164°, $[\alpha]^{20}D$ −65° (c 0.35), and was in all respects identical with the material obtained from **1**.

Rearrangement of 2a in Acetic Acid and *p*-Toluenesulfonic Acid at Room Temperature. A solution of 1.3 g of **2a** in 50 ml of glacial acetic acid was gently warmed to effect solution. Then 17 mg of *p*-toluenesulfonic acid was added, and the reaction mixture was stirred at room temperature for 3 days. The solution was poured into 500 ml of cold 2 *N* sodium hydroxide and extracted with ether. The ether extracts were washed with saturated sodium bicarbonate, then water, dried over anhydrous sodium sulfate, and finally evaporated to give a yellow oil. Chromatography on activated alumina (Alcoa F-20) with benzene afforded two products: 256 mg (20% yield) of **3** and 700 mg (53% yield) of **4b**. Recrystallization of the latter from methanol gave pure **4b**: mp 134–135°; $[\alpha]^{20}D$ −52° (c 0.715); the ir spectrum showed bands at 1742 and 1247 (acetate), 805 cm^{-1} (trisubstituted double bond); nmr δ 0.57 (18-CH_3), 1.03 (19-CH_3), 1.74 (21-CH_3), 4.64 d (23-H), 5.40 m (6-H + 22-H).

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.68; H, 9.32.

Compound **3** melted at 124–125°: $[\alpha]^{22}D$ −47° (c 1.60); λ_{max} 228 nm (ϵ 11,500). The ir spectrum showed bands at 1730 and 1250 (acetate), 1590 (conjugated diene), 898 cm^{-1} (terminal vinyl group); nmr δ 0.58 (18-CH_3), 1.04 (19-CH_3), 6.44 (22-H) d of d (J_{trans} = 17.5 Hz, J_{cis} = 11 Hz.

Anal. Calcd for $C_{25}H_{36}O_2$: C, 81.47; H, 9.85. Found: C, 81.45; H, 9.89.

Rearrangement of 2a in Glacial Acetic Acid with a Catalytic Amount of Iodine. A solution of 100 ml of acetic acid, containing 400 mg of **2a** and 8 mg of iodine, was warmed on a steam bath for 30 min. It was then cooled and worked up as described above. Chromatography on a column of neutral alumina (Woelm grade III) gave **3** and **4b** in a ratio of 1:5.

Dehydration of 2a with Phosphorus Oxychloride. To a solution of 400 mg of **2a** in 6 ml of pyridine was added dropwise 13 ml of phosphorus oxychloride in 7 ml of pyridine. The reaction mixture was heated at reflux under nitrogen on a steam bath. After cooling, the solution was poured onto ice and extracted with ether. The ether extracts were combined, washed with 2 *N* aqueous sulfuric acid, sodium bicarbonate solution, water, and finally evaporated to give 100 mg of **3** (25% yield). After recrystallization, the uv exhibited λ_{max} 228 nm (ϵ 11,500).

Formation of 3 from 2a by the Action of Sulfuric Acid in Dioxane. A solution of 480 mg of **2a** in 100 ml of dioxane containing 0.2 ml of sulfuric acid was heated at reflux for 1 hr. After cooling, the solution was extracted with ether. The ether extracts were then washed with sodium bicarbonate and water and finally evaporated. Chromatography on silica gel furnished 345 mg of **3** in a yield of 72%, identical in all respects with a sample obtained previously.

Rearrangement of 2a in Glacial Acetic Acid and *p*-Toluenesulfonic Acid at Steam Bath Temperature. A solution of 3.4 g of **2a** in 120 ml of glacial acetic acid containing 42 mg of *p*-toluenesulfonic acid was refluxed on a steam bath for 15 min. Two products were isolated as described earlier for the rearrangement performed at room temperature. Chromatographic separation on alumina furnished 1.11 g (32% yield) of **4b** and 1.97 g (58% yield) of **7**.

Compound **7**, after recrystallization from methanol, had uv λ_{max} at 240 nm (ϵ 13,000); mp 138–139.5°; $[\alpha]^{20}D$ −62° (c 0.55). The ir spectrum had bands at 1580 (conjugated diene), 910 (vinyl), and 1670 cm^{-1} (tetrasubstituted double bond).

Anal. Calcd for $C_{25}H_{36}O_2$: C, 81.47; H, 9.85. Found: C, 81.46; H, 9.93.

3α,23-Diacetate 4b from 2a by Treatment with Phosphorus Tribromide and Potassium Acetate. To 1 ml of benzene containing 4 drops of phosphorus tribromide was added 340 mg of **2a** in 9 ml of benzene. The reaction was stirred at room temperature overnight, methanol added, the solution washed with sodium bicarbonate and water, and finally the benzene layer was dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was immediately dissolved in 30 ml of redistilled acetone, 1 g of anhydrous potassium acetate was added, and the reaction mixture was refluxed for 5 hr. The potassium salts were filtered and the acetone evaporated *in vacuo*. The residue was dissolved in ether, washed with dilute potassium carbonate and water, and dried over anhydrous sodium sulfate. Finally, the ether extract was evaporated and the crude product upon chromatography on Alcoa F-20 with benzene gave a small amount of an unidentified compound, which is believed to be the 20-vinyl acetate. Continued elution gave the major product, 225 mg (66% yield), which was identified as the 3β,23-diacetate **4b**.

Hydrolysis of 4b. A solution of 400 mg of **4b** in 20 ml of methanolic potassium hydroxide was boiled for 30 min. The solution was then diluted with water and extracted with ethyl acetate. The extract was washed with water to neutrality, dried over sodium sulfate, and evaporated *in vacuo* to give 300 mg of **4a**. Recrystallization from benzene furnished the pure **4a**: mp 197–198°; $[\alpha]^{20}D$ −51° (c 0.9) (lit.[17] gives 159–161°). The ir spectrum showed bands at 3400 and 1650 (allylic alcohol) and at 800 cm^{-1} (trisubstituted double bond); nmr δ 0.58 (18-CH_3), 1.00 (19-CH_3), 1.70 (21-CH_3), 4.17 (d, 2 H_{23}, J = 7 Hz).

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.12; H, 10.30.

Oxidation of 4a to 6a. A solution of 240 mg of the 3β,23-diol **4a** and 300 mg of 2,3-dichloro-5,6-dicyanobenzoquinone in 12 ml of dioxane was allowed to react in the dark at room temperature for 36 hr. The precipitate was collected and washed with dioxane, and the combined filtrate and washings were evaporated to give an oily residue which was chromatographed on neutral alumina (Woelm grade III). The eluates with 5% ethyl acetate in benzene gave 120 mg (50% yield) of the 23-aldehyde **6a**. Recrystallization from methylene chloride–cyclohexane yielded pure **6a**: mp 187–188°; $[\alpha]^{20}D$ −45° (c 0.215); uv absorption λ_{max} 247 nm (ϵ 12,600). The ir spectrum showed bands at 3448 (hydroxyl group) and at 1642 cm^{-1} (conjugated aldehyde); nmr δ 0.63 (18-CH_3), 1.02 (19-CH_3), 2.20 (21-CH_3), 5.4 (6-H), 6.0 (d, 22-H, J = 8 Hz), 10.1 (d, 23-H, J = 8 Hz).

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.52; H, 9.96.

3β-Acetoxy-24-norchola-5,20(22)-dien-23-al (6b)[17] from 6a. The solution of 1.0 g of **6a** in 10 ml of pyridine and 1.2 ml of acetic anhydride was stirred at 25° for 20 hr. The mixture was poured on ice, and the precipitate was filtered, washed with water, and air dried. Recrystallization from acetone gave 981 mg (87%), mp 140–141°.

Anal. Calcd for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 77.98; H, 9.56.

Acknowledgment. This study was supported by U.S. Public Health Service Grant No. AM-03419 from the Institute of Arthritis and Metabolic Diseases, by a contract from the Atomic Energy Commission, AT(11-1)-3026, and by a grant from the National Science Foundation, P3B0006-000. The authors thank Dr. Thomas A. Narwid, Hoffmann-La Roche Inc., for useful discussions.

Registry No.—**1**, 1778-02-5; **2a**, 53139-43-8; **2b**, 53495-20-8; **3**, 53432-00-1; **4a**, 53495-21-9; **4b**, 53432-01-2; **5**, 3091-94-9; **6a**, 53432-02-3; **6b**, 53495-22-0; **7**, 53432-03-4; vinyl bromide, 593-60-2.

References and Notes

(1) Taken, in part, from a dissertation by M. M. L. Lo in partial fulfillment of the requirements for the M.S. Degree in Organic Chemistry, Clark University, Worcester, Mass., 1965.
(2) A. Butenandt and H. Cobler, *Z. Physiol. Chem.*, **234**, 218 (1935).
(3) F. Kohen, R. A. Mallory, and I. Scheer, *J. Org. Chem.*, **36**, 716 (1971).
(4) N. K. Chaudhuri and M. Gut, *J. Amer. Chem. Soc.*, **87**, 3737 (1965).
(5) T. A. Narwid, K. E. Cooney, and M. R. Uskoković, *Helv. Chim. Acta*, **54**, 771 (1974).
(6) For retention of acetate compare ref 5.
(7) N. K. Chaudhuri, J. A. Williams, R. Nickolson, and M. Gut, *J. Org. Chem.*, **34**, 3759 (1969).
(8) F. Sondheimer, N. Danieli, and Y. Mazur, *J. Org. Chem.*, **24**, 1278 (1959).
(9) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).
(10) H. Booker, L. X. Evans, and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940).
(11) H. H. Jaffe and M. Orchin, "Theory and Application of Ultraviolet Spectroscopy," Wiley, New York, N.Y., 1962, pp 196–204.
(12) R. B. Woodward, *J. Amer. Chem. Soc.*, **64**, 72 (1942).
(13) D. J. Faulkner, *Synthesis*, 175 (1971).
(14) Unpublished work from this laboratory.
(15) N. K. Chaudhuri, R. Nickolson, J. G. Williams, and M. Gut, *J. Org. Chem.*, **34**, 3767 (1969).
(16) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).
(17) A. O. Colonna and E. G. Gros, *J. Steroid Biochem.*, **4**, 171 (1973).

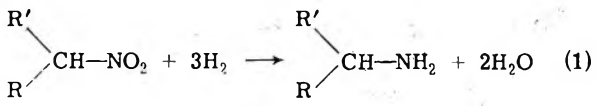
Homogeneous Catalyzed Reduction of Nitro Compounds. III. Synthesis of Aliphatic Amines

John F. Knifton

Beacon Research Laboratories, Texaco Inc., Beacon, New York 12508

Received September 16, 1974

Herein we describe the novel application of homogeneous catalysis to the selective hydrogenation of nitroalkanes to amines (eq 1), in good yields and conversions,



$$\begin{matrix} R' \\ R \end{matrix}\!\!>\!CH\!-\!NO_2 + 3H_2 \longrightarrow \begin{matrix} R' \\ R \end{matrix}\!\!>\!CH\!-\!NH_2 + 2H_2O \quad (1)$$

using a broadly defined class of ligand-stabilized ruthenium complexes. While the aim of this research has been to evaluate homogeneous catalysts for selective RNO_2 reduction,[1] in this work, particular attention has been given to tris(triphenylphosphine)ruthenium(II) chloride as a catalyst precursor, in view of (a) its proved activity for hydrogenation catalysis,[2] (b) its stability in basic media, where the formation of the more reactive nitroalkane anion should be favored,[3] and (c) the previous history of the iron-group metal complexes for catalyzing transformations of the C–NO_2 function.[4]

Nitroalkane hydrogenation catalyzed by solutions of $RuCl_2(PPh_3)_3$ has been demonstrated here in oxygen-free 1:1 benzene–ethanol mixtures (see Table I). Advantages of this technique over existing methods for reducing nitroalkanes *via* homogeneous catalysis[3,4] include the good (up to 88 mol %) yields of alkylamine obtained, with improved catalyst turnover, without the need for stringent reaction conditions or for an aqueous, acidic media which could result in competing Nef-type hydrolysis. In this work, no amine formation was detected in the absence of ruthenium complex; neither does reduction proceed in the absence of hydrogen (expt 6) even though primary alcohols are reportedly good hydrogen donors for the $RuCl_2(PPh_3)_3$ complex.[5] Preferred reaction conditions for the amine synthesis (50–150 atm of H_2, 90–130°, excess alkali) should in fact favor the formation of the intermediate hydrochlorotris(triphenylphosphine)ruthenium(II) complex[2] (eq 2), and this is

$$RuCl_2(PPh_3)_3 + H_2 + B: \rightleftharpoons RuHCl(PPh_3)_3 + B{\cdot}HCl \quad (2)$$

consistent with the observed similar hydrogenation rates for $RuHCl(PPh_3)_3$ and $RuCl_2(PPh_3)_3$ (expt 9 and 10), induction periods prior to hydrogenation with $RuCl_2(PPh_3)_3$, and the spectra of recovered catalyst samples (ν(Ru–H) 2020 cm^{-1}). Basic reaction conditions should also favor deprotonation of the nitroalkane to its anionic form,[3] by shifting the equilibrium of eq 3 further to the right. The

$$RR'CHNO_2 + B: \rightleftharpoons (RR'CNO_2)^- + BH^+ \quad (3)$$

formation of this anion has been confirmed spectroscopically.[1a] Here the effect of added alkali and triethylamine is seen primarily to improve catalyst selectivity and amine yields, rather than to increase the rate of hydrogenation (expt 2, 8, and 9). The addition of pyridine leads to catalyst deactivation,[2] as does the presence of the strongly coordinating CO molecule (expt 7 and 15).

The suggested mechanism for nitroalkane hydrogenation to amine (eq 4–6) contains several points in common with

$$RuHCl(PPh_3)_3 \rightleftharpoons RuHCl(PPh_3)_2 + PPh_3 \quad (4)$$

$$RuHCl(PPh_3)_2 + (RR'CNO_2)^- \longrightarrow RuCl(PPh)_2(RR'CNO) + OH^- \quad (5)$$

$$RuCl(PPh_3)_2(RR'CNO) + 3H_2 \longrightarrow RuHCl(PPh_3)_2 + RR'CHNH_2 + H_2O \quad (6)$$

that proposed earlier for alkene hydrogenation.[6] Initial dissociation of $RuHCl(PPh_3)_3$ to give the *trans*-hydrochlorobis(triphenylphosphine)ruthenium(II) complex[6,7] is consistent with the observed inhibition by excess triphenyl-

Table I
Hydrogenation of Nitrododecane[a,b]

Expt	Complex	Added base	Mole ratio of $C_{12}H_{25}NO_2$:(Ru, Fe):base	H_2 pressure, atm	$C_{12}H_{25}NH_2$ yield,[c] mol %	Rel rate[d]
1	$RuCl_2(PPh_3)_3$	KOH	100:1:200	90	54	
2	$RuCl_2(PPh_3)_3$	KOH	10:1:20	90	88	1–1.5
3	$RuCl_2(PPh_3)_3$	KOH	3:1:6	90	81	
4	$RuCl_2(PPh_3)_3$	KOH	3:1:6	34	59	
5	$RuCl_2(PPh_3)_3$	KOH	3:1:6	1	<5	
6	$RuCl_2(PPh_3)_3$	KOH	10:1:20	0[e]	<1	
7	$RuCl_2(PPh_3)_3$	C_5H_5N	3:1:20	90	33	
8	$RuCl_2(PPh_3)_3$	Et_3N	10:1:20	90	83	0.90
9	$RuCl_2(PPh_3)_3$	None	10:1	90	57	1.00
10	$RuHCl(PPh_3)_3$	None	10:1	90	60	0.95
11	$RuCl_3(AsPh_3)_2$	None	10:1	90	79	2.1
12	$RuCl_2(SbPh_3)_3$	None	10:1	90	77	2.9
13	$RuCl_2(diphos)_2$[g]	None	10:1	90	57	1.1
14	$RuCl_2(PPh_3)_3 + 2PPh_3$	None	10:1	90	1.7	<0.1
15	$RuCl_2(CO)_2(PPh_3)_2$	KOH	10:1:20	90	23	
16	$Ru(CO)_3Cl_2$	KOH	10:1:20	90	67[f]	
17	$Fe(CO)_5$	KOH	1:1:2	90	67[f]	
18	$Fe(CO)_3(PPh_3)_2$	KOH	2:1:4	90	16	

[a] A mixture of isomers 2- through 6-nitrododecanes. [b] Run conditions: 0.001–0.02 *M* Ru, 120°, 1–6 hr. [c] $C_{12}H_{25}NH_2$ yield data refer to maximum dodecylamine yields, based upon nitrododecane charged, for reaction times up to 6 hr. The data were estimated by both ir and glpc techniques. [d] Relative rate data are based upon the maximum observed rates of nitrododecane reduction for each experiment, as determined by glpc, with expt 9 as the base (reference) case. [e] Run under N_2 (68 atm). [f] Extensive precipitation of ruthenium or iron complex. [g] diphos, = $(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$.

phosphine (expt 14) and increasing rate with decreasing ligand strength[8] (expt 9, 11, and 12) in the order PPh_3 < $AsPh_3$ < $SbPh_3$. However, related hydridoruthenium complexes[9] may also be involved here, and recovered catalyst samples often contain ruthenium carbonyl species (ν(C≡O) 1950 cm^{-1}) as a result of ethanol decarbonylation.[6] Samples may also show new maxima at 1580 cm^{-1} assignable to NO_2 vibrations of the coordinated $RR'CNO_2^-$ anion.[10] The dependence of the hydrogenation rate upon applied H_2 pressure and substrate concentration indicates (6) to include the rate-determining step. Deoxygenation of the coordinated nitroalkane anion[1b] (eq 5) might proceed *via* a nitrene-like intermediate,[4] but this seems unlikely in view of the lack of evidence for coupling products. A more detailed examination of C–NO_2 reduction by solubilized ruthenium complexes, embodying both selective and sequential hydrogenation, has been found possible with nitroaromatic substrates.[11]

A variety of ruthenium complexes with π-bonding ligands, capable of forming hydrido species of differing lability, have been screened and found active for hydrogenation of nitroalkanes[12] (expt 9–16). Bis(triphenylphosphine)iron tricarbonyl and iron pentacarbonyl both yielded some amine[4] but were generally less effective and showed lower stability in the alkali media.

Experimental Section

Hydrogenation (prepurified) was purchased from Matheson Co., dichlorotris(triphenylphosphine)ruthenium(II) was supplied by Strem Chemical Co., and other ruthenium complexes were prepared by published methods.[13] Nitrododecane (a mixture of 2 through 6 isomers) was synthesized by liquid–vapor phase nitration of *n*-dodecane.

Synthesis Procedure. A known weight of ruthenium complex (0.1–2 mmol) was dissolved, with stirring, in 100 ml of predried, N_2-saturated, equivolume benzene–ethanol, alkali metal hydroxide was added as required, and the mixture was heated to 120° in a glass-lined pressure reactor. Nitrododecane (1–100 mmol) was injected into the reaction mixture from a side ampoule, and the H_2 pressure was adjusted (1–90 atm). The course of the reduction may be monitored by withdrawing small (1–2 ml), clear liquid samples at regular time intervals and analyzing these by glpc or ir.

On cooling, the product liquid was concentrated under reduced pressure, and the amine product was isolated by solvent extraction. Dodecylamines were identified by ir, nmr, elemental analyses, and comparison with authentic samples.

Acknowledgment. The author thanks Texaco Inc. for permission to publish this paper and T. S. Strother for experimental assistance.

Registry No.—2-Nitrododecane, 53119-34-9; 3-nitrododecane, 53608-64-3; 4-nitrododecane, 53608-65-4; 5-nitrododecane, 53608-66-5; 6-nitrododecane, 53199-35-0; 2-dodecylamine, 13865-46-8; 3-dodecylamine, 53608-67-6; 4-dodecylamine, 19031-73-3; 5-dodecylamine, 53608-68-7; 6-dodecylamine, 53608-69-8; $RuCl_2(PPh_3)_3$, 15529-49-4; $RuHCl(PPh_3)_3$, 19631-00-6; $RuCl_3(AsPh_3)_2$, 41685-48-7; $RuCl_2(SbPh_3)_3$, 15709-80-5; $RuCl_2$(diphos)$_2$, 53608-63-2; $RuCl_2(CO)_2(PPh_3)_2$, 14564-35-3; $[Ru(CO)_3Cl_2]_2$, 22594-69-0; $Fe(CO)_5$, 13463-40-6; $Fe(CO)_3(PPh_3)_2$, 21255-52-7.

References and Notes

(1) Parts I and II: (a) J. F. Knifton, *J. Org. Chem.*, **38**, 3296 (1973); (b) J. F. Knifton, *J. Catal.*, **33**, 289 (1974).
(2) P. S. Hallman, B. R. McGarvey, and G. Wilkinson, *J. Chem. Soc. A*, 3143 (1968).
(3) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N.Y., 1966, Chapter 14.
(4) See for example (a) F. L'Eplattenier, P. Matthys, and F. Calderazzo, *Inorg. Chem.*, **9**, 342 (1970); (b) J. E. Kmiecik, *J. Org. Chem.*, **30**, 2014 (1965); (c) H. Alper, *Inorg. Chem.*, **11**, 976 (1972).
(5) Y. Sasson and J. Blum, *Tetrahedron Lett.*, 2167 (1971).
(6) B. R. James, *Inorg. Chim. Acta, Rev.*, **4**, 73 (1970).
(7) B. R. James and L. D. Markham, *Inorg. Chem.*, **13**, 97 (1974).
(8) G. Hendrici-Olive and S. Olive, *Angew. Chem., Int. Ed. Engl.*, **10**, 105 (1971).
(9) T. Ito, S. Kitazume, A. Yamamoto, and S. Ikeda, *J. Amer. Chem. Soc.*, **92**, 3011 (1970).
(10) A. G. Lee, *Spectrochim. Acta, Part A*, **28**, 133 (1972).
(11) J. F. Knifton and R. M. Suggitt, French Patent 2,127,970 (1972).
(12) J. F. Knifton, U.S. Patent 3,766,271 (1973).
(13) T. A. Stephenson and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **28**, 945 (1966).

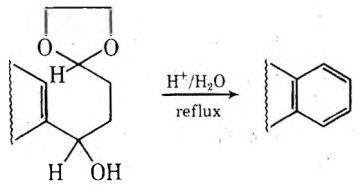
A Short Route to Functionalized Naphthalenes

Hubert J. J. Loozen

Department of Organic Chemistry, Eindhoven University of Technology, Eindhoven, The Netherlands

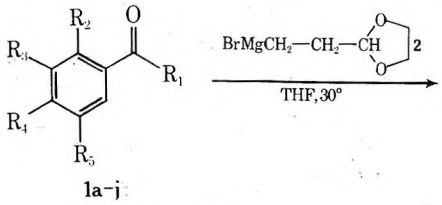
Received September 20, 1974

In recent work the synthesis of benzothiophenes and benzimidazoles from thiophenes and imidazoles, respectively, was presented.[1,2] Typical was the introduction of a suitably functionalized four-carbon atom fragment on the heterocyclic system, followed by acid-catalyzed formation of the benzene moiety as indicated below. This type of

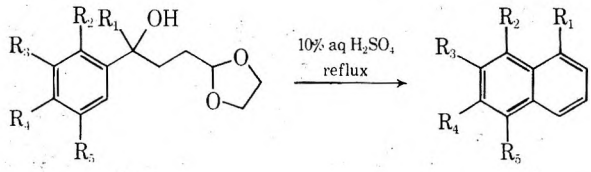


reaction seemed to be extendible to ring systems which are susceptible toward electrophilic substitution reactions.

This approach applied in the synthesis of naphthalenes proved to be successful. Reaction of the strongly activated 3,4,5-trimethoxybenzaldehyde (**1a**) with Grignard derivative **2**[3] gave alcohol **3a**, which upon treatment with refluxing 10% aqueous sulfuric acid for 1 hr afforded 2,3,4-trimethoxynaphthalene (**4a**) nearly quantitatively.[4]



1a–j



3a–j **4a–j**

In the same way products **4b–f** were obtained in excellent yields. Naphthols **4g** and **h** could be obtained under the same conditions on allowing hydroxybenzaldehydes **1g** and **h** to react with 2 equiv of **2** and following this with cyclization. Formation of the less activated products **3i** and **j** leading to 2-methylnaphthalene and naphthalene required prolonged reaction times (6 and 16 hr, respectively). It should be mentioned that in the cases where cyclization could take place at two different positions (**3c, 3e, 3f, 3h,** and **3i**) more than 90% regiospecificity was observed, leading to the least hindered products.

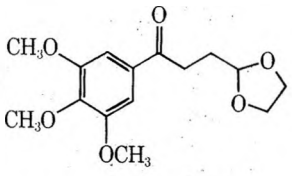
A particular case is presented by the synthesis of naphthol **6**. Treatment of **3a** with manganese dioxide[5] in refluxing benzene gave ketone **5**. Under the assumption that the deactivation of the keto group on the benzene ring was

Table I
Naphthalenes

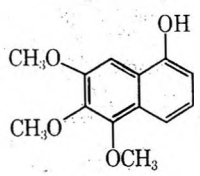
Compd	Yield, %	Mp, °C	Bp, °C	Empirical Formula
4a[a]	95		154–156 (5)	$C_{13}H_{14}O_3$
4b[b]	75	115–118		$C_{12}H_{12}O_2$
4c[c]	84	69–70		$C_{11}H_{10}O$
4d[d]	62		128–132 (1)	$C_{12}H_{12}O_2$
4e[e]	91	95–97		$C_{11}H_8O_2$
4f[f]	84			$C_{12}H_{12}O$
4g[g]	54	48–51		$C_{11}H_{10}O_2$
4h[h]	52	118–120		$C_{10}H_8O$
4i[i]	84		115–120 (1)	$C_{11}H_{10}$
4j[j]	31	78–80		$C_{10}H_8$
6[k]	30	92–95	175–185 (0.05)	$C_{13}H_{14}O_4$

[a] A. Ueno and S. Fukushima, *Chem. Pharm. Bull.*, **14**, 129 (1966). [b] Ng. Buu-Hoi and D. Lavit, *J. Org. Chem.*, **21**, 21 (1956). [c] G. A. Baramki, H. S. Chang, and J. T. Edward, *Can. J. Chem.*, **40**, 441 (1962). [d] R. Heck and C. Ellinger, *J. Amer. Chem. Soc.*, **79**, 3105 (1957). [e] W. Bonthrone and J. W. Conforth, *J. Chem. Soc. C*, 1202 (1969). [f] P. C. Mitter and D. E. Shyamakanta, *J. Indian. Chem. Soc.*, **16**, 35 (1939). [g] H. S. Chang and J. T. Edward, *Can. J. Chem.*, **41**, 1233 (1963). [h] L. Schaeffer, *Ann.*, **152**, 279 (1869). [i] K. E. Schulze, *Ber.*, **17**, 842 (1884). [j] R. Schiff, *Ann.*, **223**, 247 (1884). [k] *Anal.* Calcd for $C_{13}H_{14}O_4$: C, 66.67; H, 5.98. Found: C, 66.82; H, 5.92.

compensated by the methoxy groups, compound **5** in 10% sulfuric acid was converted to naphthol **6** in moderate



5



6

a, $R_1 = R_2 = H$; $R_3 = R_4 = R_5 = OCH_3$
b, $R_1 = R_2 = R_5 = H$; $R_3 = R_4 = OCH_3$
c, $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OCH_3$
d, $R_1 = R_2 = R_4 = H$; $R_3 = R_5 = OCH_3$
e, $R_1 = R_2 = R_5 = H$; $R_3, R_4 = O\text{-}CH_2\text{-}O$
f, $R_1 = CH_3$; $R_2 = R_4 = R_5 = H$; $R_3 = OCH_3$
g, $R_1 = R_4 = R_5 = H$; $R_2 = OH$; $R_3 = OCH_3$
h, $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OH$
i, $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = CH_3$
j, $R_1 = R_2 = R_3 = R_4 = R_5 = H$

yield. The results are summarized in Table I. Attempts made in our laboratories to achieve a facile entry into indoles and benzofurans in this particular way failed because of the instability of the pyrrole and furan ring under the cyclization conditions.

Experimental Section

General. Melting points were determined on a Mettler apparatus and are uncorrected. Nmr data were consistent with the assigned structures (Varian T-60, TMS as an internal standard). The intermediates were characterized by means of nmr and converted as is to the products offered in Table I. All starting materials were commercially available. Grignard derivative **2** was prepared according to a known procedure.[3] The preparation of the naphthalenes is illustrated by the synthesis of **4a**.

1-(1,3-Dioxolan-2-yl)-3-hydroxy-3-(3,4,5-trimethoxyphenyl)propane (3a). To a solution of **2**, prepared from 1.6 g (0.065 g-atom) of magnesium and 12.3 g (0.065 mol) of 2-(2-bromoethyl)-1,3-dioxolane in 50 ml of THF, was added dropwise with stirring a solution of 8.5 g (0.045 mol) of 3,4,5-trimethoxybenzaldehyde (**1a**) in 20 ml of THF. After additional stirring for 4 hr the reaction mixture was poured in 500 ml of a 10% NH_4Cl solution and extracted twice with $CHCl_3$. Washing, drying, and evaporation of the organic phase left a viscous oil, which upon treatment with $(i\text{-}Pr)_2O$ afforded 10.6 g of **3a** as a solid; mp [benzene–petroleum ether] 86–87°. *Anal.* Calcd for $C_{15}H_{22}O_6$: C, 60.40; H, 7.38. Found: C, 60.44; H, 7.57. Nmr ($CDCl_3$) δ 1.75 (m, 4, $-CH_2CH_2-$), 3.24 (s, 1, OH), 4.57 (m, 1, ArC*H*(OH)), 4.84 (m, 1, -OCH(R)O-), 6.60 (s, 2, Ar*H*).

1-(1,3-Dioxolan-2-yl)-3-oxo-3-(3,4,5-trimethoxyphenyl)-propane (5). To a solution of 5 g (0.017 mol) of **3a** in 75 ml of benzene was added 20 g of MnO_2. The mixture was refluxed with stirring for 2 hr. Filtration of the reaction mixture and evaporation of the solvent left 4.2 g (87%) of **5** as a white crystalline solid; mp 57–59° [$(i\text{-}Pr_2)O$–petroleum ether]. *Anal.* Calcd for $C_{15}H_{20}O_6$: C, 60.81; H, 6.76. Found: C, 60.83; H, 6.93. Nmr ($CDCl_3$) δ 2.14 (m, 2, $ArCOCH_2$), 3.01 (m, 2, $ArCOCH_2CH_2$), 4.49 (t, 1, OC(R)*H*O), 7.22 (s, 2, Ar*H*).

1,2,3-Trimethoxynaphthalene (4a). A solution of 5.96 g (0.02 mol) of **3a** in 10 ml of methanol was added in 5 min to 100 ml of stirred refluxing 10% sulfuric acid. After 1 hr the reaction mixture was cooled and extracted twice with $CHCl_3$. Washing with 5% $NaHCO_3$ solution, drying, and evaporating of the solvent left an oil, which upon distillation yielded 4.0 g (95%) of **4a**; bp 154–156° (5).

Registry No.—**1a**, 86-81-7; **1b**, 120-14-9; **1c**, 591-31-1; **1d**, 7311-34-4; **1e**, 120-57-0; **1f**, 586-37-8; **1g**, 148-53-8; **1h**, 100-83-4; **1i**, 620-23-5; **1j**, 100-52-7; **3a**, 53579-08-3; **3b**, 53597-09-4; **3c**, 53597-10-7; **3d**, 53597-11-8; **3e**, 53597-12-9; **3f**, 53597-13-0; **3g**, 53597-14-1; **3h**, 53597-15-2; **3i**, 53597-16-3; **3j**, 53597-17-4; **4a**, 5892-02-4; **4b**, 10103-06-7; **4c**, 95-04-9; **4d**, 10075-61-3; **4e**, 269-43-2; **4f**, 2825-01-6; **4g**, 1888-41-1; **4h**, 135-19-3; **4i**, 91-57-6; **4j**, 91-20-3; **5**, 53597-18-5; **6**, 53597-19-6; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4.

References and Notes

(1) H. J. J. Loozen and E. F. Godefroi, *J. Org. Chem.*, **38**, 1056 (1973).
(2) H. J. J. Loozen and E. F. Godefroi, *J. Org. Chem.*, **38**, 3495 (1973).
(3) G. Büchi and H. Wüest, *J. Org. Chem.*, **34**, 1121 (1949).
(4) For a review concerning naphthalenes, see "Chemistry of Carbon Compounds," Part IIIB, Elsevier, Amsterdam, 1956, p 1273.
(5) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

Synthesis of Prostaglandins Containing the Sulfo Group

Y. Iguchi, S. Kori, and M. Hayashi*

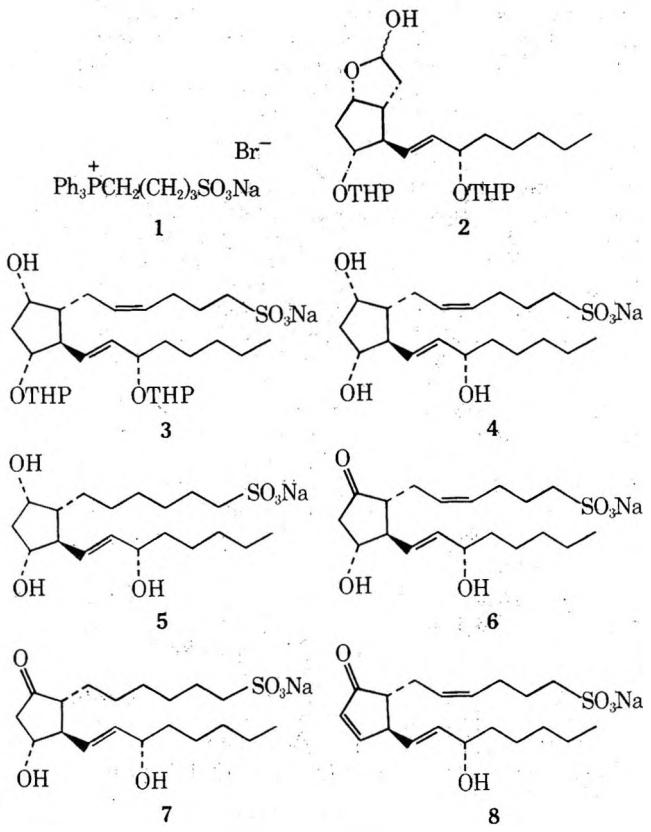
Research Institute, ONO Pharmaceutical Co., Ltd., Osaka, Japan

Received August 15, 1974

It is a matter of interest to evaluate the biological and pharmacological activities of prostaglandin analogs containing the sulfo group in place of the carboxy function (C-1). We now report the synthesis of prostaglandin sulfonic acids by the Wittig reaction with a phosphorous ylide having the sulfo group.

(4-Sodium sulfonato-*n*-butyl)triphenylphosphonium bromide (**1**) was obtained as colorless crystals, mp 268–270°, from sodium 4-bromo-*n*-butanesulfonate and triphenylphosphine in *N,N*-dimethylformamide on heating. Reaction of the corresponding ylide, prepared from **1** and a solution of sodium methylsulfinyl carbanide in dimethyl sulfoxide, with 2-oxa-3-hydroxy-6-*syn*-(3α-tetrahydropyranyloxy-1-*trans*-octenyl)-7-*anti*-tetrahydropyranyloxy-*cis*-bicyclo[3.3.0]octane[1] (**2**), an intermediate for the Corey synthesis of prostaglandins, in dimethyl sulfoxide at 30° for 3 hr afforded the sulfonic acid **3** as yellow-brown crystals in 48% yield.

According to the procedures of Corey[1,2] and Pike,[3] the sulfonic acid **3** was converted to the corresponding $F_{2\alpha}$ (**4**), $F_{1\alpha}$ (**5**), E_2 (**6**), E_1 (**7**) and A_2 (**8**).



Experimental Section

Preparation of (4-Sodium sulfonato-*n*-butyl)triphenylphosphonium Bromide (1). Sodium 4-bromo-*n*-butanesulfonate (23 g)[4] and triphenylphosphine (85 g) were dissolved in DMF (400 ml) and a solution was heated at 125° with stirring for 10 hr; the solvent was removed by distillation and the residue was washed with ether.

The residue was chromatographed on silica gel using CH_2Cl_2–MeOH (6:1) as eluent to give 1 as colorless crystals (27 g): ir (KBr tablet) ν 1210, 1180, 1038 cm^{-1}; nmr (D_2O) δ 8.02–7.35 (15 H, m), 3.60–3.10 (2 H, m), 3.25–2.80 (2 H, t), 2.42–1.60 (4 H, m).

Preparation of Sodium 6-[2β-{3α-(2-Tetrahydropyranyloxy)-1-*trans*-octenyl}-3α-(2-tetrahydropyranyloxy)-5α-hydroxycyclopent-1α-yl]-4-*cis*-hexenylsulfonate (3). Phosphonium salt (1) (10.8 g), which had been dried under reduced pressure at 100°, was dissolved in dimethyl sulfoxide (50 ml) and the solution was added at ambient temperature to sodiomethyl–sulfinylcarbanide which had been prepared from sodium hydride (1.71 g, content 63.9%) in dimethyl sulfoxide (20 ml) at 70° under nitrogen. After the addition was over, the yellow-red reaction mixture was stirred for 5 min and a solution of 1 (4.00 g) in dimethyl sulfoxide (20 ml) was added and the mixture was stirred at 30° for 3 hr. The bright red reaction mixture was diluted with ice water (500 ml), saturated with sodium chloride, and extracted with ethyl acetate–ether (1:1). The organic layer was washed with brine, dried, and concentrated *in vacuo*. The residue was submitted to column chromatography using methylene chloride–methanol (4:1) as eluent to give 3 (2.44 g, 48% yield) as pale yellow crystals: mp 178–180°; nmr ($CDCl_3$) δ 5.72–5.18 (4 H, m), 4.30–3.70 (4 H, m), 3.70–3.28 (4 H, m), 3.12–2.75 (2 H, m), 1.0–0.73 (3 H, t), 4.82–4.56 (2 H, m); ir (KBr tablet) ν 1200, 1185, 1038, 1023 cm^{-1}; homogeneous by tlc (methylene chloride–methanol 5:1, R_f 0.43).

Preparation of Sodium 6-[2β-{3α-(2-Tetrahydropyranyloxy)-1-*trans*-octenyl}-3α-(2-tetrahydropyranyloxy)-5α-hydroxycyclopent-1α-yl]hexanesulfonate. A solution of 3 (1.08 g) in methanol (60 ml) was reduced under hydrogen atmosphere (1 atm) using 5% palladium on carbon (170 mg) as a catalyst at ambient temperature for 2 hr. Concentration *in vacuo* gave sodium 6-[2β-{3α-(2-tetrahydropyranyloxy)-1-*trans*-octenyl}-3α-(2-tetrahydropyranyloxy)-5α-hydroxycyclopent-1α-yl]hexanesulfonate (913 mg).

Preparation of Sodium 6-{2β-(3α-Hydroxy-1-*trans*-octenyl)-3α,5α-dihydroxycyclopent-1α-yl}-4-*cis*-hexenesulfonate (4). To a solution of 3 (312 mg) in methanol (5 ml) was added several drops trifluoroacetic acid. The mixture was stirred at 19° for 30 min and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel using methylene chloride–methanol (4:1) as eluent to give 4 (84 mg) as colorless crystals: mp 122–125°; nmr (CD_3OD) δ 5.68–5.28 (4 H, m), 4.31–3.72 (3 H, m), 2.95–2.68 (2 H, m), 1.03–0.77 (3 H, t).

Preparation of Sodium 6-{2β-(3α-Hydroxy-1-*trans*-octenyl)-3α,5α-dihydroxycyclopent-1α-yl}hexanesulfonate (5). Using the experimental conditions described as above, sodium 6-[2β-{3α-(2-tetrahydropyranyloxy)-1-*trans*-octenyl}-3α-(2-tetrahydropyranyloxy)-5α-hydroxycyclopent-1α-yl]hexanesulfonate (283 mg) gave sodium 6-{2β-(3α-hydroxy-1-*trans*-octenyl)-3α,5α-dihydroxycyclopent-1α-yl}hexanesulfonate (59 mg) as a colorless powder: mp 182–183°; ir (KBr tablet) ν 1190, 1060 cm^{-1}; nmr (CD_3OD) δ 5.71–5.39 (2 H, m), 4.28–3.74 (3 H, m), 2.97–2.67 (2 H, m), 1.01–0.75 (3 H, t).

Preparation of Sodium 6-{2β-(3α-Hydroxy-1-*trans*-octenyl)-3α-hydroxy-5-oxocyclopent-1α-yl}-4-*cis*-hexenesulfonate (6). To a solution of sodium 6-[2β-{3α-(2-tetrahydropyranyloxy)-1-*trans*-octenyl}-3α-(2-tetrahydropyranyloxy)-5α-hydroxycyclopent-1α-yl]-4-*cis*-hexenesulfonate (766 mg) in acetone (33 ml) was added Jones reagent (1.8 ml) (prepared by dissolving chromium trioxide (2.67 g) and sulfuric acid (2.3 ml) in water and making up the total volume with water to 10 ml) at −20°, and the solution was stirred at −20 to −15° for 4 hr. 2-Propanol was added to the reaction mixture and the resulting mixture was diluted with brine and the product was extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated *in vacuo*. The residue (628 mg) in methanol (5 ml) was treated with 1 *N* hydrochloric acid (0.3 ml) and the mixture was stirred at 27° for 1.5 hr and neutralized with sodium bicarbonate. Concentration *in vacuo* at a low temperature and subjection of the residue to column chromatography on silica gel using methylene chloride–methanol (4:1) as eluent gave sodium 6-{2β-(3α-hydroxy-1-*trans*-octenyl)-3α-hydroxy-5-oxocyclopent-1α-yl}-4-*cis*-hexenesulfonate (204 mg): mp 83–84°; nmr (CD_3OD) δ 5.58–5.27 (4 H, m), 4.13–3.67 (2 H, m), 2.96–2.55 (3 H, m), 1.03–0.67 (3 H, t); homogeneous by tlc (CH_2Cl_2–MeOH 3:1, R_f 0.19).

Preparation of Sodium 6-{2β-(3α-hydroxy-1-*trans*-octenyl)-3α-hydroxy-5-oxocyclopent-1α-yl}hexanesulfonate (7). To a solution of sodium 6-{2β-(3α-hydroxy-1-*trans*-octenyl)-3α-hydroxy-5-oxocyclopent-1α-yl}hexanesulfonate (592 mg) in acetone (81 ml) at −20° was added Jones reagent (prepared as described in above example) (1.5 ml) dropwise, and the mixture was stirred at −20 to −15° for 3.5 hr. 2-Propanol was added to the reaction mixture and the resulting mixture was diluted with brine and the product was extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated under reduced pressure. The residue (497 mg) was dissolved in methanol (6 ml), treated with 1 *N* hydrochloric acid (0.36 ml), and stirred at 27° for 1.5 hr and neutralized with sodium bicarbonate. Concentration *in vacuo* at a low temperature and subjection of the residue to column chromatography on silica gel using methylene chloride–methanol (4:1) as eluent gave sodium 6-{2β-(3α-hydroxy-1-*trans*-octenyl)-3α-hydroxy-5-oxocyclopent-1α-yl}hexanesulfonate (173 mg): nmr (CD_3OD) δ 5.69–5.38 (2 H, m), 4.25–3.74 (2 H, m), 2.94–2.56 (3 H, m), 1.03–0.77 (3 H, t).

Preparation of Sodium 6-{2β-(3α-hydroxy-1-trans-octenyl)-5-oxo-3-cyclopenten-1α-yl}-4-*cis*-hexenesulfonate (8). A solution of 5 (64 mg) in 90% aqueous acetic acid (5 ml) was stirred at 55–60° for 16 hr. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate and washed with brine, and the organic layer was concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel using methylene chloride–methanol (5:1) as eluent to give sodium 6-{2β-(3α-hydroxy-1-*trans*-octenyl)-5-oxo-3-cyclopenten-1α-yl}-4-*cis*-hexenesulfonate (42 mg) as a solid: mp 80–81°; nmr ($CDCl_3$) δ 7.68–7.52 (1 H, q), 6.30–6.12 (1 H, q), 5.75–5.52 (2 H, m), 5.52–5.25 (2 H, m), 4.27–3.96 (1 H, m), 3.43–3.18 (1 H, m), 2.97–2.71 (2 H, m), 1.02–0.75 (3 H, t).

Registry No.—1, 53535-01-6; 3, 53535-02-7; 4, 53535-03-8; 5, 53535-04-9; 6, 53535-05-0; 7, 53535-06-1; 8, 53535-07-2; sodium 4-bromo-*n*-butanesulfonate, 53535-08-3; triphenylphosphine, 603-35-0; sodium 6-[2β-{3α-(2-tetrahydropyranyloxy)-1-*trans*-octenyl}-3α-(2-tetrahydropyranyloxy)-5α-hydroxycyclopent-1α-yl]hexanesulfonate, 53535-09-4.

References and Notes

(1) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

(2) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).
(3) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).
(4) J. H. Helberger and G. Manecke, German Patent 895,559.

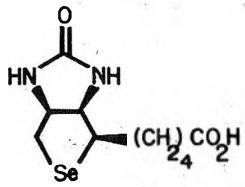
Preparation of *cis*-3,4-Ureyleneselenophane[1]

R. L. Martin and B. E. Norcross*

Department of Chemistry, State University of New York at Binghamton, Binghamton, New York 13901

Received September 3, 1974

In connection with our continuing study of the synthesis of selenobiotin we have prepared the parent fused biheterocyclic system **10**. Effective synthetic entry is based on ring closure with divalent selenium after the cis, vicinal, azide functions, precursors of the needed amine groups, are positioned in a cis relationship on **7**. Approaches utilizing 3,4-disubstituted selenophanes or varied derivatives of *meso*-erythritol other than **4** failed to produce the desired diazidoselenophane (**8**) or diaminoselenophane (**9**), and are the subject of a future communication.



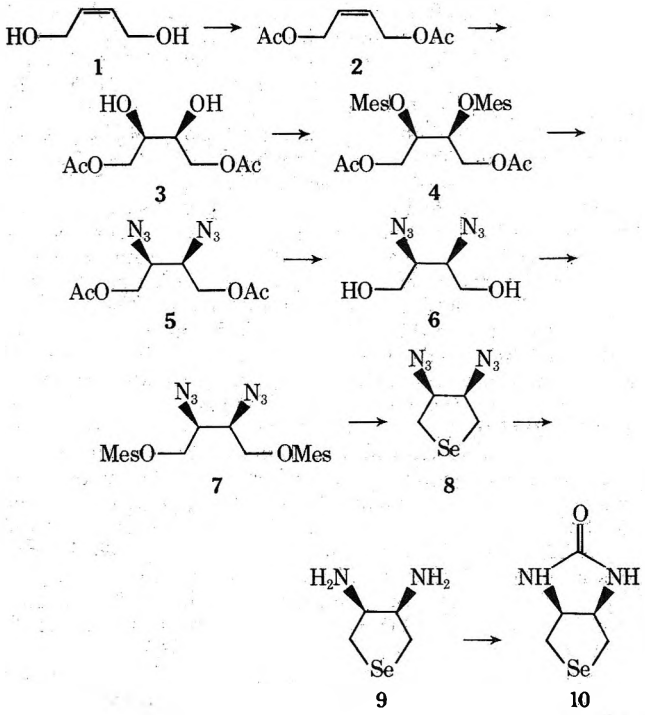
Selenobiotin

Proof of structure for the diazide **6** was realized by near-quantitative conversion to the known *meso*-2,3-diaminobutane-1,4-diol dihydrobromide[2] and dihydrochloride, by catalytic reduction and treatment with hydrogen halide.

This conversion further establishes the cis stereochemistry of the synthetic intermediates, and of the final product, since this cis arrangement of the nitrogen function is not affected by subsequent reactions. Supporting evidence for this cis, meso sterochemistry is found in the nmr spectra, which present complex multiplets resulting from the six-spin AA′BB′CC′ system, the analyses of which are beyond the scope of this report. For instance, the spectra of the noncyclic meso compounds resemble that of meso-1,2,3,4-tetrachlorobutane, rather than *d*-1,2,3,4-tetrachlorobutane,[3] while the nmr spectra of the monocyclic compounds, and *cis*-3,4-ureyleneselenophane, are consistent with that reported for the similar system: *cis*-tetrahydro-2,2-dimethylthieno[3,4-*d*]-1,3-dioxole (the acetone ketal of *cis*-3,4-dihydroxythiophane).[4]

Of the vicinal diazides subsequently described, *meso*-2,3-diazidobutane-1,4-diol (**6**) slowly polymerizes on standing to an unidentified acetone-insoluble substance; in addition, the monomer is initially obtained as a supercooled liquid with such a high heat of fusion that efficient cooling is required at the onset of solidification to avoid detonation. The unexpected stability of some of the diazides was demonstrated by their melting point behavior: the acetate and methanesulfonate diesters, **5** and **7**, give sharp, reproducible melting points, and initially melt in an open flame before deflagrating mildly; under identical conditions, the liquid heterocyclic diazide **8** detonates violently. Most reactions outlined in Scheme I are easily performed within a relatively short period of time under reasonably mild conditions.

Scheme I[a,b]



[a] Compounds **5–10** are previously unreported. [b] For all new compounds, except **6** and **8**, analytically pure samples were obtained which gave either satisfactory elemental analyses or mass spectra consistent with the structure indicated.

Evaluation of the biological activity of **10** is underway, and will be separately reported.

Experimental Section

All temperature readings were uncorrected. Ir spectra were determined on a Perkin-Elmer Model 457 spectrophotometer. Nmr spectra were recorded on a Varian A-60 or HA-100D spectrophotometer. Mass spectra were determined at Cornell University, Ithaca, N.Y. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, N.Y. Sodium selenide was purchased from Alfa Inorganics, Inc., Beverly, Mass.; *cis*-2-butene-1,4-diol was obtained from GAF Corp., Inc., Binghamton, N.Y. Those melting points taken in sealed evacuated capillaries are designated (SEC).

The diacetate **2** and the diol **3** were prepared according to literature procedures.[5]

***meso*-1,4-Di-*O*-acetyl-2,3-di-*O*-(methylsulfonyl)erythritol (4).** A solution of **3** (28.4 g; 0.140 mol) in pyridine (100 ml) is stirred at 0° and treated dropwise with methanesulfonyl chloride (34.4 g, 0.300 mol) over a 0.5-hr period. Stirring is continued 4 hr, and the mixture is then poured into 1 l. of ice water. The crystalline product which separates is collected by suction filtration, washed with several portions of cold water, and air dried to give 50.5 g (99.5%) of **4**: mp 138–140° (SEC) (lit.[7] mp 140–141°).

***meso*-1,4-Diacetyloxy-2,3-diazidobutane (5).** A solution of **4** (36.2 g, 0.100 mol) in DMSO (500 ml) is stirred and warmed to 60° in an oil bath. Finely powdered sodium azide (14.3 g, 0.220 mol) is added portionwise until solution is complete. The solution is then maintained at 90–100° for 24 hr before cooling to room temperature. The solution is poured into 1 l. of ice water. After addition of saturated sodium chloride solution (500 ml), the crystalline product is collected by suction filtration, washed with several portions of cold water, and air dried to give 24.7 g (96%) of **5**: mp (and remelt) 108.5–109.0° (SEC) (CCl_4); ir (KBr) 2180, 2120, 1730, 1320, 1240 cm^{-1}; nmr (pyridine) δ 2.04 (s, 6 H, CH_3), 4.12 (m, 2 H, CH), 4.52 (m, 4 H, CH_2).

Anal. Calcd for $C_8H_{12}N_6O_4$: C, 37.37; H, 5.02; N, 32.70. Found: C, 37.30; H, 4.68; N, 32.90.

***meso*-2,3-Diazidobutane-1,4-diol (6).** A solution of **5** (14.8 g, 0.058 mol) in 0.01% methanolic potassium hydroxide (200 ml) is stirred overnight in an open vessel. Removal of solvent and methyl acetate under reduced pressure and at room temperature produces a pale yellow, slightly opaque oil which is immediately redissolved

in methanol (100 ml). Treatment with charcoal (0.5 g), filtration, and solvent removal from the filtrate produce a clear, colorless oil which crystallizes exothermically (*caution:* vigorous cooling must be employed to avoid detonation) to give 10.0 g (99%) of **6**: mp (crude) 67–68° (SEC); ir (KBr) 3300, 2150, 2100, 1315, 1270, 1070 cm^{-1}; nmr (D_2O) δ 3.98 (m, 2 H, CH), 4.13 (m, 4 H, CH_2).

meso-**2,3-Diaminobutane-1,4-diol.** A solution of **6** (7.4 g; 0.043 mol) in methanol (200 ml) containing 5% Pd/C catalyst (1.0 g) is shaken overnight under hydrogen (125 psi). The catalyst is removed by filtration, and the filtrate is stripped of solvent to give 5.2 g (100%) of the diaminediol, mp 126–127°. A solution of this compound (1.2 g, 0.010 mol) in acetone (50 ml) treated with 40% HBr (5 ml), produces a crystalline precipitate, which was collected by suction filtration, washed with several portions of acetone and air dried to give 2.4 g (85%) of the dihydrobromide: mp 212–213° (SEC) (lit.[2] mp 214–215°). A similar solution of the diaminediol treated with concentrated HCl (3 ml) gives, upon identical workup, 1.8 g (93%) of the dihydrochloride: mp 240–242° (SEC) (lit.[2] mp 241.5–242.5°).

meso-**2,3-Diazido-1,4-dimesyloxybutane** (**7**). A solution of **6** (11.2 g; 0.065 mol) in pyridine (100 ml) is stirred at 0° and treated dropwise with methanesulfonyl chloride (16.4 g, 0.143 mol) over a 0.5-hr period. Stirring is continued 4 hr, and the mixture is then poured into 1.3 l. of ice water. The crystalline product which separates is collected by suction filtration, washed with several portions of cold water, and air dried to give 20.2 g (95%) of **7**: mp (and remelt) 92.0–92.5° (SEC) (EtOH); ir (KBr) 2125, 1360, 1290, 1175, 930, 820 cm^{-1}; nmr (acetone-d_6) δ 3.27 (s, 6 H, CH_3), 4.24 (m, 2 H, CH), 4.63 (m, 4 H, CH_2).

Anal. Calcd for $C_6H_{12}N_6O_6S_2$: C, 21.90; H, 3.92; N, 25.53; S, 19.48. Found: C, 22.20; H, 3.72; N, 25.15; S. 19.85.

cis-**3,4-Diazidoselenophane** (**8**). Sodium selenide (10.0 g; 0.080 mol) is added portionwise to a stirred, degassed solution of **7** (19.7 g, 0.60 mol) in dimethyl sulfoxide (300 ml) under a nitrogen blanket. The reaction exotherm causes the temperature to rise to 45–50°. After stirring overnight, the mixture is poured into ice water (1.5 l.) and extracted with ethyl ether (4 × 400 ml). The ether extracts are combined, washed with water (4 × 500 ml) and saturated sodium chloride solution (2 × 200 ml), and dried ($MgSO_4$). After filtration the yellow ethereal solution is stripped of solvent to produce a yellow-orange oil. The liquid is dissolved in methanol (50 ml) and eluted (MeOH) from a 1-in. diameter column packed with neutral alumina (100 g). The eluent is stripped of solvent to yield a mobile yellow liquid with a marked offensive odor. The liquid is redissolved in methanol (50 ml), serially treated with charcoal (1.5 g), and filtered until a clear, colorless solution is obtained. This solution is stripped of solvent to give 6.2 (48%) of **8** as a colorless, mobile liquid, homogeneous by tlc: ir (neat) 2110, 1335, 1265 cm^{-1}; nmr (CCl_4) δ 3.00 (m, 4 H, CH_2), 412 (m, 2 H, CH).

cis-**3,4-Diaminoselenophane** (**9**). A solution of **8** (6.2 g, 28.6 mol) in methanol (100 ml) containing Adams catalyst (0.5 g) is shaken overnight under hydrogen (125 psi). The catalyst is removed by filtration, and the filtrate is stripped of solvent to give 4.6 g (98%) of **9** as a colorless mobile liquid which readily absorbs carbon dioxide from the atmosphere. The diamine **9** is characterized as the dihydrochloride salt: mp 289–290° dec (SEC) (20% aqueous acetone); ir (KBr) 3100–2800, 1490 cm^{-1}; nmr (D_2O) δ 3.22 (m, 4 H, CH_2), 4.33 (m, 2 H, CH). Mass spectrum of the dihydrochloride gave a peak characteristic only of monoprotonated diamine **9** (70 eV), *m/e* 167 [$(M + 1)^+$].

cis-**3,4-Ureyleneselenophane** (**10**). A solution of **9** (3.3 g, 0.020 mol) in benzene (50 ml) is treated with a 12.5% solution of phosgene (3.0 g, 0.030 mol) in benzene (24 ml) followed by pyridine (50 ml). After a 3-hr reflux, an additional 9 ml of phosgene solution (1.0 g; 0.010 mol) is added, and reflux is continued overnight. After removal of solvents under vacuum, water (200 ml) is added to the particulate residue, and the resulting slurry is vigorously stirred 0.5 hr. The solids are collected by suction filtration, washed with several portions of water, and air dried to give 2.0 g (53%) of **10**: mp 256–258° (SEC) (EtOH); 53%; ir (KBr) 3200, 1690, 1260 cm^{-1}; mass spectrum (70 eV) *m/e* 191 (M^+); nmr (DMSO-d_6) δ 3.2 (m, 4 H, CH_2), 4.64 (m, 2 H, CH).

Acknowledgment. Portions of this work were generously supported by the Joint Award Council of the Research Foundation of the State University of New York (JAC-40-259A, JAC-40-7123B).

Registry No.—**3**, 53431-90-6; **4**, 53431-91-7; **5**, 53431-92-8; **6**, 53431-93-9; **7**, 53431-94-0; **8**, 53431-95-1; **9**, 53431-96-2; **9** · 2HCl, 53431-97-3; **10**, 53431-98-4; methanesulfonyl chloride, 124-63-0; *meso*-2,3-diaminobutane-1,4-diol, 53431-99-5; sodium selenide, 1313-85-5.

References and Notes

(1) Taken in part from the Ph.D. Thesis of R. L. Martin, State University of New York at Binghamton, 1974.
(2) P. F. Feit and O. T. Nielsen, *J. Med. Chem.*, **10**, 927 (1967).
(3) W. W. Simmon and M. Zanger, "The Sadtler Guide to NMR Spectra," Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1972, pp 105–106.
(4) R. Lett and A. Marguet, *Tetrahedron Lett.*, 2851, 2855 (1971).
(5) R. A. Raphael, *J. Chem. Soc.*, 401 (1952).
(6) N. A. Milas, S. Sussman, and H. S. Mason, *J. Amer. Chem. Soc.*, **61**, 1844 (1939).
(7) S. S. Brown and G. M. Timmis, *J. Chem. Soc.*, 3656 (1961).

A Convenient and Stereoselective Dithiol Synthesis

E. L. Eliel,[1a] V. S. Rao,[1a] S. Smith,[1b,2] and R. O. Hutchins*[1b]

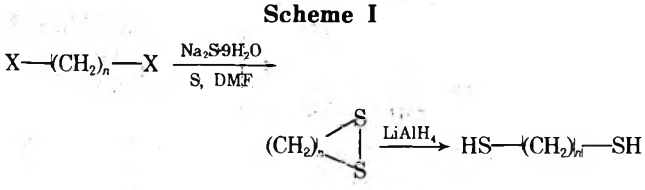
W. R. Kenan, Jr., Laboratories of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514, and Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

Received September 19, 1974

Although several procedures are available for the preparation of dithiols,[3] our experience has been that the standard methods are often unreliable or give contaminated products, especially when tertiary or other hindered thiols are desired or where stereochemical control is required for the production of particular dithiol diastereomers. The need for relatively pure samples of such dithiols as precursors for various sulfur heterocycles[4] led us to investigate several approaches toward such systems. This Note describes a convenient dithiol synthesis which is particularly attractive for hindered systems and when a maximum of stereochemical control is essential.

The procedure involves initial conversion of a dihalide or disulfonate ester to a di- or polysulfide[5] by displacement with disulfide anion (prepared *in situ* from sodium sulfide and sulfur) and subsequent reduction to the dithiol with lithium aluminum hydride without prior isolation of intermediates. The pathway is illustrated in Scheme I and

Scheme I



or oligomers

Table I presents results for a variety of dithiols chosen to illustrate the versatility of the method with difficult to prepare compounds. For instance, entries 1 and 2 represent highly hindered systems, the former involving displacement of a bifunctional neopentyl system. Furthermore, minimal racemization of chiral centers occurs, thus allowing stereochemical control for the production of diastereomers (entries 3, 4, and 5). Finally, the secondary tertiary halide, 2-methyl-2,4-dibromopentane (entry 6), gave the otherwise difficult to obtain dithiol in respectable yield, presumably *via* initial displacement at the secondary carbon followed by internal substitution.

Experimental Section

Materials. Dimethylformamide was reagent grade from a freshly opened bottle, used without further purification. The sulfonate

Table I
Preparation of Dithiols by Nucleophilic Displacement with Disulfide followed by Lithium Aluminum Hydride Reduction

Entry	Compound	Time displ, hr (temp, °C)	Time red., hr	% yield dithiol[a]
1	2,2-Dimethyl-1,3-propanediol dimesylate	60 (100)	3	61
2	2-*tert*-Butyl-1,3-propanediol ditosylate	67 (80)	3.25	70
3	*meso*-2,4-Pentanediol ditosylate	67 (80)	2.5	71[b]
4	*dl*-2,4-Pentanediol ditosylate	67 (80)	2.5	71[c]
5	*meso*-2,5-Hexanediol ditosylate	21.5 (80)	1.25	56[d]
6	2-Methyl-2,4-dibromopentane	96[e]	5	42[f]
7	1,4-Dichlorobutane	51.5 (80)	12	60

[a] Yields are for isolated and purified products. [b] Composed of 92% meso and 8% *dl* isomers as determined by glpc. [c] Contains less than 0.5% meso isomer. [d] The reaction was carried out in two steps. The intermediate *cis*-3,6-dimethyl-1,2-dithiacyclohexane was isolated in 61% yield; subsequent reduction afforded the dithiol in 91% yield. The product showed a meso/*dl* ratio of *ca.* 98:2 (glpc). [e] Conducted at room temperature for 72 hr followed by 24 hr at 80°. [f] 92% pure (glpc).

esters were prepared by standard procedures[6a] from the diols and the appropriate sulfonyl chloride in pyridine. 2-Methyl-2,4-dibromopentane was prepared in 90% yield from the diol and phosphorus tribromide.[6b] Organic solutions were dried over anhydrous $MgSO_4$.

Preparation of Dithiols. General Procedure. An equal molar portion of the dihalide or sulfonate ester was added to equal molar portions of fresh, crushed sodium sulfide nonahydrate and sulfur in DMF (200–400 ml/0.10 mol of the substrate) and heated with stirring at the temperature and for the durations listed in Table I. The reaction mixture was then poured into water and cracked ice and extracted three times with hexane. The aqueous phase was acidified with concentrated HCl and extracted again with hexane. The combined organic solution was washed with water, dried, and concentrated on a rotary evaporator. The resulting yellow oil was added dropwise to a slurry of lithium aluminum hydride (usually 0.076 mol/0.1 mol of initial substrate) at such a rate that gentle reflux was maintained. After an appropriate period (Table I), the reaction mixtures were cautiously treated with water to destroy excess hydride, then excess 10% aqueous sulfuric acid was added and the product isolated from the ether phase and purified by distillation. Representative preparations are illustrated below.

***meso*-2,4-Pentanedithiol.** *meso*-2,4-Pentanediol ditosylate (105.6 g, 0.256 mol) was added to a mixture of $Na_2S \cdot 9H_2O$ (61.4 g, 0.256 mol) and sulfur (8.29 g, 0.256 mol) in 700 ml of dry DMF and the solution was stirred in a 1-l. flask equipped with a condenser and drying tube at 80–85° for 67 hr, and then poured into 1500 ml of water and *ca.* 500 g of cracked ice. The mixture was extracted three times with hexane, then the aqueous phase was acidified with concentrated HCl and extracted with hexane. The combined hexane solution was washed twice with water, dried, and concentrated on a rotary evaporator. The resulting yellow oil was added dropwise with stirring to a slurry of lithium aluminum hydride (7.37 g, 0.195 mol) in 250 ml of anhydrous ether at such a rate that gentle reflux ensued (*ca.* 0.5 hr). The solution was then stirred at ambient temperature for 2 hr, and then refluxed for 30 min and cooled to room temperature. Approximately 7.5 ml of water was added cautiously to the mixture followed by an excess amount of 10% aqueous sulfuric acid in order to dissolve the aluminum salts. Approximately 200 ml of ether was added and the layers separated. The aqueous layer was extracted three times with ether. The combined ether solutions were washed and dried. Concentration on a rotary evaporator afforded a pale yellow oil which was distilled to yield nearly colorless product, bp 83–85° (24 mm) (lit.[7] 74.5° (12 mm)). The yield was 24.8 g (71%). Analysis by glpc (10 ft 20% Carbowax 20M column) showed the product to contain *ca.* 8% of the *dl* isomer. In contrast, the *dl*-ditosylate under the same conditions yielded product containing less than 0.5% of *meso*-dithiol.

2-Methyl-2,4-pentanedithiol. To a solution of 12 g (0.05 mol) of $Na_2S \cdot 9H_2O$ and 1.2 g (0.05 mol) of sulfur in 100 ml of dry DMF was added dropwise 12.2 g (0.05 mol) of 2-methyl-2,4-dibromopentane at room temperature. The mixture was stirred for 3 days at room temperature and 1 day at 80–85° and then poured into a mixture of 300 ml of water and 200 g of ice. The mixture was extracted three times with hexane; the aqueous phase was acidified with concentrated HCl and again extracted twice with hexane. The combined hexane extract was washed twice with water and dried, and the solvent removed on a rotary evaporator. The resulting yellow oil was dissolved in 30 ml of dry ether and added dropwise with mechanical stirring to a slurry of 5 g (0.13 mol) of lithium aluminum hydride in 150 ml of dry ether at a rate to ensure gentle reflux. The solution was stirred at room temperature for 3 hr, refluxed for 2 hr, and cooled. The excess hydride was destroyed by cautious addition of water (15 ml) and then 10% aqueous sulfuric acid was added to dissolve the aluminum salts. An additional 100 ml of ether was added and the ether layer separated. The aqueous phase was extracted twice with 50-ml portions of ether and the combined ether extracts were washed twice with water and dried. Removal of the solvent gave a pale yellow oil, 6.6 g (*ca.* 89%), which was fractionally distilled to give a colorless oil (3.1 g, *ca.* 42%), bp 78–80° (20 mm), which was *ca.* 92% pure by glpc (25 ft 30% QF-1 on Chromosorb W). The ir and nmr spectra were identical with those of an authentic sample.[8] The contaminants were not identified, but did not appear to interfere with subsequent use of the product.

***cis*-3,6-Dimethyl-1,2-dithiacyclohexane.** The procedure was a slightly modified version of that described by Dodson and Nelson[5] in that $Na_2S \cdot 9H_2O$ was used instead of the anhydrous salt. The product was obtained in 61% yield, bp 78–80° (5 mm). Analysis by glpc (20% Carbowax 20M column) indicated a cis/trans ratio of *ca.* 96/4 and traces of two lower boiling components. The nmr spectrum corresponded to that reported.[9]

***meso*-2,5-Hexanedithiol.** A solution of *cis*-3,6-dimethyl-1,2-dithiacyclohexane (4.44 g, 30 mmol) in 10 ml of anhydrous ether was added dropwise to a stirred slurry of lithium aluminum hydride (864 mg, 22.8 mmol) in 20 ml of anhydrous ether over a 15-min period. The mixture was refluxed for 1.0 hr, and then worked up as previously described above. Distillation afforded 4.08 g (91%) of colorless product, bp 76–78° (5 mm) (lit.[10] bp 87–88° (12 mm), for the mixture of diastereomers). Analysis by glpc (10 ft 20% Carbowax 20M) indicated the meso/*dl* ratio to be *ca.* 98/2.

Acknowledgment. Part of this work was supported by National Science Foundation Grant GP-35699X.

Registry No.—2,2-Dimethyl-1,3-propanediol dimesylate, 53555-41-2; 2-*tert*-butyl-1,3-propanediol ditosylate, 24330-56-1; *meso*-2,4-pentanediol ditosylate, 24347-99-7; *dl*-2,4-pentanediol ditosylate, 24348-00-3; *meso*-2,5-hexanediol ditosylate, 53585-64-1; 2-methyl-2,4-dibromopentane, 28457-08-1; 1,4-dichlorobutane, 110-56-5; 2,2-dimethyl-1,3-propanedithiol, 53555-42-3; 2-*tert*-butyl-1,3-propanedithiol, 24330-57-2; *meso*-2,4-pentanedithiol, 5954-76-7; *dl*-2,4-pentanedithiol, 5953-46-8; *meso*-2,5-hexanedithiol, 53585-65-2; *dl*-2,5-hexanedithiol, 53585-66-3; 2-methyl-2,4-pentanedithiol, 52053-49-3; 1,4-butanedithiol, 1191-08-8; *cis*-3,6-dimethyl-1,2-dithiacyclohexane, 2506-33-4; *trans*-3,6-dimethyl-1,2-dithiacyclohexane, 2242-20-8.

References and Notes

(1) (a) University of North Carolina; (b) Drexel University.
(2) Undergraduate research participant, 1973–1974.
(3) For a compilation and discussion of preparative methods for dithiols, see L. N. Owen in "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press, Elmsford, N.Y., 1961, pp 199–209.
(4) (a) For instance, substituted 1,3-dithiols are valuable for the preparation of various 1,3-dithianes (ref 4b,c) and 2-phospha-1,3-dithiacyclohexanes (ref 4d); (b) E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, **91**, 2703 (1969); (c) E. L. Eliel, A. Abatjoglou, and A. A. Hartmann, *ibid.*, **94**, 4786 (1972); (d) R. O. Hutchins and B. E. Maryanoff, *ibid.*, **94**, 3266 (1972).

(5) With 1,3- or 1,4-dihalides or sulfonates the intermediates are the corresponding cyclic five- or six-membered ring disulfides, respectively. In fact, the method provides a convenient synthesis of such compounds; see, R. M. Dodson and V. C. Nelson, *J. Org. Chem.*, **33**, 3966 (1968). For other cases where cyclization cannot readily occur, oligodisulfides or oligotrisulfides presumably result.
(6) (a) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N.Y., 1967, pp 1179–1181; (b) J. D. Bartleson, R. E. Burk, and H. P. Lankelma, *J. Amer. Chem. Soc.*, **68**, 2513 (1946).
(7) C. G. Overberger and T. Kurtz, *J. Org. Chem.*, **31**, 288 (1966).
(8) E. L. Eliel, A. A. Hartmann, and A. G. Abatjoglou, *J. Amer. Chem. Soc.*, **96**, 1807 (1974).
(9) N. Isenberg and H. F. Herbrandson, *Tetrahedron*, **21**, 1067 (1965).
(10) C. Overberger, J. Ferraro, and F. Ortland, *J. Org. Chem.*, **26**, 3458 (1961).

A New Conversion of 3,5-Disubstituted Isoxazoles to α,β-Unsaturated Ketones

Choji Kashima*

Department of Chemistry, University of Tsukuba, Sakura-mura, Niihari-gun, Ibaraki, 300-31, Japan

Yasuhiro Yamamoto and Yoshihiko Tsuda

Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo, 102, Japan

Received May 21, 1974

It is well known that 3,5-disubstituted isoxazoles are very stable compounds to acids, bases, hydrides, and oxidative reagents. Previously, we reported that 3,5-dimethylisoxazole, easily obtainable from 2,4-pentanedione and hydroxylamine, reacted regiospecifically at the methyl group in the 5 position with alkyl halides in the presence of an alkali amide in liquid ammonia.[1] Other electrophiles such as aldehydes, ketones, esters,[2] nitriles, and ketimines[3] react to give the corresponding alcohols, ketones, and amines. Recently, Büchi and his coworkers reported[4] that isoxazoles, prepared from α,β-unsaturated ketones, could be converted into α,β-unsaturated ketones (**11**) by reduction with sodium and *tert*-butyl alcohol in liquid ammonia.

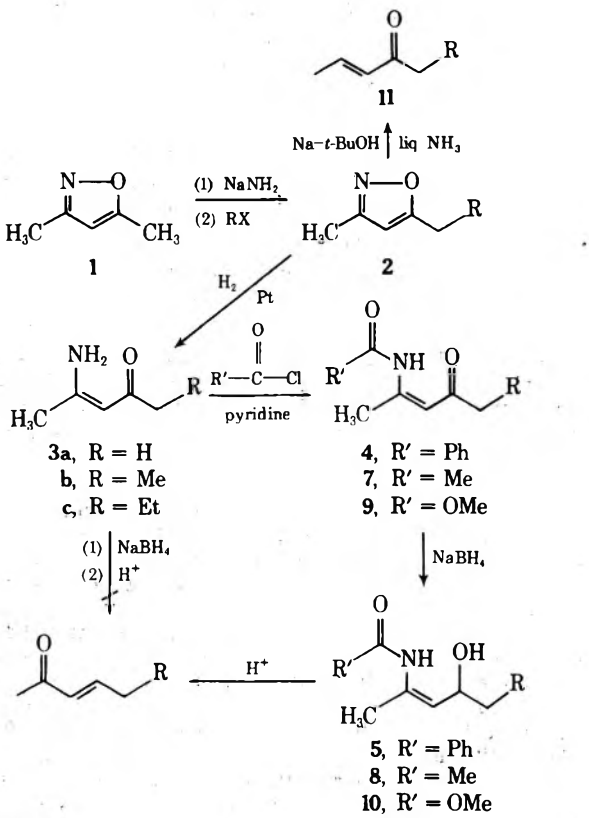
In this paper, we describe how isoxazoles can be converted regiospecifically into α,β-unsaturated ketones (**6**), which are isomeric with **11**. As a typical example, 5-ethyl-3-methylisoxazole (**2b**), prepared from 3,5-dimethylisoxazole (**1**) and methyl iodide, was hydrogenated over a platinum catalyst to afford 2-amino-2-hexen-4-one (**3b**). The reduction of **3b** with sodium borohydride was attempted, but the expected reaction did not occur and the starting material was recovered. At this point the superdelocalizability for nucleophilic reagents (Sr^N) at C-4 of **3b** was calculated by the HMO method, to give the result shown in Table I.[5] The

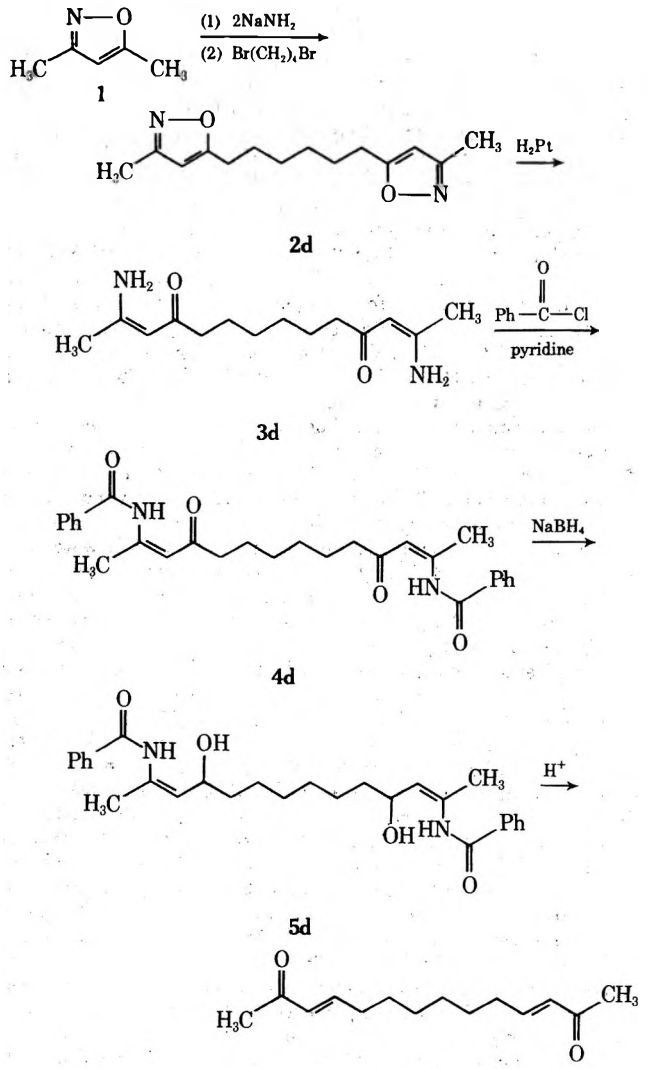
Table I

Compd	Sr^N Values at C-4	Sr^N Values at C-2
3	1.9388	1.6494
4	2.0432	1.7400
7	2.0422	1.7423
9	2.0214	1.7259

corresponding Sr^N value of the *N*-benzoyl derivative (**4b**) was also calculated and shown to be higher. Thus reduction of the carbonyl group of **4b** with sodium borohydride is expected to be easier and, indeed, on treatment with sodium borohydride, **4b** gave 2-benzamide-2-hexen-4-ol (**5b**). This

Scheme I





structure was supported by ir and nmr spectra. Without purification, **5b** was hydrolyzed with dilute sulfuric acid at room temperature. From the ir and nmr spectra, the product was found to be 3-hexen-2-one (**6b**), which had identical spectral data and retention time on vpc with an authentic sample. In addition, the semicarbazone of **6b** showed no melting point depression on admixture with an authentic sample.

Since the Sr^N values at C-4 of N-acetylated (**7b**] and *N*-carbomethoxylated derivatives (**9b**) were also calculated to be higher than that of **3b**, the reduction of **7b** and **9b** with sodium borohydride was investigated. After treatment with dilute sulfuric acid, the products from both **7b** and **9b** were identical with authentic **6b**. Similarly, 3-hepten-2-one (**6c**) and 3,11-tetradecadiene-2,13-dione (**6d**) were obtained from 3-methyl-5-*n*-propylisoxazole (**2c**) and 1,6-bis(3-methyl-5-isoxazolyl)hexane (**2d**), respectively.

In conclusion, this report, in conjunction with Büchi's report, provides a selective method for (1) isomerization of an α,β-unsaturated ketone, (2) protection and regeneration of an α,β-unsaturated ketone, or (3) conversion of a 1,3-diketone regiospecifically into an α,β-unsaturated ketone.

Experimental Section

***N*-Acylation of 3.** To a solution of **3**[1,6] (0.005 mol) in anhydrous pyridine (10 ml) was added 1 g of acyl chloride with stirring in an ice bath. Stirring was continued for another 3 hr at room temperature. The mixture was poured onto ice and extracted with methylene chloride. The extract was washed with dilute hydrochloric acid and water, dried with magnesium sulfate, and concentrated under reduced pressure. The residue was purified by recrystallization from an *n*-hexane–benzene mixture.

2-Benzamido-2-hexen-4-one (4b) was obtained from **3b** and benzoyl chloride: yield 96%; mp 33.0–34.0°; ir (KBr) 3440, 1695, 1650, 1600, and 700 cm^{-1}; nmr ($CDCl_3$) δ 5.43 (s, 1 H), 7.5 (m, 3 H), 8.02 (m, 2 H), and 13.38 (broad s, 1 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.11; H, 6.97; N, 6.26.

2-Benzamido-2-hepten-4-one (4c) was obtained from **3c** and benzoyl chloride: yield 90%; mp 44.0–45.0°; ir (KBr) 3410, 1690, 1640, 1595, 850, and 695 cm^{-1}; nmr ($CDCl_3$) δ 5.32 (s, 1 H), 7.5 (m, 3 H), 8.0 (m, 2 H), and 13.45 (broad s, 1 H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.47; H, 7.34; N, 6.17.

2,13-Bis(benzamido)tetradeca-2,12-diene-4,11-dione (4d) was obtained from **3d** and benzoyl chloride: yield 90%; mp 159.0–160.0°; ir (KBr) 3450, 1690, 1600, and 705 cm^{-1}; nmr ($CDCl_3$) δ 5.30 (s, 2 H), 7.5 (m, 6 H), 8.0 (m, 4 H), and 13.4 (broad s, 2 H).

Anal. Calcd for $C_{28}H_{32}N_2O_4$: C, 73.02; H, 7.00; N, 6.08. Found: C, 73.27; H, 7.04; N, 6.20.

2-Acetamido-2-hexen-4-one (7b) was obtained from **3b** and acetyl chloride: yield 80%; bp 210–212° (760 mm); ir (liquid film) 3425, 1720, 1645, 1600, and 890 cm^{-1}; nmr ($CDCl_3$) δ 2.13 (s, 3 H), 5.3 (s, 1 H), and 12.3 (broad s, 1 H).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.80; H, 8.44; N, 8.92.

2-Carbomethoxyamino-2-hexen-4-one (9b) was obtained from **3b** and methyl chloroformate: yield 50%; mp 63.5–65.0°; ir (KBr) 3475, 1760, 1655, 1600, and 870 cm^{-1}; nmr ($CDCl_3$) δ 3.71 (s, 3 H), 5.32 (s, 1 H), and 11.95 (broad s, 1 H).

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18. Found: C, 55.96; H, 7.64; N, 8.08.

Sodium Borohydride Reduction of 4, 7, and 9. A solution of **4, 7,** or **9** (4 mmol) in methanol (20 ml) was reduced with an excess sodium borohydride (5 mmol). After 10 hr, the mixture was poured onto water and extracted with methylene chloride. The extract was dried and evaporated. It was difficult to purify the residue by chromatography or distillation, because of its instability.

2-Benzamido-2-hexen-4-ol (5b) was obtained from **4b:** yield 80%; ir (liquid film) 3320, 1655, 1515, 1025, and 700 cm^{-1}; nmr ($CDCl_3$) δ 1.55 (m, 2 H), 2.95 (broad s, 1 H), 4.35 (m, 1 H), 4.88 (d, 1 H), and 9.05 (broad s, 1 H).

2-Benzamido-2-hepten-4-ol (5c) was obtained from **4c:** yield 67%; ir (liquid film) 3325, 1655, 1515, 1025, and 700 cm^{-1}.

2,13-Bis(benzamido)tetradeca-2,12-diene-4,11-diol (5d) was obtained from **4d:** yield 96%; ir (liquid film) 3350, 1730, 1650, 1520, 1030, and 700 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (m, 12 H), 4.3 (m, 2 H), 4.8 (d, 2 H), and 9.57 (s, 2 H).

2-Acetamido-2-hexen-4-ol (8b) was obtained from **7b:** yield 30%; ir (liquid film) 3300, 1665, 1620, 1525, and 880 cm^{-1}; nmr ($CDCl_3$) δ 0.9–1.6 (m, 5 H), 2.05 (s, 6 H), 3.43 (s, 1 H), 4.12 (q, 1 H), 4.9 (d, 1 H), and 8.03 (broad s, 1 H).

2-Carbomethoxyamino-2-hexen-4-ol (10b) was obtained from **9b:** yield 95%; ir (liquid film) 3325, 1745, 1720, 1680, and 1180 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (m, 2 H), 2.07 (s, 1 H), 2.75 (broad s, 1 H), 3.67 (s, 1 H), and 8.03 (broad s, 1 H).

Hydrolysis of 5, 8, and 10. To a solution of crude **5, 8,** or **10** in dichloromethane was added dilute sulfuric acid and the mixture was stirred for 10 hr at room temperature. This suspension was washed with water and extracted with methylene chloride. The extract was dried over magnesium sulfate and evaporated. The resulting products were purified by fractional distillation and/or silica gel column chromatography.

3-Hexen-2-one (6b) was purified by fractional distillation: yield 60% (from **5b**), 67% (from **8b**), 76% (from **10b**); bp 130–140°. The semicarbazone of **6b** was recrystallized from aqueous ethanol: mp 196° (lit.[7] 198°).

3-Hepten-2-one (6c) was purified by fractional distillation: yield 30% (from **5c**); bp 163–165°. The 2,4-dinitrophenylhydrazone of **6c** was recrystallized from aqueous ethanol: mp 122–123° (lit.[8] 125–126°).

3,11-Tetradecadiene-2,13-dione (6d) was purified by silica gel column chromatography eluting with benzene–ethyl acetate mixture: yield 42%; ir (liquid film) 1660, and 1620 cm^{-1}; nmr ($CDCl_3$) δ 1.4 (m, 8 H), 2.2 (m, 4 H), 2.25 (s, 6 H), 6.02 (d, 2 H), and 6.82 (d–t, 2 H). The bis-2,4-dinitrophenylhydrazone of **6d** was recrystallized from aqueous ethanol: mp 130° dec; ir (KBr) 3400, 1620, 1590, and 1325 cm^{-1}.

Anal. Calcd for $C_{26}H_{30}N_8O_8$: C, 53.60; H, 5.19; N, 19.24. Found: C, 53.36; H, 5.40; N, 19.54.

Registry No.—3b, 33663-57-9; **3c,** 33663-59-1; **3d,** 41027-52-5; **4b,** 53535-13-0; **4c,** 53535-14-1; **4d,** 53535-15-2; **5b,** 53535-16-3; **5c,** 53535-17-4; **5d,** 53535-18-5; **6b,** 763-93-9; **6c,** 1119-44-4; **6d,** 53535-19-6; **6d** bis (2,4-DNPH), 53535-20-9; **7b,** 53535-21-0; **8b,** 53535-22-1; **9b,** 53535-23-2; **10b,** 53535-24-3; benzoyl chloride, 98-88-4; acetyl chloride, 75-36-5; methyl chloroformate, 79-22-1.

References and Notes

(1) C. Kashima, S. Tobe, N. Sugiyama, and M. Yamamoto, *Bull. Chem. Soc. Jap.*, **46**, 310 (1973).
(2) R. G. Micetich, *Can. J. Chem.*, **48**, 2006 (1970).
(3) C. Kashima and Y. Tsuda, *Bull. Chem. Soc. Jap.*, **46**, 3533 (1973).
(4) G. Büchi and J. C. Vederas, *J. Amer. Chem. Soc.*, **94**, 9128 (1972).
(5) K. Fukui, T. Yonezawa, and C. Nagata, *Bull. Chem. Soc. Jap.*, **27**, 423 (1954); K. Fukui, T. Yonezawa, and C. Nagata, *J. Chem. Phys.*, **27**, 1247 (1957).
(6) G. Suzanne and R. Jacques, *Bull. Soc. Chim. Fr.*, 2182 (1971).
(7) C. Prevost, *Bull. Soc. Chim. Fr.*, **11**, 218 (1944).
(8) S. Powell and D. A. Ballard, *J. Amer. Chem. Soc.*, **60**, 1914 (1938).

Pyrolyses of Cyclopropylketene Dimer and Ethyl Cyclopropaneacetate

W. F. Berkowitz* and A. A. Ozorio

Chemistry Department, Queens College, City University of New York, Flushing, New York 11367

Received August 14, 1974

Photolysis of certain cyclopropyl ketones generates cyclopropylketenes[1] which have been cited as thermal precursors of the 2-cyclopentenones also formed.[1a-d,2]

We have investigated the rearrangement of cyclopropylketene (**1**) generated *in situ* by pyrolysis of its dimer (**2**) and have found, in addition to cyclopentenone (**3**), allene **4** and spirodiene **5**. Results are summarized in Table I.

There is ample evidence that ketene dimers crack thermally to the parent ketenes[4] or to allenes[5] (and carbon dioxide). Thus, we suggest that alternative cracking patterns a and b, as shown, account for the products observed. That the allene was the precursor of the spirodiene was

Table I
Pyrolysis of Dimer 2[a]

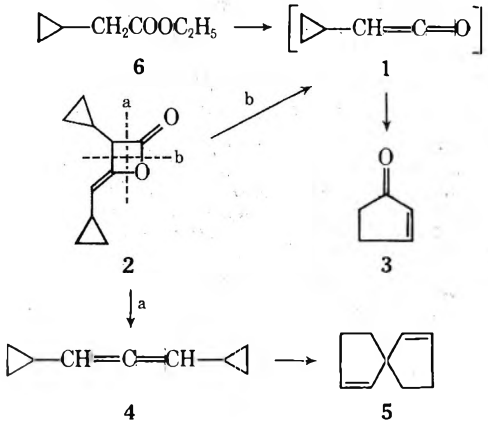
Run	T,[b] °C	Packing	% yield[c] 3	4	5
1	560	Glass wool	31	0.2	14
2	540	Glass wool	17	0	9
3	555	6-mm helices	15	20	3

[a] The pyrolysis procedure has been described previously.[3] Dimer (1–3 g) was introduced as vapor (0.2–1.8 mm) at 0.8–2.1 g/hr. [b] Temperature at the center of the hot tube, ±10°. [c] Yields are based upon glpc analysis. A 5 or 10 ft × 0.25 in. column packed with Chromosorb W coated with 20% by weight of Apiezon L was used, with ethyl benzoate or 4-methylcyclohexanone as internal standard. Identification of 3 was done by comparing glpc retention times and ir spectra with those of an authentic sample. For identification of 4 and 5, see Experimental Section.

Table II
Pyrolysis of Ethyl Cyclopropaneacetate 6[a]

Run	T,[b] °C	% 3 produced[c]	% 6 recovered
4	585	39	42
5	610	34	30
6	625	27	20

[a] The pyrolysis procedure has been described previously.[3] Ester entered the glass wool packed hot tube as vapor (0.25–2.0 mm) at *ca.* 1 g/hr. [b] Temperature at the center of the hot tube, ±10°. [c] Yields are based upon glpc analysis as described above. Yields of 3 produced are based on unrecovered 6.



suggested by the increased yield of allene at the expense of spirodiene (run 3 *vs.* run 2) with a smaller packing surface at the same rate of distillation.

Pyrolysis of ethyl cyclopropaneacetate (6)[6] also gave cyclopentenone. Results are summarized in Table II.

Acyl oxygen cleavage of esters affording ketenes is less well known than the more usual alkyl oxygen cleavage giving alkenes.[7] Phenyl esters, in particular, are prone to acyl oxygen cleavage, as are certain other esters.[8] There is some evidence that β-keto esters afford acylketenes pyrolytically in the presence of a glass surface.[3,9] Consequently we suggest that cyclopropylketene (1) may be the primary product of pyrolysis of ester 6 (although a vinylcyclopropane rearrangement of the enol form is certainly not excluded).

Experimental Section

Melting points were determined on a Mel-Temp apparatus (uncorrected). Microanalyses were performed by Spang Analytical Laboratory, Ann Arbor, Mich. Glpc results were obtained with a Varian-Aerograph Model A90-P3 thermal conductivity machine. Infrared spectra were taken on a Perkin-Elmer Model 237B or Beckman IR-20 grating spectrophotometer; ultraviolet spectra, with a Cary 14; nmr spectra, with a Varian A-60A; mass spectra, with a Varian/MAT CH-7 (at 70 eV). Pyrolyses were performed as described previously[3a] with a Hevi-Duty Electric Co. Type 77-T (600 W, "Multi-Unit") oven using a 37 × 2.5 cm Vycor tube packed as described above.

Dimer 2 (3-Cyclopropyl-4-cyclopropylmethylidene-2-oxetanone). The dimer 2 was prepared by Sauer's procedure[10] from the corresponding acid chloride[11] and triethylamine in 41% yield: bp 79–80° (0.20 mm); ir (CCl_4) 3.23, 5.32, 5.80 μ; nmr (CCl_4) δ 0.12–1.92 (m, 10, cyclopropyl CH), 3.88 (d, d, J_1 = 1.3 Hz, J_2 = 6.2 Hz, CHC*H*C=CH), 4.35 (d, d, J_1 = 1.3 Hz, J_2 = 9.1 Hz, CHC*H*=CCH); uv (EtOH) λ_{max} 210 nm (ε 2400); mass spectrum order of intensity *m/e* 82 > 54 > 39 > 164 = 41, parent ion *m/e* 164.[12] Compound 2 was converted to *N*-*p*-bromophenyl-2,4-dicyclopropyl-3-oxobutyramide, by treatment with *p*-bromoaniline, in 78% yield: mp 130–131° (ethanol–water); ir (CCl_4) 3.05, 5.95, 6.60 μ; nmr ($CDCl_3$) δ 0.35–1.67 (m, 10, cyclopropyl CH), 2.60 (d, 2, *J* = 6.5 Hz, CHCH_2), 2.83 (d, 1, *J* = 10 Hz, CHC*H*(CO–)$_2$), 7.45 (s, 4, Ar H).[12]

No cyclopentenone was observed (glpc) in the reaction mixture during preparation of the dimer.

Allene 4 (1,3-Dicyclopropyl-1,2-propadiene). The allene was trapped from the glpc effluent of the dimer pyrolysate: ir (CCl_4) 3.23, 5.11 μ; nmr (CCl_4) δ 0.10–1.43 (m, 10, cyclopropyl CH), 5.00 (d, d, 2, J_1 = 3.2 Hz, J_2 = 5.0 Hz, CHC*H*=C); uv (EtOH) λ_{max} 213 nm (ε 1490); mass spectrum order of intensity *m/e* 91 > 39 > 77 > 105 > 65 = 51 = 41 > 120, parent ion *m/e* 120.[12]

Spirodiene 5 (Spiro[4.4]nonadiene-1,6). The spirodiene[13,14] was also trapped from the glpc effluent of the dimer pyrolysate: ir (CCl_4) 3.28, 6.22 μ; nmr (CCl_4) δ 1.63–1.97 (m, 4, CH_2CH_2CH=C), 2.17–2.53 (m, 4, CH$_2$C*H*$_2$CH=C), 5.83–5.72 (m, 4, CH$_2$C*H*=C*H*–); mass spectrum order of intensity *m/e* 105 > 120 > 91 > 90 > 79 > 77 > 78 > 65 > 64, parent ion *m/e* 120, consistent with the literature values.[14a,12]

Pyrolysis of the dimer also gave 25–30% of nonvolatile material. Hydrolysis of this with hot 10% aqueous sodium hydroxide afforded small amounts of 2-pentenoic acid, cyclopropaneacetic acid, and 1,3-dicyclopropylacetone,[15] totaling about 60% of the nonvolatile fraction and presumably derived from dimer or oligomers of cyclopropylketene.

Acknowledgment. The authors gratefully acknowledge the financial assistance of Public Health Service Grant No. RO1-AM-11226.

Registry No.—2, 53432-85-2; 3, 930-30-3; 4, 53432-86-3; 5, 6569-94-4; 6, 53432-87-4; *N*-*p*-bromophenyl-2,4-dicyclopropyl-3-oxobutyramide, 53432-88-5; *p*-bromoaniline, 106-40-1.

References and Notes

(1) (a) M. J. Goldstein and B. G. Odell, *J. Amer. Chem. Soc.*, **89**, 6356 (1967); (b) O. L. Chapman and J. D. Lassila, *ibid.*, **90**, 2449 (1968); (c) O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen, and H. E. Wright, *ibid.*, **91**, 6857 (1969); (d) contrasting evidence is presented by A. S. Kende, Z. Goldschmidt, and P. T. Izzo, *ibid.*, **91**, 6858 (1969); (e) T. H. Kinstle and P. D. Carpenter, *Tetrahedron Lett.*, 3943 (1969).
(2) Also see related papers: (a) W. C. Agosta, A. B. Smith, III, A. S. Kende, R. G. Eilerman, and J. Benham, *Tetrahedron Lett.*, 4517 (1969); (b) W. C. Agosta and A. B. Smith, III, *J. Amer. Chem. Soc.*, **93**, 5513 (1971); (c) H. Hart and G. M. Love, *ibid.*, **93**, 6266 (1971).
(3) (a) W. F. Berkowitz and A. A. Ozorio, *J. Org. Chem.*, **36**, 3787 (1971); (b) W. F. Berkowitz, *ibid.*, **37**, 341 (1972).
(4) W. E. Hanford and J. C. Sauer, *Org. React.*, **3**, 108 (1946).
(5) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967).
(6) J. K. Kochi and J. D. Bacha, *J. Org. Chem.*, **33**, 2754 (1968).
(7) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).
(8) (a) H. M. Mackinnon and P. D. Ritchie, *J. Chem. Soc.*, 2564 (1957); (b) R. N. Bennett, A. A. Deans, J. G. H. Harris, P. D. Ritchie, and J. S. Shim, *ibid.*, 4508 (1958); (c) A. L. Brown and P. D. Ritchie, *J. Chem. Soc. C*, 2007, 2013 (1968).
(9) F. Leyendecker, R. Bloch, and J. M. Conia, *Tetrahedron Lett.*, 3703 (1972).
(10) J. C. Sauer, *J. Amer. Chem. Soc.*, **69**, 2444 (1947).
(11) J. H. Turnbull and E. S. Wallis, *J. Org. Chem.*, **21**, 663 (1956).
(12) A satisfactory elemental analysis was obtained for this compound.
(13) D. J. Cram and B. L. Van Duuren, *J. Amer. Chem. Soc.*, **77**, 3578 (1955).
(14) (a) H. Gerlach and W. Muller, *Helv. Chim. Acta*, **55**, 2277 (1972); (b) H. Gerlach, T. T. Huong, and W. Muller, *J. Chem. Soc., Chem. Commun.*, 1215 (1972).
(15) These materials were identified by comparison of their ir spectra and glpc retention times with those of authentic samples.

Irradiation of Benzaldehyde in 1-Hexyne[1,2]

Jerald S. Bradshaw,* Ronald D. Knudsen, and Wesley W. Parish

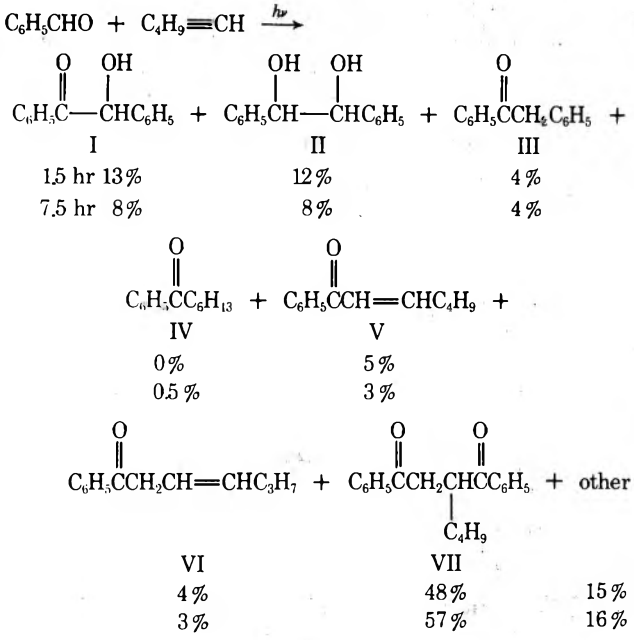
Chemistry Department, Brigham Young University, Provo, Utah 84602

Received June 27, 1974

The photoreactions of benzaldehyde have been reported extensively. Some of these include photooxidations,[3] photoreductions,[4] cycloadditions to form oxetanes[5] and suspected oxetene intermediates,[6] and mechanistic studies using chemically induced dynamic nuclear polarization (CIDNP) techniques.[7] We wish to report on the products of the ultraviolet irradiation of benzaldehyde and 1-hexyne.

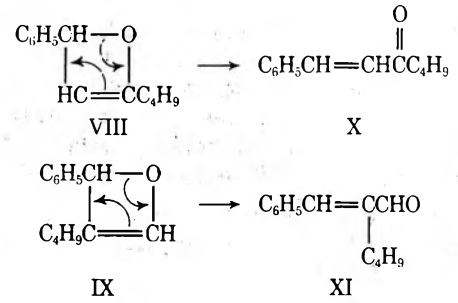
Mixtures of 1-hexyne and benzaldehyde were irradiated through Pyrex under a nitrogen atmosphere. The reaction mixture was separated by vapor phase chromatography (vpc) and the products (Scheme I) were analyzed by comparisons with authentic samples some of which were prepared in our laboratory. Products V and VI were both isolated in the course of preparing V. The structures are consistent with their nmr spectra. The aliphatic portion of the nmr spectrum for V is the same as that for 1-hexene while the aliphatic portion of the nmr spectrum for VI is the same as that for 1-pentene. We believe that compound V has the trans form because the infrared spectrum has two carbonyl bands.[8] Six per cent of the benzaldehyde was converted in 1.5 hr and 17% in 7.5 hr. The listed yields are based on the actual conversion of the benzaldehyde.

Scheme I



Products I, II, and III were formed from benzaldehyde–benzaldehyde reactions as previously reported.[2] As shown by the products, radical addition to 1-hexyne to form IV–VII dominates, but radical pair formation[7a] and hydrogen abstraction[4] mechanisms are also in evidence. We believe that benzoyl radicals formed by hydrogen abstraction from benzaldehyde add to the first carbon of 1-hexyne as has been observed for the addition of free radicals to 1-alkynes.[9] The resulting hexenyl radical ($C_6H_5C(=O)$-$CH=\dot{C}C_4H_9$) would abstract a hydrogen from another benzaldehyde or from a 1-hexyne molecule to form 2-heptenophenone (V). This reaction is similar to that reported by Wiley and Harrell for the cobalt-60 induced addition of various aldehydes to the esters of maleic and acetylenedicarboxylic acids.[10] Product IV is formed by a photochemical reduction of V. Indeed, irradiation of V gave IV probably in a similar manner as that reported by Griffin and O'Connell for the reduction of *cis*-dibenzoylethylene.[11] Product VII is formed by further addition of benzaldehyde to V as shown by the fact that irradiation of V in benzaldehyde gave a high yield of VII in a very short period of time. It is instructive to note that product VII was the major product of the overall reaction. This is probably a result of the high reactivity of V toward radical reactions. The second benzoyl radical added to the second carbon of the original 1-hexyne, giving the more stable radical α to the benzoyl group. This reaction has possible value as a preparative method for γ-diketones although we made no attempt to study the preparative aspects.[12] Product VI probably resulted from a simple photochemical isomerization of V as first shown by Yang and Jorgenson.[13] In our case, mixtures of V and VI, when irradiated, gave products which contained 95% or more of compound VI.

We do not believe that the addition of benzaldehyde to 1-hexyne involves the cycloaddition of triplet state benzaldehyde to the unsaturated system to form an oxetene as reported by Buchi and coworkers.[6] They obtained 6-benzylidene-5-decanone when benzaldehyde was irradiated in 5-decyne. They proposed an oxetene intermediate which opened to give the observed product.[6] In our reaction of benzaldehyde with 1-hexyne, two different oxetene intermediates (VIII and IX) would be possible. Ring opening of these intermediates would lead to 1-phenyl-1-hepten-3-one (X) and α-*n*-butylcinnamaldehyde (XI). Neither X nor XI was found in our reaction indicating that an oxetene intermediate is not involved.



Experimental Section

Materials and Apparatus. Spectra were obtained as follows: ir, Perkin-Elmer Model 457 spectrophotometer; nmr, Varian A60-A; uv, Cary Model 15 spectrophotometer; mass spectra, Varian MAT-111 gc–ms system using a 4 ft × ⅛ in. column packed with 3% SE-30 on Chromosorb W. A Varian Aerograph 202-B temperature programming vapor phase chromotograph (vpc) was used to analyze and separate all reaction mixtures. Accurate analytic analyses were carried out using a 4 ft × 0.25 in. stainless steel column packed with 4% Carbowax 20M on Chromosorb G/AW, 80–100 mesh. Quantitative yields were obtained by calibrating the columns with a mixture of weighed amounts of the compounds to be analyzed.[14] A Hanovia 450-W medium-pressure lamp was used for all irradiations. Benzaldehyde (J. T. Baker) and 1-hexyne (Chemical Samples Co.) were distilled prior to use.

Preparation of 2-Heptenophenone (V).[15] Phenacyltriphenylphosphonium bromide (0.65 g, 14.1 mmol), prepared from triphenylphosphine and 2-bromoacetophenone, was dissolved in 25 ml of ethanol containing about 0.1 g of potassium hydroxide. To this solution was added 0.23 g (2.68 mmol) of pentanal in 25 ml of tetrahydrofuran. This mixture was refluxed for 25 hr and evaporated leaving a yellow liquid and a white solid. The liquid was separated on the vpc to give compounds V (65%) and VI (35%). Compound V exhibited the following spectra: nmr δ 7.85 (m, 2), 7.40 (m, 3), 6.80 (m, 2), 2.20 (m, 2), 1.40 (m, 4), 0.95 (m, 3); uv λ_{max} (ethanol) 258 nm (ϵ 18,000); ir 1673 and 1625 cm^{-1}. Compound VI exhibited the following spectra: nmr δ 7.85 (m, 2), 7.40 (m, 3), 5.55 (m, 2), 3.60

(m, 2), 2.0 (m, 2), 1.40 (m, 2), 0.90 (m, 3); uv λ_{max} (ethanol) 244 nm (ϵ 9700); ir 1690 cm^{-1}.

Anal. (for a mixed V and VI sample). Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.78; H, 8.67.

Irradiation of Benzaldehyde and 1-Hexyne. A solution of 8.09 g (75 mmol) of benzaldehyde and 3.1 g (38 mmol) of 1-hexyne was placed in a Pyrex tube and purged with nitrogen for 10 min. The tube was then stoppered and irradiated at a distance of 8 in. from the light source. Aliquots were removed from the irradiated mixture at various times and analyzed by vpc. The results for 1.5 and 7.5 hr are listed in Scheme I. The vpc fractions (at 7.5 hr) were collected and the structures determined as follows. Fraction 1 proved to be 1-hexyne. Fraction 2 was benzaldehyde (83% recovered). Fraction 3 (0.5%) exhibited an ir spectrum identical with that of authentic heptanophenone (IV) (Pfaltz-Bauer Inc.). Fraction 4 (3%) exhibited ir and mass spectra identical with that of an authentic sample of 3-heptenophenone (VI). Fraction 5 (3%) exhibited ir and mass spectra identical with that of an authentic sample of 2-heptenophenone (V). Fraction 6 (4%) exhibited an ir spectrum identical with that of deoxybenzoin (III) prepared by the method of Allen and Barker.[16] Fraction 7 (8%) showed ir spectrum identical with that of an authentic sample of benzoin (I) (Heyden Chemical Co.). Fraction 8 (8%) exhibited an ir spectrum identical with that of hydrobenzoin (II) (Sadtler spectrum no. 37,405). Fraction 9 (57%) showed ir, nmr, and mass spectra identical with that of 2-*n*-butyl-1,4-diphenyl-1,4-butanedione (VI) prepared by the procedure of Sawa and coworkers.[17]

Other fractions were observed but could not be isolated in a large enough yield to characterize.

Irradiation of a Mixture of V and VI in Benzaldehyde. A mixture of V and VI (0.069, 0.32 mmol) and 10 g of benzaldehyde was irradiated as above to yield VII (67%) along with compounds I, II, and III. Compound VI was recovered.

Irradiation of V and VI Mixtures in Benzene. In two experiments a mixture of 78% VI and 22% V and a mixture of 89% V and 11% VI were irradiated in benzene through a 310–410-nm filter. Both irradiations resulted in a mixture greater than 95% VI and 5% V. Small amounts of compound IV were also formed in these reactions.

Acknowledgment. The authors wish to thank the Research Division, Brigham Young University, and Mr. Paul Parish for their generous financial support and Dr. Richard T. Hawkins for his many helpful discussions. R. D. Knudsen expresses thanks to the graduate school, Brigham Young University, for a graduate internship for 1971–1972.

Registry No.—V, 5595-63-1; VI, 53403-90-0; benzaldehyde, 100-52-7; 1-hexyne, 693-02-7; phenacyltriphenylphosphonium bromide, 6048-29-9; pentanal, 110-62-3.

References and Notes

(1) Presented at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1974.
(2) For a preliminary communication of part of this work see J. S. Bradshaw, R. D. Knudsen, and W. W. Parish, *J. Chem. Soc., Chem. Commun.*, 1321 (1972).
(3) See H. L. J. Backstrom and U. Runer, *Acta Chem. Scand.*, **20**, 630 (1966).
(4) (a) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **33**, 291 (1968); (b) T. Matsuura and Y. Kitaura, *Bull. Chem. Soc., Jap.*, **41**, 2483 (1968).
(5) (a) D. R. Arnold, R. L. Hinmon, and A. H. Glick, *Tetrahedron Lett.*, 1425 (1964); (b) N. C. Yang, J. I. Cohen, and A. Shani, *J. Amer. Chem. Soc.*, **90**, 3264 (1968); (c) J. S. Bradshaw, *J. Org. Chem.*, **31**, 237 (1966).
(6) G. Buchi, J. T. Kofron, E. Koller, and D. Rosenthal, *J. Amer. Chem. Soc.*, **78**, 876 (1956).
(7) (a) M. Cocivera and M. Trozzolo, *J. Amer. Chem. Soc.*, **92**, 1772 (1970); (b) G. L. Closs and D. R. Paulsen, *ibid.*, **92**, 7229 (1970).
(8) See R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N.Y., 1968, p 87.
(9) (a) R. M. Kpochik and J. A. Kampmeier, *J. Amer. Chem. Soc.*, **90**, 6773 (1968); Y. Amiel, *Tetrahedron Lett.*, 661 (1971).
(10) R. H. Wiley and J. R. Harrell, *J. Org. Chem.*, **25**, 903 (1960).
(11) G. W. Griffin and E. J. O'Connell, *J. Amer. Chem. Soc.*, **84**, 4148 (1962).
(12) A similar reaction has been reported for acetaldehyde; V. H. H. Schulbach, V. Frouzen, and E. Duhl, *Justus Liebigs Ann. Chem.*, **587**, 124 (1954).
(13) N. C. Yang and M. J. Jorgenson, *Tetrahedron Lett.*, 1203 (1964).
(14) F. D. Lewis and J. G. Mahyar, *J. Org. Chem.*, **37**, 2101 (1972).
(15) The method was taken from that of C. F. Hauser, T. W. Brooks, M. S. Miles, M. A. Raymond, and G. B. Butler, *J. Org. Chem.*, **28**, 372 (1963).
(16) C. H. F. Allen and W. E. Barker, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N.Y., 1967, p 156.
(17) Y. Sawa, I. Hashimoto, M. Ryaug, and S. Tstusumi, *J. Org. Chem.*, **33**, 2159 (1968).

Reaction of 2-Butynal Diethyl Acetal with Lithium Aluminum Hydride

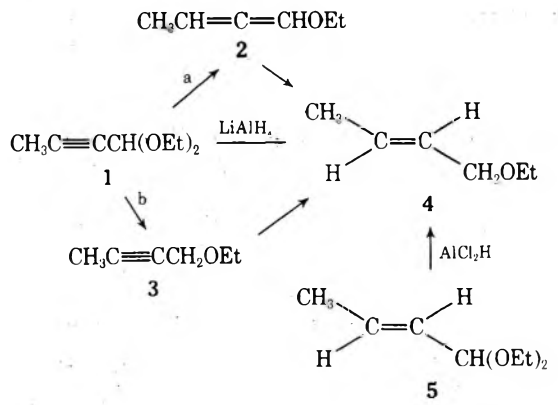
Walter W. Zajac, Jr.* and Kevin J. Byrne[1]

Department of Chemistry, Villanova University, Villanova, Pennsylvania 19085

Received August 12, 1974

The hydrogenolysis of cyclic and acyclic acetals and ketals to the corresponding ethers can be effected by alane,[2] chloroalane,[2] dichloroalane,[2] alkoxyalanes,[3] and alkoxychloroalanes.[3] Hydrogenolysis of acetals or ketals by lithium aluminum hydride (LAH) is rare. However certain allylic acetals can be reductively rearranged to vinyl ethers by $LiAlH_4$ alone. For example, hex-2-enopyranosides led to 3-deoxyglycals[4] and certain vinyl-substituted 2-vinyl-1,3-dioxolanes led to 1-propenyl 2-hydroxyethyl ethers.[5] In the light of these results and because of our continuing interest[3,6] in the hydrogenolysis of acetals and ketals, we chose to study the reactions of an acetylenic acetal, 2-butynal diethyl acetal **1**. If hydrogenolysis by LAH alone were analogous to the allylic acetal reaction, then C–O bond cleavage of the acetylenic acetal with bond migration would yield an allenic ether[7] **2** (Scheme I, path a). Otherwise C–O bond

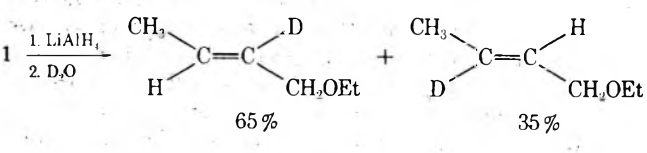
Scheme I



cleavage without bond migration would simply lead to the acetylenic ether **3** (Scheme I, path b).

In this work the reaction of **1** with LAH led to *trans*-crotyl ethyl ether **4**. To determine if the observed product resulted from reduction of allenic ether **2**, reduction of **1** with LAH was repeated and the reaction quenched with D_2O (Scheme II). There was found a 65% deuterium incor-

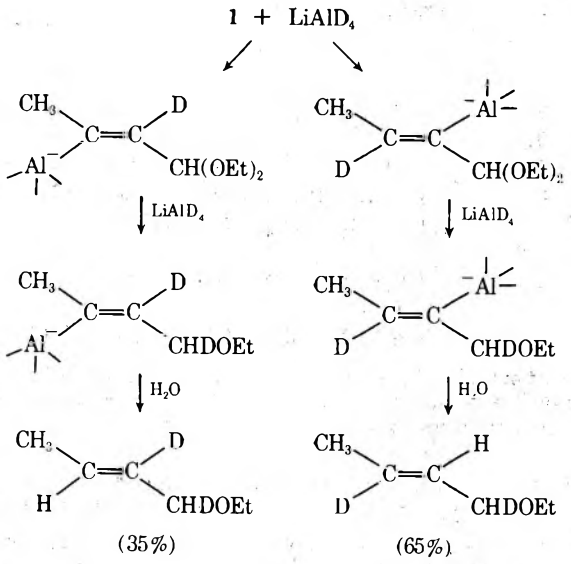
Scheme II



poration at C-2 and 35% at C-3.[8] For the allenic ether to be an intermediate 100% of the hydrogen at C-3 must come from LAH. When the reduction of **1** was repeated using $LiAlD_4$ followed by quenching with H_2O, the crotyl ethyl ether **4** was found to have 65% deuterium at C-3, 35% at C-2, and 100% at C-1[8] (Scheme III). For the allenic ether to be an intermediate, there would have to be 100% incorporation of deuterium at C-3 and C-1.

2-Butynyl ethyl ether **3** was ruled out as a possible intermediate by allowing it to react with LAH in refluxing ether for 48 hr. While **3** gave crotyl ethyl ether **4** in 65% yield, 35% of **3** remained unreacted. On the contrary no trace of

Scheme III



2-butynyl ethyl ether was found from the reaction of 1 with LAH after 24 hr. Therefore it appears that 2-butynyl ethyl ether **3** is too unreactive to be considered an intermediate in the reaction of 1 with LAH.

Based upon the results from the above experiments, the formation of the observed product *trans*-crotyl ethyl ether **4** from the reaction of 2-butynal diethyl acetal **1** with LAH can be explained by a pathway involving the nonregiospecific addition of LAH or LAD to the triple bond followed by hydrogenolysis of the acetal linkage (see Scheme III).

A number of the other experiments were also carried out. 2-Butynal diethyl acetal **1** was smoothly hydrogenolyzed by dichloroalane in ether to 2-butynyl ethyl ether **3**.

trans-Crotyl ethyl ether **4** can be obtained by the dichloroalane hydrogenolysis of *trans*-crotonaldehyde diethyl acetal **5** and is identical with the product of the LAH reduction of 2-butynal diethyl acetal **1**.

It was also determined that crotonaldehyde diethyl acetal **5** is 8 times more reactive than 2-butynal diethyl acetal **1**. Since the carbon–carbon double bond can stabilize a positive charge better than the carbon–carbon triple bond, the preceding result is consistent with the accepted mechanism of acetal hydrogenolysis which predicts the acetal producing the more stable carbonium ion to be more reactive, other factors, such as steric, being the same.[6]

Experimental Section

An F&M Model 700 gas chromatograph was used for glpc analyses. Nmr spectra were obtained with a Varian A-60 spectrometer on $CDCl_3$ solutions with TMS as an internal standard.

2-Butynal diethyl acetal **1** and 2-butynyl ethyl ether **3** were obtained from Farchan Laboratories, Willoughby, Ohio.

Trans-Crotonaldehyde diethyl acetal[9] **5** was prepared from *trans*-cortonaldehyde and triethyl orthoformate by a method previously described.[6]

trans-Crotyl ethyl ether[10] **4** was prepared by the dichloralane hydrogenolysis of *trans*-crotonaldehyde diethyl acetal by a method previously described.[5]

Competitive hydrogenolyses of **1** and **5** with alane were carried out according to the procedure of Davis and Brown.[5]

Reaction of 2-Butynal Diethyl Acetal 1 with $LiAlH_4$. This reaction was carried out by the procedure of Davis and Brown.[5] The reaction was repeated using $LiAlH_4$ but quenched with D_2O. The reaction was also carried out with $LiAlD_4$ and quenched with H_2O. In each there was obtained an 83% yield of *trans*-cortyl ethyl ether **4** and 12% of starting material. In each case the crotyl ethyl ether was subjected to nmr analysis in the following manner. In a glove bag with a nitrogen atmosphere, 63 mg of $Eu(fod)_3$ was weighed into an nmr tube and dissolved in 30 μl of $CDCl_3$. The glpc-purified crotyl ethyl ether was added to the nmr tube and the spectra were run. From the initial amount of 30 μl, the amount of crotyl ethyl ether was successively increased to 40, 50, 60, and finally 85 μl. The nmr spectra were run and analyzed as described.[8]

Registry No.—**1**, 2806-97-5; **4**, 1476-06-8; $LiAlH_4$, 16853,85-3.

References and Notes

(1) Taken from the Ph.D. thesis of K. J. Byrne, Villanova University, May 1973.
(2) M. N. Rerick, "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N.Y. 1968, pp 46–50.
(3) W. W. Zajac, Jr. and K. J. Byrne, *J. Org. Chem.*, **38**, 384 (1973).
(4) S. Y-K. Tam and B. Fraser-Reid, *Tetrahedron Lett.*, 4897 (1973); B. Fraser-Reid and B. Radatus, *J. Amer. Chem. Soc.*, **92**, 6661 (1970); B. Radatus, M. Yunker, and B. Fraser-Reid, *ibid.*, **93**, 3086 (1971); B. Fraser-Reid and B. Radatus, **93**, 6342 (1971); I. Achmatowicz and B. Szechner, *Tetrahedron Lett.*, 1205 (1972).
(5) H. A. Davis and R. K. Brown, *Can. J. Chem.*, **49**, 2563 (1971).
(6) W. W. Zajac, Jr., and K. J. Byrne, *J. Org. Chem.* **35**, 3375 (1970); **37**, 521 (1972).
(7) The intermediacy of an allenic ether has been postulated in the production of *cis*-allylic ethers *via* the hydroboration of acetylenic acetals with disiamylborane followed by protonolysis of the resulting organoborane: G. Zweifel, A. Horng, and J. E. Plamondon, *J. Amer. Chem. Soc.*, **96**, 316 (1974).
(8) The analysis was carried out by nmr. Integration of the nmr spectra of the product **4** shows the multiplet at δ 5.64 due to the vinyl protons decreasing from 2 to 1. Addition of the shift reagent $Eu(fod)_3$ shifts the C-2 hydrogen downfield relative to the C-3 hydrogen. Integration of the shifted spectra gives the relative proportion of incorporation at C-2 and C-3.
(9) J. A. Van Allen "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y., 1963.
(10) H. C. Brown and R. M. Gallivan, *J. Amer. Chem. Soc.*, **90**, 2906 (1968).

Reduction of Quaternary Ammonium Salts with Lithium Triethylborohydride. A Convenient Method for the Demethylation of Substituted Trimethylammonium Salts

Manning P. Cooke, Jr.*, and Robert M. Parlman

Department of Chemistry, Washington State University, Pullman, Washington 99163

Received July 27, 1973

Lithium triethylborohydride has recently been reported to be a source of remarkably nucleophilic hydride ion as demonstrated by its ability to rapidly reduce organic halides susceptable to SN2 displacement.[1] In light of the apparent high nucleophilicity of this reagent it seemed that lithium triethylborohydride might serve as a source of hydride ion for the displacement of groups which are much poorer leaving groups than halide ions. We now wish to report that this reagent readily effects the displacement of tertiary amines from quaternary ammonium iodides in THF.[2] Results are shown in Table I.

As can be seen from the results in Table I, aromatic trialkylammonium iodides readily react with lithium triethylborohydride at room temperature to give the tertiary amine resulting from the displacement on an alkyl group by hydride ion. It is also evident that displacement occurs predominately on a methyl group in salts containing at least two methyl groups while an appreciable amount of deethylation is observed with phenyldiethylmethylammonium iodide which contains but one methyl group. The surprising increase in deethylation in this case may be due to an increased steric hindrance to the attack on the remaining methyl group.

It is worthy of note that while the above mentioned salts are readily demethylated at 25°, these displacements are considerably slower than those involving the displacement of halide ion. Under conditions in which *n*-octyl bromide is said to be completely reduced to *n*-octane (2 min, 25°),[1] *n*-

Table I
Reduction of Quaternary Ammonium Iodides with Lithium Triethylborohydride[a]

Quaternary Salts	Registry no.	Temp, °C	Time, hr	Product(s)[b] (% yield)[c]
$C_6H_5N(CH_3)_3I$	98-04-4	25	0.75	$C_6H_5N(CH_3)_2$ (100, 92[d])
		65	0.25	(100)
$C_6H_5N(C_2H_5)(CH_3)_2I$	1006-07-1	25	0.75	$C_6H_5N(C_2H_5)CH_3$ (96) + $C_6H_5N(CH_3)_2$ (4)
$C_6H_5N(C_2H_5)_2CH_3I$	1007-67-6	25	0.75	$C_6H_5N(C_2H_5)_2$ (66) + $C_6H_5N(C_2H_5)CH_3$ (33)
$C_6H_5CH_2N(CH_3)_3I$	4525-46-6	65	7.0	$C_6H_5CH_2N(CH_3)_2$ (100, 85[d])
		25	2.0	(<5)
$CH_3(CH_2)_5N(CH_3)_3I$	15066-77-0	65	4.0	$CH_3(CH_2)_5N(CH_3)_2$ (100, 88[d])
		25	2.0	(<5)
$CH_3C(CH_3)_2CH_2C(CH_3)_2N(CH_3)_3I$	53624-41-8	65	1.0	$CH_3C(CH_3)_2CH_2C(CH_3)_2N(CH_3)_2$ (100)

[a] Reductions were performed using 1.0 mmol of salt and 1.5 mmol of $LiEt_3BH$ in 5 ml of dry THF under nitrogen. [b] All products identified by comparison with authentic samples or through preparation of known derivatives of isolated products. [c] Yields were determined by glpc analysis with the aid of an internal standard unless otherwise noted. [d] Yield of isolated picrate salt.

pentyltrimethylammonium iodide suffers less than 5% reduction.

Quaternary ammonium salts of aliphatic amines are much less readily reduced, however, owing to the increased basicity of the tertiary amine and require longer reaction times at elevated temperatures for the quantitative liberation of the dealkylated tertiary amine. The addition of hexamethylphosphoric triamide, which often accelerates the rate of SN2 processes,[3] does not affect a noticeable increase in the rate of the reaction with these substrates.

Thus, lithium triethylborohydride is an excellent reagent for the selective demethylation of quaternary ammonium salts containing methyl groups. It seems likely that this remarkable reagent will find use in other reductions involving the displacement of poor leaving groups by hydride ion.

Experimental Section

Materials. The quaternary ammonium salts employed in this work were prepared by the treatment of the corresponding tertiary amines with excess methyl iodide in benzene. The *N,N*-dimethyl amines were obtained from commercial sources or by the methylation of the corresponding primary amines.[4] Physical properties of all materials were in agreement with published values. A 1 *M* stock solution of lithium triethylborohydride in THF was prepared as previously described.[1]

General Procedure for the Dealkylation of Quaternary Ammonium Salts. *N,N*-Dimethylaniline from Phenyltrimethylammonium Iodide. The following procedure illustrates the general procedure used for the reduction of all of the quaternary ammonium iodides reported in Table I. Variations in reaction time and temperature for specific salts are shown in Table I. To a suspension of 0.265 g (1.0 mmol) of phenyltrimethylammonium iodide in 5 ml of dry THF under a nitrogen atmosphere was added 1.5 ml of 1 *M* lithium triethylborohydride stock solution. The mixture was stirred at room temperature for 0.75 hr. The resulting homogeneous mixture was treated with 1.0 ml of 10% aqueous hydrochloric acid and the THF was removed under reduced pressure. The aqueous solution was made basic by the addition of sodium hydroxide and the tertiary amine was obtained by extraction of the aqueous phase with several small portions of ether. Addition of the ethereal solution of *N,N*-dimethylaniline to 5 ml of saturated picric acid in ethanol gave 0.322 g (92%) of *N,N*-dimethylaniline picrate, mp 161–162° (lit.[5] mp 163°).

Acknowledgment. We thank Washington State University for support of this research through a grant in aid.

Registry No.—Lithium triethylborohydride, 22560-16-3.

References and Notes

(1) H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **95**, 1660 (1973).
(2) For previously developed methods for the dealkylation of quaternary ammonium salts, see R. O. Hutchins and F. J. Dux, *J. Org. Chem.*, **38**, 1961 (1973), and references cited therein.
(3) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).
(4) H. T. Clark, H. B. Gillespie, and S. Z. Weisshaus, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).
(5) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N.Y., 1956, p 298.

Carboalkoxylation of Aryl and Benzyl Halides Catalyzed by Dichlorobis(triphenylphosphine)palladium(II)

John K. Stille* and Pui Kwan Wong

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

Received July 30, 1974

With the exception of allyl halides, the carbonylation of organic halides using palladium catalysts has received little attention because of the severe reaction conditions.[1-4] A recent study[5] of the carbonylation of dichlorobis(triphenylphosphine)palladium(II) (**1**) suggests it as a potential catalyst for the carbonylation of organic halides. Carbonylation of **1** in methanol in the presence of primary or secondary amines affords a mixture of carbonylpalladium(0) complexes **2** and **3**, whereas in the presence of tertiary amines, chlorocarbomethoxybis(triphenylphosphine)palladium(II) (**4**) is formed. Treatment of **4** with methyl iodide or benzyl bromide yields the corresponding methyl ester.[5]

Since aryl, benzyl, and vinyl halides readily react with either finely divided palladium metal[6,7] or organophosphinepalladium(0) complexes[8,9] to form organopalladium(II) complexes, it appeared likely that the palladium(0) complexes **2** and **3** would react with organic halides *via* oxi-

$$L_2PdCl_2 + CO + CH_3OH \xrightarrow[RNH_2]{RR'NH} Pd(CO)L_3 + Pd_3(CO)_3L_4$$

1, L = PPh_3 **2** **3**

$$1 + CO + CH_3OH \xrightarrow{RR'R''N} L_2PdCl(CO_2CH_3)$$

4

dative addition to afford organopalladium complexes which upon carbonylation would give acylpalladium(II) derivatives. Alcoholysis of the acylpalladium(II) compounds would afford esters and regenerate a palladium(0) complex in the presence of a base.[10] A catalytic cycle for the carbonylation of organic halides could also be achieved with the carbomethoxypalladium complex **4** if dihalobis(triphenyl-

Table I
Carboalkoxylation of Aryl and Benzyl Halides[a]

RX	R'OH	Base	Reaction temp, °C	Reaction time, hr	% conversion RCO_2R'	% conversion ROR'	% conversion ROAc
PhI[b]	CH_3OH	NaOAc	60	48	80		
PhI[b]	CH_3OH	Et_3N	60	48	85		
$PhCH_2Cl$[c]	CH_3OH	NaOAc	80	24	61	19	13
$PhCH_2Cl$[c]	*n*-BuOH	NaOAc	80	36	68	Trace	Trace
$PhCH_2Cl$[c]	*n*-BuOH	NaOAc	60	36	50	Trace	Trace
$PhCH_2Cl$[c]	CH_3OH	Na_2CO_3	80	24	49	35	
$PhCH_2Cl$[c]	CH_3OH	Et_3N	80	24	36	4	
$PhCH_2Cl$[c]	CH_3OH	1,8-Bis(dimethylamino)naphthalene	80	20	91	3	
$PhCH_2Cl$[c]	CH_3OH	2,6-Lutidine	80	40		36	
$PhCOCH_2Br$[d]	CH_3OH	1,8-Bis(dimethylamino)naphthalene	80	48	64		

[a] $p(CO)$ = 200 psi at room temperature. [b] $PdCl_2(PPh_3)_2$–PhI = 1:100; PhI = 30 mmol; base = 50 mmol; CH_3OH = 100 ml. [c] $PdCl_2(PPh_3)_2$–$PhCH_2Cl$ = 1:100; $PhCH_2Cl$ = 40 mmol; base = 60 mmol; R'OH = 100 ml. [d] $PdCl_2(PPh_3)_2$–$PhCOCH_2Br$ = 1:58; $PhCOCH_2Br$ = 25 mmol; base = 29 mmol; CH_3OH = 100 ml.

phosphine)palladium(II) (**1a**) is produced from the reaction of **4** with organic halides to afford esters.

Treatment of iodobenzene with carbon monoxide (200 psi) and bases in methanol in the presence of a catalytic amount of **1** at 60° afforded good yields of methyl benzoate (Table I). The palladium catalyst was recovered as halocarbomethoxybis(triphenylphosphine)palladium(II) (**4a**) in >90% yield. Carboalkoxylation of benzyl chloride was achieved under similar conditions in the presence of a variety of bases. The best yield of ester product was obtained with 1,8-bis(dimethylamino)naphthalene, a strong base with low nucleophilicity. By-products such as benzyl methyl ether and benzyl acetate probably arose from nucleophilic displacements at either benzyl chloride or a benzylpalladium species. In the reactions of benzyl chloride which yielded esters, the palladium catalyst **1** was converted to either palladium black or an air-sensitive complex, probably a palladium(0) material. No ester was obtained in the presence of 2,6-lutidine and a 70% yield of **4** was obtained, thus suggesting a palladium(0) species as the active catalyst in the carboalkoxylation of benzyl chloride.

Carbonylation of equimolar amounts of **1** and iodobenzene afforded a 34% yield of methyl benzoate after 12 hr. Treatment of iodobenzene with an equimolar amount of **4** under similar conditions resulted in a 25% conversion to methyl benzoate. Allowing for the variation in reaction temperature, these results as well as the isolation of **4a** from the catalytic carbomethoxylation of iodobenzene are compatible with **4a** being the actual catalyst. However, the possibility that the active catalyst is a palladium(0) species present in a trace amount in the reaction mixture cannot be eliminated.

$$\mathbf{1} + PhI + CO + CH_3OH \xrightarrow[60°,\ 200\ psi]{NaOAc,\ 12\ hr} PhCO_2CH_3 + L_2PdX(CO_2CH_3)$$

34% **4a**, X = Cl or I, L = PPh_3

$$\mathbf{4} + PhI \xrightarrow[60°,\ 12\ hr]{CH_3OH} PhCO_2CH_3 + L_2PdX'Cl$$

25% **1a**, X = Cl or I, L = PPh_3

The carbonylation of α-bromoacetophenone (**5**) in methanol in the presence of 1,8-bis(dimethylamino)naphthalene was effected by treatment with a catalytic amount of **1** and carbon monoxide (200 psi) at 80°. The reaction afforded a

$$Ph{-}C(=O){-}CH_2Br \xrightarrow[\mathbf{1}]{MeOH,\ CO} Ph{-}C(=O){-}CH_2CO_2CH_3$$

64%

64% yield of α-carbomethoxyacetophenone. Carbonylation of 2-bromobutane in benzene, methanol or dimethyl sulfoxide gave no carboxylic acid derivatives.

Experimental Section

General Procedure for the Catalytic Carbonylation of Phenyl Iodide and Benzyl Chloride. In a 500-ml autoclave was placed a mixture of the organic halide, the base, dichlorobis(triphenylphosphine)palladium(II) (**1**), and alcohol. The mixture was heated at 60 or 80° under 200 psi of carbon monoxide until gas absorption stopped. The palladium catalyst was removed by gravity filtration and washed with 50 ml of methanol. The combined filtrates were concentrated by distillation through a 10 cm Vigreux column. The residue was diluted with 100 ml of water and extracted with several small portions of pentane. The combined pentane extracts were washed with 2*N* hydrochloric acid, aqueous sodium bicarbonate, and saturated aqueous sodium chloride successively. The pentane solution was dried over magnesium sulfate, concentrated by evaporation through a 10 cm Vigreux column, and then distilled under reduced pressure using a short path distillation apparatus to give the organic products. The products were characterized by nmr and vpc. Separation and quantitative analysis of organic products were achieved by vpc using a 10 ft × ⅜ in. 30% DEGS–Chromosorb W column. The results are given in Table I.

Stoichiometric Carbonylation of Iodobenzene. A mixture of 0.3 g (1.43 mmol) of iodobenzene, 0.24 g (2.9 mmol) of sodium acetate, and 1.0 g (1.43 mmol) of dichlorobis(triphenylphosphine)palladium(II) (**1**) in 15 ml of methanol was heated at 60° in a heating mantle with stirring in an autoclave which was pressurized with carbon monoxide at 200 psi. After 12 hr, the reaction mixture was filtered gravimetrically and washed with 50 ml of Skelly B to afford 1.0 g of a grayish-white complex which was identified by ir and nmr analyses as halocarbomethoxybis(triphenylphosphine)palladium(II) (**4a**): (KBr) 1665 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.39 (s, 3, CO_2CH_3), and 7.2–8.0 ppm (30). The combined filtrates were concentrated under reduced pressure and the residue was extracted with several small portions of pentane. The combined pentane extracts were washed with aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated under reduced pressure. Quantitative vpc analysis showed a 34% yield of methyl benzoate.

Reaction of Iodobenzene with Chlorocarbomethoxybis(triphenylphosphine)palladium(II) (4). A mixture of 0.29 g (1.38 mmol) of iodobenzene and 1.0 g (1.38 mmol) of **4** in 15 ml of methanol was heated at 60° in an oil bath for 12 hr. (*Anal.* Calcd for $C_{38}H_{33}ClO_2P_2Pd$: C, 62.91; H, 4.58. Found: C, 63.01; H, 4.57.) The yellow solid was collected by gravity filtration and washed with 50 ml of Skelly B to afford 1.0 g of a mixture of **1a** and **4a** as determined by ir analysis. The combined filtrates were concentrated

under reduced pressure and analyzed by vpc. The yield of methyl benzoate was 25%.

Carbonylation of α-Bromoacetophenone (5). A mixture of 5.0 g (25 mmol) of **5**, 0.3 g (0.43 mmol) of **1**, 6.0 g (29 mmol) of 1,8-bis(dimethylamino)naphthalene, and 50 ml of methanol was heated at 80° with stirring in a 500 ml autoclave which was pressurized with carbon monoxide at 200 psi. After 48 hr, the reaction mixture was filtered gravimetrically and washed with 50 ml of methanol. The combined filtrates were concentrated under reduced pressure and the residue was extracted with three 50-ml portions of dichloromethane. The combined extracts were washed with 2 *N* hydrochloric acid, aqueous sodium bicarbonate, and saturated aqueous sodium chloride successively. The dichloromethane solution was concentrated under reduced pressure and the residue was distilled using a short path distillation apparatus to afford 3.0 g (16 mmol, 64%) of a liquid which was identified as α-carbomethoxyacetophenone by comparison of its nmr spectrum with that reported for an authentic sample:[11] bp 90–94° (0.4 mm); nmr ($CDCl_3$) δ 3.72 (s, 3), 3.98 (s, 1.7), 5.64 (s, 0.3), 7.2–8.0 (m, 5), and 12.51 ppm (s, 0.3).

Acknowledgment. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**1**, 13965-03-2; **4**, 41894-01-3; **5**, 70-11-1; iodobenzene, 591-50-4; benzyl chloride, 100-44-7; α-carbomethoxyacetophenone, 614-27-7.

References and Notes

(1) P. M. Maitlis, "The Organic Chemistry of Palladium," Vol. II, Academic Press, New York, N. Y., (1971), p 18–33.
(2) L. Cassar, G. P. Chiusoli, and F. Guerrieri, *Synthesis*, 509 (1973).
(3) National Distillers and Chemical Corp., British Patent 1,149,259; *Chem. Abstr.*, **67**, 64066s (1967).
(4) R. N. Knowles, U.S. Patent 3,636,082; *Chem. Abstr.*, **76**, 85569j (1972).
(5) M. Hidai, M. Kokura, and Y. Uchida, *J. Organometal. Chem.*, **52**, 431 (1973).
(6) T. Mizoroki, K. Mori, and A. Ozaki, *Bull. Chem. Soc. Jap.*, **44**, 581 (1971).
(7) R. F. Heck and J. P. Nolley, Jr., *J. Org. Chem.*, **37**, 2320 (1972).
(8) P. Fitton and E. A. Rick, *J. Organometal. Chem.*, **28**, 287 (1971).
(9) G. W. Parshall, *J. Amer. Chem. Soc.*, **96**, 2360 (1974).
(10) J. K. Stille, L. F. Hines, R. W. Fries, P. K. Wong, D. E. James, and K. Lau, *Advan. Chem. Ser.*, **132**, 90 (1974).
(11) N. Sugiyama, M. Yamamoto, and C. Kashima, *Nippon Kagaku Zasshi*, **89**, 1268 (1968).

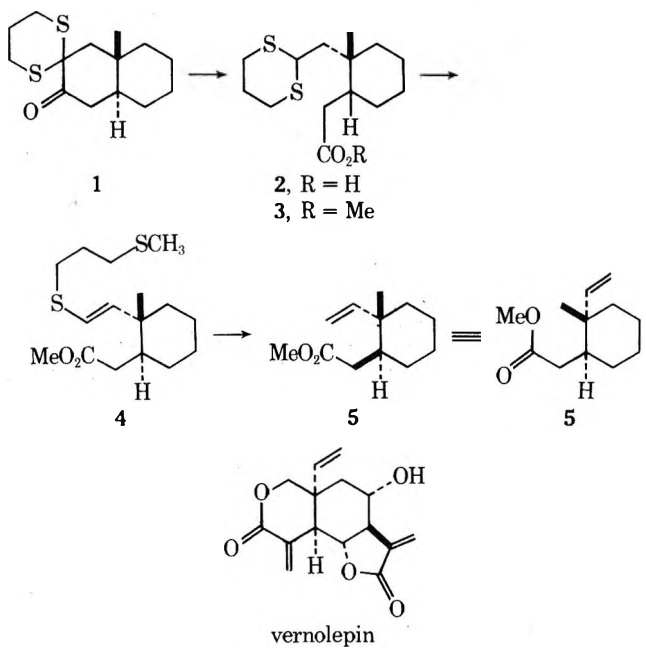
Cleavage–Elimination of 2,3-Decalindione Monothioketals Leading to Vinylic Ester and Lactone Prototypes of Vernolepin

James A. Marshall* and David E. Seitz

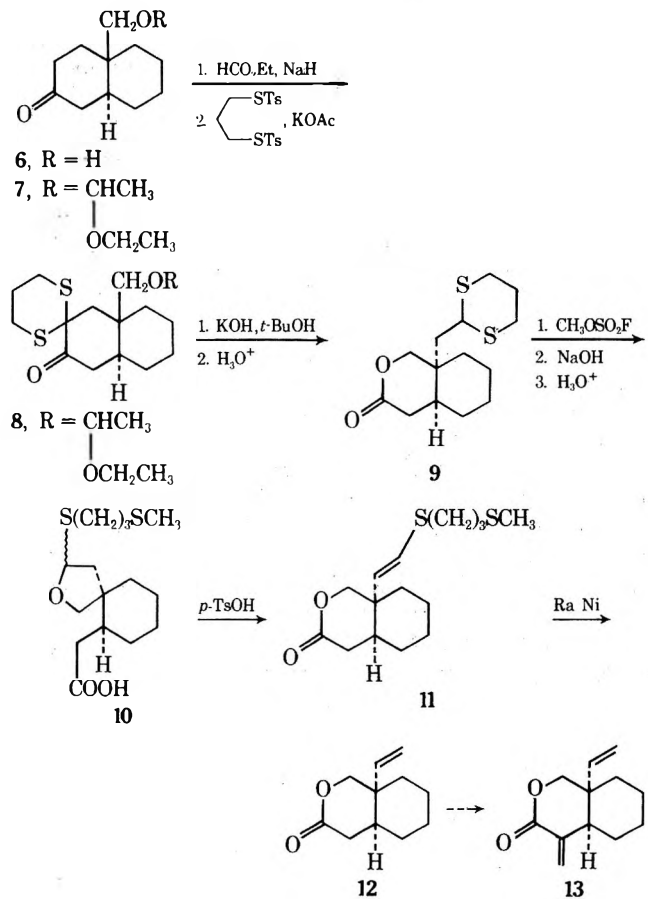
Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received September 26, 1974

A number of years ago we described a new method for the nonoxidative cleavage of carbon–carbon bonds which involved treatment of α-diketone monothioketals with nucleophilic bases.[1] In the course of subsequent studies aimed at clarifying the reaction pathway we discovered that cleavage of decalone **1** followed by the addition of methyl iodide to the basic reaction mixture led to the vinyl sulfide **4**.[2] This intermediate was smoothly converted to the vinyl compound **5** upon desulfurization with Raney nickel. Alternatively, the intermediate dithianyl acid **2** could be isolated, esterified, and then converted to the sulfonium salt with various methylating agents. Base cleavage was then best effected with sodium hydride. These facile transformations seemed well suited as a potential synthetic entree to the recently discovered growth-inhibitory elemanolide sesquiterpene dilactones vernolepin, vernodalin, and vernomenin.[3] With such goals in mind we directed our attention to the prototype lactone **13** (Scheme I) as our initial synthetic objective.[4]



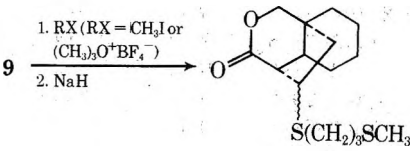
Scheme I



Attempts at dithianylation of hydroxy ketone **6**[5] *via* the hydroxymethylene derivative[6] were unsuccessful presumably because of interactions between the hydroxyl and carbonyl groupings. We therefore examined a number of hydroxyl-protected derivatives of which the mixed acetal **7** proved most suitable.[7] Basic cleavage of the derived thioketal ketone **8** followed by acid hydrolysis yielded the crystalline lactone **9**.[1]

We next explored the conversion of lactone thioacetal **9**

to the vinyl sulfide lactone **11** by S-methylation and subsequent basic elimination with sodium hydride under conditions previously optimized for the production of vinyl sulfide **4**. However except for one initial experiment which afforded this substance in about 50% yield, numerous attempts to effect this conversion met with complete failure. The principal product of these many attempts appeared to be the tricyclic lactone **14**, possibly arising *via* internal enolate alkylation or carbene insertion.



14

We eventually discovered a two-step process for the desired conversion which involved methylation of thioacetal **9** with excess methyl fluorosulfate and basic hydrolysis of the resultant (mono)methylsulfonium intermediate to give, after acidification, the hemithioacetal **10**. Previous workers have employed methylation and subsequent aqueous base treatment as a procedure for the hydrolysis of thioacetals.[8] In the present case the inertness of thioacetal **9** toward bismethylation and participation of the lactone-derived hydroxyl group to give a base-stable hemithioacetal must effectively preclude the hydrolysis pathway. Elimination to the vinyl sulfide readily occurred upon heating hemithioacetal **10** with *p*-toluenesulfonic acid in benzene. These conditions also promoted lactonization and the desired lactone sulfide **11** could thus be prepared in over 85% yield. Desulfurization with deactivated W-2 Raney nickel in acetone[9] afforded the vinylated lactone **12**[10] whose conversion to the methylene derivative **13** has been described by Grieco and Hiroi.[4]

Experimental Section[11]

Methyl 1-[2,2-(Propane-1,3-dithio)ethyl]-*cis*-1-methylcyclohex-2-ylacetate (3). An ether solution of 1.15 g (4.0 mmol) of acid **2**[1] was esterified with diazomethane. Isolation with ether afforded 1.20 g (100%) of ester **3**, bp 155° (bath temperature) at 0.02 mm: λ_{max} (film) 5.75 (CO), 6.95, 7.85, 7.90, 8.55, 8.80, 9.95 μm; δ_{TMS} (CCl_4) 4.07 (1 H, t, J = 5 Hz), 3.57 (3 H, s), 0.80 ppm (3 H, s).

Anal. Calcd for $C_{15}H_{26}O_2S_2$: C, 59.56; H, 8.66; S, 21.20. Found: C, 59.44; H, 8.89; S, 20.98.

Methyl 1-(3,7-Dithia-*trans*-1-octenyl)-*cis*-1-methylcyclohex-2-ylacetate (4). A solution of 660 mg (2.2 mmol) of ester **3** and 2 ml (32 mmol) of methyl iodide was stirred at room temperature for 12 hr. The excess methyl iodide was removed *in vacuo* and the crude sulfonium salt in 4 ml of tetrahydrofuran was transferred to a suspension of 186 mg (4.4 mmol) of sodium hydride in 2 ml of tetrahydrofuran. The mixture was stirred for 2.5 hr, water was added, and the product was isolated with ether. Chromatography on 35 g of silica gel with 1:9 ether–benzene as eluent afforded 595 mg (86%) of vinyl sulfide **4**. An analytical sample was secured by preparative layer chromatography on silica gel (1:3 ether–petroleum ether) and distillation, bp 165° (bath temperature) at 0.02 mm: λ_{max} (film) 5.75 (CO), 6.20 (C=C), 6.95, 7.85, 7.95, 8.32, 8.55, 8.75, 9.90, 10.40 μm; δ_{TMS} (CCl_4) 5.60 (2 H, AB, J = 16 Hz, $\Delta\nu_{AB}$ = 22.6 Hz), 3.57 (3 H, s), 2.04 (3 H, s), 0.90 ppm (3 H, s).

Anal. Calcd for $C_{16}H_{28}O_2S_2$: C, 60.71; H, 8.92; S, 20.26. Found: C, 60.68; H, 9.15; S, 20.00.

Methyl 1-Vinyl-*cis*-1-methylcyclohex-2-ylacetate (5). A suspension of 5 ml of W-2 Ra Ni, demineralized with ion-exchange resin[12] and deactivated by prior heating at reflux for 25 min in ethyl acetate and for 40 min in acetone, and 150 mg (0.47 mmol) of vinyl sulfide **4** in 30 ml of acetone was heated at reflux for 3 hr. The cooled reaction mixture was filtered through a pad of Celite and the solvent was removed affording 88 mg (95%) of ester **5**. Distillation at 75° (bath temperature) and 0.2 mm afforded 82 mg (89%) of ester **5** which was found to be 82% pure by gc. An analytical sample was secured by preparative gc on a 6 ft × 0.375 in. column packed with 4% DC-550 on Chromosorb G: λ_{max} (film) 5.75 (CO), 6.19 (C=C), 6.90, 10.85 μm; δ_{TMS} (CCl_4) 5.90–4.65 (3 H, m), 3.54 (3 H, s), 0.90 ppm (3 H, s).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.22; H, 10.30.

10-[2,2-(Propane-1,3-dithio)ethyl]-*cis*-3-oxa-2-decalinone (9). A solution of 2.73 g (15 mmol) of alcohol **6**,[5] 1.3 ml (25 mmol) of ethyl vinyl ether, and 120 μl of dichloroacetic acid was stirred at room temperature for 15 hr according to the procedure of Eaton.[7] Solid sodium carbonate was added and stirring was continued an additional 1 hr. The reaction mixture was filtered and the solvents were removed *in vacuo* affording 3.82 g (100%) of acetal **7** as an oil: λ_{max} (film) 5.84 (CO), 6.86, 7.24, 8.80, 9.15, 9.40, 10.65 μm; δ_{TMS} ($CDCl_3$) 4.66 (1 H, q, J = 6 Hz), 3.8–3.0 (4 H, m), 1.28 (3 H, d, J = 5.5 Hz), 1.16 ppm (3 H, t, J = 7 Hz).

A solution of 3.80 g (13.4 mmol) of the hydroxymethylene ketone obtained (92%) from the above acetal **7** by the procedure of Turner,[13] 6.67 g (16 mmol) of propane-1,3-dithiol di-*p*-toluenesulfonate,[14] and 5 g of potassium acetate in 120 ml of absolute ethanol was heated at reflux for 10 hr according to the procedure of Woodward.[6] The ethanol was removed *in vacuo* from the cooled reaction mixture, water was added to the residue, and the products were isolated with ether. The crude product was filtered through 125 g of Fisher alumina with 500 ml of benzene. Removal of the solvent afforded 3.0 g (67%) of thioketal ketone **8** as an oil: λ_{max} (film) 5.90 (CO), 6.90, 7.28, 7.85, 8.11, 8.85, 9.21, 9.50, 10.82 μm; δ_{TMS} ($CDCl_3$) 4.66 (1 H, q, J = 6 Hz), 3.8–3.0 (4 H, m), 1.28 (3 H, d, J = 5.5 Hz), 1.16 ppm (3 H, t, J = 7 Hz).

To a stirred solution of the above thioketal ketone **8** (2.95 g, 8.5 mmol) in 20 ml of *tert*-butyl alcohol was added 1.43 g (25.5 mmol) of powdered potassium hydroxide. The reaction mixture was heated at 60° for 10 hr,[1] water was added, and the mixture was extracted with ether. The aqueous phase was acidified with concentrated hydrochloric acid, acetone was added to make the mixture homogeneous, and the resulting solution was stirred for 3 hr. The acetone was removed *in vacuo* and the product was isolated with ether affording 2.11 g (87%) of lactone **9** as an oil which crystallized on standing. Recrystallization from ether afforded material of mp 75.5–77°: λ_{max} (KBr) 5.80 (CO), 6.84, 7.15, 7.95, 8.10, 8.40, 9.28, 9.50, 11.00, 11.55, 12.55 μm; δ_{TMS} ($CDCl_3$) 4.25 (2 H, AB, J = 11 Hz, $\Delta\nu_{AB}$ = 18.9 Hz), 4.05 ppm (1 H, t, J = 5 Hz).

Anal. Calcd for $C_{14}H_{22}O_2S_2$: C, 58.70; H, 7.74; S, 22.39. Found: C, 58.56; H, 7.70; S, 22.45.

10-(3,7-Dithia-*trans*-1-octenyl)-*cis*-3-oxa-2-decalinone (11). The method of Ho[8] was modified for the preparation of acid **10**. A solution of 620 mg (2.16 mmol) of lactone **9**, 242 μl (3.0 mmol) of methyl fluorosulfonate, and 5 ml of benzene was stirred at room temperature for 3.5 hr whereupon 5 ml of 10% sodium hydroxide was added and stirring was continued an additional 15 min. Water was added and the aqueous phase was extracted with ether and acidified with concentrated hydrochloric acid. The acidic product was isolated by ether extraction affording 672 mg (98%) of acid **10** as an oil: λ_{max} (film) 2.80–4.20 (COOH), 5.88 (CO), 6.90, 7.70, 8.05, 9.55, 10.90 μm; δ_{TMS} (CCl_4) 10.00 (1 H, s), 5.20 (1 H, m), 3.60 (2 H, m), 2.05 ppm (3 H, s).

The above acid **10** was refluxed with 20 mg of *p*-toluenesulfonic acid monohydrate in 20 ml of benzene for 2 hr with removal of water *via* a Dean–Stark trap. Isolation of the product with ether and chromatography on 35 g of silica gel with 1:4 ether–benzene as eluent afforded 545 mg (87%) of lactone **11**: λ_{max} (film) 5.75 (CO), 6.90, 7.90, 8.35, 9.20 μm: δ_{TMS} (CCl_4) 5.75 (2 H, AB, J = 16 Hz, $\Delta\nu_{AB}$ = 55.5 Hz), 4.10 (2 H, AB, J = 11 Hz, $\Delta\nu_{AB}$ = 13.1 Hz), 2.05 ppm (3 H, s). The analytical sample was secured by preparative layer chromatography on silica gel (1:4 ether–benzene) and distillation, bp 180° (bath temperature) at 0.02 mm.

Anal. Calcd for $C_{15}H_{24}O_2S_2$: C, 59.96; H, 8.05; S, 21.34. Found: C, 59.75; H, 8.19; S, 21.18.

10-Vinyl-*cis*-3-oxa-2-decalinone (12). The procedure outlined above for the preparation of ester **5** was followed. A suspension of 7 ml of W-2 Ra Ni, deactivated by prior heating at reflux for 25 min in ethyl acetate and for 4.5 hr in acetone, and 249 mg (0.83 mmol) of lactone **11** in 30 ml of acetone was heated at reflux for 2 hr to give 143 mg (96%) of lactone **12**. Distillation at 115° (bath temperature) and 0.02 mm afforded 135 mg (90%) of lactone **12** which was found to be 85% pure by gc. The infrared and nmr spectra of this material were identical with those of an authentic sample.[10]

Acknowledgment. We are grateful to the National Institutes of Health, Division of Cancer Research, for support of this work through a research grant (5 RO1 CA 11089).

Registry No.—**2**, 27069-39-2; **3**, 53596-99-9; **4**, 53597-00-5; **5**, 53597-01-6; **6**, 24795-49-1; **7**, 53597-02-7; **8**, 53597-03-8; **9**, 53597-04-9; **10**, 53597-05-0; **11**, 53597-06-1; **12**, 42391-78-6; propane-1,3-dithiol di-*p*-toluenesulfonate, 3866-79-3; methyl fluorosulfonate, 421-20-5.

References and Notes

(1) J. A. Marshall and H. Roebke, *Tetrahedron Lett.*, 1555 (1970); J. A. Marshall, C. T. Buse, and D. E. Seitz, *Syn. Commun.*, **3**, 85 (1973); J. A. Marshall and D. E. Seitz, *J. Org. Chem.*, **39**, 1814 (1974).
(2) H. Roebke, unpublished observations.
(3) S. M. Kupchan, R. J. Hemingway, D. Werner, A. Karim, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **90**, 3596 (1968).
(4) Two routes to this lactone have recently been described: P. A. Grieco and K. Hiroi, *Tetrahedron Lett.*, 1831 (1973); R. D. Clark and C. H. Heathcock, *ibid.*, 1713 (1974).
(5) L. S. Minckler, A. S. Hussey, and R. H. Baker, *J. Amer. Chem. Soc.*, **78**, 1009 (1956).
(6) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).
(7) P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37**, 1947 (1972).
(8) T. L. Ho and C. M. Wong, *Synthesis*, 561 (1972); T. Oishi, K. Kamemoto, and Y. Ban, Tetrahedron Lett., 1085 (1972).
(9) *Cf.* M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka, and T. Furuta, *Tetrahedron*, **21**, 733 (1965).
(10) We thank Professor C. H. Heathcock for kindly supplying us with the spectra of this compound.
(11) The apparatus described by W. S. Johnson and W. P. Schneider ["Organic Syntheses," Collect. Vol. IV, New York, N.Y., 1963, p 132] was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Infrared spectra were obtained with a Perkin-Elmer 137 spectrophotometer. Infrared absorption are reported in wavelengths (μm) and are standardized with reference to the 6.24-μm peak of polystyrene. Nuclear magnetic resonance spectra were recorded with a Varian T-60 spectrometer. Signals are reported as the chemical shift downfield from tetramethylsilane (TMS) in parts per million (ppm) of the applied field. The multiplicity of the peak is abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m. Coupling constants are reported in hertz (Hz). Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected.
(12) H. v. Driel, J. W. v. Reijendam, J. Buter and H. Wynberg, *Syn. Commun.*, **1**, 25 (1971).
(13) R. B. Turner, K. H. Gänshirt, P. E. Shaw, and J. D. Tauber, *J. Amer. Chem. Soc.*, **88**, 1776 (1966).
(14) J. C. A. Chivers and S. Smiles, *J. Chem. Soc.*, 697 (1928); R. B. Woodward, I. J. Pachter, and M. L. Scheinbaum, *Org. Syn.*, **52**, unchecked procedure 1815 (1972).

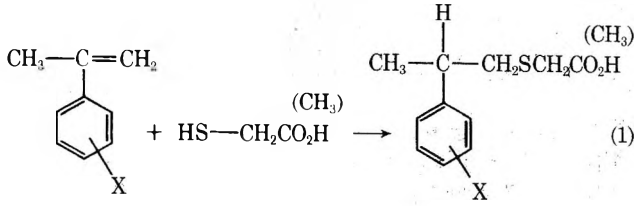
The Effect of Substituents on the Addition of Thiophenol to α-Methylstyrene[1]

Daniel F. Church and Gerald Jay Gleicher*

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

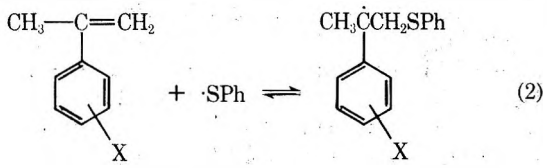
Received August 21, 1974

The additions of free radicals in general,[2] and of thiyl radicals in particular,[3] to carbon–carbon double bonds have been studied extensively over the years. Examples of the application of Hammett-type linear free-energy treatments to such a reaction, however, are rather rare.[4] In the case of thiyl radical addition, previous work[4b,c] tended to indicate that electron-donating substituents enhanced the rate of addition, while electron-withdrawing substituents retarded it. However, these studies, which dealt with the reaction (eq 1) between thioglycolic acid (or its methyl ester) and substituted α-methylstyrenes, suffer due to the small number of different substituted compounds examined and the possibility of competing ionic addition in certain cases. It was felt that a more extensive Hammett study of this reaction might be of interest.



(1)

The system chosen for study involved photoinduced competitive reactions of pairs of substituted α-methylstyrenes with thiophenol under nitrogen at reduced pressure. It was felt that the possible reversibility of addition step[2,3] (eq 2) should not affect the validity of the result from the linear free-energy treatment under these conditions. In



(2)

support of this assumption was an experiment of Cadogan and Sadler[4c] in which they found that the relative reactivity ratio for a pair of substituted α-methylstyrenes toward the thiyl radical derived from methyl thioglycolate remained constant as the relative initial concentration of methyl thioglycolate was varied.

Table I
Relative Reactivities of Substituted α-Methylstyrenes toward Thiyl Radicals at 70°

Substituent	Registry no.	σ^a	σ^{+a}	k_X/k_H
p-CH_3O	1712-69-2	−0.27	−0.778	1.85 ± 0.13
p-CH_3	1195-32-0	−0.17	−0.311	1.36 ± 0.18
m-CH_3	1124-20-5	−0.07	−0.066	1.15 ± 0.09
H	98-83-9	0.00	0.00	1.00
m-CH_3O	25108-57-0	0.12	0.047	1.02 ± 0.07
p-Cl	1712-70-5	0.23	0.114	0.98 ± 0.04
m-Cl	1712-71-6	0.37	0.399	0.69 ± 0.10
m-CF_3	368-79-6	0.47	0.52	0.58 ± 0.07
p-NO_2	1830-68-8	0.78	0.790	0.99 ± 0.10

[a] Reference 5.

Our results for the relative reactivities of substituted α-methylstyrenes toward the thiyl radical from thiophenol in benzene at 70° are listed in Table I. Nearly identical reactivity ratios were obtained when thiyl radicals were thermally, rather than photolytically, generated. In the former case, however, a lessened total reactivity was observed. When a linear free-energy treatment is applied using the Hammett σ constants, a ρ value of −0.57 ± 0.03 (correlation coefficient, $r = -0.962$) is obtained, while using the Okamoto–Brown σ^+ parameters gives ρ equal to −0.38 ± 0.02 ($r = -0.984$).[5] Both of these ρ values were obtained using all of the data points except that corresponding to the para nitro compound. A graphic presentation of the linear free-energy treatment using the σ^+ parameters is shown in Figure 1.

The anomalously high reactivity of *p*-nitro-α-methylstyrene observed in this study has also been noted in previous work[4c,d] for strongly electron-withdrawing substituents in the para position. It has been attributed to enhanced resonance stabilization of the benzylic free radical by such groups. An alternative explanation is suggested by the work of Walling, *et al.*[6] In a copolymerization study, the relative reactivities of a series of substituted styrenes toward styrene radical were determined. These results show rate enhancement by electron-withdrawing substituents and tend to correlate with the σ^- parameters. Thus, the high reactivity of the para nitro compound in the present study could be due to copolymerization taking place preferentially to,

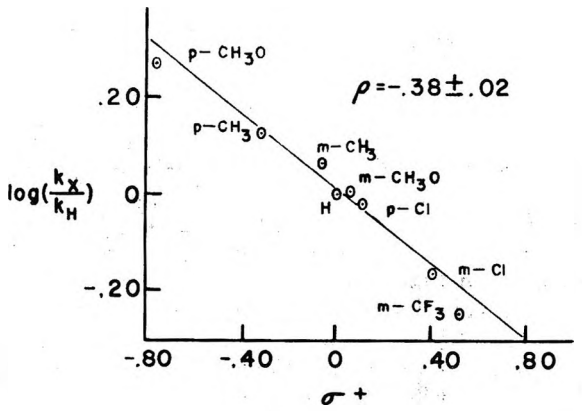
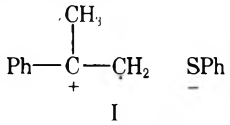


Figure 1. Correlation of log k_X/k_H and σ^+ for the addition of thiophenol to substituted α-methylstyrenes.

or together with, the desired addition process. This possibility was supported by an experiment in which a small amount of thiophenol caused more than twice the expected amount of *p*-nitro-α-methylstyrene to react.

The reaction shows a modest dependence upon the substituent in the α-methylstyrene system. The ρ value appears to be consistent with the exothermic addition step.[7] In terms of the Hammond postulate,[8] the transition state should tend to resemble the olefin plus thiyl radical more than the intermediate benzylic radical, giving rise to less sensitivity of the reaction to the substituent. Furthermore, the better correlation was obtained with the σ^+ parameters. In the formalism of Russell,[9] this result can be taken as evidence for significant contribution by structure I to the



I

transition state of the addition step. Another explanation of such substituent effects, suggested by a number of groups,[4c-e] is that they arise out of initial complex formation between the olefin and radical. However, at the present time, no definitive choice between these two interpretations can be made.

Experimental Section

Materials. Reagent benzene and *o*-dichlorobenzene were used without further purification. Commercial α-methylstyrene was distilled before use. In general, the substituted α-methylstyrenes were prepared from the appropriate aryl Grignard and acetone, followed by dehydration, according to literature methods.[10] *p*-Nitro-α-methylstyrene was prepared from cumene by nitration, followed by bromination with *N*-bromosuccinimide, and dehydrobromination.[11] Glc analysis showed the purity of all compounds to be greater than 98%. Physical properties of all compounds agreed with literature values.

Equipment. All glc analyses were performed on a Varian Aerograph Model 202B and a Sargent recorder with a disc integrator. A 0.25 in. × 12 ft aluminum column packed with 5% SE-30 on Chromosorb W or a 0.25 in. × 12 ft aluminum column packed with 8% FFAP on Chromosorb W were used.

Product Studies. An approximate 1:1:5 mixture of thiophenol, α-methylstyrene, and benzene was irradiated with a 275-w sunlamp for 1 hr at 70°. Glc analysis showed only the reactants (>94% reacted) and one other peak of considerably longer retention time. Isolation and analysis of this component showed that it was 2-phenyl-1-thiophenoxypropane.

A similar study was carried out for *p*-methoxy-α-methylstyrene. From this study it was determined that less than 4% of the olefin disappeared *via* polymerization. Total reaction was again greater than 90%.

A final study was carried out to determine whether the overall reaction was reversible. Equimolar amounts of 2-phenyl-1-thiophenoxypropane and *p*-methoxy-α-methylstyrene were allowed to react for 45 min in benzene at 70°. No α-methylstyrene was observed to be formed and the para methoxy compound decreased by no more than 2%.

Kinetics. The basic kinetic procedure has been described previously.[12] Mixtures of approximately 1:1:1:1:5 α-methylstyrene I, α-methylstyrene II, thiophenol, o-dichlorobenzene, and benzene were used. Reaction times varied from 35 to 90 min with per cent reaction 31–62%. The substituted α-methylstyrenes were run against *p*-chloro-α-methylstyrene in order to facilitate glc analysis. The rates of reaction relative to *p*-chloro-α-methylstyrene were then adjusted so that the parent hydrocarbon had a relative reactivity of 1.00.

Registry No.—Thiophenol, 108-98-5.

References and Notes

(1) Presented at the Northwest Regional Meeting of the American Chemical Society, Pullman, Wash. June 14, 1973.
(2) P. I. Abell, "Free Radicals," Vol. II, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, Chapter 13.
(3) (a) R. M. Kellog, *Methods Free-Radical Chem.*, **2**, 1 (1969); (b) F. W. Stacey and J. F. Harris, Jr., *Org. React.*, **13**, 164 (1963); (c) W. A. Pryor, "Mechanisms of Sulfur Reaction," McGraw-Hill, New York, N.Y., 1962, pp 75–93; (d) C. Walling, "Free Radicals in Solution," Wiley, New York, N.Y., 1957, pp 313–326.
(4) As representative studies see (a) M. M. Martin and G. J. Gleicher, *J. Amer. Chem. Soc.*, **86**, 233 (1964); (b) C. Walling, D. Seymour, and K. B. Wolfstirn, *ibid.*, **70**, 2559 (1948); (c) J. I. G. Cadogan and I. H. Sadler, *J. Chem. Soc. B*, 1191 (1966); (d) H. Sakurai, S. Hayashi, and A. Hosomi, *Bull. Chem. Soc. Jap.*, **44**, 1945 (1971); (e) T. Mojelsky and Y. L. Chow, *J. Amer. Chem. Soc.*, **96**, 4549 (1974).
(5) J. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N.Y., 1963, p 204.
(6) C. Walling, D. Weymour, and K. B. Wolfstirn, *J. Amer. Chem. Soc.*, **70**, 1544 (1948).
(7) See ref 3d, p 314.
(8) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).
(9) G. A. Russell and R. C. Williamson, Jr., *J. Amer. Chem. Soc.*, **86**, 2357 (1964).
(10) G. B. Bachman and L. L. Lewis, *J. Amer. Chem. Soc.*, **69**, 2022 (1947).
(11) Y. Okamoto and H. C. Brown, *J. Amer. Chem. Soc.*, **79**, 1709 (1957).
(12) G. J. Gleicher, *J. Org. Chem.*, 33, 332 (1968).

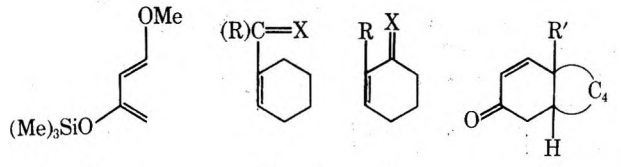
A Diels–Alder Route to Cis-Fused Δ^1-3-Octalones

Summary: Cycloaddition of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene with cyclohexene-type nucleophiles leads to *cis*-fused Δ^1-3-octalones.

Sir: Applications of the Diels–Alder reaction to the synthesis of octalones and decalones using dienophiles such as **2** and **3** (X = O, etc.) have, on the whole, proven disappointing.[1-4] High temperatures have been necessary to effect reaction, and low yields have resulted.

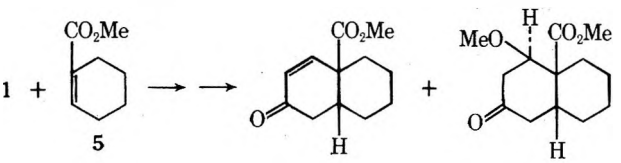
In connection with synthetic objectives directed toward vernolepin,[5,6] we sought to prepare cis-fused octalone derivatives of the type **4**. It will be recognized that such systems are not readily prepared from the corresponding *cis*-fused decalones.[7] The tendency of such decalones to undergo enolization-induced functionalizations preferentially[8] at the 4 position, or competitively at the 2 and 4 positions,[9] is well known. A recent solution to this problem in the steroid series[10] has not yet been extended to simpler systems.[11]

Recently we described[12] the preparation of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**1**). The smooth cycloadditions[12] of **1** with conventional electron-withdrawing dienophiles suggested that it might be sufficiently reactive to undergo Diels–Alder reactions with systems of the type **2** and **3** under milder conditions than have thus far been possible. The cycloadducts would be expected to suffer ready conversion to the target system, **4**.



1 **2** **3** **4**

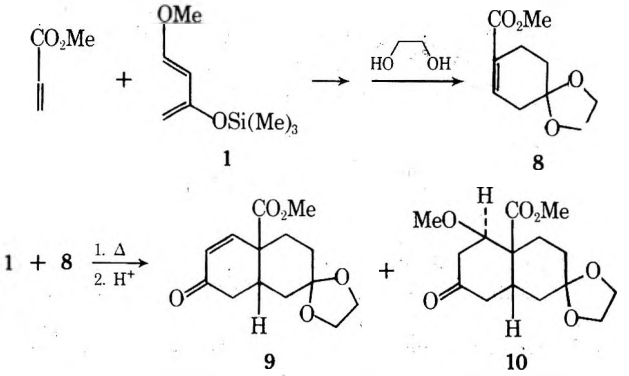
Compounds **1** and **5** were heated in a sealed tube at 190° for 30 hr. The total reaction product was added to a solution of 3:1 THF:0.005 *N* HCl at −5 to 0°. After work-up, the reaction mixture was chromatographed on silica gel. Subsequent to elution of traces of **5**, a 53% yield of enone **6** [$\bar{\nu}_{max}$ ($CHCl_3$) 1720, 1669, 1645 (sh) cm^{-1}; λ_{max} (EtOH) 229 nm (ϵ 22,500); δ ($CDCl_3$) 3.75 (s, 3 H, CO_2Me), 6.01 (d, J = 10 Hz, 1 H, O=CC**H**=CH–), 6.63 (dd, J = 10 Hz, O=C-CH=C**H**–) ppm] was obtained. Further elution afforded a 2% yield of the β-methoxy ketone **7** [$\bar{\nu}$ ($CHCl_3$) 1720 (sh), 1710 cm^{-1}; δ ($CDCl_3$) 3.24 (s, 3 H, OCH_3), 3.5–3.8 (m, containing s at δ 3.75, 4 H, OCHR + CO_2CH_3) ppm].



6 **7**

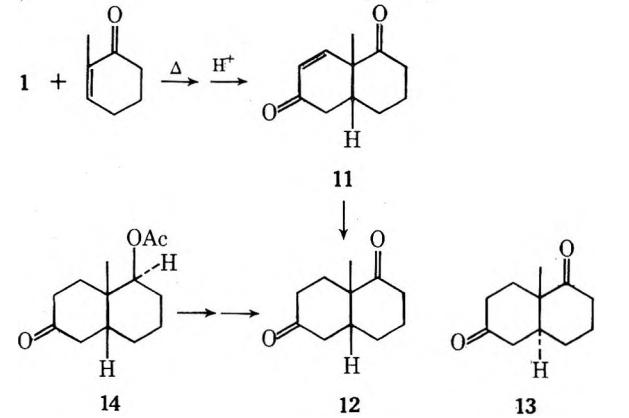
The possibilities of conducting sequential Diels–Alder reactions with diene **1** are seen in the three-step assemblage of enone ketal **9**. A solution of methyl acrylate (20 mmol) and diene **1** (23 mmol) in benzene (5 ml) was heated under reflux for 24 hr. Ethylene glycol (2 g), *p*-toluenesulfonic acid (200 mg), and additional benzene (15 ml) were added. Reflux was continued for an additional 6 hr with azeotropic removal of water. Work-up and chromatography on silica gel gave an 85% yield of ketal ester **8**, mp 40–41°. *Compound* **8**, *itself, functions as a dienophile in another Diels–Alder reaction with* **1**. The conditions required for this reaction are more severe (1 equiv of **8**, 5 equiv of **1** in xylene; sealed tube; 175–185°; 40 hr). Treatment of the total reaction mixture with 3:1 THF:0.005 *N* aqueous HCl at −5 to 0° for 10 min allowed for maintenance of the ketal while the β-methoxysilyl enol ether was unraveled to the desired enone. Chromatography on silica gel gave 11% recovered **8** and a 73% yield (65% efficiency) of enone ketal ester **9**, whose spectral properties [$\bar{\nu}_{max}$ ($CHCl_3$) 1724, 1675, 1650 (sh) cm^{-1}; λ_{max} (EtOH) 226 nm (ϵ 13,000); δ ($CDCl_3$) (3.71, s, 3 H CO_2CH_3), 3.90 (s, 4 H, dioxolane), 6.01 (d, J = 10 Hz, O=CC**H**=CH–), 6.60 (dd, J = 10 Hz, J = 1.5 Hz, 1 H, O=CCH=C**H**–)] confirm its structure. A 2% yield of the β-methoxy ketone **10** [$\bar{\nu}_{max}$ ($CHCl_3$) 1730 (sh), 1710 cm^{-1}; δ ($CDCl_3$) 3.22 (s, 3 H, OCH_3), 3.7 ~3.85 (m, containing s at δ 3.75, 4 H, OC**H**R + CO_2CH_3), 3.88 (s, 4 H, dioxolane) ppm] was obtained on further elution.

Compound **9** is a potentially valuable synthetic intermediate since it contains differentiated carbonyl systems and angular functionality.[13]



9 **10**

The cycloaddition of **1** with cyclohexene dienophiles of the type **3** was demonstrated with 2-methylcyclohexenone.[14] A solution of compound **1** (3.5 equiv) and the enone (1 equiv) in xylene was heated in a sealed tube at 200° for 20 hr. The total reaction mixture was treated with 3:1 THF:0.005 *N* aqueous HCl. Work-up and chromatography gave 11% recovered enone and 47% (42% efficiency) enedione **11**: mp 54–55°; $\bar{\nu}_{max}$ ($CHCl_3$) 1700, 1680, 1655 cm^{-1}; λ_{max} (EtOH) 227 nm (ϵ 7,000); δ ($CDCl_3$) 1.45 (s, 3 H, angular CH_3), 5.98 (d, J = 10 Hz, 1 H, O=CC**H**=CH–), 6.58 (d, J = 10 Hz, 1 H) ppm].



14 **12** **13**

In view of the rather harsh reaction conditions used in the cycloaddition, the stereochemistry of the product was confirmed in a chemical fashion. Catalytic hydrogenation of **11** gave the dihydro compound **12**, mp 65–66°. The spectral properties and melting point of **12** were different from those of the authentic trans compound, **13**, mp 57.5–59°.[15,16] A positive comparison was made starting with the ketoacetate **14**.[16] Hydrolysis and Jones oxidation of **14** gave an authentic sample of **12**[17] undistinguishable with that prepared from the Diels–Alder route.

Studies of further applications of this active diene in Diels–Alder reactions as well as utilization of the octalones are in progress.

Acknowledgments. This research was supported by P.H.S. Grant CA-12107-10. Nmr spectra were obtained on facilities supported by P.H.S. Grant R.R.-00292-03. Assistence from the Hoffmann-La Roche Corp. is gratefully acknowledged

References and Notes

(1) For this type of Diels–Alder reaction with 1,3-butadiene or alkylbutadienes, *cf., inter alia*, (a) P. D. Bartlett and G. F. Woods, *J. Amer. Chem. Soc.*, **62**, 2933 (1940); (b) W. Nudenberg and L. W. Butz, *ibid.*, **65**, 1437 (1943); (c) A. M. Gaddis and L. W. Butz, *ibid.*, **69**, 117 (1947); (d) W. G. Dauben, J. M. Logan, and E. J. Blanz, Jr., *ibid.*, **76**, 6384 (1954); (e) M. Idelson and E. I. Becker, *ibid.*, **80**, 908 (1958); (f) E. D. Bergmann and A. Becker, *ibid.*, **81**, 221 (1959); (g) H. O. House, W. F. Gann, R. S. Ro, and D. J. Wluka, *ibid.*, **82**, 1463 (1960); (h) R. R. Dueltgen, Thesis, University of Michigan, 1968.

(2) For the use of 2-alkoxybutadienes, see I. V. Torgov, I. I. Zaretskaya, G. P. Verkholetova, S. N. Ananchenko, and V. M. Andreev, *Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk*, 78 (1953) [*Chem. Abstr.*, **48**, 33324 (1954)].

(3) For successful reactions with corresponding cyclopentenoid dienophiles, see R. L. Kronenthal and E. I. Becker, *J. Amer. Chem. Soc.*, **79**, 1095 (1957).

(4) For the Diels–Alder reaction of 3-carbomethoxycyclohex-2-en-1-one, see S. Torii, T. Kunitomo, and T. Okamoto, *Bull. Chem. Soc. Japan*, **47**, 2349 (1974).

(5) (a) S. M. Kupchan, R. J. Hemingway, D. Warner, and A. Karim, *J. Org. Chem.*, **34**, 3903 (1969); (b) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).

(6) Cyclohexenones of the type 4 are readily convertible to the corresponding cis-fused δ-lactones required for vernolepin: S. Danishefsky, K. Kato, and P. Schuda, manuscript in preparation.

(7) For entries to the corresponding trans-fused Δ^1-3-decalones by bromination–dehydrobromination, see (a) R. Rinker, J. Kalvoda, D. Arigoni, A. Furst, O. Jeger, A. M. Gold, and R. B. Woodward, *J. Amer. Chem. Soc.*, **76**, 312 (1954); (b) M. Los, U. S. Patent 3,592,855 (1971) [*Chem. Abstr.*, **75**, 140371 (1971)].

(8) For a general review of the direction of functionalization of steroidal coprostanone systems where enolization in the $\Delta^{3(4)}$ sense is strongly favored, see (a) A. J. Liston, *J. Org. Chem.*, **31**, 2105 (1966), and references. For the corresponding reactions in the tricyclic (abietane) series, see (b) M. E. Kuehna, *J. Amer. Chem. Soc.*, **83**, 1492 (1961).

(9) In the case of *cis*-2-decalones, competive reactions (~1:1) have been noted for (a) enamine formation [G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963)] and (b) enol acetylation [J. A. Marshall, G. L. Bundy, and W. I. Fanta, *J. Org. Chem.*, **33**, 3913 (1968)].

(10) Y. Yanuka and G. Halperin, *J. Org. Chem.*, **39**, 3047 (1974).

(11) For another example of functionalization (oxalylation under thermodynamic control), see G. Stork and R. K. Hill, *J. Amer. Chem. Soc.*, **79**, 497 (1957).

(12) S. Danishefsky and T. Kitahara, *J. Amer. Chem. Soc.*, 96, 7807 (1974).

(13) For other entries to cis-fused Δ^1-octalones, see (a) J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, **36**, 877 (1971); (b) J. A. Marshall and R. A. Ruden, *ibid.*, **37**, 659 (1972); and (c) E. Wenkert, F. Haviv, and A. Zeitlin, *J. Amer. Chem. Soc.*, **91**, 2299 (1969).

(14) This compound is prepared through a one-step reaction—2-vinylpyridine with sodium–ammonia–ethanol followed by work-up with aqueous sodium hydroxide (P. Cain, unpublished results, University of Pittsburgh). A full account of the preparation of 2-substituted cyclohexenones will be reported in due course.

(15) V. Prelog and D. Zäch, *Helv. Chim. Acta*, **42**, 1862 (1959).

(16) We thank Professor Clayton Heathcock, Department of Chemistry, University of California at Berkeley, for generous samples of **13** and **14**.

(17) S. Swaninathan and M. S. Newman, *Tetrahedron*, **2**, 88 (1958).

Department of Chemistry **S. Danishefsy***
University of Pittsburgh **T. Kitahara**
Pittsburgh, Pennsylvania 15260

Received November 18, 1974

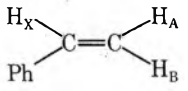
Hofmann Elimination with Diazomethane on Quaternary Curare Bases[1]

Summary: Treatment of (+)-tubocurarine, (+)-isotubocurarine, and (+)-chondocurarine at room temperature with an excess of diazomethane leads to Hofmann elimination type methine bases resulting from unique stereochemical pathways.

Sir: When O-methylating (+)-tubocurarine chloride (I) with excess diazomethane in the usual way to produce the O,O-dimethyl derivative, we observed that the crude reaction product, when examined by thin layer chromatography (tlc), showed anomalous spots which could logically be ascribed to unexpected tertiary bases on the basis of their R_f values. Additional experimentation indicated that the apparent intensities of the spots were enhanced with larger amounts of diazomethane. The same experiment repeated on (+)-isotubocurarine (II)[2] and chondocurarine chloride (III) reinforced the conclusion that a Hofmann elimination reaction had taken place to generate tertiary methine bases by the action of diazomethane on I, II, and III. This stimulated a more informative inquiry into the anomaly.[3]

The general aspects of the presently reported reaction were that the respective quaternary bases were treated in methanolic solution with a tenfold molar excess of ethereal diazomethane[4] added incrementally over a 24-hr period. The work-up of the products was essentially a separation on 1-mm precoated silica gel plates developed with a solvent system composed of 2.5% ammonia:ethyl acetate:2-propanol:methanol (0.7:3:3:4). The appropriate bands were removed and extracted with a suitable solvent mixture of methanol and ethyl acetate to yield the respective products.[5]

Examination of the nuclear magnetic resonance (nmr) spectra ($CDCl_3$, δ) of the methine bases obtained from I, II, and III provides an interesting comparison of steric factors directing the course of the Hofmann elimination (see Figure 1). The major elimination product of I isolated was the stilbene derivative (IV): 2.32 [s, 6, $N(CH_3)_2$], 2.46 (s, 3, NCH_3), 3.76 (d, 6, 2 OCH_3), 3.87 (d, 6, 2 OCH_3), 5.82–7.08 [m, 12, 10 aromatic and 2 vinyl (*i.e.*, stilbene)]. In the case of II, the methine base was exclusively a styrene derivative (V): 2.10 (s, 3, NCH_3), 2.25 [s, 6, $N(CH_3)_2$], 3.67 (d, 6, 2 OCH_3), 3.83 (d, 6, 2 OCH_3), 5.16–5.56 (4d, 2, the AB styrene protons in



J_{AX} = 9, J_{BX} = 17, J_{AB} = 1.5 Hz), 5.80–6.95 (m, 11, 10 aromatic and the X proton of the styrene product). III behaved in the expected manner to fom a monostilbene–monostyrene derivative (VI): 2.22 [s, 6, $N(CH_3)_2$], 2.34 [s, 6, $N(CH_3)_2$], 3.75 (d, 6, 2 OCH_3), 3.82 (d, 6, 2 OCH_3), 5.16–5.56 [4d, 2, the AB styrene protons (as in V)], 5.80–7.05 [m, 13, 10 aromatic, 3 vinyl (*i.e.*, 2 stilbene protons and the X proton of the styrene moiety)].

These unique stereochemical pathways become explicable by examining Dreiding models of the compounds. By orienting the molecules in their preferred conformations,[6,7] several observations account for the pathways that I, II, and III undergo in this Hofmann elimination reaction.

(1) Assuming that the eliminations proceed mostly by an E2 mechanism[8] wherein the groups must be anti-periplanar, it will be noticed that in the case of I the β hydrogens on C-4′ leading to a styrene product and those on C-a′ leading to a stilbene product can be oriented anti to the leaving quaternary group with equal ease. Thus, in I, since

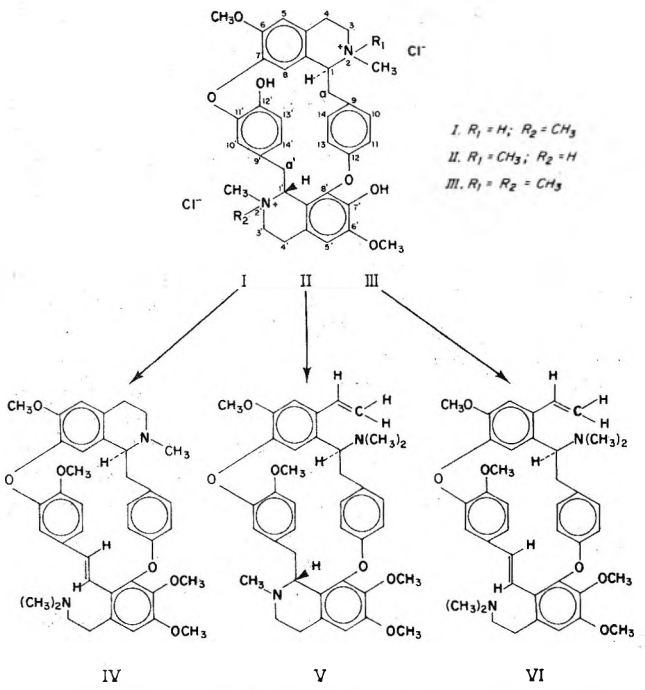


Figure 1. The generation of a stilbene derivative (IV) from (+)-tubocurarine (I), a styrene derivative (V) from (+)-isotubocurarine (II), and a stilbene-styrene derivative (VI) from (+)-chondocurarine (III) by the action of excess ethereal diazomethane on alcoholic solutions of the substrates.

the β hydrogens leading to both styrene and stilbene products are equally accessible, the driving force would be the greater stability derived from the extended conjugation when a stilbene rather than a styrene olefin is formed, and, therefore, the formation of IV is favored. In II, only the β hydrogens on C-4 leading to a styrene product can be oriented anti to the leaving group, and, thus, V is formed exclusively. It follows that VI (a stilbene on the lower portion and a styrene on the upper portion of the molecule) would be the product expected from the elimination reaction on III since no new conformational changes have been introduced.

(2) Other plausible explanations of this behavior rest on the natural structural restrictions placed on all compounds of the curine–chondocurine type.[9] This stems from the positions of the phenyl ether linkages present. In this subgroup of bisbenzyltetrahydroisoquinolines, the two phenolic junctions are not para–para (*i.e.*, symmetrical as in the isochondodendrine type) nor meta–meta (as in the hayatine type) but are, rather, meta–para. This structural feature is probably largely responsible for the unique course of reaction that I, II, and III undergo in the present Hofmann elimination. Specifically, two consequences of the restriction become evident.

(a) The conformation of the molecules is such that the phenolic ether oxygen between C-8′ and C-12 is less than 3 Å away from the β hydrogens at C-a′ (which lead to a stilbene product), whereas the other phenolic ether oxygen lying between C-7 and C-11′ is separated by more than 10 Å from the β-hydrogens at C-a. We feel that the proximity of this oxygen atom to the protons at C-a′ in I facilitates their removal and, consequently, contributes to the formation of the stilbene product (IV). This driving force is not operable to remove the protons at C-a in the case of II, hence the formation of the styrene product (V).

(b) In focusing attention on the possible olefinic products formed, the virtually exclusive formation of a stilbene product (IV) from I and a styrene product (V) from II would be expected because of the restrictions brought about by this type of phenyl ether linkage. A *trans*-stilbene[10] can only be accommodated in the lower portion of the molecule, *i.e.*, leading to IV, whereas in the upper portion only a *cis*-stilbene can be formed which would probably be unfavorable because of the resulting steric hindrance.

It may be noted that all of the above arguments rely on steric factors for their validity. We believe that electronic considerations play only a minor role, if any, in influencing the course of the Hofmann elimination in these compounds.

References and Notes

(1) This research was supported by the National Institutes of Health through Grant No. NS 08427.
(2) T. O. Soine and J. Naghaway, *J. Pharm. Sci.*, **63**, 1643 (1974).
(3) A more broadly based investigation concerning the action of diazomethane on quaternary ammonium salts is currently under way in order to obtain a better understanding of this unique reaction.
(4) All precautions (*e.g.*, drying, distillation, etc.) were taken to prevent the possibility of carryover alkalinity from the generation of diazomethane from *N*-nitroso-*N*-methylurea with strong base. No alkalinity was detected.
(5) Compounds IV, V, and VI have been characterized by analytical (C, H, N) and spectral (uv, ir, nmr) data.
(6) P. Codding and M. N. James, *J. Chem. Soc., Chem. Commun.*, 1174 (1972).
(7) R. Egan, R. Stanaszek and D. Williamson, *J. Chem. Soc., Perkin Trans. 2*, 716 (1973).
(8) We are aware that in the Hofmann elimination reaction other mechanistic pathways may be operative. Nevertheless, although one cannot be completely sure of an E2 elimination, the circumstances and product pathways seem to agree with this assumption.
(9) M. Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology," Academic Press, New York, N.Y., 1972, p 117.
(10) In general, for steric reasons, a *trans*-stilbene is more stable and is usually favored in formation over a *cis*-stilbene.

Department of Medicinal Chemistry
College of Pharmacy
University of Minnesota
Minneapolis, Minnesota 55455

Janette Naghaway
Nadim A. Shaath
Taito O. Soine*

Received November 8, 1974

The Nature of the λ 263 Chromophore in the Palytoxins[1]

Summary: Palytoxins, the toxic constituents of zoanthids of the genus *Palythoa*, are substituted *N*-(3-hydroxypropyl)-*trans*-3-amidoacrylamides.

Sir: Except for certain polypeptides and proteins from bacteria (botulinus, tetanus, and diphtheria toxins) and plants (ricin), the palytoxins are the most poisonous substances known to date. We first isolated a palytoxin from a marine coelenterate known to the Hawaiians as *limu-make-o-Hana* (the deadly seaweed of Hana)[2] and now designated *Palythoa toxica* Walsh and Bowers.[3] Since then, seemingly identical toxins have been isolated from several other species of zoanthids of the genus *Palythoa*.[4–6] The palytoxins from *P. toxica, P. mammilosa* Ellis and Solander from Jamaica, and a new species of *Palythoa* from Tahiti possess identical lethal and anticancer properties[5] and exhibit the same uv spectra (λ_{max} 233, 263 nm). Subtle differences, however, can be seen in the pmr and cmr spectra of the three toxins (Figure 1) despite their large molecular weights and absence of repetitive amino acid or sugar units.[7] We now wish to report identification of a moiety that contains two of the four nitrogens in palytoxin and exhibits the 263-nm chromophore of the toxin.

The cmr spectra of the palytoxins show signals at 169.2 and 175.6 ppm[8] which are assigned to two amide[9] carbons. The 300-MHz pmr spectra of the palytoxins in 100% DMSO-d_6[10] display two amide NH absorptions. One is a

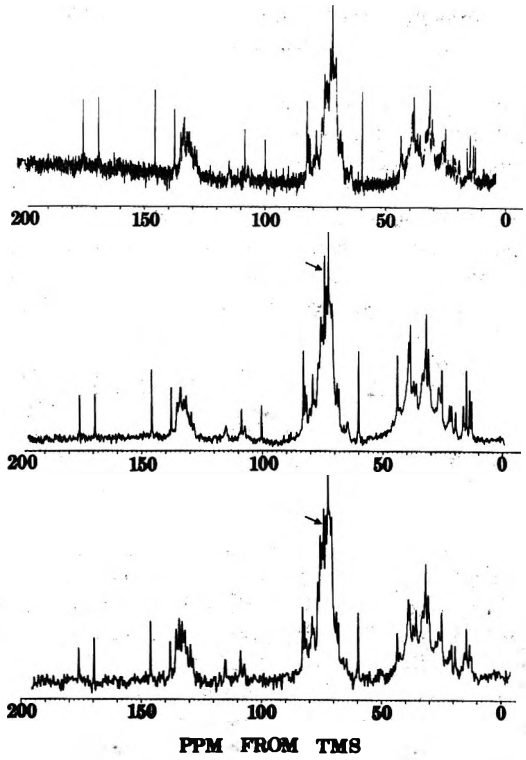
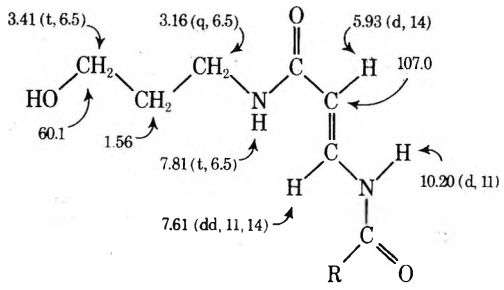


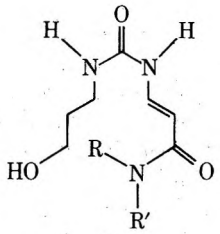
Figure 1. Comparison of the 25.2-MHz cmr spectra of palytoxins from Hawaiian *Palythoa toxica* (bottom), Jamaican *P. mammilosa* (middle), and an unknown Tahitian *P. ssp.* (top): 0.2, 0.5, and 0.4 g/2.5 ml of D_2O, respectively. Arrows point out a line at 73.5 ppm in the spectral traces of the Hawaiian and Jamaican toxins that is missing in the spectrum of the Tahitian sample. Note also that the line at 100.2 ppm in the upper and center traces is absent in the lower spectrum.

triplet (J = 6.5 Hz) at δ 7.81, which was subsequently assigned to a 3-amidopropanol residue and corroborated by nmdr and deuterium exchange experiments. The other NH signal is a doublet (J = 11 Hz) at δ 10.20 ascribed to an amido group attached to the β position of a trans disubstituted α,β-unsaturated carbonyl system. The α and β protons appear as a doublet and a doublet of doublets at δ 5.93 (J = 14 Hz) and 7.61 (J = 11 and 14 Hz). Irradiation of the NH at δ 10.20 or addition of D_2O reduces the signal for the β proton to a doublet. The doublet resonance experiment also causes an appreciable sharpening of the NH triplet at δ 7.81, showing long range coupling between the two NH protons.

These data suggested to us two partial structures 1 and 2 for palytoxin. After studying model compounds such as 3 [mp 88–89°; λ_{max} 264 nm (ϵ 22,000)], 4,[11] 5 (mp 77.5–78.5°),



1



2

and 6 it was clear that the β-amidoacrylamide (1) provides a better fit. In disubstituted ureas (6) no W coupling is observed between the two NH protons. Furthermore the chemical shifts of the NH protons and the carbonyl carbon of disubstituted ureas are observed at higher field than those for palytoxin.[12] Confirmation was achieved by acid hydrolysis and hydrogenation of palytoxin.

When a palytoxin is hydrolyzed in refluxing 2 N HCl for 4 hr the 263-nm uv band disappears as does toxicity. After ultrafiltration of the hydrolysate through a Diaflo UM-2 membrane,[13] only 3-aminopropanol is identified in the diffusate (pmr). The other products are either volatile and are lost during work-up or have molecular weights greater than 1000 and would be found in the retentate. When the palytoxin is catalytically hydrogenated (Pt/aqueous EtOH) prior to acid hydrolysis, equivalent amounts of β-alanine and 3-aminopropanol are obtained in the diffusate after ultrafiltration. These data suggest 7 and 8 as possible partial structures for hydrogenated palytoxin. Of these only 7 should yield on brief acid hydrolysis, in addition to β-alanine and 3-aminopropanol, a third ninhydrin-active product of low molecular weight, N-(3-hydroxypropyl)-3-aminopropionamide (9). In fact, synthetic N-(3-hydroxypropyl)-3-acetamidopropionamide [10, from β-alanine: (1) Ac_2O; (2) $ClCO_2Et$, Et_3N, 0°; (3) 3-aminopropanol], mp 102–103°, produces a maximum amount of 9 after a 0.5-hr reflux in 1 N HCl. In a parallel experiment, hydrolysis of hydrogenated palytoxin also gave 9 which was isolated by ultrafiltration (Diaflo UM-2 membrane) and chromatogra-

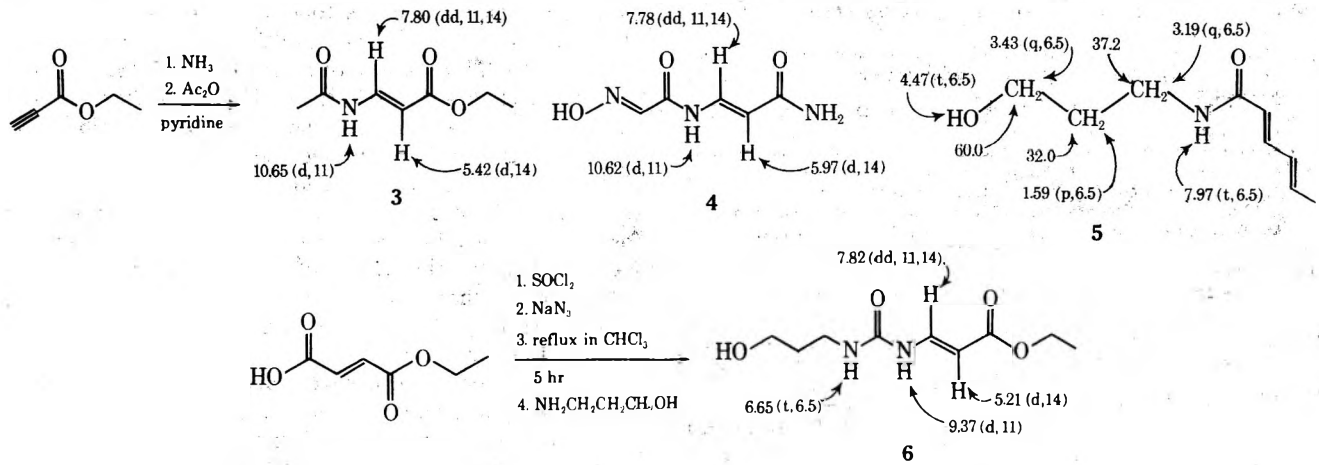
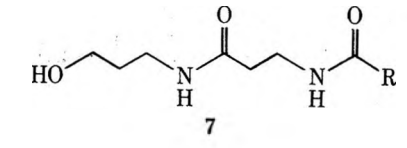
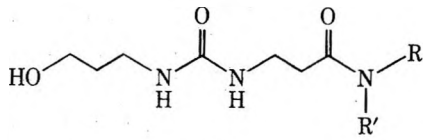


Figure 2. Nmr data and synthesis of model compounds.



7



8

phy of the diffusate on silica gel with a 7:2:1 mixture of 2-propanol–water–concentrated ammonia. Compound **9** was eluted between 3-aminopropanol and β-alanine and proved to be identical in all respects with synthetic **9** obtained by hydrolysis of **10** or by treatment of *N*-(3-hydroxypropyl)-β-phthalimidopropionamide [**11**, from β-alanine: (1) phthalic anhydride; (2) $ClCO_2Et$, Et_3N, 0°; (3) 3-aminopropanol], mp 166–167°, with hydrazine hydrate in EtOH (reflux) for 1 hr.[14]

The palytoxins are therefore substituted *N*-(3-hydroxypropyl)-*trans*-3-amidoacrylamides (1).

Acknowledgments. This work was supported by the U.S. Public Health Service. We are grateful to Lewis Cary and William Jankowski, Varian Associates, for determining the pmr and cmr spectra of Jamaican palytoxin.

Supplementary Material Available. The 300-MHz pmr spectrum of palytoxin from *Palythoa mammilosa* in 100% DMSO-d_6 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-540.

References and Notes

(1) Presented at the 9th International Symposium on Chemistry of Natural Products, IUPAC, Ottawa, Canada, June 1974, Abstract 14E.
(2) R. E. Moore and P. J. Scheuer, *Science*, **172**, 495 (1971).
(3) G. E. Walsh and R. E. Bowers, *Zool. J. Linn. Soc.*, **50**, 161 (1971).
(4) S. Kimura and Y. Hashimoto, *Publ. Seto Mar. Biol. Lab.*, **20**, 713 (1973).
(5) (a) R. J. Quinn, M. Kashiwagi, R. E. Moore, and T. R. Norton, *J. Pharm. Sci.* **63**, 257 (1974); (b) J. S. Wiles, J. A. Vick, and M. K. Christensen, *Toxicon*, **12**, 427 (1974).
(6) The palytoxin of *Palythoa tuberoulosa* Esper appears to be associated with the eggs of the female polyps [S. Kimura, Y. Hashimoto, and K. Yamazato, *Toxicon*, **10**, 611 (1972)].
(7) The molecular weight of palytoxin from *P. toxica* was estimated to be 3300 and its molecular formula $C_{145}H_{264}N_4O_{78}$ from combustion and spectral (pmr and uv) data.[1]
(8) Carbon chemical shifts are reported in δ units (parts per million) relative to *p*-dioxane (δ 67.4 relative to Me_4Si) as an internal standard in D_2O.
(9) Only amide carbonyl absorption is observed in the infrared spectrum of palytoxin (see ref 1).
(10) Proton chemical shifts are reported in δ units (2 parts per million) relative to Me_4Si (δ 0) and the residual DMSO-d_5 peak (δ 2.52) as internal standards.
(11) P. F. Wiley, R. R. Herr, F. A. MacKellar, and A. D. Argoudelis, *J. Org. Chem.*, **30**, 2330 (1965).
(12) The urea carbonyl carbon-13 signals for 1-(3-hydroxypropyl)-3-phenylurea (in DMSO-d_6), 1-(3-hydroxypropyl)-3-*n*-propylurea (in $CDCl_3$), and 4,8,14,18-tetraoxo-7,9,15-triaza-3,13,19-trioxa-*trans,trans*-heneicosa-5,16-diene (in $CDCl_3$) are found at 155.3, 160.1, and 153.4 ppm from Me_4Si. The NH protons resonate at 6.15 and 8.45, 5.75 and 5.81, and 9.39 and 6.75 ppm, respectively, in DMSO-d_6.
(13) Obtained from the Amicon Corp.
(14) All new compounds gave satisfactory elemental analyses.

Department of Chemistry
University of Hawaii
Honolulu, Hawaii 96822

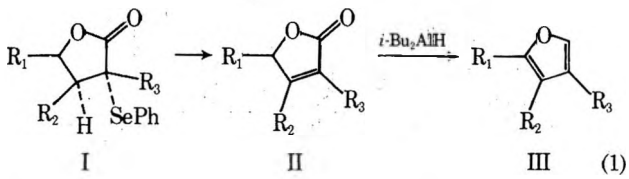
Richard E. Moore*
Robert F. Dietrich
(in part) Billie Hatton
Tatsuo Higa
Paul J. Scheuer*

Received November 1, 1974

Organoselenium Chemistry. A General Furan Synthesis

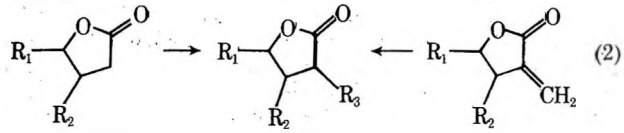
Summary: An efficient four-step synthesis of 2,4- and 2,3,4-substituted furans from γ-lactones *via* their corresponding butenolides is described.

Sir: The facile elimination of selenoxides derived from α-phenylselenenyl-γ-lactones with almost complete formation of endocyclic α,β-unsaturated butenolides suggested a general route to furans (eq 1).[1,2] We wish to report a gener-



I II III (1)

al method for the conversion of substituted γ-lactones into 2,4- and 2,3,4-substituted furans[3] *via* their corresponding butenolides (see Table I). The α-selenenylated γ-lactones of type I can be efficiently prepared by selenenylation of the corresponding α-substituted γ-lactones which are prepared by direct alkylation of lactone enolates[2,4] or by conjugate-addition of an organocopper reagent to an α-methylene-γ-lactone (eq 2).[5] The reaction sequence constitutes a



(2)

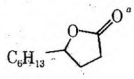
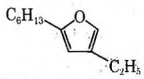
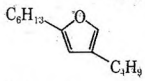
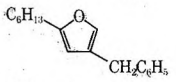
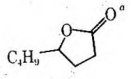
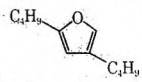
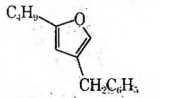
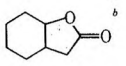
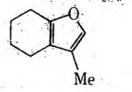
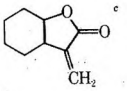
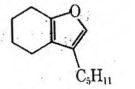
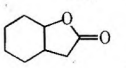
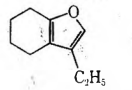
widely applicable method. As indicated in Table I, yields are generally high.

The method outlined above, however, is critically dependent upon only one of the two possible syn[6] modes of elimination predominating. α-Phenylselenenylated lactones have previously[2] been employed in the construction of fused α-methylene lactones with complete exclusion of the endocyclic double bond isomers.[7] We have observed, however, that selenoxides derived from I (R_3 = alkyl), in which there exists the possibility for two syn modes of elimination, result in >95% yield of the endocyclic olefin despite the statistical preference for exocyclic olefin formation. The high propensity for endocyclic olefin formation thus provides a useful $\Delta^{\alpha,\beta}$-butenolide synthesis as well as providing direct access to furans *via* reduction with diisobutylaluminum hydride[8] (see Table I).

A typical furan synthesis is illustrated below for the conversion of γ-decalactone[9] to 2-butyl-4-benzylfuran. The lithium enolate of γ-decalactone was prepared at −78° by slow addition (1 mmol/hr) of a solution of γ-decalactone (1 equiv, 1 *M* in THF) to a solution of lithium diisopropylamide (LDA) (1.05 equiv, 0.3 *M* in THF). After the mixture was stirred for 20 min, a solution of benzyl bromide (1.05 equiv, 1 *M* in THF) containing hexamethylphosphoramide (HMPA) (1.05 equiv) was added. The temperature was raised to *ca.* −40° and was maintained at that temperature for 3 hr. The reaction was quenched by the addition of 10% HCl and after usual work-up and chromatography on silica gel (hexanes/ether, 3:1) afforded α-benzyl-γ-decalactone (88%) [ir (film) 5.66 and 6.25 μ; nmr (CCl_4) δ 7.15 (s, 5 H), 4.18 (m, 1 H), 2.6–3.2 (m, 3 H)].

Selenenylation of α-benzyl-γ-decalactone was carried out by slowly adding (1 mmol/hr) a solution of the lactone (1.0 equiv, 1 *M* in THF) to a solution of LDA (1.1 equiv, 0.3 *M* in THF) cooled to −78°. After 20 min, the reaction mixture was treated with a solution of phenylselenenyl chlo-

Table I
Synthesis of 2,4- and 2,3,4-Substituted Furans

Example	Starting lactone	Yield[d] α-Alkylation	α-Phenylselenenylation	Elimination	Product	Yield[d] Reduction
1		72	70	80		88
2		60	80	98		75
3		88	72	85		99
4		70	72	99		84
5		98	83	85		99
6		90	88	95		66
7		99[e]	70	97		85
8		82	85	96		93

[a] See ref 9. [b] J. Klein, *J. Amer. Chem. Soc.*, 81, 3611(1959). [c] P. A. Grieco and N. Marinovic (unpublished results). [d] Yield represents pure compound isolated by chromatography; no attempt was made to optimize the yield. [e] Prepared by the addition of a solution of the α-methylene lactone (1.0 equiv, 0.25 *M* in THF) to a solution of lithium di-*n*-butylcopper (1.5 equiv, 0.15 *M* in THF) at −78°. After addition was complete, stirring was continued for 5.5 hr at −20°.[5]

ride[9] (1.1 equiv, 1 *M* in THF) containing HMPA (1.1 equiv). The temperature was maintained at −78° for 1 hr and −40° for 2 hr. Quenching with 10% HCl followed by usual work-up and purification on silica gel afforded a 72% yield of I ($R_1 = C_6H_{13}$, $R_2 = H$, $R_3 = CH_2C_6H_5$). To a solution of the above selenenylated lactone (1.0 equiv, 0.16 *M* in THF) at 0° containing a trace of acetic acid was added 30% hydrogen peroxide (*ca.* 6.0 equiv). After 30 min at 0°, the reaction was quenched by the addition of saturated $NaHCO_3$. Work-up afforded an 85% yield of butenolide II ($R_1 = C_6H_{13}$, $R_2 = H$, $R_3 = CH_2C_6H_5$) [ir (film) 5.71, 6.05, 6.24 μ; nmr (CCl_4) δ 7.18 (s, 5 H), 6.78 (m, 1 H), 4.75 (m, 1 H), 3.48 (t, J = 1 cps, 2 H)].

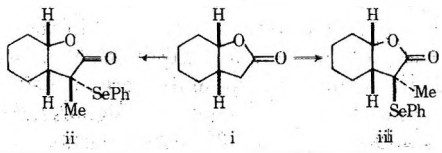
A solution of diisobutylaluminum hydride (DIBAL) (1.5 equiv, 0.5 *M* in THF) was added at −20° to a solution of the butenolide (1.0 equiv, 0.3 *M* in THF). After 3 hr at −20°, the reaction was quenched by the addition of 10% sulfuric acid and the reaction mixture was warmed to room temperature. Work-up afforded directly a 99% yield of III ($R_1 = C_6H_{13}$, $R_2 = H$, $R_3 = CH_2C_6H_5$) [nmr (CCl_4) δ 7.12 (s, 5 H), 6.90 (s, 1 H), 5.67 (s, 1 H), 3.60 (s, 2 H), 2.45 (t, 2 H)].

The high degree of endocyclic olefin formation during the elimination of the selenoxides derived from α-substituted α-selenenylated γ-lactones and the high degree of stereospecificity observed in the selenenylation of examples 6–8 associated with this approach to 3-substituted furans offers some advantages over existing methods.[3]

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (No. RO1 CA 13689-03) from the National Cancer Institute and in part by Eli Lilly & Co. We thank Mr. F. Okuniewicz for obtaining the mass spectral data.

References and Notes

(1) A report concerning the elimination of an α-phenylselenenylated γ-lactone with no alkyl group on the α carbon atom has been described by K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Amer. Chem. Soc.*, **95**, 6137 (1973). Also see H. J. Reich, I. L. Reich, and J. M. Renga, *ibid.*, **95**, 5813 (1973); D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 695 (1973).
(2) For the almost exclusive formation of an α-substituted butenolide when two possible syn[6] modes of elimination exist, see P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974).
(3) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold, New York, N.Y., 1953, p 30; F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, p 6; M. E. Garst and T. A. Spencer, *J. Amer. Chem. Soc.*, **95**, 250 (1973).
(4) J. L. Hermann and R. H. Schlessinger, *J. Chem. Soc., Chem. Commun.*, 711 (1973).
(5) We believe this to be the first report of a conjugate-addition of an organocopper reagent to an α-methylene lactone.
(6) K. B. Sharpless, M. W. Young, and R. F. Lauer, *Tetrahedron Lett.*, 1979 (1973).
(7) This route to α-methylene lactones represents a special case in that the α-methyl and α-phenylselenenyl substituents were introduced stereospecifically so as to establish an anti relationship between the α-phenylselenenyl substituent and the adjacent methine hydrogen (*e.g.*, i → ii).



Likewise one can control the stereochemistry on the α carbon atom so as to establish a syn relationship between the α-selenenyl substituent and the adjacent methine hydrogen (*e.g.*, i → iii) (see ref 2).
(8) H. Minato and T. Nagasaki, *Chem. Ind. (London)*, 899 (1965).
(9) Commercially available from Aldrich.
(10) Fellow of the Alfred P. Sloan Foundation, 1974–1976.

Department of Chemistry **Paul A. Grieco*[10]**
University of Pittsburgh **Chester S. Pogonowski**
Pittsburgh, Pennsylvania 15260 **S. Burke**

Received December 10, 1974

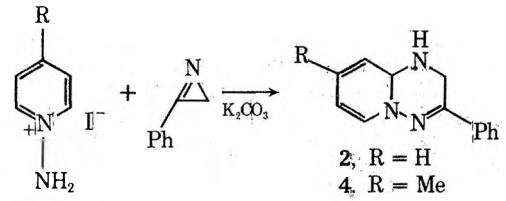
Reaction of Pyridinium *N*-Imines with 2-Phenylazirine

Summary: Pyridinium *N*-imine hydriodides **1** and **3** reacted with 2-phenylazirine in the presence of alkali to give the corresponding 3-phenyl-1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives **2** and **4** in good yields.

Sir: In the course of studies on the chemistry of pyridinium ylides, we recently reported the first synthesis of pyridotriazine derivatives from the reaction of pyridinium *N*-imines with α-haloacrylates. Mechanistic considerations suggested that the corresponding aziridine or azirine derivative as intermediate might be involved in this reaction.[1] This possibility has now confirmed by isolation of the 3-phenylpyridotriazines **2** and **4** from the reaction of pyridinium *N*-imines with the readily available 2-phenylazirine.

When the mixture of pyridinium *N*-imine hydriodide **1** with 2-phenylazirine[2] was treated with potassium carbonate in methylene chloride at room temperature for 4 days, a new compound **2** (mp 95–97°) was formed in 73% yield. *Anal.* Calcd for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 73.93; H, 6.22; N, 19.73. Similar treatment of 4-methylpyridinium *N*-imine hydriodide **3** with the azirine afforded the corresponding compound **4** (mp 112–115°) as yellow crystals in 65% yield. *Anal.* Calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.57; H, 6.69; N, 18.62. (See Scheme I.)

Scheme I



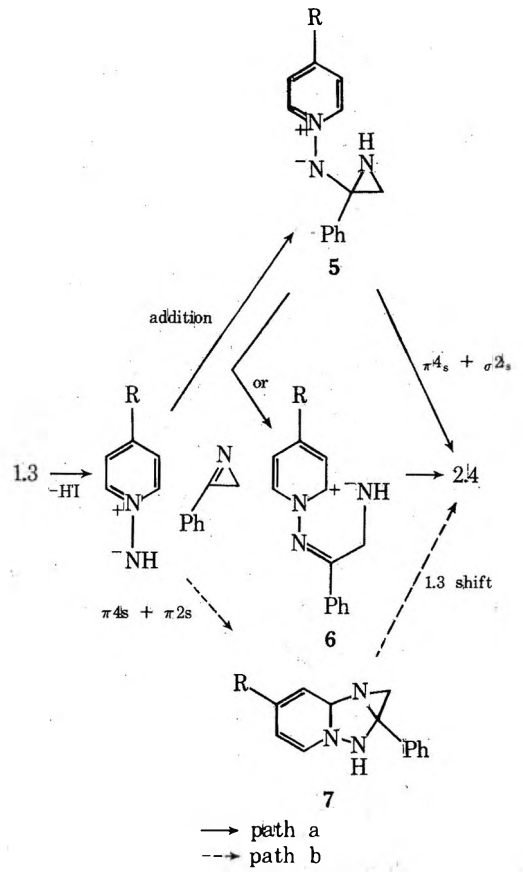
1, R = H
3, R = Me

2, R = H
4, R = Me

Compounds **2** and **4** were 1:1 adducts of the corresponding *N*-imines and 2-phenylazirine, and the ir spectra showed characteristic absorption for a secondary amino group at 3225 (**2**) or 3240 cm^{-1} (**4**) and a carbon–nitrogen or carbon–carbon double bond at 1637 (**2**) or 1654 cm^{-1} (**4**), respectively. The ^1H nmr spectrum of compound **2** exhibited signals due to five protons of the dihydropyridine ring at δ ($CDCl_3$) 4.74 (1 H, br t, J = 7.5, 7.5, 1.5 Hz, C_7 H), 5.23 (1 H, br d, J = 11.0 Hz, C_9 H), 5.42 (1 H, br s, C_{9a} H), 5.99 (1 H, m, C_8 H), and 6.62 (1 H, d, J = 7.5 Hz, C_6 H), an amino proton at δ 2.00 (1 H, br s), two methylene protons at δ 3.74 (1 H, d, J = 18.0 Hz) and 4.07 (1 H, d, J = 18.0 Hz), and five aromatic protons in the range of δ 7.1–7.5. The ^1H nmr spectrum of **4**, compared with that of **2**, showed the absence of one proton signal in the olefinic region and the presence of a new methyl signal at δ 1.79 (3 H, d, J = 1.5 Hz). These assignments were also supported by the correspondence of the ring proton signals in the spectra of **2** and **4** and of 2-methyl-3-methoxycarbonyl-1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine, prepared earlier by us.[1] From these results, we conclude that compounds **2** and **4** are 3-phenyl-1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine and its 8-methyl homolog.

The reaction probably proceeds *via* initial electrophilic addition of 2*H*-azirine to the *N*-imines, followed by homo-1,5-dipolar cyclization ($_\pi4_s + {}_\sigma2_s$) of resulting *N*-(2-aziridinium)iminopyridinium ylide **5** or by cyclization of 1,6-dipolar species **6** from **5** to give pyridotriazines **2** and **4** (path a). Similar addition reactions to azirine are well known.[3] An alternative route (path b) to **2** and **4** involves initial 1,3-dipolar cycloaddition ($_\pi4_s + {}_\pi2_s$) of the *N*-imines with the azirine followed by 1,3 shift of the amino hydrogen in the primary tricyclic adduct **7**. Since such thermal 1,3 shift is a symmetry-forbidden process,[4] the 1,3 migration should be proceed *via* not sigmatropic but ionic process under such basic condition as employed here.[5] The possible reaction mechanisms are shown in Scheme II.

Scheme II



In this reaction path a seems to be more probable than path b, because 1,3-dipolar cycloaddition of 2-phenylazirine with various N-substituted iminopyridinium ylides was unsuccessful. Further investigation of this reaction is in progress.

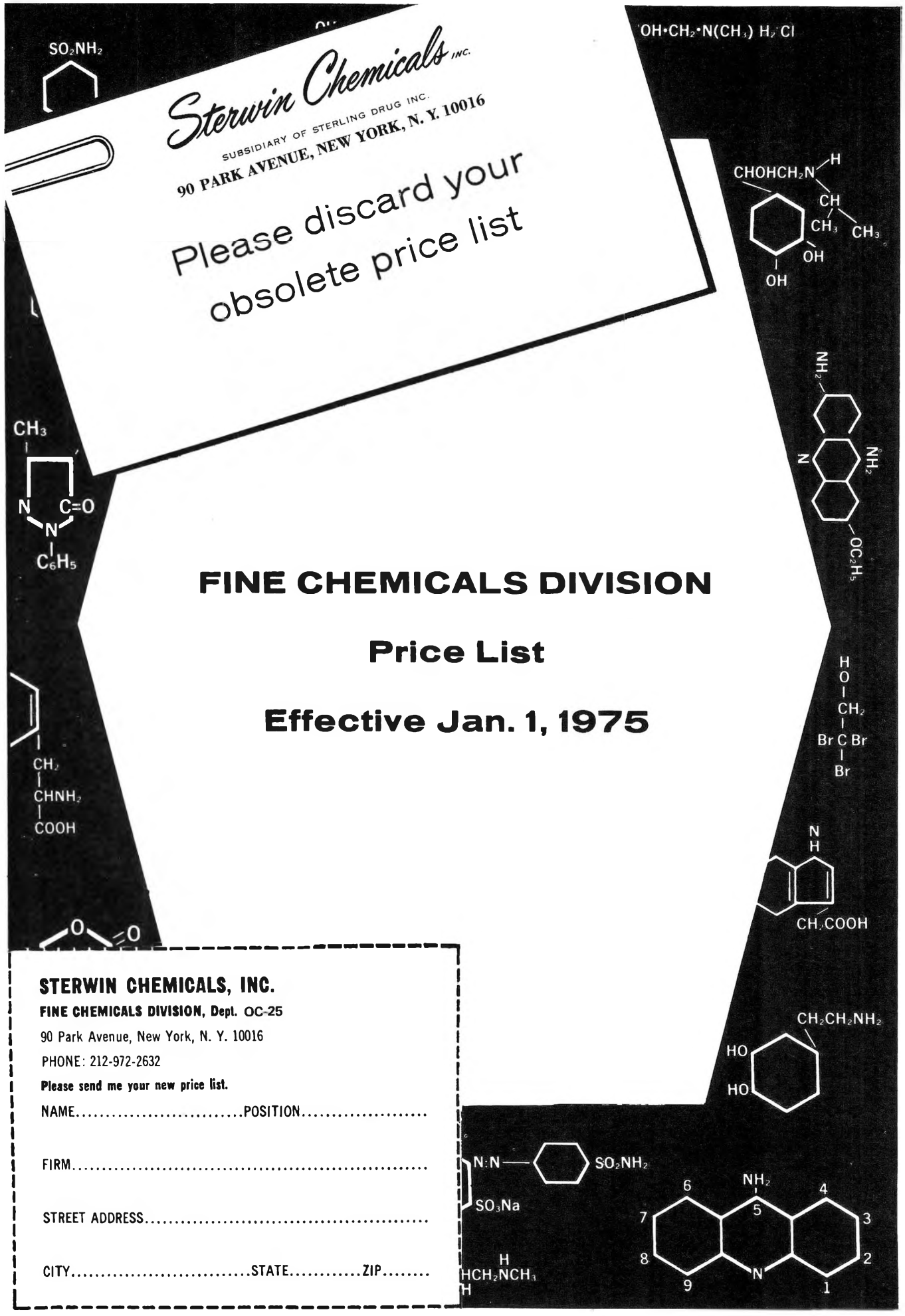
References and Notes

(1) A. Kakehi and S. Ito, *J. Org. Chem.*, **39**, 1542 (1974).
(2) (a) A. Hassner and F. W. Fowler, *Tetrehedron Lett.*, 1545 (1967); (b) A. Hassner and F. W. Fowler, *J. Org. Chem.*, **33**, 2686 (1968); (c) M. Komatsu, S. Ichijima, Y. Ohshiro, and T. Agata, *ibid.*, **38**, 4341 (1973).
(3) T. Nishiwaki and T. Sato, *Chem. Commun.*, 1479 (1970).
(4) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).
(5) (a) G. Bergsson and A. Weidler, *Acta Chem. Scand.*, **17**, 1798 (1963); (b) J. Almy, R. T. Uyeda, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 6768 (1967).

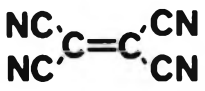
Department of Industrial Chemistry
Faculty of Engineering
Shinshu University
Wakasato, Nagano 380, Japan

Akikazu Kakehi*
Suketaka Ito
Takashi Manabe

Received December 5, 1974


Sterwin Chemicals INC.
SUBSIDIARY OF STERLING DRUG INC.
90 PARK AVENUE, NEW YORK, N. Y. 10016
Please discard your obsolete price list
FINE CHEMICALS DIVISION
Price List
Effective Jan. 1, 1975
STERWIN CHEMICALS, INC.
FINE CHEMICALS DIVISION, Dept. OC-25
90 Park Avenue, New York, N. Y. 10016
PHONE: 212-972-2632
Please send me your new price list.
NAME.....POSITION.....
FIRM.....
STREET ADDRESS.....
CITY.....STATE.....ZIP.....

TCNE and TCNQ: the electron-thirsty ones



TCNE

TCNQ

CHARGE-TRANSFER COMPLEXES — SEMICONDUCTORS

Having a high electron affinity, both **TCNE** and **TCNQ** form charge-transfer complexes with suitable electron donors, such as aromatic π-systems. Some of the solid complexes exhibit semiconductiong properties.[1] The most exciting one to date is the 1:1 complex of **TCNQ** and tetrathiofulvalene, which not only behaves like a metal over a large temperature range but has by far the largest maximum electrical conductivity of any known organic compound.[2]

CYCLOADDITION REACTIONS

TCNE is a reactive dienophile and undergoes Diels-Alder type reactions with conjugated dienes with unusual ease and at relatively low temperatures. It even reacts spontaneously with sluggish dienes such as 2-vinylnaphthalene without added catalyst or application of external heat.[1] With a diene incapable of forming a Diels-Alder product it reacts to yield a cyclobutane derivative.[1] **TCNE** undergoes 1,6-cycloaddition to 1*H*-azepines.[3]

DEHYDROGENATIONS

TCNE has been used successfully to aromatize 1,4-dihydrobenzenes[4] and to induce dehydrogenation of steroidal dienes.[5]

FOR OZONOLYSIS

Being stable to ozone, **TCNE** provides a new method for the cleavage of ozonides to produce aldehydes and ketones directly in good yields.[6]

SYNTHESIS OF HETEROCYCLIC COMPOUNDS

TCNE is a useful starting material for the synthesis of 5- and 6-membered heterocycles with one or two heteroatoms, such as thiophenes, pyrroles, isoxazoles, pyrazoles, pyridines, pyrimidines, as well as fused polynuclear heterocycles.[1]

ANALYTICAL APPLICATIONS

Its ability to form π-complexes with a variety of organic compounds instantly under mild conditions makes **TCNE** useful for determining and/or detecting many organic compounds, *e.g.*, aromatic hydrocarbons, phenols, aryl ethers.[1] Other complexometric or photometric methods for the determination of organic compounds are essentially based on the chemical reactivity of **TCNE**, such as the diene reaction and the aromatic substitution reaction.[1] **TCNQ** is a useful reagent for the colorimetric determination of free radical precursors, such as cysteine, proline, hydroxyproline, phenoxazines, and mercaptans.[7] It is also useful in locating the above amino acids, some amino acid derivatives, acridines, polynuclear aromatic hydrocarbons, mercaptans, thioamides, thiohydantoins and thiosemicarbazones on paper or thin layer chromatograms.[7] These techniques can be applied to air pollution studies.[7] A fluorimetric method using **TCNQ** to locate and detect 1-20γ of some fifty organic compounds (amines, amino acids, proteins, enzymes) on paper and silica gel chromatograms has also been described.[8] Furthermore, **TCNQ** is a color reagent for the thin layer chromatographic identification of the alkali, alkaline earth, and some post-transition metal ions. It is particularly sensitive for the detection of the univalent cations.[9]

References:

1) For a review on TCNE, see D. N. Dhar, *Chem. Rev.*, **67**, 611 (1967).
2) J. Ferraris, D. O. Cowan, V. Walatka, and J. H. Perlstein, *J. Amer. Chem. Soc.*, **95**, 948 (1973).
3) J. M. Photis, *J. Heterocycl. Chem.*, **8**, 729 (1971).
4) D. T. Longone and G. L. Smith, *Tetrahedron Lett.*, 205 (1962); J. A. Berson and M. R. Willcott III, *J. Amer. Chem. Soc.*, **87**, 2751 (1965).
5) A. L. Andrews, R. C. Fort, and P. W. LeQuesne, *J. Org. Chem.*, **36**, 83 (1971).
6) R. Criegee and P. Günther, *Chem. Ber.*, **96**, 1564 (1963); S. Munavalli and G. Ourisson, *Bull. Soc. Chim. France*, 729 (1964).
7) E. Sawicki, C. R. Engel, and W. C. Elbert, *Talanta*, **14**, 1169 (1967).
8) M. Guyer, Jr. and E. Sawicki, *Anal. Chim. Acta*, **49**, 182 (1970).
9) L. F. Druding, *Anal. Chem.*, **35**, 1582 (1963).

T880-9	**Tetracyanoethylene (TCNE)**	**10g $17.35**
		12.8g† $22.85
		25g $34.95
15,763-5	**7,7,8,8-Tetracyanoquino-**	**5g $14.50**
	dimethane (TCNQ)	**10g $27.50**
		100g $160.00

†Decimole unit

Aldrich Chemical Company, Inc.

Craftsmen in Chemistry

Corporate Offices:
Aldrich Chemical Co., Inc.
940 W. Saint Paul Ave.
Milwaukee, Wisconsin 53233

In Great Britain:
Aldrich Chemical Co., Ltd.
264 Water Rd., Wembley, Middx.
HAO 1PY, England

In Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium

In Germany:
EGA-Chemie KG
7924 Steinheim am Albuch
Germany