VOLUME 34 JULY 1969 NUMBER 7

Coden: JOCEAh

THE JOURNAL OF Organic Chemistry

PUBLISHED MONTHLY BY THE AMERICAN CHEMICAL SOCIETY

$Fe_2(CO)_9$

(Diiron nonacarbonyl; diiron enneacarbonyl)

At Alfa, we also stock technical know-how.

Ask us for any of over 2500 inorganic and organometallic research chemicals, ultrapure chemicals, and pure metals, and you'll get off-the-shelf, immediate delivery.

Ask us for technical assistance, and you'll get that too. That's what distinguishes Alfa from the order takers.

The golden yellow flakes of $Fe_2(CO)_9$ are virtually insoluble in all common solvents; even so, it is the most reactive of the three iron carbonyls. For example, only this carbonyl reacts with olefins at low enough temperatures to permit isolation of olefin-$Fe(CO)_4$ complexes. It is even possible to isolate butadiene-$Fe(CO)_4$ starting from $Fe_2(CO)_9$ (1). The higher reactivity also permits isolation of π-cyclopentadieneiron tricarbonyl, $C_5H_6Fe(CO)_3$, rather than the cyclopentadienyliron tricarbonyl dimer which results from using either of the other carbonyls (2). With proper control of conditions, $Fe_2(CO)_9$ can also accomplish the isomerization of dienes, the product being conjugated (3).

Perhaps the most interesting use of $Fe_2(CO)_9$ has been as the stabilizer (through complex formation) of unstable olefins, most notably butadiene (4) and trimethylenemethane (5). The chemistry of the butadiene complex has been particularly rich, due to its aromatic nature and its ability when decomposed in the presence of acetylenic compounds to generate Dewar benzene derivatives in great variety (6).

A selected bibliography of literature references and patents is available on request.

31132 Diiron nonacarbonyl, $Fe_2(CO)_9$
25 g. – $18.00
100 g. – 60.00

31113 $Fe(CO)_5$ 250 g. – $8.50
1000 g. – 23.00

31128 $Fe_3(CO)_{12}$ 25 g. – $19.40
100 g. – 68.00

Write for your free Alfa '69 Catalog. Alfa Inorganics, Inc., 80 Congress Street, Beverly, Mass. 01915. Tel: (617) 922-0768.

References

1. R.K. Kochhar and R. Pettit, *J. Organometallic Chem. 6*, 272 (1966).
2. "Diene-Iron Carbonyl Complexes and Related Species", R. Pettit and G.F. Emerson. ADVANCES IN ORGANOMETALLIC CHEMISTRY. Vol. I, Edited by F.G.A. Stone and R. West. Academic Press, New York, New York (1964).
3. F. Asinger, B. Fell and K. Schrage, *Chem. Ber., 98*, 372 (1965).
4. G.F. Emerson, L. Watts and R. Pettit, *J. Am. Chem. Soc., 87*, 131 (1965).
5. G.F. Emerson, K. Ehrlich, W.P. Giering and P.C. Lauterbur, *J. Am. Chem. Soc., 88*, 3172 (1966).
6. L. Watts and R. Pettit, *Adv. Chem. Ser. 62* 549 (1967).

VENTRON
ALFA INORGANICS, INC.

Western Distributor:
Wilshire Chemical Co., Inc.,
15324 So. Broadway, Gardena, Calif.
90247/(213) 323-9232.

THE JOURNAL OF Organic Chemistry

Published monthly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania

Published monthly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Easton, Pa.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Assistant Senior Production Editor, MARIANNE C. BROGAN; Assistant Editors, FERN S. JACKSON, BARBARA A. RIEGEL.

Advertising Office: Reinhold Publishing Corporation, 600 Summer St., Stamford, Conn. 06904

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

Correspondence concerning business matters should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Claims for missing numbers will not be allowed (1) if received more than 60 days from date of issue plus time normally required for postal delivery of journal and claim; (2) if loss was due to failure to notify the Subscription Service Department of a change of address; or (3) if the reason for the claim is that a copy is "missing from files."

Change of address: Notify Subscription Service Department, American Chemical Society, 1155 Sixteenth St. N.W., Washington, D. C. 20036. Such notification should include both old and new addresses and postal ZIP number, if any. Please send an old address label, if possible. Allow 4 weeks for change.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should issues of the current volume be out of print at the time the subscription order is received, the pro rata value of such issues will be refunded to the subscriber.

Subscriptions should be renewed promptly, to avoid a break in your series. Orders should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

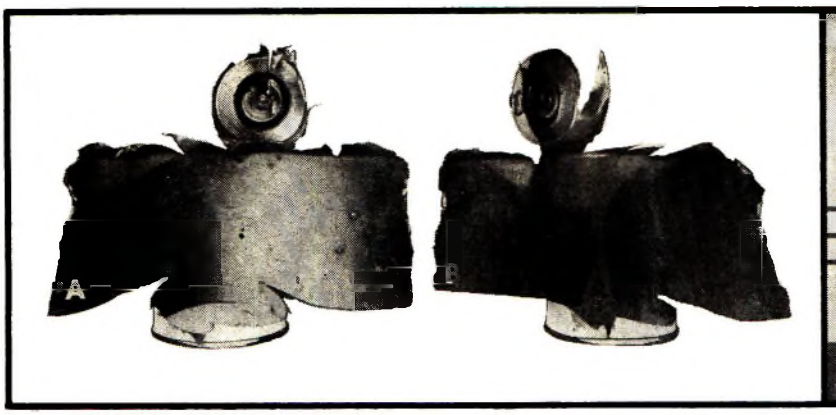
Subscription rates for 1969: $16.00 per volume to members of the ACS and $32.00 per volume to all others. Add $2.50 per subscription for Canada and countries belonging to the Postal Union, and $3.50 for all other countries.

Single copies for current year: $4.00. Postage, single copies: to Canada and countries in the Pan-American Union, $0.15; all other countries, $0.20. Rates for back issues from Volume 20 to date are available from the Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

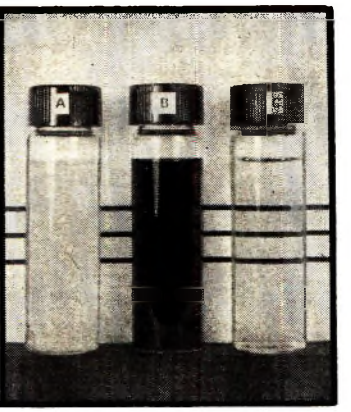
This publication and the other ACS periodical publications are now available on microfim. For information write to: MICROFILM, Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D.C. 20036.

Notice to Authors appears in January, April, July, and October issues

NEW AND INTERESTING FROM PIERCE



Unretouched photograph of the interior of two opened metal cans of currently marketed ninhydrin aerosols showing corrosion and discoloration from interaction of contents and container.

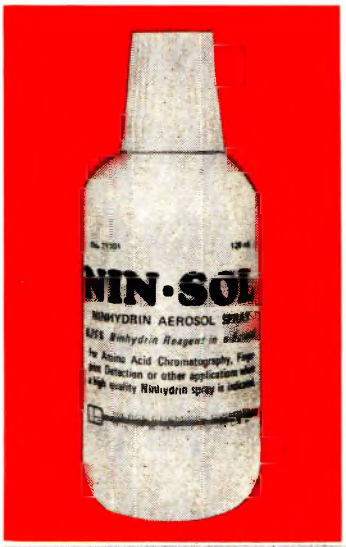


A. Contents of can A showing extreme turbidity. B. Contents of can B showing gross discoloration. C. Contents of Pierce *Nin-Sol* glass package.

NINHYDRIN AEROSOL...*In Shatterproof Glass!*

No metal ever touches the reagent in this all glass and plastic system. About 10 years ago we discontinued offering Ninhydrin aerosol because of the high incidence of corrosion and contamination in metal cans. Our new glass bomb with inert plastic valving enables us to offer an immaculate form of this fine reagent. Pierce Reagent Grade Ninhydrin is used exclusively in this product—it is never adulterated or substituted with practical grade. The glass package is shatterproofed with an adequate plastic coating and the bottle size is most convenient for a firm hand hold.

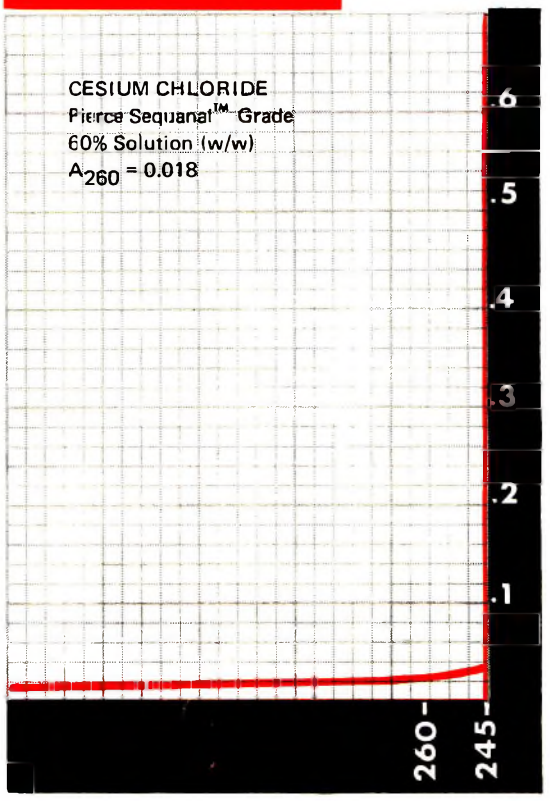
21101 NIN·SOL™ SPRAY, *Ninhydrin Aerosol*
120 ml, 0.25% Ninhydrin, Pierce Reagent Grade in n-Butanol.
$2.50/pkg; 6 pkgs, $2.25/pkg; 12 pkgs, $1.95/pkg



NOW! DENSITY GRADIENT CESIUM CHLORIDE
at Reagent Prices

Nucleic acid and protein chemists will be delighted with Pierce Sequanal™ Grade Cesium Chloride. It is an ultra-pure material showing a maximum absorbance of 0.02 at 260 mμ (60% w/w solution). It's chemical purity is such that there need be no fear of contaminating or degrading specimens. Excellent for either the most exacting analytical purposes or large prep scale work. And very economical for both.

No. 11 1547 Cesium Chloride, Sequanal Grade
$8.50/25g; $25/100g; $200/kg



THE JOURNAL OF Organic Chemistry®

VOLUME 34, NUMBER 7 JULY 1969

Perhaps needed for a fit kit in July, 1969

for making aromatic aldehydes

Formaldoxime
(EASTMAN 10766)

React this with the diazonium salt ($ArN\equiv N(Cl)$). Resulting aryl oxime ($ArCH=NOH$) yields product by acid hydrolysis. Brought to attention in 1966 with use for preparing 2-bromo-4-methylbenzaldehyde [*Org. Syn., 46,* 13].

for making ethyl esters of carboxylic acids, notably benzoic, under mild conditions

1,1-Diethoxytrimethylamine
(EASTMAN 10620)
Also known as DMF diethyl acetal

90% yield of ethyl benzoate reported in 36 hours at 20 C in acetonitrile (available as EASTMAN 488), or 5 hours at 40 C in dichloromethane (EASTMAN 342), or 1 hour at 80 C in benzene (EASTMAN 777). [*Angew. Chem., Internat. Ed. 2,* 211 and 212 (1963); *Helv. Chim. Acta, 48,* 1746 (1965)].

And for condensations with active methylenes

As in cyclopentadiene [*Ann., 641,* 1 (1961)].

And for cyclization of guanidine

To give 2,4-diamino-*s*-triazine [*Ber., 97,* 61 (1964)].

for mild brominations

Tetramethylammonium Tribromide
(EASTMAN 10480)

In benzene solution, with dibenzoyl peroxide present, benzylic hydrocarbons such as toluene (EASTMAN 325) are brominated in the benzylic methyl group. If you do it in acetic acid, the aromatic nucleus gets brominated [*J. Org. Chem. 28,* 3256 (1963)].

to make p-nitrobenzyl esters of carbobenzoxy amino acids or their peptides

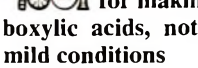
p-Nitrobenzyl p-Toluenesulfonate
(EASTMAN 10764)
Also known as p-nitrobenzyl tosylate

Reaction is run on previously prepared sodium or trialkylammonium salt of acid. Yield should be good in acetone (EASTMAN 297) or dimethylformamide (EASTMAN 5870). Protective group is stable to acid. You can remove it easily by catalytic hydrogenation [*J. Org. Chem. 29,* 2272 (1964)].

for putting thiol groups on proteins

S-Acetylmercaptosuccinic Anhydride
(EASTMAN 10528)

Add as solid to protein solution at pH 7. Remove hydrolyzed anhydride by anion exchange or dialysis. Lyophilize reacted protein. Split the acetyl-S link in dilute NaOH. Results in mercapto-



succinoylated ($HSCHCH_2CNH$-) protein. Also said to work for polyhydroxylic compounds like dextran or polyvinyl alcohol [*J.A.C.S., 81,* 3802 (1959)].

for diazo transfer and Wolff rearrangement

p-Carboxybenzenesulfonylazide
(EASTMAN 10710)

Used to introduce the diazo function at methylene positions flanked by two carbonyl groups. There are no separation problems after the reaction. Does the same thing with methine groups but not so cleanly. Several variations on these reactions allow the synthesis of most diazo ketones and esters. Phenyl and carbonyl groups flanking methylene or methine positions lead to formation of diazo compounds or Wolff rearrangement. Also primary amines can be converted into azides via their Grignard salts [*J. Org. Chem., 33,* 3610 (1968)].

Any Eastman laboratory chemical, as well as EASTMAN CHROMAGRAM® products for thin-layer chromatography, can be ordered from

B&A
CURTIN
FISHER
HOWE & FRENCH
NORTH-STRONG
SARGENT-WELCH
VAN WATERS & ROGERS
WILL

NOTES

Quarterly Reports on Sulfur Chemistry

By arrangement with the Sulphur Institute and with the organizers of the **Third International Symposium on Sulfur Chemistry,** held in Caen, France, in May, 1968, the review lectures from the Symposium will be published in Volume 5 (1970) of **Quarterly Reports on Sulfur Chemistry.**

Librarians who have not yet placed subscriptions to **Quarterly Reports on Sulfur Chemistry** are invited to do so as soon as possible to assure prompt delivery of forthcoming issues.

Back issues of "QRS" are still available – from Volume 1 (1966) to the current Volume 4 (1969). The annual library subscription rate for 1966-1970 (Volumes 1-5) is $24.00 per year (post free anywhere in the world). Please note that this also includes one subscription to the corresponding Volumes (1-5) of **Mechanisms of Reactions of Sulfur Compounds** (Annual Reports) – for the years 1966-1970.

Individual issues of "QRS" and of "Mechanisms of Reactions of Sulfur Compounds" are also available. For complete subscription information and for total listings of the contents of earlier volumes of the above publications please write the Foundation.

Librarians may request specimen copies of Quarterly Reports on Sulfur Chemistry, to be sent without charge.

INTRA-SCIENCE CHEMISTRY REPORTS

The 1969 volume of **Intra-Science Chemistry Reports** presents two integrated feature reports, covering two main themes:

Issues 1 and 2 (1969). **THE CHEMISTRY AND BIOCHEMISTRY OF STEROIDS.** These are the complete summaries of the special lectures series presented in Nov.-Dec. 1968 by **Leland J. Chinn, John S. Baran, Paul D. Klimstra,** and **Raphael Pappo,** of the steroid group, G.D. Searle and Company. Includes an overview of past and current work related to the interests of this research team.

Issues 3 and 4 (1969). **FREE-RADICAL AROMATIC SUBSTITUTION AND RELATED FREE RADICAL REACTIONS.** Presents the lectures and research papers presented at the 1968 Intra-Science Research Symposium (Dec. 1968, Santa Monica, California). Papers by **D.H. Hey** (medalist address), **Gareth H. Williams, N. Kharasch, E.K. Fields** and **S. Meyerson, J.F. Bunnett, R. Abramovitch, F.R. Mayo, W.A. Pryor,** among others are included.

Issues 1 and 2 (1969), together, on **The Chemistry and Biochemistry of Steroids,** Publication **ISCR-69-(3)-1,2** may be obtained for $8.00, postpaid anywhere in the world. Flexibound 8 1/4" x 11".

Issues 3 and 4 (1969), together, on **Free Radical Aromatic Substitution and Related Reactions,** Publication **ISCR-69-(3)-3,4** may be obtained for $8.00, postpaid anywhere in the world. Flexibound 8 1/4" x 11".

A permanently-bound library edition of **The Chemistry and Biochemistry of Steroids** (as above) is also available by arrangement with **Geron-X Press.** Requests for information on this special book-edition will be sent by return air post.

Librarians who have not as yet entered subscriptions to Intra-Science Chemistry Reports may obtain the above issues and previous and continuing ones on a subscription basis ($14.00 per year). Write for full subscription information and titles appearing in earlier volumes.

INTRA-SCIENCE RESEARCH FOUNDATION
P.O. BOX 430
SANTA MONICA, CALIFORNIA · 90406

BEILSTEIN'S HANDBUCH DER ORGANISCHEN CHEMIE

Friedrich Konrad Beilstein
4 Auflage, Berlin, Springer, 1918-44
64 vols. in 53

Main series, vols. 1–27, 30–31, pt. 1. First supplement, vols. 1–27. Subject and formula indexes to vols. 1–27 of main series and first supplement, vols. 28–29 in 4 pts. Second supplement, vols. 1–6.

This work has been published by J. W. Edwards, Publisher, Inc., since 1943 by authority of the now-disbanded Office of Alien Property Custodian, Department of Justice. These 25 sets are the last to be sold under their auspices at this advantageous price.

Entire 64 vols. in 53 **$850.00**

J. W. EDWARDS, PUBLISHER, INC.
Ann Arbor, Michigan, U.S.A.

IRRADIATION OF POLYMERS

ADVANCES IN CHEMISTRY SERIES NO. 66

- Ionization
- Radical formation
- Crosslinking
- Chain scission
- Graft copolymerization
- Homopolymerization

—Whatever the effect of high energy radiation on polymers, it is covered in this book.

Eighteen papers examine all aspects of polymer irradiation—by x-rays, beta rays, electron beams, or ultraviolet light—and report new research.

The first two papers survey radiation mechanics in polymers and the chemical nature of reactive species produced. The remainder report new work in all of the areas listed above.

275 pages clothbound (1967) $8.00
postpaid in U.S. and Canada; plus 20 cents foreign and PUAS.

Set of L.C. cards free with library orcers.

Order from:

Special Issues Sales
American Chemical Society
1155 Sixteenth St., N.W.
Washington, D.C. 20036

AUTHOR INDEX

Notice to Authors

Forwarding Address.—Manuscripts for publication should be addressed to Frederick D. Greene, Editor, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.

Correspondence regarding accepted papers, proofs, and reprints should be directed to Research Journals Production Office, American Chemical Society, 20th and Northampton Sts., Easton, Pennsylvania 18042. Manager, Editorial Production: Charles R. Bertsch.

Scope and Editorial Policies.—*The Journal of Organic Chemistry* invites original contributions on fundamental researches in all branches of the theory and practice of organic chemistry. It is not possible to publish all of the work submitted to this journal, and, in the selection by the editors of manuscripts for publication, emphasis is placed on the novelty and fundamental significance of the work.

Papers in which the primary interest lies in the implications of new compounds for medicinal, polymer, agricultural, or analytical chemistry are generally considered to be published most appropriately in specialized journals, together with information on evaluation with respect to the original reason for synthesis. Papers that deal with synthesis of new compounds by established methods and that are primarily of value as a part of the permanent chemical literature are in general more suitable for specialized journals dealing with a specific class of compounds; for compilations of data, the *Journal of Chemical and Engineering Data* may be appropriate.

In the event that new reactions or other significant chemistry have been developed in the course of a program in which large numbers of compounds were prepared, it may be suggested that extensive tables of characterization data be recorded elsewhere. It is advisable for authors to bear this possibility in mind when planning manuscripts in such situations.

Manuscripts may be classified as "Articles" or "Notes." **Articles** should be comprehensive and critical accounts of work in a given area. **Notes** should be concise accounts of studies of a limited scope. The standards of quality for Notes are the same as those for Articles. Improved procedures of wide applicability or interest, or accounts of novel observations or of compounds of special interest, often constitute useful Notes. Notes should not be used to report inconclusive or routine results or small fragments of a larger body of work but, rather, work of a terminal nature.

In particular, this journal encourages the submission of work as full accounts in the form of Articles. Presentation of results in smaller papers or Notes leads to undesirable fragmentation, especially in the case of continuing studies, and is contrary to the journal policy. When several closely related manuscripts are in preparation at about the same time, these should be submitted simultaneously. This procedure permits editors and reviewers to examine the manuscripts in an over-all context and avoids the possibility of fragmentation of the work. If additional papers in a series are projected, notification of the editors to this effect, with an approximate time table, is advisable and will be appreciated.

Republication of Preliminary Communication.—It is understood that contributions submitted to the journal will not previously have been published elsewhere, and are based upon original results. Articles based upon work previously reported as a brief preliminary communication will be considered provided that they represent a *substantial amplification* and, generally, an extension of the earlier communication. Extensive recapitulation of previously published results or experimental data should be avoided.

If significant data or conclusions in a manuscript have been published previously in preliminary form, reference to the earlier publication must be given. Three reprints or other copies of the preliminary communication are needed for use by the editors and reviewers; to avoid delays, these should be submitted with the manuscript.

Titles and Abstracts.—With the increasing importance of title and current awareness compendia, the titles of Articles or Notes should be carefully chosen to provide the maximum information on the contents.

Articles, but not Notes, must be accompanied by an abstract, placed before the main body of the text. The abstracts of Articles in this journal are used directly in *Chemical Abstracts*, and it is therefore most important that they be substantive and reflect as fully as possible the content of the paper. (CA Indexes are prepared from the full paper as in the past.) The abstract should state briefly the purpose of the research (if this is not contained in the title), and should indicate the theoretical or experimental approach (when appropriate), the principal results, and major conclusions. Reference to structural formulas or tables in the text, by number, may be made in the abstract. For a typical paper, an 80–200-word abstract is usually adequate.

Organization of Manuscripts.—An introductory paragraph or statement should be given, placing the work in the appropriate context and clearly stating the purpose and objectives of the research. The background discussion should be brief and restricted to pertinent material; extensive reviews of prior work should be avoided; and documentation of the literature should be selective rather than exhaustive, particularly if reviews can be cited.

The discussion and experimental sections should be clearly distinguished, with a separate center heading for the latter; other center headings should be used sparingly. The presentation of experimental details in the discussion section, *e.g.*, physical properties of compounds, should be kept to a minimum.

All sections of the paper must be presented in as concise a manner as possible consistent with clarity of expression. In the Experimental Section, specific representative procedures should be given when possible, rather than repetitive individual descriptions. Standard techniques and procedures used throughout the work should be stated at the beginning of the Experimental Section. Tabulation of experimental results is encouraged when this leads to more effective presentation or more economical use of space. Spectral data should be included with other physical properties and analyses of compounds in the Experimental Section or in tables. Separate tabulations of spectral values should be used only when necessary for comparisons and discussion.

Reproduction of Spectra.—Ultraviolet, infrared, nuclear magnetic resonance, electron spin resonance, and mass spectra (bar graphs) will be reproduced only if the aspects of interest cannot be discussed adequately in the absence of the actual curves or graphs, or if the compounds are inherently of special importance and can be adequately characterized only by reference to the actual curve. When presentation of spectra is deemed essential, only the pertinent section should be reproduced. These reproductions should be prepared as indicated for illustrations.

For most spectral data, an indication of band or peak positions with extinction coefficients, relative intensities, multiplicities, etc., as appropriate, suffices. The solvent or medium should be specified. Infrared data for most compounds can be restricted to major characteristic bands. The preferred format for reporting spectral values is indicated in the illustrative experimental paragraph given below (under Experimental Section).

Nomenclature should conform with American usage and, insofar as practical, with the Definitive Rules for Nomenclature, Sect. A–C, of the International Union of Pure and Applied Chemistry and with the practices of *Chemical Abstracts*. The Definitive Rules, Sect. A and B, may be found in *J. Amer. Chem. Soc.*, **82**, 5545 (1960); "IUPAC Definitives Rules for Nomenclature of Organic Chemistry," Sect. A and B, 2nd ed, Butterworth, London, 1966; Sect. C, Butterworth, London, 1965. A guide to *Chemical Abstracts* usage is found in *Chem. Abstr.*, **56**, Subject Index, In (Jan–June 1962). For cyclic systems, reference should be made to A. M. Patterson, L. T. Capell, and D. F. Walker, Ring Index, 2nd ed, American Chemical Society, Washington, D. C., 1960; and supplements I–III. Rules of carbohydrate nomenclature are found in *J. Org. Chem.*, **28**, 281 (1963).

Abbreviations for compounds should be defined when first used. In general, trade names should be avoided. Use of linear formulas for simple molecules to save space in tables and experimental sections is encouraged.

Preparation of Manuscripts.—Manuscripts should be submitted in triplicate and must be typewritten, double spaced on substantial paper. (Abstracts and footnotes should also be double spaced to allow room for copy editor's symbols and designations of type size, etc.) Clear, sharp copies made by a permanent duplication process are acceptable and are preferred, for second and third copies, to carbon copies. Authors should *consult recent issues of the journal* as a guide to format for typing, headings, etc.

Authors must assume full responsibility for all aspects of manuscript preparation. Extensive changes of minor points, or rewriting of the manuscript, cannot be undertaken in the editorial offices. Authors who are not fully familiar with idiomatic English should obtain help from a colleague in order to prepare manuscripts in proper style. Papers that appear to require ex-

tensive revision in grammar or format may be returned to authors without review.

Footnotes include both literature citations and explanatory notes and must, therefore, be numbered in one consecutive series. In the text, footnotes are indicated as unparenthesized superscripts. The footnotes may be placed, suitably offset, following the line of text in which they are cited, or they may be grouped in numerical order at the end of the manuscript. All nontechnical information (grant numbers, present address of author to whom inquiries should be directed if this information is not obvious from the heading, etc.) should be given in the subdivisions (a, b, c....) of footnote 1. Addresses of coauthors should not be included.

In literature references, journal abbreviations should be those used by *Chemical Abstracts* (see "List of Periodicals Abstracted by Chemical Abstracts"). Sample periodical reference, indicating arrangement and punctuation: (1) A. C. Cope, R. W. Gleason, S. Moon, and C. H. Park, *J. Org. Chem.*, **32**, 942 (1967). Book references must contain name of author, title, publisher, year of publication, and page. In referring to a book written by various contributors, cite author first as (1) S. F. Mason in "Physical Methods in Heterocyclic Chemistry," Vol. III, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p 59. References to the series volumes, *Organic Syntheses* (except for Collective Volumes) and *Organic Reactions*, should be in the format of journal citations, *e.g.*, L. F. Fieser, *Org. Syn.*, **46**, 44 (1966).

Tables should be numbered consecutively with Roman numerals and should be included at the proper places in the manuscript. Footnotes in tables should be given letter designations, and cited in the table by superscript letters. The sequence of letters should proceed by line rather than by column. If a footnote is cited both in the text and in a table, insert a lettered footnote in the table to refer to the numbered footnote in the text. Each table should be provided with a descriptive heading, which, together with the individual column headings, should make the table, as nearly as possible, self-explanatory. In setting up tabulations, authors are requested to keep in mind the type area of the journal page (7 × 10 in.), and the column width (approximately $3^1/_4$ in.), and to make tables conform to the limitations of these dimensions. Arrangements that leave many columns partially filled or that contain much blank space should be avoided insofar as possible.

Abbreviations and *linear* chemical formulas should be used liberally in headings and columns of tables; *structural* formulas should *not* be used in column headings or in the body of tables but may be used in the main heading.

Structural formulas should be prepared with care and with a view to the most economical use of space. All structures should be numbered in **boldface Arabic numerals.** In charts, assign numbers consecutively from left to right, top to bottom regardless of the order in which the compounds are discussed in the text. Repetition of the same structure should be avoided; the number of an earlier structure may be used alone if a compound occurs several times in formula schemes. Abbreviations such as Me for CH_3, Et for C_2H_4, Ph (but not ϕ) for C_6H_5 are acceptable.

The author should arrange structural formulas in horizontal rows so that the display or block will fill a single column width or, for very large groups, an entire page width. If this is not done, it may be necessary to rearrange the display, with possible loss of clarity, to avoid waste of space. If a satisfactory arrangement is slightly larger than the limits for a one-column presentation, it is preferable to stagger or overlap structures in successive rows rather than spread out the display to a full page. In multi-ring structures such as steroids, partial structures showing only the pertinent points are encouraged.

Structural formulas are redrawn by the printer. In structural formula layouts involving odd-shaped rings, bicyclic structures, etc., it is important that these structures be drawn exactly as they are to appear in the journal. They should also be consistent throughout, since all of the structures in a given manuscript may not be redrawn by the same person. Any special features or important points in structural drawings should be clearly indicated on the manuscript. Where needed, numbers such as nmr chemical shifts may be included directly on structural formulas.

Although fairly complicated structures can be redrawn in the standard format, unusually complex formulas, or drawings in which perspective is crucial, may be better submitted as copy suitable for direct photographic preparation of an engraving. It is *not* necessary to provide such copy for standard structural formula layouts. In the preparation of engraver's copy of complex drawings, careful lettering (*e.g.*, with a Leroy set or similar device) is required.

Illustrations should be submitted as original inked drawings or as high contrast, glossy photographic copies of drawings. Xerox or similar copies are not suitable for reproduction, but may be used for duplicate copies. All illustrations prepared as engraver's copy should be numbered as "Figures," with Arabic numerals. Blocks of structural formulas should not be designated as "Figures;" these can be designated "Charts" or "Schemes" as appropriate. Charts and schemes should be footnoted in the manner described for tables. Each illustration must be identified on the back with author, title, and figure number. The figure number (Arabic) must be typed on a separate sheet, together with the legend. More detailed information on the preparation of structural formula charts and illustrations may be found in the "Handbook for Authors" (see below).

Experimental Section.—Clear, unambiguous expression in experimental descriptions is highly important. Authors are encouraged to use the briefest style possible, consistent with clarity, in experimental descriptions. Whole sentence structure must be used, but the author should eliminate superfluous words and phrases. The title of an experiment should give the full name and formula number of the product prepared, when appropriate, but this compound may be identified thereafter by formula number. Abbreviations or chemical formulas for simple chemicals are encouraged, as well as the use of a structural formula number rather than a lengthy chemical name to identify a starting material. When a derivative is prepared by a standard procedure, no details beyond melting point, analysis, and important spectral data need be given. Repetitive descriptions of a general procedure should be avoided. Special attention should be called to hazardous compounds or operations.

Standard **abbreviations** should be used throughout the Experimental Section. *Please note that these are now used in ACS journals* **without** *periods.* The preferred forms for a few of the more commonly used abbreviations are mp, bp, min, hr, μl, ml, g, mg, cm, cps, mμ, ppm, tlc, vpc (or glpc), nmr, uv, and ir. The abbreviation for liter, l., has a period to distinguish it from the numeral "one."

Analyses must be reported in the usual format for all new compounds; in general, the deviation of "calculated" from "found" values should not exceed ±0.3%. Molecular formulas determined by accurate mass measurement ($\pm 3 \times 10^{-3}$ mass units) are acceptable if combustion analyses cannot be obtained because of sample limitations; wherever possible, mass spectral data must be supported by criteria of purity.

Physical constants and spectral data should be presented in a uniform way as illustrated in the following example.

(In nmr descriptions, s = singlet, d = doublet, t = triplet, m = multiplet.)

"The ethereal extract was dried ($MgSO_4$), concentrated, and distilled giving 10.23 g (65%) of the acetoxy ketone 12: bp 82–83° (2.9 mm); n_D^{25} 1.4266 [lit.[6] bp 80–82° (3 mm); n_D^{25} 1.4261]; d_4^{25} 0.823; $[\alpha]_D^{25}$ 0.0° (c 6, CH_3OH); uv max (95% EtOH) 275 mμ (ε 21); ir (CCl_4) 1725 (C=O), 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 3.98 (t, 2, J = 6 Hz, CH_2OAc), 2.43 (t, 2, J = 6 Hz, CH_2CO), 2.07 (s, 3), 1.97 (s, 3), and 1.6 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 158 (5), 143 (5), 115 (6), 100 (50), 99 (11), 98 (100), 85 (10)."

Proofs and Reprints.—Manuscript and proofs are sent to the author who submitted the paper. Foreign contributors may authorize a colleague in this country to correct proofs, but in this case they should bear in mind that reprint orders and page charge authorizations are handled at the time the proofs are returned.

Page Charge.—A page charge is assessed to cover in part the cost of publication. Payment is expected but is not a condition for publication. Papers are accepted or rejected only on the basis of merit, and the decision to publish a paper is made before the charge is assessed. The charge per page is $50.

Corrections.—If errors of consequence are detected in the published paper, a correction of the error should be sent by the author to the Editor, F. D. Greene, for publication in the "Additions and Corrections" section.

Registry Number.—Chemical Abstracts Service (CAS) is establishing a computer-based National Chemical Compound Registry System. Registry numbers are assigned to compounds by CAS after acceptance of a paper and appear in a separate paragraph at the end of the paper and sometimes in tables. [See *Chem. Eng. News*, 79–90 (Jan 23, 1967).]

ACS Author Handbook.—Further general information on the preparation of manuscripts for ACS journals may be found in the "Handbook for Authors," available from the Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

THE JOURNAL OF Organic Chemistry®

VOLUME 34, NUMBER 7

JULY 1969

The Relative Reactivities of Methanol and Methoxide Ion in Addition to 4-Chlorobenzyne[1]

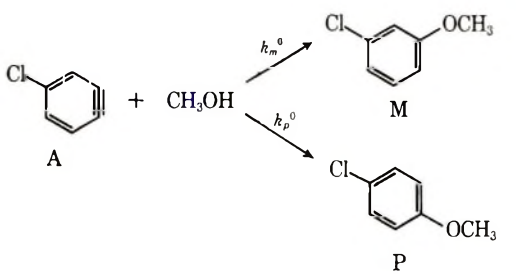
J. F. BUNNETT[2] AND CHONGSUH PYUN

Metcalf Chemical Laboratories, Brown University, Providence, Rhode Island

Received December 30, 1968

The relative reactivities of CH_3O^- and CH_3OH toward 4-chlorobenzyne can be reckoned from the variation of the chloroanisole *para/meta* ratio with $NaOCH_3$ concentration. The necessary mathematical expression is derived, and a set of experimental determinations gives the expected linear plot. Methoxide ion is estimated to be 157 times as reactive as methanol toward the carbon in 4-chlorobenzyne *meta* to chlorine, and 70 times as reactive toward the position *para* to chlorine.

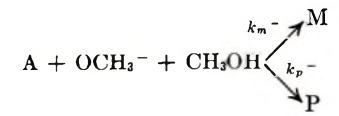
When 4-chlorobenzyne is generated in methanol solution, it adds methanol to form a mixture of *m*- and *p*-chloroanisoles (eq 1). In neutral methanol, the



(1)

p-/*m*-chloroanisole ratio is about 4.7. However, the *p*-/*m*-chloroanisole ratio decreases as the $NaOCH_3$ concentration in the medium increases; it is about 2.1 in 2 *M* $NaOCH_3$ in methanol.[3]

The change in *para/meta* ratio indicates that orientation is quantitatively different in the methoxide ion catalyzed addition (eq 2) than in addition of neutral



(2)

methanol, and that methoxide ion is much more reactive than methanol. If methoxide ion were less reactive or even approximately equally reactive, the chloroanisole product ratio would not have changed much, regardless of what *para/meta* ratio prevailed in eq 2, because even in 2 *M* methanolic $NaOCH_3$ solvent molecules are in great excess.[3]

The possibility that the altered *para/meta* ratio in 2 *M* $NaOCH_3$ is merely due to a salt effect was vitiated by demonstration that the *para/meta* ratio is essentially the same in 2 *M* $NaClO_4$ in methanol as in the pure solvent.[3]

A Method for Estimating the Relative Reactivities of Methanol and Methoxide Ion.—On the assumption that the reactions portrayed in eq 1 and 2 are first order in CH_3OH and CH_3O^-, respectively, we may write eq 3 concerning *p*-chloroanisole and an analogous expression concerning its *meta* isomer.

$$\frac{d[P]}{dt} = k_p^0[A][CH_3OH] + k_p^-[A][CH_3O^-] \quad (3)$$

Dividing one expression by the other

$$R = \frac{d[P]}{d[M]} = \frac{k_p^0[CH_3OH] + k_p^-[CH_3O^-]}{k_m^0[CH_3OH] + k_m^-[CH_3O^-]} \quad (4)$$

Let us define R as the experimental *p*-/*m*-chloroanisole ratio under any conditions (*cf.* eq 4), R^0 as k_p^0/k_m^0, the product ratio in reaction with neutral methanol, and R^- as k_p^-/k_m^-, the ratio in reaction with methoxide ion. Equation 4 is easily transformed into

$$\left(R - \frac{k_p^0}{k_m^0}\right) k_m^0[CH_3OH] = \left(\frac{k_p^-}{k_m^-} - R\right) k_m^-[CH_3O^-] \quad (5)$$

Rearranging

$$\frac{R^0 - R}{R - R^-} = \frac{k_m^-}{k_m^0} \frac{[CH_3O^-]}{[CH_3OH]} \quad (6)$$

According to eq 6, a plot of $(R^0 - R)/(R - R^-)$ *vs.* $[CH_3O^-]$ should be linear with slope equal to $(k_m^-/k_m^0) \cdot (1/[CH_3OH])$. From the slope, k_m^-/k_m^0, the ratio of methoxide to methanol reactivities toward the aryne carbon in 4-chlorobenzyne *meta* to the chlorine atom is

(1) Financial support by the National Science Foundation is gratefully acknowledged.

(2) To whom inquiries should be addressed at the University of California, Santa Cruz, Calif. 95060.

(3) J. F. Bunnett, D. A. R. Happer, M. Patsch, C. Pyun, and H. Takayama, *J. Amer. Chem. Soc.*, **88**, 5250 (1966).

TABLE I

REACTIONS OF 1-(4-CHLORO-2-IODOPHENYL)-2-BENZENESULFONHYDRAZIDE WITH $NaOCH_3$ IN CH_3OH AT 59.4°

$[NaOCH_3]_{st}$,[a] M	$[CH_3O^-]_f$,[b] M	$[Substrate]_0$,[c] M	Product yields, %				R^0	$\frac{R^0 - R}{R - R^-}$
			p- and m-chloroanisoles	m-C_6H_4ClI	C_6H_5Cl	I^-		
Part A								
0.10[d]	0	0.10	10.2	59.4	0.7	16.6	4.73	0
0.20	0.10	0.10	13.3	63.5	0.9	19.7	3.71	0.64
0.30	0.20	0.10	14.7	64.2	1.4	21.0	3.23	1.35
0.40[d]	0.30	0.10	15.5	63.4	2.0	21.2	3.01	1.93
0.50	0.40	0.10	16.2	57.4	1.9	24.9	2.85	2.58
0.60	0.50	0.10	16.8	63.5	2.2	22.1	2.72	3.35
0.70	0.60	0.10	17.2	63.7	2.4	22.1	2.65	3.92
0.80	0.70	0.10	17.0	61.5	4.6	23.1	2.58	4.67
0.90	0.80	0.10	17.2	60.1	4.1	23.3	2.52	5.52
1.00	0.90	0.10	18.1	~60	5.1	22.7	2.50	5.87
2.00[d]	1.90	0.10	20.2	66.4	~10	31.2	2.12	∞
Part B								
0.10	0.08	0.02	18.9	60.4	2.8	23.1	3.76	0.59
0.30	0.28	0.02	19.5	63.5	6.8	25.8	3.04	1.84
0.40	0.38	0.02	20.5	66.1	7.7	27.7	2.85	2.58
0.70	0.68	0.02	16.9	53.1	15.4	33.1	2.58	4.67

[a] $[NaOCH_3]_{st}$ represents the concentration that would have been obtained if there had been no reaction with substrate. [b] $[OCH_3^-]_f$ represents the "free" concentration after acid–base reaction with substrate. [c] The substrate is named in the title of the table. [d] Duplicate runs afforded R values differing by not more than 0.02. [e] *p*-/*m*-Chloroanisole ratio.

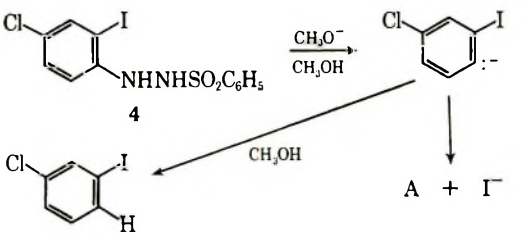
easily reckoned. (The solvent concentration is considered as constant.) The corresponding reactivity ratio toward the position *para* to chlorine is then given by

$$k_p^-/k_p^0 = (R^-/R^0)(k_m^-/k_m^0) \qquad (7)$$

In order to use eq 6 and 7, one must know R^0 and R^-. The former is easily determined by decomposition of a suitable 4-chlorobenzyne precursor in methanol not containing free methoxide ions. The latter may be estimated from the *para/meta* product ratio in a concentrated $NaOCH_3$ solution, providing that the data indicate the methoxide-catalyzed addition to be predominant at that concentration.

Although eq 6 and 7 are derived for the specific case of 4-chlorobenzyne reacting with CH_3O^- and CH_3OH, the principle should be valid for other cases in which two nucleophiles, one the conjugate base of the other, compete for a suitably constituted aryne.

Choice of Chemical System.—A precursor which would afford 4-chlorobenzyne under a wide range of $NaOCH_3$ concentrations was desired. Chlorine derivatives of benzenediazonium 2-carboxylate[4] cannot be used except in neutral methanol because in basic methanol dediazoniation to chlorobenzoic acids eclipses aryne formation.[3] However, 1-(*o*-halophenyl)-2-benzenesulfonhydrazides are decomposed to *o*-halophenyl anions over a wide range of $NaOCH_3$ concentrations,[5,6] and when the halogen is bromine or iodine the *o*-halophenyl anion reacts in part to eject halide ion and form an aryne. (The competing mode of reaction is proton capture from methanol to form an aryl halide.) A greater fraction of halide ion loss occurs the more easily the carbon–halogen bond is broken, and accordingly the easily accessible 1-(4-chloro-2-iodophenyl)-2-benzenesulfonhydrazide (**4**) was chosen as the principal 4-chlorobenzyne precursor for this study; see eq 8.



(8)

This system involves a complication which, fortunately, is of no consequence to its use for our present purposes. The *m*-chloroiodobenzene formed (see eq 8) undergoes partial loss of iodine under the conditions employed, forming chlorobenzene and iodide ion.[3,7] This side reaction should not have any effect on the reactions of 4-chlorobenzyne. Indeed, the *p*-/*m*-chloroanisole ratio in 2 *M* $NaOCH_3$–CH_3OH from the system of eq 8 was earlier shown to be substantially the same as from other 4-chlorobenzyne precursors.[3]

Experiments to Estimate Relative Reactivities.—Our experiments concerning reactions of **4** with $NaOCH_3$ in CH_3OH are summarized in Table I. This table comprises two series of runs, differing in the initial concentration of substrate. Inasmuch as a rapid acid–base reaction occurs on mixing, the data are best considered with reference to $[OCH_3^-]_f$, the free methoxide ion concentration remaining after the acid–base reaction. The *p*-/*m*-chloroanisole ratios (R) in the two series at nearly equal $[OCH_3^-]_f$ are virtually the same.

Qualitatively, the data of Table I show the same trend toward lower *p*-/*m*-chloroanisole ratios at higher methoxide concentrations that was noted earlier in a less extensive set of data concerning the same substrate.[3] Quantitatively, a plot of $(R^0 - R)/(R - R^-)$ *vs.* $[OCH_3^-]_f$ is linear, as called for by eq 6. It is presented as Figure 1. The slope by linear regression analysis is 6.67, and the correlation coefficient 0.998. From the density of methanol at 59.4° (0.754 g/ml[8]), the concen-

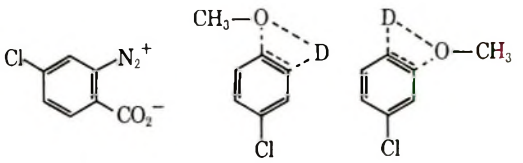
(4) M. Stiles and R. G. Miller, *J. Amer. Chem. Soc.*, **82**, 3802 (1960).
(5) J. F. Bunnett and D. A. R. Happer, *J. Org. Chem.*, **31**, 2369 (1966).
(6) J. F. Bunnett and H. Takayama, *J. Amer. Chem. Soc.*, **90**, 5173 (1968).
(7) J. F. Bunnett and C. C. Wamser, *ibid.*, **89**, 6712 (1967).
(8) "International Critical Tables," Vol. III, 1928, p 27.

tration of CH_3OH is 23.6 M. From this value, the slope in Figure 1 and eq 6 and 7, k_m^-/k_m^0, is reckoned as 157 and k_p^-/k_p^0 as 70. These are the relative reactivities of methoxide ion and methanol toward the carbons *meta* and *para* to chlorine in 4-chlorobenzyne. These results may alternatively be expressed as rate coefficients relative to k_m^0 (1.0) as follows: k_p^0, 4.7; k_m^-, 1.6×10^2; k_p^-, 3.3×10^2.

We stress that these results depend on the validity of the assumptions made in deriving eq 6. Chief among them is the assumption that the neutral and base-catalyzed methanol additions are first order in methanol and methoxide ion, respectively. However, it is noteworthy that if the respective reaction rates were proportional to $[CH_3OH]^2$ and to $[OCH_3^-][CH_3OH]$, eq 6 would still be valid because $[CH_3OH]$ would cancel from both numerator and denominator in forming eq 4.

The numerical values of the various rate coefficient ratios derived from our data also depend on the R^0 and R^- values chosen for use in the computations. The values we have used are from the data of Table I, namely, 4.73 for R^0 and 2.12 for R^-. Each of these represents the average of two independent determinations which differed by not more than 0.02 in R value. In other experiments,[3] R^0 and R^- values differed somewhat according to the aryne precursor and the experimental conditions employed. We do not fully understand those variations, but we note that the R^0 and R^- values used in the present computations are close to the average of other determinations.

Orientation of CH_3OD Addition.—From decomposition of 5-chlorobenzenediazonium 2-carboxylate (**5**) in methanol-O-*d* at reflux, *p*- and *m*-chloroanisoles were obtained in a *para*/*meta* ratio of 4.0. The similarity of this product ratio to that in ordinary methanol suggests that sundering of the O–H bond of the alcohol and/or bond formation by hydroxy hydrogen to aryne carbon are not involved prior to or during rate-limiting steps. The alternative, previously rejected on other grounds,[3] of concerted addition *via* cyclic transition states **6** and **7** would, of course, be



5 **6** **7**

subject to a kinetic isotope effect in regard to the formation of both isomers, and if each reaction were equally affected one might think the *para*/*meta* ratio to be unaffected. However, the change of hydrogen isotope would change the relative degrees of C–O and C–H bond formation in concerted, cyclic transition states, and consequently the charge distribution in the transition states, and therefore the *para*/*meta* ratio.

Reaction Mechanism.—The facts that the *p*-/*m*-chloroanisole ratio is higher for neutral methanol addition than for methoxide-catalyzed addition and that methoxide ion is more reactive than neutral methanol indicate that additions of both nucleophiles occur stepwise *via* rate-limiting transition states such as **8** and **9**.

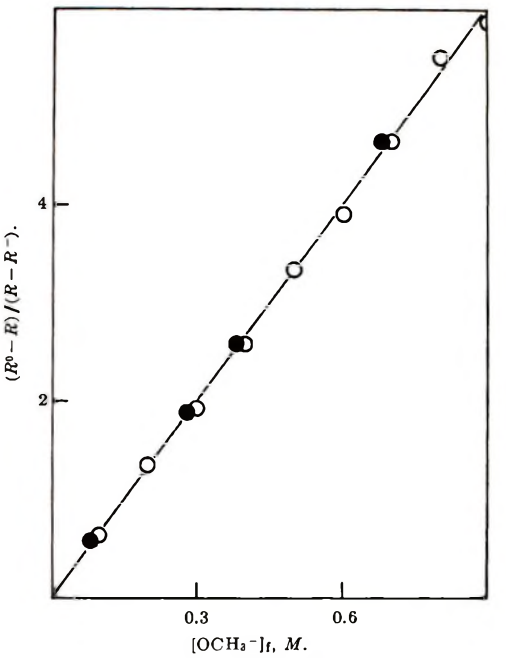
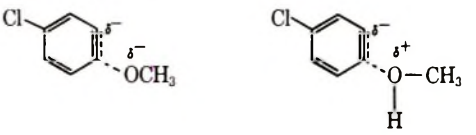


Figure 1.—Plot used to evaluate k_m^-/k_m^0; see eq 6. Data of Table I: ○, part A; ●, part B.

The arguments have been presented previously,[3] and are not repeated here.



8 **9**

Experimental Section

Materials.—1-(2-Iodo-4-chlorophenyl)-2-benzenesulfonhydrazide (**4**) was prepared as previously described,[3] and 5-chlorobenzenediazonium 2-carboxylate (**5**) after Stiles, Miller, and Burckhardt.[9] Methanol-O-*d* was prepared after Streitwieser, Verbit, and Stang[10]; it was estimated from its infrared spectrum to be 94% deuterated on oxygen.

Reactions of 4 with $NaOCH_3$ in CH_3OH.—The hydrazide **4** (0.409 g, 0.001 mole) in a 25-ml round-bottomed flask was mixed with methanolic $NaOCH_3$ (10 ml) with swirling under dry, oxygen-free nitrogen at room temperature. The hydrazide dissolved to form a solution of color varying from pale yellow with 0.1 M $NaOCH_3$ to reddish pink with 2 M $NaOCH_3$. A water-cooled condenser capped by a soda lime drying tube was affixed, and the flask was placed in a thermostat at 59.4° for 1 hr. To the cooled flask, 1.0 ml of a pentane solution containing 1×10^{-5} mole of bromobenzene and 5×10^{-5} mole of *o*-chloroanisole and then 10 ml of pentane were added through the condenser. Water (10 ml) was added, the layers were separated, the aqueous layer was extracted with a further 5 ml of pentane, and the combined pentane extracts were washed twice with water and dried over anhydrous $MgSO_4$. The dried pentane extract was analyzed by glpc on a column of 10% Carbowax 20M on Chromosorb P (80–100), at a column temperature of 115°. Relative molar responses were determined to be: chlorobenzene identically equal to bromobenzene, the three chloroanisole isomers identically equal to each other, and *o*-chloroanisole/*m*-chloroiodobenzene 1.00/0.78. Comparison of observed peak areas, corrected for molar response, and retention times with those of the bromobenzene and *o*-chloroanisole standards enable quantitative determination of yields. Iodide ion was determined by titration of the aqueous extracts with $AgNO_3$.

Registry No.—Methanol, 67-56-1; methoxide ion, 3315-60-4; A, 14091-35-1; **4**, 14173-17-2.

(9) M. Stiles, R. G. Miller, and U. Burckhardt, *J. Amer. Chem. Soc.*, **85**, 1792 (1963).

(10) A. Streitwieser, Jr., L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

Search for Acid Catalysis of the Reaction of Thiophenoxide Ion with 2,4-Dinitrofluorobenzene[1]

J. F. BUNNETT AND NORMA SBARBATI NUDELMAN

University of California, Santa Cruz, California 95060

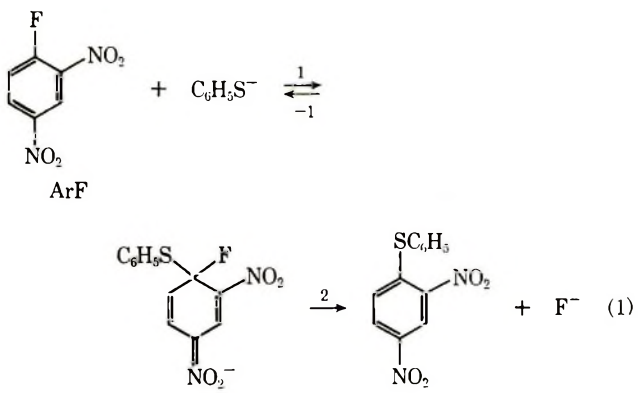
Received January 6, 1969

In five different kinds of systems designed to elicit evidence of acid catalysis of the reaction named in the title, no evidence of such catalysis has been found. No evidence was found either of general acid catalysis or of a thiophenol term in the rate law; the latter would appear if there were catalysis by the solvated proton. Inasmuch as the separation of fluoride ion from carbon is known to respond to catalysis by acids, we conclude that the first step of the intermediate complex mechanism is rate limiting for this reaction. This conclusion is contrary to one reached by other workers on the basis of thermochemical calculations.

In recent years the two-step, intermediate complex mechanism of aromatic nucleophilic substitution[2] has become generally accepted, and attention has turned increasingly toward defining the energy profiles for reactions involving various nucleophiles, leaving groups, substituents, or solvents. In part this objective has been approached experimentally, for example, by studying the incidence of base catalysis in reactions involving amine reagents, which gives information as to whether the first or second step is rate limiting.[3]

Miller[4] has approached this general problem in a different way, namely, by estimation from thermochemical data of the relative energy levels of reactants, intermediates, transition states, and products. As to the transition states (one preceding and one following the intermediate), his method requires assumptions as to the fraction of the bond dissociation energy which must be supplied to attain either transition state from the intermediate, assumptions which are made with respect to the Hammond postulate.[5] His treatment resembles in some respects that used by Hudson[6] to deal with other problems of reaction energetics. Miller's thermochemical predictions have been upheld by later experimental determinations in some cases but not in all.[7]

Having had some prior experience[8] with the reaction of sodium thiophenoxide with 2,4-dinitrofluorobenzene (eq 1), we were interested in Miller's conclusion[9] that step 2, involving expulsion of fluoride ion from the intermediate complex, is rate limiting. This was contrary to the judgment of Bunnett and Merritt,[8] which was based on leaving-group effects.



(1)

Inasmuch as the separation of fluoride ion from carbon is known to be susceptible to catalysis by acids,[10] it is possible to decide on experimental grounds which step of eq 1 is rate limiting.[11] If the first step is rate limiting, the over-all reaction should follow a simple second-order rate law, first order in 2,4-dinitrofluorobenzene (symbolized ArF) and first order in thiophenoxide ion. But, if the second step is rate limiting, the rate law should include terms representing catalysis by the solvated proton and/or general acids.

If the second step were general acid catalyzed, the over-all rate should in part be proportional to $[ArF]\cdot[C_6H_5S^-][HA]$, where HA is a general acid. If it were catalyzed by the solvated proton, proportionality in part to $[ArF][C_6H_5S^-][H^+]$ or, rather, to $[ArF]\cdot[C_6H_5SH]$ would be expected.[12] A solvent-catalyzed term would also be conceivable.

Experimental Section

Materials.—2,4-Dinitrofluorobenzene (Aldrich Reagent) was distilled at reduced pressure, mp 28°, bp 96° (0.3 mm) and 297–298° (760 mm). Thiophenol (Aldrich Reagent) was distilled at reduced pressure, bp 55–56° (9 mm), and stored in a desiccator under nitrogen atmosphere. Reagent grade methanol was further purified by the magnesium method.[13] Acetic acid (Allied Reagent, ACS), sodium acetate (Matheson Coleman and Bell reagent), chloroacetic acid (Baker Analyzed reagent), tetrapropylammonium bromide (Eastman Kodak, White Label), and lithium chloride (Matheson Coleman and Bell reagent) were used without further purification. *p*-Toluenesulfonic acid (Baker Analyzed reagent) was purified with chloroform after Perron.[14] N-Methylpiperidine (Aldrich reagent) was refluxed over sodium for 2 hr and distilled over sodium; bp 106–107°. N-Methyl-

(1) This investigation was supported by Public Health Service Research Grant No. GM 14647 from the National Institute of General Medical Sciences.

(2) J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958); A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3217 (1965); J. F. Bunnett and R. H. Garst, *ibid.*, **87**, 3879 (1965); C. R. Hart and A. N. Bourns, *Tetrahedron Lett.*, 2995 (1966).

(3) J. F. Bunnett and C. Bernasconi, *J. Amer. Chem. Soc.*, **87**, 5209 (1965); C. Bernasconi and H. Zollinger, *Helv. Chim. Acta*, **49**, 103 (1966); F. Pietra and A. Fava, *Tetrahedron Lett.*, 1535 (1963); C. F. Bernasconi, *J. Org. Chem.*, **32**, 2947 (1967); J. F. Bunnett and R. H. Garst, *ibid.*, **33**, 2320 (1968).

(4) J. Miller, *J. Amer. Chem. Soc.*, **85**, 1628 (1963); D. L. Hill, K. C. Ho, and J. Miller, *J. Chem. Soc., B*, 299 (1966).

(5) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(6) R. F. Hudson, *Chimia* (Aarau), **16**, 173 (1962).

(7) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **90**, 4982 (1968), summarizes several cases from his own work and from work of other investigators.

(8) J. F. Bunnett and W. D. Merritt, Jr., *ibid.*, **79**, 5967 (1957).

(9) K. C. Ho, J. Miller, and K. W. Wong, *J. Chem. Soc., B*, 310 (1966).

(10) W. T. Miller, Jr., and J. Berstein, *J. Amer. Chem. Soc.*, **70**, 3600 (1948); N. B. Chapman and J. L. Levy, *J. Chem. Soc.*, 1677 (1952); C. W. L. Bevan and R. F. Hudson, *ibid.*, 2187 (1953); A. K. Coverdale and G. Kohnstam, *ibid.*, 3806 (1960); C. G. Swain and R. E. T. Spalding, *J. Amer. Chem. Soc.*, **82**, 6104 (1960).

(11) *Cf.* K. B. Lam and J. Miller, *Chem. Commun.*, 642 (1966).

(12) A good example of kinetic dependence on [ArSH] which in all probability represents H^+ catalysis of reaction with ArS^- nucleophile has been reported by G. Illuminati, P. Linda, and G. Marino, *J. Amer. Chem. Soc.*, **89**, 3521 (1967).

(13) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed, D. C. Heath and Co., Boston, Mass., 1941, p 360.

(14) R. Perron, *Bull. Soc. Chim. Fr.*, 966 (1952).

piperidinium chloride was prepared by passing hydrogen chloride into an ethereal solution of N-methylpiperidine; it was crystallized twice from methanol; mp 207–208° (lit.[15] 211–212°).

Chloroacetic acid–sodium chloroacetate buffer was prepared by combining a measured volume of standard sodium methoxide solution with twice the molar amount of chloroacetic acid. The other buffer solutions were prepared by combining weighed amounts of the various compounds. 2,4-Dinitrophenyl phenyl sulfide was available in the laboratory; it was crystallized from methanol; mp 120–121°.[16] The uv and visible spectra of 2,4-dinitrofluorobenzene and 2,4-dinitrophenyl phenyl sulfide in methanol were determined in a Cary Model 14 spectrophotometer. The fluoro compound has maxima at 217 mμ (ε 12,000) and at 290 mμ (ε 6900) and the sulfide at 215 mμ (ε 19,500), 242 (sh), 265 (sh), and 328 mμ (ε 10,100).

Kinetic Procedures.—Three techniques were used, depending on the rate of the reaction being measured. In all three, the increase of absorbance at 400 mμ due to 2,4-dinitrophenyl phenyl sulfide was measured. The "infinity" absorbances agreed with those expected for quantitative conversion to that product.

The runs in Table IX were conducted by dispensing aliquots of the reaction solution into ampoules which were then sealed and immersed all at once in the thermostat bath. In preparing the reaction solutions, the required thiophenol was weighed under nitrogen, and the ampoules were flushed with nitrogen before being sealed. From 12 to 15 ampoules were used per run. Absorbances were measured in a Cary Model 14 spectrophotometer.

The runs in Table II were followed by direct observation of the absorbance of the reacting solution in the thermostated cell compartment of a Gilford spectrophotometer. The cuvettes were flushed with nitrogen before and after introduction of the reaction solution. Absorbance was recorded automatically at selected times.

The runs in Tables I and III–VIII were performed in a Durrum–Gibson stopped-flow kinetics spectrophotometer, the essential features of which are those described by Gibson and Milnes.[17]

All runs afforded linear plots of log $(A_\infty - A_t)$ *vs.* time; k_ψ values were reckoned as -2.3 times the slope as calculated by the least-squares method.

Results and Discussion

The reaction of thiophenoxide ion with 2,4-dinitrofluorobenzene is fast. In the earlier work of Bunnett and Merritt,[8] its rate could be measured only at 0° and then only by employing both the nucleophile and the substrate at very low concentrations. Ho, Miller, and Wong[9] used higher concentrations of reactants but experimental temperatures in the very low range of −82 to −65°. In the present work rates were determined at 25° under concentration conditions typical for experiments designed to afford pseudo-first-order kinetics, and the exceedingly rapid reaction rate was measured in a stopped-flow kinetics spectrophotometer.

The rate coefficients determined in four runs with constant thiophenoxide ion concentration but different thiophenol concentrations are presented in Table I. It should be noted that excess thiophenol has no discernible effect on reaction rate. These data suggest but do not prove the absence of a thiophenol term in the rate law. The reactivity of thiophenol conceivably may escape notice when it is in competition with a substantial concentration of the enormously reactive thiophenoxide ion. However, the possibility that reaction with thiophenoxide ion is catalyzed by thiophenol as a general acid is firmly denied by the data of Table I. An aspect of these data of general value is that they serve to establish the second-order rate coefficient, 780 l. mole^{-1} sec^{-1} at 25.0°, for the reaction of our principal interest.

(15) A. P. Phillips and J. Mentha, *J. Amer. Chem. Soc.*, **77**, 6393 (1955).
(16) R. W. Bost, J. O. Turner, and R. D. Norton, *ibid.*, **54**, 1985 (1932).
(17) Q. H. Gibson and L. Milnes, *Biochem. J.*, **91**, 161 (1964).

TABLE I

REACTION OF 2,4-DINITROFLUOROBENZENE WITH SODIUM THIOPHENOXIDE IN METHANOL AT 25.0°. INFLUENCE OF THE THIOPHENOL CONCENTRATION[a]

$[C_6H_5SH]$, *M*	k_ψ, sec^{-1}	k_A, l. mole^{-1} sec^{-1}
Nil	10.44	785
0.0196	10.24	770
0.0695	10.44	785
0.225	10.44	785
	Average	780

[a] $[ArF]_0$, 5.60×10^{-4} *M*; $[C_6H_5SNa]$, 1.33×10^{-2} *M*.

Table II summarizes a series of runs performed in the presence of a constant concentration of a 1:1 chloroacetate buffer and varying concentrations of thiophenol. In these runs a small concentration of thiophenoxide ion was present owing to interaction with chloroacetate ion (eq 2). The amount is controlled by

$$C_6H_5SH + ClCH_2COO^- \rightleftharpoons C_6H_5S^- + ClCH_2COOH \quad (2)$$

the equilibrium constant of eq 2, but is linearly proportional to the concentration of thiophenol. The fact that $k_\psi/[C_6H_5SH]$ is constant while thiophenol concentration is varied tenfold affirms (a) the lack of a discernible thiophenol term in the rate law and (b) the lack of a term proportional to $[C_6H_5S^-][C_6H_5SH]$, which would represent general acid catalysis by thiophenol. The data of Table II are a more sensitive test for a thiophenol term than those of Table I.

TABLE II

REACTION OF 2,4-DINITROFLUOROBENZENE WITH THIOPHENOXIDE ION IN METHANOL AT 25.0°. INFLUENCE OF THE THIOPHENOL CONCENTRATION IN A BUFFERED SYSTEM[a]

$10^2[C_6H_5SH]$, *M*	10^3k_ψ, sec^{-1}	$k_\psi/[C_6H_5SH]$, l. mole^{-1} sec^{-1}
0.95	1.8	0.190
1.60	3.3	0.206
3.80	7.8	0.205
6.0	12.0	0.200
10.0	20.0	0.200

[a] $[ArF]_0$, 5.72×10^{-4} *M*; buffer: [chloroacetic acid] = [sodium chloroacetate] = 0.01 *M*.

In Table III, some runs at constant thiophenol concentration and varying concentration of 1:1 acetate buffer are summarized. Again a small concentration of thiophenoxide ion is provided by an equilibrium analogous to that of eq 2. The fact that the pseudo-first-order rate coefficient, k_ψ, is substantially constant

TABLE III

INFLUENCE OF THE ACETATE BUFFER CONCENTRATION ON THE REACTION OF 2,4-DINITROFLUOROBENZENE WITH THIOPHENOXIDE ION IN METHANOL AT 25.0°[a]

$[CH_3COOH]$,[b] *M*	[LiCl], *M*	$10k_\psi$, sec^{-1}	pK_{HOAc}[c]
0.010	0.090	7.47	9.57
0.010	0.090	7.47	9.57
0.020	0.080	7.88	9.59
0.050	0.050	7.64	9.58
0.050	0.050	7.82	9.59

[a] $[ArF]_0$, 5.72×10^{-4} *M*; $[C_6H_5SH]$, 9.72×10^{-3} *M*. [b] $[CH_3COONa] = [CH_3COOH]$ in all runs. [c] For discussion of the pK_{HOAc}, see accompanying paper.[23]

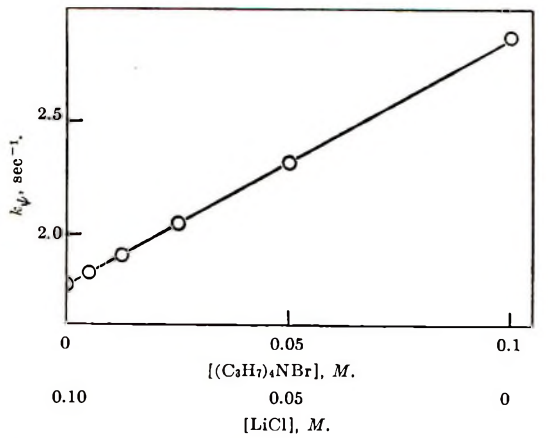


Figure 1.—Rate of reaction of ArF with thiophenoxide ion provided by thiophenol in N-methylpiperidine–N-methylpiperidinium chloride buffer (0.01 M), as affected by changing the nonreacting salt present from LiCl to tetrapropylammonium bromide. Data of Table VI.

shows the absence of general acid catalysis by acetic acid. The minor trend in k_ψ is not much greater than experimental error, and if real may stem from LiCl having a different salt effect than sodium acetate.

It seemed possible that for coulombic reasons a cationic general acid might be more effective than a neutral one, and therefore the influence of varying 1:1 N-methylpiperidine:N-methylpiperidinium chloride buffer concentration at fixed thiophenol concentration was explored, with LiCl present as needed to maintain constant salt concentration. Results are shown in Table IV. In this case there is a clear trend: the rate increases with increase in buffer concentration. This suggests general acid catalysis by the N-methylpiperidinium ion, but the possibility that it represents a difference in specific salt effects by N-methylpiperidinium chloride and LiCl must also be considered.

TABLE IV

REACTION OF 2,4-DINITROFLUOROBENZENE WITH THIOPHENOXIDE ION IN METHANOL AT 25.0°. INFLUENCE OF N-METHYLPIPERIDINE–N-METHYLPIPERIDINIUM CHLORIDE BUFFER CONCENTRATION WITH COMPENSATION BY LITHIUM CHLORIDE[a]

[NMP],[b] M	[LiCl], M	k_ψ, sec^{-1}	$10^{10}K_c$,[c] M
0.010	0.09	1.06 ± 0.01	2.31
0.020	0.08	1.25 ± 0.03	1.96
0.050	0.05	1.58 ± 0.02	1.55
0.100		2.21 ± 0.16	1.11

[a] [ArF]$_0$, 5.72×10^{-4} M; [C_6H_5SH]$_0$, 1.18×10^{-2} M. [b] NMP stands for N-methylpiperidine; [NMP·HCl] = [NMP] in all runs; each entry is the average of two runs. [c] K_c is the acid dissociation constant of N-methylpiperidinium ion; for discussion see the accompanying paper.[23]

As a test of the possibility that the salt effects of LiCl and a salt with a large organic cation might be different, a series of runs was performed with constant sodium thiophenoxide concentration and variable concentrations of tetra-*n*-propylammonium bromide and LiCl, but constant total salt concentration. These runs are summarized in Table V. There is indeed a small effect of the organic salt to accelerate the substitution as compared to the effect of LiCl, but the effect is quantitatively insufficient to account for the trend of the k_ψ values in Table IV.

TABLE V

REACTION OF 2,4-DINITROFLUOROBENZENE WITH SODIUM THIOPHENOXIDE IN METHANOL AT 25.4°. INFLUENCE OF TETRAPROPYLAMMONIUM BROMIDE *vs.* LITHIUM CHLORIDE[a]

[$(C_3H_7)_4NBr$], M	[LiCl], M	k_ψ, sec^{-1}	k_A, l. mole^{-1} sec^{-1}
	0.100	7.85 ± 0.09[b]	785
0.004	0.096	7.80 ± 0.15[c]	780
0.010	0.090	7.92 ± 0.01[c]	792
0.050	0.050	9.06 ± 0.10[c]	906
0.100		9.70 ± 0.30[c]	970

[a] [ArF]$_0$, 5.50×10^{-4} M; [C_6H_5SNa], 1.00×10^{-2} M. [b] Average of three runs. [c] Average of two runs.

The over-all rate coefficients in Table IV are, however, composite, each being the product of an equilibrium constant (for dissociation of thiophenol to thiophenoxide ion) and a rate coefficient (for the actual substitution). The possibility of a differential salt effect on the dissociation was therefore also explored. A series of runs was carried out with constant thiophenol concentration, constant concentration of 1:1 N-methylpiperidine:N-methylpiperidinium chloride buffer and variable concentrations of tetra-*n*-propylammonium bromide and LiCl, but constant total salt concentration. As shown in Table VI and also in Figure 1, there was a steady rise in reaction rate as the organic salt took the place of LiCl. The rates in Table VI are also composite of equilibrium and kinetic effects, just as those in Table IV are, but the magnitude of the kinetic differential salt effect is known from the data of Table V. Inasmuch as the over-all rate increase in Table VI (63%) is greater than in Table V (23%), a differential salt effect on the acid–base equilibrium is demonstrated.

TABLE VI

REACTION OF 2,4-DINITROFLUOROBENZENE WITH THIOPHENOXIDE ION IN METHANOL AT 25.0°. INFLUENCE OF TETRAPROPYLAMMONIUM BROMIDE *vs.* LITHIUM CHLORIDE AT CONSTANT BUFFER CONCENTRATION[a]

[$(C_3H_7)_4NBr$], M	[LCl], M	k_ψ, sec^{-1}
	0.100	1.77 ± 0.06
0.005	0.095	1.83 ± 0.04
0.0125	0.087	1.91 ± 0.04
0.025	0.075	2.05 ± 0.02
0.050	0.050	2.32 ± 0.04
0.100		2.88 ± 0.04

[a] [ArF]$_0$, 5.50×10^{-4} M; [C_6H_5SH], 1.47×10^{-2} M; [N-methylpiperidine] = [N-methylpiperidine hydrochloride] = 0.01 M.

The genesis of this effect is probably favorable London dispersion force interactions between the high polarizability thiophenoxide ion and the organic cation of rather high polarizability. The effects of London forces on acid–base equilibria have been discussed by Grunwald and Price.[18]

It was therefore to be expected that in a set of runs analogous to those of Table IV, but with tetra-*n*-propylammonium bromide as the compensating electrolyte instead of LiCl, the kinetic effect of changing the buffer concentration would be much reduced. In fact, as shown in Table VII, there was at most a very small effect; the rate pattern might also be described

(18) E. Grunwald and E. Price, *J. Amer. Chem. Soc.*, **86**, 4517 (1964).

as random variation. It is thus evident that tetra-*n*-propylammonium bromide affects over-all substitution rate to approximately the same extent as N-methylpiperidinium chloride does. The trend in Table IV therefore does not warrant interpretation as general acid catalysis of the substitution.

Table VII

Reaction of 2,4-Dinitrofluorobenzene with Thiophenoxide Ion in Methanol at 25.0°. Influence of N-Methylpiperidine–N-Methylpiperidinium Chloride Buffer Concentration with Compensation by Tetrapropylammonium Bromide[a]

[NMP],[b] *M*	[$(C_3H_7)_4NBr$], *M*	k_ψ, sec^{-1}
0.005	0.095	2.90 ± 0.20[c]
0.0125	0.087	3.05 ± 0.01[d]
0.025	0.075	3.42 ± 0.02[c]
0.050	0.050	3.52 ± 0.04[c]
0.100		3.07 ± 0.02[d]

[a] $[ArF]_0$, 5.50 × 10^{-4} *M*; [C_6H_5SH], 1.43 × 10^{-2} *M*. [b] See footnote *b*, Table IV. [c] Average of three runs. [d] Average of two runs.

A series of runs like those of Table VII was also performed in the solvent water–methanol (96:4). Results are listed in Table VIII. There was only random variation of rate as buffer concentration changed 20-fold. Again there is no evidence for general acid catalysis.[19]

Table VIII

Reaction of 2,4-Dinitrofluorobenzene with Thiophenoxide Ion in Water–Methanol (96:4) at 25.8°. Influence of N-Methylpiperidine–N-Methylpiperidinium Chloride Buffer Concentration with Compensation by Tetrapropylammonium Bromide[a]

[NMP],[b] *M*	[$(C_3H_7)_4NBr$], *M*	k_ψ, sec^{-1}
0.005	0.095	0.978 ± 0.018[c]
0.0125	0.087	0.996 ± 0.029[d]
0.025	0.075	0.981 ± 0.026[d]
0.0625	0.0375	0.975 ± 0.002[d]
0.100		0.966 ± 0.005[d]

[a] $[ArF]_0$, 2.25 × 10^{-4} *M*; [C_6H_5SH], 1.92 × 10^{-3} *M*. [b] See footnote *b*, Table IV. [c] Average of four runs. [d] Average of two runs.

Although the data of Tables I and II gave no indication of a term in the rate law proportional to thiophenol concentration, a more rigorous search for such a term was conducted by carrying out the reaction in the presence of a strong acid, *p*-toluenesulfonic acid (PTS). Such a strong acid strongly represses dissociation of thiophenol to thiophenoxide ion, but the latter is so reactive that its reaction with 2,4-dinitrofluorobenzene is nevertheless measurable. The experiments performed are summarized in Table IX.

If eq 3 and 4 both obtain, the pseudo-first-order rate coefficient, k_ψ, should depend on thiophenol and solvated proton concentrations as shown in eq 5. At constant thiophenol concentration, the product, $k_\psi \cdot [H^+]$, should be constant.

$$K_{PhSH} = [C_6H_5S^-][H^+]/[C_6H_5SH] \quad (3)$$

$$-d[ArF]/dt = k_\psi[ArF] = k_A[ArF][C_6H_5S^-] \quad (4)$$

$$k_\psi = k_A K_{PhSH}[C_6H_5SH]/[H^+] \quad (5)$$

(19) The rate coefficient for reaction of ArF with sodium thiophenoxide in water–methanol (96:4) at 25° was determined to be 512 l. $mole^{-1}$ sec^{-1}. From this value and the data in Table VIII, it is evident that the thiophenol was essentially fully dissociated under the experimental conditions employed, as was anticipated from the pH's of thiophenol and N-methylpiperidine in water.

Table IX

Reaction of 2,4-Dinitrofluorobenzene with Thiophenoxide Ion in Methanol at 25.0° in the Presence of *p*-Toluenesulfonic Acid (PTS)[a]

10^4[PTS], *M*	[LiCl], *M*	$10^5 k_\psi$, sec^{-1}	$10^9 k_\psi$[PTS], *M* sec^{-1}	pK_{PhSH}[b]
1.36	0.10	19.39	2.64	10.56
3.44	0.10	6.972	2.40	10.58
13.6	0.10	1.653	2.25	10.59
1.36	0.01	8.222	1.12	10.91
3.44	0.0097	3.167	1.09	10.92
13.6	0.0086	0.7944	1.08	10.92

[a] [ArF], 5.72 × 10^{-4} *M*; [C_6H_5SH], 0.117 *M*. [b] See accompanying paper[23] for discussion of pK_{PhSH} values.

The experiments of Table IX involve throughout a constant thiophenol concentration, 0.117 *M*. In the first set of three experiments, LiCl is present at the constant level of 0.10 *M* and *p*-toluenesulfonic acid concentration is varied tenfold, from 1.36 × 10^{-4} to 1.36 × 10^{-3} *M*. The product, k_ψ[PTS], decreases somewhat with increase in concentration of the strong acid. In the second set of three experiments, LiCl is present at a lower concentration level, approximately 0.01 *M*, but adjusted to maintain total electrolyte concentration constant at 0.01 *M*. *p*-Toluenesulfonic acid concentration is varied as in the first set. In the second set, the product, k_ψ[PTS], is constant within experimental error.

If there were a thiophenol term in the rate law, eq 5 would need to be replaced by eq 6. The product,

$$k_\psi = k_A K_{PhSH}[C_6H_5SH]/[H^+] + k^\circ[C_6H_5SH] \quad (6)$$

$k_\psi[H^+]$, would obviously increase with increase of solvated proton concentration to the extent that the thiophenol term contributed. The experimental fact that this product is constant (the lower set of three experiments in Table IX) or that it slightly decreases (the upper set of three) shows that the thiophenol term, if there is one, makes no detectable contribution to the reaction rate.

The preceding paragraph involves the implicit assumption that *p*-toluenesulfonic acid is fully dissociated in methanol at the concentrations employed. In view of the fact that the highest concentration used was only 1.36 × 10^{-3} *M*, this seems a reasonable assumption. If this assumption were not valid, relatively less dissociation would occur at the highest concentration of this acid than at the lowest, repression of thiophenol ionization would be less at the highest *p*-toluenesulfonic acid concentration, and the product, k_ψ[PTS], would increase as the concentration of the strong acid increased. The fact that this product remains constant or decreases somewhat demonstrates that the assumption is valid.

The difference in the product, k_ψ[PTS], between the first and second sets of experiments in Table IX is attributed to a salt effect on the rate and/or equilibrium constants involved. The cause of the moderate decrease in the product, k_ψ[PTS], within the first set is not evident.

Conclusions.—In five different kinds of systems, we have sought evidence for acid catalysis of the reaction

of thiophenoxide ion with 2,4-dinitrofluorobenzene. But in no case was any evidence of such catalysis found. There was no evidence of catalysis by general acids and no evidence of a thiophenol term, which would represent catalysis by the solvated proton.

Inasmuch as the separation of fluoride ion from carbon is known to respond to catalysis by acids, it follows straightforwardly that separation of fluoride ion from carbon is not involved in the rate-limiting step of this reaction. Therefore the first step of the mechanism shown in eq 1 is rate limiting.

This straightforward conclusion can be accepted, however, only after certain subtle features of the system have been considered. The compounds whose solvolysis is known to be catalyzed by acids are stable substances, and it is likely that the transition states for separation of fluoride ion from carbon involve a large extent of C–F bond rupture. In view of the high basicity of the fluoride ion, the energetic advantages of associating the departing fluoride ion with a proton are obvious.

But the intermediate in eq 1 is not a stable substance. The transition state for ejection of fluoride ion from it is therefore likely to involve a lesser degree of rupture of the C–F bond, and a lesser degree of association of a proton with it. In terms of the Brønsted catalysis law, a lower α value should be associated with step 2 of eq 1 than, say, with alkyl fluoride solvolyses. Indeed, if ejection of fluoride ion from the intermediate occurs with exceptional ease, not only general acid catalysis but even catalysis by the solvated proton may be undetectable. On this reasoning it might be contended that separation of fluoride ion from the intermediate would not necessarily require acid catalysis, and therefore that our data do not compel the straightforward conclusion drawn above.

The flaw in this hypothetical contention is that if fluoride ion separates with such exceeding ease from the intermediate, then expulsion of fluoride ion should occur faster than expulsion of thiophenoxide ion, in which case the first step of eq 1 is rate limiting. If the second step is to be rate limiting, there must be an appreciable energetic barrier to separation of fluoride ion from carbon, and in that case its separation should be acid catalyzed. The straightforward conclusion that the first step of eq 1 is rate limiting thus survives scrutiny.[20]

(20) A referee comments that the conclusion of Ho, Miller, and Wong,[9] that the second step is rate limiting, is extremely implausible on its face. We quote him: "To claim that the second step of the reaction in question is rate controlling is to claim that the SN1 reactivity of a certain α-arylthio fluoride is less than that of the corresponding α-fluoro thiophenoxide. Inasmuch as the SN1 reactivity of fluorides is much greater than that of thiophenoxides and inasmuch as α-ArS substituents increase SN1 reactivity whereas α-F substituents decrease SN1 reactivity, this claim seems quite unacceptable. The preceding two sentences, suitably amplified, seem to me to be a better argument against the interpretation of Miller, *et al.*, than is the work of the present manuscript." We agree with this referee's theoretical analysis, but we feel that experimental evidence is ultimately more decisive.

Inasmuch as Ho, Miller, and Wong[9] had concluded from thermochemical calculations that the second step of eq 1 is rate limiting, the present results require reconsideration of the basis of those calculations. In their discussion of the results of those calculations, Ho, Miller, and Wong put considerable emphasis on a report from their own laboratory[21] that thiomethoxide ion is about 3700 times as reactive with *p*-fluoronitrobenzene as with *p*-iodonitrobenzene. However, the same reactions have more recently been studied by Di Nunno and Todesco,[22] who report the reactivity difference to be less than sixfold. The latter authors did not redetermine activation parameters; they should be redetermined, in order to verify the excellent agreement between calculated and experimental activation enthalpies reported by Ho, Miller, and Wong.[9,21]

Although the one-step, SN2-like mechanism for activated aromatic nucleophilic substitution is seldom advocated any more, we note in passing that it also would call for the reaction of present interest to be catalyzed by acids. These experiments thus constitute further evidence against the one-step mechanism.

Our experimental results contribute incidentally to another topic in solution kinetics. The data of Tables IV–VII demonstrate that the kinetic effects of salts in methanol solution may be quite different from one another, and that "constant ionic strength" even at the modest level of 0.1 *M* is no guarantee of equality of salt effects in this solvent.

Finally, the data of Tables II–IV and IX contain information as to the acid dissociation constants of thiophenol, acetic acid, chloroacetic acid, and N-methylpiperidinium ion in methanol. Use of this reaction for the determination of pK_a values is developed in the accompanying paper.[23]

Registry No.—Thiophenoxide ion, 13133-62-5; 2,4-dinitrofluorobenzene, 70348.

(21) J. Miller and K. W. Wong, *J. Chem. Soc.*, 5454 (1965).

(22) L. Di Nunno and P. E. Todesco, *Tetrahedron Lett.*, 2899 (1967).

(23) J. F. Bunnett and N. S. Nudelman, *J. Org. Chem.*, **34**, 785 (1969).

An Independent, Kinetic Method for Determining Acid Dissociation Constants in Methanol[1]

J. F. BUNNETT AND NORMA SBARBATI NUDELMAN

University of California, Santa Cruz, California 95060

Received January 6, 1969

The reaction of thiophenoxide ion with 2,4-dinitrofluorobenzene (ArF) is a suitable basis for a kinetic method for determining pK's of weak acids in methanol. In a thiophenol solution buffered by the weak acid, the concentration of thiophenoxide ion and therefore the pseudo-first-order rate coefficient are governed by the pK and composition of the buffer. This method is wholly independent of other pK determinations, but gives results (for thiophenol, acetic acid, chloroacetic acid, pyridine, and N-methylpiperidine) in good agreement with the better determinations by other methods. This method is easily employed in a laboratory well equipped for spectrophotometric kinetics. It should also be applicable in other waterlike solvents and solvent mixtures.

Ionic equilibria in methanol, ethanol, and many partially aqueous solvent mixtures are similar in character to those in water. Although ion association effects are more serious in these solvents, pK_a's of weak acids can nevertheless be determined in them by methods which are familiar in aqueous chemistry.[2,3] Determinations by means of conductance measurements,[3a] or potentiometric measurements using the hydrogen electrode,[3b] or differential titrations using the glass electrode[3c,4] are all sound in principle, but chemical factors limit the scope of each method. Also, their instrumentation requirements make some of them difficult to apply in particular laboratories.

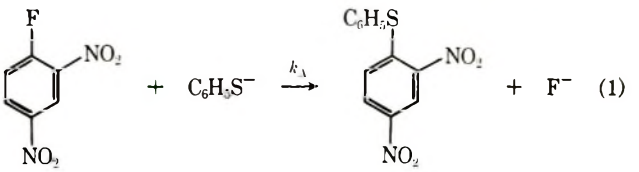
pK_a determinations by indicator methods[3d,5] are both sound in principle and convenient in practice, if a good spectrophotometer is available. However, they require knowledge of the pK_a of an indicator whose acid dissociation constant is within one or two powers of ten of the acid under study, and in a new solvent or solvent mixture some other type of measurement is generally required to establish the indicator pK_a's.

Despite the availability of these good methods, the situation is not entirely satisfactory even in the familiar solvent, methanol. For example, pK_a's reported for thiophenol within the last 15 years differ by more than 3pK_a units,[6-10] and each extreme is "confirmed" by independent measurements in another laboratory!

Kinetic methods for the determination of pK_a's are not generally held in high regard.[11a] For the most part they have concerned acid-catalyzed hydrolysis reactions, and it is possible that their low repute stems from the unawareness of early workers of the distinction between specific lyonium ion catalysis and general acid catalysis or of the significance of salt and medium effects on reaction rates.

We now describe a kinetic method for determination of acid dissociation constants which is independent of other methods, involves few assumptions, and is convenient to apply in a laboratory well equipped for rate measurements in solution.

The Reaction of Thiophenoxide Ion with 2,4-Dinitrofluorobenzene.—Thiophenoxide ion reacts rapidly with 2,4-dinitrofluorobenzene (symbolized ArF), according to eq 1. In methanol at 25.0°, the second-order rate



(1)

coefficient (k_A) is 780 l. mole^{-1} sec^{-1}. This value stems from determinations reported in Table I of an accompanying paper.[12] The rate coefficient is unaffected by the presence of excess thiophenol, and the reaction is not catalyzed by the general acids or bases of carboxylate or tertiary amine buffers, or by the solvated proton.[12]

pK_c of Thiophenol.—The reactivity of thiophenoxide ion is so great that reaction 1 occurs at a measurable rate even in a methanolic solution of thiophenol containing *p*-toluenesulfonic acid (PTS) at the level of 10^{-4} to 10^{-3} M. Data are reported in Table IX of the accompanying paper.[12] In this system, dissociation of thiophenol (eq 2) is strongly repressed by the solvated

$$C_6H_5SH \rightleftharpoons C_6H_5S^- + H^+ \qquad (2)$$

protons furnished by the virtually complete dissociation of *p*-toluenesulfonic acid. The data cited show, as discussed elsewhere,[12] that the reaction observed is entirely that of eq 1.

The pseudo-first-order rate coefficient, k_ψ, is governed by the rate coefficient for reaction 1 and the dissociation constant of thiophenol (K_{PhSH}), according to the relationship now presented as eq 3. Knowing k_ψ and the

$$k_\psi = k_A K_{PhSH}[C_6H_5SH]/[H^+] \qquad (3)$$

two concentration terms from experiment, and k_A as described above, we can calculate K_{PhSH}. From the data in the second set of three experiments in the cited Table IX, pK_{PhSH} is reckoned as 10.92 at μ 0.01, and from the first set of three pK_{PhSH} is 10.57 at μ 0.1.[13]

(1) This investigation was supported by Public Health Service Research Grant No. GM 14647 from the National Institute of General Medical Sciences.

(2) I. M. Kolthoff and S. Bruckenstein in "Treatise on Analytical Chemistry," Part I, Vol. 1, I. M. Kolthoff and P. J. Elving, Ed., The Interscience Encyclopedia, Inc., New York, N. Y., 1959, Chapter 13.

(3) E. J. King, "Acid-Base Equilibria," The Macmillan Co., New York, N. Y., 1965: (a) Chapter 2; (b) Chapter 3; (c) Chapter 4; (d) Chapter 5.

(4) E. Grunwald, *J. Amer. Chem. Soc.*, **73**, 4934 (1951).

(5) I. M. Kolthoff and L. S. Guss, *ibid.*, **60**, 2516 (1938).

(6) pK_a's reported recently for C_6H_5SH in CH_3OH are 8.65,[7] 8.3,[8] 11.63,[9] and 10.9.[10]

(7) R. F. Hudson and G. Klopman, *J. Chem. Soc.*, 1062 (1962).

(8) J. G. David and H. E. Hallam, *Trans. Faraday Soc.*, **60**, 2013 (1964).

(9) J. Hine and W. H. Brader, Jr., *J. Amer. Chem. Soc.*, **75**, 3964 (1953).

(10) B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *ibid.*, **88**, 1911 (1966).

(11) *Cf.* A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co., Ltd., London, 1962: (a) p 12; (b) p 135.

(12) J. F. Bunnett and N. S. Nudelman, *J. Org. Chem.*, **34**, 2038 (1969).

(13) μ represents the total concentration of 1:1 electrolytes. We hesitate to call it "ionic strength" because of the demonstrated inequality of salt effects in this system.

The former value is in excellent agreement with pK_{PhSH} = 10.9 at μ 0.01 or less, determined by Clare, *et al.*,[10] by an indicator method. It is close to one other determination in the recent literature, but quite far from two others.[6]

As a check on these determinations, similar experiments were performed utilizing sulfuric acid instead of PTS. Results are presented in Table I. In reckoning pK_{PhSH}, sulfuric acid was treated as a monoprotic acid. The averate pK_{PhSH} at μ 0.1 is 10.56, in superb agreement with that obtained (10.57) with PTS as the proton source. At μ 0.01, the average pK_{PhSH} in Table I is 10.84; this compares with 10.92 when PTS was the strong acid.

TABLE I

REACTION OF 2,4-DINITROFLUOROBENZENE WITH THIOPHENOXIDE ION IN METHANOL AT 25.0° IN THE PRESENCE OF SULFURIC ACID[a]

10^4[H_2SO_4], *M*	[LiCl], *M*	10^5k_ψ, sec^{-1}	10^5k_ψ·[H_2SO_4], *M* sec^{-1}	$10^{11}K_{PhSH}$, *M*	$pK_{c,PhSH}$[d]
0.242[b]	0.100	9.98	2.42	2.67	10.57
0.970[b]	0.100	2.54	2.46	2.72	10.57
2.42[b]	0.100	1.09	2.63	2.92	10.54
13.70[c]	0.100	0.200	2.62	2.90	10.54
1.31[c]	0.0100	1.03	1.35	1.49	10.83
3.27[c]	0.0097	0.441	1.44	1.60	10.80
9.70[b]	0.0090	0.132	1.29	1.42	10.86
13.10[c]	0.0760	0.0951	1.25	1.38	10.86

[a] [C_6H_5SH], 0.116 *M*. [b] [ArF] = 1.13×10^{-3} *M*. [c] [ArF] = 5.65×10^{-4} *M*. [d] Average pK_{PhSH} are 10.55 at μ 0.1, and 10.84 at μ 0.01.

The fact that these measurements agree so well with those in which PTS was the strong acid is of special significance because it shows that bisulfate ion is only slightly dissociated in methanol. We were unable to find any data in the literature concerning the second dissociation of sulfuric acid in methanol.

pK_c of Acetic Acid.—In an acetate-buffered solution, the solvated proton concentration is governed by the composition of the buffer and the dissociation constant, K_{HOAc}, of acetic acid. If thiophenol in known amount is also present, the solvated proton concentration governs the thiophenoxide ion concentration, which in turn governs k_ψ for reaction with ArF. As thiophenoxide ion is consumed by ArF, the equilibria quickly shift to restore its original concentration. The applicable mathematical expression is that of eq 4. From

$$k_\psi = \frac{k_A K_{PhSH}[C_6H_5SH][CH_3COO^-]}{K_{HOAc}[CH_3COOH]} \quad (4)$$

knowledge of k_A, K_{PhSH}, and the experimental k_ψ under various concentration conditions, one can reckon K_{HOAc}.

Appropriate data are set forth in Table III of an accompanying paper.[12] The average pK_{HOAc} is 9.58 at μ 0.1. Some other p*K*'s reported for acetic acid are 9.65,[14a] 9.34,[14b] 9.65,[5] 9.6,[10] 9.62,[14c] 9.68,[14d] and 9.72.[14e]

pK_c of Chloroacetic Acid.—By the same principles, and from the data of Table II of an accompanying paper,[12] pK_c for chloroacetic acid at μ 0.01 is reckoned as 7.33. This is the average value from the five runs; the individual values ranged from 7.31 to 7.34. This compares with pK_c = 7.7 from indicator measurements reported by Clare, *et al.*,[10] and 7.4 as reported by Ogston and Brown.[15]

pK_c of Pyridine.—Relevant experimental data are set forth in Table II of this paper. The principles discussed above again apply, but a new factor is superimposed, namely, the variation of K_{PhSH} and k_A as LiCl is replaced as an electrolyte by an amine hydrochloride. This factor is discussed in an accompanying paper.[12] Because of it, the K_c values reckoned from the four experiments of Table II are not constant, even though the "ionic strength" is constant. A plot of K_c *vs.* the square root of buffer concentration[16] is presented as Figure 1; it is approximately linear, and the intercept of the line drawn gives a K_c of 5.6×10^{-6} *M* at zero buffer concentration and a LiCl concentration of 0.10 *M*. pK_c is then 5.25. Rochester[17] has reported pK_a for pyridine, determined by an indicator method, as 5.37 and pK_c in 0.1 *M* NaCl as 5.7.

TABLE II

REACTION OF 2,4-DINITROFLUOROBENZENE WITH THIOPHENOXIDE ION IN METHANOL AT 25.0° IN THE PRESENCE OF PYRIDINE–PYRIDINIUM CHLORIDE BUFFERS[a]

[Pyridine],[b] *M*	[LiCl], *M*	[C_6H_5SH], *M*	10^4k_ψ, sec^{-1}	10^6K_c,[c] *M*
0.0080	0.0920	0.118	4.95	4.95
0.0200	0.0800	0.123	5.10	5.01
0.0400	0.0600	0.119	5.98	4.14
0.100	Nil	0.118	7.30	3.36

[a] [ArF], 5.72×10^{-4} *M*. [b] [$C_5H_5N \cdot HCl$] = [C_5H_5N] in all experiments. [c] Extrapolation to zero buffer concentration (and [LiCl] 0.10 *M*) gives K_c for pyridinium ion 5.6×10^{-6} *M*.

pK_c of N-Methylpiperidine.—We now consider the data of Table IV of an accompanying paper.[12] Again because of the dependence of K_{PhSH} and k_A on whether the electrolyte is LiCl or amine hydrochloride, K_c is not constant as the electrolyte composition is varied, even though the total concentration of 1:1 electrolyte is held constant. A plot of K_c *vs.* the square root of buffer concentration[16] is approximately linear (Figure 2), and the intercept gives a K_c value of 2.8×10^{-10} *M* at zero buffer concentration and 0.10 *M* LiCl. pK_c is then 9.56. To our knowledge, the p*K* of N-methylpiperidine in methanol has not previously been determined. However, we note that the pK_c difference between N-methylpiperidine and pyridine in methanol is 4.3 according to our measurements, while the difference in water is 4.9.[18] An actual equality of differences would not be expected because of differential solvation effects.

On the Dissociation of HF in CH_3OH.—In several runs, the rate of reaction of 2,4-dinitrofluorobenzene (initial concentration 5.6×10^{-4} *M*) with thiophenol in N_2-flushed, unbuffered methanol was measured. Representative runs are presented in Table III of this paper.

(14) (a) N. Bjerrum, A. Unmack, and L. Zechmeister, *Kgl. Danske Videnskab. Selskab, Mat. Fys. Medd.*, **5** (11), 34 (1925); *Chem. Abstr.*, **19**, 3196 (1925); (b) L. D. Goodhue and R. M. Hixon, *J. Amer. Chem. Soc.*, **56**, 1329 (1934); (c) M. Kilpatrick and R. D. Eanes, *ibid.*, **75**, 586 (1953); (d) I. D. Tabagua, *Tr. Sukhumsk. Gos. Ped. Inst.*, **15**, 119 (1962); *Chem. Abstr.*, **60**, 14373 (1964); (e) R. Gaboriaud, *Compt. Rend.*, *C*, **263**, 911 (1966).

(15) A. G. Ogston and J. F. Brown, *Trans. Faraday Soc.*, **31**, 574 (1935).

(16) This extrapolation procedure has been utilized because it is empirically useful. The intercepts in plots of k_ψ *vs.* the first power of buffer concentration led to nearly the same K_c values.

(17) C. H. Rochester, *J. Chem. Soc.*, *B*, 33 (1967).

(18) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth and Co. Ltd., London, 1965, pp 139, 141.

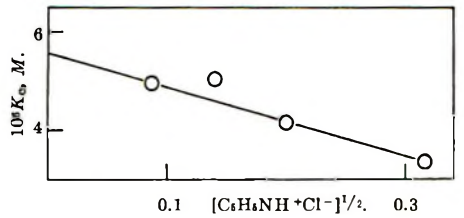


Figure 1.—Dissociation of pyridinium ion; plot of K_c *vs.* $[C_5H_5NH^+Cl^-]^{1/2}$.

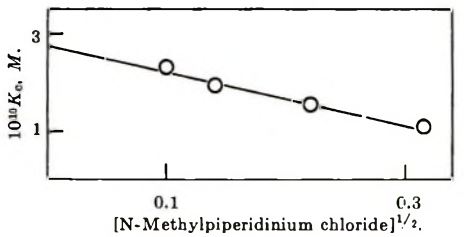


Figure 2.—Dissociation of *N*-methylpiperidinium ion; plot of K_c *vs.* square root of N-methylpiperidinium chloride concentration.

TABLE III

REACTION OF 2,4-DINITROFLUOROBENZENE WITH THIOPHENOL IN UNBUFFERED METHANOL AT 25.0°[a]

$[C_6H_5SH]$, *M*	Obsd 10^3k_ψ, sec^{-1}	10^3k_ψ, sec^{-1}, expected if no HF dissocn[b]
0.044	0.28	0.56
0.050	0.19	0.61
0.092	0.94	0.83
0.220	1.7	1.3
0.350	2.15[c]	1.6
0.540	7.6	2.0

[a] All solutions were bubbled with N_2, and cuvettes were flushed with N_2. [b] Based on K_{PhSH} 1.2×10^{-11} *M*. [c] Average of two runs.

In these runs, two solute acids were present: thiophenol and HF, the latter a by-product of the formation of 2,4-dinitrophenyl phenyl sulfide. If the HF were extensively dissociated, the solvated protons generated by the reaction would soon be present in concentration (*ca.* 10^{-4} *M*) about two orders of magnitude greater than from dissociation of the thiophenol. The increased solvated proton concentration would repress dissociation of the thiol and cause a pronounced decrease in slope of plots of log $(A_\infty - A_t)$ *vs.* time. However, these first-order kinetic plots were for the most part good straight lines. An example is presented as Figure 3. In this example, only a modest decrease in slope occurs, and then only commencing in the second half-life. Moreover, if $[H^+]$ is assumed to be *ca.* 10^{-4} *M*, the observed k_ψ values are about two orders of magnitude greater than they ought to be with respect to the known values of k_A and K_{PhSH}. Thus HF, even at the concentration level of 10^{-4} *M*, is but slightly dissociated in methanol.

If HF is assumed not to dissociate at all, the k_ψ values predicted from knowledge of $[C_6H_5SH]$, K_{PhSH}, and k_A are close to those observed; see Table III. The discrepancies between predicted and observed values are perhaps due to adventitious acidic or basic impurities, to which this unbuffered system should be quite sensitive.

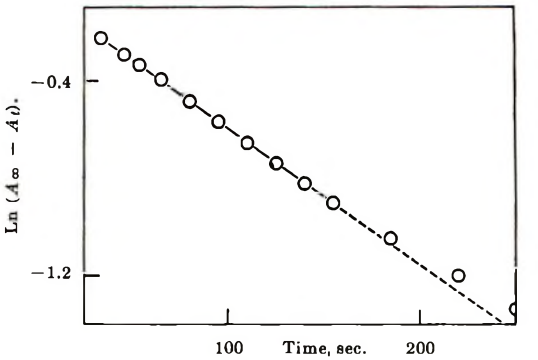


Figure 3.—Reaction of ArF with thiophenol in unbuffered methanol. First-order kinetic plot for a typical run; initial concentrations: ArF, 5.6×10^{-4} *M*; C_6H_5SH, 4.30×10^{-1} *M*. The first-order rate coefficient is 5.57×10^{-3} sec^{-1}.

To our knowledge, the pK_a of HF in methanol has not been measured. However, Chapman, *et al.*,[19] obtained kinetic evidence showing that aniline hydrofluoride is largely dissociated to free aniline in ethanol, whereas piperidine hydrofluoride is not appreciably dissociated in that solvent.

Discussion

In this study, this new method for determining p*K*'s in methanol has been applied to four acids or bases in addition to the key acid, thiophenol. In one case no comparison p*K* is available, but in all of the other four cases the p*K*'s determined in this work are in good agreement with the better determinations in the literature. On the basis of its performance, this method appears to be at least as accurate as any of the others.

Remarkably few assumptions are involved in this method. The chief one, as we have applied it, has been neglect of activity coefficient effects. The values we have determined are therefore concentration dissociation constants, designated K_c. Thermodynamic dissociation constants, K_a, referred to infinite dilution in methanol, could no doubt be determined by this method if measurements were made at a series of electrolyte concentrations so as to allow extrapolation to infinite dilution.

Limitations.—Qualitatively, this method would be difficult if not impossible to apply if the acid under study or its conjugate base were reactive enough with either 2,4-dinitrofluorobenzene (ArF) or thiophenoxide ion to compete substantially with the reaction of eq 1. For example, we would anticipate complications in applying this method to certain primary and secondary amines which are quite reactive with ArF. Piperidine, for instance, is about $^1/_{120}$ as reactive as thiophenoxide ion with ArF in methanol.[20] On the other hand, it was applied easily and successfully to determination of pK_c for chloroacetic acid; although the latter undoubtedly reacts with thiophenoxide ion, the reaction rate is evidently too low to interfere.

Quantitatively, this method is limited to acids stronger than thiophenol and, at the other extreme, by the very low rate of reaction of thiophenol with ArF when the solvated proton concentration is as high as

(19) N. B. Chapman and R. E. Parker, *J. Chem. Soc.*, 3301 (1951); N. B. Chapman, R. E. Parker, and P. W. Soanes, *ibid.*, 2109 (1954).

(20) J. F. Bunnett, T. Kato, and N. S. Nudelman, *J. Org. Chem.*, **34**, 785 (1969); N. S. Nudelman, unpublished observations.

10^{-3} *M*; *cf.* Table I. It is thus useful for determination of p*K*'s approximately in the range of 3–10. No doubt its range could be extended at the weak acid limit by using an aliphatic mercaptan instead of thiophenol. In water, alkanethiols have pK_a's about four units greater than thiophenol.[11b] However, in that case it might be necessary to determine the p*K* of the thiol in methanol by reaction with ArF in a buffered solution (*e.g.*, acetate buffer) rather than in a solution of PTS or sulfuric acid.

The odor of thiophenol or another thiol might be thought a severe disadvantage. In our experience, odor problems can virtually be eliminated if most transfers are made in the fume hood, if transfers are made neatly, and particularly if all thiol-containing residues and rinsings are first poured into a jar containing water and an oxidizing agent (*e.g.*, $KMnO_4$) rather than directly into the laboratory sink.

Other Solvents.—Although our determinations were all made in methanol, this method should be applicable with equal ease and rigor to other waterlike solvents including especially mixtures of water with organic cosolvents. The indicator method, which is perhaps the chief rival of this kinetic method in regard to convenience of application, suffers from the disadvantage in a new solvent that first the pK_a of the indicators be used must be determined. Conventionally, that would imply conductimetric or potentiometric measurements preceding the actual photometric work with the indicator. With this kinetic method, the same general type of technique, photometric kinetics, is used throughout.

Experimental Section

For the most part, materials and methods were as described in an accompanying paper.[12] Pyridine (Aldrich reagent) was refluxed over sodium for 2 hr and distilled over sodium; bp 115°. Pyridine–pyridinium chloride buffer was prepared by mixing a standard solution of hydrogen chloride in methanol (titrated after László[21]) with twice its molar amount of a standard solution of pyridine in methanol. The ampoule technique was used for the runs of Table I and direct observation of reacting solutions in a Gilford spectrophotometer for those of Tables II and III.

Registry No.—Methanol, 67-56-1; 2,4-dinitrofluorobenzene, 70-34-8; thiophenoxide ion, 13133-62-5; thiophenol, 108-98-5.

(21) N. László, *Gyógyszerészet*, 215 (1966).

Reactions of Chloro Olefins with Difluoramine[1]

KURT BAUM

Environmental Systems Division, Aerojet-General Corporation, Azusa, California 91703

Received December 5, 1968

The reaction of 2-chloro-2-penten-4-one with difluoramine and fuming sulfuric acid gave 2,2,4,4-tetrakis(difluoramino)pentane, 2-chloro-2,4,4-tris(difluoramino)pentane, and 2-chloro-3,4,4-tris(difluoramino)pentane. *cis*-3-Chlorocrotonic acid gave 3-chloro-3-(difluoramino)butyric acid but ethyl 3-chlorocrotonate did not react. 1,1-Dichloro-1-buten-3-one gave 1,1-dichloro-3,3-bis(difluoramino)-1-butene when a very large excess of difluoramine was used and N-[2,2-dichloro-1,2-bis(difluoramino)ethyl]acetamide with less difluoramine. A possible mechanism for the formation of the latter compound is presented. The reaction of 1,1-dichloroethylene with difluoramine and fuming sulfuric acid gave 1,1-dichloro-1-(difluoramino)ethane and 1-chloro-1,1-bis(difluoramino)ethane.

In a previous paper[2] it was demonstrated that *gem*-bis(difluoramino)alkanes can be prepared in a reversible reaction of ketones and aldehydes with difluoramine in the presence of sulfuric acid. Acrylic acid and its esters underwent Michael addition of difluoramine under these conditions, whereas methyl vinyl ketone underwent Michael addition and subsequent replacement of the carbonyl group. This investigation has been extended to chlorinated substrates with the prospect of exploring chemical similarities between chlorine and difluoramino groups. Halogenlike electronic effects of difluoramino groups have been discussed previously.[3] The reversibility of the *gem*-bis(difluoramino)alkane formation shows that difluoramino groups as well as halogens can act as leaving groups in sulfuric acid. Graham, Freeman, and Johnson[4] have also obtained a low yield of 2,2-bis(difluoramino)propane from 2-chloro-2-(difluoramino)propane and difluoramine in sulfuric acid.

2-Chloro-2-penten-4-one was found to react with difluoramine and fuming sulfuric acid to give three products which could not be separated by distillation (Scheme I). The components, comprising 90, 5, and 5% of the sample (15, 0.9, and 0.9% yields), were separated by gas chromatography and were identified by elemental analysis and ir and nmr spectra as 2,2,4,4-tetrakis(difluoramino)pentane, 2-chloro-2,4,4-tris(difluoramino)pentane, and 2-chloro-3,4,4-tris(difluoramino)pentane, respectively. The expected product of Michael addition of difluoramine to 2-chloro-2-penten-4-one is 2-chloro-2-difluoramino-4-pentanone, and replacement of the carbonyl group with two difluoramino groups would give 2-chloro-2,4,4-tris(difluoramino)-pentane. Ionization of chloride ion from this product and alkylation of difluoramine by the resulting carbonium ion would give 2,2,4,4-tetrakis(difluoramino)-pentane. The formation of 2-chloro-3,4,4-tris(difluoramino)pentane can be rationalized on the basis of a 1,2-hydride shift in a chlorocarbonium ion followed by alkylation of difluoramine by the resulting secondary carbonium ion.

The reaction of *cis*-3-chlorocrotonic acid with refluxing difluoramine (bp −23°) in the presence of fuming sulfuric acid gave the Michael adduct, 3-chloro-3-

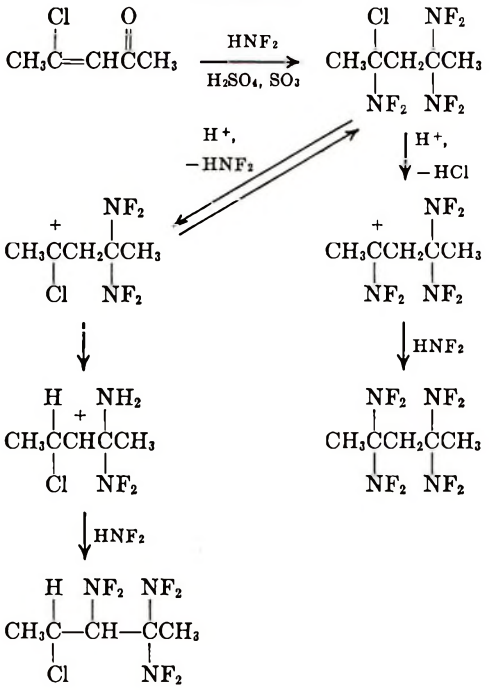
(1) This work was supported by the Office of Naval Research and the Advanced Research Projects Agency.

(2) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083 (1968).

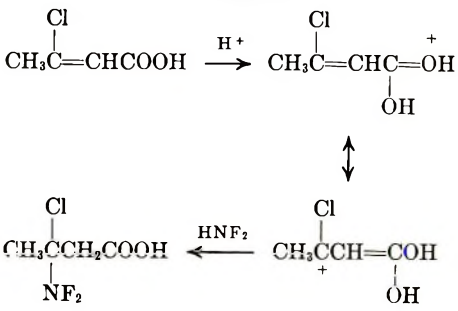
(3) K. Baum, *J. Org. Chem.*, **32**, 3648 (1967).

(4) W. H. Graham, J. P. Freeman, and K. E. Johnson, private communication.

SCHEME I

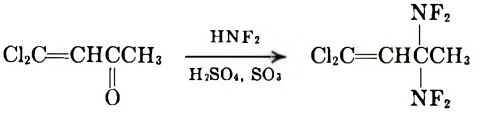


SCHEME II



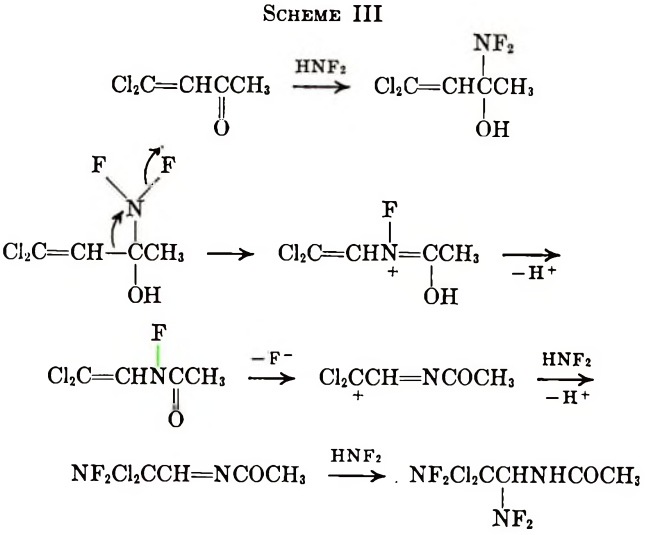
(difluoramino)butyric acid, in 59% yield (Scheme II). Ethyl 3-chlorocrotonate, on the other hand, did not react under these conditions, and the starting material was recovered. The stability of 3-chloro-3-(difluoramino)butyric acid in sulfuric acid, and the failure of chlorine to leave, is attributed to protonation of the carboxy group; subsequent chloride ionization would give a doubly charged cation. Failure of ethyl 3-chlorocrotonate even to add difluoramine is probably due to the greater stability of the protonated starting material, rendering the carbonium-ion center unreactive.

The reaction of 1,1-dichloro-1-buten-3-one with difluoramine took two entirely different courses, depending upon the conditions. In the presence of fuming sulfuric acid and such a large excess of liquid difluoramine that the latter was essentially the solvent (weight ratio of substrate/difluoramine/acid, 1:9:6.3), 1,1-dichloro-3,3-bis(difluoramino)-1-butene was isolated in 57% yield.



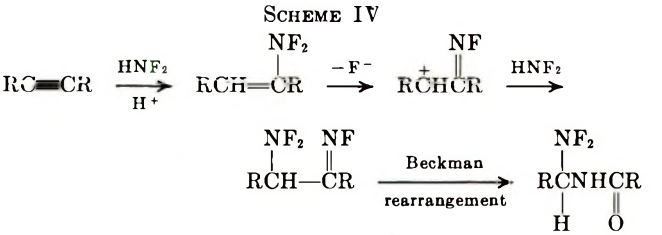
When this reagent ratio was changed to 1:1.3:6.2, no 1,1-dichloro-3,3-bis(difluoramino)-1-butene was obtained, but a product identified as N-[2,2-dichloro-1,2-bis(difluoramino)ethyl]acetamide was isolated in 24% yield. This product could be formed from the difluoraminocarbinol resulting from addition of difluoramine to the carbonyl group. Loss of fluoride and migration of the vinyl group would give a fluorimonium ion, which is also a protonated N-fluoroamide. Ionization of the "allylic" fluorine of the latter and the alkylation of difluoramine by the resulting carbonium ion center would give 1,1-dichloro-1-difluoramino-2-N-acetyliminoethane. The addition of difluoramine would then give N-[2,2-dichloro-1,2-bis(difluoramino)ethyl]-acetamide (Scheme III).

SCHEME III



Difluoraminocarbinols have been prepared by the uncatalyzed addition of difluoramine to carbonyl compounds[5] and are assumed to be intermediates in the formation of *gem*-bis(difluoramino)alkanes in the presence of sulfuric acid.[2] Alkyldifluoramines rearrange to fluorimonium ions under the same conditions,[3,6] and in this example the high mobility of vinyl groups in nucleophilic rearrangements[7] serves to make rearrangement competitive with hydroxyl removal. The ionization of the "allylic" fluorine of the resulting N-fluoroamide is similar to that of vinyldifluoramines formed by the addition of tetrafluorohydrazine[8-10] or difluoramine[11] to acetylenes. In the latter reaction a product of difluoramine alkylation by the resulting fluoriminocarbonium ion was isolated (Scheme IV).

SCHEME IV



(5) J. P. Freeman, W. H. Graham, and C. O. Parker, *J. Amer. Chem. Soc.*, **90**, 121 (1968).
(6) K. Baum and H. M. Nelson, *ibid.*, **88**, 4459 (1966).
(7) P. A. S. Smith, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, p 574.
(8) R. C. Petry, C. O. Parker, F. A. Johnson, T. E. Stevens, and J. P. Freeman, *J. Org. Chem.*, **32**, 1534 (1967).
(9) G. N. Sausen and A. L. Logothetis, *ibid.*, **32**, 2261 (1967).
(10) W. H. Graham, Abstracts of Papers, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.
(11) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7089 (1968).

In the presence of a high concentration of difluoramine, removal of the hydroxyl group of the difluoraminocarbinol and alkylation of difluoramine to give the geminal derivative is favored over fluorimonium-ion formation. The failure of 1,1-dichloro-1-buten-3-one to undergo simple 1,4 addition of difluoramine is in accord with reports of the resistance of conjugated ω-dichlorovinyl compounds to acid-catalyzed additions.[12,13] The reactivity of the double bond of 1,1-dichloro-3,3-bis(difluoramino)-1-butene is reduced by the steric and inductive effects of the two adjacent difluoramino groups.

The ability of a dichlorovinyl group to undergo difluoramine addition and of the adduct to undergo substitution of chlorine was demonstrated using a simpler substrate. The reaction of difluoramine and fuming sulfuric acid with 1,1-dichloroethylene at the reflux temperature of difluoramine gave an 8% yield of 1,1-dichloro-1-(difluoramino)ethane. When the reaction was conducted in a closed reactor at ambient temperature for a prolonged period, a mixture of 1,1-dichloro-1-(difluoramino)ethane (7.2% yield) and 1-chloro-1,1-bis(difluoramino)ethane (3.3% yield) was obtained. The compounds had little difference in boiling point, but were separated by gas chromatography. Further extension of the reaction time, however, did not result in replacement of the remaining chlorine.

$$CH_2{=}CCl_2 \longrightarrow CH_3CCl_2NF_2 \longrightarrow CH_3CCl(NF_2)_2$$

These results can be related to the fact that the difluoramino group is more electronegative than chlorine,[14] yet can provide mesomeric stabilization of adjacent positive charge.[3] Since both chlorine and difluoramino groups were shown to function as leaving groups in sulfuric acid, one would expect the chlorine of 1-chloro-1,1-bis(difluoramino)ethane to undergo substitution in the presence of a large excess of difluoramine. Molecular models indicate, however, that in the bis(difluoramino)carbonium ion both difluoramino groups cannot be in the same plane, as required for mesomeric stabilization. The additivity of the inductive effect of two difluoramino groups but not the mesomeric effect serve to favor the alternative reverse reaction to give the unstrained difluoraminochlorocarbonium ion.

Extensive attempts were not made to optimize yields in this work. It is apparent that experimental conditions have a profound effect not only on yields but on the type of products formed. The tendency toward rearrangement at lower difluoramine concentrations, as observed for the 1,1-dichloro-1-buten-3-one reactions, may have more general synthetic utility in difluoramine reactions.

Experimental Section

Difluoramine.—The previously described procedure for the generation of difluoramine was used.[2,3] *Explosion shielding adequate to withstand detonation of the quantity of difluoramine used is essential.* Manipulations were conducted remotely. Similar care is required in handling the potentially explosive products.

2,2,4,4-Tetrakis(difluoramino)pentane, 2-Chloro-2,4,4-tris(difluoramino)pentane and 2-Chloro-3,4,4-tris(difluoramino)pentane.—2-Chloro-2-pentan-4-one[15] (3.0 g, 0.028 mol) was treated with 18 g of difluoramine and 10 ml of 20% fuming sulfuric acid for 4 hr at ambient temperature with stirring in a 200-ml reactor fitted with needle valves.[2] Difluoramine was vented and the product, insoluble in the acid, was taken up in 50 ml of pentane and treated with sodium sulfate. Distillation through a 25-cm Holzmann column gave 1.30 g of colorless liquid, bp 30° (1 mm). Gas chromatography (8 ft × 1/4 in. column, 10% dioctyl phthalate on Fluoropak 80, 95°, 75 ml/min He) gave three components with retention times of 56, 66, and 81 min, comprising 90, 5, and 5% of the sample. The components were characterized as 2,2,4,4-tetrakis(difluoramino)pentane (15% yield), 2-chloro-2,-4,4-tris(difluoramino)pentane (0.9% yield), and 2-chloro-3,4,4-tris(difluoramino)pentane (0.9% yield).

The proton nmr spectrum of 2,2,4,4-tetrakis(difluoramino)-pentane consisted of a quintet (J = 3 cps) at δ 1.77 for the methyls and a broadened singlet at 2.90 for the methylene. The fluorine spectrum consisted of a singlet at ϕ^* −28.24. The infrared spectrum showed strong NF bands at (μ) 10.0 and 11.1.

Anal. Calcd for $C_5H_8N_4F_8$: C, 21.74; H, 2.90; N, 20.3. Found: C, 21.80; H, 3.20; N, 20.0.

The proton nmr spectrum of 2-chloro-2,4,4-tris(difluoramino)-pentane consisted of a quintet (J = 2.5 cps) at δ 1.79 for $CH_3C(NF_2)_2$, a triplet (J = 2 cps) at 1.97 for $CH_3C(NF_2)Cl$, and a broadened singlet at 2.93 for the methylene. Infrared bands in the NF region were at (μ) 10.0 (s), 11.13 (s), and 11.45 (m).

Anal. Calcd for $C_5H_8ClN_3F_6$: C, 23.13; H, 3.09; N, 16.2; F, 44.0. Found: C, 23.50; H, 3.34; N, 15.9; F, 42.9.

The proton nmr spectrum of 2-chloro-3,4,4-tris(difluoramino)-pentane consisted of a quintet (J = 2.5 cps) at δ 1.91 for $CH_3C(NF_2)_2$, two doublets (J = 6.3 cps) at 1.58 and 1.62 attributable to CH_3CHCl in two diastereomers, a poorly resolved multiplet at 4.55 for CH_3CHCl, and a broad multiplet at 4.13 for $CH(NF_2)$. Infrared bands in the NF region were at (μ) 10.06 (s), 10.30 (s), 10.85 (sh), 11.1 (s), and 11.50 (s).

Anal. Calcd for $C_5H_8ClN_3F_6$: C, 23.13; H, 3.09; N, 16.2; F, 44.0. Found: C, 23.59; H, 3.28; N, 15.7; F, 43.7.

3-Chloro-3-(difluoramino)butyric Acid.—*cis*-3-Chlorocrotonic acid (2.4 g, 0.020 mol) was added dropwise to 27 g of refluxing difluoramine and 10 ml of 20% fuming sulfuric acid. After 4.5 hr, the excess difluoramine was removed and the solution was quenched with 50 ml of ice. The product was extracted with three 20-ml portions of methylene chloride, dried, and distilled to give 2.05 g (59% yield) of colorless liquid which solidified in the receiver: mp 29–30°, bp 68° (0.2 mm).

Anal. Calcd for $C_4H_6NF_2ClO_2$: C, 27.68; H, 3.49; N, 8.09; F, 21.9. Found: C, 27.50; H, 3.24; N, 8.02; F, 20.1.

The proton nmr spectrum consisted of a triplet (J = 2 cps) at δ 2.07 for the methyl, a broadened singlet at 3.16 for the methylene, and a singlet at 11.74 for the OH. The fluorine spectrum consisted of an AB quartet (J_{FF} = 563 cps) with ϕ^*_A −32.63 and ϕ^*_B −36.16.

When ethyl 3-chlorocrotonate was treated as above, it was recovered unchanged in 70% yield.

1,1-Dichloro-3,3-bis(difluoramino)-1-butene.—1,1-Dichloro-1-buten-3-one[12] (3.0 g, 0.028 mol) was added dropwise with stirring to 27 g of refluxing difluoramine and 10 ml of 20% fuming sulfuric acid. After 3 hr, 50 ml of pentane was added and the unreacted difluoramine was removed. The pentane layer was separated, dried over sodium sulfate, and distilled through a 25-cm Holzmann column to give 3.64 g (57% yield) of 1,1-dichloro-3,3-bis-(difluoramino)-1-butene, bp 51° (18 mm).

Anal. Calcd for $C_4H_4N_2F_4Cl_2$: C, 21.14; H, 1.76; N, 12.3; F, 33.5. Found: C, 20.91; H, 2.04; N, 12.2; F, 34.1.

The proton nmr spectrum consisted of a quintet (J = 2.5 cps) at δ 1.97 for the methyl and a broadened singlet at 6.31 for the olefinic hydrogen. The fluorine spectrum consisted of a singlet at ϕ^* −30.02. The infrared spectrum showed an olefin band at (μ) 6.15 and NF bands at 9.92, 10.15, 10.40, 10.70, 11.02, 11.3, and 11.7.

N-[2,2-Dichloro-1,2-bis(difluoramino)ethyl]acetamide.—1,1-Dichloro-1-buten-3-one (20 g, 0.144 mol) was added dropwise with stirring to 27 g of difluoramine and 65 ml of 20% fuming sulfuric acid. After 3 hr, 60 ml of pentane was added and the excess difluoramine was removed. The acid layer was drained onto 200 ml of ice and the mixture was extracted with three 30-ml

(12) I. M. Heilbron, E. R. H. Jones, and M. Julia, *J. Chem. Soc.*, 1430 (1949).

(13) P. Straus, L. Kollek, and W. Heyn, *Ber.*, **63**, 1877 (1930).

(14) R. Ettinger, *J. Phys. Chem.*, **67**, 1558 (1963).

(15) M. Julia, *Ann. Chim.* (Paris), [12] **5**, 595 (1950).

portions of methylene chloride. Distillation of the pentane layer gave no products. The methylene chloride solution was dried over sodium sulfate and the solvent was removed. An undistillable oil (14.6 g) remained. Crystallization and recrystallization from cyclohexane gave 8.8 g (24% yield) of N-[2,2-dichloro-1,2-bis(difluoramino)ethyl]acetamide, mp 92–93°.

Anal. Calcd for $C_4H_5N_3F_4OCl_2$: C, 18.60; H, 1.94; N, 16.3; F, 29.4. Found: C, 19.04; H, 2.04; N, 16.2; F, 28.4.

The proton spectrum showed a singlet at δ 2.19 for the methyl, a broad doublet (J = 9 cps) at 6.86 for the NH, and a five-line pattern centered at 6.19 for $NHCH(NF_2)$. The latter signal is interpreted as double doublet splitting (J = 22.3, 11.3 cps) by the nonequivalent NF_2 fluorines and doublet splitting by the NH. Near equality of coupling to the NH and one of the fluorines results in overlapping to give five evenly spaced lines. When D_2O was added to remove the amide hydrogen, the δ 6.86 doublet disappeared and the 6.19 signal reverted to a doublet of doublets (J = 11.8, 23.4 cps). The fluorine nmr spectrum in $DCCl_3$ showed a "doublet" (J = 23 cps) at ϕ^* −42.66 for NF_2CCl_2 which is interpreted in terms of the rotational nonequivalence of the two fluorines, with the outer members of the resulting AB quartet invisible over the background. The other difluoramino group, attached to an asymmetric center, gave an AB quartet, with each member split by the adjacent hydrogen [ϕ^*_A −27.37, ϕ^*_B −45.34 (J_{AB} = 614 cps, J_{AH} = 22.3 cps, J_{BH} = 11.4 cps)]. The infrared spectrum showed the expected amide bands, and bands in the NF region at (μ) 9.73 (s), 10.13 (m), 10.56 (m), 11.18 (s), 11.42 (s), 11.80 (s), and 12.0 (s).

1,1-Dichloro-1-(difluoramino)ethane and 1-Chloro-1,1-bis(difluoramino)ethane.—1,1-Dichloroethylene (3.0 g, 0.031 mol) was added to 27 g of difluoramine and 10 ml of 20% fuming sulfuric acid in a 500-ml glass reactor fitted with needle valves[2] and the mixture was allowed to stand at ambient temperature for 18 hr. Difluoramine was removed and the product was extracted with 50 ml of pentane. Distillation through a 25-cm Holzmann column gave 0.51 g of colorless liquid, bp 30° (160 mm). Gas chromatography (10 ft × 1/4 in. column, 10% dioctyl phthalate on Fluoropak 80, 60 ml/min He, 25°) showed that the distillate consisted of 66% 1,1-dichloro-1-(difluoramino)ethane (7.2% yield), retention time 27 min, and 33% 1-chloro-1,1-bis(difluoramino)ethane (3.3% yield), retention time 18 min.

Anal. Calcd for $C_2H_3Cl_2NF_2$: C, 16.00; H, 2.00; N, 9.34; F, 25.3. Found: C, 15.80; H, 2.26; N, 8.91; F, 25.3.

The proton nmr spectrum of 1,1-dichloro-1-(difluoramino)-ethane in CCl_4 consisted of a triplet (J = 2.2 cps) at δ 2.31, and the fluorine spectrum consisted of a broadened singlet at ϕ^* −43.4. Infrared bands in the NF region were at (μ) 9.90 (s), 10.35 (w), 11.0 (s), and 11.8 (m).

Anal. Calcd for $C_2H_3N_2F_4Cl$: N, 16.8. Found: N, 17.3.

The proton nmr spectrum of 1-chloro-1,1-bis(difluoramino)-ethane in CCl_4 consisted of a quintet (J = 2.3 cps) at δ 1.61 and the fluorine spectrum consisted of a broadened singlet at ϕ^* −27.7. Infrared bands in the NF region were at (μ) 9.9 (m), 10.25 (s), 11.0–11.4 (vs).

In another experiment 3.0 g (0.031 mol) of 1,1-dichloroethylene was added to 6 g of refluxing difluoramine and 4 ml of 20% fuming sulfuric acid. After 1 hr, 15 ml of *n*-decane was added and the acid layer was quenched with ice. Distillation of the *n*-decane solution gave 0.35 g (8% yield) of 1,1-dichloro-1-(difluoramino)-ethane, bp 35° (250 mm), identical with the above product.

Registry No.—Difluoramine, 10405-27-3; 2,2,4,4-tetrakis(difluoramino)pentane, 19955-08-9; 2-chloro-2,4,4-tris(difluoramino)pentane, 19955-09-0; 2-chloro-3,4,4-tris(difluoramino)pentane, 19955-10-3; 3-chloro-3-(difluoramino)butyric acid, 19955-11-4; 1,1-dichloro-3,3-bis(difluoramino)-1-butene, 19955-12-5; N-[2,2-dichloro-1,2-bis(difluoramino)ethyl]acetamide, 19955-13-6; 1,1-dichloro-1-(difluoramino)ethane, 19955-14-7; 1-chloro-1,1-bis(difluoramino)ethane, 19955-15-8.

Acknowledgment.—The author is grateful to Dr. H. M. Nelson for nmr analyses, Mr. K. Inouye for elemental analyses, and Mr. F. J. Gerhart for assistance in the synthesis work.

Reactions of Nitro and Nitroso Compounds with Difluoramine[1]

KURT BAUM

Environmental Systems Division, Aerojet-General Corporation, Azusa, California 91703

Received December 5, 1968

Nitro and nitroso compounds were used as alkylating agents for difluoramine in the presence of strong acid. 1,1-Dibromo-1-nitrobutane, 1,1-dichloro-1-nitrobutane, 1-bromo-1-fluoro-1-nitropropane, and α,α-dibromo-α-nitrotoluene gave 1,1-dibromo-1-(difluoramino)butane, 1,1-dichloro-1-(difluoramino)butane, 1-bromo-1-difluoramino-1-fluoropropane, and α,α-dibromo-α-(difluoramino)toluene, respectively. Prolonged reactions converted the dibromo derivatives into 1-bromo-1,1-bis(difluoramino) compounds. 2-Halo-2,4,4-trinitropentane gave 3,5-dimethylisoxazole and 2,2,4,4-tetrakis(difluoramino)pentane, rationalized by a mechanism involving intramolecular nitro O alkylation. 1-Chloro-1-nitrosocyclohexane and 1-nitro-1-nitrosocyclohexane gave 1,1-bis(difluoramino)cyclohexane with fuming sulfuric acid but, with $BF_3 \cdot H_3PO_4$ as catalyst, 1-nitro-1-nitrosocyclohexane gave nitrocyclohexane and 1-nitrocyclohexyl-N′-fluorodiimide N-oxide. The latter was shown not to be an intermediate in the sulfuric acid catalyzed reaction. Unstable nitroso derivatives were prepared from 1-chloro-1-nitroalkanes, which reacted with difluoramine and fuming sulfuric acid to give 1-chloro-1,1-bis(difluoramino)alkanes. Alkyl nitrites acted as nitrosation agents toward difluoramine.

In a study of reactions of carbonyl compounds with dilfuoramine in sulfuric acid, several nitro ketones were examined.[2] Although 5-nitro-2-pentanone, 5,5-dinitro-2-hexanone, and 5,5,5-trinitro-2-pentanone gave the corresponding *gem*-bis(difluoramino)alkanes with nitro groups intact, 5-methyl-5-nitro-2-hexanone gave 2-difluoramino-2,5,5-trimethyltetrahydrofuran, rationalized on the basis of a carbonium-ion intermediate resulting from the protonation of the nitro group and loss of nitrous acid. Nitroso compounds are known to react with difluoramine in the presence of pyridine to give N′-fluorodiimide N-oxides,[3] but acid-catalyzed reactions have not been reported previously. In the present study, the scope of utility of nitro and nitroso compounds as alkylating agents for difluoramine was explored.

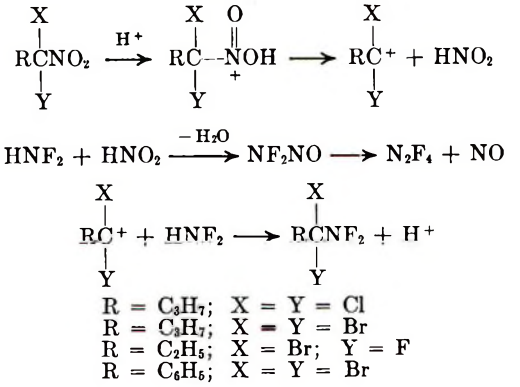
α,α-Dihalonitro Compounds.—1,1-Dihalo-1-nitroalkanes were found to react readily with difluoramine and fuming sulfuric acid to give 1,1-dihalo-1-(difluoramino)alkanes (Scheme I). Thus, 1,1-dichloro-1-(difluoramino)butane, 1,1-dibromo-1-(difluoramino)butane, 1-bromo-1-difluoramino-1-fluoropropane, and α,α-dibromo-α-(difluoramino)toluene were prepared

(1) This work was supported by the Office of Naval Research and the Advanced Research Projects Agency.

(2) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083 (1968).

(3) T. E. Stevens and J. P. Freeman, *J. Org. Chem.*, **29**, 2279 (1964).

SCHEME I

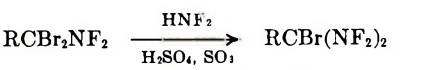


from 1,1-dichloro-1-nitrobutane, 1,1-dibromo-1-nitrobutane, 1-bromo-1-fluoro-1-nitropropane, and α,α-dibromo-α-nitrotoluene, respectively, in yields of 33–61%.

Transient blue-purple colorations in the solutions were indicative of nitrosyl difluoramine, formed by the nitrosation of difluoramine. Nitrosyl difluoramine has been prepared reversibly from NO and N_2F_4 at low temperatures.[4]

1,1,1-Bromodinitroalkanes and chlorodinitroalkanes did not react with difluoramine in fuming sulfuric acid. 1-Iodo-1-nitrocyclohexane[5] was degraded under these conditions, but did not react with neat difluoramine.

The reaction of vinylidene chloride with difluoramine and fuming sulfuric acid gave 1,1-dichloro-1-(difluoramino)ethane and 1-chloro-1,1-bis(difluoramino)ethane.[6] The reaction of dihalonitroalkanes with difluoramine thus provided a convenient source of starting material to determine the scope of reactivity of halogens in α,α-dihalodifluoramines toward substitution. Only the dibromo derivatives were found to undergo halogen substitution. In fact, to obtain a sample of 1,1-dibromo-1-(difluoramino)butane free of the bis(difluoramino) derivative, it was necessary to quench the reaction (conducted at -10 to $-20°$) within 10 min. On the other hand, the corresponding dichloro derivative gave no chlorine substitution product after 4 days in a sealed reactor at ambient temperature. α,α-Dichloro-α-(difluoramino)toluene was previously prepared from benzotrichloride and difluoramine in trifluoroacetic acid.[7] In the present work the same product was obtained using fuming sulfuric acid and no chlorine substitution took place under forcing conditions. Likewise, no further substitution products could be obtained from 1-bromo-1-difluoramino-1-fluoropropane. The greater reactivity of 1,1-dichloro-1-(difluoramino)ethane compared with the butane and toluene analogs must be attributed to steric factors.

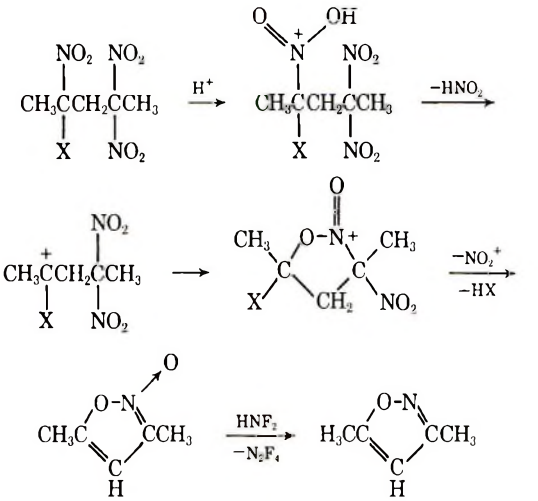


R = C_3H_7 (13% yield)
R = C_6H_5 (72% yield)

2-Halo-2,4,4-trinitropentanes.—Because of the demonstrated inertness of *gem*-dinitro compounds, 2-halo-2,4,4-trinitropentanes were expected to undergo replacement only of the 2-nitro and possibly the halogen. The starting materials were prepared by adding bromine and chlorine *in situ* to the adduct of the sodium salt of 1,1-dinitroethane and 2-nitropropene.[8] The chloro and bromo compounds both reacted with difluoramine in fuming sulfuric acid to give the same products, 2,2,4,4-tetrakis(difluoramino)pentane[6] (5–8% yield) and 3,5-dimethylisoxazole (26–34% yield). Even when reaction conditions were used that resulted in the recovery of some unreacted starting materials, no other products were isolated. The isoxazole also gave 2,2,4,4-tetrakis(difluoramino)pentane, but it is not known whether the reaction proceeded entirely through this intermediate.

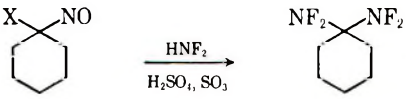
A possible path for the formation of 3,5-dimethylisoxazole is given in Scheme II. Protonation of the

SCHEME II



most basic nitro group and loss of nitrous acid would give a halocarbonium ion. Intramolecular alkylation of the oxygen of a nitro group, followed by loss of nitronium ion and HX would give 3,5-dimethylisoxazole N-oxide, which could be reduced to the isoxazole by difluoramine. Amine oxides are deoxygenated by a variety of reagents,[9] and, since isoxazoles are resistant to oxidation,[10] the deoxygenation of this oxide should be particularly facile. Difluoramine has been shown to act as a reducing agent toward reagents such as ferric ion[11] and diazonium salts.[12]

Nitroso Compounds.—The only product isolated from the reactions of 1-chloro-1-nitrosocyclohexane or 1-nitro-1-nitrosocyclohexane with difluoramine and fuming sulfuric acid was 1,1-bis(difluoramino)cyclo-



X = Cl or NO_2

(4) C. B. Colburn and F. A. Johnson, *Inorg. Chem.*, **1**, 715 (1962).

(5) An undistillable oil prepared according to L. W. Seigle and H. B. Haas, *J. Org. Chem.*, **5**, 100 (1940). Analytically pure material was obtained by low temperature crystallization.

(6) K. Baum, *ibid.*, **34**, 2046 (1969).

(7) W. H. Graham and J. P. Freeman, *J. Amer. Chem. Soc.*, **89**, 716 (1967).

(8) S. S. Novikov, *et al.* [*Dokl. Akad. Nauk SSSR*, **125**, 560 (1959)] reported a similar synthesis of 2-bromo-2,4,4,4-tetranitrobutane by adding nitroform to 2-nitropropene and brominating the resulting acidic *aci*-nitro compound.

(9) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, p 27.

(10) K. K. Kochetkov and S. D. Sokolov, *Advan. Heterocycl. Chem.*, 418 (1963).

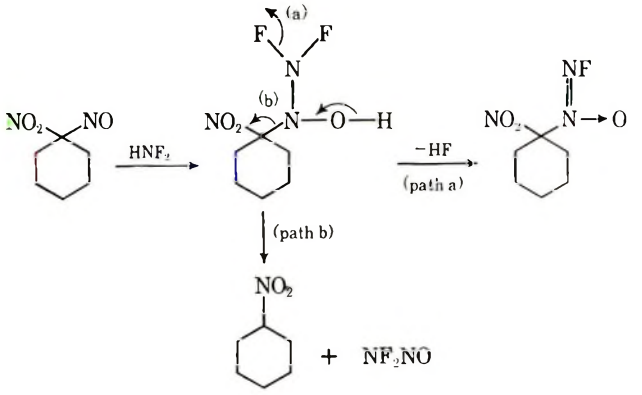
(11) K. J. Martin, *J. Amer. Chem. Soc.*, **87**, 394 (1965).

(12) K. Baum, *J. Org. Chem.*, **33**, 4333 (1968).

hexane, even when the reaction, in the latter case, was quenched within 5 min.

With the objective of isolating possible intermediates, the reaction of 1-nitro-1-nitrosocyclohexane with difluoramine was repeated using a more selective catalyst, the boron trifluoride complex of phosphoric acid.[7,12] Under these conditions,[13] 1,1-bis(difluoramino)cyclohexane was not formed, but nitrocyclohexane and 1-nitrocyclohexyl-N′-fluorodiimide N-oxide were isolated. These products could be formed from a common intermediate, the adduct of difluoramine to the N=O bond, by cleavage of either the N–F or the C–N bond (Scheme III).

SCHEME III



A sample of 1-nitrocyclohexyl-N′-fluorodiimide N-oxide was treated with difluoramine in fuming sulfuric acid to determine if this compound could be an intermediate in the formation of 1,1-bis(difluoramino)cyclohexane. The unchanged starting material was recovered. The reaction thus appears to involve initial solvolysis of a protonated nitro or nitroso group, or of the hydroxylamine function postulated above. When one group is replaced, the remaining one becomes sufficiently reactive that intermediates are not isolated.

This reaction was used to prepare 1-chloro-1,1-bis(difluoramino)alkanes not obtainable from the dichloronitroalkanes. The 1-chloro-1-nitro-1-nitrosoalkanes have not been reported previously. Nitrosation of aqueous solutions of the sodium salts of 1-chloro-1-nitropropane and 1-chloro-1-nitrobutane at 0° gave dark blue oils which were too unstable for the isolation of analytical samples. Reactions of the crude oils with difluoramine in fuming sulfuric acid gave 1-chloro-1,1-bis(difluoramino)propane and 1-chloro-1,1-bis(difluoramino)butane, respectively.

R = C_2H_5 or C_3H_7

Alkyl Nitrites.—Octyl nitrite reacted with liquid difluoramine to give a blue-purple solution indicative of nitrosyldifluoramine. Removal of the difluoramine left *n*-octanol. No catalyst was necessary for this reaction. The nitrite thus acted as a nitrosation agent rather than an alkylating agent toward difluoramine.

(13) Methylene chloride was used as a solvent for the 1-nitro-1-nitrosocyclohexane; thus the catalyst was present as a separate phase. The diimide N-oxide was obtained in one uncatalyzed reaction, but this result was not repeatable.

Experimental Section

Difluoramine.—The previously described[2,14] apparatus for the difluoramine reaction was used. *Adequate explosion shielding is essential* for the difluoramine reactions and for isolation of the products.

1,1-Dichloro-1-(difluoramino)butane.—1,1-Dichloro-1-nitrobutane (4.0 g, 0.0232 mol) was added with stirring to 27 g of difluoramine and 11 ml of 20% fuming sulfuric acid in a 500-ml reactor fitted with glass and Teflon needle valves.[2] The reaction was allowed to proceed for 1 hr at the reflux temperature of difluoramine; a purple color developed during this period. The valves were closed and the reaction was continued at room temperature for 2 hr. The mixture was drained onto 100 ml of ice and extracted with three 30-ml portions of methylene chloride. The solution was dried over sodium sulfate and distilled through a 25-cm Holzmann column to give 2.80 g (61% yield) of 1,1-dichloro-1-(difluoramino)butane, bp 45° (40 mm).

Anal. Calcd for $C_4H_7NF_2Cl_2$: C, 26.97; H, 3.96; H, 7.86; F, 21.4. Found: C, 27.10; H, 4.03; N, 7.65; F, 20.7.

The proton nmr spectrum showed an irregular triplet (J = 6 cps) at δ 1.03 for the methyl and complex multiplets at 1.82 and 2.21 for the methylenes. The fluorine spectrum consisted of a broadened singlet at ϕ^* −41.92. Infrared bands in the NF region were (μ) 9.90 (m), 10.98 (m), 11.30 (s), and 11.69 (m).

1,1-Dibromo-1-(difluoramino)butane.—To 6 g of refluxing difluoramine and 5 ml of 20% fuming sulfuric acid, 1.0 g (0.00384 mol) of 1,1-dibromo-1-nitrobutane was added dropwise with stirring. After 10 min, the mixture was drained onto 100 ml of ice. The product was extracted with two 20-ml portions of methylene chloride, dried over sodium sulfate, and distilled through a 25-cm Holzmann column to give 0.48 g (47% yield) of 1,1-dibromo-1-(difluoramino)butane, bp 24° (1 mm).

Anal. Calcd for $C_4H_7NF_2Br_2$: C, 17.98; H, 2.62; N, 5.24. Found: C, 18.21; H, 2.60; N, 5.26.

The proton nmr spectrum consisted of a triplet (J = 7 cps) for the methyl at δ 1.05, a distorted triplet at 2.52 for $CH_2CBr_2NF_2$, and a multiplet centered at 1.84 for the other methylene. The fluorine spectrum consisted of a broadened singlet at ϕ^* −56.0. Infrared bands in the NF region were (μ) 10.0 (s), 10.80 (w), 10.93 (m), 11.09 (m), 11.40 (s), and 11.78 (m).

1-Bromo-1-difluoramino-1-fluoropropane.—A mixture of 5.0 g (0.268 mol) of 1-bromo-1-fluoro-1-nitropropane,[15] 14 ml of 20% fuming sulfuric acid, and 27 g of difluoramine was stirred at ambient temperature and autogenous pressure for 30 min. Decane (40 ml) was added and difluoramine was removed. The decane solution was heated at 77° for 1.5 hr at 22-mm pressure and the product, 1.95 g of colorless liquid, was collected in a −80° trap. Elemental analysis and gas chromatography showed that the product consisted of 98% 1-bromo-1-difluoramino-1-fluoropropane (37% yield) and 2% *n*-decane. Distillation of the mixture at 50° (209 mm) did not change its composition. An analytical sample was obtained by gas chromatography ($^3/_{16}$ in. × 6 ft column, 10% dibutyl phthalate on Chromosorb W, 30 ml/min helium, 63°, retention time 118 sec).

Anal. Calcd for $C_3H_5NBrF_3$: C, 18.77; H, 2.62; N, 7.30. Found: C, 19.07; H, 2.19; N, 7.72.

The proton nmr spectrum consisted of a triplet (J_{HH} = 7.6 cps) at δ 1.3 for the methyl and an overlapping quartet (J_{HH} = 7.6 cps) of doublets (J_{HF} = 16.5 cps) of triplets (J_{HNF_2} = 1.5 cps) at 2.39 for the methylene. The fluorine spectrum consisted of a broad symmetrical band at ϕ^* −34.3 for the NF_2 and a quintet (J_{FF} = 16.5 cps = J_{CH_2F}) at 102.0 for CF. Infrared bands in the NF region were (μ) 10.10 (s), 10.49 (s), 10.75 (m), 10.80 (m), 11.00 (s), 11.25 (s), and 11.73 (s).

1-Bromo-1,1-bis(difluoramino)butane.—1,1-Dibromo-1-nitrobutane (4.0 g, 0.0153 mol) was added to 27 g of difluoramine and 11 ml of 20% fuming sulfuric acid in a glass pressure reactor. The mixture was stirred at atmospheric pressure for 2 hr and then at autogenous pressure at ambient temperature for 2 hr. Bromine color in this solution became pronounced. Pentane (100 ml) was added and difluoramine was removed. Distillation of the pentane solution gave 0.47 g (13% yield) of 1-bromo-1,1-bis(difluoramino)butane, bp 36° (15 mm).

Anal. Calcd for $C_4H_7N_2F_4Br$: C, 20.08; H, 2.93; N, 11.70. Found: C, 20.52; H, 3.15; N, 11.40.

The proton nmr spectrum consisted of an irregular triplet at δ 0.99 for the methyl and multiplets at 2.3 and 1.8 for the methy-

(14) K. Baum, *J. Org. Chem.*, **32**, 3648 (1967).

(15) K. Baum, paper in preparation.

lenes. The fluorine spectrum consisted of an AB quartet, ϕ^*_A −35.11, ϕ^*_B −46.27 (J_{AB} = 604 cps). Infrared bands in the NF region were (μ) 9.80 (m), 9.93 (m), 10.62 (s), 10.80 (sh), 11.38 (s), 11.5 (sh), 12.2 (m), and 12.3 (m).

α-Bromo-α,α-bis(difluoramino)toluene.—α,α-Dibromo-α-nitrotoluene (5.0 g, 0.0170 mol) was added dropwise with stirring to 27 g of refluxing difluoramine and 12 ml of 20% fuming sulfuric acid. After 4 hr, 50 ml of methylene chloride was added and difluoramine was removed. The methylene chloride solution was dried over sodium sulfate and distilled to give 3.35 g (72% yield) of α-bromo-α,α-bis(difluoramino)toluene, bp 32° (0.4 mm).

Anal. Calcd for $C_7H_5N_2F_4Br$: C, 30.77; H, 1.83; N, 10.25; F, 27.8. Found: C, 30.90; H, 1.84; N, 10.40; F, 28.3.

The fluorine nmr spectrum consisted of an AB quartet, ϕ^*_A −42.17, ϕ^*_B −45.04 (J_{FF} = 601 cps). Infrared bands in the NF region were (μ) 9.95 (m), 10.19 (m), 10.28 (m), 10.50 (m), 10.70 (m), 11.05 (s), 11.25 (s), and 11.50 (vs).

α,α-Dibromo-α-(difluoramino)toluene and α-Bromo-α,α-bis(difluoramino)toluene.—α,α-Dibromo-α-nitrotoluene (15 g, 0.051 mol) was added dropwise with stirring to 58 g of refluxing difluoramine and 36 ml of 20% fuming sulfuric acid. After 4 hr, 100 ml of pentane was added and difluoramine was removed. The pentane solution was dried over sodium sulfate and distilled to give 5.52 g (40% yield) of α-bromo-α,α-bis(difluoramino)toluene and 4.98 g (32.5% yield) of α,α-dibromo-α-(difluoramino)toluene, bp 53° (0.25 mm).

Anal. Calcd for $C_7H_5Br_2NF_2$: C, 27.91; H, 1.66; N, 4.65; F, 12.62. Found: C, 28.02; H, 1.63; N, 4.70; F, 12.80.

The fluorine nmr spectrum consisted of a singlet at ϕ^* −57.5. Infrared bands in the NF region were (μ) 10.0 (m), 10.73 (w), 10.96 (m), 11.52 (s), and 12.34 (s).

α,α-Dichloro-α-(difluoramino)toluene.—Benzotrichloride (15.0 g, 0.078 mol) was treated with 40 g of refluxing difluoramine and 36 ml of 20% fuming sulfuric acid for 4 hr. Pentane (100 ml) was added and difluoramine was removed. Distillation of the pentane solution gave 10.55 g (64% yield) of α,α-dichloro-α-(difluoramino)toluene, bp 38° (0.4 mm).

Anal. Calcd for $C_7H_5NF_2Cl_2$: C, 39.63; H, 2.36; N, 6.60; F, 17.9. Found: C, 39.60; H, 2.02; N, 6.64; F, 17.8.

The fluorine nmr spectrum consisted of a singlet at ϕ^* −44.88. The infrared spectrum showed NF bands at (μ) 9.98 (m), 10.65 (w), 10.83 (m), 11.14 (s), 11.40 (vs), and 11.80 (s).

1-Iodo-1-nitrocyclohexane.[5]—Nitrocyclohexane (3.87 g, 0.030 mol) was dissolved in 6.6 ml of 5 *N* sodium hydroxide at 50°. The solution was cooled to room temperature and was added dropwise to a solution of 7.62 g (0.030 mol) of iodine and 4.98 g (0.030 mol) of potassium iodide in 30 ml of water. After 10 min, the dark oil which separated was crystallized from pentane at −80° and recrystallized twice. The residual solvent was removed at 20 mm. The product, 1-iodo-1-nitrocyclohexane (5.4 g, 64% yield), was an amber oil at room temperature.

Anal. Calcd for $C_6H_{10}NO_2I$: C, 28.25; H, 3.93; N, 5.50. Found: C, 28.19; H, 3.82; N, 5.32.

This compound did not react with difluoramine in the absence of catalysts, and, in the presence of sulfuric acid, no products extractable from water were formed.

2-Bromo-2,4,4-trinitropentane.—2-Nitropropene (17.4 g, 0.2 mol) was added with stirring to a solution of 8.8 g (0.22 mol) of sodium hydroxide and 24.0 g (0.20 mol) of 1,1-dinitroethane in 200 ml of water at 5°. A yellow salt precipitated. Bromine (32.0 g, 0.20 mol) was added dropwise over a 25-min period at 0–5°. The solid product was filtered, washed with water, and recrystallized from 200 ml of ethanol to give 34.3 g of white solid, mp 54–55°. Concentration of the ethanol gave an additional 4.8 g, mp 53–54° (68% total yield).

Anal. Calcd for $C_5H_8N_3O_6Br$: C, 20.99; H, 2.80; N, 14.69. Found: C, 20.67; H, 2.67; N, 14.36.

The nmr spectrum consisted of singlets at δ 4.06, 2.29, and 2.12, assigned to the CH_2, $CH_3C(NO_2)_2$, and CH_3CNO_2Br, respectively.

2-Chloro-2,4,4-trinitropentane.—The slurry prepared from dinitroethane, sodium hydroxide, and 2-nitropropene, as above, was saturated with chlorine. A green oil which separated was diluted with 80 ml of methylene chloride and washed with sodium bicarbonate solution and with water. Distillation gave 28 g of green oil, bp 82° (0.06 mm). Crystallization and recrystallization from ethanol gave 5.9 g (12.2% yield) of 2-chloro-2,4,4-trinitropentane, a white solid, mp 31–31.5°.

Anal. Calcd for $C_5H_8N_3O_6Cl$: C, 24.85; H, 3.31; N, 17.39. Found: C, 24.59; H, 3.32; N, 16.99.

The nmr spectrum showed an AB quartet centered at δ 4.00 (J_{AB} = 16.8 cps, inner member separation (6.2 cps) for the methylene, a sharp singlet at 2.22 for $CH_3C(NO_2)_2$, and a slightly broadened singlet at 2.15 for CH_3CNO_2Cl.

Reactions of 2-Chloro-2,4,4-trinitropentane and 2-Bromo-2,4,4-trinitropentane with Difluoramine.—2-Chloro-2,4,4-trinitropentane (5.0 g. 0.0207 mol) in 10 ml of methylene chloride was stirred at ambient temperature, under autogenous pressure, with 14 ml of 20% fuming sulfuric acid and 27 g of difluoramine for 18 hr. The mixture was drained onto 250 ml of ice and extracted with four 30-ml portions of methylene chloride. The methylene chloride solution was dried and distilled through a 25-cm Holzmann column to give 0.60 g of colorless liquid, bp 37–50° (13 mm), and 0.53 g, bp 50–58° (13 mm). Gas chromatography (10% six-ring polyphenyl ether on Chromosorb W, 110°) and nmr analysis showed that the first fraction consisted of 0.064 g (0.123 mmol) of 2,2,4,4-tetrakis(difluoramino)pentane[6] and 0.537 g (5.53 mmol) of 3,5-dimethylisoxazole while the second fraction consisted of 0.39 g (1.41 mmol) of 2,2,4,4-tetrakis(difluoramino)pentane and 0.14 g (1.45 mmol) of 3,5-dimethylisoxazole (total yields, 8 and 34%, respectively). Infrared spectra were identical with those of authentic samples.

The reaction of 2-bromo-2,4,4-trinitropentane (5.0 g, 0.0175 mol) with difluoramine as above gave a 5% yield of 2,2,4,4-tetrakis(difluoramino)pentane and a 26.5% yield of 3,5-dimethylisoxazole.

Reaction of 1-Chloro-1-nitrosocyclohexane with Difluoramine.—1-Chloro-1-nitrosocyclohexane (5.0 g, 0.040 mol) was added dropwise to 27 g of refluxing difluoramine and 10 ml of 20% fuming sulfuric acid. The blue color of the nitroso compound disappeared instantaneously. After 2 hr, the reaction was quenched with 100 ml of ice and the product was extracted with three 30-ml portions of methylene chloride and dried over sodium sulfate. Distillation through a 25-cm Holzmann column gave 2.06 g (31% yield) of 1,1-bis(difluoramino)cyclohexane, identical with an authentic sample.[2]

Reaction of 1-Nitro-1-nitrosocyclohexane with Difluoramine and Fuming Sulfuric Acid.—A solution of 5.0 g (0.0316 mol) of 1-nitro-1-nitrosocyclohexane in 15 ml of methylene chloride was added with stirring to 27 g of refluxing difluoramine and 11 ml of 20% fuming sulfuric acid. The nitroso color disappeared instantaneously. Five minutes after the addition was completed, the mixture was worked up as above to give 1.92 g (31% yield) of 1,1-bis(difluoramino)cyclohexane.[2]

Reaction of 1-Nitro-1-nitrosocyclohexane with Difluoramine and Boron Trifluoride–Phosphoric Acid Complex.—Boron trifluoride complex of phosphoric acid (2 ml) was added dropwise to a solution of 5.0 g (0.0316 mol) of 1-nitro-1-nitrosocyclohexane in 27 g of refluxing difluoramine. After 45 min, 80 ml of methylene chloride was added and difluoramine was removed. The methylene chloride solution was dried over sodium sulfate and distilled to give 1.50 g (39.4% yield) of nitrocyclohexane, bp 30° (3 mm), and 3.22 g (53.4% yield) of 1-nitrocyclohexyl-N′-fluorodiimide N-oxide, bp 69° (3 mm).

Anal. Calcd for $C_6H_{10}N_3O_3F$: C, 37.70; H, 5.23; N, 22.0; F, 9.95. Found: C, 38.09; H, 5.57; N, 21.7; F, 10.0.

The infrared spectrum showed a nitro band at 6.4 (μ), an azoxy band at 6.68, and bands in the NF region at 9.70 (m), 9.90 (s), 10.46 (m), 10.98 (m), and 11.40 (s).

1-Chloro-1,1-bis(difluoramino)propane.—1-Chloro-1-nitropropane (10.0 g, 0.081 mol) was dissolved in a solution of 5.0 g (0.125 mol) of sodium hydroxide in 40 ml of water at 0–5° with vigorous stirring (1.5 hr). This solution was added dropwise to a partially frozen nitrous acid solution prepared by slowly adding 8.6 g. (0.122 mol) of sodium nitrite to a solution of 15 g of concentrated sulfuric acid in 100 ml of water with intermittent cooling in a −80° bath. A dark blue oil (7.6 g) separated; it was extracted with 25 g of pentane and stored overnight at −80°.

The pentane solution was added dropwise to 27 g of refluxing difluoramine and 13 ml of 20% fuming sulfuric acid. After 4 hr, the mixture was drained onto 200 ml of ice. The pentane layer was separated and the aqueous layer was extracted with 25 ml of pentane. The pentane solution was dried and distilled to give 0.2 g of colorless liquid, bp 31° (60 mm). Gas chromatography (10 ft × 1/4-in. column, 10% Ucon 50HB100 on Fluoropak 80, 70°) was used to isolate the major component (60% of the sample).

Anal. Calcd for $C_3H_5N_2F_4Cl$: C, 20.3; H, 2.82; N, 15.8. Found: C, 20.4; H, 3.33; N, 16.1.

The proton nmr spectrum consisted of a triplet (J = 7.0 cps) at δ 1.26 for the methyl and a quartet (J = 7.0 cps) at 2.45, with additional coupling detectable to the fluorines. The fluorine spectrum consisted of an AB quartet with ϕ^*_A −29.91, ϕ^*_B −36.91 (J_{AB} = 611 cps).

1-Chloro-1,1-bis(difluoramino)butane.—1-Chloro-1-nitrobutane (5.0 g, 0.0364 mol) was dissolved in a solution of 1.64 g (0.041 mol) of sodium hydroxide in 50 ml of water at 0–5° (2 hr) and 3.79 g (0.055 mol) of sodium nitrite was added. A 25% sulfuric acid solution (20 ml) was added slowly at 0–5°. A dark blue oil (6.2 g) separated and was stored overnight at −80° in 25 g of pentane.

The pentane solution was added to 10 ml of 20% fuming sulfuric acid and 27 g of refluxing difluoramine. After 4 hr the mixture was drained onto 100 ml of ice and pentane layer was separated. The aqueous layer was extracted with two 50-ml portions of methylene chloride. The combined organic solution was distilled to give 0.82 g of colorless liquid, bp 33–34° (35 mm). Gas chromatography (10 ft × 1/4 in. column of 10% Ucon 50-HB100 on Fluoropak 80, 70°) was used to trap the major component (90% of the sample, 10% yield), identified as 1-chloro-1,1-bis(difluoramino)butane.

Anal. Calcd for $C_4H_7N_2F_4Cl$: C, 24.7; H, 3.60; N, 14.4. Found: C, 24.9; H, 3.89; N, 14.0.

The proton nmr spectrum consisted of an irregular triplet at δ 1.01 for the methyl, a multiplet at 1.78 (approximately a septet) for CH_3CH_2, and a multiplet at 2.24 for the other methylene. The fluorine spectrum consisted of an AB quartet, ϕ^*_A −30.42, ϕ^*_B −37.35 (J_{AB} = 609 cps). The infrared spectrum showed peaks in the NF region at (μ) 9.80 (m), 10.60 (s), 11.2–11.4 (s), 12.03 (m), and 12.30 (m).

Reaction of *n*-Octyl Nitrite with Difluoramine.—*n*-Octyl nitrite (5.0 g, 0.0314 mol) was added dropwise to 27 g of refluxing difluoramine. A purple solution was formed, which became colorless after 30 min. After 4 hr, difluoramine was removed and the residue was distilled to give 3.14 g (77% yield) of *n*-octanol, bp 54° (1 mm), infrared spectrum identical with that of an authentic sample.

Registry No.—Difluoramine, 10405-27-3; 1,1-dichloro-1-(difluoramino)butane, 19955-19-2; 1,1-dibromo-1-(difluoramino)butane, 19955-20-5; 1-bromo-1-difluoramino-1-fluoropropane, 19955-21-6; 1-bromo-1,1-bis(difluoramino)butane, 19955-22-7; α-bromo-α,α-bis(difluoramino)toluene, 19955-23-8; α,α-dibromo-α-(difluoramino)toluene, 19955-24-9; 1-chloro-1,1-bis(difluoramino)butane, 19955-25-0; α,α-dichloro-α-(difluoramino)toluene, 14092-53-6; 2-bromo-2,4,4-trinitropentane, 19955-54-5; 2-chloro-2,4,4-trinitropentane, 19955-55-6; 1-nitrocyclohexyl-N′-fluorodiimide N-oxide, 19955-56-7; 1-chloro-1,1-bis(difluoramino)-propane, 19955-57-8.

Acknowledgment.—The author is indebted to Mr. F. J. Gerhart and Mr. H. F. Shuey for assistance in the synthesis work, to Dr. H. M. Nelson and Mr. L. A. Maucieri for nmr analyses, and to Mr. K. Inouye for elemental analyses.

Heterocyclic Ring-Closure Reactions. II.[1] Reactions of α-Mercapto Acids with Cyanogen[2a]

S. C. MUTHA[2b] AND ROGER KETCHAM[2c]

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94122

Received October 10, 1968

The reaction of α-mercapto acids with cyanogen has been studied and shown to give 2-[(S-carboxyalkyl)-thioimidyl]-Δ^2-thiazolin-4-one in good yields. The reaction product undergoes unusual N-methylation in addition to esterification when treated with diazomethane and could be cyclized to afford bicyclic symmetrical 4,4′-diketo-Δ^2-bithiazolinyl, which could be converted into its dienol diacetate. Proof of structure has been obtained by X-ray crystallography and supporting evidence obtained from uv, ir, nmr, and pK_a determinations and dipole moment measurements.

Cyanogen reacts with mercaptans in the presence of catalytic amounts of *n*-butylamine at low temperature to yield S,S′-disubstituted dithiooxaldiimidates.[1,3] This is a general reaction for the preparation of dithiooxaldiimidic esters.

Primary aliphatic amines react with cyanogen to yield symmetrically disubstituted oxamidines,[4] whereas secondary amines normally give only cyanoformamidines and under vigorous conditions oxamidine derivatives.[5] But when ethylenediamine and its C-alkyl derivatives are allowed to react with cyanogen the product obtained was characterized as bis(Δ^2-2-imidazolinyl).[6]

In the light of these results it was interesting to investigate the behavior of α-mercapto acids (**1**) with cyanogen, since the geminal mercapto and carboxylic acid groups could react separately or in conjunction. When 2 mol of mercaptoacetic acid (**1a**) were treated with 1 mol of cyanogen, a white crystalline product, henceforth referred to as the monocyclic product, was obtained. This substance analyzed for condensation of these three molecules accompanied by loss of 1 mol of water ($C_6H_6N_2S_2O_3$). This indicated that the expected diaddition product (**2a**) was formed but reacted further to afford a monocyclic product. Cyclization of **2a** can result in formation of **3a** having a five-membered ring or **4a** having a six-membered ring. When it is dissolved in water and treated with 5% aqueous sodium bicarbonate, carbon dioxide is liberated, indicating the presence of a strongly acidic function. It has a neutralization equivalent of 109 when titrated with sodium hydroxide (potentiometric titration) and has two acidic functions of apparent pK_a = 4.1 and 6.7 (50% acetone in water). It gives a red color when treated with a solution of ferric chloride, which indicates that the compound may be phenolic although there are other possibilities for complex formation with the various functional groups in either of the two structures. The

(1) A. R. Martin and R. G. Ketcham, *J. Org. Chem.*, **31**, 3612 (1966).

(2) (a) Supported by National Institute of Mental Health Grant MH 08787. (b) A portion of the Ph.D. thesis of S. C. M. (c) To whom inquiries should be sent.

(3) H. M. Woodburn and C. E. Sroog, *J. Org. Chem.*, **17**, 371 (1952).

(4) H. M. Woodburn, B. A. Morehead, and C. M. Chih, *ibid.*, **15**, 535 (1950).

(5) H. M. Woodburn, B. A. Morehead, and W. H. Bonner, *ibid.*, **14**, 555 (1949).

(6) H. M. Woodburn and R. C. O'Gee, *ibid.*, **17**, 1235 (1952).

uv, ir, and nmr spectra do not distinguish unambiguously between the two structures **3a** or **4a**.

A 1-mol sample of the monocyclic compound (**3a** or **4a**) reacts with 2 mol of diazomethane and gives a product (**5a** or **6a**), mp 71–72°, which analyzes for $C_8H_{10}N_2O_3S_2$. The ir spectrum showed two peaks at 1740 and 1720 cm^{-1}, indicating two different carbonyl groups. Unexpectedly, there was no band at 3230 cm^{-1} corresponding to the imino N–H group. Disappearance of a group of small bands between 3000 and 2500 cm^{-1} indicated that the acid had been converted into the ester. The nmr spectrum of this ester in deuteriochloroform showed a singlet at 3.84 ppm (methylene group on the sulfur side chain, 3.88 ppm in the unmethylated compound), a singlet at 3.71 ppm (methyl ester), and another singlet at 3.06 ppm integrating for two, three, and three protons, respectively, and an AB quartet (J_{AB} = 16 cps) at 3.56 ppm assigned to ring methylene protons (3.92 ppm in the unmethylated compound) integrating for two protons. Disappearance of the =NH frequency in the ir spectrum coupled with appearance in the nmr spectrum of a singlet at 3.06 ppm integrating for three protons leads to the assignment of this signal to the $N-CH_3$ group.

The uv spectrum of this compound in ethanol showed an absorption maximum at 220 mμ (ϵ 7800) which is different from that of the parent compound. One would have expected the uv spectra to be similar since both contain the same chromophore. The differences might be explained if the carboxylic acid containing side chain were zwitterionic.

Further proof for concurrent N methylation and esterification was obtained from the reaction of diazomethane on the analogous monocyclic product (**3c** or **4c**) obtained from α-mercaptoisobutyric acid (**1c**) and cyanogen. In this case also two methyl groups are introduced although there is no possibility of enol formation, hence the possibility of O methylation of the enol is eliminated. All the above facts are consistent with either structure (**3a** or **4a**). In order to know more about this unusual N methylation some model compounds such as S,S′-dibenzyl dithiooxaldiimidate, S,S′-dimethyl dithiooxaldiimidate, and S,S′-dicarbomethyoxymethyl dithiooxaldiimidate were treated with diazomethane. In each case no reaction was observed and starting material was recovered. Therefore, no explanation can be offered for this N methylation accompanying esterification, except that the carboxylic acid group apparently facilitates the reaction. This suggests that the zwitterion may be required.

In order to obtain further information bearing on the question of formation of a five- or a six-membered ring, it was thought that, if a second ring could be closed, **3a** or **4a** would give rise to bicyclic product **7a** or **8a**, respectively. Although both structures are symmetrical, **7a** has free rotation around its central C–C bond whereas **8a** is more rigid; therefore, the former should have an appreciable dipole moment and the latter should have no dipole moment so long as the enol form does not exist in significant concentration. Molecular models of **8a** indicated that some of its conformations would have dipole moments. Thus one might be able to assign a structure to the condensation product of mercaptoacetic acid and cyanogen.

On refluxing the monocyclic product (**3a** or **4a**) with acetic anhydride for 10 min a white crystalline product, mp 152–175°, was obtained. Repeated crystallization from dioxane raised the melting point to 180–183°. Elemental analysis indicated the molecular formula $C_6H_4N_2S_2O_2$, resulting from loss of 1 mol of water in agreement with formation of a second ring. (Henceforth, this product will be referred to as the bicyclic product, **7a** or **8a**). At this stage considerable information on the bicyclic product (**7a** or **8a**) could be brought to bear on the question of formation of five- or six-membered rings. The fact that cyanogen reacts with mercaptoacetic acid to yield a monocyclic product, which under vigorous conditions loses a second mole of water to give a bicyclic product, suggests formation of first one and then a second six-membered ring. Once one six-membered ring was formed, subsequent closure of the second six-membered ring under similar conditions might be more difficult since it would give rise to a rigid fused bicyclic system. That is, the conformational requirements of the first six-membered ring would decrease the ease of formation of the second ring. In the case of the five-membered ring system, the existence of the first ring should have no obvious effect on formation of the second ring. The nmr data also favor a six-membered fused bicyclic structure (**8a**), since conformational differences in the geminal protons are more logically expected in the puckered six-membered ring compound than in the relatively more coplanar five-membered ring compound. The carbonyl frequency at 1775 cm^{-1} in the ir spectrum is in better accord with a five-membered bicyclic structure (**7a**), since the carbonyl frequency of five-membered cyclic ketones is observed between 1770 and 1800 cm^{-1}. Dipole moment data (2.6 D) are consistent with either **7a** or **8a**. If the dienol diacetate of the bicyclic compound could be prepared its nmr spectrum might indicate whether it is composed of five-membered rings (aromatic) or fused six-membered rings (less aromatic). The reaction of α-mercaptoisobutyric acid with cyanogen would yield a product incapable of enolization, whose dipole moment would indicate whether the product has five- or six-membered rings.

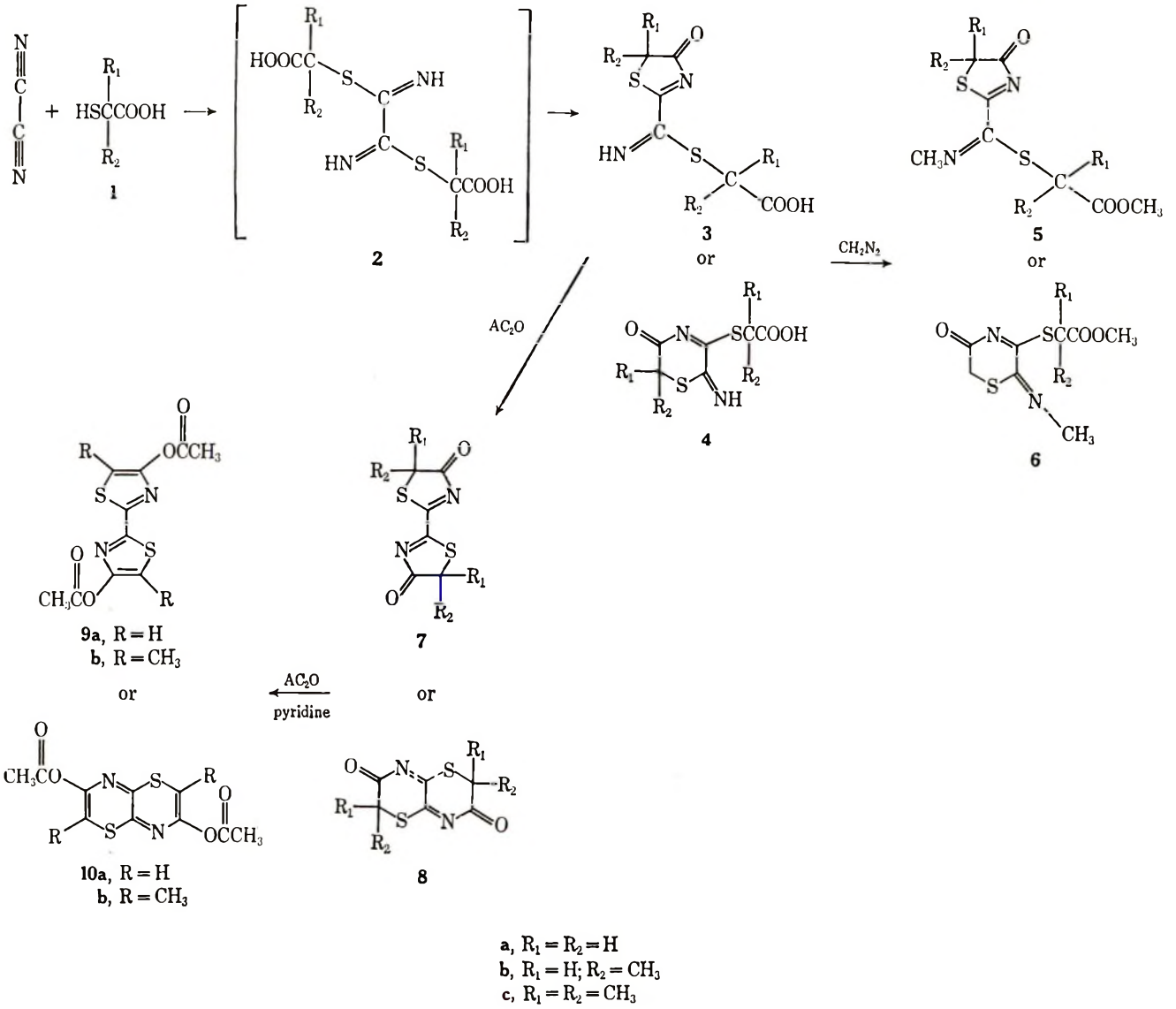
On refluxing the bicyclic product (**7a** or **8a**) with acetic anhydride and pyridine, a product (**9a** or **10a**), mp 215–26°, was obtained (Scheme I) which analyzed for $C_{10}H_8N_2O_4S_2$, indicating that two acetyl groups have been incorporated in place of the two enolic hydrogens.

The bicyclic product (**7c** or **8c**) from the α-mercaptoisobutyric acid–cyanogen reaction product (**3c** or **4c**) has a sharp melting point 109–110° and does not exhibit keto–enol tautomerism because of the replacement of geminal hydrogens by methyl groups. The dipole moment of this compound was found to be 3.2 D and could be best explained by the structure having free rotation around the central C–C bond. This is strong evidence that the bicyclic product has structure **7c**. However, the conformational differences for the methyl groups indicate that the rings are not flat, and that there may still be two six-membered rings.

For unequivocal assignment of structure, the dienol diacetate (**9b**) of the bicyclic product obtained from thiolactic acid and cyanogen was subjected to X-ray diffraction studies,[7] which conclusively proved that the

(7) X-Ray crystallographic studies were done by Dr. K. J. Palmer of Western Regional Research Laboratory, Albany, Calif., and will be published separately.

SCHEME I



molecule has a center of symmetry and has two five-membered rings joined by a C–C bond, and is represented by structure **9b** (Figure 1). Thus it has been proved that the reaction of cyanogen and α-mercapto acids gives rise to a monocyclic product (**3a**) containing one five-membered ring which on treatment with diazomethane affords **5a** and on dehydration a bicyclic product (**7a**) having two five-membered rings is obtained, and that the dienol diacetate (**9a**) is a derivative of **7a**.

The results of the X-ray diffraction studies (Figure 1) have not only provided the proof of structure for the above compounds, but also supply confirmation for a number of structures proposed in the literature beginning in 1891. In each of these cases the same question of two five-membered rings or two fused six-membered rings exists. In none of these cases was an unequivocal proof of structure provided.

Forsell[8] reported that the thermal condensation of dithiooxamide with ethylenediamine affords bis(Δ²-2-imidazolinyl) (**11**). The assignment of this structure was completely arbitrary. In a later publication[9] he commented that the product could also have structure **12** but concluded that this is highly improbable although possible. In 1944, Lehr and Erlenmeyer[10] condensed the dithioamide of adipic acid with ethylenediamine and obtained 1,4-bis(Δ²-2-imidazolinyl)butane and concluded that Forsell's product was bis(Δ²-2-imidazolinyl). They also condensed the dithioadipamide with α-bromoacetophenone and obtained α,ω-di[4-phenylthiazolyl-(2)]butane. Karrer and coworkers[11] condensed dithiooxamide with chloroacetone and on the basis of Lehr and Erlenmeyer's work[10] assigned structure **13** to the reaction product. In 1952, Woodburn and O'Gee reported that condensation of ethylenediamine with cyanogen yielded a product identical with **11** and, quoting Lehr and Erlenmeyer,[10] also assigned the structure bis(Δ²-2-imidazolinyl). Forsell,[8,9] Lehr, and Erlenmeyer[10] and Woodburn and O'Gee[6] ignored the possibility of formation of **12** or a tautomer thereof.

The model compound (dithioadipamide) used by Lehr and Erlenmeyer for assignment of structure to the condensation product of Forsell is not as unique as dithiooxamide, while the latter has the possibility of form-

(8) G. Forsell, *Ber.*, **24**, 1846 (1891).
(9) G. Forsell, *ibid.*, **25**, 2132 (1892).
(10) H. Lehr and H. Erlenmeyer, *Helv. Chim. Acta*, **27**, 489 (1944).
(11) P. Karrer, P. Leiser, and W. Graf, *ibid.*, **27**, 624 (1944).

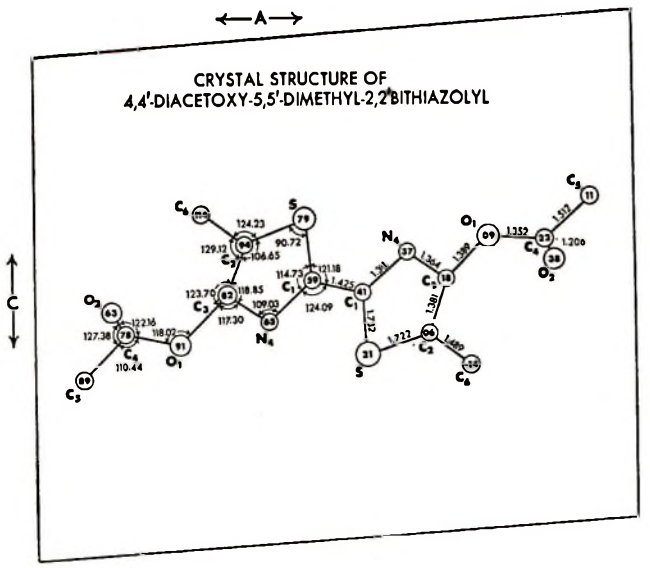
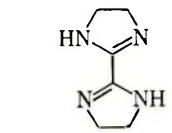
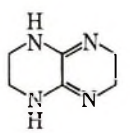


Figure 1.—The molecule has a center of symmetry. The angles are shown on the left side, the interatomic distances on the right. The number within each circle is the value of the y parameter. The unit cell dimensions are a = 13.125 Å, b = 4.830 Å, c = 10.995 Å, and β = 94.09°. Space group $P2_1/c$.

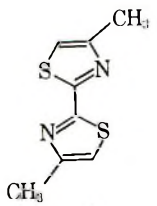
ing five- or six-membered rings the former can only form five-membered rings and hence is not compelling evidence for the formation of **11**. Therefore, the possibility of structures such as **12** cannot be ruled out. The same argument can be used in the assignment of structure to the condensation product of dithiooxamide and chloroacetone and the possibility of alternate structure **14** cannot be excluded.



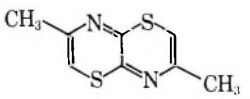
11



12



13



14

On mechanistic and structural grounds, the reaction of mercaptoacetic acid and cyanogen is not much different from that of ethylenediamine and cyanogen, and dithiooxamide and chloroacetone, hence the results in one case provide support for five-membered ring structures in the other similar cases. Thus the X-ray diffraction studies support formation of structures containing two five-membered rings.

Experimental Section[12,13]

Reactions of α-Mercapto Acids with Cyanogen (Synthesis of Monocyclic Products).—The procedure is the same as that reported earlier,[1,3] except that the reaction is carried out in ether instead of hexane because of the low solubility of α-mercapto acids in hexane.

2-[(S-Carboxymethyl)thioimidyl]-Δ²-thiazolin-4-one (3a).—In a 300-ml three-necked flask, fitted with a Dry Ice–acetone condenser, a magnetic stirring bar, and a gas inlet tube cooled to −80°, were placed 18.4 g (0.2 mol) of mercaptoacetic acid, 2 drops of n-butylamine, and 200 ml of anhydrous ether. Cyanogen gas (5 g, 0.1 mol, previously frozen and weighed) was passed into the above solution. After addition of cyanogen was complete (20 min) the reaction mixture was maintained at −80° for 2 hr, and then allowed to warm to room temperature. At this stage the reaction became slightly exothermic and the reaction product precipitated as a white solid, which was collected, washed with ether, and crystallized from acetone or acetic acid to give 16.8 g (77%) of a white crystalline material: mp 164–165° dec; ir 3230 (NH), 3000–2400 (OH, CO_2H dimer), 1730 (ring C=O) and 1700 cm^{-1} (C=O of CO_2H); nmr (acetone-d_6) δ 4.4 (broad s, 2, NH and CO_2H), 3.92 (AB quartet, 2, J = 15.5 Hz, ring CH_2), and 3.88 (s, 2, S–CH_2); uv max (95% EtOH) 314 mμ (ε 7540) and 365 (10), 314 (7850, in acid), 365 (7900, in base); neut equiv (potentiometric titration), 109 (calcd 109); pK_a = 4.1 and 6.7 (50% aqueous acetone).

Anal. Calcd for $C_5H_6N_2O_3S_2$: C, 33.04; H, 2.77; N, 12.84; S, 29.34. Found: C, 33.36; H, 2.78; N, 12.76; S, 29.38.

2-[S-(2-Carboxyethyl)thioimidyl]-Δ²-thiazolin-4-one (3b).—This product (monocyclic) could not be isolated in pure state from the reaction of thiolactic acid and cyanogen. It was always accompanied by 4,4′-dihydroxy-5,5′-dimethyl-2,2′-bithiazolyl (bicyclic). However, its presence was shown by treating this mixture with diazomethane whereby the monocyclic product was methylated and dissolved, whereas the unreactive bicyclic product remained behind. The N-methylated ester (**5b**) of the monocyclic product thus obtained could be characterized. The procedure described below is one which gave rise to the above-mentioned mixture.

Cyanogen gas (5 g, 0.1 mol) was passed into a stirred solution of 21.2 g (0.2 mol) of thiolactic acid and 2 drops of n-butylamine in 200 ml of anhydrous ether maintained at −80°. The reaction mixture was continuously stirred at −80° for 2 hr and then allowed to warm to room temperature. At this stage the colorless reaction mixture became pale yellow. On removing the ether under vacuum, there was obtained 24 g of solid, mp 190–220°. The heterogenous nature of the product could be observed by the presence of both yellow and white crystals. All attempts to separate the white product (presumably the monocyclic product) from yellow product (bicyclic) were unsuccessful, *e.g.*, fractional crystallization from a variety of solvents (benzene, acetone, ether, and ethanol) and chromatography on activated florisil and alumina (neutral).

5,5-Dimethyl-2-[S-(2-carboxyisopropyl)thioimidyl]-Δ²-thiazolin-4-one (3c).—Into a stirred solution of 10 g (0.083 mol) of α-mercaptoisobutyric acid and 2 drops of n-butylamine in 100 ml of anhydrous ether maintained at −80° was passed 2.2 g (0.042 mol) of cyanogen gas. The reaction mixture was stirred at −80° for 2 hr and then allowed to warm to room temperature. Ether was removed on a rotary evaporator leaving behind a white crystalline product, mp 170–174°. Two crystallizations from methanol afforded 9.6 g (80%) of a white crystalline product: mp 177–178°; ir 3280 (NH), 3000–2400 (OH of COOH dimer), 1720 (ring C=O), and 1675 cm^{-1} (C=O of COOH); nmr δ 4.4 (broad, s, 2, NH and COOH), 1.96 (s, 3) and 1.73 (s, 3) (ring CH_3 groups), and 1.63 (s, 3) and 1.58 (s, 3) (side chain CH_3); neut equiv (potentiometric titration), 275.1 (calcd 274); pK_a = 4.1.

Anal. Calcd for $C_{10}H_{14}N_2O_3S_2$: C, 43.80; H, 5.15; N, 10.22; S, 23.35. Found: C, 43.98; H, 5.30; N, 9.99; S, 23.12.

(12) Melting points were measured using a Thomas–Hoover capillary melting point apparatus, and are corrected. Elemental analyses were carried out by the micro-analytical laboratory of the University of California at Berkeley. The ultraviolet spectra were determined in 95% ethanol using a Carey Model-11 spectrophotometer. Absorption is reported in millimicrons, intensities as the molar extinction coefficient (ε). The infrared spectra were determined using a Perkin-Elmer 337 spectrophotometer. Potassium bromide was used for solids. The nuclear magnetic resonance spectra were measured in deuteriochloroform unless indicated otherwise, with tetramethylsilane as the internal standard, using a Varian A60-A spectrometer. Chemical shifts are reported as δ values (part per million); coupling constants (J values) are given in cycles per second. Potentiometric titrations were done on a Metrohm Herisau potentiograph at 25° in 50% aqueous acetone. Dipole moment measurements were made on a WTW dipolimeter DE01 using DLF-2 cells at 25° in dioxane. Calculations were done by the method of Kumler and Halverstadt[13] using an IBM 360 computer.

(13) I. F. Halverstadt and W. D. Kumler, *J. Amer. Chem. Soc.*, **64**, 2933 (1942).

Reactions of Monocyclic Compounds with Diazomethane. 2-[N-Methyl-(S-carbomethoxymethyl)thioimidyl]-Δ^2-thiazolin-4-one (5a).—To an ice cold suspension of 2.2 g (0.01 mol) of **3a** in 15 ml of anhydrous ether was added an ethereal solution of diazomethane[14] (0.9 g, 0.021 mol) in small portions until evolution of nitrogen ceased and the solution acquired a pale yellow color. As reaction proceeds the suspended starting material dissolves and at the end a clear solution is obtained. The solvent was evaporated leaving behind a white crystalline product and an oil. The residue was dissolved in methanol and set aside for crystallization. On cooling it afforded 2.3 g (92%) of a white crystalline product, mp 69–71°. Two crystallizations from methanol afforded a product: mp 71–72°; ir 1780 (ring C=O) and 1700 (ester C=O), 1600 cm^{-1} (C=N); nmr δ 3.84 (s, 2, S–CH_2) and 3.71 (s, 3, methyl ester), 3.56 (AB quartet, 2, J = 16 Hz, ring CH_2), 3.06 (s, 3, N–CH_3); neut equiv (potentiometric titration), 247 (calcd 246); pK_a = 6.65.

Anal. Calcd for $C_8H_{10}N_2O_3S_2$: C, 39.23; H, 4.09; N, 11.38; S, 26.00. Found: C, 39.53; H, 4.36; N, 11.38; S, 25.60.

5-Methyl-2-[N-methyl-S-(2-carbomethoxyethyl)thioimidyl]-Δ^2-thiazolin-4-one (5b).—The reaction product of thiolactic acid and cyanogen (**3b**) (5 g) was suspended in 20 ml of anhydrous ether. To this suspension was added an ethereal solution of 0.42 g of diazomethane in small portions until the evolution of nitrogen ceased. As the reaction proceeded part of the mixture dissolved and part remained in suspension. The reaction mixture was filtered at this stage and a yellow product, mp 242–243°, was collected. This yellow product was identical in all respects with the bicyclic product (**7b**) obtained from cyanogen and thiolactic acid. The filtrate on evaporation afforded a crystalline product, mp 95–97°. This was recrystallized from methanol to afford 1.37 g of colorless needles, mp 98–99°, and represents 1.25 g of the corresponding unmethylated compound. On the basis of this yield of N-methylated ester, the percentage of monocyclic product in the mixture (5 g) was estimated to be 25%: ir 1780 (ring C=O), 1720 (ester C=O), 1610 cm^{-1} (C=N); nmr δ 4.07 (q, 1, J = 7 Hz, CH next to CH_3), 3.8 (s, 3, methyl ester), 3.71 (q, 1, J = 7 Hz, CH next to CH_3), 3.1 (s, 3, =NCH_3) and 1.63 (d, 3, J = 7 Hz, CH_3), 1.36 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{10}H_{14}N_2O_3S_2$: C, 43.80; H, 5.15; N, 10.22; S, 23.35. Found: C, 43.93; H, 5.40; N, 10.18; S, 23.50.

5,5-Dimethyl-2-[N-methyl-(S-carbomethoxyisopropyl)thioimidyl]-Δ^2-thiazolin-4-one (5c).—To an ice cold solution of 2.8 g (0.01 mol) of **3c** in 15 ml of anhydrous ether was added an ethereal solution of diazomethane (0.9 g, 0.021 mol) in small portions until gas evolution ceased and the solution became yellow. The solvent was evaporated leaving behind a white crystalline product. Two recrystallizations from methanol afforded 2.85 g (95%) of crystalline product: mp 120–121°; ir 1780 (ring C=O) and 1710 cm^{-1} (ester C=O); nmr δ 3.70 (s, 3, methyl ester), 3.06 (s, 3, =NCH_3), 1.96 (s, 3, CH_3) and 1.73 (s, 3, CH_3) (nonequivalent geminal methyl groups of the ring), 1.60 (s, 6, geminal methyl groups on side chain).

Anal. Calcd for $C_{12}H_{18}N_2O_3S_2$: C, 47.68; H, 6.00; N, 9.27; S, 21.96. Found: C, 47.52; H, 5.91; N, 9.02; S, 21.80.

Syntheses of Bicyclic Compounds. 4,4'Diketo-2,2'-Δ^2-bithiazolinyl (7a).—2-[(S-Carboxymethyl)thioimidyl]-Δ^2-thiazolin-4-one (4.36 g, 0.02 mol) was refluxed in 10 ml of acetic anhydride for 10 min. The reaction mixture was cooled and set aside for crystallization. It afforded 3.8 g (95%) of a white crystalline product, mp 152–175°. On repeated recrystallization from dioxane the melting point could be improved to 180–182°: ir 1775 cm^{-1} (ring C=O); nmr (pyridine-d_5) δ 4.2 (AB quartet, nonequivalent ring methylene protons) (deuterium oxide exchange resulted in disappearance of the AB quartet); uv max (95% EtOH) 314 mμ (ϵ 7850) and 365 (1700), 314 (8200 in acid), 365 (8100 in base); neut equiv (potentiometric titration), 100 (calcd 100.05); pK_a = 6.7; dipole moment 2.6 D.

Anal. Calcd for $C_6H_4N_2O_2S_2$: C, 36.01; H, 2.01; N, 14.00; S, 31.98. Found: C, 36.20; H, 2.19; N, 14.20; S, 31.98.

4,4'-Dihydroxy-5,5'-dimethyl-2,2'-bithiazolyl (7b).—Cyanogen gas (5 g, 0.1 mol) was passed into a stirred solution of 21.2 g (0.2 mol) of thiolactic acid and 2 drops of n-butylamine in 200 ml of anhydrous ether maintained at −80°. The reaction mixture was stirred at −80° for 2 hr and then allowed to warm to room temperature. The reaction mixture was then refluxed on a water bath for 30 min and ether removed at the water pump leaving behind a yellow solid. Two recrystallizations from dimethyl sulfoxide yielded 20 g (87%) of a yellow crystalline product: mp 242–243° dec; ir 3500–2500 (H bonded OH) and 1580 cm^{-1} (conjugated C=C); nmr (TFA) δ 2.20 (s, CH_3); neut equiv (potentiometric titration), 114 (calcd 114); pK_a = 6.7.

Anal. Calcd for $C_8H_8N_2O_2S_2$: C, 42.11; H, 3.53; N, 12.28; S, 31.56. Found: C, 42.28; H, 3.64; N, 12.20; S, 31.72.

4,4'-Diketo-5,5,5',5'-tetramethyl-2,2'-Δ^2-bithiazolinyl (7c).—5,5-Dimethyl-2-[S-(2-carboxyisopropyl)-thioimidyl]-Δ^2-thiazolin-4-one (2.8 g, 0.01 mol) was refluxed in 5 ml of acetic anhydride for 10 min and set aside for crystallization. On cooling it afforded 2.1 g (81.5%) of a white crystalline product, mp 105–108°. Two recrystallizations from benzene yielded a product of mp 109–110°; ir 1780 cm^{-1} (ring C=O); nmr δ 1.93 (s) and and 1.68 (s) (nonequivalent methyl groups); dipole moment 3.2 D.

Anal. Calcd for $C_{12}H_{12}N_2O_2S_2$: C, 46.88; H, 4.72; N, 10.93; S, 24.98. Found: C, 47.01; H, 4.78; N, 10.75; S, 24.72.

Syntheses of Dienol Diacetates. 4,4'-Diacetoxy-2,2'-bithiazolyl (9a).—4,4'-Diketo-2,2'-Δ^2-bithiazolinyl (1 g, 0.005 mol) was dissolved in a mixture of 3 ml of acetic anhydride and 1 ml of pyridine and gently refluxed for 30 min. On cooling it afforded 700 mg (50%) of a white crystalline product, mp 210–212°. Two recrystallizations from benzene afforded a product of mp 215–216°; ir 1750 (acetoxy C=O), 1210 cm^{-1} (C–O stretch); nmr δ 6.5 (s, 1, aromatic CH), 2 (s, 3, acetoxy CH_3); uv max (95% EtOH) 345 mμ (ϵ 25,200).

Anal. Calcd for $C_{10}H_8N_2O_4S_2$: C, 42.26; H, 2.84; N, 9.86; S, 22.52. Found: C, 42.21; H, 2.73; N, 9.71; S, 22.60.

4,4'-Diacetoxy-5,5'-dimethyl-2,2'-bithiazolyl (9b).—4,4'-Dihydroxy-5,5'-dimethyl-2,2'-bithiazolyl (5 g, 0.02 mol) was dissolved in a mixture of 8 ml of acetic anhydride and 2 ml of pyridine and gently refluxed for 20 min. On cooling it afforded a white crystalline product, mp 240–241°. Two recrystallizations from benzene yielded a product of mp 242–243°; ir 1750 (C=O), 1210 cm^{-1} (C–O stretch); nmr δ 2.33 (s, 3, acetoxy group), 2.28 (s, 3, methyl); uv max (95% EtOH) 346 mμ (ϵ 25,300).

Anal. Calcd for $C_{12}H_{12}N_2O_4S_2$: C, 46.16; H, 3.87; N, 8.97; S, 20.50. Found: C, 46.24; H, 4.07; N, 9.14; S, 20.60.

Registry No.—Cyanogen, 460-19-5; **3a**, 19639-58-8; **3b**, 19639-59-9; **3c**, 19639-60-2; **5a**, 19639-61-3; **5b**, 19639-62-4; **5c**, 19639-63-5; **7a**, 19639-64-6; **7b**, 19639-65-7; **7c**, 19639-66-8; **9a**, 19639-67-9; **9b**, 19639-68-0.

(14) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green & Co., London, 1956, pp 971 and 973.

Rearrangements of 5-Nitronorbornenes. II. 6-Phenyl- and 6-Methyl-5-nitro-2-norbornenes

WAYLAND E. NOLAND, RICHARD B. HART,[1a] WILLIAM A. JOERN,[1b] AND R. GERALD SIMON[1c]

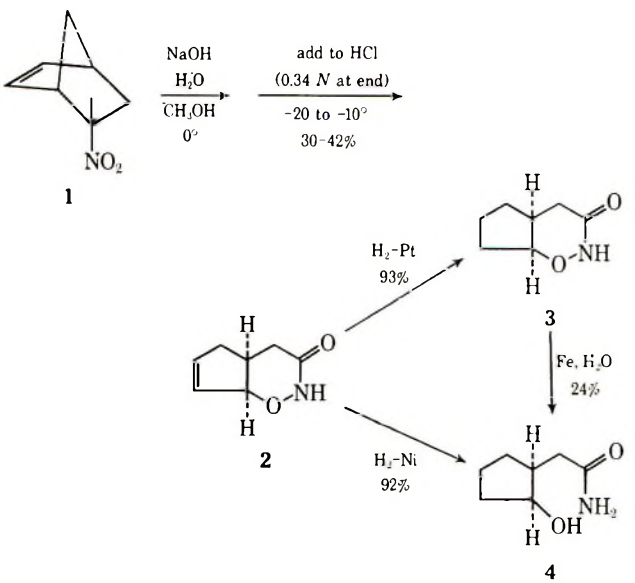
School of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received July 12, 1968

Rearrangement of the salts of 6-phenyl- (**5a**) and 6-methyl-5-nitro-2-norbornenes (**5b**) in aqueous methanolic hydrochloric acid gave isomeric rearrangement products **6a** and **6b**. Hydrogenation of **6a** and **6b** over platinum gave dihydro derivatives **9a** and **9b** and over Raney nickel gave dihydrodeoxo derivatives **12a** and **12b**, the hydrogenolysis in the latter cases supporting the assignment of hydroxamide structures to **6a** and **6b**. Ozonolysis of **6a** to the known 1-phenylpropane-1,2,3-tricarboxylic acid (**19**), and an independent synthesis of the 3 epimer (**17**) of the dihydrodeoxo derivative (**12a**) of **6a**, established the structure of **6a** as 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-hexahydro-1-hydroxy-3-phenylcyclopenta[*b*]pyrrol-2-one. By analogy the corresponding 3-methyl structure is assigned to **6b**. The lactam structure of **12a** was extremely resistant to acidic hydrolysis or reduction with $LiAlH_4$, but epimerized (to **17**), particularly under alkaline conditions, whereas **12b** did not epimerize, but was readily hydrolyzed (to amino acid hydrochloride **41**) and reduced with $LiAlH_4$ to the amine, 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-methylcyclopenta[*b*]pyrrole (**42**). The mechanism of formation of the rearrangement products is discussed.

It has been shown previously in this laboratory that the product of rearrangement under acidic conditions of the sodium salt of 5-nitro-2-norbornene (**1**) is 2,3,4,4a-*cis*-5,7a-*cis*-hexahydrocyclopenta[*e*]-1,2-oxazin-3-one (**2**).[2] Two key degradation products, of interest in the discussion which follows, are the dihydro derivative (**3**), derived from hydrogenation over platinum, and the tetrahydro derivative (**4**), derived from hydrogenation over Raney nickel. In order to determine the effect of substitution on the rearrangement, we have now subjected the salts of the 6-phenyl (**5a**) and 6-methyl (**5b**) derivatives of **1**, which, like **1**, are available from the Diels–Alder reaction of cyclopentadiene with the appropriate nitroolefins, to the acidic rearrangement.

Phenyl Rearrangement Product (6a).—Rearrangement of the sodium or potassium salt of the 6-phenyl derivative (**5a**) in aqueous methanolic hydrochloric acid gave a crystalline product (**6a**), isomeric with the starting material, in yields as high as 43–57%. The transformations **6a** → **18** shown in Scheme I,[3] and the additional data included in the Experimental Section, are consistent with the assignment to **6a** of a hydroxamide structure [-C(=O)N(OH)-], in contrast to the cyclic hydroxamate structure established for **2**.



Ozonolysis of the phenyl rearrangement product (**6a**) at −78° in methanol, followed by oxidative work-up with performic acid, gave in 55% yield a key degradation product, the known 1-phenylpropane-1,2,3-tricarboxylic acid (**19**), identical with a synthetic sample prepared *via* sodium ethoxide catalyzed condensation of mandelonitrile with ethyl cyanoacetate, and then with ethyl chloroacetate, according to the procedure of Chatterjee and Barpujari.[4]

Among the most likely structures for the phenyl rearrangement product are **6a**, **20a**, **21a**, and **22**. If the intermediate nitronic acid of **5a** is considered as the N-oxide of an oxime, which might undergo a Beckmann-type rearrangement, then structures **20a** and **21a** are potentially derivable from migration of the 4 and 6 carbons of **5a**, respectively, to nitrogen. Structure **20a** is also derivable by a ring reclosure reaction, as will be discussed later in the Mechanism Section. Structure **22** is the phenyl-substituted analog of the unsubstituted rearrangement product[2] (**2**), and is potentially derivable in a manner completely analogous to that of **2** by a ring reclosure reaction through oxygen acting as the nucleophile. Structure **6a** is potentially derivable by an analogous ring reclosure reaction through nitrogen rather than oxygen acting as the nucleophile. Structure **22**, although consistent with the ozonolysis product, can be eliminated immediately because it is not a hydroxamide, would not give a positive ferric chloride test, and, by analogy with **2** (which gave a tetrahydro derivative), would not be expected to give a dihydrodeoxo (or deoxo) derivative. The hydroxamide structure **21a** can be eliminated because, with a nitrogen

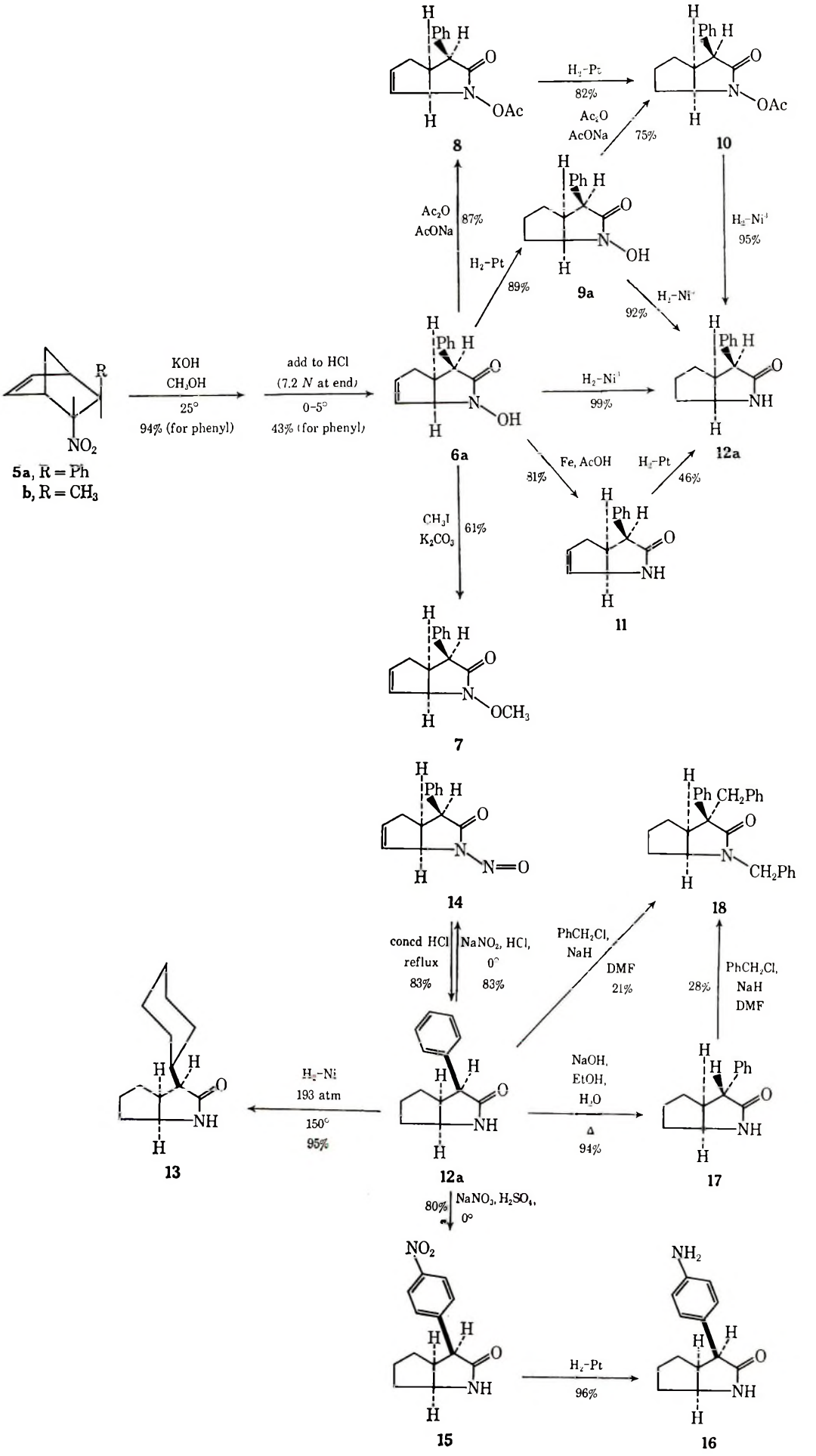
(1) (a) Taken in large part from the Ph.D. thesis of Richard B. Hart, University of Minnesota, August 1964; *Dissertation Abstr.*, **26**, 695 (1965). It is a pleasure to acknowledge support of much of this work through fellowships to R. B. H. from the George Macpherson Fellowship of the Graduate School of the University of Minnesota (academic year 1962–1963), the Sun Oil Co. Fellowship (academic year 1963–1964), the National Science Foundation Summer Fellowships (summers of 1962, 1963, and 1964), and the Monsanto Co. (second summer session 1961); taken in part from initial exploratory studies by (b) William A. Joern, M.S. degree research, University of Minnesota, 1959–1960; and (c) R. Gerald Simon, research, University of Minnesota, Jan–Feb 1961.

(2) (a) Paper I: W. E. Noland, J. H. Cooley, and P. A. McVeigh, *J. Amer. Chem. Soc.*, **81**, 1209 (1959); (b) *ibid.*, **79**, 2976 (1957).

(3) Hydrogenolysis of hydroxamides and alkoxamides over Raney nickel at low pressure is well known. For numerous illustrations see, for example, W. E. Noland and R. J. Sundberg, *J. Org. Chem.*, **28**, 3150 (1963); *Tetrahedron Lett.*, 295 (1962).

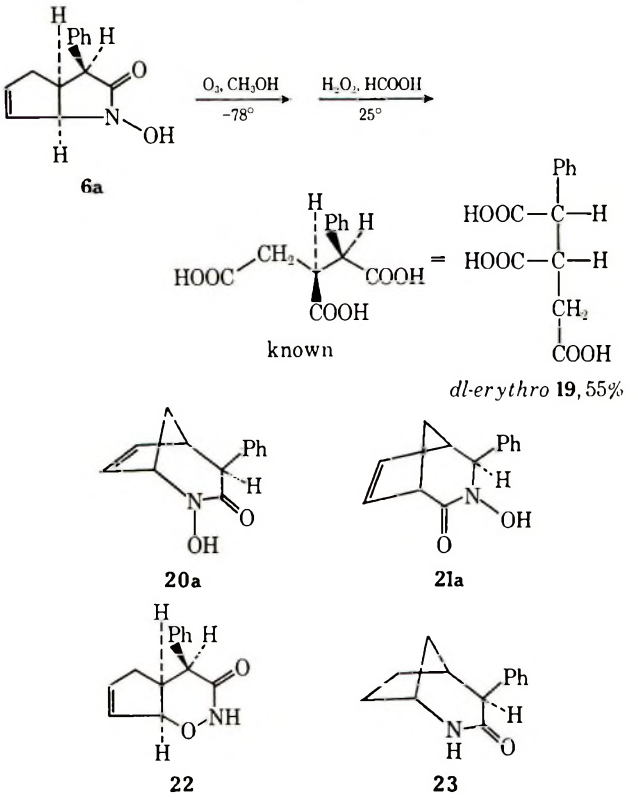
(4) N. N. Chatterjee and G. N. Barpujari, *J. Indian Chem. Soc.*, **17**, 292 (1940).

SCHEME I


5a, R = Ph
b, R = CH3
KOH
CH3OH
25°
94% (for phenyl)
add to HCl
(7.2 N at end)
0–5°
43% (for phenyl)
6a
8
9a
10
11
12a
7
H2–Pt
82%
Ac2O
AcONa
75%
Ac2O
AcONa
87%
H2–Pt
89%
H2–Ni
92%
H2–Ni
95%
H2–Ni
99%
Fe, AcOH
31%
H2–Pt
46%
CH3I
K2CO3
61%
14
concd HCl
reflux
83%
NaNO2, HCl,
0°
83%
PhCH2Cl,
NaH
DMF
21%
PhCH2Cl,
NaH
DMF
28%
18
H2–Ni
193 atm
150°
95%
NaOH,
EtOH,
H2O
Δ
94%
13
17
80%
NaNO2, H2SO4,
0°
15
16
H2–Pt
96%

rather than a carbonyl attached to the benzyl carbon, it could not give rise to the substituted phenylacetic acid structure present in the ozonolysis product. The hydroxamide structures **6a** and **20a** are consistent with the ozonolysis product, and with the epimerization and benzylation data, which seem to require that the phenyl substituent be on a carbon α to a carbonyl group for the necessary enolate anion to form (Scheme II). Efforts were then directed toward differentiating between the two possible structures (**6a** and **20a**) for the phenyl rearrangement product.

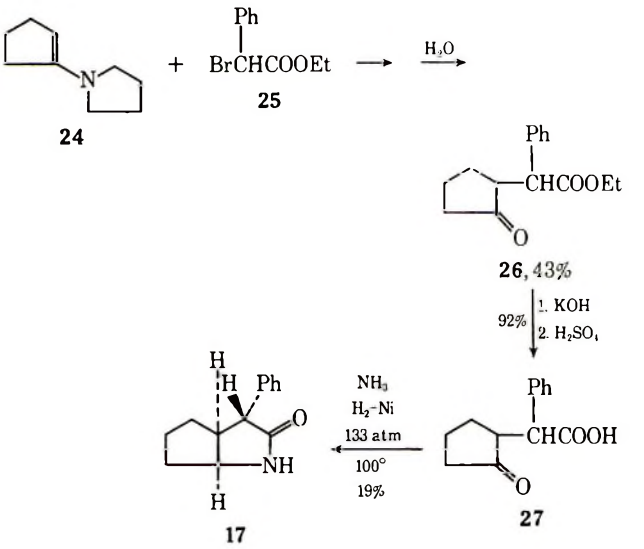
SCHEME II



Because of the complex functionality of the rearrangement product, efforts were directed toward independent syntheses of the simpler dihydrodeoxo derivatives **12a** and **23**[5] derivable from **6a** and **20a**. Synthesis of the epimer (**17**) of the dihydrodeoxo derivative **12a** was accomplished from the pyrrolidine enamine of cyclopentanone (**24**), as shown in Scheme III. The product (**17**, mp 128.5–129.5°) was different from the dihydrodeoxo derivative (**12a**, mp 171–172°) and, although it had the proper melting point, it was also first thought to be different from epimer **17** because of substantial differences in the infrared spectra in Nujol.[1a] These differences led to the incorrect formulation of the phenyl rearrangement product (**6a**) and its derivatives (**7**–**18**) in the Hart thesis[1a] as the alternate structure **20a** and its corresponding derivatives (including **23**). Hart found subsequently, however, that the nmr spectra of the two samples of **17** in chloroform-*d* were identical, and that the differences in the Nujol infrared spectra were attributable to the existence of dimorphic forms, both of which were isolated at various times from epimerization of the dihydrodeoxo derivative (see the

(5) Four unsuccessful approches to the synthesis of the alternate structure **23** are described in the Hart thesis.[1a]

SCHEME III



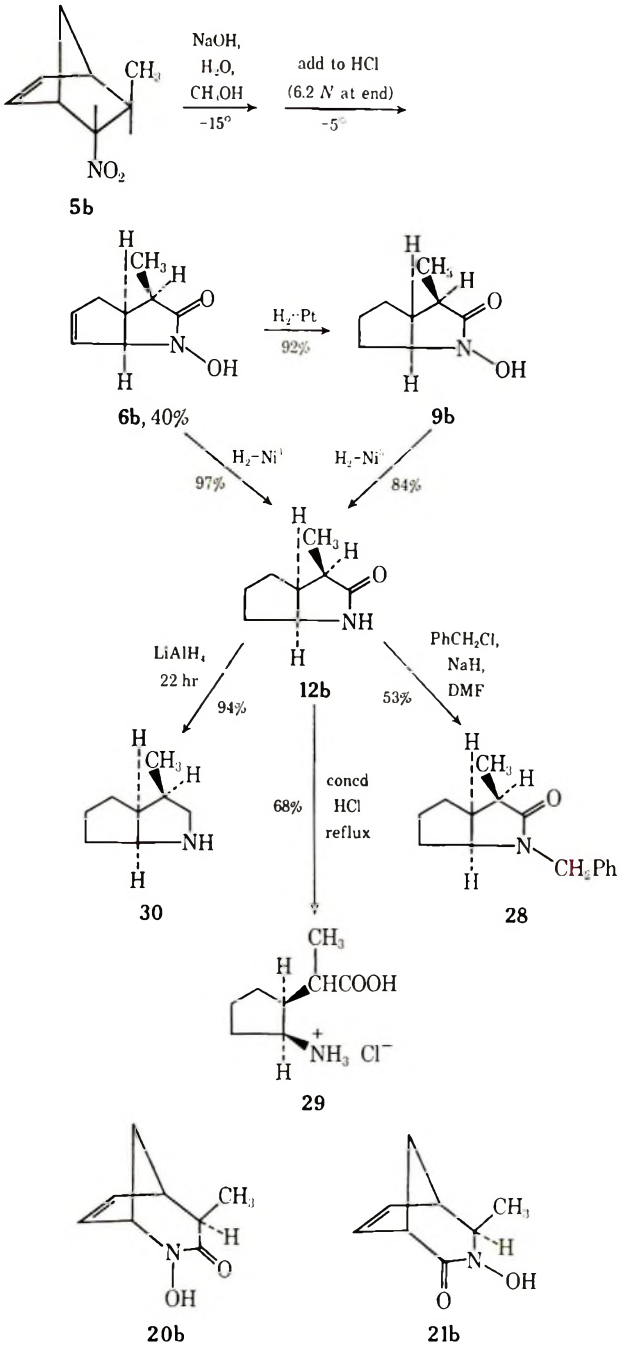
Experimental Section). Thus it follows that the dihydrodeoxo derivative has structure **12a** and its precursor, the phenyl rearrangement product, must have structure **6a**.

Methyl Rearrangement Product (6b).—Rearrangement of the sodium salt of 6-methyl-5-nitro-2-norbornene (**5b**) in aqueous methanolic hydrochloric acid also gave a crystalline product (**6b**), isomeric with the starting material, in 40% yield. The transformations **6b** → **30** shown in Scheme IV, and the bright purple ferric chloride tests given by **6b** and **9b** (like **6a** and **9a**), show that **6b** has a hydroxamide structure like the phenyl rearrangement product (**6a**). The methyl dihydrodeoxo derivative **12b**, having a less acidic hydrogen α to the carbonyl group, does not epimerize or undergo C benzylation under the basic conditions where the phenyl derivative **12a** does. Also in contrast to **12a**, in which the phenyl substituent sterically prevents hydrolysis or hydride reduction at the carbonyl group, **12b** hydrolyzed in refluxing concentrated hydrochloric acid to the amino acid hydrochloride **29**, and reduced with lithium aluminum hydride to the cyclic secondary amine **30**.

By analogy with structure **6a** established for the phenyl rearrangement product, the methyl rearrangement product is assigned structure **6b** rather than the alternative hydroxamide structures **20b** and **21b** (analogous to **20a** and **21a**), although all three structures are consistent with the chemical data presented.

Effect of Reaction Conditions.—The rearrangement product (**2**) from 5-nitro-2-norbornene (**1**) was obtained under milder conditions of acidity (2.6 *N* HCl at the start and 0.3 *N* at the end) than the rearrangement products **6a** (from the 6-phenyl derivative **5a**; 12 *N* HCl at the start and 7.2 *N* at the end) and **6b** (from the 6-methyl derivative **5b**; 12 *N* HCl at the start and 6.2 *N* at the end), which were isolated under similar conditions. Developmental work[1b,c] carried out on the rearrangement of the salt of the 6-phenyl derivative (**5a**) showed that the reaction is favored by (1) high acid concentration (6–12 *N* HCl), (2) slow addition of the salt solution to the acid, (3) the presence of methanol as a solubilizing agent, (4) probably by reaction temperatures in the range of 0–10°, and (5) use of freshly prepared salt. The latter factor is probably

SCHEME IV



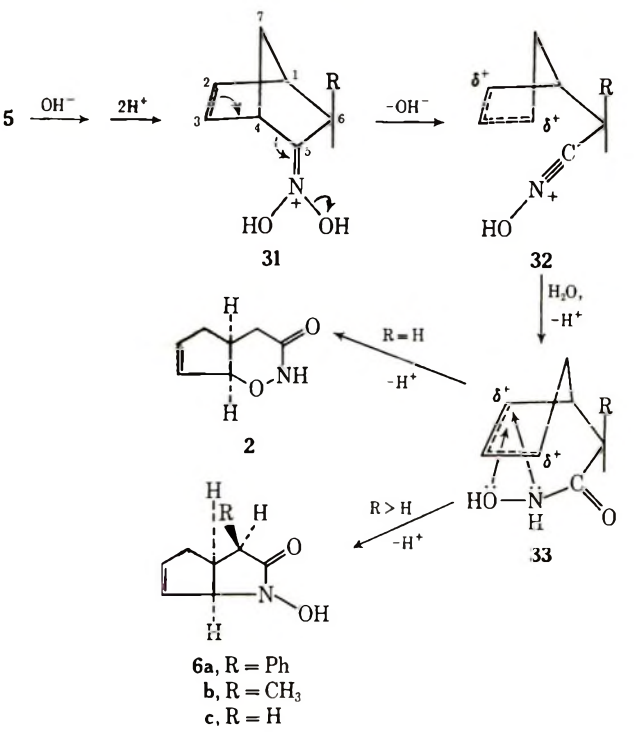
favored because of a slow autoxidation of the nitro compound salt to nitrite,[6] which otherwise probably leads during the acidification to increased amounts of nitrosation by-products (such as pseudonitroles).

Mechanism.—The mechanism previously proposed[2] to account for formation of the unsubstituted rearrangement product (**2**) can be adapted to account for all three rearrangement products. The mechanism probably proceeds through the doubly protonated nitronate anion (**31**), the conjugate acid of the nitronic acid, which undergoes ring opening and elimination of hydroxide ion to give an allylic carbonium ion–nitrile oxide, or its conjugate acid (**32**) (Scheme V). Cristol and Freeman[7] have reported a ring fission reaction of 5-norbornen-2-one (**34**) with sodium amide or potassium

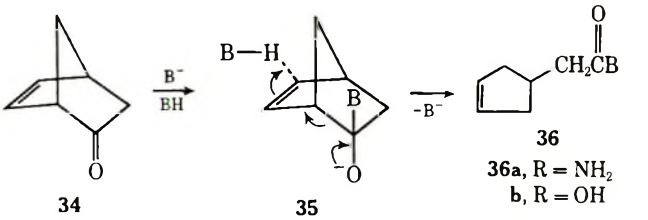
(6) (a) G. A. Russell, *J. Amer. Chem. Soc.*, **76**, 1595 (1954). (b) For additional examples, see W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).

(7) S. J. Cristol and P. K. Freeman, *J. Amer. Chem. Soc.*, **83**, 4427 (1961).

SCHEME V



t-butoxide to give 3-cyclopentene-1-acetamide (**36a**) or 3-cyclopentene-1-acetic acid (**36b**) in which, as they have noted, the electron flow (**35**) is just the reverse of that which we have postulated[2] for the ring-fission process **31** → **32**.



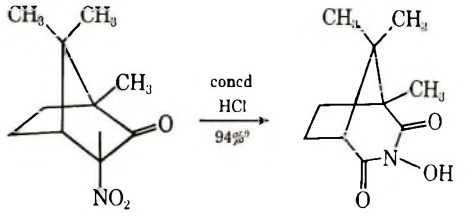
Hydrolysis of the protonated nitrile oxide (**32**) should give the corresponding hydroxamic acid (**33**). This intermediate could then react along one of several subsequent pathways, depending on steric and possibly electronic factors.

One possible reaction pathway (type 1 rearrangement), which has not so far been observed when an alternate pathway is present (as in our examples), would be nucleophilic attack by the hydroxamic nitrogen on the same (now positive) carbon from which the original ring fission occurred. In our examples this would be the allylic, original C-4 bridgehead carbon in **5**. This pathway would regenerate a bicyclic system, giving one (**20a**, **20b**) of the two types of hydroxamide suggested earlier also as possible products of a Beckmann-type rearrangement. The type 1 rearrangement has been observed in the acid-catalyzed rearrangements of the α-nitro ketones 3-*endo*-nitro-2-bornanone[8] (**37**) and 3β-hydroxy-16-nitroandrost-5-en-17-one (**39**, a 1:1 mixture of the 16α- and 16β-nitro epimers) and its 5,6-dihydro derivative, which have been shown to give N-hydroxycamphorimide[9] (**38**) and 3β,N-dihydroxy-16,17-secoandrost-5-ene-16,17-dioic imide (**40**) and its 5,6-

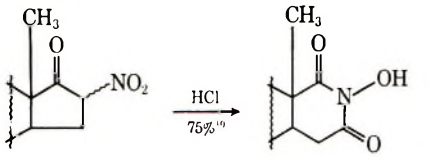
(8) A. A. Griswold and P. S. Starcher, *J. Org. Chem.*, **30**, 1687 (1965).

(9) H. O. Larson and E. K. W. Wat, *J. Amer. Chem. Soc.*, **85**, 827 (1963).

dihydro derivative,[10] respectively. Hassner and Larkin[10] have suggested that these rearrangements may also proceed through cleavage to a nitrile oxide (analogous to **32**) and thence to a hydroxamic acid intermediate (analogous to **33**). In these examples, the acidity of the hydrogen α to both the carbonyl and nitro groups is sufficiently great that it is not necessary, as in our examples, to first form the salt in order to generate the nitronic acid upon acidification; with the α-nitro ketones the nitronic acid must form directly by acid-catalyzed enolization. The rearrangements also proceed with benzoyl chloride under Schotten–Baumann reaction conditions, giving the benzoate of **38**,[9] and with acetic anhydride, giving the 3β,N-diacetate of **40** or its 5,6-dihydro derivative.[10] Hassner and Larkin[10] have made the plausible suggestion that these examples may also proceed through the nitrile oxide mechanism, in which an acyl group replaces a proton as catalyst and an anhydride molecule (or more probably an acylate ion or its conjugate acid) replaces a water molecule as a co-catalyst. The opposite type of ring closure reaction to the type 1 rearrangement to form bicyclic systems, in which a nucleophilic center (double bond) *in a ring* attacks an *exocyclic* electrophilic center, has been studied extensively by Bartlett and coworkers.[11]



37 **38**



39 **40**

A second possible reaction pathway (type 2 rearrangement), which is observed in our examples, involves ring closure through nucleophilic attack at the other end of the allylic carbonium ion system, at the original C-2 vinyl carbon in **5**. Thus, ring closure through the hydroxamic oxygen (type 2a rearrangement) would give the hydroxamate type of structure (**22**) previously observed[2] (**2**) in the unsubstituted case. This reaction pathway was not observed when the 6-*exo*-phenyl[12] (**5a**) or methyl (**5b**) substituents are present in **5**, as the products (**6a**, **6b**) are hydroxamides. Instead, for reasons which may relate to protonation of the oxygen in the more strongly acidic media employed,[13] ring closure occurs in the corresponding fashion, but through nitrogen (type 2b rearrangement) rather than oxygen, giving 5:5 fused ring products (**6a**, **6b**). Since the yields of rearrangement products (43–57% of **6a**, and 40% of **6b**) exceeded the amounts of 5-*exo*-nitro-6-*endo*-substituted minor stereoisomers present in the starting mixtures,[12] the products must be derived from the major stereoisomers **5a** and **5b**. It follows from the mechanism proposed that the 6-*exo* substituents in **5a** and **5b** become the 3-substituents in **6a**[14] and **6b** and their derivatives and remain *trans* to the 3a-hydrogen at the adjacent ring junction. Thus, epimerization of the dihydrodeoxo derivative **12a** to **17** relieves the serious *peri*-1,3-steric interaction between the inward-pointing 3-phenyl and 4-hydrogen substituents in **12a**.[15,16]

Experimental Section

Melting points were determined on calibrated hot stages. Ultraviolet spectra were determined on Bausch and Lomb Spectronic 505 or Cary Model 11 recording spectrophotometers. Infrared spectra were determined on Beckman IR5, Perkin-Elmer 21, or Unicam SP-200 spectrophotometers. Nuclear magnetic resonance (nmr) spectra were determined on a Varian A-60 spectrometer. Microanalyses were performed largely at the University of Minnesota by Mrs. Olga Hamerston and Dr. T. S. Prokopov and their assistants, particularly Mrs. Kathleen Nelson Juneau and Lawrence L. Landucci, and at the Scandinavian Microanalytical Laboratory in Herlev, Denmark.

The Potassium Salt of 5-Nitro-6-phenyl-2-norbornene.—5-Nitro-6-phenyl-2-norbornene[17] (60.0 g, 0.279 mol) was added dropwise with vigorous stirring at room temperature to a solution of potassium hydroxide (17.3 g, 0.308 mol) in methanol (300 ml). The resulting yellow solution was stirred for 12 hr. Then the methanol was removed carefully in a rotary evaporator, keeping the temperature below 40°, leaving a red gummy residue. This residue was cooled and washed with ether–acetone (>3:1, 200–300 ml) at 0°, causing formation of a yellowish white solid (66.4 g, 94%): ν_{max}^{Nujol} (cm^{-1}) 3280 and 3140 (m, OH), 1615 (s, C=N), 1590 (ms, C=C). The solid was insoluble in ether but somewhat soluble in water. It was used in the next step without further purification.

Rearrangement of the Salt of 5-Nitro-6-phenyl-2-norbornene in Aqueous Methanolic Hydrochloric Acid. 1,2,3-*cis*-3a-*cis*-Hexahydro-1-hydroxy-3-phenylcyclopenta[*b*]pyrrol-2-one (6a).—A solution of the potassium salt of 5-nitro-6-phenyl-2-norbornene (89.0 g, 0.351 mol) in water (200 ml) and methanol (300 ml) at 0° was added dropwise with vigorous stirring over 2 hr to concentrated hydrochloric acid (800 ml, 9.60 mol) cooled to 0° in an ice–salt bath, never allowing the temperature to rise above 5°. During the addition, the reaction solution became opaque and light blue-green, and a considerable amount of blue-green oil formed,

(10) A. Hassner and J. Larkin, *J. Amer. Chem Soc.*, **85**, 2181 (1963).

(11) (a) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *ibid.*, **87**, 1288 (1965); (b) P. D. Bartlett and G. D. Sargent, *ibid.*, **87**, 1297 (1965); (c) P. D. Bartlett, W. S. Trahanofsky, D. A. Bolon, and G. H. Schmid, *ibid.*, **87**, 1314 (1965).

(12) W. E. Noland, B. A. Langager, J. W. Manthey, A. G. Zacchei, D. L. Petrak, and G. L. Eian, *Can. J. Chem.*, **45**, 2969 (1967).

(13) The type of rearrangement product formed (such as **22** or **20**) may depend on the conditions of acidity employed. As noted in the section on Effect of Reaction Conditions, product **2** was isolated previously[2] under markedly lower conditions of acidity than **6a** or **6b**. It has recently been shown also that **2** is the crystalline product (isolated in 25% yield) from rearrangement of the sodium salt of **1** under higher conditions of acidity (12 *N* HCl at the start and 3.3 *N* at the end) than used previously in the isolation of **2**: John M. Olson, senior thesis research, University of Minnesota, fall 1967, NSF Undergraduate Academic Year Research Participant. From the sodium salt of **1** under conditions of acidity the same as those used in the isolation of **6a** (12 *N* HCl at the start and 7.2 *N* at the end) an oily product, mp 95.5–96°, was isolated (in 54% crude yield), which is different from **2** and gives a positive ferric chloride test, suggesting that it is hydroxamide **6c** (R = H). The nature of this new product is currently under investigation.

(14) Based on the stereochemistry of **6a** deduced above, the ozonolysis product triacid (**19**) should be the *dl-erythro* stereoisomer. It is fortunate, from the viewpoint of the proof of structure, that the synthetic sample had the same stereochemistry as the ozonolysis product, since both *dl-erythro* and *dl-threo* stereoisomers are theoretically possible.

(15) The nmr spectra support the stereochemistry assigned to **12a** and its epimer **17**. In **12a** $J_{1,3a}$ = 10 Hz, consistent with the very small dihedral angle between the nearly eclipsed 3- and 3a-hydrogens, since the Karplus equation predicts a coupling constant of 10 Hz when the dihedral angle is zero.[16] In epimer **17**, $J_{1,3a}$ = 4 Hz, while the dihedral angle should be about 120°, which again is consistent with the prediction of a coupling constant of 4 Hz.[16]

(16) (a) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963); (b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 49–51.

(17) W. E. Parham, W. T. Hunter, and R. Hanson, *J. Amer. Chem. Soc.*, **73**, 5068 (1951).

coating the walls of the flask and the stirrer. At the end of the addition, the blue-green reaction mixture was allowed to come to room temperature and was stirred for 18 hr. At the end of this time the mixture had become light yellow and a brownish white precipitate was present, but there was none of the blue-green oil observed earlier. The precipitate was filtered and dried, giving a brown amorphous solid (43.6 g, 78%). This solid was dissolved in ethanol–benzene (1:1, 500 ml), producing a black solution, which was treated repeatedly with charcoal until the color became light yellow. The solution was concentrated to 250 ml and allowed to cool, causing separation of fluffy white needles (32.7 g, 43%), mp 198–201° dec. Four recrystallizations from ethanol–benzene gave fine white needles: mp 202–204° dec; $\lambda_{max}^{95\%\ EtOH}$ (a toluene chromophore[18]) mμ (log ε) 248 infl (2.18), 253 (2.24), 259 (2.30), 265 (2.18), 268 infl (1.86); ν_{max}^{Nujol} (cm^{-1}) 2640 (m, OH), 1667 (s, C=O), 1531 (mw); nmr (14% w/w in $(CH_3)_2SO$) τ 8.25 (m, 2.0, CH_2), 6.7 (m, 0.8, 3a-CH), 5.97 (d, 1.0, J = 11 Hz, 3-CH), 5.40 (bd, 1.0, J = 8 Hz, 6a-CH), 4.09 (m, 2.0, CH=CH), 2.73 (m, 5.0, C_6H_5), and 0.19 (s, OH). The compound was insoluble in sodium bicarbonate solution, but soluble in 5% sodium hydroxide solution and gave a bright purple color with ethanolic ferric chloride solution.

Anal. Calcd for $C_{13}H_{13}NO_2$ (215.24): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.31; H, 6.32; N, 6.37.

Methyl Derivative of 6a. 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-Hexahydro-1-methoxy-3-phenylcyclopenta[*b*]pyrrol-2-one (7).—A mixture of 1,-2,3-*cis*-3a-*cis*-4,6a-*cis*-hexahydro-1-hydroxy-3-phenylcyclopenta-[*b*]pyrrol-2-one (1.00 g, 4.65 mmol), potassium carbonate (0.55 g, 3.98 mmol), and methyl iodide (6.67 g, 47.0 mmol) in acetone (50 ml) was refluxed on a steam bath for 12 hr. Then more methyl iodide (6.67 g, 47.0 mmol) was added and refluxing was continued for 6 more hr. The acetone and excess methyl iodide were evaporated on a steam bath in a steam of air, leaving a yellow semisolid residue. The residue was extracted with hot water (25 ml). The resulting yellow oil was dissolved in methylene chloride and the aqueous layer was extracted with more methylene chloride. The methylene chloride solutions were combined, dried ($MgSO_4$), and evaporated, leaving a yellowish white solid (0.65 g, 61%), mp 107–111°. Two crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave long white needles: mp 113–114°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 248 infl (2.20), 253 (2.25), 259 (2.30), 265 (2.19), 268 infl (1.84); ν_{max}^{Nujol} (cm^{-1}) 1695 (s, C=O); nmr (22% w/w in $CHCl_3$-*d*) τ 8.00 (m, 2.2, CH_2), 6.74 (m, 1.4, 3a-CH), 6.12 (s, 3.3, OCH_3) superimposed on the upfield half of 6.04 (d, downfield half 0.4, J = 11 Hz, 3-CH), 5.33 (bd, 1.0, J = 8 Hz, 6a-CH), 4.08 (m, 2.0, CH=CH), and 2.76 (m, 4.7, C_6H_5). The compound was insoluble in 5% hydrochloric acid and 5% sodium hydroxide solution, and gave no color reaction with ethanolic ferric chloric solution.

Anal. Calcd for $C_{14}H_{15}NO_2$ (229.27): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.18; H, 6.47; N, 5.98.

Acetyl Derivative of 6a. 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-Hexahydro-2-oxo-3-phenylcyclopenta[*b*]pyrrol-1-yl Acetate (8).—A solution of 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-hexahydro-1-hydroxy-3-phenylcyclopenta[*b*]pyrrol-2-one (0.50 g, 2.32 mmol) and anhydrous sodium acetate (0.1 g) in acetic anhydride (15 ml, 159 mmol) was stirred at room temperature for 24 hr. The solution was poured into cold water (25 ml) and stirred to hydrolyze the excess acetic anhydride, causing an exothermic reaction. The warm solution was cooled in an ice bath, causing precipitation of a white solid (0.52 g, 87%), mp 115–117°. Three crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave white needles: mp 118–119°; ν_{max}^{Nujol} (cm^{-1}) 1785 and 1704 (s, C=O).

Anal. Calcd for $C_{15}H_{15}NO_3$ (257.28): C, 70.02; H, 5.88; N, 5.44. Found: C, 69.99; H, 5.61; N, 5.66.

Dihydro Derivative of 6a. 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-1-hydroxy-3-phenylcyclopenta[b]pyrrol-2-one (9a).—A solution of 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-hexahydro-1-hydroxy-3-phenylcyclopenta[*b*]pyrrol-2-one (0.50 g, 2.32 mmol) in methanol (100 ml) was hydrogenated at 2 atm over platinum oxide at room temperature for 36 hr. Filtration of the catalyst and evaporation of the pink solution left a reddish orange oil. The oil was dissolved in methylene chloride and precipitated with hot petroleum ether (bp 60–68°), giving a pink solid (0.45 g, 89%), mp 153–155°. Three recrystallizations from methylene chloride–petroleum ether gave fine white needles: mp 156.5–158°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 247 infl (2.18), 253 (2.23), 259 (2.29), 265 (2.17), 268 infl (1.88); ν_{max}^{Nujol} (cm^{-1}) 2680 (m, OH), 1668 (s, C=O), 1522 (m); nmr (12% w/w in $CHCl_3$-*d*) τ 8.50 (m, 5.2, 2.5 CH_2), 7.82 (m, 1.0, 0.5 CH_2), 6.99 (m, 0.9, 3a-CH), 5.87 (d, 1.2, J = 10 Hz, 3-CH) superimposed on part of 5.70 (m, 0.7, 6a-CH), and 2.67 (5.1, C_6H_5). The hydroxyl proton was not determined. The compound gave a bright purple color with ethanolic ferric chloride solution.

Anal. Calcd for $C_{13}H_{15}NO_2$ (217.26): C, 71.86; H, 6.96; N, 6.45. Found: C, 71.74; H, 7.05; N, 6.49.

Oxidation of **9a** with chromic acid in acetic acid gave benzoic acid (26%) as the only recognizable product.[1a] Attempted hydrolysis of **9a** in refluxing concentrated sulfuric acid for 24 hr (92% recovery) or in refluxing ethanolic aqueous sodium hydroxide for 4 hr (76% recovery) was unsuccessful, giving unchanged **9a**.[1a] The compound was also recovered unchanged (93%) after being heated in polyphosphoric acid solution at 115–120° for 15 min, and then poured into cold water.[1a] Attempted reduction of **9a** with lithium aluminum hydride in refluxing ether for 12 hr was also unsuccessful, giving unchanged **9a** in 87% recovery.[1a]

Acetyl Derivative of 8. 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-2-oxo-3-phenylcyclopenta[*b*]pyrrol-1-yl Acetate (10). A. From Acetylation of 9a.—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-1-hydroxy-3-phenylcyclopenta[*b*]pyrrol-2-one (0.20 g, 0.92 mmol) and anhydrous sodium acetate (0.05 g) in acetic andydride (10 ml, 106 mmol) was stirred at room temperature for 5 hr. The solution was then poured into cold water (15 ml) and stirred. The warm solution resulting from exothermic hydrolysis of the acetic anhydride was cooled in an ice bath and scratched vigorously, causing separation of white needles (0.18 g, 75%), mp 108–110°. Several recrystallizations from methylene chloride–petroleum ether (bp 60–68°) gave fine white needles: mp 108–109°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 247 (2.17), 252 (2.24), 258 (2.31), 264 (2.17); ν_{max}^{Nujol} (cm^{-1}) 1785 and 1706 (s, C=O).

Anal. Calcd for $C_{15}H_{17}NO_3$ (259.29): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.34; H, 6.76; N, 5.47.

B. From Hydrogenation of 8.—A solution of 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-hexahydro-2-oxo-3-phenylcyclopenta[*b*]pyrrol-1-yl acetate (0.13 g, 0.51 mmol) in 95% ethanol (35 ml) was hydrogenated at 2 atm over platinum oxide at room temperature for 24 hr. Filtration of the catalyst and evaporation of the solvent left a light green solid (0.11 g, 82%), mp 100–103°. Two crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave white needles, mp 108–109°. There was no depression in mmp 108–109° with the sample prepared by acetylation of **9a**, and the infrared spectra in Nujol were identical.

Deoxo Derivative of 6a. 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-Hexahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (11).—1,2,3-*cis*-4,6a-*cis*-Hexahydro-1-hydroxy-3-phenylcyclopenta[*b*]pyrrol-2-one (1.00 g, 4.65 mmol) was added to a mixture of iron filings (0.80 g, 14.3 mg-atom) in boiling glacial acetic acid (25 ml), and the resulting dark red mixture was refluxed for 48 hr. Most of the acetic acid was removed by distillation, water (200 ml) was added to the residue, and the mixture was cooled in an ice bath and basified with 2 *N* sodium hydroxide solution. The red, gelatinous iron (III) hydroxide was removed by gravity filtration and the light yellow filtrate was extracted exhaustively with methylene chloride. The extracts were dried ($MgSO_4$) and evaporated, leaving a yellowish white solid (0.75 g, 81%), mp 120–124°. Two crystallizations from ethanol–water gave white needles: mp 124.5–126°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 242 (2.00), 248 (2.06), 253 (2.19), 259 (2.30), 265 (2.18), 268 (1.98); ν_{max}^{Nujol} (cm^{-1}) 3330 (m, NH), 1689 and 1653 (s, C=O); nmr (21% w/w in $CHCl_3$-*d*) τ 7.56 (m, 2.0, CH_2), 6.99 (m, 1.1, 3a-CH), 6.65 (d, 1.0 , J = 7 Hz, 3-CH), 6.45 (bd, 0.9, J = 8 Hz, 6a-CH), 4.23 (m, 2.0, CH=CH), 2.70 (4.9, C_6H_5), and 1.60 (bs, NH). An ethanolic ferric chloride test was negative.

Anal. Calcd for $C_{13}H_{13}NO$ (199.24): C, 78.36; H, 6.58; N, 7.03. Found: C, 78.19; H, 6.50; N, 7.01.

Dihydrodeoxo Derivative of 6a. 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (12a).—A solution of 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-hexahydro-1-hydroxy-3-phenylcyclopenta[*b*]pyrrol-2-one (2.00 g, 9.28 mmol) in methanol (200 ml) was hydrogenated at 2 atm over Raney nickel at room temperature for 24 hr. Filtration of the catalyst and evaporation of the solvent left a white solid (1.85 g, 99%), mp 168–171°. Four crystallizations from methylene chloride–petroleum ether (bp

(18) Reported for toluene: $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 250 infl (1.98), 256 (2.15), 262 (2.28), 265 (2.10), 269 (2.19) [T. W. Campbell, S. Linden, S. Godshalk, and W. G. Young, *J. Amer. Chem. Soc.*, **69**, 880 (1947)]; $\lambda_{max}^{abs\ EtOH}$ mμ (log ε) 249 (2.11), 256 (2.27), 260 infl (2.33), 262 (2.40), 265 (2.24), 269 (2.33) [A. Fehnel and M. Carmack, *ibid.*, **71**, 84 (1949)].

60–68°) gave fine white needles: mp 171–172°; $\lambda_{max}^{95\% EtOH}$ mμ (log ε) 243 (1.88), 248 (2.08), 253 (2.21), 259 (2.30), 265 (2.18), 268 infl (1.88); ν_{max}^{Nujol} (cm^{-1}) 3150 (mw, NH), 1684 (s, C=O); nmr (15% w/w in $CHCl_3$-*d*) τ 8.5 (m, 6.2, 3 CH_2), 7.0 (m, 0.9, 3a-CH), 5.92 (d, 1.9, J = 10 Hz, 3-CH) superimposed on 5.86 (m, 6a-CH), 2.65 (5.3, C_6H_5), and 2.11 (bs, 0.7, NH). That the 3 proton is coupled to the 3a proton was shown by a standard field sweep decoupling experiment with H_2 = 3 mG and a difference frequency of +64 Hz, which collapsed the doublet at 5.92.[19] The compound was soluble in concentrated hydrochloric acid but insoluble in aqueous sodium hydroxide. An ethanolic ferric chloride test was negative.

Anal. Calcd for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.72; H, 7.66; N, 7.11.

Similar hydrogenations with Raney nickel also gave the dihydrodeoxo derivative **12a** from the dihydro derivative **9a** (92%) in methanol, from the acetyldihydro derivative **10** (95%) in 95% ethanol, and with platinum oxide from the deoxo derivative **11** (46% yield after separation of some unchanged **11**), as shown by mixture melting point and infrared comparison in Nujol of the products with the sample prepared from hydrogenation of **6a**. Attempted oxidation of **12a** with chromium trioxide in glacial acetic acid at 0° gave unchanged **12a** in 100% recovery, but boiling with alkaline potassium permanganate solution gave benzoic acid (51%).[1a]

The lactam carbonyl group of **12a** was extremely resistant to hydrolysis and to reduction with lithium aluminum hydride, probably because of the steric hindrance of the adjacent phenyl substituent. Attempted hydrolysis gave unchanged **12a** from concentrated sulfuric acid at room temperature for 45 min (86% recovery) or from refluxing concentrated hydrochloric acid for 20 hr (96%).[1a] Attempted reduction with lithium aluminum hydride gave unchanged **12a** under the following conditions: (a) in ether for 24 hr (67% recovery), (b) with aluminum chloride in ether for 5 hr (70%), (c) in tetrahydrofuran for 24 hr (89%), and (d) in dioxane for 18 hr (38%).[1a]

Octahydrodeoxo Derivative of 12a. 3-Cyclohexyl-1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydrocyclopenta[*b*]pyrrol-2-one (13).—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (5.00 g, 24.9 mmol) in 95% ethanol (200 ml) was hydrogenated at 133 atm over Raney nickel (3 g) in an Aminco manganese-steel bomb. The temperature was raised gradually to 150° over a period of 2 hr (during which the pressure rose to 193 atm after 45 min), and heating was continued at this temperature for 2.5 more hr, with constant shaking. Cooling, filtration of the catalyst, evaporation of the solvent to one-third of its original volume, and addition of hot water (50 ml) caused precipitation of a white solid (4.90 g, 95%), mp 155–157°. Three crystallizations from ethanol–water gave white needles, mp 157.5–159°. The ultraviolet spectrum in 95% ethanol contained only rising end absorption; ν_{max}^{Nujol} (cm^{-1}) 3150 (ms, NH), 1678 (s, C=O).

Anal. Calcd for $C_{13}H_{21}NO$ (207.31): C, 75.31; H, 10.21; N, 6.76. Found: C, 75.39; H, 10.32; N, 6.70.

Attempted oxidation of **13** with chromic acid in acetic acid at room temperature for 1 hr was unsuccessful, giving unchanged **13** in 80% recovery.[1a]

N-Nitroso Derivative of 12a. 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-1-nitroso-3-phenylcyclopenta[*b*]pyrrol-2-one (14).—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (1.00 g, 4.97 mmol) in concentrated hydrochloric acid (8 ml) was cooled to 0° in an ice bath. A solution of sodium nitrite (1.60 g, 23.3 mmol) in water (10 ml) was added dropwise with stirring, the temperature being maintained at 0°. The resulting yellow solid was filtered, washed repeatedly with water, and dried (0.95 g, 83%), mp 89–92°. Three crystallizations from 95% ethanol gave yellow needles: mp 92–94°; $\lambda_{max}^{95\% EtOH}$ mμ (log ε) 251 (3.78), 430 (1.7), 451 (1.7); ν_{max}^{Nujol} cm^{-1} 1757 (s, C=O), 1497 (ms, N=O), 1347 (ms).

Anal. Calcd for $C_{13}H_{14}N_2O_2$ (230.20): C, 67.81; H, 6.13; N, 12.17. Found: C, 68.13; H, 6.02; N, 11.95.

The electronic spectrum of **14** is similar to that of 1-nitroso-2-pyrrolidinone [λ_{max} mμ (log ε) 252 (3.8), 423 (1.8)][20] and the N-nitroso derivative of **2** [$\lambda_{max}^{95\% EtOH}$ mμ (log ε) 261 (3.64), 402 (1.97), 418 (2.11), 439 (2.06)].[2a] Attempted nitrosation of **12a** in dilute, aqueous methanolic hydrochloric acid was unsuccessful.[1c] Solutions of **12a** (0.15 g, 0.75 mmol) in methanol (25 ml) and sodium nitrite (2.8 g, 41 mmol) in water (50 ml) were mixed, cooled to −2° in an ice–salt bath and added slowly to 3.3 *N* hydrochloric acid (13.8 ml) also at −2°, the temperature not being allowed to rise above 3°. Only unchanged **12a** was recovered, as a white solid, mp 170–171°. There was no depression in mmp 170–171°, with the starting material, and the infrared spectra in Nujol were identical.

Denitrosation of 14 to 12a.—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-1-nitroso-3-phenylcyclopenta[*b*]pyrrol-2-one (1.45 g, 6.29 mmol) in concentrated hydrochloric acid (25 ml) was refluxed for 24 hr. The solution was cooled and poured into cold water, causing precipitation of a yellowish white solid (1.05 g, 83%), mp 144–150°. Three crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave a sample, mp 171–172°. There was no depression in mmp 171–172° with the sample of **12a** prepared from hydrogenation of **6a** over Raney nickel, and the infrared spectra in Nujol were identical.

***p*-Nitro Derivative of 12a. 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-3-(*p*-nitrophenyl)cyclopenta[*b*]pyrrol-2-one (15).**—A solution of sodium nitrate (0.40 g, 4.7 mmol) in concentrated sulfuric acid (20 ml) was added dropwise with stirring to a solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (1.00 g, 4.97 mmol) in concentrated sulfuric acid (30 ml) at 0° over a period of 0.5 hr. The resulting light yellow solution was stirred for 1 hr at 0° and then poured over chipped ice, causing precipitation of a light yellow solid (0.98 g, 80%), mp 135–150°. Three crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave pale yellowish white needles: mp 201–203°; $\lambda_{max}^{95\% EtOH}$ mμ (log ε) 273 (4.03); ν_{max}^{Nujol} (cm^{-1}) 3140 (m, NH), 1694 (s, C=O), 1517 and 1350 (s, NO_2).

Anal. Calcd for $C_{13}H_{14}N_2O_3$ (246.26): C, 63.40; H, 5.73; N, 11.38. Found: C, 63.11; H, 5.80; N, 10.80, 11.53.

The ultraviolet spectrum is similar to that of *p*-nitrotoluene [$\lambda_{max}^{abs. EtOH}$ mμ (log ε) 273 (3.98)].[21,22]

***p*-Amino Derivative of 12a. 3-(*p*-Aminophenyl)-1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydrocyclopenta[*b*]pyrrol-2-one (16).**—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-(*p*-nitrophenyl)cyclopenta[*b*]pyrrol-2-one (0.25 g, 1.01 mmol) in 95% ethanol (100 ml) was hydrogenated at 2 atm over platinum oxide at room temperature for 48 hr. Filtration of the catalyst and evaporation of the solvent left a cream-colored solid, which was dissolved in methylene chloride and filtered to remove a small amount of insoluble material. Hot petroleum ether (bp 60–68°) was added to the filtrate, causing precipitation of a pink solid (0.21 g, 96%), mp 185–203°, having an infrared spectrum in Nujol identical with that of the analytical sample. Six crystallizations from methylene chloride–petroleum ether gave cream-colored needles: mp 206–208°; $\lambda_{max}^{95\% EtOH}$ mμ (log ε) 241 (4.02), 290 (2.9); ν_{max}^{Nujol} (cm^{-1}) 3360, 3300, 3160 (w, m, m, all NH), 1692 (s, C=O).

Anal. Calcd for $C_{13}H_{16}N_2O$ (216.27): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.15; H, 7.27; N, 13.11.

Epimer of the Dihydrodeoxo Derivative. 1,2,3-*trans*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (17).

A. From Refluxing Ethanolic Aqueous Sodium Hydroxide.—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (0.50 g, 2.48 mmol) and sodium hydroxide (0.60 g, 15 mmol) in ethanol (30 ml) and water (20 ml) was refluxed for 6 hr. The resulting deep yellow solution was acidified with 10 *N* sulfuric acid (6 ml), causing the solution to become colorless. The ethanol was evaporated on a steam bath, and keeping and cooling the residual solution caused precipitation of a white solid (0.47 g, 94%), mp 120–123°. Three crystallizations from methylene chloride–petroleum ether (pb 60–68°) gave white needles: mp 124–125°; $\lambda_{max}^{95\% EtOH}$ mμ (log ε) 242 (2.00), 248 (2.09), 253 (2.22), 259 (2.31), 262 infl (2.20), 265 (2.19), 268 (2.02); ν_{max}^{Nujol} (cm^{-1}) 3300 (m, NH), 1690 and 1658 (s, C=O); nmr (11% w/w in $CHCl_3$-*d*) τ 8.32 (6.1, 3 CH_2), 7.17 (bm, 1.1, 3a-CH), 6.68 (d, 1.0, J = 4 Hz, 3-CH), 5.83 (m, 1.1, 6a-CH), 2.69 (5.0, C_6H_5), and 2.31 (b, 0.7, NH).

Anal. Calcd for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.48; H, 7.51; N, 7.22.

(19) We are indebted to Richard F. Sprecher for carrying out this experiment.

(20) R. Huisgen and J. Reinertshofer, *Ann. Chem.*, **575**, 197 (1952).

(21) W. A. Schroeder, P. E. Wilcox, K. N. Trueblood, and A. O. Dekker, *Anal. Chem.*, **23**, 1740 (1951). This reference reports for *o*-nitrotoluene: $\lambda_{max}^{abs EtOH}$ mμ (log ε) 257 (3.73).

(22) For *m*-nitrotoluene: $\lambda_{max}^{abs EtOH}$ mμ (log ε) 264 (3.83); G. N. Jean and F. F. Nord, *J. Org. Chem.*, **20**, 1370 (1955).

Epimerization of **12a** was also observed (a) during attempted Hofmann rearrangement in methanolic aqueous sodium hydroxide containing bromine (67% yield of **17**), (b) during attempted reduction with lithium aluminum hydride for 7 days in refluxing ether (53%), (c) in refluxing hydrazine for 12 hr (84%), and (d) in refluxing hydrobromic acid in acetic acid for 4 days (90%).

B. From Refluxing Ethanolic Aqueous Potassium Hydroxide. Isolation of a Dimorphic Form.—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (0.75 g, 3.73 mmol) and potassium hydroxide (1.00 g, 17.8 mmol) in ethanol (30 ml) and water (20 ml) was refluxed for 3 hr. The solution was cooled to room temperature and neutralized by dropwise addition of concentrated sulfuric acid, causing precipitation of a white solid (K_2SO_4; soluble in water, insoluble in methylene chloride, leaves a residue upon ignition). The solid was filtered, and the filtrate was diluted with water and extracted repeatedly with methylene chloride. The extracts were dried ($MgSO_4$), evaporated almost to dryness, and diluted with petroleum ether (bp 60–68°), causing separation of a white precipitate (0.67 g, 89%), mp 120–124°. Three crystallizations from methylene chloride–petroleum ether gave white needles, mp 126.5–128.5°, having an infrared spectrum in Nujol different from that of the samples described in part A, not only in the "fingerprint region" but also in the facts that there is a single band in the carbonyl region while the NH absorption is split: ν_{max}^{Nujol} (cm^{-1}) 3160 and 3050 (m, NH), 1695 (s, C=O).

Dibenzyl Derivative of the Dihydrodeoxo Derivative or of Its Epimer. 1,3-*cis*(?)-Dibenzyl-1,2,3,3a-*cis*-4,5,6,6a-*cis*-octahydro-3-*trans*(?)-phenylcyclopenta[*b*]pyrrol-2-one (18). A. From the Dihydrodeoxo Derivative.—Sodium hydride dispersed in oil (2.1 g, containing 0.96 g, 40 mmol of NaH) was added to a solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (4.00 g, 19.9 mmol) in N,N-dimethylformamide (75 ml), and the mixture was stirred for 15 min. Benzyl chloride (2.53 g, 20.0 mmol) was added and the mixture was refluxed for 3 hr. Additional benzyl chloride (2.53 g, 20.0 mmol) was added and refluxing was continued for 12 more hr. The bulk of the N,N-dimethylformamide was removed by distillation at reduced pressure, leaving a dark brown, viscous oil. Water (25 ml) and methylene chloride (75 ml) were added, and the methylene chloride layer was separated, dried ($MgSO_4$), and concentrated. The resulting dark brown oil was dissolved in a minimum of benzene and chromatographed on alumina which had been packed wet with petroleum ether (bp 60–68°). Elution with petroleum ether and mixtures with benzene removed nothing, but elution with benzene removed a yellowish white solid (1.56 g, 21%), mp 101–102.5°. Three crystallizations from ethanol–water gave fine white needles: mp 102–103°; ν_{max}^{Nujol} (cm^{-1}) 1679 (s, C=O).

Anal. Calcd for $C_{27}H_{27}NO$ (381.49): C, 85.00; H, 7.13; N, 3.67. Found: C, 84.68; H, 7.27; N, 3.83.

Attempted reduction with lithium aluminum hydride in refluxing ether for 8 hr was unsuccessful, giving unchanged **18** in 90% recovery.[1a]

B. From the Epimer of the Dihydrodeoxo Derivative. 1,2,3-*trans*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (1.00 g, 4.97 mmol) was added to a mixture of sodium hydride dispersed in oil (0.50 g, containing 0.24 g, 10 mmol of NaH) and N,N-dimethylformamide (25 ml), and the mixture was stirred for 15 min. Benzylation with two portions of benzyl chloride (0.63 g, 4.98 mmol each) separated by 3 hr of refluxing, followed by an additional 24 hr of refluxing and work-up in the general manner described for benzylation of the dihydrodeoxo derivative (part A above), gave from chromatography a yellowish white solid (0.53 g, 28%), mp 98–101°. Three crystallizations from ethanol–water gave white needles, mp 102–103°. There was no depression in mmp 102–103° with the sample prepared from the dihydrodeoxo derivative, and the infrared spectra in Nujol were identical.

Independent Synthesis of the Epimer of the Dihydrodeoxo Derivative. A. Ethyl 2-Oxo-α-phenylcyclopentaneacetate (26).—The general method is that of Stork and coworkers.[23] Ethyl α-bromophenylacetate[24] (99.5 g, 410 mmol; $n^{26}D$ 1.5336; ν_{max}^{neat} (cm^{-1}) 1740 (s, C=O)) was added dropwise to a solution of freshly prepared 1-(1-cyclopenten-1-yl)pyrrolidine (50.0 g, 364 mmol; obtained[23,25] in 99% yield, bp 85–89° (14 mm), $n^{25}D$ 1.5126) in dry methanol (300 ml) and the solution was refluxed for 18 hr. Water (15 ml) was added and the solution was refluxed for 1 additional hr. The cooled solution was diluted with water (800 ml) and extracted with methylene chloride, and the extracts were dried ($MgSO_4$) and evaporated, leaving a red oil. Fractional distillation at reduced pressure gave a light yellow oil (38.7 g, 43%): bp 148–152° (0.3–0.4 mm); $n^{24}D$ 1.5188; ν_{max}^{neat} (cm^{-1}) 3420 (w, C=O overtone), 1724 (s, broad, C=O).

2,4-Dinitrophenylhydrazone of 26.—A solution of ethyl 2-oxo-α-phenylcyclopentaneacetate (0.50 g, 2.03 mmol) in 95% ethanol (10 ml) was added to a warm solution of 2,4-dinitrophenylhydrazine (0.41 g, 2.07 mmol) and concentrated sulfuric acid (2 ml) in water (3 ml) and 95% ethanol (10 ml), and the solution was allowed to cool to room temperature, producing a light yellow precipitate (0.79 g, 91%), mp 196–198°. Four crystallizations from methanol–chloroform gave fine yellow needles: mp 198–200°; ν_{max}^{Nujol} (cm^{-1}) 3300 (w, NH), 1726 (s, C=O), 1520, 1344, 1314 (s, NO_2).

Anal. Calcd for $C_{21}H_{22}N_4O_6$ (426.24): C, 59.15; H, 5.20; N, 13.14. Found: C, 59.10; H, 5.18; N, 13.24.

B. Saponification of 26 to the Acid. 2-Oxo-α-phenylcyclopentaneacetic Acid (27).—A solution of ethyl 2-oxo-α-phenylcyclopentaneacetate (10.0 g, 40.6 mmol) and aqueous 10% potassium hydroxide (91.2 g, 164 mmol) in the minimum amount of ethanol was refluxed for 24 hr. The solution was cooled, acidified with dilute sulfuric acid, and extracted with ether. The ether extract was extracted exhaustively with saturated sodium bicarbonate solution, and the bicarbonate extracts were acidified with dilute sulfuric acid and extracted with ether. Evaporation of the ether left a yellow oil, which crystallized after being kept for a time, giving a sample (6.36 g), mp 142–145°. Evaporation of the original reaction solution gave another crop of yellowish white crystals (1.85 g), mp 141–145°. The combined crops (8.21 g, 92%) were recrystallized to constant melting point from acetone–water, giving white needles: mp 143.5–145°; ν_{max}^{Nujol} (cm^{-1}) 2700 (mw, broad, OH), 1738 and 1701 (s, C=O).

Anal. Calcd for $C_{13}H_{14}O_3$ (218.24): C, 71.54; H, 6.47. Found: C, 71.52; H, 6.63.

C. Reductive Amination and Lactamization of 27 to the Epimer of the Dihydrodeoxo Derivative. 1,2,3-*trans*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-3-phenylcyclopenta[*b*]pyrrol-2-one (17).—The compound was prepared according to the general method of Bertho and Rödl[26] for the model compound, octahydrocyclopenta[*b*]pyrrol-2-one. A solution of 2-oxo-α-phenylcyclopentaneacetic acid (2.00 g, 9.15 mmol) in concentrated ammonium hydroxide (15 ml) was saturated at −10° with liquid ammonia. The cold solution was placed in a manganese–steel bomb and cooled to Dry Ice–acetone temperature. Raney nickel (0.5 g) was added and the bomb was sealed, charged with hydrogen at 133 atm, and heated gradually to 100° with constant shaking. The bomb was then heated quickly to 150° and kept at this temperature for 2 hr. Then the bomb was allowed to cool, opened, and the catalyst removed by filtration. The dark brown filtrate was evaporated in a rotary evaporator, leaving a brown solid, which was washed with water, filtered, and dried (0.35 g, 19%), mp 112–123°. Three crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave white needles (11%), mp 128.5–129.5°. There was no significant depression in mmp 125.5–128.5°, with the dimorphic form (mp 126.5–128.5°) of the epimer of the dihydrodeoxo derivative (part B), and the infrared spectra in Nujol were identical. The nmr spectrum of a 10% by weight solution in $CHCl_3$-*d* was identical with that of the original dimorph of the epimer (part A), and the ultraviolet spectra in 95% ethanol were also essentially identical.

Anal. Calcd for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.33; H, 7.50; N, 7.02.

Ozonolysis of 6a. 1-Phenylpropane-1,2,3-tricarboxylic Acid (19). A. Followed by Performic Acid Oxidation at Room Temperature.—A stream of ozonized oxygen from a Welsbach T-23 ozonizer was bubbled through a well-stirred suspension of 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-hexahydro-1-hydroxy-3-phenylcyclopenta[*b*]pyrrol-2-one (4.00 g, 18.6 mmol) in methanol (200 ml) at −78° until all the solid had disappeared and the solution had become dark blue. The resulting cold solution was then flushed with oxygen for 0.5 hr and allowed to come to room temperature.

(23) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(24) (a) R. Anschütz, C. Hahn, and P. Walter, *Ann. Chem.*, **354**, 127 (1907); (b) C. S. Marvel, E. J. Prill, and D. F. DeTar, *J. Amer. Chem. Soc.*, **69**, 52 (1947).

(25) M. E. Kuehne, *ibid.*, **81**, 5400 (1959).

(26) A. Bertho and G. Rödl, *Chem. Ber.*, **92**, 2218 (1959).

The methanol was carefully removed at room temperature in a rotary evaporator under high vacuum, leaving a light yellow, viscous oil. The oil was dissolved in 90% formic acid (25 ml), and 30% hydrogen peroxide (8.00 g, 70.5 mmol) in 90% formic acid (15 ml) was added dropwise with vigorous stirring. The resulting yellow solution was stirred at room temperature for 24 hr. The formic acid was carefully removed at room temperature in a rotary evaporator under high vacuum, leaving a viscous brown oil. The oil was dissolved in saturated sodium bicarbonate solution (75 ml), washed with ether, and acidified with concentrated hydrochloric acid. The acidified solution was extracted with ether in a continuous liquid–liquid extractor for 24 hr. The ether extract was dried ($MgSO_4$) and evaporated, leaving a light yellow glassy oil, which crystallized on scratching to a light yellow solid (2.58 g, 55%), mp 175–185°. Three recrystallizations from acetone–acetonitrile and one from water gave fine white needles, mp 202–203°. The infrared spectrum in Nujol was identical with that of the sample isolated by performic acid oxidation under exothermic conditions. There was no depression in mmp 202–204° with the synthetic sample, and the infrared spectra in Nujol were identical.

B. Followed by Performic Acid Oxidation under Exothermic Conditions.—1,2,3-*cis*-3a-*cis*-4,6a-*cis*-Hexahydro-1-hydroxy-3-phenylcyclopenta[*b*]pyrrol-2-one (6.00 g, 27.9 mmol) in methanol (300 ml) was ozonized in the manner described in part A, giving, after evaporation of the methanol, a light pink, viscous oil. The oil was dissolved in 90% formic acid (25 ml), and 30% hydrogen peroxide (12.0 g, 106 mmol) in 90% formic acid (15 ml) was added dropwise with vigorous stirring. The resulting yellow solution was heated gradually to 53°, at which point the reaction became quite exothermic, and the temperature rose rapidly to 110°. After the initial reaction had subsided, the solution was refluxed for 1 hr, during which it became quite dark. The formic acid was removed in a rotary evaporator, leaving a viscous brown tar. The tar was extracted with saturated sodium bicarbonate solution (75 ml), causing most of the tar to dissolve but leaving behind a dark brown gum. The bicarbonate solution was washed with benzene and chloroform, acidified with concentrated hydrochloric acid, and extracted as described in part A, giving a tan solid (1.66 g, 24%), mp 170–190°, having an infrared spectrum in Nujol identical with that of the analytical sample. Four crystallizations from acetone–acetonitrile and one from acetone–water gave fine white needles: mp 203–205°; ν_{max}^{Nujol} (cm^{-1}) 3070 (ms) and 2640 (m, OH), 1704 (s) and 1670 (ms, C=O).

Anal. Calcd for $C_{12}H_{12}O_6$ (252.22): C, 57.14; H, 4.80. Found: neutralization equivalent, 88.5; C, 57.14; H, 4.88.

The infrared spectrum in Nujol was identical with that of the sample isolated by performic acid oxidation at room temperature. There was no depression in mmp, 203–205°, with the synthetic sample, and the infrared spectra in Nujol were identical.

Synthesis of the Ozonolysis Product. 1-Phenylpropane-1,2,3-tricarboxylic Acid (19). A. Mandelonitrile.—The compound was obtained[27] in 84% yield as a yellow oil: ν_{max}^{neat} (cm^{-1}) 3410 (s, OH), 2250 and 2210 (w, C≡N), 1701 (s, C=O, probably from unreacted benzaldehyde).

B. Diethyl 2,3-Dicyano-3-phenylpropane-1,2-dicarboxylate.—The compound was prepared[4] by sodium ethoxide catalyzed condensation of benzaldehyde (liberated *in situ* from mandelonitrile) with ethyl cyanoacetate, followed by nucleophilic addition of cyanide ion (also derived from the mandelonitrile) and nucleophilic attack of the resulting anion on ethyl chloroacetate. Through an apparent omission in print, the original reference[4] fails to mention that the product, after dilution with water, was worked up by extraction with ether. In the present work, the extract was subsequently dried ($MgSO_4$), the ether evaporated, and the viscous orange residue distilled, giving the product in 35% yield as a viscous, glassy syrup: bp 165–175° (0.2–0.35 mm); ν_{max}^{neat} (cm^{-1}) 3470 (mw, C=O, probably an overtone), 3370 (w, OH, possibly from the ethanol solvent), 2240 (m, C≡N), 1740 (vs, broad, C=O) [lit.[4] yield 39%, bp 205–207° (4 mm)].

C. 1-Phenylpropane-1,2,3-tricarboxylic Acid (19).—The compound was prepared from the diethyl dicyano ester by hydrolysis first in boiling aqueous (1:1 by volume) sulfuric acid and then in 15% sodium hydroxide solution according to the procedure of Chatterjee and Barpujari.[4] It was obtained as a light red oil which crystallized on cooling and scratching, giving a light yellow solid in 76% yield, mp 184–188°, having an infrared spectrum in Nujol identical with that of the purified sample. Two recrystallizations from acetone–acetonitrile and two from water gave fine white needles, mp 204–206° [lit. (no yield stated[4]) mp 199°,[28] 204°[4]]; monohydrate mp (rapid heating) 110°, decomposes strongly at 125.[29]

Rearrangement of the Sodium Salt of 6-Methyl-5-nitro-2-norbornene in Aqueous Methanolic Hydrochloric Acid. 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-Hexahydro-1-hydroxy-3-methylcyclopenta[*b*]pyrrol-2-one (6b).—A solution of 6-methyl-5-nitro-2-norbornene[30] (12.0 g, 78.3 mmol) and aqueous 20% sodium hydroxide (31.2 g, 155 mmol of NaOH) in methanol (20 ml) was kept overnight in a freezer (at about −15°). The cold solution was then added dropwise with vigorous stirring over 0.5 hr to concentrated hydrochloric acid (75 ml, 900 mmol) cooled to −5° in an ice–salt bath. The yellow solution was allowed to come to room temperature and was stirred for 24 hr. The now dark red solution was diluted to twice its volume with cold water and was extracted exhaustively with methylene chloride. The extracts were dried ($MgSO_4$) and evaporated, leaving a dark red oil. The oil was continuously triturated with small amounts of hot petroleum ether (bp 90–100°) until the extracts were no longer colored, leaving a black, foul smelling, tarry residue. The extracts were concentrated on a rotary evaporator, leaving a light yellow oil (5.30 g) which, upon being kept for a time, partially crystallized to a yellow waxy solid. Trituration with a very small amount of cold (0°) ether gave a white solid (4.78 g, 40%), mp 80–85°. Four crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave fluffy white needles: mp 88–89.5°; ν_{max}^{Nujol} (cm^{-1}) broad OH band obscured by CH bands, 1686 and 1664 (s, C=O), 1524 (m); nmr (21% w/w in $CHCl_3$-*d*) τ 8.87 (d, 3.0, J = 7 Hz, $CHCH_3$), 7.62 and 7.51 (2.1, CH_2), 7.42–6.82 (m, 1.9, 3a-CH and 3-CH), 5.35 (finely split d, 1.1, J = 7 Hz, 6a-CH), and 3.98 (s, 1.9, CH=CH). The hydroxyl proton was not determined. The compound gave a bright purple color with ethanolic ferric chloride.

Anal. Calcd for $C_9H_{11}NO_2$ (153.18): C, 62.72; H, 7.24; N, 9.14. Found: C, 62.37; H, 7.34; N, 8.93.

Ozonolysis of **6b** and work-up in the manner described for the phenyl derivative gave an acidic, reddish black oil (16 wt %). An attempt to characterize the oil by formation of an amide by treatment with thionyl chloride and then ammonia gave no solid product.

Dihydro Derivative of 6b. 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-1-hydroxy-3-methylcyclopenta[*b*]pyrrol-2-one (9b).—A solution of 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-hexahydro-1-hydroxy-3-methylcyclopenta[*b*]pyrrol-2-one (0.15 g, 0.98 mmol) in 95% ethanol (50 ml) was hydrogenated at 2 atm over platinum oxide at room temperature for 6 hr. Filtration of the catalyst and evaporation of the solvent left a clear oil, which upon cooling and scratching crystallized to a white solid (0.14 g, 92%), mp 101–105°. Four recrystallizations from methylene chloride–petroleum ether (bp 60–68°) gave fine white needles: mp 106–107°; ν_{max}^{Nujol} (cm^{-1}) broad OH band obscured by CH bands, 1687 and 1653 (s, C=O), 1530 (m); nmr (12% w/w in $CHCl_3$-*d*) τ 8.89 (d, 3,2, J = 7 Hz, $CHCH_3$), 8.40 (m, 5.0, 2.5 CH_2), 7.84 (m, 0.8, 0.5 CH_2), 7.3 (m, 2.0, 3a-CH and 3-CH), and 5.80 (b, 1.0, 6a-CH). The hydroxyl proton was not determined. The compound gave a bright purple color with ethanolic ferric chloride solution.

Anal. Calcd for $C_8H_{13}NO_2$ (155.19): C, 61.91; H, 8.44; N, 9.03. Found: C, 61.76; H, 8.48; N, 9.23.

Dihydrodeoxo Derivative of 6b. 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-3-methylcyclopenta[*b*]pyrrol-2-one (12b). A. From Hydrogenation of 6b.—A solution of 1,2,3-*cis*-3a-*cis*-4,6a-*cis*-hexahydro-1-hydroxy-3-methylcyclopenta[*b*]pyrrol-2-one (0.50 g, 3.26 mmol) in 95% ethanol (50 ml) was hydrogenated at 2 atm over Raney nickel at room temperature for 20 hr. Filtration of the catalyst and evaporation of the solvent left a white solid (0.44 g, 97%), mp 80–85°. Three crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave white plates: mp 85–86°, which gave a depression in mmp 48–55°, with the starting material; ν_{max}^{Nujol} (cm^{-1}) 3170 (ms, NH), 1678–1655 (s, broad, C=O); nmr (12% w/w in $CHCl_3$-*d*) τ 8.85 (d, 3.4, J = 7 Hz, $CHCH_3$), 8.32 (6.1, 3 CH_2), 7.3 (m, 1.9, 3a-CH and 3-CH), 5.91 (m, 0.9,

(27) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, pp 97–99.

(28) H. Stobbe and R. Fischer, *Ann. Chem.*, **315**, 239 (1901).

(29) J. Hecht, *Monatsh. Chem.*, **24**, 367 (1903).

(30) E. E. van Tamelen and R. J. Thiede, *J. Amer. Chem. Soc.*, **74**, 2615 (1952).

6a-CH), and 2.53 (b, 0.7, NH). An ethanolic ferric chloride test was negative.

Anal. Calcd for $C_8H_{13}NO$ (139.19): C, 69.03; H, 9.41; N, 10.06. Found: C, 69.25; H, 9.41; N, 9.98.

Compound **12b** did not epimerize, being recovered unchanged in 67% yield from refluxing ethanolic aqueous sodium hydroxide for 6 hr under conditions which caused the phenyl dihydrodeoxo derivative (**12a**) to epimerize to **17**.[1a]

B. From Hydrogenation of 9b.—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-1-hydroxy-3-methylcyclopenta[*b*]pyrrol-2-one (0.10 g, 0.64 mmol) in 95% ethanol (20 ml) was hydrogenated at 2 atm over Raney nickel at room temperature for 24 hr. Filtration of the catalyst and evaporation of the solvent left a white solid (0.075 g, 84%), mp 76–82°. Three crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave colorless plates, mp 85–86°. There was no depression in mmp 85–86° with the sample prepared from hydrogenation of **6b** (part A above), and the infrared spectra in Nujol were identical.

Monobenzyl Derivative of the Dihydrodeoxo Derivative. 1-Benzyl-1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-methylcyclopenta[*b*]pyrrol-2-one (28).—Sodium hydride dispersed in oil (0.74 g, containing 0.35 g, 14.6 mmol of NaH) was added to a solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-methylcyclopenta[*b*]pyrrol-2-one (1.00 g, 7.18 mmol) in N,N-dimethylformamide (25 ml), and the mixture was stirred for 15 min. Benzyl chloride (0.91 g, 7.19 mmol) was added and the mixture was refluxed for 3 hr. Additional benzyl chloride (0.91 g, 7.19 mmol) was added and refluxing was continued for 24 more hr. Work-up and chromatography in the manner described for preparation of the dibenzyl derivative **18** gave a light yellow liquid (0.87 g, 53%). Distillation under high vacuum gave a colorless liquid: bp 80–100° (0.001 mm); $n^{30}D$ 1.5388; ν_{max}^{neat} (cm^{-1}) 3400 (mw, C=O overtone(?), 1669 (s, C=O).

Anal. Calcd for $C_{15}H_{19}NO$ (229.31): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.62; H, 8.34; N, 6.13.

Hydrolysis of the Dihydrodeoxo Derivative with Concentrated Hydrochloric Acid. 2-*cis*-Amino-α-methylcyclopentaneacetic Acid Hydrochloride (29).—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-methylcyclopenta[*b*]pyrrol-2-one (0.30 g, 2.16 mmol) in concentrated hydrochloric acid (20 ml) was refluxed for 16 hr. The solvent was removed in a rotary evaporator, leaving white needles (0.28 g, 68%), mp 184–191°. Three recrystallizations from absolute ethanol–ether gave white needles: mp 189.5–191°; ν_{max}^{Nujol} (cm^{-1}) 2570 (m), 2450 (mw), 2020 (mw), 1990 (mw), 1890 (w), 1621 (s), 1572 (m), 1532 (s), all NH_3^+, and 1720 (s, C=O).

Anal. Calcd for $C_8H_{16}NO_2Cl$ (193.67): C, 49.61; H, 8.33; N, 7.23. Found: C, 49.18; H, 8.42; N, 7.33.

Reduction of the Dihydrodeoxo Derivative with Lithium Aluminum Hydride. 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-3-methylcyclopenta[*b*]pyrrole (30).—A solution of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-methylcyclopenta[*b*]pyrrol-2-one (1.00 g, 7.19 mmol) in dry ether (25 ml) was added dropwise under nitrogen at a rate to maintain a steady reflux to a suspension of lithium aluminum hydride (0.62 g, 16.3 mmol) in dry ether (25 ml). The mixture was then refluxed for 20 hr, stirred at room temperature for 2 hr, cooled in an ice bath, and the excess lithium aluminum hydride was destroyed by cautious addition of cold water. The ether layer was decanted and the solid residue was extracted twice with warm ether. The extracts were combined with the ether decantate, and the ether was removed in a rotary evaporator at room temperature, leaving a yellow oil. The oil was dissolved in 5.6% hydrochloric acid (25 ml), washed with ether, basified with aqueous 5% sodium hydroxide, and extracted exhaustively with ether. The ether extracts were dried (KOH) and evaporated in a rotary evaporator at room temperature, leaving a colorless oil (0.85 g, 94%): $n^{24}D$ 1.4776; ν_{max}^{neat} (cm^{-1}) 3240 (s, NH), 1695 (m, NH).

***p*-Toluenesulfonyl Derivative of 30. 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-Octahydro-3-methyl-1-(*p*-toluenesulfonyl)cyclopenta[*b*]pyrrole.**—*p*-Toluenesulfonyl chloride (0.16 g, 0.84 mmol) was added to a suspension of 1,2,3-*cis*-3a-*cis*-4,5,6,6a-*cis*-octahydro-3-methylcyclopenta[*b*]pyrrole (0.10 g, 0.80 mmol) in aqueous 5% sodium hydroxide (5 ml, 6.2 mmol). The mixture was stirred at room temperature for 8 hr, giving a precipitate (0.21 g, 94%), mp 106–109°. Two crystallizations from ethanol–water gave white plates: mp 110–111°; ν_{max}^{Nujol} (cm^{-1}) no NH, 1338 and 1160 (s, C=O).

Anal. Calcd for $C_{15}H_{21}NO_2S$ (279.39): C, 64.48; H, 7.58; N, 5.01; S, 11.48. Found: C, 64.11; H, 7.59; N, 4.83; S, 11.79.

Registry No.—**6a**, 19759-07-0; **6b**, 19759-08-1; **7**, 19759-09-2; **8**, 19759-10-5; **9a**, 19759-11-6; **9b**, 19759-12-7; **10**, 19759-13-8; **11**, 19759-14-9; **12a**, 19759-15-0; **12b**, 19759-16-1; **13**, 19765-72-1; **14**, 19765-73-2; **15**, 19765-74-3; **16**, 19765-75-4; **17**, 19765-76-5; **18**, 19765-77-6; **19**, 19765-78-7; **26** (2,4-dinitrophenylhydrazone), 19755-90-9; **27**, 19775-91-0; **28**, 19759-17-2; **29**, 19759-18-3; **30** (*p*-toluenesulfonyl deriv), 19759-19-4.

Acknowledgment.—In addition to the acknowledgments in ref 1a, the senior author is grateful to the Chemistry Department of the University of Wisconsin at Madison for its hospitality during the writing of much of this paper while he held a single quarter leave from the University of Minnesota.

Acid-Catalyzed Aromatic Nucleophilic Substitution. II. The Reaction of 2-Halo-3-nitropyridines and 2-Halo-5-nitropyridines with Water in Sulfuric Acid

JOHN D. REINHEIMER, JAMES T. MCFARLAND,[1,2] RICHARD A. AMOS,[1] JOHN M. WOOD,[2] MARK ZAHNISER,[1] AND WAYNE BOWMAN[2]

Department of Chemistry, The College of Wooster, Wooster, Ohio 44691

Received October 4, 1968

The reaction rate constants for the reaction of several 2-halo-5-nitropyridines and 2-halo-3-nitropyridines have been determined. The plot of k_ψ *vs.* molarity of sulfuric acid shows a maximum. φ values from the Bunnett–Olsen plot indicate that a slow proton transfer to water is involved. Some limitations for preparation of halopyridines by an acid-catalyzed halogen exchange are indicated.

A mechanism has been proposed for the hydrolysis of 2-halo-5-nitropyridines to 2-hydroxy-5-nitropyridine in acid solution.[3] This mechanism was based on four considerations: (1) the reaction is an aromatic nucleophilic substitution reaction; (2) the reaction is acid catalyzed; (3) there is a deuterium isotope effect; and (4) four molecules of water are involved in the transition state. The reaction rate constants in this earlier investigation were determined by wet chemical methods, so the rate constants could not be conveniently measured at very low substrate concentrations. Spectrophotometric methods, with the requirement of very low substrate concentrations, can be applied to this system at both high and low acid concentrations and hence at both high and low percentage protonation of the pyridine nitrogen.

The previous kinetic relationships between the activity of water, a_{HOH}, and the protonated substrate were deduced from a plot of (k_ψ/F) *vs.* $(a_{HOH})^n$, where k_ψ was the observed pseudo-first-order rate constant and F was the fraction of the pyridine protonated. A linear plot was obtained with $n = 4$ for the substrate 2-chloro-5-nitropyridine. Our interest in studying other closely related substrates was to find answers to some of the following questions. Is the power of 4 on a_{HOH} applicable to other 2-halo-5-nitropyridines? Will the 2-halo-3-nitropyridines show the same kinetic relationship with respect to a_{HOH}? Can the *o*-nitro group replace one or more of the waters of solvation? How good is the bromo- and iododechlorination reaction; can one prepare the corresponding bromo and iodo compounds in a pure state from 2-chloro-5-nitropyridine and 2-chloro-3-nitropyridine. To answer these questions, 2-halo-5-nitropyridines and 2-halo-3-nitropyridines were synthesized (or purified) and their reaction rates with aqueous sulfuric acid were investigated.

Results

pK_a Determination.—The pK_a's of the halonitropyridines were determined by the method of Davis and Geissman[4] or Katritzky[5] or Bunnett and Olsen.[6] The pK_a's were determined by adding concentrated sulfuric acid from a weight buret to a fixed amount of the halonitropyridine. Readings were taken, and the cuvette carefully rinsed to ensure that no sample was lost before the next addition of sulfuric acid. This procedure was followed for all the substrates except 2-bromo-5-nitropyridine. The Davis and Geissman procedures were carried out by different investigators at Wooster with variations on the technique of adding known volumes of concentrated sulfuric acid to an aliquot of the sample. This technique was not satisfactory for the Katritzky or Bunnett and Olsen method, for slight changes in the value of the absorbance caused disproportionate changes in the calculated pK_a. The results are displayed in Table I.

The order of pK_a is roughly that expected. The steric inhibition of resonance of *ortho* group in the 2-halo-3-nitropyridines would be expected to decrease the electron-withdrawing effectiveness of the 3-nitro group as compared to the 5-nitro group. The chloro-substituted compounds are the least basic in both the 3-nitro and the 5-nitro series; this is in the order of the electronic effects of the halogens.

There are some differences in these pK_a values. For 2-chloro-5-nitropyridine, the Bunnett–Olsen pK_a is somewhat lower than the other values. The ratio $(C_{BH^+}/C_B) = 1.0$ occurs between $H_0 = 2.96$ and $H_0 = -2.78$. The extrapolation of a plot of $[H_0 + \log (H^+)]$ *vs.* $H_0 + \log [(C_{BH^+})/(C_B)]$ with the same data does not yield a Kp_a of the above range. The more negative value of -2.85 seems to be more consistent with the remainder of the data.

The rate data are displayed in Table II. In Table III the variation of k_ψ with temperature and the Arrhenius activation energies are given.

The H_0 data were taken from the review of Long and Paul.[7] The more recent data of Noyce and Jorgensen[8] were not needed, since our experiments were in the range of lower acidities where the two functions have the same value. (H^+) was taken to be the molarity of the sulfuric acid. The fraction protonated was calculated as $F = h_0/(h_0 + K_{SH^+})$.

The first attempted correlation of the pseudo-first-order rate constants with pK_a and a_{HOH} was a plot of log (k_ψ/F) *vs.* log (a_{HOH}). The slope of such a plot would give "n," the power on a_{HOH}. These plots showed evidence of curvature at both high and low per cent protonation. The central portion of such plots

(1) Participant in the Undergraduate Research Participation Program of the National Science Foundation, 1966, 1968.

(2) Taken in part from the Independent Study thesis of James McFarland, 1964, John Wood, 1968, and Wayne Bowman, 1962.

(3) J. D. Reinheimer, J. T. Gerig, R. Garst, and B. Schrier, *J. Amer. Chem. Soc.*, **84**, 2770 (1962).

(4) C. T. Davis and T. A. Geissman, *J. Amer. Chem. Soc.*, **76**, 3507 (1954).

(5) C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakir, and A. M. White, *Tetrahedron*, **21**, 1055 (1965).

(6) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899 (1966).

(7) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 1 (1957).

(8) D. S. Noyce and M. J. Jorgenson, *J. Amer. Chem. Soc.*, **84**, 4312 (1962).

TABLE I

pK_a AND φ FOR SUBSTITUTED PYRIDINES AT 30°

Compound	pK_a			φ[b]	φ[b]
	H_0 method	Davis & Geissman	Bunnett & Olsen	Bunnett & Olsen	from[c] pK_a
2-Chloro-5-nitro	−2.85	−2.95[a]	−2.42	0.66 (25°)	0.76
2-Bromo-5-nitro	−2.40[a]	−2.50[a]	−2.60[a]	0.68	
2-Iodo-5-nitro	−1.43	−1.70	−1.40	0.64	0.62
2-Chloro-3-nitro	−2.44		−2.39	0.63	0.67
2-Bromo-3-nitro	−2.05	−2.25	−2.02	0.68	
				0.69 (25°)	

[a] Temperature was 25°. [b] Temperature was 80° unless noted otherwise. [c] Plot of log (k_ψ/F) *vs.* $[H_0 - \log (H^+)]$ where $F = h_0/(h_0 + K_{BH^+})$.

TABLE II

RATE CONSTANTS AT 80° FOR 2-HALO-*x*-NITROPYRIDINES

$M_{H_2SO_4}$	k_ψ, sec^{-1}
2-Iodo-5-nitropyridine	
0.892	5.31×10^{-5}
1.784	11.9×10^{-5}
2.689	17.6×10^{-5}
3.142	19.3×10^{-5}
3.594	19.0×10^{-5}
4.047	17.9×10^{-5}
4.500	16.2×10^{-5}
5.404	10.2×10^{-5}
6.311	6.0×10^{-5}
2-Bromo-3-nitropyridine at 80.8°	
1.50	10.5×10^{-5}
2.45	20.1×10^{-5}
3.38	29.3×10^{-5}
4.16	31.6×10^{-5}
5.10	30.4×10^{-5}
6.03	21.5×10^{-5}
6.91	14.0×10^{-5}
7.82	7.45×10^{-5}
2-Bromo-3-nitropyridine at 25°	
1.50	4.15×10^{-7}
2.45	8.10×10^{-7}
3.38	11.8×10^{-7}
4.16	12.5×10^{-7}
5.10	12.1×10^{-7}
6.03	8.6×10^{-7}
6.91	5.5×10^{-7}
7.82	3.0×10^{-7}
2-Chloro-3-nitropyridine at 80.2°	
1.44	6.55×10^{-5}
2.40	13.0×10^{-5}
3.36	21.6×10^{-5}
4.32	26.7×10^{-5}
5.28	27.5×10^{-5}
6.24	22.7×10^{-5}
7.20	13.8×10^{-5}
8.16	6.8×10^{-5}
2-Bromo-5-nitropyridine	
2.40	1.23×10^{-4}
3.36	1.90×10^{-4}
4.32	2.46×10^{-4}
5.28	2.66×10^{-4}
6.21	2.11×10^{-4}
6.24	2.12×10^{-4}
7.20	1.52×10^{-4}
8.16	0.751×10^{-4}
9.12	0.438×10^{-4}

TABLE III

RATE CONSTANT AT DIFFERENT TEMPERATURES FOR 2-HALO-*x*-NITROPYRIDINES

Molarity	Temp, °C	k_ψ, sec^{-1}	Activation energy, kcal
2-Iodo-5-nitropyridine			
1.78	102.3	7.56×10^{-4}	
	89.9	2.78×10^{-4}	
	80.1	1.19×10^{-4}	
	60.0	0.195×10^{-4}	21.3
3.59	102.3	11.8×10^{-4}	
	89.9	4.58×10^{-4}	
	80.1	1.90×10^{-4}	
	60.0	1.02×10^{-4}	21.9
5.40	102.3	6.23×10^{-4}	
	89.9	2.61×10^{-4}	
	80.1	1.02×10^{-4}	
	60.0	0.144×10^{-4}	23.1
2-Bromo-3-nitropyridine			
2.45	100.7	74.2×10^{-5}	
	80.8	20.1×10^{-5}	
	70.7	8.91×10^{-5}	20.1
6.91	100.7	64.8×10^{-5}	
	80.8	14.0×10^{-5}	
	70.7	5.19×10^{-5}	21.4
2-Chloro-3-nitropyridine			
3.36	100.2	10.1×10^{-4}	
	80.2	2.16×10^{-4}	
	59.6	0.368×10^{-4}	20.6
4.32	100.2	12.5×10^{-4}	
	80.2	2.67×10^{-4}	
	59.6	0.479×10^{-4}	20.5
5.28	100.2	12.2×10^{-4}	
	80.2	2.74×10^{-4}	
	59.6	0.481×10^{-4}	20.0
6.24	100.2	10.5×10^{-4}	
	80.2	2.27×10^{-4}	
	59.6	0.343×10^{-4}	21.1
2-Bromo-5-nitropyridine			
3.36	99.9	8.54×10^{-4}	
	80.0	1.90×10^{-4}	
	60.1	3.18×10^{-5}	19.4
4.32	99.9	1.13×10^{-3}	
	80.0	2.46×10^{-4}	
	60.1	4.00×10^{-5}	19.7
5.28	99.9	1.47×10^{-3}	
	80.1	2.67×10^{-4}	
	60.1	4.21×10^{-5}	20.7

approximated a straight line; these plots were regarded as unsatisfactory.

The next approach was to apply the empirical method of Bunnett and Olsen.[6] Their plot of $[\log k_\psi - \log (C_{BH^+}/C_{st})]$ *vs.* $[H_0 + \log (H^+)]$ does not use the pK_a. The concentration of the protonated species and stoichiometric concentration are obtained from the spectra in the acid solution. A similar plot, log (k_ψ/F) *vs.* $[H_0 + \log (H^+)]$, was also made for each substrate.

Bunnett and Olsen have argued that the use of $F = [h_0/(h_0 + K_{BH^+})]$ is not as accurate as the use of $F = (C_{BH^+}/C_{st})$. The latter F may be obtained from pro-

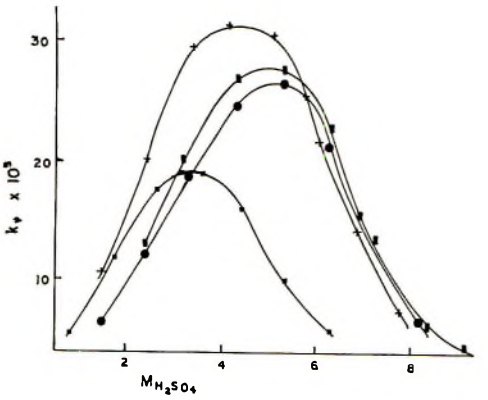


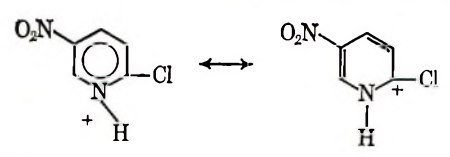
Figure 1.—k_ψ (sec^{-1}) *vs.* $M H_2SO_4$: ●, 2-bromo-5-nitropyridine; ■, 2-chloro-3-nitropyridine; ■, 2-iodo-5-nitropyridine; +, 2-bromo-3-nitropyridine.

tonation data directly without the intervention of a pK_a to determine K_{SH^+}. Further, if the substrate does not obey the acidity function that is applied, the pK_a that is determined may or may not give the proper F from $(h_0/(h_0 + K_{SH^+})]$. In the present case, both pyridine and pyridine N-oxides are Hammett bases.[9] Both types of plots were linear, and their slopes are in reasonable agreement. These results are displayed in Table I, columns 5 and 6.

Discussion

The acid-catalyzed bromodechlorination reaction is only a fair method for the preparation of the bromonitropyridines from chloronitropyridines. The reaction is acid catalyzed, for no reaction took place in the absence of acid and only partial exchange in the presence of acid.[10,11] However, iododechlorination is effective for the preparation of 2-iodo-5-nitropyridine from 2-chloro-5-nitropyridine. This was also an acid-catalyzed reaction; refluxing 2-chloro-5-nitropyridine with KI in methyl ethyl ketone gave no product. There is some indication that the halodechlorination reaction may be quite sensitive to the nature of the nucleophile. For example, $NaHF_2$ gave a 3% yield, but KHF_2 gave a 74% yield in the fluorodechlorination of 2-chloropyridine with no solvent.[12] It is possible that the use of CsI or some other alkali metal halide could give higher yields than we have been able to achieve.

The pseudo-first-order rate constants for the halonitropyridines *vs.* acid concentration are given in Figure 1. The shape of this curve may be qualitatively understood on the basis of two competing effects: protonation of the substrate and the activity of water. If the active species in solution is the protonated substrate, the rate should increase as the fraction protonated (F) increases. The activity of water, the nucleophile, decreases with increasing acid concentration. If $k_\psi = kF(a_{HOH})^n$, where k is the rate constant, a composite k_ψ results. At low acid concentrations, where a_{HOH} changes slightly with changing acid concentration, (F) is the major factor with its larger value (with increasing acid concentration) controlling the over-all rate. However, at higher acid concentrations, the decreasing a_{HOH} becomes more important and the over-all rate decreases with increasing acid concentration. During a particular experiment, both a_{HOH} and (F) remain constant.



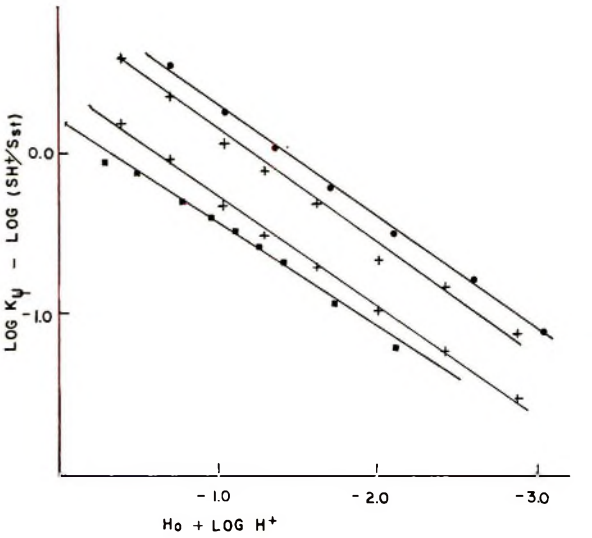


Figure 2.—[Log k_ψ − log (SH^+/S_{st})] *vs.* [H_0 + log (H^+)]: ●, 2-bromo-5-nitropyridine (80°); +, 2-bromo-3-nitropyridine (upper curve 80°, lower curve 25°); ■, 2-iodo-5-nitropyridine (80°).

It is interesting to note that the maximum is not the result of complete protonation of the substrate. The fraction protonated at the maximum value of k_ψ varies from 0.33 for 2-bromo-3-nitropyridine to 0.42 for 2-iodo-5-nitropyridine. These maxima occur between 3 and 5 M sulfuric acid.

There does not seem to be a good basis for the comparison of the rate constants of these reactions. The maximum values for k_ψ seem to be the most reasonable comparison. Chlorine and bromine are replaced at approximately equal rate, with iodine the slowest. This is the order expected for an activated aromatic nucleophilic substitution.[13]

Attempts to evaluate the role of water in the reaction were made with two plots. The method of Bunnett and Olsen gave reasonable straight lines with slopes which varied from 0.64 to 0.76. These slopes (φ) are in the range in which rate-determining proton transfer to water is indicated. It is of interest to note that the slope of the line depends upon the value of the pK_a which is used. Before the pK_a of 2-chloro-3-nitropyridine was determined, several rough estimates of −2.12, −2.25, and −2.50 were made and the kinetic data [log (H^+) + H_0 *vs.* log (k_ψ/F)] were plotted. The lines for each plot were equally good, with slopes (φ) of 0.58, 0.62, and 0.67, respectively. In another plot, the Bunnett–Olsen plot was made for the same substrate with k_ψ (80°) and also k_ψ (25°). The experimental data for 2-bromo-3-nitropyridine were measured at 80.8° and were extrapolated to 25.0° in order to use the H_0 and pK_a data that were obtained the the lower tem-

(9) C. D. Johnson, A. R. Katritzky, and B. J. Ridgewell, *J. Amer. Chem. Soc.*, **21**, 1057 (1965).

(10) A. H. Berrie, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 2042 (1952).

(11) Y. Yamamoto, *J. Pharm. Jap.*, **71**, 662 (1951).

(12) M. M. Boudakin, *J. Heterocycl. Chem.*, **4**, 381 (1967).

(13) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 173 (1951).

perature. The plots were both linear, but $\varphi_{80.8} = 0.68$ and $\varphi_{25.0} = 0.69$. This difference is not regarded as highly significant. It has been suggested by Yates and Riordan[14] that kinetic data at temperatures other than 25° can be combined with acidity function data and a_{HOH} data at 25° without serious error for weakly basic substrates. Our observations do suggest that the combination of a poor estimate of pK_a and collection of data far removed from 25° may cause considerable differences in the slopes obtained (see Figure 2).

Some conclusions which may be drawn from this body of data are as follows.

(1) The hydrolysis reactions of 2-halo-5-nitropyridines and 2-halo-3-nitropyridines have the same mechanism.

(2) The mechanism involves a rate-determining proton transfer to water. The mechanism offered in ref 3 is supported, but the number of waters of hydration cannot be as definite as these authors have indicated.

(3) The role of the 3-nitro group in contrast to that of the 5-nitro group cannot be evaluated from this data. On the extreme hypothesis of hydration,[6] 4.5φ should give the hydration change for the reaction in terms of number of molecules of water.[8] Values of φ for 3-nitro compounds are 0.63 and 0.67; for 5-nitro they are 0.66, 0.67, and 0.64. There seems to be no difference in φ (where the same halogen is displaced) with change in position of the nitro group. A greater change in φ occurs when the iodine atom is displaced. This may suggest a steric factor is involved, but there are not sufficient data to draw a firm conclusion.

Experimental Section

Kinetic Methods. 2-Iodo-5-nitropyridine.—A stock solution of the reagent was prepared by dissolving 2-iodo-5-nitropyridine in concentrated sulfuric acid. A 9.85-ml sample was pipeted into a volumetric flask, and the desired concentration attained by suitable dilution in an ice bath (final dilution at room temperature). Nitrogen was used to deaerate the solution and to fill the sample tubes. Samples (10 ml) were sealed in Pyrex glass ampoules which were then placed in a constant-temperature bath. The reaction was stopped by plunging the tube into ice. The tubes were opened and the contents were rinsed into a 50-ml volumetric flask with 9 M H_2SO_4; the absorbance at 2840 Å was determined on a Beckman D.U. spectrophotometer. The rate constants were determined from eq 1.

$$2.303 \log [A_\infty/(A_\infty - A_t)] = k_\psi t \quad (1)$$

2-Bromo-3-nitropyridine and 2-Chloro-3-nitropyridine.—The procedures were the same as above, except that the use of nitrogen was not required. The samples were read without dilution on a Beckman D.U. spectrophotometer which had a Gilford phototube and electronics. The wavelength was 3480 Å.

2-Bromo-5-nitropyridine.—The procedures were the same as above, but certain complications ensued. The product and reagent absorbed at the same wavelengths, and their absorptivities were similar. Since the absorptivity changed slightly with acid concentration, it was necessary to prepare absorbance *vs.* wavelength curves for each product and reagent at each kinetic acid concentration. The wavelength that gave the greatest ($A_{reagent} - A_{product}$) was selected for analysis. This procedure allowed one to "read" the absorbance of the kinetic sample without dilution. The modified Beckman D.U. spectrophotometer was used. The wavelengths were approximately 2500–2600 Å in these experiments.

Precautions and Product Identification.—The sulfuric acid was standardized by titration against tris(hydroxymethyl)methylamine. The products were shown to follow Beer's law at several concentrations. The infinity samples were found to have the calculated absorbance within 2% in all cases; generally the agreement was to 1%. Qualitatively, the spectrum of the product was the same as that of the authentic sample—this comparison was made for the infinity samples of both 2-hydroxy-5-nitropyridine and 2-hydroxy-3-nitropyridine. The product was shown to be stable to the kinetic conditions by placing an authentic sample of the 2-hydroxy-3-nitropyridine in the kinetic medium at 102° for 24 hr. The absorbance of the sample did not change. All pipets and thermometers have been calibrated. All rate constants were determined by a least-squares regression analysis. The rate constants reported in Table II are the average of two or more experiments; those in Table III are singlet experiments.

Preparation of Substrates. Hydrolysis of 2-Chloro-3-nitropyridine.—2-Chloro-3-nitropyridine (1 g) was dissolved in 8 ml of 9 M sulfuric acid. The mixture was refluxed for 3 hr. Sodium hydroxide solution (6 M) was added to the cooled mixture until a precipitate formed; the still acidic solution was filtered. The product was isolated in 91% yield [0.89 g of 2-hydroxy-3-nitropyridine, mp 220–224° (lit.[10] mp 224°)]. In a second experiment, 20 g of 2-chloro-3-nitropyridine was added to 200 ml of glacial acetic acid and 200 ml of concentrated HCl and refluxed for 3 hr. The solvent was distilled away, and the product filtered. The product was recrystallized from methanol to give a product, mp 223–225°, in a yield of 16.0 g (89%). Thin layer chromatography on alumina with benzene showed no trace of the starting material in the product. Attempts to hydrolyze in basic solution gave a viscous oil which slowly crystallized and melted above 300°.

2-Iodo-5-nitropyridine was prepared by the method of Reinheimer, *et al.*[2] The final product was purified by column chromatography on alumina with benzene: purified yield 27%; mp 162.5–164.5°.

2-Bromo-5-nitropyridine.—Several attempts to prepare 2-bromo-5-nitropyridine by the reaction of LiBr with 2-chloro-5-nitropyridine in different solvents gave a product of mp 132–133°. Attempts to purify this material by column chromatography were unsuccessful. Finally, the method of Yamamoto[11] was used. 2-Hydroxy-5-nitropyridine (2.5 g), red phosphorus (0.8 g), and 0.83 ml of toluene were mixed and 3.82 ml of bromine was slowly added over a period of 2.5 hr while the temperature was maintained at 120–130°. The reaction mixture was cooled and poured on ice; the solid was filtered and dried. Purification on an alumina column with benzene as the eluting agent gave 1.0 g (29%) of 2-bromo-5-nitropyridine, mp 136.5–138°. In a second preparation, bromobenzene was substituted for toluene in the above preparation to avoid the formation of benzyl bromide. During chromatographic work-up, several bands appeared and the crude product melted over a considerable range, 122–133° (61% yield). With further purification on the alumina column and acetone as the eluting agent, the crude product separated into two bands; the desired product moved with the solvent front and the impurity remained at the origin. Two recrystallizations from acetone–ligroin gave 4.7 g (34% yield), mp 138–139.5° (lit.[5] mp 138°).

Anal. Calcd for $C_5H_3BrN_2O_2$: C, 29.58; H, 1.49; N, 13.80. Found: C, 29.57; H, 1.42; N, 13.81.

2-Bromo-3-nitropyridine was prepared by the procedure of Berrie, Newbold, and Spring.[10] The product was recrystallized six times, mp 122–124° (lit.[10] mp 124°). Thin layer chromatography gave no indication of impurities, and a bromide analysis indicated a purity of 98%.

Bromodechlorinations of 2-Chloro-5-nitropyridine.—2-Chloro-5-nitropyridine (13.16 g, 0.0083 mol) was dissolved in 480 ml of anhydrous methyl ethyl ketone. LiBr (36.15 g, 0.415 mol) and 4 ml of concentrated sulfuric acid were added and the mixture was refluxed for 1.5 hr. The reaction mixture was cooled, poured on ice, and the organic layer separated. After drying, concentration (by evaporation of the solvent under reduced pressure) to one-third the original volume, and cooling, 13.5 g (80% yield) of a crude product, mp 120–125°, was obtained. Three recrystallizations from benzene–ligroin gave a product of mp 132–133°. In a similar reaction, 0.02 mol of 2-chloro-5-nitropyridine and 0.10 mol of LiBr in 60 ml of glacial acetic acid gave 35% yield of white crystals, mp 130–132°. Recrystallization from benzene–ligroin gave a product melting at 131.5–132.5°.

Iododechlorination of 2-Chloro-5-nitropyridine.—The procedure of Klingsberg[15] was followed. 2-Chloro-5-nitropyridine

(14) K. Yates and J. C. Riordan, *Can. J. Chem.*, **43**, 2333 (1965).

(15) E. Klingsberg, *J. Amer. Chem. Soc.*, **72**, 1031 (1950).

(25 g) and KI (75 g) were refluxed in 350 ml of methyl ethyl ketone. The solvent was evaporated, the residue washed with water, and recrystallized from benzene to give starting material.

Attempted Bromodechlorination of 2-Chloro-3-nitropyridine.—The molar ratio was 0.08 mol of aryl chloride and 0.416 mol of LiBr. In three experiments, methyl ethyl ketone, glacial acetic acid, and dimethyl sulfoxide were used as the solvent. Starting material was recovered when no acid was added to methyl ethyl ketone. In each case, the reaction mixture was refluxed for several hours, then the product isolated by pouring the reaction mixture on ice. If the product did not precipitate immediately, the solvent was removed by evaporation to obtain the solid product. The melting point of the product was 118–120°, and did not change with recrystallization. Potentiometric titration of the halide by silver nitrate showed the presence of both bromide and chloride ions.

Registry No.—Sulfuric acid, 7664-93-9; 2-bromo-5-nitropyridine, 4487-59-6; 2-chloro-3-nitropyridine, 5470-18-8; 2-iodo-5-nitropyridine, 19755-52-3; 2-bromo-3-nitropyridine, 19755-53-4.

The Photochemistry of Unsaturated Nitrogen Containing Compounds. II. The Mechanism of Benzonitrile and Benzaldimine Formation during Irradiation of Benzalazine

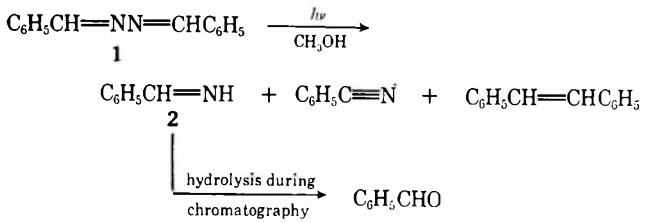
ROGER W. BINKLEY

Department of Chemistry, The Cleveland State University, Cleveland, Ohio 44115

Received April 1, 1968

The photochemical reaction of benzalazine (1) to give benzonitrile and benzaldimine (2) was studied in the presence of various hydrogen donors in an effort to obtain information which would determine whether the mechanism for this photochemical transformation is inter- or intramolecular. These studies showed that with the addition of effective hydrogen donating agents such as benzhydrol and decyl mercaptan a definite decrease in product yield occurred; however, a limiting value in the decrease of this yield was reached beyond which further addition of trapping agents had no effect. These results are interpreted as indicative of both intra- and intermolecular reaction being operative in the photochemical conversion of benzalazine (1) to benzonitrile and benzaldimine (2). Mechanisms for these two processes are presented and discussed.

In the previous publication in this series[1] it was shown that benzalazine (1) reacted photochemically to produce benzonitrile, benzaldimine (2), and *trans*-stilbene. Benzaldimine (2) was discovered to be an

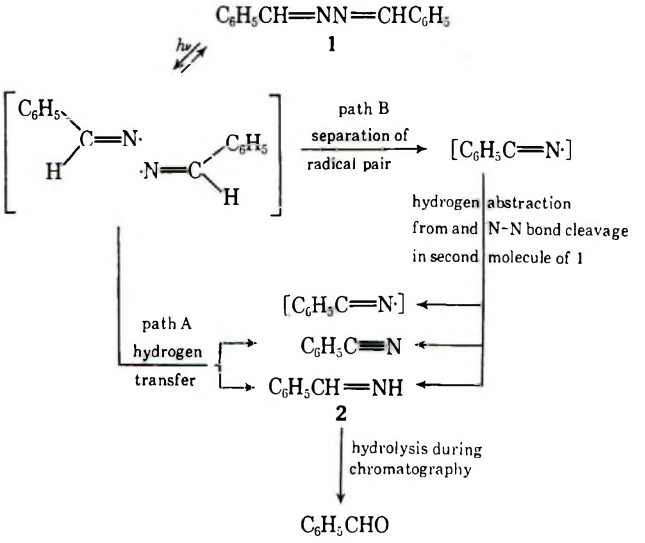


unstable photoproduct which hydrolyzed to benzaldehyde during chromatography. Two mechanisms were proposed at the time of the previous study in order to rationalize the apparently coupled benzonitrile–benzaldimine (2) formation (Scheme I); unfortunately, it was not feasible at that time with the evidence available to make a choice between these two mechanistic possibilities.

The fundamental difference between the two pathways under consideration (Scheme I) exists in the fact that path A postulates an intramolecular reaction mechanism with a hydrogen transfer which occurs within the solvent cage (a disproportionation within the solvent cage of the photochemically produced radical pair) while path B, in contrast, proposes an intermolecular reaction which requires the diffusion of the $C_6H_5CH{=}N$ radical through solution (*i.e.*, escape of the radical species from the solvent cage prior to further reaction) to react with a second molecule of benzalazine (1) in a hydrogen abstraction process. Accordingly, reaction *via* path A should be effectively insensitive to the presence of radical trapping agents in solution while a process such as that indicated by path B should show

SCHEME I

FORMATION OF BENZONITRILE AND BENZALDEHYDE FROM BENZALAZINE (1)



a change in reaction course in a solution where the $C_6H_5CH{=}N$ radical could be intercepted and could undergo reaction before reaching a benzalazine (1) molecule. As a basis for selection between these two possible pathways, a series of irradiations was undertaken in which alcohols with different hydrogen-donating abilities were used as reaction solvents; in addition, a number of reactions were also conducted in which decyl mercaptan was present in the reaction mixtures in various concentrations.

Results

The data given in Table I described the Vycor-filtered irradiations of benzalazine (1) with four dif-

(1) R. W. Binkley, *J. Org. Chem.*, **33**, 2311 (1968).

TABLE I

PHOTOCHEMICAL REACTIVITY OF BENZALAZINE (1)[a]

Run no.	Time, hr	% completion	Solvent	Trapping agent	% yield of products[b] Benzonitrile	Benzaldehyde
1	11	25	2-Methyl-2-propanol	None	46	44
2	12	26	Methanol[c]	None	40	46
3	10	26	Ethanol	None	40	44
4	9	27	2-Propanol	None	35	48
5	10	25	2-Propanol	2.00 mmol of benzhydrol	25	48
6	10	22	2-Propanol	4.00 mmol of benzhydrol	25	52

[a] All runs made with a Vycor filter which removes light of wavelength shorter than 210 mμ. In each run 1.00 mmol of benzalazine was irradiated. [b] The per cent yield of a product is calculated by dividing the millimoles of product by millimoles of reactant consumed and multiplying by 100. [c] Product yield is slightly greater then reported earlier (ref 1) due to improved isolation procedure.

ferent alcohols as reaction solvents and irradiations in which a fifth alcohol was present in the reaction mixtures. A clear decrease in the yield of benzonitrile is apparent as one proceeds from run 1 to run 6 in Table I. The yield of benzaldehyde, on the other hand, shows little change under these different reaction conditions. (Since each molecule of benzalazine is potentially capable of producing both a molecule of benzonitrile and one of benzaldehyde, a 100% yield of each of these products is theoretically possible in any reaction.)

In Table II are listed the results of the irradiation of benzalazine (1) in 2-propanol with various amounts of added decyl mercaptan. An inspection of this table reveals that the addition of the mercaptan causes an initial decrease of 10% in the benzonitrile yield when compared to an irradiation run in pure 2-propanol; however, once the nitrile yield reaches 25% it remains constant and is not further changed by addition of more mercaptan. The effect of added decyl mercaptan on the yield of benzaldehyde is noticeably different from its effect on the benzonitrile yield since the amount of benzaldehyde isolated progressively decreases as more mercaptan is added.

TABLE II

THE PHOTOCHEMICAL REACTIVITY OF BENZALAZINE (1) IN THE PRESENCE OF DECYL MERCAPTAN

Run	Mercaptan concn, mmol/l.	% completion	% yield of products Benzonitrile	Benzaldehyde
1	0.00	27	35	45
2	0.10	25	27	44
3	0.33	25	24	40
4	0.66	25	25	40
5	3.33	25	25	33

Discussion

As was described in the introductory portion of this paper, the two proposed mechanisms for conversion of benzalazine (1) into benzonitrile and benzaldimine differ in that one occurs entirely within the solvent cage (path A, Scheme I) and the other requires escape from this solvent shell (path B, Scheme I). A logical method for distinguishing between these two possibilities consists of conducting irradiations of 1 in the presence of a substance capable of intercepting the $C_6H_5CH{=}N$ radical and, thereby, stopping any intermolecular process involving this species; unfortunately, selection of a suitable trapping agent is not an easy task since common free radical traps such as 2,2-diphenyl-1-picrylhydrazyl, galvinoxyl, and I_2 used in normal free radical reactions absorb light and are photochemically decomposed.[2] Two different types of compounds were found, however, which were acceptable as trapping agents under the conditions of these irradiations.

It is important to note in connection with the interpretation of the experimental results from this work that the yield of benzonitrile and not benzaldehyde is taken as the critical indicator of the ability of a trapping agent to affect the photochemical conversion of benzalazine (1). The reason for this choice can be seen from a consideration of Scheme I. In the proposed intermolecular reaction mechanism for decomposition of 1 (path B, Scheme I), the mechanism representing the reaction pathway assumed to be sensitive to radical traps, benzonitrile can only arise *via* diffusion of the $C_6H_5CH{=}N$ radical (or other radical species) through solution to abstract a hydrogen atom from a molecule of benzalazine (1); in contrast, benzaldimine (2), the precursor of benzaldehyde, might arise by hydrogen abstraction of the $C_6H_5CH{=}N$ radical from the solvent or other hydrogen donor present. Therefore, if path B is operative, only the yield of benzonitrile is necessarily dependent upon diffusion through solution of a radical species capable of abstracting a hydrogen atom from benzalazine (1). In considering B as a pathway for understanding benzonitrile production, it is important to emphasize that a hydrogen transfer resulting in benzonitrile formation can occur from benzalazine (1) to radical species other than the $C_6H_5CH{=}N$ radical; therefore, in order for the hydrogen donors used in this work to be effective radical traps, they must react with a $C_6H_5CH{=}N$ radical or other radicals present to give stable molecules and new radical species, ones which are not capable of abstracting a hydrogen atom from benzalazine (1).

The first method used in attempting to intercept the $C_6H_5CH{=}N$ radical consisted of a series of irradiations using various alcohols and mixtures of alcohols as reaction solvents. Unlike ionic reactions of alcohols in which an oxygen–hydrogen bond is generally more readily broken than carbon–hydrogen bond, radical-induced hydrogen atom abstractions favor loss of a hydrogen atom attached to the alcohol carbon if such a hydrogen exists;[3,4] presumably this phenomenon is

(2) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1967, p 603.

(3) W. H. Urry, F. W. Stacey, E. S. Huyser, O. O. Juveland, *J. Amer. Chem. Soc.*, **76**, 450 (1954).

(4) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 219.

due to the ability of the hydroxyl group to participate in the stabilization of the radical center being formed.[5] With this fact in mind, methanol, ethanol, 2-propanol, and 2-methyl-2-propanol were closed as irradiation solvents. Of these four alcohols only 2-methyl-2-propanol has no hydrogen directly attached to an alcohol carbon; consequently, it among the four should be most resistent to free radical attack.[4,5] Methanol, ethanol, and 2-propanol, on the other hand, each have at least one hydrogen attached to the hydroxyl carbon and, therefore, are much more effective hydrogen donors.[6,7] Benzhydrol, which was added to two of the irradiations in 2-propanol, represents the most effective hydrogen donor of the alcohols used since in benzhydrol the radical center formed by hydrogen abstraction is not only adjacent to an OH group but it also stabilized by delocalization involving the benzene rings. Using these five alcohols as hydrogen donors provides at least three distinctly different levels of effectiveness in the hydrogen-donating ability of the reaction medium.

From an inspection of Table I it is clear that the yield of benzonitrile decreases as the hydrogen-donating ability of the solvent increases; however, even with benzhydrol present in a fourfold greater concentration than benzalazine (1), the yield of benzonitrile remains substantial. Comparing run 5 with run 6 of Table I reveals that a certain limiting value is apparently reached in the decrease of benzonitrile yield; thus, although addition of benzhydrol to an irradiation in 2-propanol reduces the benzonitrile formed, doubling the amount of benzhydrol present from 2.00 (run 5) to 4.00 mmol (run 6) does not change the yield further. It is necessary to be careful in placing too great an emphasis on reactions conducted in the presence of benzhydrol since it alone among the alcohols used absorbs light during irradiation. (In a control experiment benzhydrol also showed slight photochemical decomposition.) Although this fact does not necessarily negate the effectiveness of benzhydrol in these reactions, it does suggest that independent confirmation of these results by a second trapping agent would be valuable.

The second hydrogen donor selected as a trapping agent was decyl mercaptan. Mercaptans are well known for their ability to donate hydrogen atoms in radical abstraction reactions;[8] in addition, to this necessary qualification the problem of light absorption by the trapping agent is greatly reduced by the selection of this compound.

The results of irradiations of benzalazine (1) in the presence of various amounts of mercaptan are shown in Table II. A clear and significant parallel exists between the previously described irradiations using various alcohols and the results shown for the decyl mercaptan irradiations; namely, in each set of reactions the benzonitrile yield decreases until a limiting value is reached. This value is the same (25%) both in the presence of decyl mercaptan and in the presence of the most effective of the alcohols, benzhydrol.

On the basis of the considerations made thus far the following facts are clear. (a) The yield of benzonitrile in the photochemical reactions of benzalazine (1) is the best available indicator of the intervention of hydrogen donors in a potential intermolecular benzonitrile–benzaldimine (2) forming process. (b) The yield of benzonitrile decreases as the hydrogen-donating effectiveness of the medium increases; however, a limiting value exists beyond which further dimunition in yield does not occur. (c) The limiting value beyond which further reduction of yield of benzonitrile by hydrogen donors does not appear possible is the same whether benzohydrol of decyl mercaptan is used as the hydrogen-donating agent.

The first conclusion which reasonably can be drawn from these three facts is that since the majority of the benzonitrile (25%) arises *via* a pathway insensitive to effective hydrogen donors, the major reaction pathway is, logically, intramolecular. In terms of the mechanisms shown in Scheme I, therefore, the predominate mode of reaction can be represented by path A.

Although in path A a two-step sequence is proposed involving first the cleavage of a nitrogen–nitrogen bond and, second, the transfer of a hydrogen atom, there are no experimental facts requiring this particular timing. It is possible that these two processes could occur, at least in part, simultaneously. It is also conceivable that hydrogen transfer could precede nitrogen–nitrogen bond cleavage. The precise timing of these events is not known. The important factor is that the major process operative here occurs within the solvent cage and that path A (Scheme I) represents a reasonable conception for the mode of occurrence of such a reaction.

In addition to the portion of benzalazine (1) to benzaldimine (2) and benzonitrile reaction which gives evidence of being intramolecular, a substantial amount of this reaction is decidely influenced by the presence of solvents of different hydrogen-donating abilities and also by the addition of radical trapping agents to reaction mixture. The fact that a clear minimum in benzonitrile yield is reached beyond which further hydrogen donor addition has no effect argues well for the existence of an inter- as well as an intramolecular process. Clearly a reaction exists which is first hindered and then essentially stopped by the addition of hydrogen donors. If the benzonitrile yield were being decreased simply by an increase in the consumption of benzalazine (1) due to new reactions in the presence of effective hydrogen donors, the decrease in yield logically would have continued as greater amounts of hydrogen donors were added. Since such a continued decrease was not observed, the most reasonable explanation is that, in the absence of effective hydrogen donors, intermolecular reaction contributes to benzonitrile formation.

It is of interest to note two other studies on azine photochemistry. The vapor phase irradiation of both formaldazine[9] and acetaldazine[10] have been reported, although only the latter was studied in detail. Similar to benzalazine (1) irradiations, the major products from

(5) S. G. Cohen and H. M. Chao, *J. Amer. Chem. Soc.*, **90**, 165 (1968).

(6) 2-Propanol is probably the most widely used hydrogen atom source in photochemical reactions; in fact, it has been referred to in at least one text[7] as a "standard hydrogen donor."

(7) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1967, p 144.

(8) F. W. Stacey and J. F. Harris, Jr., in "Organic Reactions," Vol. 13, A. C. Cope, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, pp 166–167; (b) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 216; (c) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 314.

(9) J. F. Ogilvil, *Chem. Commun.*, 359 (1965).

(10) R. K. Brinton, *J. Amer. Chem. Soc.*, **77**, 842 (1955).

acetaldazine photolyses are acetonitrile and acetaldimine. In studying the mechanism of formation of these photoproducts[10] it was concluded that acetonitrile and acetaldimine were formed in these reactions in an intramolecular process. The differences in reaction medium and reactant structure make unprofitable at this time a comparison of the present work on benzalazine with that previously reported[10] for acetaldazine.

In summary, the results from study of the mechanism of the benzalazine (1) to benzonitrile–benzaldimine (2) conversion suggest that this reaction is capable of taking place *via* both intra- and intermolecular pathways. This conclusion is based primarily upon the fact that addition of radical trapping agents to the reaction mixtures decreases the amount of benzonitrile formation initially but a definite minimum is reached beyond which further addition of the trapping agents is ineffective.

Experimental Section[11]

Irradiation of Benzalazine (1) in 2-Methyl-2-propanol Using a Vycor Filter.—In a typical run 208.3 mg (1.000 mmol) of benzalazine[12] (1) in 300 ml of 2-methyl-2-propanol at 25.0° was irradiated with constant stirring for 11 hr using a 100-W Hanovia high-pressure quartz mercury-vapor lamp which had been lowered into a water-cooled quartz immersion well. A Vycor filter was introduced between this light source and the reaction mixture. Prepurified nitrogen was passed through the solution for 1 hr prior to irradiation and a slow stream of nitrogen was continued during photolysis.

After 11 hr, the solvent was removed by distillation *in vacuo* below 30° producing a distillate which was transparent in the uv spectrum and leaving a yellow solid. This solid was chromatographed on an 80 × 2.5 cm florisil column slurry packed in 1:9 ether–hexane; 20-ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane, 0.5 l. of 1:99 ether–hexane, 0.5 l. of 1:49 ether–hexane, 1.0 l. of 1:24 ether–hexane, 0.5 l. of 1:12 ether–hexane and 0.5 l. of 1:6 ether–hexane.

Fractions 90–122 yielded 156 mg of benzalazine (1) as yellow crystals, mp 92–94°. Fractions 123–133 afforded 11.7 mg (44%) of clear oil which gave the ir spectrum of benzaldehyde. Treatment of these fractions with semicarbazide hydrochloride according to the method of Shriner, Fusion, and Curtin[13] produced benzaldehyde semicarbazone, mp 219–222° (lit.[13] mp 222°). Fractions 134–170 gave 11.8 mg (46%) of a clear oil identical in ir and iv spectra with a known sample of benzonitrile. Control experiments concerned with the stability of the reactant and products under isolation conditions have been previously described.[1]

Irradiation of Benzalazine (1) in Methanol Using a Vycor Filter.—The procedure and material involved were the same as those described for the irradiation in 2-methyl-2-propanol. The only change was methanol was used as the reaction solvent.

Fractions 81–120 produced 160 mg of yellow solid, mp 86–89°, recrystallized from hexane to give 153 mg of benzalazine, mp 90–93°. Fractions 121–134 gave 12.7 mg of benzaldehyde, identified by ir spectroscopy. Fractions 135–154 afforded 10.7 mg of benzonitrile, identified by ir and uv spectroscopy.

Irradiation of Benzalazine (1) in Ethanol Using a Vycor Filter.—The procedure and materials used were the same as those described for the irradiation in 2-methyl-2-propanol except ethanol was used as the reaction solvent.

Fractions 89–119 gave 155 mg of benzalazine, mp 91°. Fractions 121–134 afforded 11.4 mg of benzaldehyde, identified by ir spectroscopy. Fractions 139–159 produced 10.7 mg of benzonitrile, identified by ir and uv spectroscopy.

Irradiation of Benzalazine (1) in 2-Propanol Using a Vycor Filter.—The procedure and substances used were the same as those described for the irradiation in 2-methyl-2-propanol. The only change was that 2-propanol was used as the solvent.

Fractions 91–125 afforded 162 mg of yellow solid, mp 80–85°, recrystallized from hexane to give 152 mg of benzalazine, mp 90–91°. Fractions 126–135 gave 13.0 mg of benzaldehyde, identified by ir spectroscopy. Fractions 140–160 gave 9.5 mg of benzonitrile, identified by ir and uv spectroscopy.

Irradiation of Benzalazine (1.00 Mmol) and Benzhydrol (2.00 Mmol) in 2-Propanol Using a Vycor Filter.—Benzalazine (208.3 mg, 1.000 mmol) and benzhydrol (358 mg, 2.00 mmol) in 300 ml of 2-propanol at 25.0° were irradiated in the normal manner. The isolation scheme was the same as that used in the irradiation run in 2-methyl-2-propanol.

Fractions 60–83 gave 320 mg of benzhydrol, mp 60–65°. Fractions 95–122 yielded 146 mg of benzalazine, mp 90–94°. Fractions 123–135 afforded 14.4 mg of benzaldehyde identified by ir spectroscopy. Fractions 136–154 gave 7.5 mg of benzonitrile, identified by ir and uv spectroscopy.

Irradiation of Benzalazine (1.00 Mmol) and Benzhydrol (4.00 Mmol) Using a Vycor Filter.—The procedure and materials used were the same as in the above irradiation with added benzhydrol except that the benzhydrol concentration was doubled. The isolation procedure and results were essentially the same.

Irradiation of Benzalazine (1.00 Mmol) and Decyl Mercaptan (1.00 Mmol) in 2-Propanol.—Benzalazine (208.3 mg, 1.00 mmol) and decyl mercaptan (174 mg, 1.00 mmol) in 300 ml of 2-propanol at 25.0° were irradiated in the usual manner. The isolation procedure was the same as that used in the irradiation run in 2-methyl-2-propanol.

Fractions 22–40 afforded 144 mg of decyl mercaptan, identified by ir spectroscopy. Fractions 90–121 gave 167 mg of yellow solid, mp 85–89°, recrystallized from hexane to give 146 mg of benzalazine, mp 89–91°. Fractions 122–135 produced 14.1 mg of benzaldehyde, identified by ir spectroscopy. Fractions 136–160 produced 7.5 mg of benzonitrile, identified by ir and uv spectroscopy.

Irradiation of Benzalazine (1.00 Mmol) and Decyl Mercaptan (2.00 Mmol) in 2-Propanol.—The procedure and materials used were the same as in the above irradiation with added decyl mercaptan except that the mercaptan concentration was doubled. The isolation procedure and results were essentially the same.

Irradiation of Benzalazine (1.000 Mmol) and Decyl Mercaptan (10.0 Mmol) in 2-Propanol.—The procedure and materials used were the same as in the above irradiation with added decyl mercaptan except that the mercaptan concentration was doubled. The isolation procedure and results were essentially the same.

Registry No.—1, 588-68-1; 2, 16118-22-2; benzonitrile, 100-47-0.

Acknowledgment.—Appreciation is gratefully expressed to the Research Corp. for support of this work.

(11) All melting points were taken on a Fisher-Johns block and are corrected.

(12) T. Curtius and R. Jay, *J. Prakt. Chem.*, **39**, 45 (1889).

(13) R. L. Shriner, R. C. Fusion, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1956, pp 218 and 283.

The Alkaline Hydrolysis of Yellow Azomethine Dyes

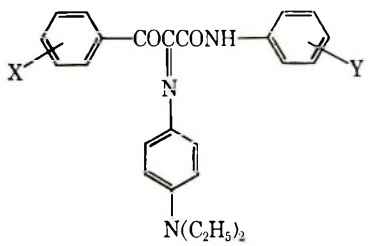
KAZUYA SANO

Ashigara Research Laboratories, Fuji Photo Film Co., Ltd., Minamiashigara, Kanagawa, Japan

Received October 1, 1968

The reaction of substituted 1-{N-[*p*-(diethylamino)phenyl]-2-phenylglyoxylimidoyl}formanilides (I) with sodium hydroxide in 50 vol % aqueous acetone was studied. The decomposition is first order in dye but not in hydroxide unless dilute. Instead, its reciprocal gives a straight line when plotted against $1/[OH^-]$. This, together with other evidence such as substituent effects, indicates that the decomposition is preceded by rapid establishment of an equilibrium. The equilibrium constant depends largely on the substituent in the anilide ring, whereas the rate of decomposition appears to be affected only by the substituent in the benzoyl group. These observations are consistent with the following two mechanisms. One proceeds through an anilide anion which attacks an adjacent water molecule to form a cyclic transition state that breaks down with the formation of the substituted benzoic acid. The other mechanism involves the rate-determining attack of hydroxide ion at the keto carbon atom of the undissociated substrate.

The fugitivity of color-photographic image dyes has long attracted the interest of photographic chemists. Efforts have been made to clarify the aspects of the reaction of these dyes in the bulk phase.[1] Recently, De Hoffmann and Bruylants[2] have made a kinetic study of the acid hydrolysis of a series of 1-{N-[*p*-(dimethylamino)phenyl]-2-phenylglyoxylimidoyl}formanilides, which are widely used as image dyes in color photography. They tried the alkaline hydrolysis too, but "encountered a very serious difficulty."[2] Our preliminary study[3] with analogous 1-{N-[*p*-(diethylamino)-phenyl]-2-phenylglyoxylimidoyl}formanilides I has suggested a remarkable difference of the aspects of these two reactions, and this has conducted us to a more detailed study of the alkaline hydrolysis of I.



I

Results and Discussion

All the measurements were carried out in 50 vol % aqueous acetone unless otherwise specified. The logarithm of the absorbance of the dye solution decreases linearly with time, and the slope is independent of the initial dye concentration, indicating that the reaction is first order in dye. It is not first order in hydroxide, however, and at higher alkali concentration the rate rapidly tends to converge to a limiting value specific to each dye. The relationship is illustrated in Figure 1.

Table I lists values of the rate constants, $k = -[(1/A)(dA/dt)]$, where A is the absorbance at the wavelength of the maximum visible absorption (λ_{max}) of the original dye solution and t is time in seconds, at a sufficiently low concentration of sodium hydroxide (0.026 M) where the rate is almost a linear function of the hydroxide concentration. The observed rate appears to be affected neither by substituents in the anilide ring nor by modification of the *p*-diethylaminophenylimino moiety but by substituents in the benzoyl group with a Hammett ρ value[4] exceeding 3. This suggests that the rate-determining reaction occurs at a site close to the benzoyl group, and hence one may reasonably expect the hydrolytic cleavage of the benzoyl–iminomethyl bond. Indeed, *m*-nitrobenzoic acid was the sole isolable product of the hydrolysis of the corresponding dye. Similarly, aqueous sodium hydroxide converted 2-benzoyl-2-chloroacetanilide into benzoic acid and 2-chloroacetanilide. It should be noted that the acid hydrolysis of these dyes which results in the formation of α,β-diketonanilides is markedly retarded by introduction of a 2-methyl group in the 4-diethylaminophenyl moiety,[5] whereas it is

TABLE I

APPARENT RATES OF FADING OF I AT 25.0°, $[OH^-] = 0.026\ M$

Compd no.	X	Y	Log *k*
1	H	H	−3.31
2	H	*p*-OCH_3	−3.20
3	H	*p*-Cl	−3.28
4	H	*m*-CF_3	−3.43
5	H	*m*-Br	−3.32
6	H	*o*-OCH_3	−3.32
7	H	2-CH_3-6-OCH_3	−3.22
8	H	2,6-$(CH_3)_2$	−3.23
9	*p*-NH_2	H	*a*
10	*p*-OCH_3	H	−4.23
11	*p*-CH_3	H	−3.86
12	*m*-CH_3	H	−3.34
13	*p*-F	H	−3.30
14	*p*-Cl	H	−1.0
15	*m*-NO_2	H	*b*
16	*o*-OCH_3	H	−3.69
17	*o*-CH_3	H	−3.31
18	*o*-F	H	−0.4
19	*o*-Cl	H	0
20	2,4,6-$(CH_3)_3$	H	*a*
21	*c*	H	−4.43
22[d]	H	H	−3.17
23[e]	H	H	−3.19

[a] Too slow reaction. [b] Too rapid reaction. [c] $(CH_3)_3CCO$– instead of X–C_6H_4CO–. [d] –$N(C_2H_5)(CH_2CH_2OH)$ instead of –$N(C_2H_5)_2$). [e] –C_6H_3(2-CH_3)[4-$N(C_2H_5)_2$] instead of –C_6H_4·[*p*-$N(C_2H_5)_2$].

(1) *E.g.*, R. L. Reeves and L. K. J. Tong, *J. Amer. Chem. Soc.*, **84**, 2050 (1962).

(2) E. De Hoffmann and A. Bruylants, *Bull. Soc. Chim. Belg.*, **75**, 91 (1966).

(3) K. Sano, *Tetrahedron Lett.*, 3203 (1968).

(4) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 184.

(5) Our unpublished work.

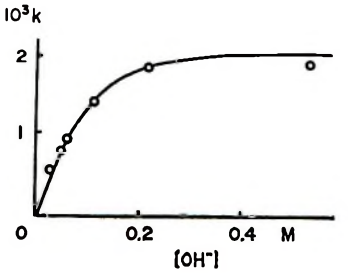


Figure 1.—Fading rate of **1** at various concentrations of sodium hydroxide at 25.0°.

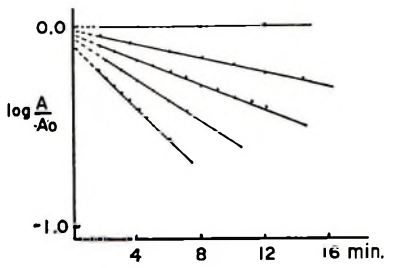


Figure 2.—Plot of log A for **23** against time at various concentrations of sodium hydroxide at 25.0°. The absorbances were measured at 455 mμ.

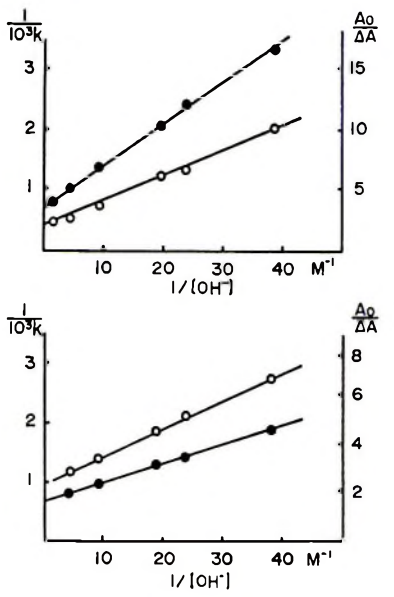


Figure 3.—Fading rate and $A_0/\Delta A$ of **1** (upper) and **4** (lower) at 25.0° as functions of $1/[OH^-]$: ○, $1/k$; ●, $A_0/\Delta A$. In both cases the absorbances were measured at 440 mμ.

affected only slightly by substituents in the benzoyl and anilide rings.[2]

The dye extinction extrapolated to $t = 0$ does not assume a constant value but decreases with increasing alkali concentration, and this decrease again tends to converge to a value specific to each dye (Figure 2). This decrease appears to parallel the deviation of the rate from linearity, and indeed the reciprocal of the fractional decrease ($A_0/\Delta A$, where $A_0 = A_{[OH^-]=0,t=0}$ and $\Delta A = A_0 - A_{t=0}$) and that of k gives two straight lines of an identical slope–intercept ratio when plotted against $1/[OH^-]$ (Figure 3).

The initial dropping of the extinction is too rapid to be followed. The decrease of the extinction extrapolated to $1/[OH^-] = 0$ varies within the range of 6–40% of the original extinction A_0 (at the λ_{max} of the original

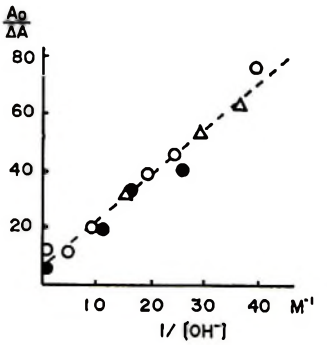


Figure 4.—Effect of solvent composition on $A_0/\Delta A$ of **9** at 25.0°; acetone–water ratio; ○, 2.0; △, 1.0; ●, 0.5. The absorbances were measured at 430 mμ.

dye solution), depending on the dye structure. This range and the decrease itself is too large to be accounted for in terms of the change of the electrolyte concentration. Variation of acetone–water ratio from 0.5 to 2.0 brought about a considerable change of the fading rate of **9**, but the ratio $A_0/\Delta A$ remained unchanged as illustrated in Figure 4. Obviously water is not playing an important role in the equilibration step.

The ultraviolet and visible absorption spectra of the dye solutions in the presence and absence of sodium hydroxide differ slightly. Compound **9** for example shows peaks at 341 mμ (ε 26,600) and 437 (19,600) in 1:1 (in volume) ethanol–water, and at 340 (24,700) and 434 (14,200) in 1:1 ethanol–1 N aqueous sodium hydroxide mixture. Although the difference is small when we consider the possible marked difference of the electronic states, the occurrence of a second species is implied. Rapid equilibration prior to hydrolysis was observed in the acid hydrolysis of analogous dyes too, but in this case the protonated species was colorless.[2]

SCHEME I

$$\text{dye} \underset{\text{fast}}{\overset{k_1[OH^-]}{\underset{k_2}{\rightleftharpoons}}} \text{dye}' \xrightarrow[\text{slow}]{k_3} \text{product}$$

$$\frac{1}{k} = \frac{1}{k_3} + \frac{k_2}{k_1 k_3 [OH^-]} \quad (1)^6$$

$$\frac{A_0}{\Delta A} = \frac{\epsilon_1}{\epsilon_1 - \epsilon_2}\left(1 + \frac{k_2}{k_1[OH^-]}\right) \quad (2)^6$$

(6) These equations were obtained in the following way.

$$k = -\frac{1}{A}\frac{dA}{dt} = \frac{1}{\epsilon_1[\text{dye}] + \epsilon_2[\text{dye}']}\frac{d(\epsilon_1[\text{dye}] + \epsilon_2[\text{dye}'])}{dt}$$

Since $[\text{dye}'] \simeq k_1[OH^-][\text{dye}]/k_2$, and $[OH^-]$ is in large excess

$$k = -\frac{1}{[\text{dye}]}\frac{d[\text{dye}]}{dt}$$

According to Scheme I

$$-\frac{d([\text{dye}] + [\text{dye}'])}{dt} = k_3[\text{dye}]$$

Substitution of $[\text{dye}']$ by $k_1[OH^-][\text{dye}]/k_2$ gives eq 1. Equation 3 is obtained from

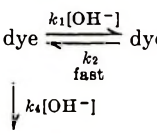
$$-\frac{d([\text{dye}] + [\text{dye}'])}{dt} = k_4[OH^-][\text{dye}]$$

in an analogous way. At the extrapolated (hypothetical) zero time when the equilibration is complete but no decomposition has started

$$\frac{A_0}{\Delta A} = \frac{\epsilon_1([\text{dye}] + [\text{dye}'])}{\epsilon_1([\text{dye}] + [\text{dye}']) - (\epsilon_1[\text{dye}] + \epsilon_2[\text{dye}])} = \frac{\epsilon_1[\text{dye}'](1 + k_2/k_1[OH^-])}{\epsilon_1[\text{dye}'] - \epsilon_2[\text{dye}']}$$

which is identical with eq 2.

SCHEME II



$$\frac{1}{k} = \frac{k_1}{k_2 k_4} + \frac{1}{k_4[OH^-]} \qquad (3)^6$$

$$\frac{A_0}{\Delta A} = \frac{\epsilon_1}{\epsilon_1 - \epsilon_2}\left(1 + \frac{k_2}{k_1[OH^-]}\right) \quad \text{(same as eq 2)}$$

TABLE II

RATE AND EQUILIBRIUM CONSTANTS AT 25.0°, CALCULATED ON SCHEMES I AND II

Compd no.	$10^3 k_3$, sec^{-1}	$10^3 k_4$, sec^{-1}	k_1/k_2[a]
1	3.0	23	7.5
2	4.3	24	5.4
3	1.7	28	16
4	1.0	22	21
5	1.3	29	22
6	4.5	20	4.5
7	2.5	31	13
8	2.6	28	11
9	b	b	2.4[c]
10	0.43	2.6	6.0
11	1.1	6.1	5.5
12	2.5	21	8.6
13	5.0	49	9.7
16	2.0	8.5	4.2
17	3.6	22	6.2
20	b	b	16[c]
21	0.38	2.1	5.3
22	3.2	33	10
23	5.0	28	5.6

[a] Determined from $1/k$ *vs.* $1/[OH^-]$ curves unless otherwise indicated. The two schemes lead to the identical k_1/k_2 values. [b] The reaction was too slow for the rate measurement. [c] Determined from $A_0/\Delta A$ *vs.* $1/[OH^-]$ curves.

The features discussed so far lead to the following two possibilities, namely a consecutive (Scheme I) and a parallel (Scheme II) mechanism.

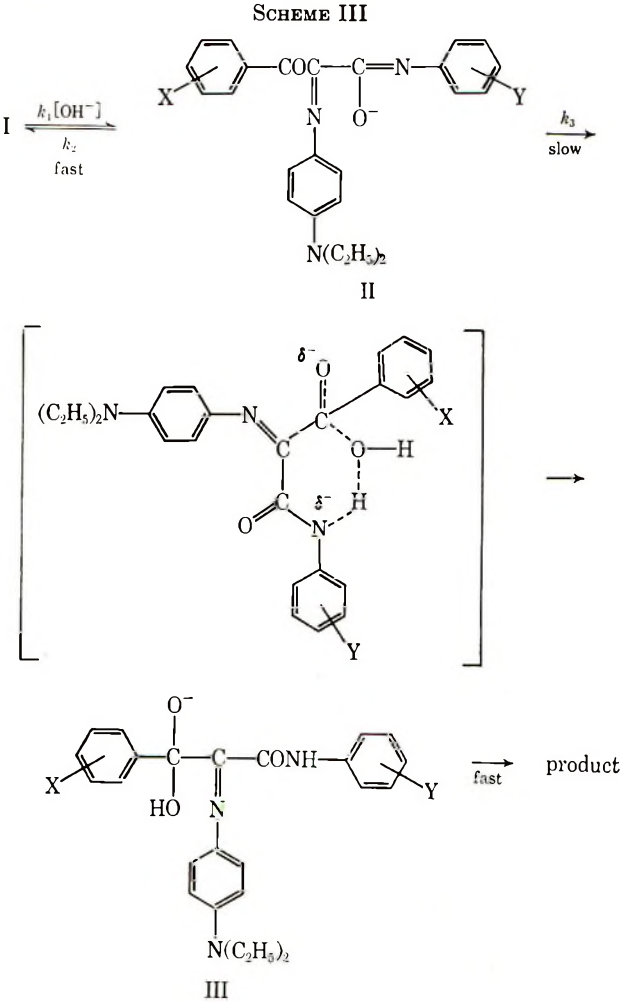
Here, ϵ_1 and ϵ_2 denote the molar absorptivities of dye and dye′ at the λ_{max} of the original dye solution, respectively. The expression "product" does not necessarily mean the final decomposition product.

In Table II are summarized the rate and equilibrium constants calculated on these schemes. Most of the equilibrium constants have been calculated from $1/k$ curves and not from $A_0/\Delta A$ curves since the latter seemed to be subject to greater experimental error at low hydroxide concentration where ΔA's are considerably smaller.

The data cited in this table can be interpreted by either of the two schemes. The equilibrium constant k_1/k_2 is more susceptible to Y substituent effect than to X substituent effect and to modification of the *p*-diethylaminophenyl moiety. In addition, the compounds with sterically crowded keto groups such as **16**, **17**, and **21** (with the exception of **20**) exhibit no extraordinary k_1/k_2 value. These facts indicate that the equilibration reaction is not taking place in the vicinity of the keto group in contrast to the decomposition reaction, and hence that dye′ is formed by dissociation of the anilide hydrogen.

Thus, Scheme I proposes a mechanism involving the attack of the anilide anion on an adjacent water molecule with simultaneous attack by oxygen on the carbonyl group which leads to the fission of the benzoyliminomethyl bond (Scheme III).

SCHEME III

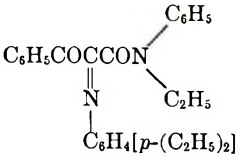


Since k_3 involves proton transfer to anilide anion one may reasonably expect a good Brønsted relation between k_3 and k_2/k_1.[7] This is in fact observed (Figure 5) and $\beta = 0.8$ suggesting that the protonation is nearly complete at the transition state.

The rate constant k_3 also involves the attack by a partially formed hydroxide ion on the carbonyl group. Accordingly the Hammett ρ value is expected to be positive with respect to X whereas it should be negative with respect to Y. Figure 6 shows reasonable ρ values of +3.0 and −0.9, respectively.

At the base concentration cited in Table I, k_3 was approximately $k_1k_3[OH^-]/k_2$. Since k_3 tends to decrease as k_1/k_2 increases, the seemingly small effect of Y on k must have been the consequence of this compensation effect.

The N-ethyl derivative **24**, which is incapable of forming an anion, showed no initial rapid dropping of



24

(7) J. N. Brønsted and K. J. Pedersen, *Z. Phys. Chem.*, **108**, 185 (1924).

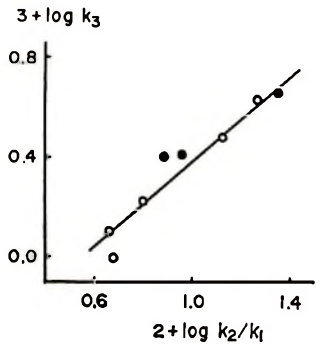


Figure 5.—The Brønsted relationship between k_3 and k_2/k_1, temperature = 25.0°. ○, 1–5; ●, 6–8.

extinction. The remarkable resistance of this compound toward hydrolysis is consistent with the above-mentioned reaction pathway.

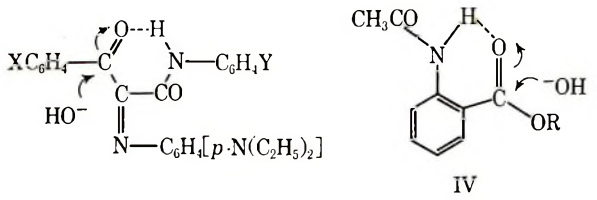
According to Scheme II, k_4 is correlated with X by a large Hammett ρ value of +3.6 (Figure 7). This suggests the rate-determining attack of hydroxide ion on the carbonyl carbon which results in the formation of the intermediate III and in the subsequent cleavage of the benzoyl–iminomethyl bond.

$$\text{I} \underset{k_2}{\overset{k_1[OH^-]}{\rightleftharpoons}} \text{II}$$

$$\downarrow k_4[OH^-] \text{ (slow)}$$

$$[\text{III}] \xrightarrow[\text{fast}]{} \text{product}$$

The extremely slow reaction of **24** can be interpreted in terms of the absence of the acceleration by intramolecular hydrogen bonding. At present we cannot decide which mechanism is really operating. An alkaline hydrolysis study of *o*-acetaminobenzoic ester IV, which is now under progress, might offer some in-



IV

formation on the possibility of the latter mechanism. It should be noted that the substrates can exist in conformational isomers at the imino function. Since we have no knowledge of the geometry of the species undergoing hydrolysis, we may have been discussing the composite constants of the two possible isomers.

It is surprising that 1-{N-[*p*-(diethylamino)phenyl]-2-phenylglyoxylimidoyl}formyl group is so strongly electron withdrawing despite that the conjugation system is expected to increase the electron density of the central carbon atom[8] or that of the keto oxygen.[9] The large values of k_1/k_2 of 2,6-disubstituted anilides are worth noting. The 2′,6′-disubstituted benzoylacetanilides have been found to have smaller acid dissociation constants of the active methylene group than the

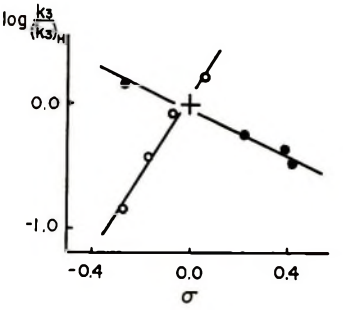


Figure 6.—The Hammett plots of k_3 against X (○) and Y (●), temperature = 25.0°.

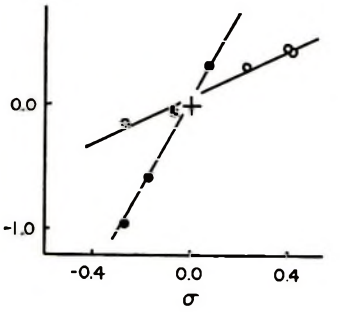


Figure 7.—The Hammett plots of k_1/k_2 (○) and k_4 (●) against Y and X, respectively, temperature = 25.0°; abscissa, log k_1/k_2 − log $(k_1/k_2)_H$ and log $k_4/(k_4)_H$.

corresponding 2′,4′-disubstituted ones.[10] Presumably the liberation of the anilide hydrogen relieves the steric strain.

Experimental Section

Rate Measurement.—Solutions of 10^{-4} *M* dye in acetone and 1.0, 0.40, 0.20, 0.10, 0.075 and 0.05 *N* sodium hydroxide in distilled water were prepared. One volume of the dye solution was mixed with one volume of fresh aqueous sodium hydroxide to make 1.92 volumes, and the absorbance was followed in an optical cell thermostated by means of circulating water, using Hitachi EPS-II spectrophotometer.

Hydrolysis of 15.—A 1-g sample of **15** was dissolved in 20 ml of acetone, and to the warmed solution was added 4 ml of 5 *N* aqueous sodium hydroxide. After the solution had become colorless, 12 ml of 1 *N* hydrochloric acid was added. *m*-Nitrobenzoic acid that precipitated was collected, washed with water, and recrystallized from methanol. Identification was made by infrared spectrometry.

Hydrolysis of 2-Benzoyl-2-chloroacetanilide.—A 1-g sample of 2-benzoyl-2-chloroacetanilide was dissolved in 20 ml of 1 *N* sodium hydroxide and was heated on a steam bath for 10 min, during which period 2-chloroacetanilide began to separate. The precipitates were collected, recrystallized from aqueous methanol, and subjected to mixture melting point measurement. The alkaline filtrate was acidified with concentrated hydrochloric acid to separate benzoic acid, which was identified by infrared spectrometry.

Materials. Dyes. General Procedure A.—In a 1-l. three-necked flask equipped with a stirrer was added a solution of 0.04 mol of *p*-amino-N,N-dialkylaniline and 0.02 mol of 2-acylacetanylide dissolved in 300 ml of 2% aqueous sodium hydroxide. To the stirred mixture was added a solution of 0.01 mol of ammonium persulfate in 200 ml of water during 1 hr.

(8) J. J. Jennen, *Chim. Ind.*, **86**, 400 (1961).

(9) G. H. Brown, J. Figueras, R. J. Gledhill, C. J. Kibler, F. C. McCrossen, S. M. Parmerter, P. W. Vittum, and A. Weissberger, *J. Amer. Chem. Soc.*, **79**, 2919 (1957).

(10) Private communication from Y. Oishi of our laboratory, who reported the p*K* values of 10.16, 9.53, 9.38, and 8.25 for 2′,6′-dimethyl-, 2′,4′-dimethyl, 2′,6′-dichloro-, and 2′,4′-dichloro-2-benzoylacetanilide, respectively, in 60 vol % aqueous ethanol at 25°.

Stirring was continued for another 30 minutes and the precipitates were collected, dried, and recrystallized from ethanol or other suitable solvents.

General Procedure B.—Some of the dyes were prepared by condensation of the acylacetanylide with *p*-nitroso-N,N-dialkylaniline in the same fashion as the procedure of De Hoffmann, *et al.*[11] This procedure was suitable for the components that were unreactive toward oxidized *p*-amino-N,N-dialkylaniline although very cautious purification of the product was necessary in order to avoid contamination with azomethine N-oxide.

Compound **24** did not crystallize from the reaction mixture and was purified by repeated thin layer chromatography on silica gel using 1:4 methanol–benzene mixture. The acetone extract was directly used for the measurement.

Table III lists the melting points and nitrogen analyses of the dyes. Further structural confirmation was given by comparison of the infrared spectra with that of authentic **23** reported by Brown, *et al.*[9]

Most of the benzoylacetanilides were already reported by these authors, and unreported members were prepared in an analogous way.

Registry No.—**1**, 4754-85-2; **2**, 19650-46-5; **3**, 19650-47-6; **4**, 19755-72-7; **5**, 19779-37-4; **6**, 19755-73-8; **7**, 19755-74-9; **8**, 19755-79-4; **9**, 19755-80-7; **10**, 19650-48-7; **11**, 19755-82-9; **12**, 19755-83-0; **13**, 19755-84-1; **14**, 19755-85-2; **15**, 19779-38-5; **16**, 19650-49-8; **17**, 19755-87-4; **18**, 19755-88-5; **19**, 19755-89-6; **20**, 19759-05-8; **21**, 19759-06-9; **22**, 4754-88-5.

(11) E. De Hoffmann and A. Bruylants, *Bull. Soc. Chim. Belg.*, **74**, 609 (1965).

TABLE III
MELTING POINTS, SYNTHETIC PROCEDURES, AND ANALYSES OF DYES

Compd no.	Mp, °C	Synthetic procedure	N analysis, % Calcd	Found
1	209	A	10.52	10.38
2	162	A	9.78	10.07
3	192	A	9.66	9.72
4	118	A	8.99	9.14
5	147	A	8.79	8.63
6	149	A	9.78	9.72
7	157	B	9.48	9.51
8	183	B	9.84	9.82
9	203	A	13.52	13.90
10	131	A	9.78	9.53
11	162	A	10.16	10.09
12	182	A	10.16	10.03
13	220	A	10.06	10.17
14	114	A	9.66	9.43
15	139	A	12.61	12.27
16	144	A	9.74	9.79
17	171	A	10.16	10.10
18	207	A	10.06	10.16
19	182	A	9.66	9.55
20	180	B	9.44	9.52
21	119	A	11.07	11.03
22	155	A	10.11	10.19

Acknowledgment.—The author wishes to thank Professor Y. Yukawa and Dr. Victor P. Vitullo for helpful discussions and comments. The author also extends his gratitude to Dr. K. Hirayama for advice in preparing the manuscript.

The Conformational Preferences of Sulfur and Oxygen in Hemithioketals[1]

MATHIAS P. MERTES,[2] HYUK-KOO LEE, AND RICHARD L. SCHOWEN[2]

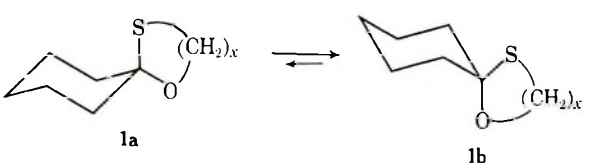
The Department of Medicinal Chemistry, School of Pharmacy, and Department of Chemistry, The University of Kansas, Lawrence, Kansas 66044

Received October 21, 1968

Both second-order catalytic rate constants and isomer ratios at equilibrium for boron trifluoride catalyzed interconversion of the equatorial oxygen and sulfur ethylene hemithioketals of 3,3,5-trimethylcyclohexanone are independent of catalyst concentration in the range of 0.016–0.095 *M* BF_3. Thus no catalyst complex with the hemithioketal forms to a significant extent and the equilibrium constant of 0.285 ± 0.005 favoring the equatorial oxygen species is a true measure of conformational preference in the hemithioketal.

The early conformational analysis studies of divalent sulfur attached to cyclohexyl systems were performed by Chiurdoglu and coworkers.[3] Subsequent studies by Eliel and coworkers,[4,5] using nuclear magnetic resonance suggested the opposite; values of 0.8 kcal/mol for SC_6H_5, 0.7 kcal/mol for SCH_3, and 0.9 kcal/mol for SH were found. Thus, the authors concluded that the nature of the substituent on sulfur (C_6H_5, CH_3, or H) appeared to have little effect on its conformational preference, which was for the equatorial position. Earlier studies on oxygen derivatives had given similar results.

A comparison of the conformational preferences of oxygen ($-\Delta G_{av} \sim 0.6$ kcal/mol) and sulfur ($-\Delta G_{av} \sim 0.8$ kcal/mol) derivatives leads to the prediction that sulfur should prefer the equatorial position, over oxygen, by about 200 cal/mol. On this basis, spiro systems containing oxygen and sulfur geminally bound to a cyclohexyl ring (**1**) should consist, at equilibrium, of a greater proportion of the sulfur equatorial isomer **1b**.



1a **1b**

(1) This research was supported by the University of Kansas Research Fund. Further details may be found in M.S. Thesis in Medicinal Chemistry of H.-K. Lee, The University of Kansas, 1967.

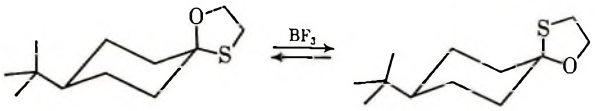
(2) Holders of Research Career Development Awards of the National Cancer Institute (M.P.M.) 1K3-CA-10,739 and the National Institute of General Medical Sciences (R.L.S.) 1-K4-GM-10,913.

(3) G. Chiurdoglu, J. Reisse, and M. VanderStichelen Rogier, *Chem. Ind.* (London), 1874 (1961). Interpretation of the infrared and Raman spectra of cyclohexanethiol resulted in the assignment of a conformational free-energy difference ($-\Delta G = G_{ax} - G_{eq}$) of −0.4 kcal/mole to the SH group, a remarkable preference for the axial position.

(4) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(5) (a) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962); (b) E. L. Eliel and B. P. Thill, *Chem. Ind.* (London), 88 (1963).

This assumes no strain or compression of the cyclohexyl ring imposed by the oxythio ring. Conformational equilibration of such compounds with five-membered heterocyclic rings ($x = 2$ in **1**) has, in fact, shown oxygen to be preferred over sulfur in the equatorial position. Eliel and coworkers[6] equilibrated the ethylene hemithioketals of 4-*t*-butylcyclohexanone (**2**) and found 58% of **2b** at equilibrium ($-\Delta G = 0.4$ kcal/mol for sulfur if $-\Delta G \cong 0.6$ kcal/mol is assumed for oxygen), if a catalytic quantity of boron trifluoride etherate was employed, whereas equal amounts of **2a** and **2b** resulted

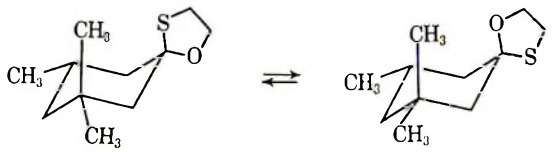


2a **2b**

from use of excess catalyst. Additional studies[7] with boron trifluoride etherate catalyst at 34° in ether revealed the equilibrium mixtures of the ethylene hemithioketals of 3-methylcyclohexanone, 3,3,3-trimethylcyclohexanone, and 3-*t*-butylcyclohexanone to consist of 76–79% of the equatorial oxygen isomer ($-\Delta G \cong -0.2$ kcal/mole for sulfur relative to 0.6 kcal/mole for oxygen). At 80° (*p*-toluenesulfonic acid catalyst in benzene), the equatorial oxygen isomer constituted 80% of the equilibrium mixture for these compounds.

In contrast to the above results, the trimethylene hemithioketal of 4-*t*-butylcyclohexanone yields, after equilibration, with boron trifluoride etherate catalyst at 34° in ether, 55% of the equatorial sulfur isomer[8] ($-\Delta G \cong 0.8$ kcal/mole for sulfur relative to 0.6 for oxygen), comparing favorably with the conformational free-energy values for sulfur derived from nmr studies. The conclusion was drawn that the six-membered ring of the trimethylene hemithioketal produced a strain-free system, which reflected the true conformational free-energy differences for sulfur and oxygen. The five-membered ring of the ethylene hemithioketal, however, bends the axial ring member away from the interfering 3-axial substituents; the outward displacement of the sulfur exceeds that for the oxygen, for the same angle deformation, because the carbon–sulfur bond is longer ("leverage effect[8]"). Thus the sulfur comes relatively to prefer the axial position.

It is nevertheless possible that the apparent preference of oxygen for the equatorial position in the ethylene hemithioketals might result from extensive complexation with the catalyst.[9] To establish whether this is so, we decided to examine the kinetics and apparent equilibrium isomer composition of the ethylene hemithioketals of 3,3,5-trimethylcyclohexanone (**3**) in ether, as a function of catalyst concentration.



3a **3b**

(6) (a) E. L. Eliel and L. A. Pilato, *Tetrahedron Letters*, 103 (1962); (b) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Am. Chem. Soc.*, **84**, 2377 (1962).

(7) M. P. Mertes, *J. Org. Chem.*, **28**, 2320 (1963).

(8) (a) E. L. Eliel, E. W. Della, and M. Rogić, *ibid.*, **30**, 855 (1965); (b) a similar argument for the oxirane ring has been made by R. G. Carlson and N. S. Behn, *Chem. Commun.*, 339 (1968).

(9) (a) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957); (b) E. L. Eliel and M. Renick, *ibid.*, **82**, 1367 (1960).

Results

Kinetics.—The conversion of pure **3a** into the equilibrium mixture of **3a** and **3b** in ether solution at 34.6°, as followed by glpc analysis, proceeded according to a simple first-order kinetic law within any given run, yielding the rate constants shown in Table I for various

TABLE I
RATE AND EQUILIBRIUM CONSTANTS FOR CONFORMATIONAL EQUILIBRATION OF 0.159 *M* **3** IN ETHER AT 34.6 ± 0.1°, CATALYZED BY BORON TRIFLUORIDE

$[BF_3]$, *M*	[3]/$[BF_3]$	k_{obsd}, hr^{-1}	K_{app}
0.016	10.0	0.063	0.288
0.032	5.0	0.139	0.276
0.048	3.3	0.198	0.284
0.064	2.5	0.246	0.289
0.079	2.0	0.337	0.291
0.095	1.7	0.347	0.290

concentrations of boron trifluoride catalyst. These data are accurately described by eq 1, showing the reactions to be first order in catalyst throughout this concentration range. The small intercept presumably corresponds to an uncatalyzed reaction or to catalysis by adventitious impurities.

$$k_{obsd}\ (sec^{-1}) = (4.2 \pm 3.9) \times 10^{-6} + (1.03 \pm 0.06) \times 10^{-3}[BF_3] \quad (1)$$

Equilibrium.—The apparent conformational equilibrium constant, $K_{app} = [\mathbf{3b}/\mathbf{3a}]$, is shown in Table I as a function of boron trifluoride concentration. A least-squares fit of these data (as a linear function) yields eq 2, showing K_{app} to be, within experimental error, independent of catalyst concentration. The true equilibrium constant is thus $K_c = 0.285 \pm 0.005$.

$$K_{app} = (0.285 \pm 0.005) + (0.001 \pm 0.008)[BF_3] \quad (2)$$

From this value, which is equal to the ratio of forward and reverse rate constants and the catalytic constant (eq 1) for boron trifluoride, which equals their sum, we calculate $k_{for} = (2.3 \pm 0.8) \times 10^{-4}\ M^{-1}\ sec^{-1}$ and $k_{rev} = (8.0 \pm 0.5) \times 10^{-4}\ M^{-1}\ sec^{-1}$.

Discussion

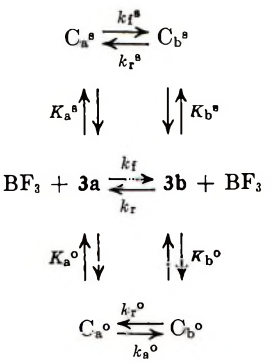
It is in principle possible that either **3a** or **3b** could complex with boron trifluoride and that the latter could bind either to sulfur or to oxygen. All of these possibilities may be considered by defining four complex-formation constants K_a^o, K_a^s, K_b^o and K_b^s where the subscript identifies the isomer (**3a** or **3b**) and the superscript the binding site. The apparent equilibrium constant is then given, in the most general form, by eq 3. Our observation is that K_{app} does not change as the boron trifluoride concentration is varied. This means that either (a) all the complexation constants in eq 3 are small enough to contribute negligibly to K_{app} (*i.e.*, no complexes form under these conditions), (b) all the complexation constants are equal in eq 3 (*i.e.*, all com-

$$K_{app} = K_c \frac{1 + K_b^o[BF_3] + K_b^o[BF_3]}{1 + K_a^s[BF_3] + K_a^s[BF_3]} \quad (3)$$

plexes are of equal stability), or (c) some complexation constants may be negligible and others equal (*e.g.*, K_a^s and K_b^s might be negligible if the Lewis acid prefers oxygen to sulfur, while K_a° and K_b° might be equal if the presence of the BF_3 causes no change in the conformational preference of oxygen).

The simple first-order dependence of the rate of equilibration on boron trifluoride gives less ambiguous information about complexation. Scheme I shows a highly

SCHEME I



general mechanistic formulation for boron trifluoride catalyzed interconversion of **3a** and **3b**, either directly (*via* the k_f and k_r route) or through the various possible complexes, denoted by C_a^s, C_a°, C_b^s, and C_b° with the superscript again indicating the site of binding and the subscript indicating the isomer involved. For this scheme the observed, pseudo-first-order rate constants are given by eq 4. No assumption is made as to whether complexes

$$k_{obsd} = [BF_3] \times \left\{ \frac{k_f^s K_a^s + k_f^\circ K_a^\circ + k_f}{1 + (K_a^s + K_a^\circ)[BF_3]} + \frac{k_r^s K_b^s + k_r^\circ K_b^\circ + k_r}{1 + (K_b^s + K_b^\circ)[BF_3]} \right\} \quad (4)$$

are reactive or unreactive; unreactive complexes will simply have zero rate constants associated with them. But if *any* of the complexation equilibria were nonnegligible, the $[BF_3]$ term in the denominator of eq 4 would lead to a less than first-order dependence on boron trifluoride. Such is not found, which unambiguously excludes significant complexation under these conditions.

From $K_c = 0.285 \pm 0.005$, we calculate $\Delta G^\circ = G_{3b} - G_{3a} = 0.77 \pm 0.1$ kcal/mole, corresponding to a value of $-\Delta G$ for sulfur of -0.2 kcal/mole relative to 0.6 for oxygen in the five-membered hemithioketal ring of cyclohexanones. We conclude that no effect of catalyst is responsible for this preference of oxygen over sulfur for the equatorial position.

Experimental Section

The ethylene hemithioketal of 3,3,5-trimethylcyclohexanone was prepared as described[7] and the isomers were separated on alumina by elution with petroleum ether (30–60°). The nmr ($CDCl_3$) of the first isomer collected showed triplets centered at δ 3.00 (axial S-CH_2) and 4.17 (equatorial O-CH_2). The second isomer showed the corresponding triplets at δ 3.05 (equatorial S-CH_2) and 4.12 (axial O-CH_2); corresponding shifts are reported for similar systems.[6]

Equilibrations and Kinetic Studies.—Solutions (0.159 *M*) of either pure isomer or a mixture of isomers of the ethylene hemithioketal of 3,3,5-trimethylcyclohexanone containing freshly distilled boron trifluoride etherate in varying concentrations (0.016, 0.032, 0.048, 0.064, 0.079, and 0.095 *M*) were maintained at 34.6 ± 0.1° by immersion in a constant temperature bath. Portions for analysis (1.5 ml) were withdrawn and immediately shaken with 1 ml of 0.1 *N* sodium hydroxide. Gas chromatographic analysis using 10% diethylene glycol adipate on Firebrick gave optimum separation of the isomers. The peak areas were estimated using a disk integrator and assuming equal sensitivities for the two isomers. Rate constants were obtained from semilogarithmic plots of fraction of reaction *vs.* time.

Registry No.—**3a**, 19765-68-5; **3b**, 19765-69-6.

Addition of Arylsulfinic Acids to N,N-Dialkylquinone Diimines[1]

K. Thomas Finley, Robert S. Kaiser, Richard L. Reeves, and Grant Werimont

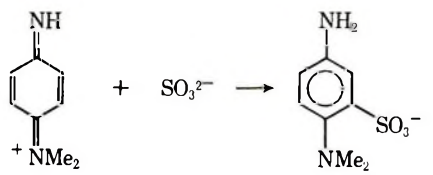
Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received January 2, 1968

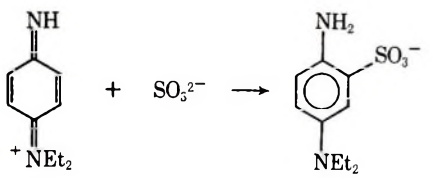
The addition of arylsulfinates (2) to N,N-dialkylquinone diimines (1) under anaerobic conditions can result in four products. Sulfonamide **3** is produced in good yield under a variety of conditions (pH 5–9; temperature 0–50°). One of the possible sulfones (**4**, the 3 isomer) is found in significant amounts at pH 5–6 at room temperature and below; the 2 isomer is not found. At pH 7–9 detectable quantities of the N′,N′-disulfonamide (**5**) and *p*-phenylenediamine (**6**) are obtained from the reactions of benzenesulfinate and sulfinates with electron-donating substituents. Significantly larger amounts of **5** and smaller amounts of **3** were obtained at 0 and 50° than at 24°. The relationship of product yield to acidity is discussed in terms of the mechanisms of analogous reactions. The reported yields were obtained from the uv spectra of reaction mixture extracts by novel matrix methods involving characteristic vectors. A linear regression technique and a calibration with the spectra of pure compounds were required. The errors in yield lie in the range of 1–5% based on starting material.

N,N-Dialkylquinone diimines are ambident cations which show a high degree of specificity in reactions with anionic nucleophiles. Thus, dye-forming reactions with phenolates give only the product arising from attack at the unsubstituted imino nitrogen,[2] reaction with hydroxide ion gives only the product resulting from displacement of the substituted imino group,[3] and reaction with sulfite ion appears to give only ring addition.[4] We have extended these studies to include reactions with arylsulfinates since stable products result from reaction of these nucleophiles at more than one site. We have made systematic variations in structure, reaction pH (5–9), and reaction temperature (0–50°) to learn how these factors influence the competition between the single-step nitrogen attack and the two-step ring addition. The reactants and products are shown in Scheme I.

Sulfite is reported to show a remarkable selectivity in its final orientation on addition to N,N-dimethyl- and to N,N-diethylquinone diimine, giving **9** and **10**, respectively.[5] We find that phenylsulfinate ion, which



7 **9**



8 **10**

has a formal resemblance to sulfite ion, gives a single sulfone isomer from both quinone diimines (**4a** and **4f**).

Results

Product Isolation and Identification.—The quinone diimines were generated *in situ* by oxidation of the appropriate *p*-phenylenediamine with stoichiometric amounts of potassium ferricyanide in deaerated phosphate buffer solutions. It was shown that the presence of the sulfinates during the oxidation had no significant effect on the total yield of products; therefore no oxidation of the sulfinate by ferricyanide was taking place. Self-condensation reactions were minimized by using low concentrations of quinone diimine (2×10^{-3} *M*). The competing deamination of the tertiary imino group was not significant in the pH range used in this study.

Because two of the products are sensitive to air (**4** and **6**), nitrogen was constantly bubbled into the reaction solutions. Extractions with chloroform and dilution of the extracts for spectrophotometric analysis were carried out with deaerated solvents in a nitrogen atmosphere. If these precautions were not taken, significant errors in the product analyses resulted.

The products were all poorly soluble in the aqueous buffers and precipitated in large-scale product-isolation experiments. The major products were isolated from such runs and were characterized by elemental analysis and by nmr, ir, and mass spectral analysis.

The ir spectra of the sulfonamides showed a strong single band at approximately 3.1 μ indicative of NH. Several strong bands in the regions, 7.4–7.9 and 8.4–8.9 μ, can be assigned to SO_2 stretching. The sulfones showed a strong split band at approximately 3 μ indicative of NH_2. The SO_2 stretching bands were similar to those present in the sulfonamides. The disulfonamides showed no absorption in the 3-μ region and this was taken as the absence of NH. The strong SO_2 bands were present.

An AA′BB′ pattern (6.7 ppm) which on integration showed the presence of four aryl protons was found with both sulfonamide and disulfonamide. The latter compounds showed twice as many protons associated with the arylsulfonyl group as the corresponding monosulfonamide. The sulfones gave a complicated multiplet between 7 and 8 ppm. The protons of both aryl groups are involved in this absorption pattern.

All three classes of compounds gave a parent peak in the mass spectrum corresponding to the expected molecular weight. In the case of the disulfonamide it was necessary to introduce the sample directly into the ion source. If the sample was allowed to pass through the molecular leak, only the monosulfonamide parent peak was observed although larger amounts of Ar and SO_2 fragments were found. This was attributed to

(1) Presented in part before the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 13, 1968.

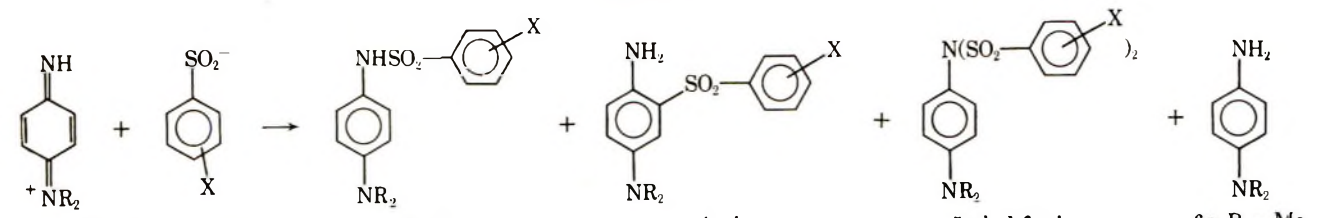
(2) L. K. J. Tong and M. C. Glesmann, *J. Amer. Chem. Soc.*, **90**, 5164 (1968).

(3) L. K. J. Tong, M. C. Glesmann, and R. L. Bent, *ibid.*, **82**, 1988 (1960).

(4) K. T. Finley and L. K. J. Tong in "The Chemistry of the Carbon–Nitrogen Double Bond," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., in press.

(5) K. H. Bauer, *J. Prakt. Chem.*, **4**, 65 (1958).

SCHEME I



1a, R = Me
b, R = Et

2a, X = H
b, X = 4-Me
c, X = 4-Cl
d, X = 3,4-Me$_2$
e, X = 4-CN

3a–j

4a–j

5a,b,d,f,g,i

6a, R = Me
b, R = Et

a, R = Me; X = H
b, R = Me; X = 4-Me
c, R = Me; X = 4-Cl
d, R = Me; X = 3,4-Me$_2$
e, R = Me; X = 4-CN
f, R = Et; X = H
g, R = Et; X = 4-Me
h, R = Et; X = 4-Cl
i, R = Et; X = 3,4-Me$_2$
j, R = Et; X = 4-CN

thermal decomposition and was also observed in glpc. The most significant fragment ions from sulfonamide and sulfone were rationalized as M − SO_2Ar and as Ar. The sulfones also showed a peak corresponding to M − Me.

The mass spectra of the sulfones are of special interest in connection with the question of structure. The only sulfones for which a rigorous chemical proof was carried out are **4a** and **4f**. In the former case the alternative 2 isomer (**23**) was also prepared. The mass spectra of these two compounds differed in some important details as shown in Table I. The other sulfones

TABLE I

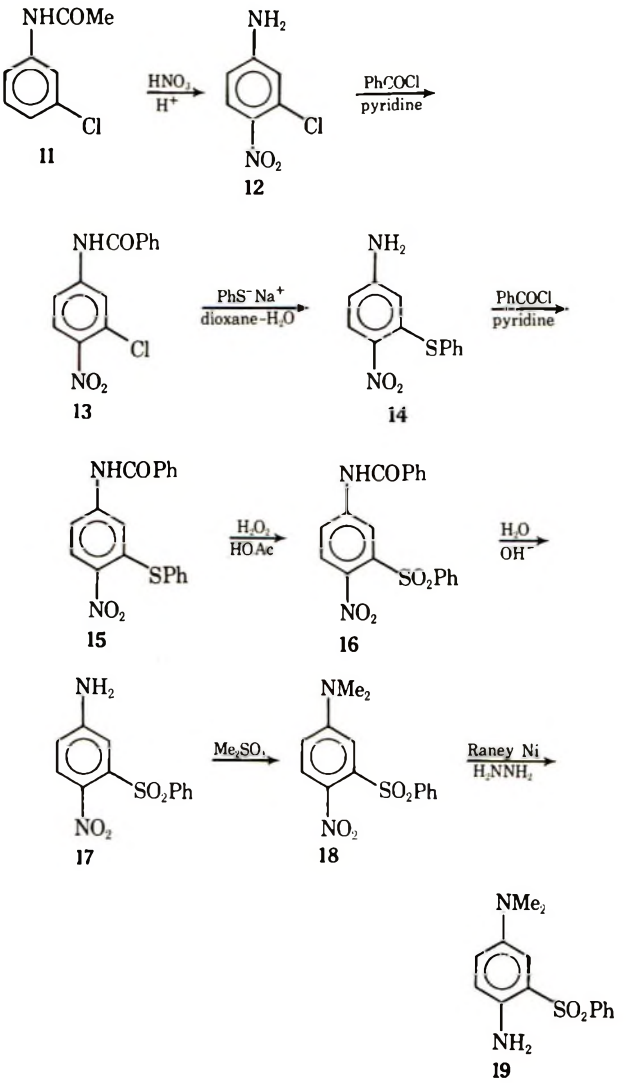
		Rel intensity		
m/e	Probable structure	**4a**	**19**	**23**
276	M	100	100	100
261	M − Me	12.3	12.4	12.4
259	M − OH	0.2	0.2	7.9
135	M − O_2SPh	18.8	19.3	9.0
134	M − HO_2SPh	3.8	3.9	27.8
133	M − H_2O_2SPh	3.6	3.6	45.7

containing a dimethylamino group gave spectra analogous to those of **4a** and **19**. The mass spectra of **4f** and **25** were identical and the other sulfones containing a diethylamino group showed similar fragmentation patterns.

In addition to being isolated from reaction mixtures, all of the sulfonamides (**3a–j**) were prepared from the appropriate *p*-phenylenediamine and arylsulfonyl chloride in pyridine. These products were shown to be identical with those formed in the addition reaction by melting point, tlc, and spectra.

The structure of the sulfone produced by the addition of benzenesulfinate to N,N-dimethylquinone diimine was demonstrated by unambiguous synthesis. By analogy with the reported addition of sulfite, the expected product would be 4-amino-N,N-dimethyl-2-phenylsulfonylaniline (**23**). For comparison we prepared 4-amino-N,N-dimethyl-3-phenylsulfonylaniline (**19**) according to Scheme II. The synthetic compound **19** proved to be identical in all respects with the sulfone isolated from the corresponding addition reaction. The isomeric material **23** and the N,N-diethyl compound **25** were prepared by a similar sequence of reactions shown in Scheme III. Compound **25** proved to be identical with the sulfone isolated from

SCHEME II

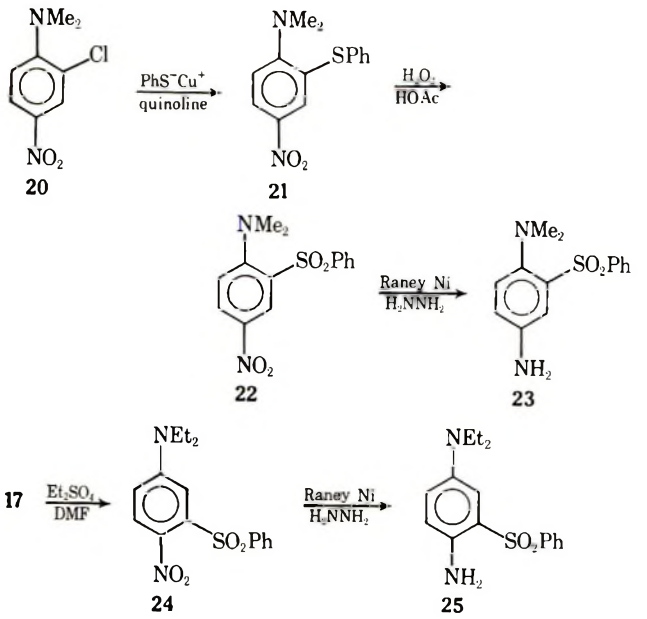


11 12 13 14 15 16 17 18 19

the addition of sodium benzenesulfinate to N,N-diethylquinone diimine.

The pair of isomeric sulfones of known structure (**19** and **23**) are separated by tlc on alumina when developed with 20% ethyl acetate in benzene. Furthermore, on standing in air, the isomer corresponding to the isolated product (**19**) rapidly becomes colored (magenta) while the 2 isomer does not. The authentic N,N-diethyl structure **25** turns cyan on standing. Since tlc of the

Scheme III



isolated sulfones (**4a–j**) showed only a single material and all gave the characteristic color on standing, we take this together with the mass spectral evidence as confirmation that all have structure **4**. The 2 isomers, if formed at all, must be below the limit of detection, which we established as 0.3 μg (0.5% yield).[6] The R_f values of the reaction products were within experimental error of those for purified analytical samples ($\pm$0.03).

Yields. Method of Analysis and Errors.—Of the various methods tried for obtaining quantitative estimates of product yields from the relatively dilute reaction mixtures, spectrophotometry was most satisfactory. The uv absorption curves for the four products from reaction of **1a** with **2a** are shown in Figure 1 for relative concentrations close to those found in some mixtures. It can be seen that the four curves are rather similar in some wavelength regions. This fact, along with the instability to oxygen of two of the products (**4** and **6**), required a sophisticated method of preparing the solutions and analyzing the absorption curves of the product mixtures.

Initially we were unaware of the presence of the two minor products, **5** and **6**, and attempted to determine the sulfonamide **3** and sulfone **4** by the standard method of solving for the two concentrations from two simultaneous equations, using absorbances at two different wavelengths. We found that the calculated concentrations varied according to the two wavelengths selected. A careful search of the product mixture by tlc led us to the additional compounds. Using the data available from the entire absorption curve seemed to offer hope of resolving this rather complicated product mixture.

It is well known that absorption curves can be written as matrices and, further, that they can be described by characteristic vectors.[7] Absorption curves (225–360 nm) were obtained for each of the pure products. Absorbance values at 28 wavelengths (every 5 nm) throughout each curve were subjected to the matrix transformations needed to derive characteristic

(6) K. T. Finley and R. S. Kaiser, *J. Chromatogr.*, **39**, 195 (1069).
(7) G. Wernimont, *Anal. Chem.*, **39**, 554 (1967).

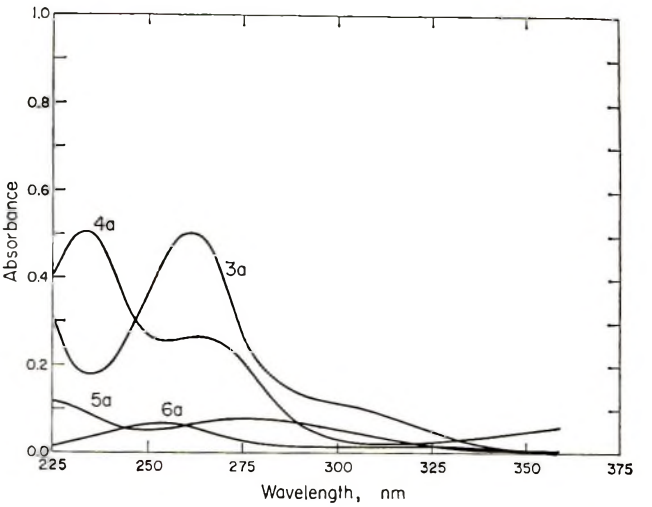


Figure 1.—Spectra of the individual components of a typical reaction mixture. Solvent: 1% chloroform in ethanol–methanol (95:5). Concentration $\times 10^5$ *M*: **3a** = 3.00, **4a** = 2.12, **5a** = 0.48, **6a** = 0.52.

vectors and their associated scalar multiples. These derived parameters were used in a linear regression to calculate concentrations of the four components required to give the best fit to the observed absorption curves for mixtures of known composition and for those obtained from the extracts of addition reactions. A comparison of the actual and the calculated concentrations for a typical prepared mixture is given in Table II.

Table II
Analysis of a Prepared Mixture by Characteristic Vectors

Compd	Concn $\times 10^7$ *M* Actual	Concn $\times 10^7$ *M* Calcd
3a	150	149
4a	64	64
5a	10	8.4
6a	105	99

Similar results were obtained for all pure compounds and analogous prepared mixtures for the other nine pairs of reactants, a total of 94 spectra. The calculated concentrations were then recombined with the vector parameters to calculate a theoretical absorption curve for those concentrations. The theoretical curves always agreed with the observed curves (for pure compounds and prepared mixtures) to within 0.002 absorbance unit, which is well within the error range for spectrophotometry. The differences for reaction mixture extracts were higher, depending upon the reactivity of the sulfinates and the similarity of the absorption curves of the products. With the exception of the reaction of **1b** with **2e**, the greatest difference amounted to 0.015 absorbance unit, which was an acceptable error for determining yields. The extract from the reaction of N,N-diethylquinone diimine (**1b**) with 4-cyanobenzenesulfinate (**2e**) was shown by tlc to contain traces of additional products. The disagreement between the theoretical and observed spectra varied from 0.024 to 0.040 absorbance unit depending on pH.

Since the reconstructed curves for the reaction mixture extracts do not agree with the observed curves to within expected spectrophotometric error, it is difficult

TABLE III

PER CENT PRODUCT YIELDS FROM THE ADDITION OF ARYLSULFINATES TO N,N-DIALKYLQUINONE DIIMINES[a,b]

R	X	pH	% product 3	4	5	6
		5	31	54		2
		6	54	32	1	4
Me	H	7	80	4	2	5
		8	88		4	8
		9	85		4	7
		5	18	60	2	5
		6	45	46	2	6
Me	4-Me	7	74	11	3	10
		8	82		6	12
		9	85		6	13
		5	26	54	1	1
		6	45	39		2
Me	3,4-Me_2	7	74	14	1	2
		8	86	3	2	4
		9	81	3	4	4
		5	35	45		
		6	55	23		
Me	4-Cl	7	82	6		
		8	87	1		
		9	86	2		
		5	56	25		
		6	71	8		
Me	4-CN	7	88			
		8	89			
		9	76			
		5	48	40	1	1
		6	75	16	2	4
Et	H	7	94		2	3
		8	90		4	8
		9	92		4	6
		5	39	43		
		6	67	24		
Et	4-Me	7	82	3	2	
		8	86		5	
		9	85	1	4	
		5	42	54		
		6	54	24		1
Et	3,4-Me_2	7	72	7	1	2
		8	83		1	3
		9	81	1	2	1
		5	52	22		
		6	72	9		
Et	4-Cl	7	81	2		
		8	86	2		
		9	83	3		
		5	64	27		
		6	70	10		
Et	4-CN	7	76	3		
		8	75	5		
		9	68	5		

[a] At 24 ± 1°. [b] Where no yield is recorded, the product was not detected by tlc.

to assign exact estimates of errors in the analytical results. We have adopted two estimates as being most informative. First, if we consider the calculated concentrations from single-component solutions prepared from analytical samples, the regression equations show low concentrations of the three absent components. The magnitude of these errors corresponds to yields of ±1%. Second, the calculated concentrations of minor components of the reaction mixture extracts occasionally indicates a negative value which would correspond to a yield error of ±5%. The error in any computed yield should lie within this range, *i.e.*, 1–5% yield based on starting materials.

The average total yield of products for the 62 experiments reported in Tables III and IV is 89%. In view of the scope of the study and the probable errors just discussed, we feel that an acceptable material balance has been achieved. We were unable to detect any disulfonamide (**5**) or *p*-phenylenediamine (**6**) in the reactions of arylsulfinates containing electron-withdrawing substituents. These reaction mixtures were analyzed for two components (**3** and **4**).

TABLE IV

EFFECT OF TEMPERATURE ON THE ADDITION OF BENZENESULFINATE TO N,N-DIALKYLQUINONE DIIMINES[a]

R	pH	% product 3	4	5	6
		At 0 ± 1°			
	6	30	54	4	3
Me	7	51	26	13	2
	8	65	6	23	1
	6	47	38	8	
Et	7	76	9	14	
	8	72		26	
		At 50 ± 1°			
	6	64	19	9	4
Me	7	55		15	6
	8	63		20	6
	6	75	8	8	
Et	7	64	1	18	
	8	68	3	24	2

[a] Where no yield is recorded, the product was not detected by tlc.

The effect of temperature on yield was examined for the addition of benzenesulfinate to N,N-dimethyl- and N,N-diethylquinone diimine. These data are presented in Table IV.

4-Nitrobenzenesulfinate was also added to the two quinone diimines, but the reaction appeared to be relatively slow and tlc indicated the presence of eight to ten minor by-products. Since the 4-cyanobenzenesulfinate reacted more cleanly, and attempts to improve the 4-nitro reaction failed, no yields were measured. The major 4-nitro products are probably the sulfone and sulfonamide as indicated by tlc comparison with authentic samples.

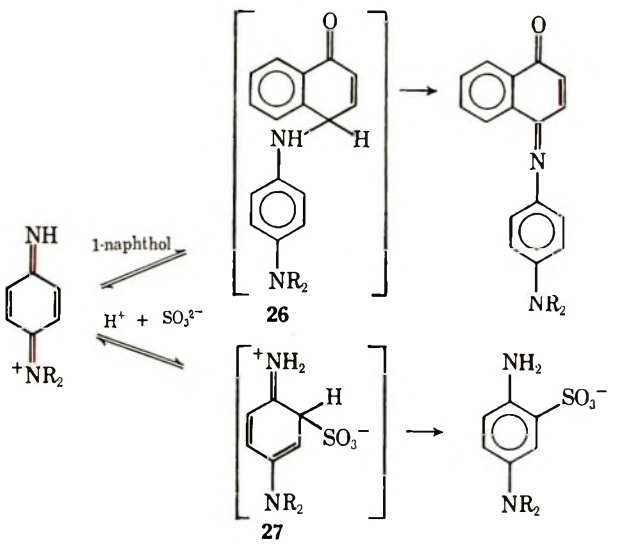
We have shown, in separate experiments, that the reaction products **3**–**5** are not interconverted under reaction conditions.

The yield data presented in Tables III and IV indicate certain general trends: (1) sulfone **4** decreases with increasing pH and temperature, (2) sulfonamide **3** and disulfonamide **5** increase with pH, (3) sulfonamide decreases and disulfonamide increases with temperatures either above or below 24°, and (4) sulfone increases with electron-donating substituents in the arylsulfinate and with the N,N-dimethylamino group in

the quinone diimine (compared with the N,N-diethylamino group). The fourth trend is less marked than the other three, but is still outside the limits of experimental error.

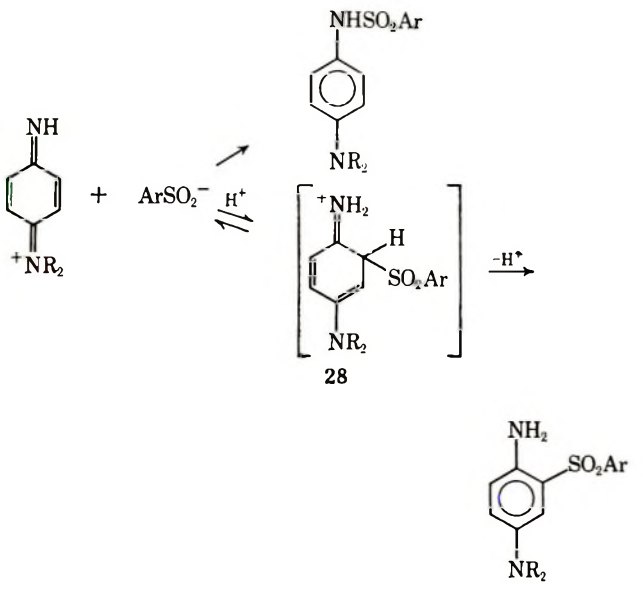
The addition of phenolate and sulfite ions to quinone diimine provides useful models with which to discuss the mechanisms of the observed reactions (Scheme IV). It seems reasonable that the pathway for sulfone

Scheme IV



formation might correspond rather closely to that for sulfonation. Similarly we might compare the formation of the coupling intermediate **26** with sulfonamide formation (Scheme V). Kinetic studies of the sulfona-

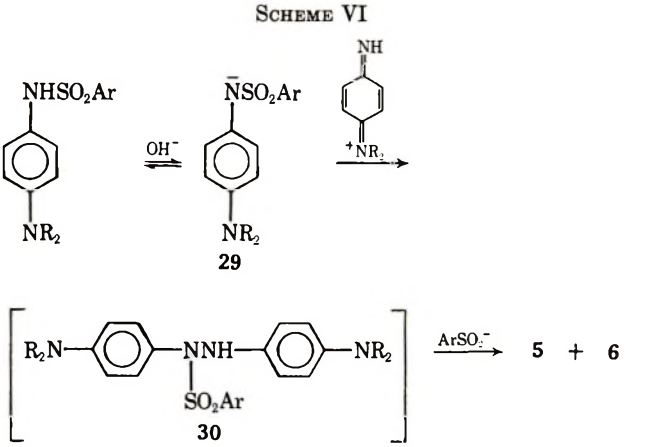
Scheme V



tion reaction show that the ring addition is subject to general acid catalysis by acid phosphate salts. This has been interpreted mechanistically as base-catalyzed removal of a ring proton from the protonated intermediate **27**. The rate of addition of phenolate ions, on the other hand, is independent of pH. By analogy, it seems reasonable that the sulfonamide:sulfone ratio would change with pH in the direction which we observe.

While the disulfonamides **5** are very minor products, they are intriguing because the reaction by which they might be formed is less obvious. We noticed that the disulfonamides were obtained at high pH and that the yields of sulfonamide often dropped slightly above pH 8. The effect of temperature on the yields of sulfonamide and disulfonamide also suggest a connection between these two products. At temperatures both above and below 24° the sulfonamide yield drops and the disulfonamide yield increases. We have considered Scheme VI to account for these facts. This scheme

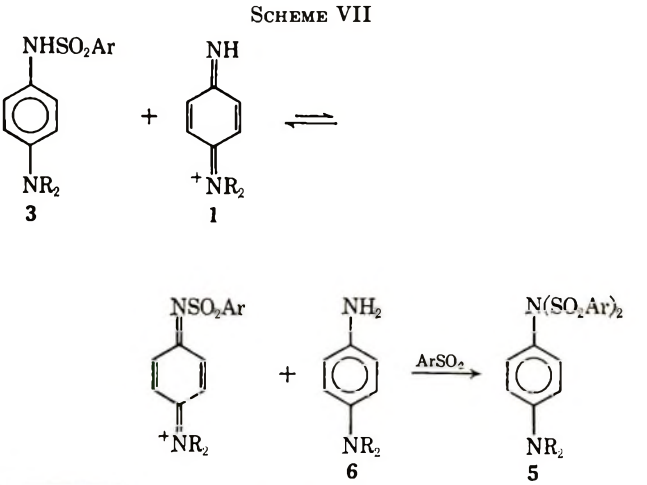
Scheme VI



predicts the observed products and the pH dependence. It has been suggested that the formation of hydrazobenzenes from partially oxidized *p*-phenylenediamines involves the reaction of quinone diimines with ionized *p*-phenylenediamines.[8] The subsequent attack of a second arylsulfinate would be expected to occur at the nitrogen bearing the electron-withdrawing arylsulfonyl group. The scheme requires that the rate of addition of sulfonamide anion to unreacted quinone diimine be comparable to the rates of addition of sulfinate. Attempts to investigate this route have been unsuccessful in that we were unable to prepare the intermediate **30**. An earlier study of such compounds indicated that the addition of sulfinic acids to azobenzenes is not a general reaction.[9]

An alternative reaction path to the disulfonamide would involve a cross oxidation of the sulfonamide **3** by quinone diimine **1** (Scheme VII). We have found that

Scheme VII



(8) C. A. Bishop and L. K. J. Tong, *Phot. Sci. Eng.*, **11**, 30 (1967).
(9) W. Bradley and J. D. Hannon, *J. Chem. Soc.*, 2713 (1962).

treatment of **3** with ferricyanide gives only recovered starting material. Therefore the quinone diimine–quinone diimide equilibrium must lie very far to the left, *i.e.*, toward reactants, and would not be a feasible mode of formation for **5**.

Experimental Section[10]

Materials.—Mono-, di-, and tribasic potassium phosphate and potassium ferricyanide (Baker and Adamson Reagent Grade) were used as received. N,N-Diethyl-*p*-phenylenediamine hydrochloride was recrystallized to a constant melting point of 237–238.5°. N,N-Dimethyl-*p*-phenylenediamine dihydrochloride (Eastman Grade), chloroform (Eastman Spectro Grade), and absolute ethanol denatured with 5% methanol were used as received. Sodium benzenesulfinate and *p*-toluenesulfinate (Eastman Grade and Practical Grade) were used without further purification. The other sulfinic acids were prepared by the reduction of the appropriate sulfonyl chlorides with sodium sulfite.[11–13] 4-Chloro- and 4-nitrobenzenesulfonyl chlorides (Eastman Technical and Eastman Grade) were used without purification. 4-Cyano- and 3,4-dimethylsulfonyl chlorides were prepared by chlorosulfonation as described in the literature.[14,15] All of these compounds were recrystallized to the literature melting points. Solvents for reactions and recrystallizations were Eastman Grade and were used without further purification except as specifically indicated.

Determination of Products.—The appropriate *p*-phenylenediamine (0.2 mmole) was dissolved in 110 ml of deaerated phosphate buffer solution (I = 0.75 M) containing a fivefold excess of the arylsulfinate. Ten milliliters of a deaerated solution containing 0.4 mmole of potassium ferricyanide was added and the reaction was allowed to proceed for approximately 15 min during which time nitrogen was bubbled through the reaction mixture. The products were extracted in 50 ml of deaerated chloroform and after dilution of the solution with deaerated alcohol, the uv spectrum (225–360 nm) was recorded. The reaction vessel was a 250-ml separatory funnel fitted with a long, narrow delivery tip. The extractions were carried out under nitrogen and the extract was delivered directly into a volumetric flask being flushed with nitrogen.

Isolation of Products.—To keep the concentrations of reactants low and still obtain enough product for isolation and analysis large-scale reactions were run at high dilution. Solutions (4×10^{-3} M) of the *p*-phenylenediamine and ferricyanide were added slowly from separate addition funnels to a well-stirred solution of the appropriate arylsulfinate in the desired buffer. At pH 7 it was possible to isolate the sulfonamides in purified yields of approximately 80%. More acidic conditions (pH 4 or 5) gave lower, but still useful, yields of sulfones. The sulfones were generally chromatographed on silica gel and eluted with 15% ethyl acetate in benzene. The same procedure was employed at pH 9 to obtain samples of N′,N′-disulfonamides.

Preparation of Products.—The various sulfonamides **3a–j** were prepared by the reaction of the appropriate *p*-phenylenediamine and arylsulfonyl chloride in pyridine which had been distilled from BaO.[16] It was very important to keep the reaction cold in most cases since warming produced only a deep purple dye. Some of the sulfonamides appeared to be appreciably more soluble in acid than others and it was necessary to neutralize the aqueous mixture before they could be isolated. A number of the sulfones were prepared by the ferric chloride oxidation of the *p*-phenylenediamines in the presence of sulfinates under acidic conditions.[17] The physical properties and elemental analyses of the sulfonamides and sulfones studied are presented in Table V.

N-Benzoyl-3-chloro-4-nitroaniline (13).—3-Chloro-4-nitroaniline (**12**) was prepared[18] and 20.4 g (118 mmoles) was treated with benzoyl chloride in pyridine. Recrystallization from ethanol gave 24.2 g (74%) of **13**, mp 161.5–163°.

Anal. Calcd for $C_{13}H_9ClN_2O_3$: C, 56.4; H, 3.3; Cl, 12.8; N, 10.1. Found: C, 56.3; H, 3.5; Cl, 13.0; N, 9.9.

4-Nitro-3-phenylmercaptoaniline (14).—To a solution of 24.0 g (87 mmoles) of **13** in 90 ml of 1,4-dioxane was added 14.1 g (128 mmoles) of thiophenol and the mixture was made alkaline with 60 g of NaOH in 400 ml of water. The reaction mixture was then refluxed for 16 hr and poured over cracked ice and water. The precipitate was collected, dried, and recrystallized from ethanol–water giving 17.8 g (83%) of **14**, mp 162–163°.

Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.5; H, 4.1; N, 11.4; S, 13.0. Found: C, 58.4; H, 4.0; N, 11.2; S, 13.2.

N-Benzoyl-4-nitro-3-phenylmercaptoaniline (15).—By the method used for the preparation of **13**, 17.8 g (72.4 mmoles) of **14** was converted to 20.5 g (81%) of **15**, mp 193–194°.

Anal. Calcd for $C_{19}H_{14}N_2O_3S$: C, 65.1; H, 4.0; N, 8.0; S, 9.2. Found: C, 65.0; H, 4.0; N, 7.8; S, 9.3.

N-Benzoyl-4-nitro-3-phenylsulfonylaniline (16).—A suspension of 23.2 g (66 mmoles) of **15** in 250 ml of glacial acetic acid was treated with 18 g of 30% hydrogen peroxide (*ca.* an eightfold excess) and refluxed for 2 hr. Analysis by tlc showed two substances, neither of which was **15** (silica gel developed with 20% ethyl acetate in benzene). A partial separation on a column of silica gel gave samples whose ir and mass spectra suggested that they were the desired sulfone **16** and the corresponding sulfoxide. The addition of 85 g of 30% peroxide in portions over a reflux period of *ca.* 56 hr gave 19 g (76%) of crystalline product, mp 252–256°. Only a trace of the sulfoxide was found in this material and recrystallization from acetic acid gave an analytical sample of **16**, mp 255–257°.

Anal. Calcd for $C_{19}H_{14}N_2O_5S$: C, 59.7; H, 3.7; N, 7.3; S, 8.4. Found: C, 59.6; H, 3.6; N, 7.4; S, 8.2.

4-Nitro-3-phenylsulfonylaniline (17).—A suspension of 18 g of **16**, containing a trace of sulfoxide, in 700 ml of 1,4-dioxane, was treated with 350 ml of water containing 47 g of NaOH and refluxed for 4 hr. After standing and cooling, a crystalline material was collected and tlc (silica gel, 20% ethyl acetate in benzene) indicated that all of the amide had been hydrolyzed and that a trace of a second product (sulfoxide) was present. Careful recrystallization from ethanol gave 6.8 g (52%) of analytically pure **17**, mp 234.5–236°.

Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.8; H, 3.6; N, 10.1; S, 11.5. Found: C, 52.0; H, 3.4; N, 10.1; S, 11.2.

N,N-Dimethyl-4-nitro-3-phenylsulfonylaniline (18).—A suspension of 5.0 g (18 mmoles) of **17** in 50 ml of dimethyl sulfate was heated in an oil bath to 90°. After a short time the aniline dissolved and an additional 25 ml of freshly distilled dimethyl sulfate was added. The reaction mixture was heated at 70–90° for 3 hr and then poured over ice. A yellow oil formed which solidified on standing. Recrystallization from chloroform–ethanol (1:1 v/v) gave 2.0 g (36%) of **18**, mp 236–237.5°.

Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.9; H, 4.6; N, 9.1; S, 10.4. Found: C, 55.1; H, 4.7; N, 8.8; S, 10.7.

4-Amino-N,N-dimethyl-3-phenylsulfonylaniline (19).—A mixture of 500 mg (1.6 mmoles) of **18** and 1 g of wet Raney nickel in *ca.* 75 ml of hot methanol was stirred in a water bath. During a period of 15 min, 3 ml of hydrazine hydrate (64%) was added dropwise. The reaction was continued for about 1.5 hr until no ammonia was detected. The catalyst was removed by filtration and the methanol evaporated under vacuum. Recrystallization from methanol gave 200 mg (44%) of **19**, mp 128–130°; a mixture melting point with the sulfone obtained from the addition of benzenesulfinate to N,N-dimethylquinone diimine showed no depression.

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.8; H, 5.8; N, 10.1; S, 11.6. Found: C, 60.5; H, 5.9; N, 10.0; S, 11.3.

N,N-Dimethyl-4-nitro-2-phenylmercaptoaniline (21).—Cuprous thiophenolate was prepared by Adams' procedure[19] and 18.5 g (0.11 mole) was suspended with 20.0 g (0.1 mole) of 2-chloro-N,N-

(10) The corrected melting points were obtained by using a Thomas–Hoover apparatus. Ultraviolet spectra were recorded with a Beckman DK-2A spectrophotometer, nmr with a Varian 60A instrument operated at 60 MHz (TMS internal standard), ir using a Baird Atomics spectrophotometer, Model NK-1 with NaCl optics, and mass spectra using either a 60° sector-type, or a Consolidated Electrodynamics Model 21-110B mass spectrometer both with an all-glass heated inlet operated at 235°.

(11) S. Smiles and C. M. Bere in "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 7.

(12) A. T. Fuller, I. M. Tonkin, and J. Walker, *J. Chem. Soc.*, 633 (1945).

(13) We are indebted to Mr. Victor Stead of the Color Organic Laboratory for the preparation of 4-chloro- and 4-nitrobenzenesulfinic acids.

(14) I. Remsen, R. N. Hartman, and A. M. Muckenfuss, *Amer. Chem. J.*, **18**, 150 (1896).

(15) E. H. Huntress and J. S. Antenrieth, *J. Amer. Chem. Soc.*, **63**, 3446 (1941).

(16) R. Adams and J. H. Looker, *ibid.*, **73**, 1145 (1951).

(17) S. Pickholz, *J. Chem. Soc.*, 685 (1946).

(18) H. H. Hodgson and A. Kershaw, *ibid.*, 2917 (1929).

(19) R. Adams, W. Reifschneider, and M. D. Nair, *Croat. Chem. Acta*, **29**, 277 (1957).

Table V

Physical Properties and Analytical Data for Sulfonamides, Sulfones, and Disulfonamides

Compd	Mp, °C[a]	λ_{max}, nm[b]	$\epsilon \times 10^{-4}$[b]	Calcd, % C	H	N	S	Cl	Found, % C	H	N	S	Cl
3a	129.5–130	262, 300 sh	1.71, 0.390	60.9	5.8	10.2	11.6		60.7	6.2	10.2	11.4	
b	127–129	225, 262, 300 sh	1.52, 1.72, 0.370	62.0	6.2	9.7	11.0		61.9	6.4	9.7	11.0	
c	120–121	230, 262, 300 sh	1.82, 1.82, 0.432	54.1	4.8	9.0	10.3	11.4	54.2	4.9	9.2	10.1	11.5
d	148.5–150	228, 262, 300 sh	1.36, 1.70, 0.355	63.1	6.6	9.2	10.5		62.9	6.4	9.0	10.6	
e	158.5–159.5	240, 261, 305 sh	2.06, 2.10, 0.339	59.9	5.0	14.0	10.6		60.0	5.1	14.1	10.8	
f	124–125.5	268, 300 sh	1.80, 0.421	63.2	6.6	9.2	10.5		63.1	6.5	9.2	10.5	
g	160.5–161 dec	226, 268, 300 sh	1.55, 1.98, 0.484	64.2	6.9	8.8	10.1		64.2	6.9	8.6	10.2	
h	153–154.5 dec	230, 268, 300 sh	1.78, 2.10, 0.489	56.8	5.6	8.3	10.5	9.5	56.8	5.4	8.3	10.7	9.6
i	151.5–152.5	228, 268, 300 sh	1.43, 2.07, 0.490	65.1	7.2	8.4	9.6		65.4	7.2	8.5	9.5	
j	135–136.5	240, 268, 300 sh	1.96, 2.56, 0.417	62.1	5.8	12.8	9.7		62.2	5.6	13.0	9.7	
4a	130–131	233, 265	2.44, 1.27	60.9	5.8	10.2	11.6		61.0	5.8	10.2	11.4	
b	173–175	238, 265 sh	2.49, 1.19	62.0	6.2	9.7	11.0		61.9	6.2	9.8	10.8	
c	164.5–166	241, 265 sh	2.85, 1.38	54.1	4.8	9.0	10.3	11.4	53.9	4.8	9.2	10.0	11.3
d	148–149.5	241, 265 sh	2.56, 1.30	63.1	6.6	9.2	10.5		62.8	6.8	9.3	10.4	
e	189.5–190.5	248, 275 sh	2.44, 1.27	59.9	5.0	14.0	10.6		59.8	5.3	13.9	10.7	
f	118.5–120	234, 270	2.06, 1.39	63.2	6.6	9.2	10.5		62.9	6.4	9.0	10.4	
g	156–157.5	239, 270	2.55, 1.60	64.2	6.9	8.8	10.1		63.8	6.7	8.9	9.7	
h	155.5–156.5	242, 270	2.84, 1.60	56.8	5.6	8.3	9.5	10.5	56.9	5.5	8.1	9.5	10.6
i	97.5–99	241, 270	2.08, 1.61	65.1	7.2	8.4	9.6		65.3	7.2	7.9	9.4	
j	118–119.5	248, 275 sh	2.40, 1.61	62.1	5.8	12.8	9.7		61.8	5.8	12.6	9.9	
5a	161.5–162.5	275	1.70	57.6	4.8	6.7	15.4		57.7	5.2	6.7	15.5	
b	208–210 dec	236, 275	2.56, 1.55	59.5	5.4	6.3	14.4		59.9	5.9	6.3	14.1	
d	198.5–199.5 dec	238, 275	2.60, 1.80	61.0	5.9	5.9	13.5		60.8	5.9	5.9	13.6	
f	140.5–142	275	1.63	59.5	5.4	6.3	14.4		59.8	5.2	6.1	14.5	
g	200–202 dec	236, 275	2.90, 2.44	61.0	5.9	5.9	13.6		60.8	5.8	5.8	13.7	
i	196–197.5 dec	238, 280	2.42, 1.99	62.4	6.4	5.6	12.8		62.2	6.1	5.6	12.7	

[a] Corrected. [b] Molar absorptivity measured in 1% chloroform in ethanol (denatured with 5% methanol) with a Beckman DK-2A spectrophotometer.

dimethyl-4-nitroaniline (**20**, Frinton Laboratories) in 100 ml of quinoline containing 2 ml of pyridine. The mixture was refluxed for *ca.* 20 hr and then poured over crushed ice and excess hydrochloric acid. A black tar was decanted and, after air drying, was extracted with ether in a Soxhlet extractor until the extract returning to the pot was colorless. The aqueous mother liquors were also extracted and the ether solutions were combined and washed with 0.1 *N* HCl and then with water. The ether was removed under vacuum after the solution had been dried with anhydrous $MgSO_4$. A dark oil remained which crystallized on cooling. A benzene solution of the product was rapidly passed over a column of Florisil. The benzene was allowed to evaporate and the product was recrystallized from methanol to give 6.6 g (24%) of **21**, mp 69–70°.

Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.4; H, 5.1; N, 10.2; S, 11.7. Found: C, 61.5; H, 5.5; N, 9.9; S, 11.7.

N,N-Dimethyl-4-nitro-2-phenylsulfonylaniline (22).—A solution of 1.05 g (3.8 mmoles) of **21** and 1.5 ml of 30% hydrogen peroxide in 25 ml of glacial acetic acid was refluxed for 2 hr. The solvent was removed under vacuum and the resulting gum was dissolved in benzene and passed rapidly over a column of Florisil. Three products were successively eluted by benzene; the third was 500 mg (43%) of **22**, mp 89.5–90.5°.

Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.9; H, 4.6; N, 9.1; S, 10.5. Found: C, 54.9; H, 4.4; N, 9.0; S, 10.8.

4-Amino-N,N-dimethyl-2-phenylsulfonylaniline (23).—By the method used with **19**, 120 mg (0.39 mmole) of **22** was converted to 80 mg (75%) of **23**, mp 132–133°.

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.8; H, 5.8; N, 10.1; S, 11.6. Found: C, 60.8; H, 5.7; N, 10.3; S, 11.4.

N,N-Diethyl-4-nitro-3-phenylsulfonylaniline (24).—A suspension of 4.0 g (14.4 mmoles) of **17** in 100 ml of freshly distilled diethyl sulfate was stirred at about 90° for 3 hr. After cooling it was poured over ice and a yellow powder was removed by filtration and recrystallized from chloroform–ethanol (1:1 v/v). Tlc (silica gel, 20% ethyl acetate in benzene) showed it to be **17** containing a small amount of a second yellow material. All of the recovered material was dissolved in 25 ml of dimethylformamide (DMF) and heated to *ca.* 100°. Diethyl sulfate (20 ml) was added with rapid stirring. After 1 hr another 20 ml of diethyl sulfate was added. Stirring and heating was continued for 2 more hr. The reaction mixture was poured over ice and a fine yellow solid and a yellow-brown gum were obtained, the latter solidifying after standing for several days. Tlc indicated that more of the product observed earlier, plus a second component, were present. This mixture of products and **17** were once again dissolved in DMF, treated with two 25-ml portions of diethyl sulfate, and heated (90–100°) for approximately 8 hr. The reaction mixture was poured over ice and the yellow powder which formed was recrystallized from ethanol. All of the starting material (**17**) was gone, but tlc still indicated the presence of two products. Several attempts to separate these by column chromatography failed and preparative tlc was used. The two bands overlapped and both had to be chromatographed a second time. The two products showed only a trace of the other component by analytical tlc and this was removed by recrystallization from ethanol. The major component proved to be **24**, mp 158–159°. The second product was the N-ethyl homolog, mp 182–183°. The mass spectra of both products showed the required molecular ion and fragment ions expected, *i.e.*, M − Me and M − NO.

4-Amino-N,N-diethyl-3-phenylsulfonylaniline (25).—Since the precursor **24** was proving so difficult to separate from the monoethyl compound, it was decided to reduce the mixture. The method used with **19** was applied to 500 mg of the mixture. Chromatography on a column of Woelm polyamide and elution with DMF gave a solid product with only a trace of a second component. Recrystallization from ethanol failed to remove the impurity. Preparative tlc on silica gel eluted with 20% ethyl acetate in benzene gave **25**, mp 117–118.5°.

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.1; H, 6.6; N, 9.2. Found: C, 62.5; H, 6.6; N, 9.1.

Registry No.—**3a**, 19766-54-2; **3b**, 19766-55-3; **3c**, 19770-72-0; **3d**, 19770-73-1; **3e**, 19770-74-2; **3f**, 19770-75-3; **3g**, 19770-76-4; **3h**, 19770-77-5; **3i**, 19770-78-6; **3j**, 19770-79-7; **4a**, 19770-80-0; **4b**, 19789-51-6; **4c**, 19770-81-1; **4d**, 19770-82-2; **4e**, 19789-52-7; **4f**, 19771-02-9; **4g**, 19770-83-3; **4h**, 19789-54-9; **4i**, 19789-55-0; **4j**, 19789-56-1; **5a**, 19770-84-4; **5b**, 19770-85-5; **5d**, 19770-86-6; **5f**, 19770-87-7; **5g**, 19770-88-8; **5i**, 19770-89-9; **13**, 5925-26-8; **14**, 19770-91-3; **15**, 19770-92-4; **16**,

19770-93-5; **17**, 19770-94-6; **18**, 19770-95-7; **19**, 19770-80-0; **21**, 19770-97-9; **22**, 19770-98-0; **23**, 19770-99-1; **24**, 19771-00-7; **24** (N-ethyl homolog), 19771-01-8; **25**, 19771-02-9.

Acknowledgment.—The authors are especially indebted to Dr. L. K. J. Tong for his interest in this work and for many helpful discussions. The assistance of Dr. T. H. Regan and Mr. R. L. Young (nmr), Mr. D. P. Maier (mass spectra), Miss T. J. Davis (ir), and Mr. D. F. Ketchum (microanalysis) is very much appreciated. Professor E. C. Taylor, of Princeton University, offered several helpful suggestions during the course of this work.

Linear Free-Energy Relationship Involving *ortho* Substituents in Gas-Phase Reactions. XVII[1]

G. G. SMITH, KIN K. LUM, J. A. KIRBY, AND J. POSPOSIL

Department of Chemistry, Utah State University, Logan, Utah 84321

Received November 12, 1968

Rate constants, and in most cases Arrhenius parameters (E_a and $\Delta S^{\ddagger}$ values), have been determined in the gas-phase pyrolysis of sixteen 1-arylethyl benzoates, sixteen 1-arylethyl acetates, and sixteen 1-arylethyl methyl carbonates. In each case the rates for the pyrolysis of the *meta* and *para* isomers were correlated in a Hammett plot using σ^+ constants. Furthermore, linear free-energy relationships involving *ortho* substituents were obtained in these gas-phase reactions when the log (k/k_0) for the pyrolysis of 1-arylethyl methyl carbonate was plotted as a function of log (k/k_0) for the pyrolysis of 1-arylethyl acetate or 1-arylethyl benzoate, each including *ortho* substituents. This demonstrates that proximity effects are minimal or nonexistent in these reactions. From this study the following σ_o^+ substituent constants have been obtained: *o*-MeO, −0.411; *o*-Me, −0.233; *o*-Br, +0.551; *o*-Cl, +0.452; *o*-NO_2, +0.749.

Equations of the Hammett type have been very successful in correlating equilibrium and rate data for reactions of *meta*- and *para*-substituted benzene derivatives. These equations, however, do not apply for similar reactions of *ortho*-substituted benzene derivatives in the condensed phase because of "proximity effects." Evaluation of *ortho*-substituent constants is extremely difficult since proximity effects for a given *ortho* substituent vary with the nature of the adjacent reaction center, the particular reaction, and especially with the reaction conditions (*e.g.*, solvent). It has been demonstrated, however, that proximity effects are not evident in a study of steric effects in the gas-phase pyrolysis of isopropyl benzoates.[2] From a vapor-phase kinetic study of the pyrolysis of *ortho*-substituted isopropyl benzoates, σ_o^0 constants have been obtained which correlate very well with Taft's calculated values[3] and with other data obtained from reactions thought to be free of the major contributing factor to the proximity effects.[4]

In the present investigation the objective was to evaluate σ^+ values for *ortho* substituents. Previous pyrolysis studies[5,6] have established that the unimolecular vapor-phase pyrolysis of *meta*- and *para*-substituted 1-arylethyl acetates and their methyl carbonates are correlated with the equation log $(k/k_0) = \rho\sigma^+$ using the standard σ^+ values. Assuming that proximity effects for *ortho* substituents in these gas-phase reactions are either negligible or equal, a linear free-energy relationship would result if log (k/k_0) for *ortho*-substituted 1-arylethyl acetates were plotted as a function of log (k/k_0) for *ortho*-substituted 1-arylethyl methyl carbonates. A preliminary report of the data on some of these compounds has been given.[6] In the present study, kinetic data of the gas-phase pyrolysis of sixteen *ortho*-, *meta*-, and *para*-substituted 1-arylethyl benzoates are presented along with some revised data from the gas-phase pyrolysis of the corresponding acetates and methyl carbonates. Linear free-energy relationships for *ortho* as well as *meta* and *para* substituents in these three reactions in the gas phase are reported. From these plots Hammett σ^+ constants are presented for the *ortho* substituents in reactions essentially free of proximity effects.

Experimental Section

Preparation of 1-Arylethyl Alcohols.—All the alcohols, except 1-phenylethyl alcohol, which was purchased from Aldrich Chemical Co., were prepared by sodium borohydride reduction of the substituted acetophenone in 70% aqueous methanol.

Preparation of 1-Arylethyl Benzoates.—The benzoates were prepared by benzoylation of the appropriate alcohols with benzoyl chloride in chloroform in the presence of pyridine. The alcohol (0.1 mole) was mixed with a slight excess of pyridine (0.11 mole) in a three-necked flask fitted with a water condenser and a thermometer. The mixture was cooled externally by an ice–water bath and was stirred by a magnetic bar driven by a motor. Redistilled benzoyl chloride (0.11 mole) in chloroform (80 ml) was added a drop at a time through a dropping funnel, while the temperature of the mixture was kept below 15°. After all the benzoyl chloride was added, the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ether and washed with dilute NH_4OH solution, water, dilute HCl solution, and then again with water. It was dried over magnesium sulfate prior to solvent removal. The desired benzoates were obtained either by fractional distillation at reduced pressure or by recrystallization from pentane. A shorter fractionation column was used in distilling high-boiling benzoates, *e.g.*, 1-*p*-methoxyphenylethyl benzoate [bp 140° (0.09 mm)], to avoid decomposition at the high temperature. Benzoates thus obtained were characterized by infrared and nmr spectra and refractive indices, and where practical the purity was checked by vpc or thin layer chromatography. The physical constants are listed in Table I.

(1) Paper number XVI: B. L. Yates and G. G. Smith, *J. Chem. Soc.*, 7242 (1965). Abstract, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p 5100. Presented in part at the Second Conference on Linear Free Energy Relationships, University of California, Irving, March 27–29, 1968.

(2) D. A. K. Jones and G. G. Smith, *J. Org. Chem.*, **29**, 3531 (1964).

(3) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

(4) (a) M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964). (b) K. K. Lum and G. G. Smith, *Chem. Commun.*, 1208 (1968).

(5) R. Taylor, G. G. Smith, and W. H. Wetzel, *J. Amer. Chem. Soc.*, **84**, 4817 (1962).

(6) G. G. Smith and B. L. Yates, *J. Org. Chem.*, **30**, 434 (1965).

TABLE I
PHYSICAL CONSTANTS OF 1-ARYLETHYL BENZOATES

Substituent[a]	Mp or bp, °C (mm)	$n^{20.5}D$	Yield, %
H	115–116 (0.19)[b]	1.5568	66
p-MeO	140 (0.09)	1.5575	64
o-MeO	34.0–34.4		70
p-Me	117–118 (0.05)	1.5516	66
o-Me	128–132 (0.5)	1.5562	78
m-Me	126–127 (0.23)	1.5524	84
p-Br	142–144 (0.07)	1.5785	83
m-Br	139–141 (0.13)	1.5793	50
p-Cl	152–156 (0.7)	1.5642	72
o-Cl	131–132 (0.07)	1.5669	70
m-Cl	141–143 (0.25)	1.5651	76
p-NO_2	94.8–95.5		82
m-NO_2	65.0–65.5		64

[a] Satisfactory analytical data have been obtained for all compounds except those with H and *p*-Me substitutes. [b] A. Klages and P. Allendorff [*Ber.*, **31**, 1003 (1898)] reported bp 189° (21 mm).

Preparation of 1-Arylethyl Acetates.—The acetates were prepared by either of the following methods. (A) Equal molar quantities of the appropriate alcohol and pyridine were diluted with anhydrous ether (60 ml/0.1 mole of alcohol). The mixture was put into the same apparatus used in benzoylation and was cooled externally with an ice–water bath. A slight excess of acetyl chloride in ether (50 ml/0.1 mole of chloride) was added a drop at a time while the mixture was stirred magnetically. After the addition was complete, the reaction mixture was stirred overnight at room temperature. From then on the treatment was the same as in the preparation of benzoates. (B) Ketene, generated by pyrolyzing acetone over a glowing platinum wire, was bubbled directly into the appropriate alcohol either with or without a solvent (petroleum ether, bp 60–90°). The reaction was catalyzed by adding trace amounts of *p*-toluenesulfonic acid to the alcohol. The approximate duration of bubbling was 1.5–2 hr/0.1 mole of alcohol. The reaction mixture was diluted with ether and was washed with dilute NH_4OH solution and water. It was then treated as in the preparation of benzoates. The acetates were characterized by their infrared and nmr spectra. Their physical constants are given in Table II.

Preparation of 1-Arylethyl Methyl Carbonates.—The carbonates were prepared by either of the following methods. (A) A large excess of methyl chloroformate was added to the alcohol and the mixture was refluxed for 10–12 hr. The reaction was initiated by adding a few drops of pyridine before refluxing the mixture. After the reaction was stopped and cooled to room temperature, it was treated in a manner similar to that employed in the preparation of acetates by ketenization. This method was used in the preparation of nitro- and halo-substituted 1-phenylethyl alcohols. (B) The methyl carbonates of unsubstituted or methyl- and methoxy-substituted 1-phenylethyl alcohols were prepared in a way similar to method A in the preparation of 1-arylethyl acetates. Yields were relatively low compared with those from the next method. (C) A large excess of methyl chloroformate was added a drop at a time to a solution of the alcohol in excess pyridine while it was stirred vigorously and cooled externally with an ice–water bath. A finger condenser with Dry Ice–alcohol as coolant was connected to the reaction flask. After the addition was completed, the mixture was refluxed for 1.5–2 hr. The reaction mixture separated as in method B. This method proved applicable to all the alcohols. The physical constants of 1-arylethyl methyl carbonates are given in Table III.

Method of Pyrolysis.—All esters were pyrolyzed in a stainless steel, constant-volume reactor possessing an automatic pressure monitoring system previously described.[7] The reactor, in this study, was used empty and also packed with enough stainless steel gauze to increase the reactor surface by a factor of ten to check for any surface reactions. None was observed in a seasoned reactor. The temperature of the reactor was measured to a precision of ±0.05°. About 200–300 μl of a liquid sample or equivalent amounts of a solid sample in purified chlorobenzene was used. Each ester was pyrolyzed at least three times at one temperature and repeated at several temperatures over a range of 30°. The temperatures used in the calculations for Arrhenius parameters are given in Table IV.

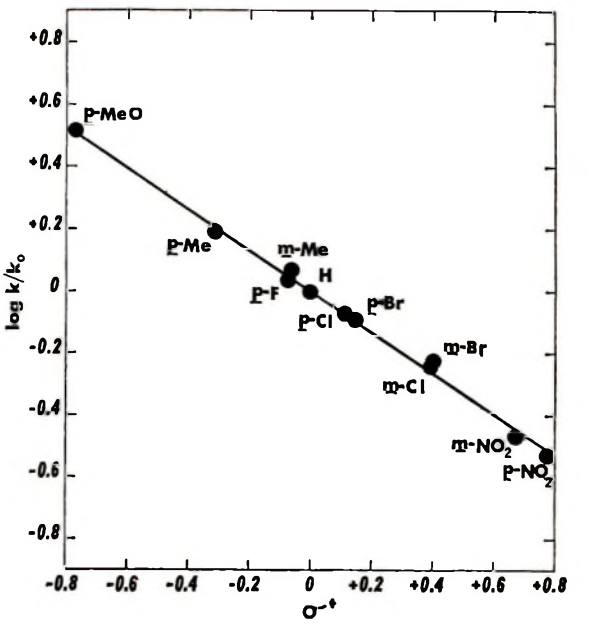


Figure 1.—Linear free-energy correlation, Hammett $\rho\sigma^+$ plot, for pyrolysis of 1-arylethyl acetates. $\rho = -0.663$, correlation coefficient = −0.998.

Kinetics.—Since the reaction was followed by measuring pressure change *vs.* time by means of a pressure transducer, the output, E, varied linearly with the absolute pressure, P. First-order rate constants were calculated directly from the slope of plots of log $(E_\infty - E_t)$ against time for four to six half-lives. Values of E and the elapsed time, t, were obtained directly from the recorder chart, usually at 1-min intervals. The reproducibility of rate constants thus obtained was within ±2%, except for those of nitro-substituted esters, which were within ±10% due to secondary decomposition. The Arrhenius plots were linear (correlation coefficients >0.996) for all the esters pyrolyzed.

The Arrhenius parameters were calculated by combining the experimental rate equation with Eyring's rate expression assuming that $E_a = \Delta H^{\ddagger}$ and that the transmission coefficient is equal to one. Hence, $k_{expt} = (\mathbf{k}T/\mathbf{h})e^{\Delta S^{\ddagger}/R}e^{-E_a/RT}$. E_a was evaluated from a plot of log k_{expt} *vs.* $1/T$.

Results

The pyrolyses of all the esters followed first-order kinetics up to six half-lives except for the nitro esters; in these, secondary decomposition occurred later in the reaction. For nitro esters the initial slope of the first-order plot (for 50–75% reaction) was used to estimate the rate constants. The relative rates of pyrolysis, energies, and entropies of activations are given in Table IV.

Figures 1–3 show the linear free-energy relationship in a Hammett σ^+ correlation in the pyrolysis of 1-arylethyl acetates, 1-arylethyl methyl carbonates, and 1-arylethyl benzoates, respectively. The linear correlation coefficient for these three plots are 0.998, 0.996, and 0.990, respectively. It has already been reported that the pyrolysis of acetates follows a σ^+ correlation.[5,8] The mechanism for ester pyrolysis has been studied extensively in the last 20 years and the available data has been reviewed recently.[9] There seems little doubt that charge separation occurs in the transition state in

(7) (a) G. G. Smith and F. D. Bagley, *Rev. Sci. Instr.*, **32**, 703 (1961); (b) J. A. Kirby, Ph.D. Thesis, Utah State University, Logan, Utah, June 1967; (c) G. G. Smith and J. A. Kirby, *Analyst*, **94**, 242 (1969).

(8) A. Maccoll, *Advan. Phys. Org. Chem.*, **3**, 91 (1965).

(9) K. K. Lum and G. G. Smith, *J. Chem. Kinetics*, in press.

TABLE II

PHYSICAL CONSTANTS OF 1-ARYLETHYL ACETATE

Substituent	Mp or bp, °C (mm)	$n^{20.5}D$	Yield, % (method)	Lit. bp, °C (mm)	Lit. n_D (°C)
H	49 (0.04)	1.4940	Purchased		
o-Me	59.0–59.5 (0.08)	1.4981	67 (A)	80 (2)[a]	1.4991 (25)[a]
m-Me	80–80.5 (0.76)	1.4943	84 (B)[b]		
p-Br	84–85 (0.16)	1.5297	60 (B)	108 (2)[a]	1.5351 (25)[a]
m-Br	75.0–75.5 (0.14)	1.5294	79 (B)	96 (1.1)[a]	1.5295 (25)[a]
o-Cl	70.0–70.5 (0.08)	1.5100	66 (A)	64–65 (0.05)[c]	1.5011 (20)[c]
m-Cl	67.5–68.0 (0.18)	1.5091	82 (B)	65–66 (0.5)[a]	1.5116 (25)[a]
p-NO_2	55.5–56		81 (B)[d]		
m-NO_2	105–106 (0.16)	1.5227	65 (A)	131 (1.6)[a]	1.5225 (25)[a]

[a] Reference 5. [b] *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.91. Found: C, 74.38; H, 8.07. [c] Reference 6. [d] *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.69. Found: C, 57.41; H, 5.31; N, 6.62.

TABLE III

PHYSICAL CONSTANTS OF 1-ARYLETHYL METHYL CARBONATES

Substituent	Bp, °C (mm)	$n^{20.5}D$	Yield, % (method)	Lit. bp, °C (mm)	Lit. $n^{20}D$
H	64.0–64.5 (0.25)	1.4912	64 (C)	85 (0.4)[a]	1.4930[a]
p-MeO	99.5–100 (0.23)	1.5011	59 (C)	88 (0.2)[a]	1.5021[a]
o-MeO	87–88 (0.2)	1.5012	25 (B)	76–77 (0.1)[a]	1.5078[a]
p-Me	67.5–68.5 (0.08)	1.4910	24 (B)	62–64 (0.3)[a]	1.4920[a]
m-Me	74.5–76.0 (0.22)	1.4914	70 (C)[b]		
m-Br	90–91 (0.19)	1.5257	46 (C)[c]		
o-Cl	81.0–81.5 (0.17)	1.5055	90 (A)	74–75 (0.5)[a]	1.5068[a]
m-Cl	82–83 (0.24)	1.5059	62 (C)	80–82 (0.1)[a]	1.5074[a]
o-NO_2	123 (0.4)	1.5175 (22)	81 (A)[d]		

[a] Reference 6. [b] *Anal.* Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.07; H, 7.16. [c] *Anal.* Calcd for $C_{10}H_{11}BrO_3$: C, 46.31; H, 4.28; Br, 30.81. Found: C, 46.09; H, 4.51; Br, 30.56. [d] *Anal.* Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.03; H, 5.19; N, 6.15.

TABLE IV

LOG OF THE RELATIVE RATES AND ENERGIES AND ENTROPIES OF ACTIVATION OF PYROLYSES OF 1-ARYLETHYL BENZOATES, ACETATES, AND METHYL CARBONATES

	Acetates (374.1°)					Benzoates (374.1°)					Carbonates (346.0°)				
Substituent	Registry no.	Log (k/k_0)	E_a	$\Delta S^{\ddagger}$	r	Registry no.	Log (k/k_0)	E_a	$\Delta S^{\ddagger}$	r	Registry no.	Log (k/k_0)	E_a	$\Delta S^{\ddagger}$	r
H	93-92-5	0.00	43.1	−2.9	0.999	13358-49-1	0.00	42.6	−2.5	0.998	1796-59-4	0.00	41.2	−1.8	0.999
p-MeO	945-89-1	0.52	38.9	−7.4	0.998	19771-09-6	0.77	43.9	3.4	0.999	1678-47-3	0.61	41.1	0.56	0.999
o-MeO	19759-39-8	0.26				19771-03-0	0.38	46.6	5.7	0.998	2016-97-9	0.33	37.9	−5.7	0.998
p-Me	19759-40-1	0.19	43.2	−1.32		19771-04-1	0.25	47.2	6.0	0.997	1796-67-4	0.23	41.0	−1.1	0.999
o-Me	19759-21-8	0.17	44.4	−0.3	0.999	19771-05-2	0.21				1678-48-4	0.20	42.7	1.6	0.998
m-Me	19759-22-9	0.07	43.6	−1.9	0.997	19771-06-3	0.08	44.1	0.65	0.999	19759-33-2	0.09	44.2	3.3	0.999
p-F	2928-12-3	0.035									1796-57-2	0.02			
p-Br	19759-23-0	−0.09	46.2	1.2	0.999	19771-07-4	−0.105	44.8	7.4	0.999	1796-69-6	−0.14			
o-Br	1796-61-8	−0.33									1796-70-9	−0.40			
m-Br	6948-02-3	−0.23	45.7	−7.1	0.999	19771-10-9	−0.25	44.7	−0.10		19759-34-3	−0.25	44.0	1.3	0.999
p-Cl	19759-43-4	−0.07				19771-11-0	−0.09				1796-71-0	−0.085			
o-Cl	1996-62-9	−0.28	46.1	0.32	0.999	19771-12-1	−0.30	43.1	−2.8	0.996	1796-56-1	−0.32	42.9	−0.55	0.999
m-Cl	19759-26-3	−0.24	44.9	−1.3	0.999	19771-13-2	−0.27	45.9	1.6	0.999	1796-72-1	−0.26	44.0	1.3	0.999
p-NO_2	19759-27-4	−0.53	40.5	−9.8	0.999	19771-14-3	−0.50	43.5	−3.5	0.999	19759-49-0	−0.50	42.4	−2.3	0.998
o-NO_2											19759-37-6	−0.51	41.2	−4.2	0.999
m-NO_2	19759-28-5	−0.47	41.3	−8.3	0.999	19771-15-4	−0.48	44.7	−1.6	0.999	1796-68-5	−0.46	41.7	−3.5	0.998

TABLE V

σ_0^+ SUBSTITUENT CONSTANTS FROM GAS-PHASE PYROLYSIS OF ESTERS

	σ_0^+					
Substituent	A[a]	B[b]	C[c]	Av	σ_p^+	σ_m^+
MeO	−0.382	−0.46	−0.435	−0.426	−0.78	−0.047
Me	−0.246	−0.24	−0.251	−0.246	−0.31	−0.066
Br	+0.508		+0.594	+0.551	+0.15	+0.405
Cl	+0.433	+0.45	+0.482	+0.455	+0.11	+0.399
NO_2			+0.749	+0.749	+0.778	+0.674

[a] (A) Pyrolysis of acetates, $\rho = -0.663$, correlation coefficient = −0.999. [b] (B) Pyrolysis of benzoates, $\rho = -0.795$, correlation coefficient = −0.990. [c] (C) Pyrolysis of carbonates, $\rho = -0.709$, correlation coefficient = −0.996.

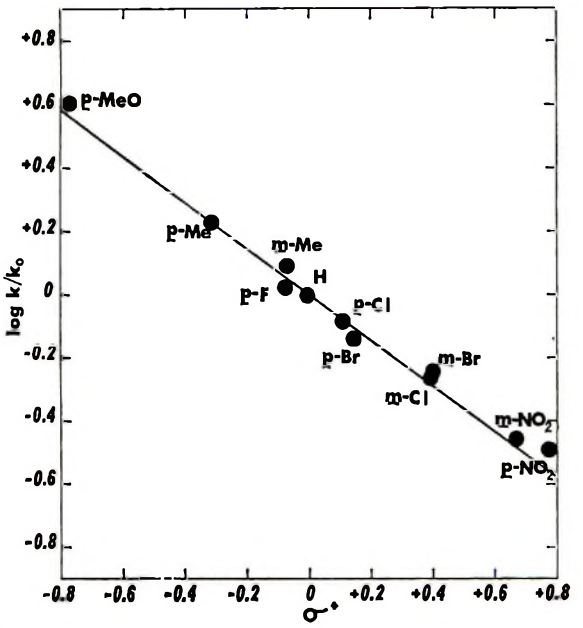


Figure 2.—Linear free-energy correlation, Hammett $\rho\sigma^+$ plot, for the pyrolysis of 1-arylethyl carbonates. $\rho = -0.709$, correlation coefficient = −0.996.

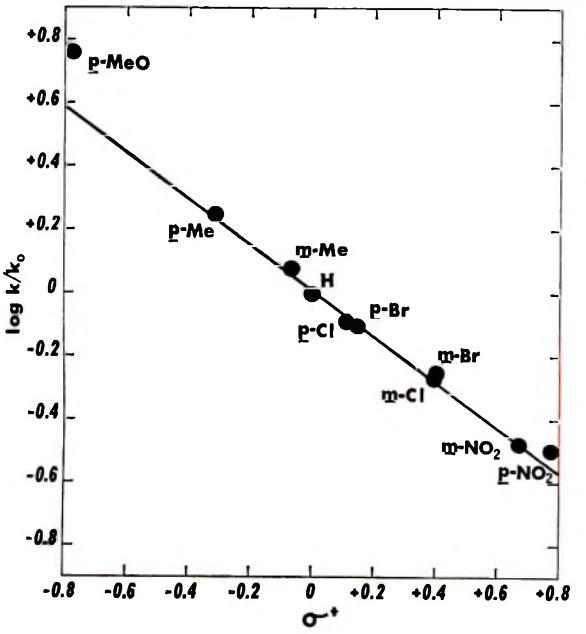


Figure 3.—Linear free-energy correlation, Hammett $\rho\sigma^+$ plot, for the pyrolysis of 1-arylethyl benzoates. $\rho = -0.795$, correlation coefficient = = 0.990.

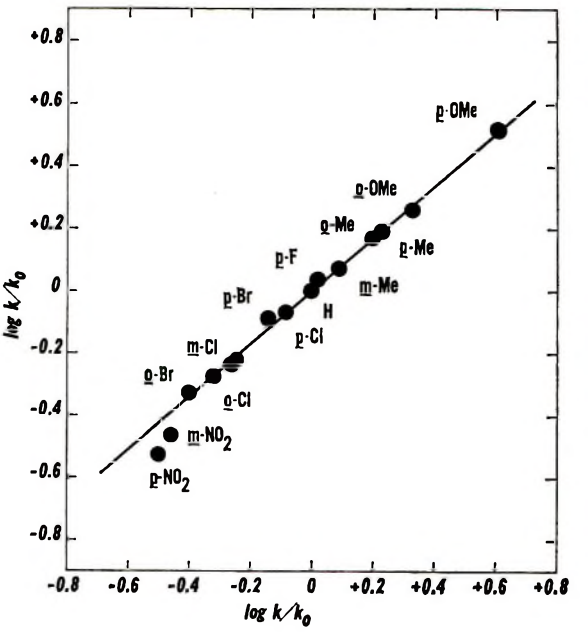


Figure 4.—Linear free-energy correlation, log (k/k_0) for the pyrolysis of 1-arylethyl acetates *vs.* log (k/k_0) for the pyrolysis of 1-arylethyl carbonates, including *ortho* substituents. $\rho = 0.833$, correlation coefficient = 0.994.

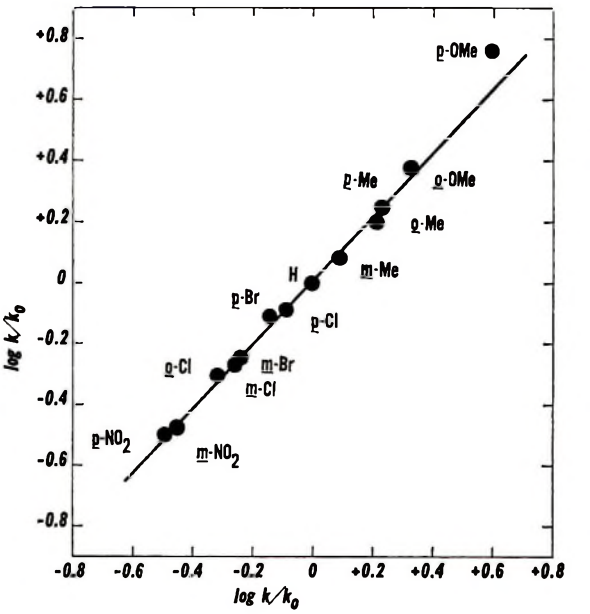


Figure 5.—Linear free-energy correlation, log (k/k_0) for the pyrolysis of 1-arylethyl benzoates *vs.* log (k/k_0) for the pyrolysis of 1-arylethyl carbonates, including *ortho* substituents. $\rho = 1.00$, correlation coefficient = 0.996.

this unimolecular gas-phase reaction, but a serious question has been raised about the formation of an ion-pair intermediate, which has been proposed for reactions of this type.[10]

Figures 4 and 5 are linear free-energy plots for the pyrolysis of acetates *vs.* carbonates and benzoates *vs.* carbonates with linear correlation coefficients of 0.994 and 0.996, respectively. The *ortho* substituents, as well as the *para* and *meta* substituents, are all correlated with a degree precision. These plots demonstrate that substituent effects in all three gas-phase pyrolysis reactions are directly comparable, and any proximity effects by the *ortho* substituents are constant or perhaps even negligible.

In such a situation, σ^+ constants could be determined for *ortho* substituents from the rate data of each individual reaction using the ρ value for the equation log $(k/k_0 = \rho\sigma^+$ for the *para* and *meta* substituents). The σ^+ values for *ortho* substituents thus calculated are listed in Table V. The σ_o^+ values obtained from these different reactions agree reasonably well with each other. Included for comparison are σ^+ constants for the corresponding *meta* and *para* substituents.[11]

(10) (a) M. Hanack, H.-J. Schneider, and H. Schneider-Bernlohr, *Tetrahedron*, **23**, 2195 (1967); (b) J. C. Scheer, E. C. Kooyman, and F. L. J. Sixma, *Rec. Trav. Chim.*, **82**, 1123 (1963); (c) C. A. Bunton, K. Khaleeluddin, and D. Whittaker, *Nature*, **190**, 715 (1961).

(11) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

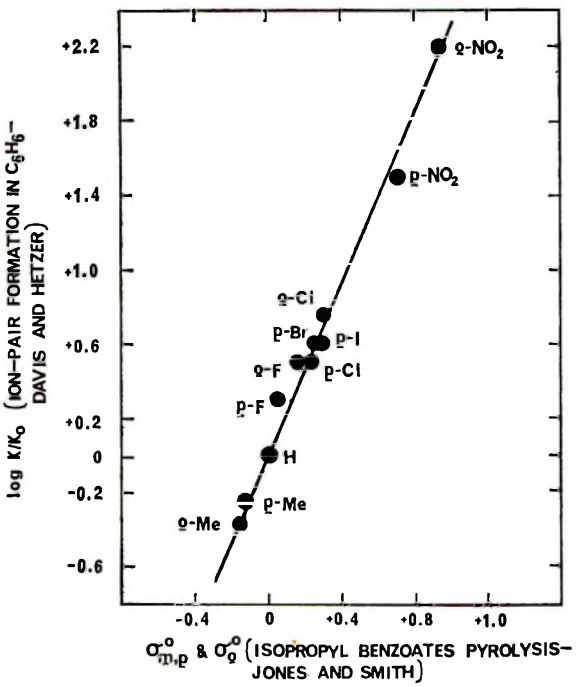


Figure 6.—Linear free-energy correlation, log (k/k_0) for the ion-pair formation of benzoic acid with 1,3-diphenylguanidine in benzene (Davis and Hetzer[24]) against $\sigma_{m,p}^0$ and σ_o^0 (Jones and Smith[2]) determined from the pyrolysis of substituted isopropyl benzoates.

Discussion

Evidence for Proximity Effects.—Relating structure to reactivity for rigid systems, where the substituent is located *meta* or *para* to the reactive site in benzene derivatives, has been remarkably well accomplished with linear free-energy relationships of the Hammett type.[12] Results in the less rigid aliphatic systems and in *ortho*-substituted benzene derivatives, where the problem is substantially more complex, have not been as fruitful. *Ortho* substituents are considered to involve a variety of effects in addition to the well-known inductive, field, and resonance effects generally acknowledge with *meta*- and *para*-substituted derivatives. These additional effects are frequently referred to as "proximity effects" and have been reported in measurements of half-wave potential in polarographic analysis;[13] ir,[14a] uv,[14b] and nmr[14c,d] spectra; diffraction patterns;[15a] and, of course, in many chemical reactions such as the ionization of acids, hydrolysis of esters and amides, and numerous addition reactions to carbonyl compounds.[15b]

Explanations for Proximity Effects.—In an attempt to explain these complicating proximity effects many hypotheses have been suggested such as primary[16] and secondary steric effects,[17] intramolecular hydrogen bonding,[18] field effects,[14d,19] and effects of substitution on solvation,[20] as well as several less understood concepts such as ponderal effects,[21] London forces,[22] and miserable effects.[23]

Brown, *et al.*,[16] have emphasized the importance of primary steric effects (compression between the reactant and the neighboring substituent in bimolecular reactions). In contrast and opposition to Brown, a long series of papers published by Chapman, Shorter, and coworkers deal with attempts to separate polar, resonance, and steric effects in systems involving *ortho* substituents. This group has stressed recently[20i] the importance of the solvent participation, including steric inhibition of solvation, in both the ground state and transition state, the polar facilitation of solvation, and the ring solvation effects. Solvation effects alter both the entropy and enthalpy of activation. Many other scientists have also spoken of the importance of steric interference with solvation of the transition state.[20] Hojo, *et al.*,[20d] have shown that the extent of solvent participation is dependent on the solvent as well as the reaction. For example, proximity effects are present but constant in various solvents in reactions such as the alkaline hydrolysis of *ortho*-substituted ethyl benzoates, whereas the solvent effect on the *ortho*-proximity effect (or *vice versa*) is marked and variable in the ionization of aryl acids.

There is little doubt that the medium plays a very important role in reactivity in the condensed phase and that this role is dependent on the *ortho* substituent. Studies of *ortho*-substituent effects in the condensed phase are, therefore, very formidable, particularly when polar solvents are involved.

Whatever the explanation for proximity effects, the problem of evaluating *ortho*-substituent constants is appreciably eased in studies of unimolecular reactions where the primary steric effects have been excluded and the reacting molecules are sufficiently separated

(12) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp 184–199.

(13) D. H. Geske, J. L. Ragle, M. A. Bambenek, and A. L. Balch, *J. Amer. Chem. Soc.*, **86**, 987 (1964); W. H. Hussey and A. J. Diefenderfer, *ibid.*, **89**, 5359 (1967).

(14) (a) L. J. Bellamy and R. L. Williams, *J. Chem. Soc.*, 4294 (1957); 3465 (1958); M. L. Josein and C. Castinel, *Bull. Soc. Chim. France*, 801 (1958); I. R. Solomon and R. Filler, *J. Amer. Chem. Soc.*, **85**, 3492 (1963); G. Elington, G. Ferguson, K. M. Islam, and J. S. Glasley, *J. Chem. Soc., B*, 1141 (1967); (b) R. C. Cookson, *ibid.*, 282 (1954); I. R. Solomon and R. Filler in ref 14a; E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; H. Foster, *J. Amer. Chem. Soc.*, **82**, 3780 (1960); (c) V. J. Kowalewski and D. G. de Kowalewski, *J. Chem. Phys.*, **37**, 1009 (1962); F. C. Stehling, *Anal. Chem.*, **35**, 773 (1963); (d) N. Boden, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, *Mol. Phys.*, **8**, 133 (1964); M. T. Tribble and J. G. Traynham, 2nd Conference on Linear Free Energy Relationships, University of California, Irvine, March 27–29, 1968.

(15) (a) G. Ferguson and J. M. Robertson, *Advan. Phys. Org. Chem.*, **1**, 203 (1963), and references contained therein; G. Eglington, G. Ferguson, K. M. Islam, and J. S. Glasley, in ref 14a; (b) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, pp 192–194, 593; N. B. Chapman, M. G. Rodgers, and J. Shorter, *J. Chem. Soc., B*, 164 (1968), and earlier papers.

(16) H. C. Brown and B. Kanner, *J. Amer. Chem. Soc.*, **88**, 986 (1966).

(17) (a) G. G. Smith and D. V. White *J. Org. Chem.*, **29**, 3533 (1964); (b) J. F. Dippy, S. R. C. Hughes, and J. W. Laxton, *J. Chem. Soc.*, 1470 (1954); (c) N. B. Chapman, J. Shorter, and J. H. P. Utley, *ibid.*, 1824 (1962).

(18) R. Stewart and M. R. Granger, *Can. J. Chem.*, **39**, 2508 (1961).

(19) The importance of the field effect between the reaction site and the substituent is gaining recognition and is dependent on the distance and direction between the reacting site and the substituent: (a) P. R. Wells and W. Adcock, *Australian J. Chem.*, **18**, 1365 (1965); (b) M. J. S. Dewar and T. G. Squires, *J. Amer. Chem. Soc.*, **90**, 210 (1968); (c) H. D. Holtz and L. M. Stock, *ibid.*, **86**, 5183, 5188 (1964); **87**, 2404 (1965); R. Golden and L. M. Stock, *ibid.*, **88**, 5928 (1966); (d) M. J. S. Dewar, *Chem. Commun.*, 547 (1968); (e) K. Bowden, *Can. J. Chem.*, **44**, 661 (1966).

(20) (a) J. G. Watkinson, W. Watson, and B. L. Yates, *J. Chem. Soc.*, 5437 (1963); (b) C. C. Price and D. C. Lincoln, *J. Amer. Chem. Soc.*, **73**, 5836 (1951); (c) J. B. Hyne and R. Wills, *ibid.*, **85**, 3650 (1963); (d) M. Hojo, M. Utaka, and Z. Yoshida, *Tetrahedron Letters*, 19 (1966); *Yuki Gosei Kagaku Kyokai Shi*, **23**, 1034 (1965); *Chem. Abstr.*, **64**, 4916 (1966); (e) K. Yates and R. Stewart, *Can. J. Chem.* **37**, 664 (1959); (f) C. H. Rochester and B. Rossall, *J. Chem. Soc., B*, 743 (1967); (g) F. E. Condon, *J. Amer. Chem. Soc.*, **87**, 4494 (1965); (h) C. L. De Ligny, *Rec. Trav. Chim.*, **85**, 1114 (1966); (i) N. B. Chapman, M. G. Rogers, and J. Shorter, ref 15b; (j) S. Ehrenson, 2nd Conference on Linear Free Energy Relationships, University of California, Irvine, March 27–29, 1968.

(21) C. K. Ingold, *Quart. Rev.* (London), **11**, 1 (1957).

(22) J. D. Reinheimer and J. F. Bunnett, *J. Amer. Chem. Soc.*, **81**, 315 (1959).

(23) J. F. Bunnett and J. Y. Bassett, Jr., *J. Org. Chem.*, **27**, 2354 (1962).

from one another to avoid interaction with the solvent or other reacting molecules. This has been accomplished in gas-phase reactions. σ_o^0 substituent constants obtained in the gas-phase pyrolysis of isopropyl benzoates[2] correlate very well with other polar *ortho*-substituent constants obtained from Davis and Hetzer's work on the reaction of benzoic acid with 1,3-diphenylguanidine in benzene.[24] This correlation is shown in Figure 6.

As solvent molecules apparently play a major role in proximity effects, it is not surprising that *ortho*-substituent effects in one gas-phase reaction correlate with *ortho*-substituent effects in another, particularly if the reactions both utilize a similar pathway. Unimolecular gas phase reactions correlated by σ^+ substituent constants, therefore, afford an approach to establishing σ^+ substituent constants for *ortho* substituents free from solvent participation and, of course, primary steric effects. Apparently the secondary steric effects for such reactions are negligible or similar and cancel out. Earlier studies[17a] showed that two methyl groups, flanking a *p*-methoxy substituent, exhibited steric inhibition of resonance in the gas-phase pyrolysis of 1-arylethyl acetates.

The general applicability of these *ortho*-substituent constants will be shown as other similar systems are studied where different bonds are broken such as in the thermolysis of 1-arylethyl methyl xanthates, amine oxides, and β-hydroxy olefins (CH_2=C(Ar)CH_2CH_2OH, $ArCHOHCH_2CH$=CH_2).

Strong support has already been obtained for these *ortho*-substituent constants in an electron-impact study of substituted benzophenones. Mass spectral data for *ortho*-, *meta*-, and *para*-substituted benzophenones, log (Z/Z_0) (Z = $[C_6H_5CO^+]/[XC_6H_4COC_6H_5^+]$, Z_0 = $[C_6H_5CO^+]/2X[C_6H_5COC_6H_5^+]$) were plotted *vs.* σ^+ constants for *meta* and *para* substituents, and for the *ortho* σ^+ constants reported from this study. The correlation coefficient in this study, which is reported elsewhere,[25] is 0.984.

Acknowledgment.—This work was supported in part by two National Science Foundation Grants, GP 2940 and GP 6006. Grateful acknowledgment is given for this support.

(24) M. M. Davis and H. B. Hetzer, *J. Res. Natl. Bur. Std.*, **60**, 569 (1958).

(25) K. K. Lum and G. G. Smith, *J. Org. Chem.*, **34**, 2095 (1969).

Linear Free-Energy Relationship Involving *ortho* Substituents in Mass Spectrometry

KIN K. LUM AND GRANT GILL SMITH

Department of Chemistry, Utah State University, Logan, Utah 84321

Received November 12, 1968

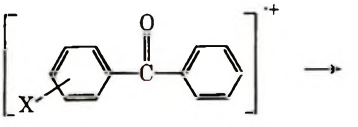
A linear free-energy relationship involving *ortho* substituents has been found between the benzoyl ion intensities in the mass spectra of substituted benzophenones and σ^+ substituent constants. This good correlation indicates that proximity effects are equivalent or negligible in gas-phase electron-impact reactions of benzophenones.

The evaluation of *ortho* σ^0 [1] and σ^+ constants[2] has been carried out in this laboratory by studying the gas-phase pyrolysis of esters which is a unimolecular, homogeneous reaction. The correlation of the σ_o^0 constants with the ion-pair formation of benzoic acid in benzene[3] is remarkable.[2] The present study was designed to test whether σ_o^+ constants previously obtained from kinetic data of pyrolysis of various esters[2] could be correlated in another gas-phase reaction which is unimolecular and homogeneous.

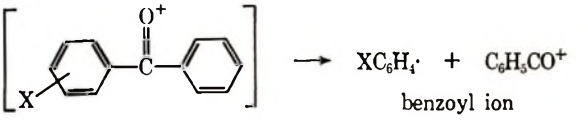
Mass spectrometry provides a system for this purpose. Lossing, *et al.*,[4] have shown that the ionization potentials of benzyl radicals, eq 1, can be correlated in a linear free-energy relationship involving σ^+ substituent

$$XC_6H_4CH_2I \xrightarrow{\Delta} XC_6H_4CH_2\cdot \xrightarrow{e^-} XC_6H_4CH_2^+ + 2e^- \quad (1)$$

constants. They limited their study to *meta* and *para* substituents. McLafferty, *et al.*,[5] have investigated substituent effects in benzophenones and acetophenones by studying the ratio of ion intensities in mass spectrometry. They also limited their study to *meta* and *para* substituents. In the present investigation the method of McLafferty, *et al.*, of correlating relative ion intensities with σ^+ substituent constants was adopted. Mass spectral data for *ortho*-, *meta*-, and *para*-substituted benzophenones, log (Z/Z_0), (Z = $[C_6H_5CO^+]/[XC_6H_4COC_6H_5^+]$, Z_0 = $[C_6H_5CO^+]/2[C_6H_5COC_6H_5^+]$) were plotted *vs.* σ^+ constants for *meta* and *para* substituents, and the recently reported *ortho* σ^+ constants were determined from pyrolysis of esters.[2]



molecular ion



benzoyl ion

Experimental Section

Preparation of Benzophenones.—Substituted benzophenones commercially available were recrystallized two or three times from spectral grade methanol or fractionally redistilled at reduced pressure. *o*-Hydroxy, *m*-chloro-, and *m*- and *o*-bromobenzophenones were prepared by a Friedel–Craft reaction with the

(1) D. A. K. Jones and G. G. Smith, *J. Org. Chem.*, **29**, 3531 (1964).

(2) G. G. Smith, K. K. Lum, J. A. Kirby, and J. Pospisil, *ibid.*, **34**, 2090 (1969).

(3) M. M. Davis and H. B. Hetzer, *J. Res. Natl. Bur. Std.*, **60**, 569 (1958); G. G. Smith and K. K. Lum, *Chem. Commun.*, 1208 (1968).

(4) A. G. Harrison, P. Kebarle, and F. P. Lossing, *J. Am. Chem. Soc.*, **83**, 777 (1961).

(5) (a) M. M. Bursey and F. W. McLafferty, *ibid.*, **88**, 529 (1966); (b) F. W. McLafferty, *Chem. Commun.*, 956 (1968), and references therein.

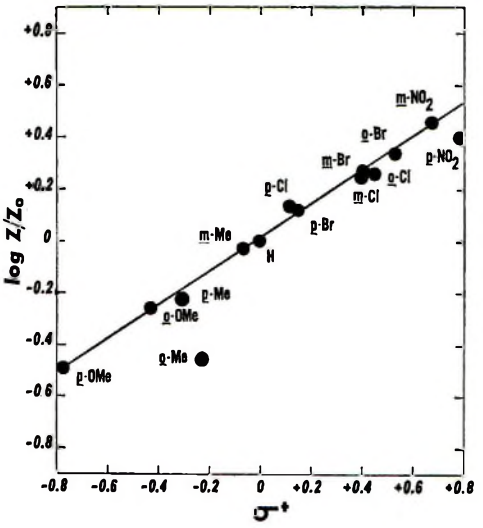


Figure 1.—Linear free-energy correlation of the benzoyl ion intensity, $Z = [C_6H_5CO^+]/[C_6H_5COC_6H_4Y]^+$ in the mass spectra of *ortho*-, *meta*-, and *para*-substituted benzophenones with σ^+ constants. $\rho = +0.619$; linear correlation coefficient = 0.984.

corresponding benzoyl chloride, benzene, and aluminum chloride. *o*-Methoxybenzophenone was prepared by methylation of *o*-hydroxybenzophenone with dimethyl sulfate in alcoholic sodium hydroxide solution. No indication of appreciable impurities was detected in the mass spectrum of any compound.

Mass Spectra.—All the mass spectra were recorded on a Hitachi RMU-6E single-focusing instrument using 80-eV electrons at an emission current of 80 μA. All solid samples were introduced at a suitable temperature inside the sample heater (25–45°) to give enough vapor pressure for recording. Liquid samples were injected at 170°. The source temperature was maintained at 175 ± 2°. It has been reported that benzophenones do not undergo thermal decomposition under 185°.[5] The standard deviation for four to eight replicate recordings of the same sample was, on the average, 2.5%; ratios of fragment ion intensities to molecular ion intensities were constant to within 3% from day to day for all the compounds except *p*-nitrobenzophenone, a phenomenon also observed by McLafferty, *et al.*[5]

Results and Discussion

The application of the kinetic approach to mass spectra has been discussed in detail by McLafferty, *et al.*[5] The decomposition of the molecular ion in the gas phase is a unimolecular, homogeneous reaction. Table I shows the data for substituted benzophenones in

TABLE I

Substituent	Log (Z/Z_0)
p-NO_2	0.40 (0.35–0.45)
m-NO_2	0.46
p-Br	0.12
m-Br	0.37
o-Br	0.34
p-Cl	0.135
m-Cl	0.25
o-Cl	0.26
H	0.00
m-Me	−0.03
p-Me	−0.22
o-MeO	−0.26
o-Me	−0.46
p-MeO	−0.50

which Z equals the ratio of the intensity of the m/e 105 ion ($C_7H_5O^+$) to that of the molecular ion as stated above. When log (Z/Z_0) was plotted against σ^+ constants, including those for *ortho* substituents previously determined, a straight line was obtained ($\rho = 0.619$); the linear correlation coefficient equals 0.984 as shown in Figure 1.

The fact that a good correlation of σ_o^+ constants was obtained with the ion intensities in mass spectra of benzophenones indicated that proximity effects are equivalent or negligible in gas-phase pyrolysis of esters and gas-phase electron-impact reactions of benzophenones. These results are surprising considering the complexity of the factors which affect ion abundance.[6b] An explanation for the failure of the *o*-Me substituent to correlate in this study is given in a recent paper by Ballantine and Pillinger[6a] who have studied the mass spectra of *ortho*-substituted benzophenones. Based on their paper the *o*-OH substituent would also show a marked deviation. With *o*-Me and *o*-OH substituents a hydrogen migration occurs and a large M − 1 peak appears as the base peak. Meyerson, *et al.*, discussed the mass spectra of *ortho*-substituted diarylmethanes.[6b] This proximity effect causes a marked deviation as shown in the figure. The result of this investigation, however, supports the suggestion that σ_o^+ constants are obtainable for gas-phase, unimolecular, homogeneous reactions. One of the differences between these two reactions is that the reactant of the latter is an unsolvated cation, whereas in pyrolysis the reactant is an unsolvated molecule.

It has often been emphasized that reactions which follow a $\rho\sigma^+$ relationship involve a negative ρ value. This is because the reaction involves an electron-deficient intermediate, transient or otherwise, which can be stabilized in the rate-determining transition state by electron release from an aromatic ring. Examples of this are cumyl chloride solvolyses,[7] the pyrolysis of 1-arylethyl acetates,[8] and the appearance potential studies in mass spectroscopy of benzyl radicals.[4]

The ρ value in this mass spectral study, however, is positive even though it too follows a σ^+ correlation. An explanation for this is that the positive charge which is stabilized by the electron-releasing substituent is located on the starting material, $[ArCOPh]\cdot^+$. Hence, these substituents stabilize these species and decrease the reaction rate. To our knowledge this reaction is the only reported example where this point has been observed. The ρ value reported by McLafferty, *et al.*,[5a] was also positive (0.66 linear correlation coefficient = 0.963); they proposed a different explanation for the positive ρ value and found as good a correlation using σ as σ^+.

The fact that proximity effects are equivalent or reduced to a minimum in gas-phase reactions may be mainly because the transition state is unsolvated as compared with reactions in the condensed phase. The steric effect of the *ortho* substituent, which contributes greatly to the proximity effects, may be overcome in the transition state by lack of solvation.[9] Based on this

(6) (a) J. A. Ballantine and C. T. Pillinger, *Org. Mass Spectrmy.*, **1**, 425 (1968); (b) S. Meyerson, H. Drews, and E. K. Fields, *J. Amer. Chem. Soc.*, **86**, 4964 (1964).

(7) H. C. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958).

(8) R. Taylor, G. G. Smith, and W. H. Wetzel, *ibid.*, **84**, 4817 (1962).

(9) It has been reported that the anomalous influence of *ortho* substituents in the condensed phase is partially due to its steric interference with solvation of the transition state [C. C. Price and D. C. Lincoln, *ibid.*, **73**, 5836 (1951); J. B. Hyne and R. Wills, *ibid.*, **85**, 3650 (1963); J. G. Watkinson, W. Watson, and B. L. Yates, *J. Chem. Soc.*, 5437 (1963)].

reasoning, McLafferty, *et al.*,[5] explained their data of *p*-phenylbenzophenone from electron-impact reactions. In their case, the transition state also receives excess vibrational energy from electron impact to overcome the steric strain. The suggestion that proximity effects can be reduced by overcoming steric strain in the transition state is also revealed in Weale's[10] study of the reaction between *o*-methyl-N,N-dimethylaniline and methyl iodide in dry methanol. He found that the "*ortho* effect" is decreased by increasing the pressure on the system. He explained this observation as due to the contribution from compression energy which overcomes the steric strain in the transition state. Certainly this study and other gas-phase studies[2] demonstrate the advantages of gas-phase studies when relating structure to chemical reactivity.

(10) K. E. Weale, *J. Phys. Soc.*, 2959 (1954).

Acknowledgment. —This work was supported in part by two National Science Foundation Grants, GP 6006 and an equipment grant for the purchase of the mass spectrometer. The Utah State University Research Council also supported this study. We wish to express our appreciation for these generous supports.

Carboxylate-Facilitated Acetylation of Hydroxy Acids in Aqueous Solution

ROLF B. PAULSSEN, IAN H. PITMAN, AND TAKERU HIGUCHI

Department of Pharmaceutical Analytical Chemistry and Pharmaceutics, University of Kansas, Lawrence, Kansas 66044

Received October 16, 1968

Interactions of acetic anhydride with glycolate, malate, salicylate, and similar hydroxy acid anions in dilute aqueous solutions have been shown to lead to significant formation of corresponding acetyl esters. Thus, when acetic anhydride (initial concentration 0.02 *M*) was added to 0.5 *M* solutions of sodium salicylate or sodium glycolate, 22.6% of the acetic anhydride reacted to form aspirin (acetylsalicylic acid) and 48.4% to form acetylglycolic acid, respectively. The reactions which take place competitively with the hydrolysis of the acetic anhydride are believed to be mediated by initial attack of the carboxylate function followed by an O (carboxyl) to O (hydroxy) transacetylation reaction. Salicylate ions, for example, appear to form mixed salicylic acetic acid anhydride species, which preferentially undergo rearrangement to aspirin rather than hydrolysis. These mechanisms appear to play a part in the slow hydrolysis of the corresponding acetyl esters.

In an earlier paper[1] we reported that small amounts of acetylmalate ion were obtained when acetic anhydride was added to dilute aqueous solutions of sodium malate. Further investigation of this reaction and studies on similar acetylations of other hydroxy acid anions strongly indicate that the responsible mechanism involved an O to O transacetylation process mediated by the carboxylate function. Relevant data on these systems are presented in this article.

Although unsubstituted alcohols and phenols can be acetylated by acetic anhydride in inert solvents, or in the absence of solvents, the acetylation of the hydroxy group normally competes unsuccessfully with the hydrolysis of acetic anhydride in water. For example, when acetic anhydride (0.02 *M*) was added to a solution of ethanol (0.50 *M*) in water, more than 99% of the acetic anhydride was hydrolyzed to acetic acid.

The present investigation was undertaken to examine what role a carboxylate group in the alcohol or phenol molecule played in the reaction sequence which led to the significant acetylation of these molecules by acetic anhydride in water.

Results and Discussion

Formation of Ester.—One of the simpler indications of rapid concomitant ester formation during apparent hydrolysis of acetic anhydride in, for example, aqueous sodium glycolate, is the observed reduction in the amount of acetic acid found. Thus the solution obtained 1 hr after adding acetic anhydride (0.02 *M*) to aqueous solutions of sodium glycolate (0.5 *M*) at 25° (solution 1) required a 24% smaller titer of standard sodium hydroxide solution to raise its pH to the phenolphthalein end point than did a solution obtained 1 hr after adding acetic anhydride (0.02 *M*) to water (solution 2).

When solution 1 was acidified with mineral acid and chromatographed on a silicic acid column, it was found to contain the ester, acetylglycolic acid, together with acetic and glycolic acids. The composition of solution 1 did not change appreciably between 30 min and 2 hr after mixing acetic anhydride with the sodium glycolate solution. The slow hydrolysis of acetylglycolic acid in neutral solutions has been investigated by Senter and Ward.[2]

Similar behavior was observed following addition of acetic anhydride to aqueous solutions of other hydroxy acid anions. Errors in the titration of the salicylic acid reaction mixture due to the hydrolysis of acetylsalicylic acid proved to be within the experimental error.

The per cent yield of ester, relative to moles of added acetic anhydride (relative yield, R), was calculated from the titration data on the assumption that the lower titer of sodium hydroxide against the reaction mixture (solution 1) was due to the fact that some of the acetic acid, which would result from the hydrolysis of acetic anhydride, was tied up as an acetyl group in the ester. Results in Table I show the per cent relative yield of ester obtained following the addition of acetic anhydride to aqueous solutions of hydroxy acid anions and alcohols at 25°. The importance of a carboxylate group in the molecules is evident in the fact that the un-ionized hydroxy acids and simple alcohols and phenol were not acetylated to an appreciable extent under the experimental conditions. The failure of tri-

(1) I. H. Pitman, R. B. Paulssen, and T. Higuchi, *J. Pharm. Sci.*, **57**, 239 (1968).

(2) G. Senter and T. J. Ward, *J. Chem. Soc.*, 2535 (1912).

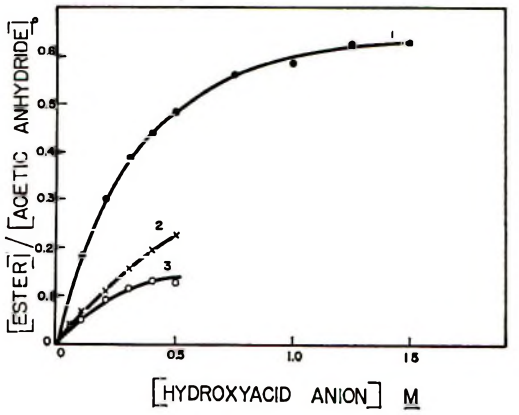


Figure 1.—Yield of (1) acetylglycolic acid, (2) aspirin, and (3) acetylmalic acid plotted against concentration of the respective hydroxy acid anions. Initial concentration of acetic anhydride = 0.02 M, T = 25°, and I = 1.50 M.

TABLE I

RELATIVE YIELDS OF ACETYL ESTERS FROM HYDROXY ACIDS AND ALCOHOLS AT 25° AND IONIC STRENGTH = 1.50 M. INITIAL CONCENTRATION OF ACETIC ANHYDRIDE 0.02 M AND OF SUBSTRATE 0.5 M

	Initial pH	[Ester]/[Ac_2O]$_T$ ×100
Acid		
Glycolic	5.50	48.4
Glycolic	1.45	<1[a]
Lactic	5.50	36.4
Lactic	2.00	<1
α-Hydroxy-*n*-butyric	7.00	45.4
β-Hydroxy-*n*-butyric	7.00	31.0
γ-Hydroxy-*n*-butyric	7.00	75.0
Salicylic	5.10	22.6
Malic	6.60	12.8
Malic	1.85	<1
Tartaric	5.70	25.6
Tartaric	1.60	<1
Citric	6.00	<1
Alcohols		
Ethanol		<1
Isopropyl alcohol[b]		<1
Xeopentyl alcohol[b]		<1
Glucose		2.0
Phenol[c]	1.60	<1

[a] Measured at 40°. [b] Concentration 0.3 M. [c] Indicator, Bromcresol purple.

ionized citric acid to be acetylated will be discussed later.

The relative yield of ester was found experimentally to be a function of the concentration of hydroxy acid anion but was independent of the initial acetic anhydride concentration between 0.01 and 0.02 M. These results indicate that the over-all reaction leading to formation of the ester and the hydrolysis of acetic anhydride are of different orders in hydroxymonocarboxylate ion, but are all first order in acetic anhydride. Plots of yield of ester relative to the initial acetic anhydride concentration against [hydroxy acid anion] are shown for several systems in Figure 1. When the data in Figure 1 were plotted as (reciprocal of yield of ester) against (reciprocal of [hydroxy acid anion]) straight lines which intersected the Y axis at values greater than 1 were obtained. Plots of this type are shown in Figure 2.

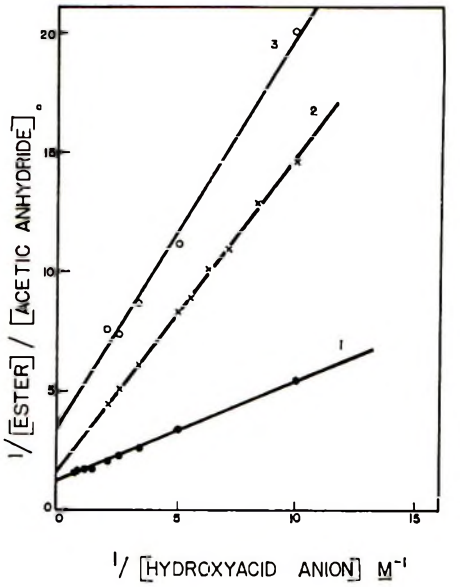


Figure 2.—Plots of 1/yield of (1) acetylglycolic acid, (2) aspirin, and (3) acetylmalic acid against 1/concentration of the respective hydroxy acid anions.

Rate of Consumption of Acetic Anhydride.—At constant pH and in the presence of a considerable excess of ionized hydroxy acids, acetic anhydride appeared to be consumed by a pseudo-first-order process. This was apparent for the glycolate and malate systems from corresponding changes in the uv spectra of the reacting solutions. The reaction with sodium salicylate could not be observed optically, but exhibited essentially the same behavior when followed titrimetrically on a pH-stat.

The second-order rate constants, k_{B^-} and $k_{B^{2-}}$, attributable to hydroxymonocarboxylate (B^-) and hydroxydicarboxylate (B^{2-}) ions, respectively, were calculated from the pseudo-first-order rate constants, k_{obsd} values, by using the equation

$$k_{obsd} = k_0 + k_{NaCl}[NaCl] + k_{B^-}[B^-] + k_{B^{2-}}[B^{2-}] \quad (A)$$

In this equation k_0 is the first-order rate constant for the hydrolysis of acetic anhydride in water and k_{NaCl} is the catalytic (negative) constant for NaCl on the observed reactions. This latter term was included because different amounts of NaCl were added to each system to maintain an ionic strength of 1.5 and NaCl is known[3a,4] to be a negative catalyst on the hydrolysis of acetic anhydride. Any catalytic effect of un-ionized hydroxycarboxylic acids was neglected because independent experiments revealed that it was very much smaller than that attributable to ionized species. The method of calculating k_{B^-} and $k_{B^{2-}}$ values is given in the Experimental Section and results are shown in Table II.

Proposed Reaction Scheme.—The proposed reaction scheme for the consumption of acetic anhydride in solutions of hydroxydicarboxylate ions is shown in Scheme I, using malate ion as an example. Similar reactions are suggested to occur in systems containing hydroxymonocarboxylate ions except that the cyclization reaction (reaction 6) would not be possible.

(3) (a) A. R. Butler and W. Gold, *J. Chem. Soc.*, 2305 (1961). (b) M. Kilpatrick, *J. Amer. Chem. Soc.*, **50**, 2891 (1928). (c) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y. 1966.

(4) C. A. Bunton, N. A. Fuller, S. G. Perry, and I. H. Pitman, *J. Chem. Soc.*, 4478 (1962).

TABLE II

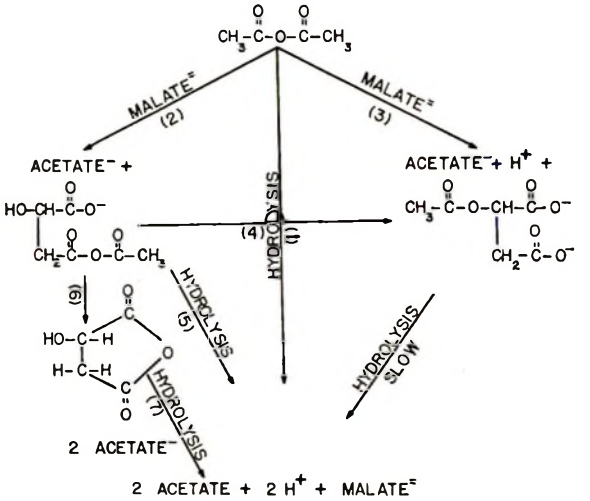
OVER-ALL EFFECT OF HYDROXY ACIDS ANIONS ON THE DISAPPEARANCE OF ACETIC ANHYDRIDE IN AQUEOUS SOLUTIONS, EXPRESSED AS SECOND-ORDER RATE CONSTANTS (I = 1.50 M, T = 25°)

Buffer acid	k_B^-, M^{-1} sec^{-1} × 10^3	K_B^{2-}, M^{-1} sec^{-1}
Glycolic	7.1	
Salicylic	1.8	
Malic[a]		32

[a] See ref 1.

SCHEME I

REACTIONS OF ACETIC ANHYDRIDE IN MALIC ACID BUFFERS[a]



[a] All reactions are expected to be subject to general acid–base catalysis and reaction 3 is likely to also be subject to intramolecular general-base catalysis by a carboxylate group.

All the reactions in Scheme I are acyl transfer reactions and must be expected[3] to be subject to general acid, general base catalysis by the un-ionized and ionized hydroxycarboxylic acids. It is also known that salts, including inert salts such as sodium chloride,[4] effect the rate of hydrolysis of acid anhydrides. In our present treatment we have been unable to determine the effects of general acids, general bases, and salts on the individual reactions. However, we have determined the over-all effect of the concentration of hydroxycarboxylate ions on the relative yield of ester and on the rate of consumption of acetic anhydride.

The ester could be formed by either reactions 2 and 4 or by reaction 3. This latter reaction would involve attack of the hydroxy oxygen atom of the hydroxycarboxylate ion on acetic anhydride. Although such a reaction would be facilitated by the carboxylate group (general base) in the attacking molecule, we still believe that the carboxylate group would be the more nucleophilic center and that reaction 2 would predominate. There is qualitative evidence[5] to suggest that, in nonhydroxylic solvents, the carboxylate function is the more nucleophilic. Thus when salicylic acid was allowed to react with potassium hydroxide and dimethyl sulfate, only the methyl ester could be identified as a product. Therefore, it is proposed that acetic anhydride is consumed by hydrolysis, reaction 1, and by attack of the carboxylate group of the hydroxycarboxylate ion, reaction 2, to yield a mixed acetic–hydroxycarboxylic acid anhydride. To differentiate between the nucleophilic participation of hydroxycarboxylate ions, reaction 2, and the general base effect exerted by these ions on reactions 1 and 2, a specific analytical technique is required. For example, when Bunton and Fendler[6] studied the catalytic effect of fluoride ions on the hydrolysis of acetic anhydride in water at 0°, they were able to distinguish between such mechanisms by isolating acetyl fluoride which was formed by nucleophilic attack of fluoride ions on the acetic anhydride. We have made no attempts to separate the nucleophilic catalysis from the general base catalyzed component of hydrolysis because of the instability of the mixed anhydride which would be formed.

There are numerous examples of related cases of formation of mixed acid anhydrides. Reactions of acetic anhydride with ions such as propionate,[7] malate,[1] citrate,[8] and phosphate[9] have been shown to yield mixed anhydrides, and formation of similar high energy species have been postulated during carboxylate catalyzed oxidation of thioethers of sulfoxides.[10,11]

The rearrangement of the mixed anhydride to the ester reaction (reaction 4) could occur through a tetrahedral intermediate or activated complex similar to the type proposed[12] during the intramolecular nucleophilic catalyzed hydrolysis of aspirin. When discussing the likelihood of the mixed acetic salicylic anhydride being formed during the hydrolysis of aspirin, Fersht and Kirby[13] made the point that such a molecule would be very much less stable than the ester and its rate of conversion to the ester would be very rapid. Thus it seems likely that if it were formed following reaction of salicylate ion and acetic anhydride it would rapidly rearrange to yield aspirin. Analogous rearrangement of mixed anhydrides by an O (carboxy) to N (amino) acyl transfer has been utilized as a step in the synthesis of cephalosporin C.[14] In peptide synthesis this rearrangement is usually prevented by protecting the amino group in the mixed anhydride.[15a]

Kinetic Test of the Proposed Mechanism.—Hydrolysis and rearrangement of the mixed anhydrides (reactions C, D, and E) were assumed to be essentially first-order reactions with rate constants k_4, k_5, and k_6 sec^{-1}, respectively.

Thus, in the presence of fully ionized hydroxymonocarboxylic acids, the yield of ester relative to the moles of added acetic anhydride, R, would be

$$R = \frac{k_B^{-\prime} k_4 [B]_T}{(k_4 + k_5)(k_0 + 1.50k_{NaCl}) + (k_4 + k_5)(k_B^- - k_{NaCl})[B]_T} \quad (B)$$

or

$$1/R = \frac{(k_4 + k_5)(k_0 + 1.50k_{NaCl})}{k_B^{-\prime} k_4 [B]_T} + \frac{(k_4 + k_5)(k_B^- - k_{NaCl})}{k_B^{-\prime} k_4} \quad (C)$$

(5) R. Nodzu, M. Hamada, M. Hosino, and T. Kinosita, *J. Chem. Soc. Jap.*, **60**, 1189 (1939); *Chem. Abstr.*, **36**, 6513 (1942).

(6) C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, **32**, 1547 (1967).

(7) M. Kilpatrick and M. L. Kilpatrick, *J. Amer. Chem. Soc.*, **52**, 1418 (1930).

(8) A. J. Repta, J. R. Robinson, and T. Higuchi, *J. Pharm. Sci.*, **55**, 1200 (1966).

(9) T. Higuchi, G. L. Flynn, and A. C. Shah, *J. Amer. Chem. Soc.*, **89**, 616 (1967).

(10) T. Higuchi and K.-H. Gensch, *ibid.*, **88**, 3874 (1966).

(11) K.-H. Gensch, I. H. Pitman, and T. Higuchi, *ibid.*, **90**, 2096 (1968).

(12) M. L. Bender, F. Chlouprek, and M. C. Neveu, *ibid.*, **80**, 5384 (1958).

(13) A. R. Fersht and A. F. Kirby, *ibid.*, **89**, 4857 (1967).

(14) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *ibid.*, **88**, 852 (1966).

(15) (a) N. F. Albertson, *Org. Reactions*, **12**, N. Y., 1962. (b) T. Higuchi and A. Drubulis, *J. Pharm. Sci.*, **50**, 905 (1961).

where k_{B^-}' is the second-order rate constant for nucleophilic attack of hydroxymonocarboxylate ion on acetic anhydride as distinct from the over-all catalytic effect of the ions on the consumption of acetic anhydride. A plot of $1/R$ against $1/[B]_T$ should give a straight line with a value of slope/intercept on the Y axis.

$$\frac{\text{slope}}{\text{intercept}} = \frac{k_0 + 1.50k_{NaCl}}{k_{B^-} - k_{NaCl}} \quad (D)$$

Equation D was derived on the basis that as $[B^-]$ varied, appropriate amounts of sodium chloride were added or deleted to maintain the ionic strength at 1.50 M. The salt effect has to be taken into account in our results, but if it could be ignored, the slope/intercept ratio would be approximately equal to the ratio of the specific rate of spontaneous hydrolysis of acetic anhydride to the over-all second-order reaction rate constant of the attacking hydroxymonocarboxylate ion.

For reactions in the presence of hydroxydicarboxylate ions a similar straight line relationship would be expected and the slope/intercept would be

$$\frac{\text{slope}}{\text{intercept}} = \frac{k_0 + 1.50k_{NaCl}}{k_{B^{2-}} - 3k_{NaCl}} \quad (E)$$

It is possible to check the approximate validity of eq D for the glycolate system for which we have the most data. The ratio of slope to intercept for this system as plotted in Figure 2 corresponds to 0.3 M. Independently determined value of $(k_0 + 1.50k_{NaCl})$ is 1.90×10^{-3} and k_{B^-} from Table II is 7.1×10^{-3} M^{-1} sec^{-1}. The measured value of $-k_{NaCl}$ for acetic anhydride at 25° in water was 6×10^{-4} M^{-1} sec^{-1}. Thus the directly determined value of $(k_0 + 1.50k_{NaCl})/(k_{B^-} - k_{NaCl})$ is 0.2 M.

The comparison for the salicylate system is much less satisfactory, being 0.7 M *vs.* 1.6 M, respectively. This may be due, at least in part, to the known[15b] role of salicylate anion in greatly modifying the thermodynamic activities of other organic solutes in solution. The malate system shows somewhat greater discrepancy. The very large corrections associated with ionic strength adjustments in these systems make more than qualitative agreements for this crude test rather difficult.

Effect of Structure of the Hydroxy Acid on the Degree of Acetylation.—The proposed reaction scheme contains a number of competitive reactions and the relative amount of acetic anhydride which reacts by a given route will be largely influenced by the structures of the hydroxy acid anions and the mixed anhydrides which would be formed.

Thus the first competitive process would be between hydrolysis of acetic anhydride and nucleophilic attack of a hydroxy acid anion on acetic anhydride to yield a mixed anhydride. To a first approximation, the more nucleophilic the hydroxy acid anion, the more acetic anhydride would be expected to be consumed *via* formation of a mixed anhydride. Comparison of rate constants in Table II shows that the rate of mixed anhydride formation in these systems would be in the order malate > glycolate > salicylate. The ultimate yield of ester will not be determined by this reaction alone and will also depend on the result of competition between intramolecular acetylation, hydrolysis, and other reactions of the mixed anhydride. Thus malate ions are probably stronger nucleophiles than glycolate ions and would be expected to react with acetic anhydride to form more mixed anhydride. However, the resulting anhydride readily cyclizes to give malic anhydride[1] and the yield of acetyl malate is therefore considerably smaller than that of acetyl glycolate. The mixed anhydride precursor of this latter species could not cyclize in a similar way to acetic–malic anhydride. Similarly, the failure of citrate ions to yield any acetyl citrate is believed to be due to the fact that, at this pH value, the mixed citric acetic anhydride would preferentially cyclize to yield highly reactive citric anhydride[8] rather than rearrange to the ester.

The position of the hydroxy group relative to the acetyl group in the mixed hydroxy acid–acetic acid anhydride also affects the competition between intramolecular acetylation and hydrolysis. Thus, β- and γ-hydroxy-*n*-butyric acids have similar pk_a values and the nucleophilicities of their ions are expected to be very close. The higher yield of γ-acetyl butyrate ions relative to β-acetyl butyrate ions suggests that intramolecular acetylation of the mixed anhydride precursor is more favorable compared to hydrolysis in the former case than in the latter.

The number of hydroxy groups also appears to be important and thus the per cent yield of ester obtained from reactions of tartarate ion (2,3-dihydroxy succinate) is approximately double that obtained from reactions on malate ion (2-hydroxy succinate), although the former is expected to be the weaker nucleophile.

The Y intercept for the salicylate system (Figure 2) is 1.75, corresponding to 57% consumption of the acetic anhydride in formation of aspirin in an infinite concentration of sodium salicylate, assuming acetic anhydride only formed the mixed acetic–salicylic acid anhydride. Thus the limiting value indicates that intramolecular acetylation of the mixed anhydride was preferred to direct hydrolysis of this species. Any positive catalytic effect by sodium salicylate on the hydrolysis of acetic anhydride, reaction 1, would increase the value of $k_4/(k_4 + k_5)$ which reflects the preferred rearrangement of the mixed anhydride to the hydrolysis of the same species.

Experimental Section

Equipment.—Spectrophotometric studies were performed using commonly employed technique on Cary Models 11 and 14. pH-Stat experiments were done on a Radiometer TTT1 automatic titrator utilizing a SBR titrigraph and an ABU1 autoburet with a TTA3 titration assembly. All thermostated water baths were regulated within ±0.1°. In tlc, Eastman chromagram sheet 6060, silica gel, was employed.

Reagents.—All reagents used were of analytical grade unless otherwise stated. α- and β-hydroxy-*n*-butyric acids were obtained from K & K Laboratories, Plainview, N. Y., and employed without further purifications. The sodium salt of γ-hydroxybutyric acid was made from γ-butyrolactone. Acetic anhydride was distilled over magnesium turnings and the fraction boiling between 137.8 and 138.2° was collected and sealed in ampoules. Commercial grade *p*-dioxane was purified by the method described in Vogel.[16] All water used was redistilled from acid permanganate using an all-glass still. Acetylglycolic acid was synthesized[17] by refluxing glycolic acid with acetyl chloride, mp 65.5–66.5° (lit.[18] mp 67–68°).

Acetyllactic Acid.—Freshly distilled lactic acid was refluxed with acetyl chloride and the acetyllactic acid formed was purified

(16) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1962.

(17) A. Anschutz and W. Bertram, *Chem. Ber.*, **36**, 467 (1903).

(18) M. S. Kharasch, H. N. Friedlander, and W. H. Urry, *J. Org. Chem.*, **16**, 533 (1951).

by fractionated distillation.[19] α- and β-acetoxy-*n*-butyric acids were synthesized by refluxing the parent acid with excess acetyl chloride. The liquid products were isolated by vacuum distillation. Nmr and ir spectra were consistant with the assumed structure. Salicylic acid was recrystallized from hot water, mp 158–159°. Titration with sodium hydroxide showed 99.69% salicylic acid. Acetylsalicylic acid was recrystallized from benzene and the crystals were washed with cyclohexane, mp 133–134.5°. Titration with sodium hydroxide showed 100.21% acetylsalicylic acid.

Isolation and Identification of Reaction Products.—In order to isolate reaction products, the amount of reactants was scaled up, but the [hydroxy acid] was kept in large excess over [acetic anhydride] by repeatedly adding small aliquots of acetic anhydride to the reaction mixture. The pH of the solution was kept constant by addition of sodium hydroxide.

Glycolic Acid.—The final reaction mixture was evaporated to dryness, and the crystalline residue was dissolved in 3 *M* sulfuric acid. Inorganic salt was precipitated by adding methanol. The filtrate was again evaporated to dryness and after acidification, extracted with benzene. Upon concentration and cooling, the mixture solidified and acetylglycolic acid was obtained after recrystallization from benzene, mp 66.5–67°. No depression in melting point was observed when isolated material was mixed with synthesized material. Paper chromatography (*n*-butyl alcohol form sprayed with bromcresol green) and tlc (ethyl ether–formic acid–water, 18:5:9 v/v, sprayed with bromcresol green) of isolated material showed spots corresponding to synthesized acetoxyglycolic acid.

α- and β-Hydroxy-*n*-butyric Acids.—The reaction mixture was acidified with sulfuric acid and extracted several times with ethyl ether. The residues after evaporation of the ether were tested for acetoxy derivatives by tlc. In three different solvents (*n*-butyl alcohol–formic acid–water, 10:2:5 v/v, acetone, and ethyl acetate), R_f values were obtained identical with those of the synthesized acetyl esters. The acetoxy derivatives always moved faster than the parent acid on the tlc sheets.

Acetylsalicylic Acid.—An 8.0-ml sample of 1.2 *M* acetic anhydride in dioxane was added to 50.0 ml of 0.5 *M* salicylate buffer of pH 5.1. This addition was repeated four times with 20-min intervals. The reaction mixture was shaken with chloroform after acidification with sulfuric acid and the chloroform was evaporated. The residue was suspended in water and 6.0 ml of 3 *N* sulfuric acid was added. Precipitated salicylic acid was filtered off and the filtrate was shaken with chloroform until no more salicylic acid could be detected with ferric chloride. The collected chloroform was pooled and shaken with 1% ferric chloride until the water layer was no longer purple. The chloroform solution, this way freed for salicylic acid, was dried and evaporated to dryness. The residue was recrystallized from isopropyl alcohol and melted at 135–137° (lit.[13] mp 135°). No depression in the melting point was observed when the isolated crystals were mixed with authentic acetylsalicylic acid. Uv spectrum of the isolated material matched that of known acetylsalicylic acid. λ_{CHCl_3} 278 mμ (log ε = 3.125). (A value of log ε = 3.120 was found for authentic material.)

Acetylation Followed by Titration.—A 0.1-ml sample of 0.6 *M* acetic anhydride in dioxane was allowed to react with 3.0 ml of buffer solution in a closed vial for 1 hr. The reaction mixture was then diluted with 2.0 ml of water and titrated with standard solution of sodium hydroxide to phenolphthalein (or phenol red) end point, volume of required titrant = *a* ml. A 3.0-ml sample of buffer solution and 2.0 ml of water was titrated to the same end point, volume of titrant = *b* ml. An equivalent amount of acetic anhydride was titrated after hydrolysis in 5.0 ml of water, volume of titrant = *c* ml. Error in the titration was estimated to be less than ±2%.

$$\frac{[\text{ester}]}{[Ac_2O]_{added}} = 2\,\frac{c-(a-b)}{c}$$

Spectrophotometric Determination of Aspirin in the Presence of Salicylic Acid.—Aspirin, ASA (20 mg), dissolved in 1 ml of dioxane was added to 25.0 ml of salicylate buffer of pH 5.40. Sulfuric acid (6 *N*, 2 ml) was added and the precipitated salicylic acid, SA, was filtered off. A 20.0-ml sample of the filtrate was then extracted with chloroform to 100.0 ml of solution. After a proper dilution, the absorbance was read at 277.5 and 308 mμ. The concentration of aspirin, c_{ASA}, was calculated from

$$c_{ASA} = \frac{A_{277.5}\,\epsilon_{SA}^{308} - A_{308}\,\epsilon_{SA}^{277.5}}{\epsilon_{ASA}^{277.5}\,\epsilon_{SA}^{308} - \epsilon_{SA}^{308}\,\epsilon_{SA}^{277.5}}$$

TABLE III
MOLAR ABSORPTIVITIES, ε VALUES, OF SALICYLIC AND ACETYLSALICYLIC ACIDS[a]

	Wavelength, mμ	
	277.5	308
Acid	ε	ε
Salicylic acid	725	4125[b]
Acetylsalicylic acid	1325[b]	15

[a] Measured in chloroform. [b] Maxima in the absorbance.

Comparison of the Spectrophotometric and the Titrimetric Determination of Aspirin in the Reaction Mixture.—A 1.0 ml sample of 1.2 *M* acetic anhydride was added to 25.0 ml of salicylate buffer of pH 5.40. After 1 hr the reaction mixture was worked up as described above. The expected amount of aspirin was calculated on the basis of a simultaneous titration of acetic acid in an aliquot of the reaction mixture. The analysis showed that 85% of the calculated aspirin was found by the spectrophotometric determination compared to 87% recovery of aspirin added to the salicylate buffer.

Calculation of Rate Constants.—The pseudo-first-order rate constants for the reactions of acetic anhydride in aqueous hydroxymonocarboxylate ions could be accounted for by eq A. Because the ionic strength of each system was 1.5, [NaCl] could be related to [B^-] by the identity

$$[\text{NaCl}] = 1.5 - [B^-]$$

Also, the total buffer concentration $[B]_T$ was related to concentrations of un-ionized and ionized buffer species by the identity

$$[B]_T = [BH] + [B^-]$$

Using these two identities, eq A could be rearranged to

$$k_{obsd} = k_0 + 1.5k_{NaCl} + (k_{B^-} - k_{NaCl})\,\frac{[B]_T K_a}{K_a + [H^+]}$$

Plots of $[B]_T K_a/(K_a + [H^+])$ against k_{obsd} for systems in which either $[B]_T$ or $[H^+]$ was varied and the other term kept constant gave straight lines from whose slope and intercept on the *Y* axis values of $(k_{B^-} - k_{NaCl})$ and $(k_0 + 1.5k_{NaCl})$, respectively, were calculated. By using an independently measured value of the rate constant for hydrolysis of acetic anhydride in pure water at 25°, $k_0 = 2.80 \times 10^{-3}$ sec^{-1}, values of k_{B^-} could then be calculated. This method is only valid if the hydrolysis of acetic anhydride is not subject to specific acid or base catalysis in the pH region being investigated. Outside of this pH region, only $[B]_T$ can be varied, and the effective rate constant for acetic anhydride hydrolysis at the particular pH value used as k_0.

Determination of Ionization Constants.—The ionization constant of salicylic acid was determined spectrophotometrically[20] in aqueous solutions of sodium chloride. At 25° and $I = 1.50$ *M*, $pK_a = 2.55 \pm 0.06$. The ionization constant of glycolic acid was determined potentiometrically under the same conditions, $pK_a = 3.44 \pm 0.04$.

Registry No.—Glycolic acid, 79-144; lactic acid, 50-21-5; α-hydroxy-*n*-butyric acid, 565-70-8; β-hydroxy-*n*-butyric acid, 300-85-6; γ-hydroxy-*n*-butyric acid, 591-81-1; salicylic acid, 69-72-7; malic acid, 97-67-6; tartaric acid, 526-83-0; citric acid, 77-92-9; ethanol, 64-17-5; isopropyl alcohol, 67-63-0; neopentyl alcohol, 75-84-3; glucose, 50-99-7; phenol, 108-95-2.

Acknowledgment.—The authors gratefully acknowledge partial support of this program from the National Institute of Health (GM-15910-01) and by Warner-Lambert Laboratories of Morris Plains, N. J. R. B. P. also acknowledges partial financial support from the Norwegian Research Council for Science and the Humanities.

(19) B. B. Dey and T. R. Govindachari, *Arch. Pharm.*, **275**, 383 (1937).

(20) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, N. Y., 1962.

Pyrimido[5,4-*e*]-*as*-Triazines. III. The Preparation and Some Reactions of 5-Substituted Pyrimido[5,4-*e*]-*as*-Triazines[1]

CARROLL TEMPLE, JR., CONRAD L. KUSSNER, AND JOHN A. MONTGOMERY

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received September 26, 1968

Reaction of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (**1**) with NaN_3 gave directly the heteroaromatic 5-aminopyrimido[5,4-*e*]-*as*-triazine (**2**). The amino group of **2** underwent exchange with both $EtNH_2$ and H_2N-NH_2 in the presence of HCl to give 5-ethylamino- and 5-hydrazinopyrimido[5,4-*e*]-*as*-triazine (**7** and **8**), respectively. In the absence of acid the pyrimidine ring was opened to give 6-amino-*as*-triazine-5-carboxamidine derivatives **9** and **10**. Alkylation of 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine with $C_6H_5CH_2Cl$ gave the corresponding 5-benzylamino derivative **11**. Treatment of **2** with aqueous NaOH hydrolyzed the amino group to give pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (**12**). Reduction of **12** with $Na_2S_2O_4$ in HOAc resulted in ring contraction to give 9-acetamidohypoxanthine (**14**). Reaction of **12** with Et_3N cleaved the pyrimidine ring to give 6-amino-*as*-triazine-5-carboxamide (**20**), which was cyclized with diethoxymethyl acetate to give **12** and with the phosgene–pyridine complex to give pyrimido[5,4-*e*]-*as*-triazine-5,7(6H,8H)-dione (**23**). Methylation of **23** gave the antibiotic, fervenulin (**24**).

The identification of the biologically active antibiotics toxoflavin and fervenulin[2-4] has stimulated interest in the chemistry of the pyrimido[5,4-*e*]-*as*-triazine (7-azapteridine) ring system. The difficulties encountered in the preparation and cyclization of 5-amino-4-hydrazinopyrimidines[2,4] to give pyrimido[5,4-*e*]-*as*-triazines led us to examine some of the reactions of both the 1,2-dihydro and heteroaromatic derivatives of this ring system and to synthesize the parent ring system, pyrimido[5,4-*e*]-*as*-triazine-5,7(6H,8H)-dione (**23**)[5] from the previously unknown 6-amino-*as*-triazine-5-carboxamide (**20**).

Although the ultraviolet (uv) spectrum indicated that treatment of 4,5-diamino-6-hydrazinopyrimidine[6] with the $(EtO)_3CH$–HCl reagent[7] gave some 5-aminopyrimido[5,4-*e*]-*as*-triazine (**2**), this compound was not separated pure from the other reaction products. However, the reaction of 5-chloro-1,2-dihydropyrimido-[5,4-*e*]-*as*-triazine (**1**)[7] with NaN_3 in aqueous EtOH, either at room temperature or at reflux, gave directly the 5-amino compound **2** (Scheme I). Although the intermediates and the order of their occurrence in this reaction are unknown, this transformation probably involves either (1) oxidation of **1** by the azide group[8] to give **3** and ammonia which then combine to give **2** or (2) azido-5-dechlorination of **1** followed by oxidation of the 1,2-dihydro-*as*-triazine ring and conversion of the azido group into an amino group. The latter could occur either by autoxidation or disproportionation. Prior air oxidation of **1** to **3** was eliminated from consideration by treatment of **1** with aqueous ethanolic NaCl, which resulted in ring opening of the 1,2-dihydrotriazine ring to give the pyrimidine **5**. Reaction sequence 2 is supported by (a) the nitrosation of the 5-hydrazino compound **8** (see below) at room temperature to give **2**, presumably *via* an azido intermediate, (b) the formation of a dihydro derivative by reaction of **1** with a nucleophile in a reducing medium (NaSH),[9] and (c) the reaction of **1** with diethylamine to give a 17% yield of **6** presumably formed *via* oxidation of a dihydro intermediate of **6**.[10] The recovery of 1-benzyl-5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine[11] in 79% yield from its reaction with NaN_3 would appear to provide support for route 1; however, this result might indicate that the facility with which **1** and NaN_3 react is related to the delocalization of the charge at N-1 as in the intermediate anionic adduct **4**. The importance of charge delocalization in the adjoining ring has been noted in other heterocyclic systems.[12]

Previously it was shown that the 5-amino group of heteroaromatic pyrimido[5,4-*e*]-*as*-triazines will undergo exchange with primary amines.[13] Treatment of **2** with excess alcoholic $EtNH_2$ in a bomb at 125° gave a mixture containing the 5-ethylamino compound **7** as a minor component. The major component was identified as the *as*-triazine-5-carboxamidine **9** by elemental analyses and its pmr spectrum. Reaction of **2** with $EtNH_2$ at 65° gave a 69% yield of recovered **2** and a 22% yield of crude **7**. Addition of HCl to this reaction, however, gave a 63% yield of **7**, identified by elemental analyses and its pmr spectrum. At this temperature it appears that the exchange reaction, but not the cleavage reaction, is catalyzed by HCl.[14] Also the results described above indicate that only **7** and not **2** is involved in the cleavage reaction. Similar products were obtained by treatment of **2** with alcoholic hydrazine. In hot propanol, **2** and hydrazine gave the *as*-triazine-5-carboxamidine hydrazone **10**. Although little or no reaction occurred between **2** and hydrazine in hot MeOH, addition of HCl to this reaction gave a 59% yield of the 5-hydrazino compound **8**. As described

(1) This work was supported by the C. F. Kettering Foundation and by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

(2) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Amer. Chem. Soc.*, **84**, 1724 (1962).

(3) E. C. Taylor and F. Sowinski, *ibid.*, **90**, 1374 (1968) and references therein.

(4) T. K. Liao, F. Baiocchi, and C. C. Cheng, *J. Org. Chem.* **31**, 900 (1966), and references therein.

(5) Part of this work has appeared as a preliminary report. See C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Heterocycl. Chem.*, **5**, 581 (1968).

(6) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **30**, 829 (1965).

(7) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *ibid.*, **28**, 923 (1963).

(8) E. S. Gould, "Inorganic Reactions and Structure," Henry Holt and Co., New York, N. Y., 1955, p 236.

(9) This reaction gave 1,2-dihydropyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione; it will be described in a forthcoming paper.

(10) The oxidation of reduced pteridines is retarded by chloro groups and accelerated by amino groups. See E. C. Taylor and W. R. Sherman, *J. Amer. Chem. Soc.*, **81**, 2464 (1959).

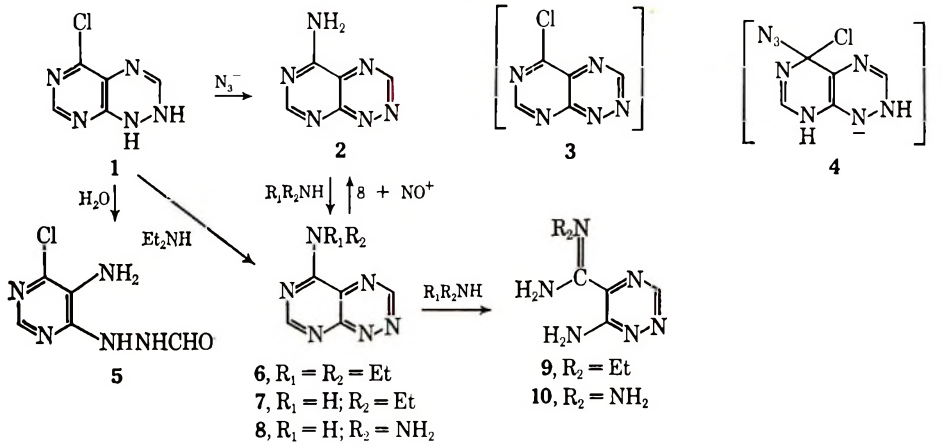
(11) J. A. Montgomery and C. Temple, Jr., *ibid.*, **82**, 4592 (1960).

(12) E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *ibid.*, **82**, 6058 (1960).

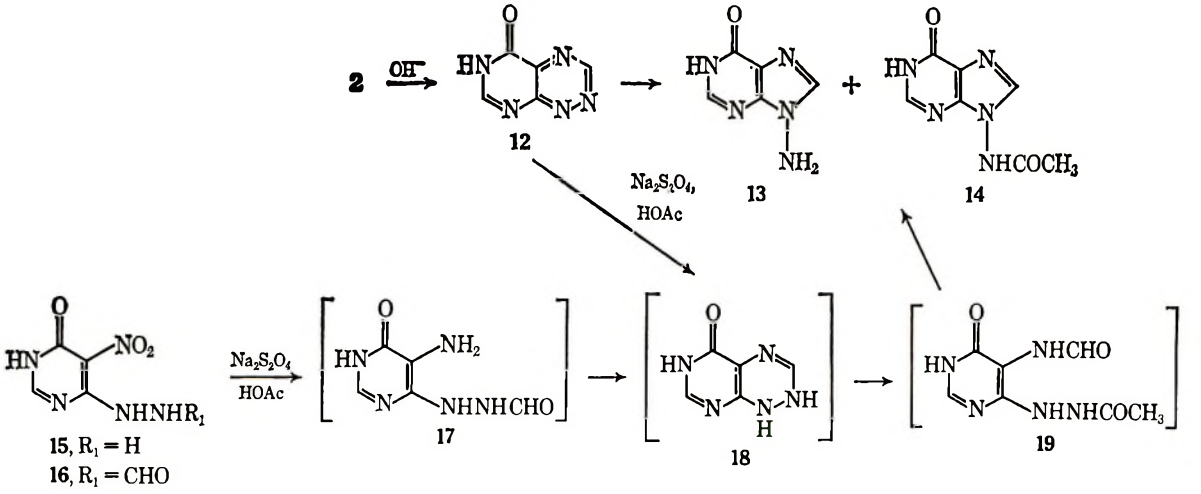
(13) C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **28**, 3038 (1963).

(14) C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **82**, 3971 (1960).

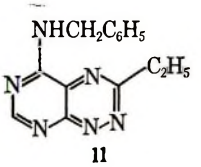
SCHEME I



SCHEME II



above, the nitrosation of **8** gave **2** in 42% yield. Addition of **2** to 10% NaOH gave a precipitate, presumably a sodium salt of a hydrated derivative of **2**.[15] That the 5-amino group of this ring system was acidic, however, was shown by alkylation of 5-amino-3-ethylpyrimido-[5,4-*e*]-*as*-triazine with NaH and $C_6H_5CH_2Cl$ in DMF to give a 16% yield of pure **11**.[13]



11

Reaction of **2** with an equivalent amount of aqueous NaOH at room temperature hydrolyzed the amino group to give **12** (Scheme II).[13] An earlier study on the preparation of **12** from the 4-hydrazinopyrimidine **15**[6] was unsuccessful. Formylation of **15** with formic acid to give **16**, followed by the reductive cyclization of **16** with $Na_2S_2O_4$ in HOAc, gave mainly 9-acetamidohypoxanthine (**14**), which was also prepared from 9-aminohypoxanthine (**13**)[11] and acetic anhydride. In addition acid hydrolysis of the reaction product gave **13**, which on nitrosation gave hypoxanthine. Apparently the conversion of **16** into **14** involved (1) reduction of the nitro group of **16** to give **17**, (2) cyclization of **17** to give **18**, (3) acetylation and opening of the *as*-triazine of **18** to give **19**, and (4) recyclization of **19** to give **14**.[16] Support for this mechanism was obtained by treatment of **12** with $Na_2S_2O_4$ in HOAc to give a mixture of **13** and **14**, presumably formed *via* **18** and **19**. In other studies reaction of (1) 5-amino-4-hydrazinopyrimidin-6(1H)-one[6] with the $(EtO)_3CH$–HCl reagent, (2) 4-chloro-5-ethoxymethyleneaminopyrimidin-6(1H)-one with hydrazine,[13] and (3) compound **1** with aqueous NH_4OH gave only low yields of crude **12**.

Treatment of **12** with aqueous ethanolic Et_3N cleaved the pyrimidine ring to give 6-amino-*as*-triazine-5-carboxamide (**20**) (Scheme III).[17] A 6% yield of the corresponding carboxylic acid **21** was also obtained in this reaction. The recyclization of **20** to **12** was carried out with hot diethoxymethyl acetate. Also, treatment of **20** with a HCO_2H–Ac_2O mixture gave **22**, which was converted into **12** (tlc) in DMF containing K_2CO_3. No reaction occurred on treatment of **20** with hot formic acid, which was explained when it was found that the formamide group of **22** was hydrolyzed in hot formic acid to give **20**. Although the fusion of **20** with urea gave mainly decomposition products containing a trace amount of **23**, the reaction of **20** with the phosgene–pyridine complex[18] gave a 37% yield of pure **23**.[5]

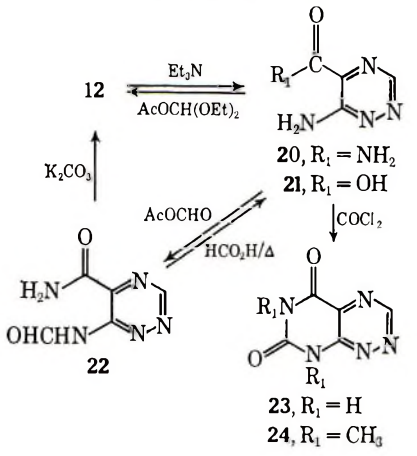
(15) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951), reported that 4-aminopteridine forms an anion in 0.2 *N* NaOH.

(16) A similar sequence of reactions for the conversion of 5-amino-4-chloro-6-hydrazinopyrimidine into 9-formamidohypoxanthine has been demonstrated. See ref 7.

(17) J. Clark and G. Neath, *J. Chem. Soc., C*, 1112 (1966).

(18) C. Scholtissek, *Ber.*, **89**, 2562 (1956).

SCHEME III



This structure was confirmed by alkylation with CH_3I in DMF containing K_2CO_3 to give the antibiotic, fervenulin **24**.[2,3]

Experimental Section

Melting points were determined on a Kofler Heizbank apparatus and are corrected. The uv absorption spectra of solutions were determined with a Cary Model 14 spectrophotometer, whereas the infrared (ir) absorption spectra were determined in pressed potassium bromide disks with Perkin-Elmer Models 221-G and 521 spectrophotometers. The proton magnetic resonance (pmr) spectra were obtained on a Varian A-60A spectrometer in DMSO-d_6 using tetramethylsilane as an internal reference. Descending paper chromatograms were developed in water saturated butanol (A), butanol–glacial acetic acid–water (5:2:3, v/v) (B), isopropyl alcohol–concentrated ammonium hydroxide–water (70:5:25, v/v) (C), and acetate buffer pH 6.1 (D). Thin layer chromatograms were prepared from silica gel H (Brinkmann) and were usually developed with mixtures of chloroform and methanol.

5-Aminopyrimido[5,4-*e*]-*as*-triazine (2). A.—A mixture of 1[7] (32 g) and NaN_3 (20 g) in 1:1 EtOH–H_2O (1300 ml) was refluxed with stirring for 2 hr. After cooling the solid was collected by filtration, washed with water, and dried *in vacuo* over P_2O_5 to give practically pure product: yield 26 g (93%). The analytical sample was obtained by recrystallization from MeOH: mp >264°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] 0.1 *N* HCl, 217 (13.8), 243 (10.0), 353 (10.5), 358 (sh) (10.3); $\bar{\nu}_{max}$ in cm^{-1}, 3225, 3045 (NH), 1670 (NH_2), 1650, 1575, 1540, 1500 (C=C, C=N); pmr, τ −0.11, 1.32 (1, 1, CH), 1.12 (2, NH).

Anal. Calcd for $C_5H_4N_6$: C, 40.55; H, 2.70; N, 56.75. Found: C, 40.57; H, 2.80; N, 56.87.

At room temperature for 24 hr 1 (1.0 g) and NaN_3 (0.61 g) gave an 87% yield of 2.

B.—To a suspension of 8 (500 mg) in 1:1 EtOH–H_2O (20 ml) was added with stirring a solution of $NaNO_2$ (250 mg) in 1 *N* HCl (3.1 ml). After 18 hr the solid (190 mg, 42%) was collected by filtration and identified as 2 by comparison of its uv spectrum and chromatographic behavior (tlc) with those described in A.

C.—A suspension of 4,5-diamino-6-hydrazinopyrimidine[6] (1.0 g) and ethyl orthoformate (20 ml) containing concentrated HCl (0.62 ml) was stirred at room temperature for 20 hr. The solid (1.15 g) was collected by filtration and was shown to contain 2 by comparison of its uv spectrum and chromatographic behavior (tlc) with those described in A. The isolation of pure 2 from this solid by recrystallization was unsuccessful.

5-Amino-4-chloro-6-(2-formylhydrazino)pyrimidine (5).[7]—A suspension of 1 (1.0 g) in 1:1 EtOH–H_2O (64 ml) containing NaCl (0.52 g) was refluxed for 2.5 hr. The unreacted 1 (0.47 g) was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. Tlc (9:1 $CHCl_3$–MeOH) showed that the resulting solid contained mainly 5 contaminated with 1 and 12. Extraction of this residue with hot EtOAc (25 ml) and recrystallization of the solid from the extract from C_6H_6 gave the product containing a trace amount of 1: yield 0.22 g (38% based on recovered 1).

Anal. Calcd for $C_5H_6ClN_5O$: C, 32.00; H, 3.20; N, 37.30. Found: C, 32.25; H, 3.17; N, 37.01.

5-Diethylaminopyrimido[5,4-*e*]-*as*-triazine (6).—A suspension of 1 (5.0 g) in *n*-PrOH (100 ml) containing Et_2NH (15 ml) was refluxed for 5 hr. After filtration the dark filtrate was evaporated to dryness, and the residue was triturated with H_2O (20 ml). The remaining solid (1.2 g) was extracted with EtOAc, and the extract was evaporated to dryness to give 6: yield 1.0 g (17%); mp 123° (recrystallization of a portion of this sample from hexane raised the melting point to 127°); λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] 0.1 *N* HCl, 233 (11.6), 373 (11.6); $\bar{\nu}_{max}$, in cm^{-1}, 2975, 2930 (aliphatic CH), 1570, 1515 (C=C, C=N).

Anal. Calcd for $C_9H_{12}N_6$: C, 52.93; H, 5.92; N, 41.15. Found: C, 52.98; H, 6.03; N, 41.15.

5-Ethylaminopyrimido[5,4-*e*]-*as*-triazine (7).—A suspension of 2 (1.0 g) in MeOH (20 ml) and 1.0 *N* HCl (6.8 ml) containing $EtNH_2$ (1.0 ml) was heated with stirring at 68° for 8 hr. The resulting solution was evaporated to dryness, and the residue was recrystallized from benzene: yield 0.75 g (63%); mp 170° with presoftening from 130°. Recrystallization of a portion of this solid from petroleum ether (bp 85–105°) gave the analytical sample: mp 172°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] 0.1 *N* HCl, 224 (12.5), 249 (sh) (4.51), 363 (10.7); $\bar{\nu}_{max}$, in cm^{-1}, 2975, 2950 (aliphatic CH), 1605 (NH), 1565, 1490 (C=C, C=N); pmr, τ −0.15, 1.22 (1, 1, CH), 0.44 (m, 1, NH), 6.35 (m, 2, CH_2), 8.73 (t, 3, CH_3).

Anal. Calcd for $C_7H_8N_6$: C, 47.72; H, 4.58; N, 47.71. Found: C, 47.99; H, 4.55; N, 47.61.

A similar reaction without HCl gave 0.69 g of recovered 2 and only 0.26 g (22%) of impure 7.

5-Hydrazinopyrimido[5,4-*e*]-*as*-triazine (8).—A suspension of 2 (1.0 g) in MeOH (20 ml) and 1.0 *N* HCl (6.8 ml) containing 95+% hydrazine (0.5 ml) was heated with stirring at 80° for 5 hr. After the mixture was cooled, the solid was collected by filtration, washed with MeOH, and dried *in vacuo* over P_2O_5: yield 0.65 g (59%); mp >264°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] 0.1 *N* HCl, 365 (7.33); $\bar{\nu}_{max}$, in cm^{-1}, 3400, 3270 (NH), 1625 (NH), 1610, 1550 (C=C, C=N); pmr, τ 1.03, 2.63 (1, 1, CH), *ca.* 1.5 (NH).

Anal. Calcd for $C_5H_5N_7$: C, 36.81; H, 3.09; N, 60.10. Found: C, 37.00; H, 3.41; N, 59.81.

In a similar reaction without HCl 0.84 g of 2 was recovered after 20 hr.

6-Amino-N-ethyl-*as*-triazine-5-carboxamidine (9).—A mixture of 2 (5.2 g), ethylamine (25 ml), and *n*-PrOH (170 ml) in a Parr bomb was heated at 100° for 9 hr, then at 125° for 4 hr. The resulting solution was evaporated to dryness, and the residue was recrystallized from C_6H_6 to give 9 in two crops: yield 2.0 g (35%) mp 179°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] pH 7, 240 (9.34), 347 (4.06); $\bar{\nu}_{max}$, in cm^{-1}, 2965, 2930, 2865 (aliphatic CH), 1640 (NH), 1600, 1585, 1520 (C=C, C=N); pmr, τ 0.98 (1, CH), 1.53, 3.20 (2, 2, NH), 6.76 (q, 2, CH_2), 8.76 (t, 3 CH_3).

Anal. Calcd for $C_6H_{10}N_6$: C, 43.36; H, 6.06; N, 50.57. Found: C, 43.43; H, 6.03; N, 50.39.

The C_6H_6 filtrate gave 0.87 g (14%) of crude 7, mp 160–163°.

6-Amino-*as*-triazine-5-carboxamide Hydrazone (10).—A mixture of 2 (1.0 g) and 95+% anhydrous hydrazine (1.0 ml) in *n*-PrOH (20 ml), protected with drying a tube, was refluxed under a Dry Ice condenser for 20 hr. The solid was collected by filtration and recrystallized from MeOH: yield 0.32 g (31%); mp 245° dec; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] pH 7, 357 (9.04); $\bar{\nu}_{max}$, in cm^{-1}, 3420, 3370, 3340, 3315, 3185 (NH), 1640, 1600 (NH_2), 1560, 1495 (C=C, C=N); pmr, τ 1.05 (1, CH), 2.15, 3.83, 4.10 (2,2, NH).

Anal. Calcd for $C_4H_7N_7$: C, 31.37; H, 4.60; N, 64.03. Found: C, 31.44; H, 4.62; N, 63.98.

5-Benzylamino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (11).[13]—Solid NaH (0.30 g), 51.5% dispersed in mineral oil, was added with stirring to a suspension of 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine[13] (1.0 g) in DMF (10 ml), which was cooled in an ice bath. After the initial reaction had subsided, benzyl chloride (0.8 ml) was added. Then the mixture was stirred at room temperature for 1.5 hr and evaporated *in vacuo* to give a gum. This residue was extracted with CCl_4 (50 ml), the extract was evaporated to dryness *in vacuo*, and the resulting oil was extracted with three 300-ml portions of hot petroleum ether (bp 85–105°). The combined extracts were decanted from the gum that deposited, then evaporated to dryness to give the crude

(19) Each solution contains 10% dissolving solvent and 90% appropriate aqueous solvent: a, MeOH; b, 8%methanolic DMSO; c, H_2O.

product: yield 0.40 g; mp ~141° dec. Two recrystallizations of this material from petroleum ether gave the pure product: yield 0.25 g (16%); mp 152–153° dec (lit.[13] mp 153–154° dec); pmr, τ 0.18 (t,1, NH), 1.30 (1, CH), 2.65 (5, C_6H_5), 5.17 (d,2, CH_2), 6.63 (q,2, CH_2), 8.51 (t,3, CH_3).

Pyrimido[5,4-*e*]-*as*-triazin-5(6H)-one (12). **A.**—A suspension of **2** (10 g) in H_2O (100 ml) containing 1 *N* NaOH (73 ml) was stirred at room temperature for 3 hr. A trace amount of solid was removed by filtration, and with cooling and stirring the filtrate was acidified with 1 *N* HCl (146 ml). After 0.5 hr the product was collected by filtration: yield 5.7 g (57%). The analytical sample was obtained by recrystallization from H_2O: mp 256° dec; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19c] 0.1 *N* HCl, 232 (8.19), 264 (4.49), 329 (5.42); $\bar{\nu}_{max}$, in cm^{-1}, 1715 (CO), 1605, 1595, 1535 (C=C, C=N); pmr, τ −0.08, 1.52 (1,1, CH), *ca.* −2.0 (NH).

Anal. Calcd for $C_5H_3N_5O$: C, 40.27; H, 2.03; N, 46.97. Found: C, 40.48; H, 2.28; N, 47.16.

B.—A suspension of 5-amino-4-hydrazinopyrimidin-6(1H)-one[6] (500 mg) in $(EtO)_3CH$ (10 ml) containing concd HCl (0.3 ml) was stirred at room temperature for 6 hr. The solid was collected by filtration, washed with hot CH_3OH (25 ml), and dissolved in 0.1 *N* NaOH (20 ml). After filtration the filtrate was acidified to pH 1 with 1 *N* HCl to give 25 mg of **12**.

C.—A suspension of **1** (500 mg) in 1 *N* NH_4OH (10 ml) was stirred at room temperature for 1 hr. The solid was collected by filtration and washed with H_2O (10 ml) and EtOH (10 ml), to give 250 mg of crude **12**.

D.—A suspension of 4-chloro-5-ethoxymethyleneaminopyrimidin-6(1H)-one (1.0 g) in EtOH (20 ml) containing 95% anhydrous hydrazine (0.16 ml) was refluxed for 3 hr, and the mixture was evaporated to dryness to yield 810 mg of a slightly gummy solid. Paper chromatograms in four solvent systems indicated that this material was mainly 5-amino-4-chloropyrimidin-6(1H)-one[6] containing a trace amount of **12**.

E.—A solution of **20** (1.0 g) in diethoxymethyl acetate (20 ml) was heated at 100° for 4 hr and evaporated to dryness *in vacuo*. This residue was dissolved in 1.5 *N* NH_4OH (11 ml), and the resulting solution was acidified to pH 4 with 1 *N* HCl to deposit **12**: yield 0.82 g (77%); mp 251° dec (95% pure by uv spectrum).

4-Chloro-5-ethoxymethylenaminopyrimidin-6(1H)-one.—A suspension of 5-amino-4-chloropyrimidin-6(1H)-one hydrochloride[6] (5.0 g) in diethoxymethyl acetate (25 ml) was stirred at room temperature for 2.5 hr. An additional 5 ml of diethoxymethyl acetate was added to the mixture at the end of the first hour. The solid was collected by filtration, washed with ether (25 ml), and dried *in vacuo* over P_2O_5: yield 0.77 g; mp 181–183° dec with the evolution of gas (the melt solidified and did not remelt below 264°); λ_{max}, in mμ ($\epsilon \times 10^{-3}$), EtOH, 259 (5.50), 300 (7.92); $\bar{\nu}_{max}$, in cm^{-1}, 1700 (C=O), 1635, 1610, 1500 (C=C, C=N).

Anal. Calcd for $C_7H_8ClN_3O_2$: C, 41.65; H, 3.97; Cl, 17.61; N, 20.80. Found: C, 41.36; H, 4.30; Cl, 17.76; N, 20.82.

The diethoxymethyl acetate filtrate was evaporated to dryness under reduced pressure, and the remaining oil was distilled under high vacuum. The fraction that boiled at 121–155° was collected and extracted with petroleum ether (bp 85–105°) (35 ml), and the extract was evaporated to dryness to give an oil that solidified on cooling: yield 2.91 g; mp 181–183° dec with the evolution of fumes. The total yield was 3.67 g (66%).

9-Acetamidohypoxanthine (14). **A.**—A mixture of 9-aminohypoxanthine (**13**,[11] 900 mg) and Ac_2O (50 ml) was heated for 1 hr, the unreacted material (620 mg) was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*: yield 450 mg. This residue was dissolved in 1 *N* NH_4OH, the solution was filtered, and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was triturated with a small amount of H_2O and dried *in vacuo* over P_2O_5: yield 180 mg (50%, based on recovered **16**); mp >264°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19c] 0.1 *N* NaOH, 256 (11.8); $\bar{\nu}_{max}$, in cm^{-1}, 1715, 1700 (C=O), 1585, 1560, 1535, 1515 (C=C, C=N); paper chromatogram solvent (R_f). A (0.24), B (0.53), C (0.34), D (0.78).

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.55; H, 3.63; N, 36.25. Found: C, 43.76; H, 3.66; N, 36.02.

B.—Solid sodium hydrosulfite (3 g) was added in several portions with stirring to a suspension of **16** (1.0 g) in glacial AcOH (20 ml) at 100°, and the mixture was refluxed for 18 hr. After the addition of concentrated HCl (7 ml), the solid was removed by filtration, and the filtrate was evaporated to dryness *in vacuo* to yield 1.4 g of colored solid. Chromatographic data indicated that the major absorbing spot was **14**: paper chromatogram solvent (R_f), A (0.23), B (0.51), D (0.80). Similar treatment of **12** gave **14** containing a small amount of **13**.

In another experiment the isolated solid was boiled for 10 min in 2 *N* HCl to give mainly **13**, identified by its paper chromatographic behavior: A (0.12), B (0.42), C (0.23), D (0.68). Nitrosation of this sample gave hypoxanthine: A (0.26), B (0.51), C (0.36), D (0.58).

4-(2-Formylhydrazino)-5-nitropyrimidin-6(5H)-one (16).—A suspension of **15**[6] (2.3 g) in 98% HCO_2H (20 ml) was refluxed for 30 min and diluted with methanol (75 ml). The yellow solid that deposited was collected by filtration and dried *in vacuo* over P_2O_5: yield 2.10 g (78%); mp 263–265° dec; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19b] pH 7, 260 (5.9), 335 (6.22); $\bar{\nu}_{max}$, in cm^{-1}, 1715, 1670 (C=O), 1615, 1485 (C=C, C=N).

Anal. Calcd for $C_5H_5N_5O_4$: C, 30.15; H, 2.51; N, 35.15. Found: C, 30.28; H, 2.42; N, 35.01.

6-Amino-*as*-triazine-5-carboxamide (20).—A mixture of **12** (50 g) in 10:1 EtOH–H_2O (1100 ml) containing Et_3N (100 ml) was refluxed for 18 hr and cooled in an ice bath. The solid was collected by filtration and dried *in vacuo* over P_2O_5: yield 28 g (60%); mp 253–254° with sublimation (recrystallization from MeOH did not raise the melting point); λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] pH 7, 239 (11.7), 357 (4.11); $\bar{\nu}_{max}$, in cm^{-1}, 1705 (CO), 1615 (NH_2); pmr, τ 0.85 (1, CH), 1.52, 1.95, 2.20 (1,1,2, NH).

Anal. Calcd for $C_4H_5N_5O$: C, 34.53; H, 3.63; N, 50.35. Found: C, 34.64; H, 3.83; N, 50.25.

The filtrate was evaporated to dryness, and the resulting residue was recrystallized from EtOH to give crude, unreacted **12** (10 g). The ethanol filtrate was evaporated to dryness, and the residue was dissolved in H_2O (100 ml). The aqueous solution was acidified to pH 2 with concentrated HCl to deposit **21**·H_2O: yield 3.0 g (6%); this sample did not melt, but decomposed >250°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19c] 0.1 *N* NaOH, 244 (10.3), 342 (3.33); pmr (CF_3CO_2D), τ 0.75 (CH).

Anal. Calcd for $C_4H_4N_4O_2 \cdot H_2O$: C, 30.39; H, 3.83; N, 35.43. Found: C, 30.51; H, 3.90; N, 35.57.

6-Formamido-*as*-triazine-5-carboxamide (22).—A solution of **20** (1.0 g) in 2:3 Ac_2O–HCO_2H (25 ml) mixture was stirred at room temperature for 18 hr and evaporated to dryness under reduced pressure. This residue was dissolved in hot EtOAc (570 ml), and the resulting solution was evaporated to dryness to give **22**: yield 1.2 g (100%); mp 210°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] pH 7, 244 (16.7), 315 (3.40); $\bar{\nu}_{max}$, in cm^{-1}, 3340, 3220 (NH), 1670 (CO), 1600, 1545 (C=C, C=N); pmr, τ 0.32 (1, CH), 0.47 (m,1, CHO), −1.05 (m,1, NH), 1.18, 1.60 (1,1, NH).

Anal. Calcd for $C_5H_5N_5O_2$: C, 35.93; H, 3.02; N, 41.91. Found: C, 36.06; H, 3.18; N, 41.60.

Pyrimido[5,4-*e*]-*as*-triazine-5,7(6H,8H)-dione (23).—Phosgene was bubbled slowly for 0.5 hr into a solution of pyridine (1.8 ml) in anhydrous dioxane (225 ml), and the resulting mixture was refluxed for 15 min to remove excess phosgene. After adding **20** (3.0 g), the mixture was refluxed with stirring for 4.5 hr and evaporated to dryness *in vacuo*. This residue was extracted with hot glacial HOAc (two 125-ml portions), and the combined extracts were evaporated to dryness to give crude **23**: yield 2.5 g (70%). This solid was recrystallized once from glacial HOAc, then from water, and dried *in vacuo* over P_2O_5 at 140° to give the analytical sample: yield 1.3 g (37%); mp >264°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19c] 0.1 *N* HCl, 232 (14.4), 265 (sh), 332 (4.97), pH 7, 236 (sh), 248 (11.5), 264 (sh) (9.22), 350 (2.60), 385 (2.89), 0.1 *N* NaOH, 259 (19.4), 312 (2.03), 394 (3.92); $\bar{\nu}_{max}$, in cm^{-1}, 3180, 3085, 2985, 2790 (NH), 1715 (broad) (CO), 1570, 1555 (C=C, C=N); pmr, τ 0.32 (1, CH), −2.13 (broad) (2, NH).

Anal. Calcd for $C_5H_3N_5O_2$: C, 36.37; H, 1.83; N, 42.42. Found: C, 36.14; H, 2.08; N, 42.13.

Fervenulin (24).—A solution of **23** (495 mg) in DMF (5 ml) containing K_2CO_3 (830 mg) and CH_3I (0.39 ml) was stirred at room temperature for 36 hr. An additional amount of CH_3I (0.20 ml) was added at the end of 18 hr. The mixture was evaporated to dryness *in vacuo*, the residue was treated with 1 *N* HCl (6 ml), and the solid was collected by filtration: yield 162 mg (28%); mp 176°. Extraction of the residue obtained from evaporation of the acidic filtrate with $CHCl_3$ (two 25 ml portions) gave crude product (265 mg), which was purified by recrystallization from H_2O: yield 146 mg; mp 177° (lit. mp 175.7°,[3] 178–179°[2]) [total yield 308 mg (53%)]; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), EtOH, 239 (16.8), 275 (1.60), 340 (4.33); pmr, τ 0.17 (1, CH), 6.34, 6.68 (3.3, CH_3).

Registry No.—**2**, 19359-15-0; **6**, 19359-59-2; **7**, 19359-60-5; **8**, 19359-61-6; **9**, 19359-62-7; **10**, 19359-63-8; **12**, 19359-64-9; **14**, 19359-65-0; **16**, 19359-66-1; **20**, 19359-67-2; **22**, 19359-68-3; **23**, 19359-69-4; 4-chloro-5-ethoxymethylenaminopyrimidin-6-(1H)-one, 19359-70-7.

Acknowledgment.—The authors are indebted to Dr. W. J. Barrett and the members of the Analytical and Physical Chemistry Division of Southern Research Institute for the spectral and microanalytical determinations. Some of the analyses reported were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Base-Catalyzed Reactions. XXXIII.[1] Sodium- and Potassium-Catalyzed Reactions of Methylnaphthalenes with Ethylene

BOZIDAR STIPANOVIC AND HERMAN PINES

The Ipatieff High Pressure and Catalytic Laboratory, Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received August 26, 1968

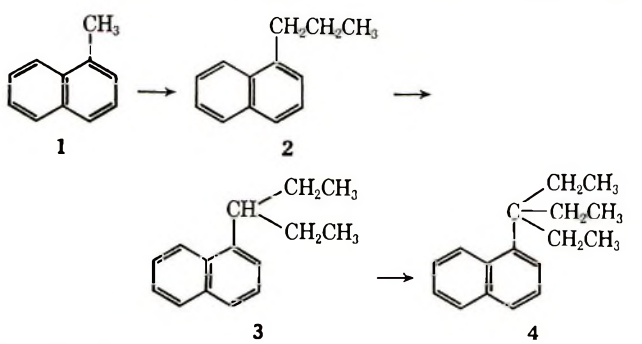
Sodium or potassium dispersed in 1- or 2-methylnaphthalene are active catalysts for the reaction of these hydrocarbons with ethylene, under pressure and at temperatures from 90 to 210°. To form an active sodium catalyst a promoter is needed, while in the case of potassium the initiator is not always required. The reaction in the presence of sodium results exclusively in side-chain ethylation (compounds **2**–**4**, **6**, and **8**–**10**). All hydrogen atoms at the α carbon of the side chain can be replaced with ethyl groups, though in case of 1-alkylnaphthalenes steric hindrance can considerably retard the reaction. The potassium-catalyzed reaction with ethylene is more complex. In addition to the side-chain ethylation reaction, products of cyclization (**12**, **17**, and **18**) and nuclear alkylation (**11** and **16**) were isolated. Also, all of these primary products undergo further alkylation (**13** and **14**) and formation of higher boiling hydrocarbons can take place.

The sodium- and potassium-catalyzed side-chain alkylation and alkenylation of alkylbenzenes and alkylpyridines have been the subject of extensive studies in this laboratory.[1,2] The present investigation is extended to the study of the reactions of ethylene with 1- and 2-alkylnaphthalenes, these being representatives of alkylpolycyclic hydrocarbons. The search of the literature had revealed only a noncatalytic reductive methylation of sodium 1- and 2-methylnaphthalenes with methyl bromide.[3]

The ethylation reactions were carried out under pressure using catalytic amounts of either sodium or potassium in the presence of small amounts of *o*-chlorotoluene as a promoter. The major reaction products were separated by a combination of fractional distillation and gas chromatography and the structures were established by nmr, by ir, and in some cases by means of mass spectra and synthesis.

Results

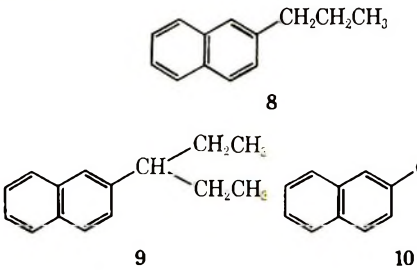
Sodium-Catalyzed Reactions.—Sodium has been found to be a very selective catalyst for the side chain ethylation of alkylnaphthalenes (Table I). With 1-methylnaphthalene (**1**), mono- and diadducts of ethylene were the only products obtained (expt 1 and 2). 3-(1-Naphthyl)pentane (**3**) underwent further ethylation very slowly and only after all of the *n*-propylnaphthalene (**2**) had reacted (expt 3). Prolonged heating and stirring for several hours resulted in the formation of only 2% 3-ethyl-3-(1-naphthyl)pentane (**4**).[4]



1 2 3 4

1,5-Dimethylnaphthalene (**5**) in the presence of sodium and an excess of ethylene produced 1,5-di(3-pentyl)naphthalene (**6**) in a 94% yield (expt 5).

2-Methylnaphthalene (**7**) formed mono- (**8**), di- (**9**), and triethylated (**10**) compounds; the last one was produced in a 62% yield (expt 7, Table I).



8 9 10

Unlike **1**, 2-methylnaphthalene (**7**) reacts readily with three molecules of ethylene to produce 3-ethyl-3-(2-naphthyl)pentane (**10**). The difference in the reactivity of **1** and **7** is due to steric effects which in 1-methylnaphthalene had been estimated to be 1.6 kcal/mol, greater than in *o*-xylene (0.5 kcal/mol) and almost equal to that of 1,2,3-trimethylbenzene (2.0 kcal/mol).[5] Molecular models show that in compound

(1) Paper XXXII: H. Pines and J. Oszczapowicz, *J. Org. Chem.*, **32**, 3138 (1967).

(2) For general literature review, see H. Pines and L. A. Schaap, *Advan. Catal.*, **12**, 117 (1960).

(3) W. Hückel and R. Cramer, *Justus Liebigs Ann. Chem.*, **630**, 89, (1960); W. Hückel, and C. M. Jennewein, *Chem. Ber.*, **95**, 350 (1962).

(4) 1-Isopropylnaphthalene and 1-*sec*-butylnaphthalene were ethylated much more easily under the same conditions. More details about the products, 2-methyl-2-(1-naphthyl)butane and 3-methyl-3-(1-naphthyl)pentane, will be published in a separate paper.

(5) J. Packer, J. Vaughan, and E. Wong, *J. Amer. Chem. Soc.*, **80**, 905 (1958).

TABLE I
SODIUM-CATALYZED REACTIONS OF ALKYLNAPHTHALENES WITH ETHYLENE

Expt	Starting material[a]	Reaction temp, °C	Duration, hr	Convn,[a] %	Yields[b] of products,[c] % 2	3	4	6	8	9	10	Other
1	1-Methylnaphthalene (1)	210	8	53.1	49.8	47.1						3.1
2	1-Methylnaphthalene (1)	196	36	99.8	10.5	84.7						4.8
3	1-Methylnaphthalene (1)	208	48	100		91.7	2.1					6.2
4	1-*n*-Propylnaphthalene (2)	195	36	99.4		96.3						3.7
5[d]	1,5-Dimethylnaphthalene (5)	204	40	99.9				94.2				5.8
6	2-Methylnaphthalene (7)	178	10	75.9					25.8	64.8	3.0	6.3
7	2-Methylnaphthalene (7)	175	48	100					Trace	31.3	62.6	6.1

[a] Sodium (0.2–0.3 g) and *o*-chlorotoluene (0.2–0.4 ml) were stirred in 0.15 mol of alkylnaphthalene plus 0.0375 mol of *sec*-butylcyclohexane (internal standard) at 120° for 3–4 hr (12 hr expt 6 and 7). Initial pressure of ethylene was 30–35 atm. [b] Molar % based on reacted alkylnaphthalenes. [c] For the names of the compounds, consult Table VI. [d] About 0.1 g of sodium, 0.2 ml of *o*-chlorotoluene, 0.032 mol of starting material, and 0.0075 mol of *sec*-butylcyclohexane; after sodium was dispersed, the mixture was diluted with 10 ml of dry benzene.

TABLE II
ANALYTICAL DATA OF THE PRODUCTS OBTAINED IN THE PRESENCE OF SODIUM AS CATALYST

Compound[b]	Nmr Spectra,[a] δ, ppm CH₃	CH₂	CH	Aromatic protons	Bp, °C (mm)	Analysis, % Calcd C	Calcd H	Found C	Found H	Refract. index[c]
2	1.00 (3), t	1.77 (2), m 3.02 (2), t		7.20–8.16 (7), m	81–82 (1)					1.5923[d]
3	0.82 (6), t	1.82 (4), m	3.37 (1), m	7.30–8.32 (7), m	117–119 (4–5)	90.85	9.15	90.55	9.41	1.5782
4	0.63 (9), t	2.00 (6), q		7.00–8.44 (7), m	44–45[f]	90.20	9.80	90.42	9.97	
6	0.83 (12), t	1.84 (8), m	3.46 (2), m	7.29–7.64 (4), m 8.01–8.24 (2), q	171–172 (6) 33.5–34.5[f]	89.49	10.51	89.70	10.41	
8	0.95 (3), t	1.71 (2), m 2.71 (2), t		7.14–7.91 (7), m						1.5863[g]
9	0.78 (6), t	1.76 (4), m	2.45 (1), m	7.08–7.83 (7), m	102–104 (1.5)	90.85	9.15	91.08	9.19	1.5720
10	0.66 (9), t	1.77 (6), q		7.17–7.52 7.55–7.72 (7), m	133–134 (3–4)	90.20	9.80	89.74	10.08	1.6110

[a] Numbers in parentheses are proton integrations; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. [b] For the names of the compounds, consult Table VI. [c] Measured at 20.0°. [d] Lit.[e] n^{20}D 1.5922. [e] S. H. Morrell, G. B. Pickering, and J. C. Smith, *J. Inst. Petr.*, **34**, 677 (1948). [f] Melting point. [g] Lit.[e] n^{20}D 1.5872.

3 there is a considerable interaction between the C-8 hydrogen and 3-pentyl group, which hinders further alkylation.

In the case of 1- and 2-methylnaphthalenes, monoethylated products could not be obtained free of the higher ethylated methylnaphthalenes. The rate of ethylation of the *n*-propyl group in naphthalene seems to be faster than that of the methyl group, which is in agreement with the data obtained from the study of the relative rates of ethylation of toluene *vs.* *n*-propylbenzene[6] and γ-picoline *vs.* γ-*n*-propylpyridine.[7]

The other minor products from the reaction of methylnaphthalenes with ethylene catalyzed by sodium were not isolated. However, the vpc relative retention times of these products were similar to those obtained in larger amounts in the presence of potassium.

The nmr spectra of the side-chain ethylated alkylnaphthalenes, obtained from the reactions catalyzed by sodium, gave unequivocal proof of their structures (Table II). Compounds **3**, **4**, **9**, and **10** have not been previously reported in the literature.

Potassium-Catalyzed Reactions.—The reaction of ethylene with 1- and 2-methylnaphthalene in the presence of potassium proceeded at temperatures of 90 to 160°, which is 50 to 100° lower than in the presence of sodium (Table III). Although the potassium-catalyzed reactions did not require *o*-chlorotoluene as a promoter, nevertheless its presence facilitated the ethylation.

The product obtained from the ethylation of methylnaphthalenes with potassium as a catalyst is much more complex than that derived from sodium (Table III). Besides the side-chain alkylation, cyclization and nuclear alkylation have also taken place. In addition all of these compounds also underwent further ethylation. Only 65 and 78% of the products from the reaction of 1- and 2-methylnaphthalene, respectively (expt 9 and 12, Table III), were identified. The remainder consisted of viscous material and tar. Besides **2** and **8**, compounds **11**, **12**, **16**, and **17** are the main products from the respective ethylation of methylnaphthalenes (see Scheme I).

The reaction of methylnaphthalenes with ethylene in the presence of potassium was accompanied by the formation of considerable amount of ethane, which diluted the ethylene and slowed down the rate of reaction. To complete the reaction the ethane–ethylene mixture was released during the course of the experi-

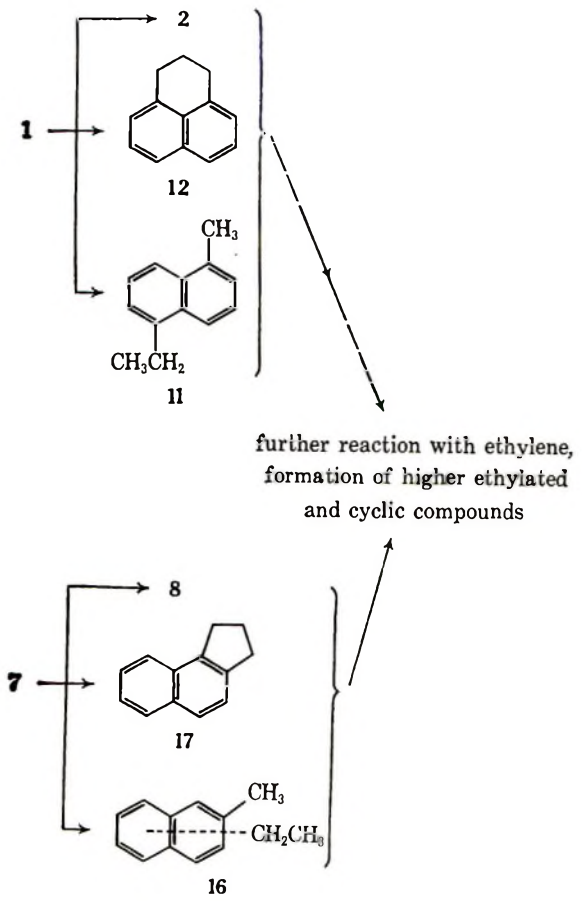
(6) H. Pines and L. Schaap, *J. Amer. Chem. Soc.*, **80**, 3076 (1958).
(7) B. Notari and H. Pines, *ibid.*, **82**, 2945 (1960).

TABLE III
POTASSIUM-CATALYZED REACTIONS OF ALKYLNAPHTHALENES WITH ETHYLENE

Expt	Starting material[a]	Catalyst prepared,[b] °C, (hr)	Reaction temp, °C	Duration, hr	Ethane ratio[c]	Convn, %	Yields[d] of products,[e] %							
							2	3	11	12	13	14	15	Other + higher alkylated
8	1-Methylnaphthalene (1)	110(1.5)	165	4		41.5	18.3	2.2	4.0	9.7	12.3			53.4
9	1-Methylnaphthalene (1)	40 (3)	105	18	1.6	25.6	24.8	2.6	6.2	19.0	11.9			35.4
10	1-*n*-Propylnaphthalene (2)	90 (2)	160	12		49.3		19.8			25.7	9.0		46.9
11	3-(1-naphthyl)-pentane (3)	90 (2)	140	8		59.3						62.8	2.3	34.9
							8	9	10	16	17	18		
12	2-Methylnaphthalene (7)	40 (18)	90	36	0.7	49.4	22.4	2.4	0	10.4	41.7	3.1		21.7

[a] Alkylnaphthalene (0.15 mol) plus *sec*-butylcyclohexane (0.0375 mol) (internal standard); initial pressure of ethylene was 30–35 atm. [b] About 0.3–0.5 g of potassium in alkylnaphthalene was stirred without promoter, except in expt 8 and 11 where 0.2 and 0.4 ml, respectively, of *o*-chlorotoluene was added. [c] Molar ratio between the ethane produced and the total amount of cyclic plus higher alkylated product. [d] Molar per cent based on reacted alkylnaphthalene. [e] For the names of the compounds, consult Table VI.

SCHEME I



ment and the autoclave was recharged with fresh ethylene. The amount of ethane produced is an indicator of the extend of cyclization. Similar formation of ethane and cyclic compounds in the presence of potassium, but not in the presence of sodium, has been observed previously in connection with the ethylation of alkylbenzenes.[8] Cyclization in the presence of potassium had also been reported in the case of the rearrangement of ω-phenylalkenes.[9,10]

1-Methylnaphthalene yielded about 30% dihydrophenalene **12** and its ethyl derivative **13**, while 2-methylnaphthalene gave 45% indan-type compounds **17** and **18** (Table III). If we assume that at least the same distribution may exist among the unidentified higher boiling products, then the percentage of cyclic hydrocarbons formed would be even higher. Only one of the two possible cyclization compounds of 1- and 2-methylnaphthalene was found, as the attack was exclusively on the α position of the naphthalene ring; dihydrophenalene **12** and dihydrobenz[*e*]indene **17** were produced, respectively. The β position of the naphthalene ring seems inert to cyclization.

From expt 11 about 3% benz[*e*]indene **18**, a product of dehydrogenation of **17**, was also isolated; this type of dehydrogenation by alkali metals had been reported previously.[11–13] It is therefore very possible that phenalene itself must have undergone dehydrogenation (expt 8 and 9); however, owing to its high reactivity, it was not detected.

Previous studies have indicated that in base-catalyzed reactions alkylbenzenes having a benzylic hydrogen do not undergo nuclear alkylations with olefins.[2] However, in the case of methylnaphthalenes, ring alkylation in the presence of potassium did occur; 4–10% of the product consisted of ring-alkylated material (expt 8, 9, and 12). 2-Methylnaphthalene produced three isomeric methylethylnaphthalenes which were not separable into pure compounds by gas chromatography. Nuclear alkylation was the main reaction when 3-(1-naphthyl)pentane (**3**) was allowed to react with

(8) L. Schaap and H. Pines, *J. Amer. Chem. Soc.*, **79**, 4967 (1957).

(9) H. Pines, N. C. Sih, and E. Lewicki, *J. Org. Chem.*, **30**, 1457 (1965).

(10) N. C. Sih and H. Pines, *ibid.*, **30**, 1462 (1965); H. Pines, J. A. Vesely, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **77**, 347 (1955).

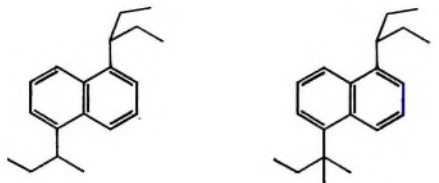
(11) H. Pines and H. E. Eschinazi, *ibid.*, **77**, 6314 (1955).

(12) M. Kolobielski and H. Pines, *ibid.*, **79**, 5820 (1957).

(13) T. M. O'Grady, R. M. Alm, and M. C. Hoff, Division of Petroleum Chemistry of the American Chemical Society, Preprints 4, No. 4, B65-B69, 1959.

ethylene (expt 11); about 63% compound **14** was produced.

From the same experiment, a small amount of pure compound was separated which had a higher boiling point than the main product to which structure **15** was assigned. The nmr spectrum of **15** represents almost a

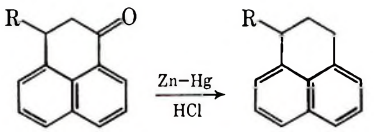


14 **15**

superimposure of the spectra of 3-(1-naphthyl)pentane (**3**) and 3-methyl-3-(1-naphthyl)pentane[4,14] (Figure 1).

Analytical data of the products formed by the nuclear alkylation and cyclization using potassium as a catalyst are given in Table IV, where **13**, **14**, and **15** are new compounds. Some of the hydrocarbons were synthesized and their nmr and ir spectra were compared with those of the products of the reaction and found to be identical.

Dihydrophenalene **12** and ethyldihydrophenalene **13** were synthesized by a Clemmensen reduction of the corresponding ketones.[15] Compound **13** could not be



19, R = H
20, R = C_2H_5

12, R = H
13, R = C_2H_5

synthesized directly from 1,2-dihydrophenalen-3-one **19** by means of a Grignard reaction because the dehydration of the corresponding alcohol leads to the isomerization of the ethyl group.[16]

Ketone **20** was prepared from 1-(1-naphthyl)-1-propanol (**21**), following the procedure of Bachmann and Edgerton.[17] Compound **11** was synthesized according to the method of Harvey, *et al.*,[18] with a few modifications. Hydrocarbon **14** was synthesized by reacting 1-methyl-5-ethylnaphthalene (**11**) with ethylene in the presence of sodium as a catalyst.

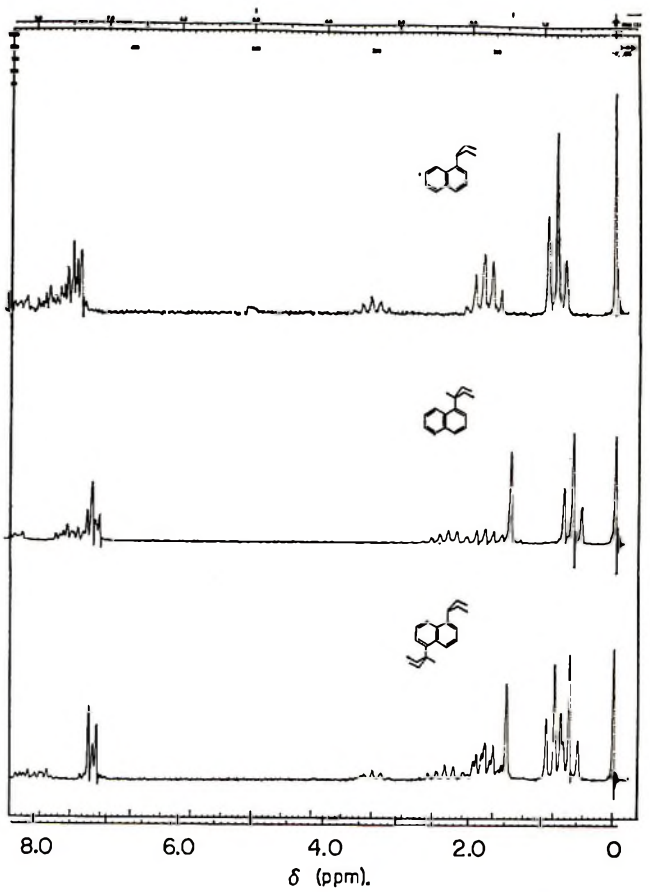
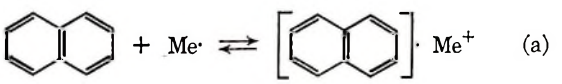


Figure 1.—Nmr spectra of 3-(1-naphthyl)pentane, 3-methyl-3-(1-naphthyl)pentane, and 1-(3-pentyl)-5-[(3-methyl)-(3-pentyl)]-naphthalene.

Discussion

The course of the reaction of alkylnaphthalenes with ethylene depends on alkali metal being used as a catalyst, which confirms the previously obtained results with alkylbenzenes,[8] and with ω-phenylalkenes.[9] Unlike alkylbenzenes, alkylnaphthalenes do not require the presence of a promoter to form an active potassium catalyst (expt 8, Table III). This can be attributed to the fact that fused polycyclic aromatic hydrocarbons undergo an addition reaction with a reactive alkali metal to form a mononegative ion.[19] The solutions of



(a)

Me = alkali metal

such ions in tetrahydrofuran and 1,2-dimethoxyethane were strongly paramagnetic[19b] and esr spectra unambiguously proved that the added electron is not localized on a particular carbon atom, but is distributed and delocalized over the whole π-electron system of the molecule.[19c] The electrontransfer from the alkali metal to the hydrocarbon may thus lead to uni- or divalent ions depending on the solvent.[19b]

In the case of alkylnaphthalenes with at least one relatively acidic proton on the α-carbon atom (benzylic

(14) The nmr spectrum indicated that the CH_2 hydrogens in 3-methyl-3-pentyl group are not magnetically equivalent (Figure 1). Nonequivalence apparently arises because the methylene group is attached to a carbon bearing three different substituents and an AB quartet of lines is further coupled to the adjacent methyl group. As a result of overlap, however, the full 16-line multiplet is not obtained. ("Nuclear Magnetic Resonance for Organic Chemists," D. W. Mathieson, Ed., Academic Press, London–New York, 1967, pp 39, 121).

(15) L. F. Fieser and F. C. Novello, *J. Amer. Chem. Soc.*, **62**, 1855 (1940); L. F. Fieser and M. D. Gates, *ibid.*, **62**, 2334 (1940).

(16) D. H. Reid, *Quart. Rev.* (London), **19**, 274 (1965); V. Boekelheide and C. E. Larrabee, *J. Amer. Chem. Soc.*, **72**, 1240, 1245 (1950); M. Nakazaki, *U.S. At. Energy Comm. Repts.*, U.C.R.L. 3700 (1959).

(17) W. E. Bachmann and R. O. Edgerton, *J. Amer. Chem. Soc.*, **62**, 2219 (1940).

(18) J. Harvey, I. M. Heilbron, and D. G. Wilkinson, *J. Chem. Soc.*, 423, (1930).

(19) E. de Boer, *Advan. Organometal. Chem.*, (a) 115 (1964); (b) 117 (1964); (c) 140 (1964).

TABLE IV
ANALYTICAL DATA OF THE PRODUCTS OBTAINED IN THE PRESENCE OF POTASSIUM AS CATALYST

Compound[b]	Nmr spectra,[a] δ, ppm: CH_3	CH_2	CH	Aromatic protons	Bp (mm) or mp, °C, or refractive index
11	1.33 (3), t 2.72 (3), s	3.04 (2), q		7.00–7.50 7.55–7.97 } (6), m	Mp 35–38[c]
12		1.99 (2), m 3.01 (4), t		6.93–7.55 (6), m	Mp 64–65[d]
13	0.96 (3), t	1.73 (2), m 1.95 (2), m 2.86 2.96 (3), m		7.00–7.30 (6), m	$n^{20}D$ 1.6114
14	0.81 0.92 } (9), q	1.36 (3), d	3.42 (2), m	7.20–7.64 7.83–8.10 } (6), m	Bp 125–130 (1–1.5) $n^{20}D$ 1.5637
15	0.61 0.82 } (12), m 1.48 (3), m	1.78 1.82 } (8), m 2.33	3.33 (1), m	7.15–8.42 (6), m	
17		2.18 (2), q 3.02 3.13 } (4), q		7.13–7.81 (6), m	$n^{20}D$ 1.6130[e]
18		3.40 (2), m		6.42–6.63 6.80–7.00 7.22–7.47 7.62–7.87 } (8), m	

[a] Numbers in parentheses are proton integrations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. [b] For the names of the compounds, consult Table VI. [c] Lit.[18] mp 40.0°; identical with an synthetic sample (11; see Experimental Section). [d] Mp 65.1–65.4°: L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, **60**, 1658 (1938). [e] $n^{19.7}D$ 1.6323. [f] J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 1098 (1933).

type of proton), reactions b–d can occur. The species like IV and V can then initiate the catalytic side-chain alkylation.

$$\underset{\text{I}}{C_{10}H_7CH_3} + Me\cdot \longrightarrow \underset{\text{II}}{|C_{10}H_7CH_3|\cdot}\ {}^-Me^+ \qquad \text{(b)}$$

$$\underset{\text{II}}{|C_{10}H_7CH_3|\cdot}\ {}^-Me^+ + \underset{\text{I}}{C_{10}H_7CH_3} \longrightarrow \underset{\text{III}}{|C_{10}H_8CH_3|\cdot} + \underset{\text{IV}}{C_{10}H_7CH_2}{}^-Me^+ \qquad \text{(c)}$$

$$\underset{\text{III}}{|C_{10}H_8CH_3|\cdot} + \underset{\text{II}}{|C_{10}H_7CH_3|\cdot}\ {}^-Me^+ \longrightarrow \underset{\text{V}}{|C_{10}H_8CH_3|}\ {}^-Me^+ + \underset{\text{I}}{C_{10}H_7CH_3} \qquad \text{(d)}$$

Me = alkali metal

Potassium having a lower ionization potential than sodium is able to transfer the electron to a naphthalene molecule and form an anion radical. However, promoters are necessary for the reactions in the presence of sodium since radical anions are formed less readily with this metal, particularly in the nonpolar solutions, and at higher temperature.[19–21]

High selectivity of the sodium-catalyzed ethylation of alkylnaphthalenes is an indication that only carbanions at the α-carbon atom of the side chain are involved in the addition to ethylene (eq e and f). A monoethylated

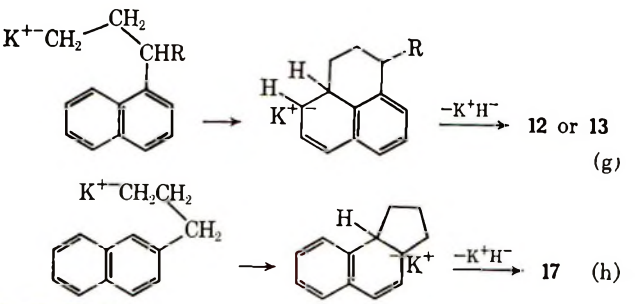
$$ClC_6H_4CH_3 \xrightarrow[(-NaCl)]{2Na} C_6H_5CH_2{}^-Na^+ \xrightarrow{C_{10}H_7CH_3} C_{10}H_7CH_2{}^-Na^+ + C_6H_5CH_3 \qquad \text{(e)}$$

$$C_{10}H_7CH_2{}^-Na^+ \xrightarrow{CH_2=CH_2} C_{10}H_7CH_2CH_2CH_2{}^-Na^+ \xrightarrow{C_{10}H_7CH_3} C_{10}H_7CH_2CH_2CH_3 + C_{10}H_7CH_2{}^-Na^+ \qquad \text{(f)}$$

product can further undergo an abstraction of the secondary proton and then add to another molecule of ethylene. This mechanism is similar to the one proposed previously to explain the side-chain alkylation of toluene with olefins.[2,22]

The potassium-catalyzed reaction of alkylnaphthalenes and ethylene is more complex than that with sodium. More than 15 compounds were formed from the reaction of 1-methylnaphthalene with ethylene. The great difference between the catalytic properties of the alkali metals as catalysts may be related to the ionic characters of the carbon–metal bonds. Organolithium compounds are least ionized while cesium–carbon bonds show a large extent of ionic character.[23] A more ionic species is probably more dissociated and the carbanion is thus of higher reactivity.[9] It also appears probable that the extent of ion pairing[24] and the field effect of the cation[25] may determine to a certain degree the catalytic properties of an alkali metal.

The formation of 1,2-dihydrophenalene (13) (eq g)



(20) G. J. Hoijtink and P. H. van der Meij, *Z. Phys. Chem.* (Frankfurt), **20** (1/2), 1 (1959).

(21) A. Rembaum, A. Eisenberg, and R. Haack, *J. Amer. Chem. Soc.*, **87**, 2291 (1965); A. Rembaum, A. Eisenberg, R. Haack, and R. F. Landel, *ibid.*, **89**, 1062 (1967).

(22) H. Pines and V. Mark, *ibid.*, **78**, 4316 (1956).

(23) E. G. Rochow, D. T. Hurd, and R. N. Lewis, "The Chemistry of Organometallic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1957, p 25.

(24) K. H. J. Buschow, J. Dielman, and G. J. Hoijtink, *J. Chem. Phys.*, **42**, 1993 (1965); N. H. Velthorst and G. J. Hoijtink, *J. Amer. Chem. Soc.*, **87**, 4529 (1965).

(25) E. Warhurst and R. Whittaker, *Trans. Faraday Soc.*, **62**, 707 (1966).

TABLE V
DESCRIPTION OF VAPOR PHASE CHROMATOGRAPHIC COLUMNS

Column	Liquid phase	Solid support	Mesh	Length, m	Outside diameter, in.
A	15% silicone gum SE-30	Gas Pack WAB	60–80	2.13	0.25
B	15% silicone gum SE-30	Gas Pack WAB	60–80	2.44	0.375
C	15% Versamid	Gas Pack WAB	60–80	2.44	0.375
D	15% Carbowax 20M	Chromosorb P	60–80	2.13	0.25
E	15% LP-122 silicone gum rubber GE-SE-52	Chromosorb W	60–80	10.00	0.25

TABLE VI
RELATIVE RETENTION TIMES OF IDENTIFIED REACTION PRODUCTS[a]

Reaction product	Compound no.	Column[b,c] A[d]	Column[b,c] A[e]	Column[b,c] D[d]
Standard		1.00	1.00	1.00
1-Propylnaphthalene	2	1.45		1.15
3-(1-Naphthyl)pentane	3	2.11		1.36
3-Ethyl-3-(1-naphthyl)pentane	4	3.97	1.95	2.57
1,5-Di(3-pentyl)naphthalene	6		3.25	
2-Propylnaphthalene	8	1.48		1.16
3-(2-Naphthyl)pentane	9	2.20		1.48
3-Ethyl-3-(2-naphthyl)pentane	10	4.36		3.05
1-Methyl-5-ethylnaphthalene	11	1.68		1.45
1,2-Dihydrophenalene	12	2.18		2.37
1-Ethyl-1,2-dihydrophenalene	13	3.49		3.24
1-(2-Butyl)-5-(3-pentyl)naphthalene	14		2.90	
1-(3-Pentyl)-5-[(3-methyl)-3-pentyl]naphthalene	15		4.44	
2-Methyl-*x*-ethylnaphthalene	16	1.50		1.27
2,3-Dihydro-1H-benz[*e*]indene	17	2.24		2.28
*x*H-Benz[*e*]indene[f]	18	2.36		

[a] F & M 720 chromatograph; helium flow 100 ml/min at 35 psi; injection port and detector temperature 300°. [b] Column temperature 220°. [c] Description of the columns in Table V. [d] Biphenyl as a standard. [e] Fluorene as a standard. [f] 1H- and/or 3H-benz[e]indene.

and 2,3-dihydro-1H-benz[*e*]indene (**17**) (eq f) could be explained according to the earlier proposed mechanism as an intramolecular alkylation of the aromatic ring by a carbanion.[8] Potassium hydride from the cyclization reaction may add to an ethylene and form ethylpotassium, which by abstraction of a proton from an α-carbon atom leads to the formation of a carbanion and ethane (eq i). A concerted mechanism for such a cyclization reaction has been recently proposed.[26]

$$K^+H^- + CH_2{=}CH_2 \longrightarrow CH_3CH_2{}^-K^+ \xrightarrow{C_{10}H_7CH_3} CH_3CH_3 + C_{10}H_7CH_2{}^-K^+ \quad \text{(i)}$$

R = H, alkyl

Product **18** resulting from the dehydrogenation of **17** was isolated from the reaction of 2-methylnaphthalene (expt 12, Table III). This dehydrogenation could be explained by a mechanism suggested previously.[11]

The nuclear alkylation, one of three major reactions of alkylnaphthalenes and ethylene in the presence of potassium, was also found to occur in ethylation reactions of alkylbenzenes, although in relatively small yields. For this reaction two possible carbanion mechanisms were suggested.[8,22] The formation of ethylpotassium by the addition of potassium hydride to ethylene may result either in a direct attack of the ethyl carbanion on the aromatic nucleus, or in a metalation of the aromatic ring. The arylpotassium thus formed could then add to ethylene.[27]

The addition of an aromatic mononegative ion to ethylene could also be assumed and there is some evidence in favor of such a mechanism. The structure of the isolated product **14** from the reaction of 1-methylnaphthalene suggests that the carbon atom in position 5 is presumably more reactive than the others. This is in agreement with the calculated higher spin densities at the α rather than at the β position of the symmetrically substituted dimethylnaphthalene mononegative ions.[28] It is, however, difficult to visualize such a reaction as a catalytic process. Only a catalytic reaction can lead to the formation of more than 60% ring-alkylated compound **14** (expt 11, Table III) and for that reason the mechanism involving ethylpotassium is favored.

Experimental Section

The pure reaction products were separated by means of preparative vapor phase chromatography (columns B and C, Table V). The structures of various hydrocarbons were determined from the nmr spectra, while the ir spectra[29] were compared with those of synthesized compounds or with known spectra from the literature. The vpc columns are described in Table V, and the retention times of identified products are given in Table VI. All melting and boiling points are uncorrected.

Apparatus and General Procedure.—In a three-necked, round-bottom flask with a thermocouple well, equipped with a high speed stirrer,[30] condenser with a drying tube, and an inlet for inert gas (nitrogen or helium), was placed 0.15 mol of alkylnaphthalene and 0.0375 mol of *sec*-butylcyclohexane as an in-

(26) G. G. Eberhardt, *J. Org. Chem.*, **29**, 643 (1964).

(27) Recently, R. L. Eppley, and J. A. Dixon [*J. Amer. Chem. Soc.*, **90**, 1606 (1968)] have found that *t*-butyllithium reacts with naphthalene, initially forming a complex $(RLi)_2(C_{10}H_8)$. Subsequent reaction of this complex leads to the formation of 1- and 2-*t*-butylnaphthalene. A similar intermediate complex might be found in the reaction of ethylpotassium and alkylnaphthalene.

(28) F. Gerson, P. Wiedmann, and E. Heilbroner, *Helv. Chim. Acta*, **47**, 1951 (1964).

(29) The ir spectra were taken in a microcell with capillary thickness (liquid products) and in KBr pellet (solids) with a Baird Model 4-55 spectrophotometer. Nmr spectra were measured in carbon tetrachloride using tetramethylsilane as an internal standard with a Varian A-60.

(30) H. Pines and N. C. Sih, *J. Org. Chem.*, **30**, 280 (1965).

ternal standard. Under a nitrogen (or helium in case of potassium) atmosphere approximately 0.01–0.02 g-atom of alkali metal was cut (under dry *n*-pentane) and placed into the flask. Then, if necessary, 0.2–0.4 ml of *o*-chlorotoluene was added and the reaction mixture was heated to the desired temperature and stirred until a dark brown or black suspension was formed (the reaction conditions for particular experiments are given in Table I and III). The mixture was then cooled and transferred (under nitrogen) to a Magne-Dash autoclave of 100-cc capacity. After flushing the air with nitrogen, ethylene was introduced from a calibrated charger (pressure of about 30 atm at room temperature). The autoclave content was agitated and heated to that temperature at which the pressure started to decrease. At the end the autoclave was cooled down to room temperature. In some experiments the gaseous products, after releasing the pressure, were collected in a gas bottle and analyzed on column E (Table V) at room temperature.

The remaining alkali metal and organometallic catalyst was decomposed with abs ethanol (under nitrogen). The resulting reaction mixture was dissolved in ether, washed with water and salt solution, dried over anhydrous magnesium sulfate, and finally distilled in vacuum under nitrogen. The samples for the vpc analysis were taken before distillation. The conversions and molar per cent compositions of the products were calculated according to the internal standard. Thermal conductivity coefficients for separated and identified products were taken into account for those calculations.

Reagents.—1-Methylnaphthalene (Aldrich, bp 240–243°) and 2-methylnaphthalene (Aldrich, mp 34–36°) were distilled and stored under nitrogen until they were used for the reaction. 1,5-Dimethylnaphthalene was supplied by courtesy of Dr. A. W. Weitkamp, American Oil Co., Whiting, Ind. 3-(1-Naphthyl)-pentane was synthesized from 1-methylnaphthalene and ethylene in the presence of sodium as a catalyst.

3-(1-Naphthyl)pentane (3).—A mixture of 71.0 g (0.5 mol) of 1-methylnaphthalene, about 1–1.5 g (0.1 g-atom) of freshly cut (under dry *n*-pentane) metallic sodium, and 0.5 ml of *o*-chlorotoluene were placed in the previously described apparatus (250-cc capacity). The reaction mixture was stirred at 110–120° under a slow stream of nitrogen for 4 hr. The content was then cooled down and transferred into a 250-cc Magne-Dash autoclave, and after flushing the air with nitrogen ethylene was introduced (about 32 atm). The reaction was carried out at 205° for 48 hr. More ethylene was added during that time. After the reaction was completed, unreacted ethylene was released and the sodium and organosodium compounds destroyed with ethanol. The reaction products were dissolved in ether, washed, dried ($MgSO_4$), and distilled. After a small amount of 1-propylnaphthalene was distilled off, the main reaction product, a viscous, colorless liquid, 3-(1-naphthyl)pentane, distilled at 133–134° (4–5 mm). The yield was 69.8 g (82.2%).

Synthesis of the Reaction Products. A. 1,2-Dihydrophenalene (12). 1,2-Dihydrophenalen-3-one (19).—Ketone **19** was synthesized according to the method of Fieser and Gates,[15] with the modification that 1-bromoethylnaphthalene was used as a starting material: 52% over-all yield, mp 80–82°. The bromide was prepared in 91% yield, mp 54–55°, by the method of Horner and Winkelmann.[31]

1,2-Dihydrophenalene (12).—This hydrocarbon was prepared in 66% yield, mp 64.5–65.5°, by the Clemmensen reduction[15] of **19**.

B. 1-Ethyl-1,2-dihydrophenalene (13). 1-(1-Naphthyl)propan-1-ol (21).—Carbinol **21** was synthesized from 0.1 mol of 1-bromonaphthalene and 0.1 mol of propionaldehyde *via* a Grignard reaction, according to the procedure described.[32] The yield of alcohol **21** was 82%, bp 139–142° (2–2.5 mm), $n^{20}D$ 1.6096.[33]

1-Bromo-1-(1-naphthyl)propane (22).—Bromide **22** was prepared from 0.08 mol of **21** according to the method of Bachmann and Edgerton:[17] yield 72%, mp 37–38.5°.[33]

β-(1-Naphthyl)valeric acid (23).—Acid **23** was synthesized from 0.052 mol of **22** and diethyl sodiomalonate:[17] yield 69%, mp 69–70°.[33]

1-Ethyl-1,2-dihydrophenalen-3-one (20).—Acid **23** (0.038 mol) was cyclized by means of hydrogen fluoride according to Ansell and Berman.[33] A brown oil (6.9 g) was obtained, which was chromatographed in *n*-hexane on an alumina column (4 × 15 cm). Ketone **20** was eluted by a 4:1 *n*-hexane–ether solution. The column and the elute were kept under nitrogen, and he column was protected from the light. After the solvent was distilled off, 4.05 g (50%) of **20** was obtained: 2,4-dinitrophenylhydrazone mp 182.5–184°.[33]

1-Ethyl-1,2-dihydrophenalene (13).—A mixture of 25 g of amalgamated zinc, 50 ml of methyl alcohol, 50 ml of benzene, 10 ml of concentrated hydrochloric acid, and 4.0 g of ethyldihydrophenalenone (**20**) was refluxed for 9 hr. During that period an additional 10 ml of hydrochloric acid were added in two portions. After cooling, the aqueous layer was extracted with ether, washed, dried ($MgSO_4$), and concentrated. 1-Ethyl-1,2-dihydrophenalene (**13**) was separated from 10–15% of impurities by a preparative vpc using column B (Table V) at 210° and helium flow of 100 ml/min: $n^{20}D$ 1.6110. *Anal.* Calcd for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 92.02; H, 8.15.

C. 1-Methyl-5-ethylnaphthalene (11). Diethyl 2-Methylbenzylmalonate (24).—2-Methylbenzylbromide (0.4 mol) was added slowly to a paste of ethyl sodiomalonate prepared from 0.75 mol of diethyl malonate in 200 ml of benzene and 0.4 g-atom of sodium. The mixture was stirred and refluxed for 12 hr and cooled and the sodium bromide was washed with water. Ester **24**, obtained in 89% yield, distilled at 151–154° (4–5 mm): $n^{20}D$ 1.4910. *Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.37; H, 7.64.

1-Methylhydrocinnamic Acid (26).—Ester **24** (0.35 mol) was hydrolyzed for 4 hr at reflux temperature with 1 mol of potassium hydroxide in 200 ml of water. The solution was cooled and neutralized with dilute hydrochloric acid, using congo red as an indicator. On filtration a quantitative yield of 1-methylbenzylmalonic acid **25** was obtained. Without further purification the acid **25** (0.34 mol) was heated for ~0.5 hr at 170–180°, until the evolution of carbon dioxide ceased. The residue was recrystallized from an acetic acid–water solution and 49.5 g (88%) of 1-methylhydrocinnamic acid, mp 103–104°,[34] was obtained.

3-(1-Methylphenyl)propan-1-ol (27).—Acid **26** (0.3 mol) was placed in a thimble of a continuous extractor and reduced with 0.26 mol of lithium aluminum hydride in 300 ml of ether.[35] Alcohol **27**, 94.5% yield, distilled at 109–111° (3 mm): urethan mp 57–58° [lit.[18] bp 136° (15 mm), urethan mp 58°].

3-(1-Methylphenyl)-1-bromopropane (28).—To 0.28 mol of **27**, cooled with ice, was added dropwise 46 g of phosphorus tribromide. After standing overnight the reaction mixture was kept for 1.5 hr in a warm-water bath, then poured on ice, and extracted with ether. Bromide **28**, yield 85% distilled at 121–123° (15 mm) [lit.[18] bp 124° (17 mm)].

γ-(1-Methylphenyl)butyric acid (29).—From 0.115 mol of bromide **28** and potassium cyanide, according to the procedure of Harvey, *et al.*,[18] acid **29** was obtained in 84% yield: mp 59–60° (lit.[18] mp 60°).

3,4-Dihydro-5-methyl-1(2H)-naphthalenone (30).—A solution of 0.095 mol of **29** in 150 g of anhydrous hydrogen fluoride was stirred for 8 hr at room temperature, then poured on ice, and extracted with ether. After it was washed (H_2O, $NaHCO_3$) and dried ($MgSO_4$), the ethereal extract was distilled. Ketone **30** was obtained in 89% yield: bp 117–120° (3–4 mm), mp 48–50° [lit.[36] bp 115–117° (3 mm), mp 50–51°[18]].

1-Methyl-5-ethylnaphthalene (11).—Compound **11** was prepared from 0.075 mol of ketone **30** by the procedure of Harvey, *et al.*[18] The tertiary alcohol, obtained by allowing **30** to react with ethylmagnesium bromide, was dehydrated with boiling acetic anhydride to 1-ethyl-5-methyl-3,4-dihydronaphthalene. The latter was then heated with selenium metal at 300° for 24 hr. A solid obtained after distillation over sodium was purified *via* picrate. Compound **11** in the form of white crystals was obtained in 61% over-all yield: mp 38–39° (lit.[18] mp 40°). The synthetic hydrocarbon was identical with 1-methyl-5-ethylnaphthalene separated from the reaction (Table IV).

D. 1-(2-Butyl)-5-(3-pentyl)naphthalene (14).—A mixture of 5 g (0.0294 mol) of 1-methyl-5-ethylnaphthalene (**11**) and 6.5 g (0.0706 mol) of toluene was stirred for 5 hr with 0.2 g of sodium and 0.35 ml of *o*-chlorotoluene at 110° in a slow stream of nitro-

(31) L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 349 (1959).

(32) H. Gilman, N. B. St. John, and F. Schulze, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 425.

(33) M. F. Ansell and A. M. Berman, *J. Chem. Soc.*, 1792 (1954).

(34) W. E. Bachmann and E. K. Raunio, *J. Amer. Chem. Soc.*, **72**, 2530 (1950).

(35) R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 2548 (1947).

(36) I. Ochiai, T. Okamoto, M. Sekijima, M. Nishikawa, and K. Shono, *Pharm. Bull.* (Tokyo), **5**, 48 (1957); *Chem. Abstr.*, **51**, 16387 (1957).

gen. The dark brown reaction mixture was then cooled and transferred to a 100-ml capacity Magne-Dash autoclave with an agitator. After this was flushed with nitrogen, 40 atm of ethylene was introduced and the autoclave was heated at 208° until the uptake of ethylene ceased. The sodium was then decomposed with ethanol and the reaction product was dissolved in ether, washed, dried ($MgSO_4$), and distilled. Title compound 11 distilled at 125–128° (1–1.5 mm) and was purified by preparative vpc: $n^{20}D$ 1.5640. *Anal.* Calcd for $C_{19}H_{26}$: C, 89.70; H, 10.30. Found: C, 89.98; H, 10.28. The synthetic sample was identical with the isolated product 14 (expt 10 and 11, Table III).

Registry No.—Ethylene, 74-85-1; **2**, 2765-18-6; **3**, 3042-56-6; **4**, 19990-00-2; **6**, 19990-01-3; **8**, 2027-19-2; **9**, 3042-57-7; **10**, 19990-03-5; **11**, 17057-92-0; **12**, 479-58-3; **13**, 19990-06-8; **14**, 19990-07-9; **15**, 19990-08-0; **17**, 4944-94-9; **18**, 232-54-2; **24**, 6619-57-4.

Base-Catalyzed Reactions. XXXIV.[1] The Alkali Metal Catalyzed Side-Chain Aralkylation of 2- and 4-Alkylpyridines with Styrene, α-Methylstyrene, and *cis*- and *trans*-β-Methylstyrene

HERMAN PINES AND NELSON E. SARTORIS[2]

The Ipatieff High Pressure and Catalytic Laboratory, Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received September 25, 1968

The sodium- and potassium-catalyzed side-chain aralkylation reactions of 2- and 4-alkylpyridines with styrene, α-methylstyrene, and *cis*- and *trans*-β-methylstyrene were performed using the alkylpyridines in a 5:1 molar excess. For the most part, the reactions proceed readily at 0–25° to yield monoaddition products *via* a Michael-type addition mechanism, as well as di- and triaddition products in some cases. As the length and branching of the alkylpyridine are increased, the yields of the higher adducts decrease. The yields of the higher adducts, as well as the relative rates of reaction, also decrease as the steric hindrance of the reacting olefin increases on going from styrene to α-methylstyrene to β-methylstyrene. 4-Alkylpyridines react more readily than 2-alkylpyridines. Also formed, in some cases, are diaddition products resulting from a chain-lengthening process. With 2- and 4-picoline and 2- and 4-ethylpyridine, *trans*-β-methylstyrene reacts faster than *cis*, due to the greater conjugation of the *trans* olefin. With 4-isopropylpyridine, however, the results are reversed.

The sodium- and potassium-catalyzed side-chain aralkylations of alkylbenzenes having a benzylic hydrogen have been studied extensively in our laboratory.[3] These reactions proceed in the presence of a promoter at 100–125° to give the expected monoaddition products, and diadducts in some cases, *via* a carbanion mechanism. As the length and branching of the alkylbenzene is increased, and as the steric hindrance of the olefin increases on going from styrene to α-methylstyrene to β-methylstyrene, the yields of the aralkylation products decrease while the competitive dimerization and polymerization of the olefin increases.[4] The potassium-catalyzed aralkylation of *n*-alkylbenzenes with β-methylstyrene at 105° gives only fair yields (19–52%) of the monoaddition products, while isopropylbenzene fails to react with β-methylstyrene. Instead, the β-methylstyrene undergoes dimerization by both anionic and anionic free-radical mechanisms.[5,6]

It has been reported that alkylpyridines can undergo alkali metal catalyzed side-chain alkylation reactions similar to the side-chain alkylations of alkylbenzenes.[3,7] The sodium- and potassium-catalyzed aralkylation reactions of 2- and 4-alkylpyridines with styrene, α-methylstyrene, and *cis*- and *trans*-β-methylstyrene were studied in order to compare the results with those of the analogous reactions with alkylbenzenes.

Discussion of Results

The reactions of 2- and 4-alkylpyridine with styrene, α-methylstyrene, and *cis*- and *trans*-β-methylstyrene were carried out in the presence of catalytic amounts of sodium and potassium. Details and results of the aralkylations are given in Tables I and II. The course of the reactions was followed by vapor phase chromatography. The products were separated by preparative gas chromatography and their structures were established by nmr and ir spectroscopy, elemental analyses, and occasionally by comparison with known compounds.

The metallic sodium or potassium was dispersed in the alkylpyridine for 3–5 hr to ensure complete dispersion, resulting in the formation of a seemingly homogeneous solution of organoalkali metal catalyst, R^-M^+. The olefin was then added dropwise. For the most part the reactions proceed readily at 0–25°.

The mechanism of the aralkylation is proposed to be similar to that of the side-chain aralkylation of alkylbenzenes[8] and the side-chain alkenylation of 4-alkylpyridines.[7d] The initial step is suspected to be the formation of a radical anion.[1]

The aralkylation reaction can be described by the following equation. If R_1 and/or R_2 = H, further aralkylation of the alkylpyridine does occur, resulting in the formation of normal di- and triadducts. The diaddition products can also be formed to a smaller extend *via* a chain-lengthening process similar to that which has previously been reported.[8,9]

In Table I are listed the results of the reactions of various alkylpyridines with styrene and α-methylstyrene. As the length and branching of the alkylpyri-

(1) (a) Paper XXXIII: B. Stipanovic and H. Pines, *J. Org. Chem.*, **34**, 2106 (1969); (b) paper V of the series Alkylation of Heteroaromatics.

(2) Predoctoral Fellow, National Institutes of Health, 1964–1968.

(3) For literature references, see H. Pines and L. Schaap, *Advan. Catalysis*, **12**, 116 (1960).

(4) J. Shabtai and H. Pines, *J. Org. Chem.*, **26**, 4225 (1961).

(5) J. Shabtai, E. M. Lewicki, and H. Pines, *ibid.*, **27**, 2618 (1962).

(6) J. Shabtai and H. Pines, *ibid.*, **29**, 2408 (1964).

(7) (a) H. Pines and D. Wunderlich, *J. Amer. Chem. Soc.*, **81**, 2568 (1959); (b) H. Pines and B. Notari, *ibid.*, **82**, 2209 (1960); (c) *ibid.*, **82**, 2945 (1960); (d) H. Pines and J. Oszczapowicz, *J. Org. Chem.*, **32**, 3183 (1967).

(8) H. Pines and D. Wunderlich, *J. Amer. Chem. Soc.*, **80**, 6001 (1958).

(9) H. Pines and N. Sih, *J. Org. Chem.*, **30**, 280 (1965).

TABLE I

ALKALI METAL CATALYZED SIDE-CHAIN ARALKYLATION OF 4-ALKYLPYRIDINES WITH STYRENE

Expt	4-Alkyl	Mole	Styrene, mole	Catalyst	g[a]	Temp, °C	Intern. std[b]	Product distribn,[c] % Mono-adduct	Diad-duct	Triad-duct	Other
1	CH_3	0.375	0.075	Na	0.30	0	A	41.1	41.8	12.7	4.4
2		0.375	0.075	K	0.30	0	A	40.0	40.9	16.0	3.1
3	CH_2CH_3	0.375	0.075	Na	0.30	0	A	83.0[d]	17.0	Trace	
4		0.190	0.038	K	0.15	0	A	89.2[d]	10.8	Trace	
5	$CH_2CH_2CH_3$	0.20	0.04	Na	0.20	0	D	76.0	24.0		
6	$CH(CH_3)_2$	0.190	0.038	Na	0.15	0	B	74.9	25.1[e]		
7		0.190	0.038	K	0.15	0	B	74.3	25.7[e]		
			α-Methyl-styrene, mole								
8	CH_3	0.375	0.075	Na	0.30	0	A	65.1	26.8[e]		8.1
9		0.375	0.075	K	0.30	0	A	55.2	35.2[e]		9.6
10	CH_2CH_3	0.190	0.038	Na	0.15	0	A	76.6[d]	21.4[e]		2.1
11		0.375	0.075	K	0.30	0	A	84.7[d]	13.3[e]		2.0
12	$CH(CH_3)_2$	0.175	0.035	Na	0.15	0	B	85.7	14.3[b,f]		
13		0.175	0.035	K	0.15	0	B	85.4	14.6[b,f]		
			β-Methyl-styrene,[g] mole								
14	CH_3	0.125	0.025	Na	0.10	0	C	98.0			2.0
15		0.125	0.025	K	0.10	0	C	99.0			1.0
16	CH_2CH_3	0.190	0.038	Na	0.15	0	B	96.9			3.1
17		0.190	0.038	K	0.15	0	B	99.0			1.0
18	$CH(CH_3)_2$	0.140	0.028	Na	0.10	25	B	93.0			7.0
19		0.140	0.028	K	0.10	25	B	94.0			6.0
20		0.050	0.010	K	0.05	75	B	92.5			7.5

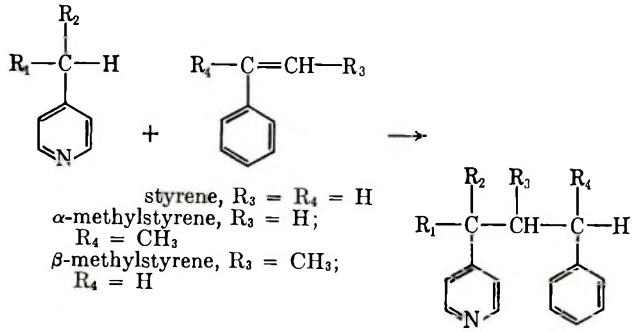
[a] Weight of catalyst is approximate. [b] Amount of internal standard used = 0.01 mole. A = *sec*-butylcyclohexane, B = ethylcyclohexane, C = *n*-butylcyclohexane. [c] Percentages were based on vpc peak area, uncorrected by thermal conductivity factors, calculated by triangulation method after 100% reaction of α-methylstyrene. [d] Monoadduct consisted of two compounds, a pair of diastereoisomers, resolvable by vapor phase chormatography. [e] Product actually a mixture of stereoisomers, unresolvable by vapor phase chromatography. [f] Diadduct suspected to be 2,4-dimethyl-4,6-diphenyl-2-(4-pyridyl)heptane, produced *via* a chain-lengthening process. [g] β-Methylstyrene used was a mixture of 81% *trans*-, 17.5% *cis*-, and 1.5% allylbenzene.

TABLE II

SODIUM-CATALYZED SIDE-CHAIN ARALKYLATION OF 2-ALKYLPYRIDINES WITH *cis*- AND *trans*-β-METHYLSTYRENE

Expt	2-Alkyl	Mole	Styrene, mole	Na, g[a]	Temp, °C	Intern. std[c]	Products, %[d] Mono-adduct	Diad-duct	Others
21	CH_3	1.00	0.20	1.0	25	A	69.0	26.0	5.0[h]
			β-Methyl-styrene,[b] mole						
22	CH_3	0.125	0.025	0.15	55	D	>99		
23	CH_2CH_3	0.125	0.025	0.15	55	D	>99		≃72[f,g]
24	$CH(CH_3)_2$	0.10	0.020	0.10	115	B	0[e]		≃72[f,g]

[a] Weight of catalyst is approximate. [b] β-Methylstyrene used was a mixture of 81% *trans*-, 17.5% *cis*-, and 1.5% allylbenzene. [c] Amount of internal standard used = 0.01 mole. A = *sec*-butylcyclohexane, B = ethylcyclohexane, D = isopropylcyclohexane. [d] Percentages were based on vpc peak areas, uncorrected by thermal conductivity factors, calculated by triangulation method after 100% reaction of β-methylstyrene. [e] No aralkylation reaction occurred; instead, both the β-methylstyrene and 2-isopropylpyridine underwent self-condensation reactions. [f] Product shown to be a dimer of β-methylstyrene, *i.e.*, *trans*-4-methyl-1,5-diphenyl-1-pentene (**17**). [g] Remainder of β-methylstyrene underwent further reaction to polymeric products. [h] Triadduct.



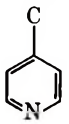
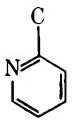
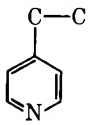
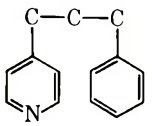
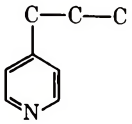
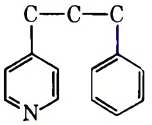
dine increases the relative rate of the reaction decreases, as do the amounts of the higher adducts. Little difference is noticed between sodium and potassium as catalysts.

Even though the molar ratio of 4-picoline to styrene was 5:1, both di- and triaddition products were found. This indicates that the secondary carbanion of the monoadduct, once formed, reacts faster than 4-picoline carbanion with the remaining styrene. Similar observations have been made in the reaction of alkylbenzenes with styrene[8] and in the ethylation[7c] and competitive alkenylation of 4-alkylpyridines.[10] Also, in the Michael addition of unsymmetrical ketones to α,β-unsaturated carbonyl compounds, reaction occurs largely at the more highly substituted α carbon of the unsymmetrical ketone.[11]

(10) H. Pines and W. M. Stalick, unpublished results.

(11) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 208–210.

TABLE III
COMPETITIVE SODIUM-CATALYZED SIDE-CHAIN ARALKYLATION OF ALKYLPYRIDINES WITH STYRENE

Expt	Alkylpyridines used X	Alkylpyridines used Y	Molar ratio[a] X:Y:styrene	Temp, °C	Intern. std[b]	Molar ratio of monoadducts[c] X:Y
25			10:10:1	0	A	99:1[d]
26			10:10:1	0	A	1:1
27			10:10:1	0	D	1:2.5

[a] 0.20 mol of alkylpyridine and 0.1 g of sodium were used. [b] Amount of internal standard used = 0.01 mol. A = *sec*-butylcyclohexane, D = isopropylcyclohexane. [c] Percentages corrected by thermal conductivity factors. [d] Also formed is small amount of diadduct from X.

In the reactions of both 4-ethylpyridine and 4-*n*-propylpyridine with styrene, the diaddition product consisted of two compounds formed in roughly equal amounts, unresolvable by preparative gas chromatography, one of which in each case results from a normal diaddition process and the other from a chain-lengthening diaddition. In a similar reaction, Chumakov and Ledovskikh reported only the normal diaddition product.[12]

In Tables I and II, expt 14–24, are given the results of the reactions of alkylpyridines with *cis*- and *trans*-β-methylstyrene. The reactions of β-methylstyrene are much slower than the corresponding reactions of styrene and α-methylstyrene, presumably because of a more pronounced steric effect with a β-methyl as compared to an α-methyl substituent in the styrene molecule.[5,13] These increased steric factors are also responsible for the almost exclusive formation of monoaddition products.

In the reactions of 2- and 4-picoline and 2- and 4-ethylpyridine with a mixture of *cis*- and *trans*-β-methylstyrene, *trans*-β-methylstyrene was detected by vpc to react much faster than *cis*. These kinetic differences between *cis*- and *trans*-β-methylstyrene probably are related to a difference in the conjugation of the double bond with the ring in the two compounds. Molecular models indicate that steric hindrance exists between the methyl group and the *o*-hydrogen of the phenyl ring in the *cis* compound. This prevents complete conjugation of the π-electron orbitals of the double bond and the ring by restricting coplanarity.[13,14] In the *trans* compound no such internal interactions are present. That *trans*-β-methylstyrene is more conjugated than the *cis* is reflected in the ultraviolet spectra.[15]

In the reaction of 4-isopropylpyridine and *cis*- and *trans*-β-methylstyrene, however, the results are reversed and the *cis* compound reacts faster. To explain these results it is necessary to assume that change in the rate-determining step must take place due to the increased steric requirements of 4-isopropylpyridine. The possibility also exists that only *trans*-β-methylstyrene undergoes the aralkylation reaction and that *cis–trans* isomerization is occurring.

An unsuccessful attempt was made to treat β-methylstyrenes with 2-isopropylpyridine below 100°. As the temperature was increased to 115°, the β-methylstyrene underwent an anionic dimerization reaction leading to *trans*-1,5-diphenyl-4-methyl-1-pentene (**17**),[6] and the reaction was further complicated by self-condensation reactions of two molecules of 2-isopropylpyridine.

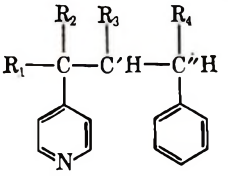
In an effort to confirm the greater reactivity of 4-alkylpyridines *vs.* 2-alkylpyridines,[7c] a competitive sodium-catalyzed reaction was carried out between 2- and 4-picoline with styrene (Table III). The monoadduct of 4-picoline was formed almost exclusively. Also performed were competitive reactions with styrene of 4-ethylpyridine and 4-*n*-propylpyridine, respectively, with 1-phenyl-3-(4-pyridyl)propane. The relative rate of aralkylation of 4-ethylpyridine as compared to 1-phenyl-3-(4-pyridyl)propane was about 1:1, while 4-*n*-propylpyridine reacts slower than 1-phenyl-3-(4-pyridyl) propane by a relative ratio of 1:2.5. The relative reaction rate of 4-ethylpyridine *vs.* 4-*n*-propylpyridine is then calculated to be 2.5:1. This ratio is consistent with the figures of 1.9:1 and 2.5:1 obtained in the competitive ethylation[7c] and alkenylation,[10] respectively, of these two alkylpyridines.

Of particular note is that 1-phenyl-3-(4-pyridyl)propane reacts 2.5 times faster than 4-*n*-propylpyridine, although steric factors are apparently greater in the former. In an analogous situation, it was found that the butenylation of 1-(4-pyridyl)-3-pentene occurred 4.5 times faster than 4-*n*-propylpyridine.[7d] This difference in the rates of alkenylation was explained in terms of the greater acidity of 1-(4-pyridyl)-3-pentene, due to π-electron bonding of the picolyl hydrogen with the double bond of the alkenyl group. A somewhat similar situation may exist with 1-phenyl-3-(4-pyridyl)-propane, where the phenyl ring assists in the removal of

(12) Yu. I. Chumakov and V. M. Ledovskikh, *Ukr. Khim. Zh.*, **31**, 506 (1965); *Chem. Abstr.*, **63**, 5594a (1965).
(13) D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3883 (1948).
(14) G. Favini and M. Simonetta, *Theoret. Chim. Acta*, **1**, 294, (1963).
(15) C. G. Overberger, D. Tamer, and E. M. Pearce, *J. Amer. Chem. Soc.* **80**, 4566 (1958).

TABLE IV

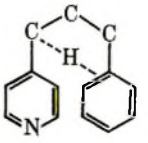
CHEMICAL SHIFTS IN NMR SPECTRA OF PRODUCTS OF CLASS I[a]



Compd[c]	δ, ppm[b] C	C'H	C''H	R_1	R_2	R_3	R_4
1, R_1–R_4 = H	2.50 (2) m	1.94 (2) m	2.50 (2) m				
2, R_1 = CH_2CH_2Ph; R_2–R_4 = H	2.28 (1) m	1.85 (4) m	2.28 (4) m				
3, R_1 = R_2 = CH_2CH_2Ph; R_3 = R_4 = H		1.90 (6) m	2.22 (6) m				
4, R_1 = CH_3; R_2–R_4 = H	2.56 (1) m	1.90 (2) m	2.56 (2) m	1.22 (3) d (J = 6.8)			
5, R_1 = R_2 = CH_3; R_2 = R_4 = H		1.82 (2) m	2.26 (2) m	1.29 (3) s	1.29 (3) s		
6,[g] R_1 = R_2 = CH_3; R_3 = H; R_4 = CH_2CH_2Ph		1.90 (2) m	2.40 (1) m	1.14 (3) s	1.02 (3) s		1.90 (2) m, 2.20 (2) m
7, R_1–R_3 = H; R_4 = CH_3	2.40 (2) m	1.85 (2) m	2.58 (1) m				1.22 (3) d (J = 6.8)
8,[i] R_1 = $CH_2CHPhCH_3$; R_2 = R_3 = H; R_4 = CH_3	2.35 (1) m	1.95 (4) m	2.35 (2) m				0.90–1.30 (6) m
9A,[k] R_1 = R_4 = CH_3; R_2 = R_3 = H	2.40 (1) m	1.85 (2) m	2.40 (1) m	1.16 (3) d (J = 6.8)			1.16 (3) d (J = 6.8)
9B,[k] R_1 = R_4 = CH_3; R_2 = R_3 = H	2.50 (1) m	1.82 (2) m	2.50 (1) m	1.18 (3) d (J = 6.8)			1.20 (3) d (J = 6.8)
10,[j] R_1 = $CH_2CHPhCH_3$; R_2 = R_4 = CH_3; R_3 = H		1.95 (4) m	2.40 (2) m		0.85–1.30 (3) m		0.85–1.30 (6) m
11,[h] R_1 = R_2 = R_4 = CH_3; R_3 = H		1.97 (2) m	2.45 (1) m	1.21 (3) m	1.10 (3) s		1.06 (3) d (J = 6.0)
12, R_1 = R_2 = R_4 = H; R_3 = CH_3	2.47 (2) m	2.10 (1) m	2.47 (2) m			(J 6.0)	
13,[e] R_1 = R_3 = CH_3; R_2 = R_4 = H	2.60 (1) m	2.00 (1) m	2.45 (2) m	1.24 (3) d (J = 7.0)		0.72 (3) d[d] (J = 7.5)	
14,[f] R_1–R_3 = CH_3; R_4 = H		2.60 (1) m	2.15 (2) m	1.34 (3) s	1.29 (3) s	0.70 (3) d[d] (J = 6.0)	
18, R_1 = CH_2CH_3; R_2–R_4 = H	2.32 (2) m	1.90 (2) m	2.32 (2) m	1.80 (2) m, 0.73 (3) t (J = 7.0)			

[a] All products in this class result from addition of styrene, α-methylstyrene, or β-methylstyrene to 4-alkylpyridines. Their spectra therefore show two α-hydrogens and two β-hydrogens of an α-substituted pyridine ring in the regions 8.3–8.7 and 6.7–7.1 ppm, respectively, and phenyl hydrogens of monosubstituted phenyl rings in the region 6.9–7.3 ppm. [b] Numbers in parentheses refer to integrated number of protons: s = singlet, d = doublet, t = triplet, m = multiplet. J values are given cycles per second. [c] Refer to Table VII for compound names. [d] Actually two sets of doublets due to asymmetric center. [e] Contain two asymmetric carbon atoms, therefore two stereoisomers are present. The enantiomers were not resolvable by vpc and as a result the nmr is that of a mixture of both stereoisomers. Both methyl groups are in different magnetic environment and they appear as two doublets. This type of spectral patterns has been previously reported: J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice Hall, Inc., Englewood Cliffs, N. J., 1965, pp 119–122: P. M. Nair and J. D. Roberts, *J. Amer. Chem. Soc.*, **79**, 4565 (1957); J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 58–60. [f] Contains one asymmetric carbon atom. Therefore, the two methyl groups, R_1 and R_2, although seemingly identical, appear as two singlets as a result of the molecular asymmetry. [g] Diadduct formed *via* a chain lengthening. The nmr situation is similar to that of footnote *f*. [h] The two methyl groups, R_1 and R_2, appear as two singlets at 1.10 and 1.21 ppm, the former overlapping one peak of the doublet of the other methyl group centered at 1.06 ppm. [i] The following stereoisomers exist in **8** (E. L. Eliel, "Stereochemistry, of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 28): *R*, *R* (enantiomer), *S*, *R R* (enantiomer), (2*), *S* (*meso*), *R* (S*), *S* (*meso*). These isomers were unresolvable by vpc, and therefore the nmr is that of a mixture of the above stereoisomers. As a result, the methyl groups, being magnetically nonequivalent in the various stereoisomers, appear as a series of peaks integrating to the expected six hydrogens in the region from 0.90 to 1.30 ppm. [j] This compound presents a situation similar to **8** (footnote *i*), but the methyl, R_2, further complicates the nmr in this region. The three methyl groups integrate to the expected nine hydrogens. [k] Compounds **9A** and **9B** are enantiomers, formed in a ratio of 2:3, and were resolved by preparative gas chromatography (column H).

this hydrogen by the π-electron bonding postulated, although in this case the π-electron system is one carbon further removed.

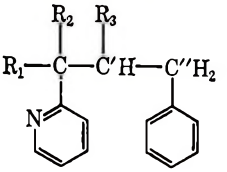


An alternative explanation for the apparent greater reactivity of 1-phenyl-3-(4-pyridyl)propane can be postulated in terms of the stability of the resultant carbanion, by assuming π-electron overlap of the two aromatic rings involved. The negative charge on the α carbon of the pyridine ring is therefore partially delocalized over both rings as opposed to only one in 4-*n*-propylpyridine. Molecular models indicate that such overlap is sterically favorable.

Structure Determination.—The primary tool for structure determination of the products was nmr. The ir spectra were all consistent with the proposed structures and will not be discussed except where

TABLE V

CHEMICAL SHIFTS IN NMR SPECTRA OF PRODUCTS OF CLASS II[a]



Compd[c]	δ, ppm[b] C	C'H	C''H$_2$	R$_1$	R$_3$
15, R$_1$ = R$_2$ = H; R$_3$ = CH$_3$	2.55 (2) m	2.35 (1) m	2.55 (2) m		0.82 (3) d (J = 5.5)
16,[c] R$_1$ = R$_3$ = CH$_3$; R$_2$ = H	2.75 (1) m	2.15 (1) m	2.75 (2) m	1.32 (3) d[e] (J = 7.0)	0.75 (3) d[d] (J = 6.0)
19, R$_1$–R$_3$ = H	2.68 (2) m	2.08 (2) m	2.68 (2)m		
20, R$_1$ = CH$_2$CH$_2$Ph; R$_2$ = R$_3$ = H	2.55 (1) m	2.04 (4) m	2.44 (4) m		
21, R$_1$ = R$_2$ = CH$_2$CH$_2$Ph; R$_3$ = H		1.96 (6) m	2.34 (6) m		

[a] All products in this class result from addition of 2-alkylpyridine to styrene or β-methylstyrene. Their spectra therefore show one α-, and γ-, and two β-hydrogens of an α-substituted pyridine ring in the regions 8.4–8.5, 7.3–7.4, and 6.8–7.0, respectively, and phenyl hydrogens from monosubstituted phenyl rings in the region 6.9–7.2 ppm. [b–e] See corresponding footnotes in Table IV.

TABLE VI

VAPOR PHASE CHROMATOGRAPHIC DETAILS OF ARALKYLATION REACTIONS

Expt[a]	Products[b]	Vpc column[c]	Programming rate, °C/min	Temp limits, °C	Column[d]	Temp, °C
2	**1–3**	A	13	100–290	D[e]	280
3, 4	**4**[f]	A	13	90–290	D	210
6, 7	**5, 6**	A	13	100–290	D	240
8, 9	**7, 8**	A	13	100–290	D	260
10, 11	**9A, 9B, 10**	A	13	80–290	D[g]	240
12, 13	**11**[h]	A	13	100–290	B	270
14, 15	**12**	A	13	85–280	D	180
16, 17	**13**	A	9	85–275	C	200
18–20	**14**	F	15	100–235	B	230
22	**15**	A	9	70–275	C	200
23	**16**	A	9	75–275	B	230
24	**17**[i]	G	9	70–275	K	235
5	**18**[j]	G	9	90–275	D	230
21	**19–21**	G	9	80–280	D[e]	270
25	**1, 19**[k]	G	9	80–275		
26	**2, 4**[k]	G	6.4	70–275		
27	**2, 18**[k]	A	9	90–275		

[a] Refer to Tables I–III for reactants. [b] Refer to Table VII. [c] Chromatographic column was used to follow progress of reaction. [d] Preparative chromatographic column was used to separate products. [e] Compounds **3** and **21** were recycled on column E at 270°. [f] Two diaddition products, unresolvable by preparative gas chromatography, are also produced, presumably 3-methyl-1,5-diphenyl-3-(4-pyridyl)pentane and 1,3-diphenyl-5-(4-pyridyl)hexane. [g] Compounds **9A** and **9B** were collected together and then separated on column H at 200°. [h] A diaddition product, believed to be 2,4-dimethyl-4,6-diphenyl-2-(4-pyridyl)heptane, was also produced. [i] Self-condensation products of 2-isopropylpyridine were not isolated. [j] Two diaddition products unresolvable by preparative gas chromatography, are also produced, presumably 3-ethyl-1,5-diphenyl-3-(4-pyridyl)pentane and 1,3-diphenyl-5-(4-pyridyl)heptane. [k] Products identified by comparison of their relative retention times on columns F and G with previously identified compounds.

particularly pertinent. For the most part, the nmr spectra are quite explicit for the proposed structures and can be divided into two general classes, Tables IV and V. Asymmetric centers were generated in the formation of many products. As a result, their nmr spectra show significant characteristics arising from the molecular nonequivalence caused by the molecular asymmetry.

Not belonging to either class I or II the dimerization product of β-methylstyrene, *trans*-4-methyl-1,5-diphenyl-1-pentene (**17**), formed in the reaction of 2-isopropylpyridine with β-methylstyrene. This compound was identified by its similar relative retention time on columns F, G, and I with a known sample available in our laboratory. It was further characterized by nmr, which shows ten phenyl hydrogens of two different monosubstituted phenyl rings at 7.13 and 7.20 ppm. Two vinyl hydrogens are centered at 6.20 ppm, while the two benzylic methylene hydrogens are centered at 2.52 ppm. The two allylic methylene hydrogens and the methine hydrogen overlap in the region 1.80–2.30 ppm. The methyl group appears as a doublet (J = 6.0 cps) centered at 0.90 ppm. The strong band at 10.41 μ in the infrared spectrum indicates the olefin is *trans*.

Experimental Section

Reagents.—2- and 4-picoline, 2- and 4-ethylpyridine, 4-*n*-propylpyridine, and 4-isopropylpyridine were obtained from Reilly Tar and Chemical Co. They were distilled and dried over Linde 13X Molecular Sieves before use. Isopropylpyridine was synthesized.[16]

Internal standards, ethylcyclohexane, isopropylcyclohexane,

(16) H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, **73**, 3308 (1951).

TABLE VII
PHYSICAL CONSTANTS AND ELEMENTAL ANALYSES OF REACTION PRODUCTS

No.	Compound	Formula	Calcd, %			Found, %			$n^{22}D$ (lit.[8] $n^{20}D$)
			C	H	N	C	H	N	
1	1-Phenyl-3-(4-pyridyl)propane	$C_{14}H_{15}N$	85.24	7.66	7.10	85.06	7.54	7.06	1.5604 (1.5620)
2	1,5-Diphenyl-3-(4-pyridyl)pentane	$C_{22}H_{23}N$	87.66	7.69	4.65	87.80	7.77	4.63	1.5809 (1.5810)
3	1,5-Diphenyl-3-(2-phenylethyl)-3-(4-pyridyl)pentane	$C_{30}H_{31}N$	88.84	7.71	3.45	88.59	7.77	3.57	1.5875
4	1-Phenyl-3-(4-pyridyl)butane	$C_{15}H_{17}N$	85.26	8.11	6.63	85.13	8.16	6.68	1.5543 (1.5545)
5	3-Methyl-1-phenyl-3-(4-pyridyl)butane	$C_{16}H_{19}N$	85.28	8.50	6.22	85.49	8.60	6.12	1.5522
6	5-Methyl-1,3-diphenyl-5-(4-pyridyl)hexane	$C_{24}H_{27}N$	87.50	8.25	4.25	87.29	8.17	4.08	1.5732
7	3-Phenyl-1-(4-pyridyl)butane	$C_{15}H_{17}N$	85.26	8.11	6.63	85.21	8.17	6.54	1.5543
8	2,6-Diphenyl-4-(4-pyridyl)heptane	$C_{24}H_{27}N$	87.50	8.25	4.25	87.57	8.46	4.08	1.5763
9A	2-Phenyl-4-(4-pyridyl)pentane	$C_{16}H_{19}N$	85.28	8.50	6.22	85.40	8.56	6.12	1.5456
9B	2-Phenyl-4-(4-pyridyl)pentane	$C_{16}H_{19}N$	85.28	8.50	6.22	85.45	8.52	6.15	1.5471
10	4-Methyl-2,6-diphenyl-4-(4-pyridyl)heptane	$C_{25}H_{29}N$	87.41	8.51	4.08	87.48	8.66	4.03	1.5710
11	2-Methyl-4-phenyl-2-(4-pyridyl)pentane	$C_{17}H_{21}N$	85.31	8.84	5.85	85.59	8.84	5.72	1.5485
12	2-Methyl-1-phenyl-3-(4-pyridyl)propane	$C_{15}H_{17}N$	85.26	8.11	6.63	84.97	8.20	6.54	1.5545
13	2-Methyl-1-phenyl-3-(4-pyridyl)butane	$C_{16}H_{19}N$	85.28	8.50	6.22	85.16	8.59	6.14	1.5536
14	2,3-Dimethyl-1-phenyl-3-(4-pyridyl)butane	$C_{17}H_{21}N$	85.31	8.84	5.85	85.21	8.76	5.69	1.5560
15	2-Methyl-1-phenyl-3-(2-pyridyl)propane	$C_{15}H_{17}N$	85.26	8.11	6.63	85.16	8.11	6.75	1.5533
16	2-Methyl-1-phenyl-3-(2-pyridyl)butane	$C_{16}H_{19}N$	85.28	8.50	6.22	85.15	8.57	6.32	1.5518
17	*trans*-4-Methyl-1,5-diphenyl-1-pentene	$C_{18}H_{20}$	91.47	8.53		91.48	8.43		1.5728 (lit.[6] 1.5710)
18	1-Phenyl-3-(4-pyridyl)pentane	$C_{16}H_{19}N$	85.28	8.50	6.22	85.40	8.60	6.27	1.5507
19	1-Phenyl-3-(2-pyridyl)propane	$C_{14}H_{15}N$	85.24	7.66	7.10	85.25	7.85	7.23	1.5610 (1.5585)
20	1,5-Diphenyl-3-(2-pyridyl)pentane	$C_{22}H_{23}N$	87.66	7.69	4.65	87.95	7.85	4.50	1.5796 (1.5773)
21	1.5-Diphenyl-3-(2-phenylethyl)-3-(2-pyridyl)pentane	$C_{30}H_{31}N$	88.84	7.71	3.45	88.62	7.98	3.37	1.5874

n-butylcyclohexane, and *sec*-butylcyclohexane, were obtained by hydrogenation of the corresponding alkylbenzenes. *cis*- and *trans*-β-methylstyrene were obtained by dehydration of phenylethylcarbinol over alumina. The olefins consisted of 73% *trans* and 23% *cis* isomers and 3% of allylbenzene. Pure *cis*- and *trans*-β-methylstyrene were separated by preparative gas chromatography on column J (see below) at 120°. All reagents were at least 99.5% pure, adjudged by vpc.

General Procedure for Aralkylation Reactions.—The catalyst was prepared by dispersion of freshly cut alklai metal in the alkylpyridine for 3–5 hr to ensure complete dispersion. The reactions were performed under a slow stream of dry N_2 on a three-necked flask equipped with reflux condenser and a self-sealing rubber septum. The active catalyst was a brown-black solution, seemingly homogeneous. An inert nonaromatic hydrocarbon was added as internal standard, followed by the slow addition of reacting olefin by syringe at the reaction temperature. During the reaction samples were withdrawn periodically, decomposed with methanol, and analyzed by vpc. At the conclusion of the reaction, the catalyst was decomposed with methanol at 0°. The reaction mixture was then taken up in ether and washed with water. The organic layer was dried over $MgSO_4$ and then distilled under reduced pressure to remove excess methanol, alkylpyridine, and internal standard. The products, contained in the residue, were then separated and collected by preparative gas chromatography.

Vapor Phase Chromatography (Table VI).—F & M Model 300 programmed-temperature gas chromatograph was used for analytical determination, while aerograph Model A-700 chromatograph was employed for separation of reaction products. Helium was used as a carrier gas with a rate of 85–90 ml/min. The progress of all reactions was followed.

Description of Columns.—**Substrates** for the columns were 15% silicone gum rubber SE-30 (A–F), 10% (G), 15% Versamid 600 (F, K), 10% (H), 15% Carbowax 20M (I, J).

Solid supports for the columns were Gas Pack WAB 60–80 mesh (A–G), 60–100 mesh (K), Gas Pack W 80–100 mesh (H), Chromosorb P 30–60 mesh (I, J).

Dimension of copper tubings were 0.75 ft × 3/8 in. (E), 1.5 ft × 3/8 in. (D), 3 ft × 1/8 in. (C), 5 ×0.25 in. (A, F), 5 × 3/8 in. (B, K), 6 × 0.25 in. (I), 6 × 3/8 in. (J), 8 × 0.25 in. (G), 13 × 3/8 in. (H); helium flow rate: 85 ml/hr.

Spectroscopic Analyses.—The infrared spectra of all products were taken as films between sodium chloride disks on a Baird Model 4-55 spectrophotometer. A Varian A-60 nmr spectrometer was used. All nmr spectra were taken in CCl_4 solvent using TMS as internal standard. The ultraviolet spectra of *cis*- and *trans*-β-methylstyrene, respectively, were taken in a 1-cm cell on a Cary 14R recording spectrophotometer in 2,2,4-trimethylpentane solvent purified by passing through silica gel.

Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich., and Micro-Tech Laboratories, Inc., Skokie, Ill. These analyses and refractive indices of the products appear in Table VII.

Registry No.—Styrene, 100-42-5; α-methylstyrene, 98-83-9; *cis*-β-methylstyrene, 766-90-5; *trans*-β-methylstyrene, 873-66-5; **1**, 2057-49-0; **2**, 2057-47-8; **3**, 19991-09-4; **4**, 2057-45-6; **5**, 19991-11-8; **6**, 19991-12-9; **7**, 19991-13-0; **8**, 19991-14-1; **9**, 19991-15-2; **10**, 19991-16-3; **11**, 19991-17-4; **12**, 19991-18-5; **13**, 19991-19-6; **14**, 19991-20-9; **15**, 19991-21-0; **16**, 19991-22-1; **18**, 19991-23-2; **19**, 2110-18-1; **20**, 2110-16-9; **21**, 19991-26-5.

Base-Catalyzed Reactions. XXXV.[1] The Alkali Metal Catalyzed Reactions of 2- and 4-Picoline with 2- and 4-Vinylpyridine. Disproportionation and Transaralkylation Reactions

NELSON E. SARTORIS[2] AND HERMAN PINES

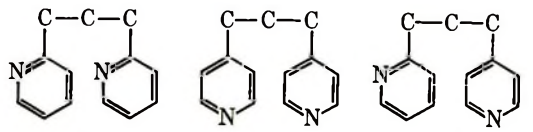
The Ipatieff High Pressure and Catalytic Laboratory, Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received September 25, 1968

In the sodium- and potassium-catalyzed reactions of 2-picoline with 2-vinylpyridine and 4-picoline with 4-vinylpyridine, polymerization of the vinylpyridines is the initial reaction to occur. At temperatures near 100°, depolymerization occurs, followed by rapid addition reactions to yield 1 and 2, respectively, as well as diaddition products. The reactions of 2-picoline with 4-vinylpyridine and 4-picoline with 2-vinylpyridine owing to disproportionation give a mixture of the three dipyridylpropanes. The disproportionation of 3 proceeds to yield 4-picoline and 2-picoline in a 2.6:1 ratio, indicating the greater acidity of 4-picoline *vs.* 2-picoline.

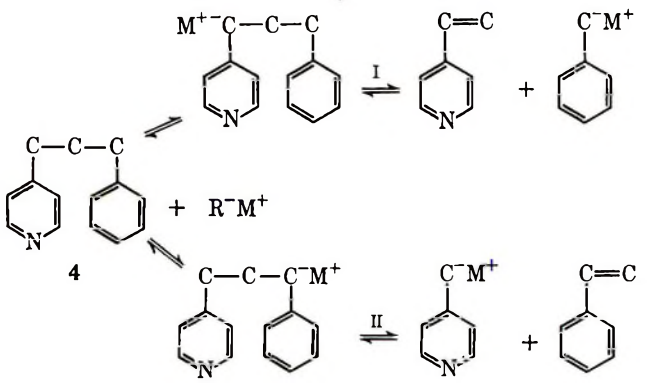
The preparation of 1,3-di(2-pyridyl)propane[3] (1) and of 1,3-di(4-pyridyl)propane[4,5] (2) from the corresponding picolines and vinylpyridines have been reported.

The preparation of the mixed dipyridylpropane, 1-(2-pyridyl)-3-(4-pyridyl)propane (3), by the sodium-catalyzed reaction of 2-picoline with 4-vinylpyridine and 4-picoline with 2-vinylpyridine, has also been reported.[5] In a more recent publication, however, Michalski and Zając[6] reported a 42% yield of 3 from 2-picoline and 4-vinylpyridine at reflux temperature. More surprising is their report that 4-picoline and 2-vinylpyridine with sodium did not give the expected mixed dipyridylpropane, but rather resulted in a 27% of 2.



1 2 3

In view of these contradictory results, these reactions were reinvestigated. In the course of the aralkylation reactions studied in the preceding paper,[1] the question of the reversibility of the reaction has also emerged. If the disproportionation reaction can be forced to occur, the question of the path of disproportionation arises, for it is conceivable that the adduct, once formed, may disproportionate *via* two paths, I and II.



4

To elucidate the answer to these questions, the disproportionation reaction of 1-phenyl-3-(2-pyridyl)propane (5) and 1-phenyl-3-(4-pyridyl)propane (4) were undertaken. Depending on the relative ease of disproportionation of these two compounds an insight into the relative acidities and nucleophilicities of the compounds involved might be achieved. The disproportionation reaction of 3 was also performed. Depending on the relative amounts of 2- and 4-picoline produced, conclusions concerning their relative acidities may be made.

Discussion of Results

The alkali metal catalyzed reactions of 2- and 4-picoline were performed by first dispersing the alkali metal in the picoline and then adding the vinylpyridine slowly with a syringe. The progress of the reaction was followed by vapor phase chromatography, something which was not done in previous studies.

The reaction of 2-picoline and freshly distilled 2-vinylpyridine was attempted at 0–120° with a 5:1 to 10:1 molar excess of 2-picoline. In each case, polymerization of the 2-vinylpyridine occurred immediately. The reaction was also attempted using undistilled 2-vinylpyridine, which contained *t*-butylcatechol as stabilizer, and by adding significant amounts of hydroquinone to the catalyst, as previous authors[3,6] had done, before the addition of 2-vinylpyridine.

Although polymerization is the primary reaction to take place at all temperatures, in the reactions at 100 and 120° secondary reactions occur with time, leading to the expected 1,3-di(2-pyridyl)propane (1). A catalytic depolymerization takes place. The polymers unzips to produce 2-vinylpyridine and immediately undergoes an addition reaction with 2-picoline to yield 1. Also formed is a significant amount of diaddition product, presumably 1,3,5-tri(2-pyridyl)pentane (6). It is reasonable to conclude, therefore, that in work done by previous workers,[3,6] polymerization and depolymerization, although unnoticed, also occurred.

Also given in Table I are the results of a sodium-catalyzed reaction of 4-picoline with 4-vinylpyridine at 90°. In this reaction and in others attempted at various temperatures from 0 to 120°, polymerization of 4-vinylpyridine occurs initially.

Depolymerization occurs more readily with 4-vinylpyridine, since at temperatures near 70° the polymer starts to unzip leading to rapid addition reactions pro-

(1) (a) Paper XXXIV: H. Pines and N. E. Sartoris, *J. Org. Chem.*, **34**, 2113 (1969). (b) Paper VI of the series Alkylation of Heteroaromatics. For other papers see 1a.

(2) Predoctoral Fellow, National Institutes of Health, 1965–1968.

(3) N. J. Leonard and J. H. Boyer, *J. Amer. Chem. Soc.*, **72**, 4818 (1950).

(4) L. M. Jampolsky, M. Baum, S. Kaiser, L. N. Sternbach, and M. W. Goldberg, *J. Amer. Chem. Soc.*, **74**, 5222 (1952).

(5) G. Magnus and R. Levine, *J. Org. Chem.*, **22**, 270 (1957).

(6) J. Michalski and H. Zając, *J. Chem. Soc.*, 593 (1963).

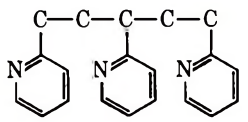
TABLE I

SODIUM-CATALYZED REACTIONS OF 2- AND 4-PICOLINE WITH 2- and 4-VINYLPYRIDINE

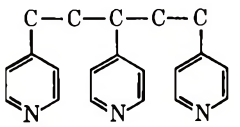
Expt	Picoline	Mole	Vinylpyridine	Mole	Sodium, g	Temp, °C	Time, hr	Conversion,[b,c] %	Product distribution,[a] % 1	3	2	Diadduct
1	2-	0.20	2-	0.04	0.1	110	4	71	70			21[d]
2	4-	0.20	4-	0.04	0.1	90	2.5	69			93	7[e]
3	2-	0.20	4-	0.03	0.15	105	0.5	16	15.5	84.5		[f]
							1.0	37	44.4	55.6		
							1.5	49	68.3	31.2	0.5	
							2.0	60	78.2	20.8	1.0	
4	4-	0.20	2-	0.03	0.15	105	1.0	9.3	1.0	81.0	18.0	
							2.0	18.4	4.0	65.0	31.0	
							3.0	25.5	7.5	56.9	35.6	
							5.0	38.1	9.0	48.4	42.6	

[a] *sec*-Butylcyclohexane (0.005 mole) was used as internal standard. [b] Percentages are corrected by thermal conductivity factors. [c] Based on vinylpyridine reacted. [d] The product is presumed to be 1,3,5-tri(2-pyridyl)pentane. [e] The product is presumed to be 1,3,5-tri(4-pyridyl)pentane. [f] Also formed small amounts of diaddition products.

ducing **2**, and, presumably, 1,3,5-tri(4-pyridyl)pentane (**7**).



6



7

In an attempt to prepare the mixed dipyridylpropane **3**, the alkali metal catalyzed reaction of 2-picoline with 4-vinylpyridine was studied. At temperatures necessary to affect the depolymerization, however, the reaction is complicated by disproportionation of the mixed dipyridylpropane into 4-picoline and 2-vinylpyridine. The 2-vinylpyridine then undergoes an addition reaction with the excess 2-picoline to yield **1**, while the 4-picoline reacts with depolymerizing 4-vinylpyridine to give **2** (Scheme I). Also produced are small amounts of diaddition products, presumably 1,3,5-tripyridylpentanes. The distribution of the 1,3-dipyridylpropanes changes substantially with contact time (expt 3 and 4, Table I). This type of reversal and resynthesis in the 1,3-dipyridylpropane system has recently been reported.[6,7]

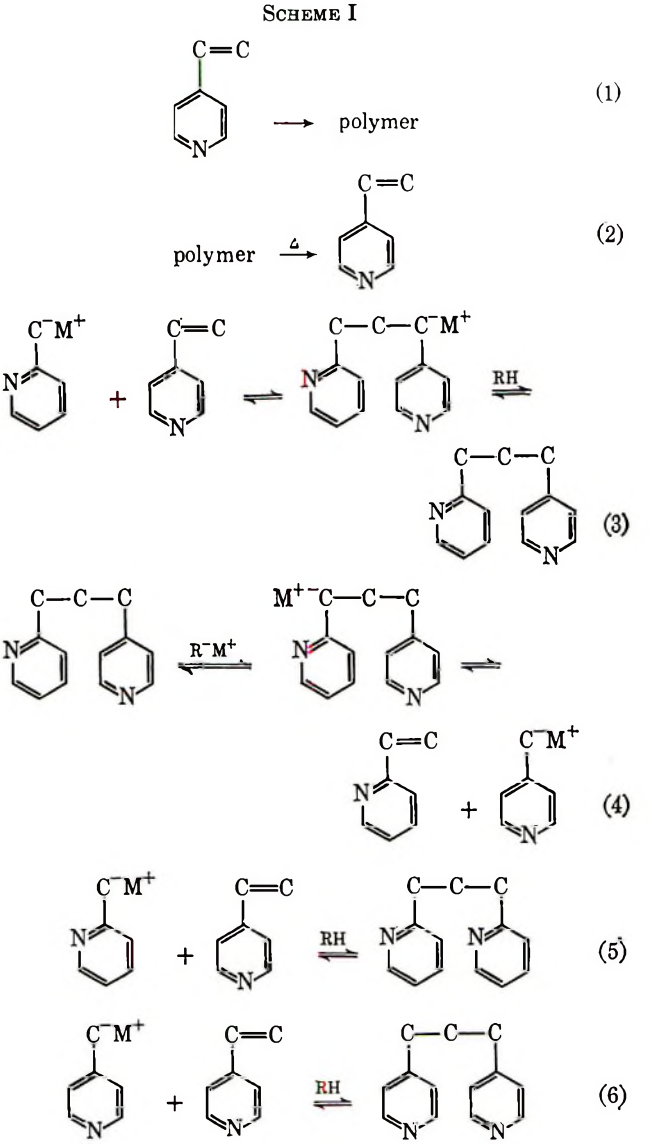
It should be noted that Michalski and Zając[6] reported the formation of **3** upon refluxing 2-picoline and 4-vinylpyridines. Since vpc was not used in their study, it is conceivable that the product isolated in 42% yield is actually a mixture of 1,3-dipyridylpropanes.

The preparation of pure **3** was also attempted using 4-picoline and 2-vinylpyridine (Expt **4**, Table I). Again, the course of the reaction was similar to that reported above.

Disproportionation and Transaralkylation Reactions. —The sodium-catalyzed disproportionation reactions of **4** and 1-phenyl-3-(2-pyridyl)propane (**5**), respectively, were studied by adding them to a dispersion of catalyst in a "scavenger" alkylpyridine. The olefin product of disproportionation, either styrene or a vinylpyridine, should then be picked up by the "scavenger" alkylpyridine or by another molecule of **4** or **5** in an addition reaction. In effect, a transaralkylation would take place.

In preliminary reactions of **4** using 2-picoline as the "scavenger," the temperature was raised slowly as the progress of the reaction was followed by vpc. At 100°, the disproportionation is slow and proceeds exclusively

SCHEME I

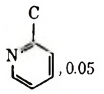
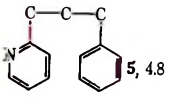
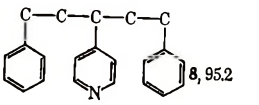
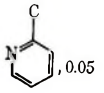
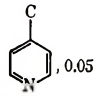
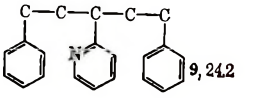
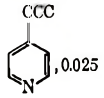
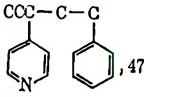
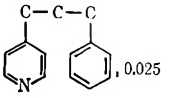
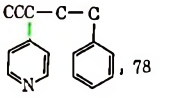


in one direction to give 4-picoline and styrene. The styrene reacts immediately with the "scavenger" 2-picoline to yield **5**, or more favorably (by 20:1) with another molecule of **4** to give 1,5-diphenyl-3-(4-pyridyl)-pentane (**8**) (Table II). At 120°, the disproportionation is considerably faster. The styrene is picked up again more readily by **4** (by 3:1) than by 2-picoline, although the selectivity is reduced in this case due to the higher temperature and by the fact that at these

(7) J. Michalski and R. Bodalski, *Roczniki Chem.*, **41**, 549 (1967).

TABLE II

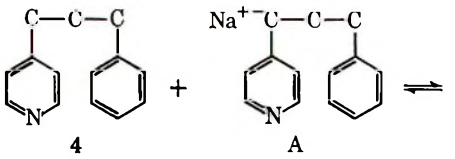
SODIUM-CATALYZED DISPROPORTIONATION AND TRANSARALKYLATION REACTIONS

Expt	Reactants,[a] moles		Temp, °C	Time, hr	Conversion,[b] %	Products,[b,c] %	
5	 0.05	4, 0.05	100	48	9.0[d]	 5, 4.8	 8, 95.2
6	 0.05	4, 0.05	120	24	21.3[d]	5, 27.0	8, 73.0
7	 0.05	5, 0.05	120	21	7.1[e]	4, 75.8	 9, 24.2
8	 0.025	4, 0.025	118	7	5.8[d]	 47	8, 53
9	 0.025	5, 0.025	118	7	2.9[e]	 78	9, 22

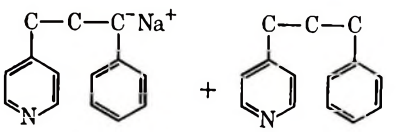
[a] Isopropylcyclohexane (0.025 mol) was used as internal standard and 0.05 g of sodium as catalyst in expt 8 and 9 and *sec*-butylcyclohexane (0.005 mol) and 0.1 g of sodium in expt 5–7. [b] Percentages corrected by thermal conductivity factors. [c] A trace of toluene was detected in reactions made at 118 and 120°. [d] Based on 4-picoline produced. [e] Based on 2-picoline produced.

higher conversions of **4**, the greater relative concentration of 2-picoline becomes more important.

If the stability of the initial carbanion was the important factor in determining the path of disproportionation, *i.e.*, if the transition state more closely resembles



4 **A**



B

the reactants, then the expected path of disproportionation would be of carbanion A to give toluene and 4-vinylpyridine. This is not the predominant path of disproportionation, however. Apparently, it is the stability of the resultant carbanion, and not that of the initial carbanion, that governs the path of disproportionation, *i.e.*, the transition states more closely resemble the products. The reaction proceeds to give the more stable carbanion of 4-picoline than of toluene, which is in agreement with their relative acidities.

Therefore, carbanion A, even though present in large concentration, does not tend to disproportionate. Instead, higher temperatures are necessary to shift the equilibrium toward greater amounts of the less stable carbanion B, which then reacts.

These results are not without precedent, since Pines and Eschinazi[8] found that the stability of the resultant carbanion governs the reaction path in the sodium-catalyzed dealkylation of geminal alkylcyclohexadienes.

The disproportionation of 1-phenyl-3-(2-pyridyl)-propane (**5**), using 4-picoline as the "scavenger" alkylpyridine, was studied. In contrast to **4**, the disproportionation of **5** does not proceed at an appreciable rate until the temperature nears 115–120°. Again, the predominant path of disproportionation is in the direction that yields the more stable carbanion, *i.e.*, the carbanion of 2-picoline rather than of toluene. Only a trace of toluene is detected.

The styrene produced is immediately captured by "scavenger" 4-picoline to yield **4**, or by another molecule of **5** to yield 1,5-diphenyl-3-(2-pyridyl)pentane (**9**) (Table II). At this temperature and conversion, the former route of capture is favored by 3:1. If the stability of the resultant carbanion is the important factor in determining the ease of disproportionation, then this would suggest that the carbanion of 4-picoline is more stable than that of 2-picoline, *i.e.*, 4-picoline is more acidic than 2-picoline.

To determine for certain the relative ease of disproportionation of **4** *vs.* **5**, these reactions were performed under identical catalytic conditions. This was accomplished by dispersing sodium in "scavenger" 4-*n*-propylpyridine, dividing the dispersion in two, and then adding **4** and **5**, respectively, to each half of the dispersion. Results of the reactions are given in expt 8 and 9, Table II. The disproportionation of **4** is twice as rapid as that of **5**.

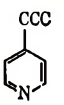
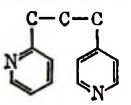
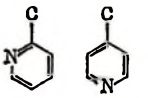
To further examine the relative stabilities of the carbanions of 2- and 4-picoline, the disproportionation of **3** was also performed in the presence of 4-*n*-propylpyridine as scavenger of the vinylpyridines produced (Table III). The formation of 4-picoline was favored by about 2.6:1 over 2-picoline, and thus it can be concluded that 4-picoline is more acidic than 2-picoline. Also produced are adducts of 4-*n*-propylpyridine and 2- and 4-vinylpyridine, presumably, 1,3-di(4-pyridyl)pentane and 1-(2-pyridyl)-3-(4-pyridyl)pentane.

In contrast to these results is the work of Michalski and Zając,[6] who reported the preferred formation of

(8) H. Pines and H. E. Eschinazi, *J. Amer. Chem. Soc.*, **78**, 5950 (1956).

TABLE III

SODIUM-CATALYZED DISPROPORTIONATION REACTION OF 1-(2-PYRIDYL)-3-(4-PYRIDYL)PROPANE

		Reactants,[a] mole				Products,[b,d] %	
Expt	Time, hr			Temp, °C	Conversion,[b,c] %		
10	0.5	0.05	0.01	100	18.5	27.5	72.5
	1.0				27.5	28.5	71.5
	1.5				36.0	27.0	73.0

[a] Isopropylcyclohexane (0.005 mole) was used as internal standard and 0.05 g of sodium as catalyst. [b] Percentages corrected by thermal conductivity factors. [c] Based on 2- and 4-picoline produced. [d] Also produced were adducts of 2- and 4-vinylpyridine with *n*-propylpyridine.

TABLE IV

PHYSICAL CONSTANTS AND ELEMENTAL ANALYSES OF REACTION PRODUCTS

		Calcd, %			Found, %			
Compound	Formula	C	H	N	C	H	N	$n^{22}D$ or mp, °C
1,3-Di(2-pyridyl)propane (1)	$C_{13}H_{14}N_2$	78.75	7.22	14.13	78.94	7.22	13.94	1.5600 (lit.[3] 1.5607)
1,3-Di(4-pyridyl)propane (2)	$C_{13}H_{14}N_2$	78.75	7.12	14.13	78.75	7.11	14.09	61–63[a] (lit. 57–60,[4] 62–65[5])
1-(2-pyridyl)-3-(4-pyridyl)propane (3)	$C_{13}H_{14}N_2$	78.75	7.12	14.13	78.98	7.20	14.21	1.5585

[a] Product was recrystallized from hexane after separation by preparative gas chromatography.

2-picoline over 4-picoline by a 4:1 ratio in the potassium-catalyzed reaction of **3** at reflux temperature for 5 hr. It is believed that the starting material **3** used by these authors might have been impure and contaminated with 1,3-di(2-pyridyl)propane, which upon disproportionation would give only 2-picoline.

Experimental Section[9]

Reagents.—2- and 4-picoline, 2- and 4-vinylpyridine, 1-phenyl-3-(4-pyridyl)propane, and 4-*n*-propylpyridine were obtained from Reilly Tar and Chemical Co. 1-Phenyl-3-(2-pyridyl)-propane was prepared from 2-picoline and styrene in the reactions described in the preceding paper.[1] All reagents were at least 99.5% pure.

General Reaction Procedure.—The catalyst was prepared and the reactions performed in an apparatus similar to that used in the preceding paper.[1]

Vapor Phase Chromatography.—The progress of all reactions was followed by vpc on an 8 ft × 0.25 in., 10% silicone gum rubber, SE-30, on Gas Pack WAB (60–80) column, programming at 9°/min from 80 to 275°, helium flow rate 85 ml/min. 1,3-Di-(2-pyridyl)propane (**1**) and 1,3-di(4-pyridyl)propane (**2**) were separated by preparative gas chromatography on a 1.5 ft × 3/8 in., 15% silicone gum rubber, SE-30, on Gas Pack WAB (60–80) column, at 200°. 1-(2-Pyridyl)-3-(4-pyridyl)propane (**3**) was separated on a 3 ft × 3/8 in., 15% Carbowax 20M and 5% KOH on Gas Pack W (60–80) column, at 210°.

(9) Experimental analyses were performed by M-H-W Laboratories, Garden City, Mich., and Micro-Tech Laboratories, Inc., Skokie, Ill.

Product Identification.—Compounds **1–3** were identified by ir and nmr spectroscopy, elemental analyses, and by comparison of physical constants. Elemental analyses and physical constants are given in Table IV.

1,3-Di(2-pyridyl)propane (**1**).—The nmr spectrum shows two α-, two γ-, four β-hydrogens of two α-substituted pyridine rings centered at 8.33, 7.36, and 6.88 ppm, respectively. Centered at 2.70 ppm are the four equivalent methylene hydrogens adjacent to the pyridine rings, while the other two methylene hydrogens are centered further upfield at 2.20 ppm.

1,3-Di(4-pyridyl)propane (**2**).—The nmr spectrum indicates four α- and four β-hydrogens of two γ-substituted pyridine rings centered at 8.28 and 6.88 ppm, respectively. The four equivalent methylene hydrogens adjacent to the pyridine rings are centered at 2.50 ppm, while centered further upfield at 1.93 ppm are the other two methylene hydrogens.

1-(2-Pyridyl)-3-(4-pyridyl)propane (**3**).—The nmr spectra show three α-, one γ-, and four β-hydrogens of one α- and one γ-substituted pyridine ring centered at 8.32, 7.38, and 6.90 ppm, respectively. Centered at 2.64 ppm are the four overlapping methylene hydrogens adjacent to the pyridine rings, while the other two methylene hydrogens are centered further upfield at 2.06 ppm.

Spectroscopic Analyses.—The infrared spectra of liquid products were taken as films between sodium chloride disks, while that of the only solid, **2**, was taken in a KBr pellet on a Baird Model 4-55 spectrophotometer. A Varian A-60 nmr spectrophotometer was used. All nmr spectra were taken in CCl_4 solvent using TMS as an internal standard.

Registry No.—**1**, 15937-81-2; **2**, 17252-51-6; **3**, 19978-13-3; 2-picoline, 109-06-8; 4-picoline, 108-89-4; 2-vinylpyridine, 100-69-6; 4-vinylpyridine, 100-43-6.

Intramolecular Rearrangements. V.[1] Formation and New Acyl Rearrangement of Isoindolo[2,1-*a*]quinazoline-5,11-dione to Isoindolo[1,2-*b*]quinazoline-10,12-dione

MASARU KURIHARA

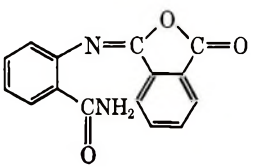
Basic Research Laboratories, Toyo Rayon Co., Ltd., Tebiro, Kamakura, Japan

Received September 16, 1968

2′-Carbamoylphthalanilic acid (I) was prepared by the reaction of anthranilamide with phthalic anhydride; the treatment of I in acetic anhydride–pyridine has been shown to yield isoindolo[2,1-*a*]quinazoline-5,11-dione (III) and *o*-phthalimidobenzamide (II). The thermal treatment of III afforded isoindolo[1,2-*b*]quinazoline-10,12-dione (IV) by an intramolecular acyl rearrangement. New synthetic methods and the mechanism for the formation of IV were investigated.

The preparation of isoindolo[2,1-*a*]quinazoline-5,11-dione (III) by the reaction of anthranilamide with phthalic anhydride has been reported by Crippa and Caracci[2] in connection with the phthaloylation of amines. Recently, Gaudemaris, *et al.*,[3] reported the formation of III in connection with the synthesis of poly(isoindoloquinazolinediones). In the course of a study on ladder polymers,[4] the model reaction of anthranilamide with phthalic anhydride was reinvestigated. The spectral properties of the products and melting points appeared inconsistent for the reported structure III.[2,3] I wish to report that the correct structure of one of the products is that of isoindolo[1,2-*b*]quinazoline-10,12-dione (IV). We have prepared isoindolo[2,1-*a*]quinazoline-5,11-dione (III) by treatment of 2′-carbamoylphthalanilic acid (I) in acetic anhydride–pyridine, and studied its rearrangement to IV. Structures III and IV were assigned on the basis of nmr, infrared, ultraviolet, and elemental analyses. A similar study on 1,2,4-benzothiazine has been reported recently by Bell, *et al.*,[5] and Kratzl, *et al.*[6]

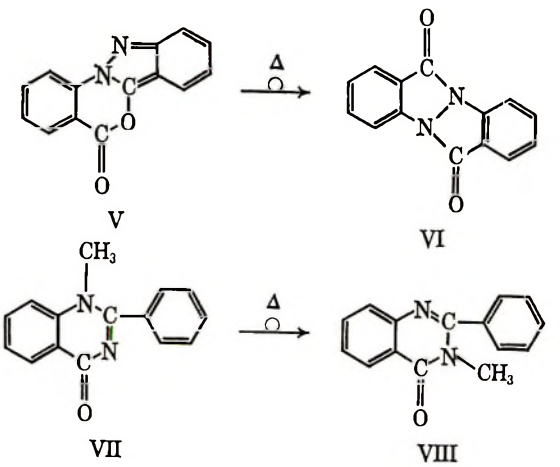
The reaction of anthranilamide with phthalic anhydride in N-methylpyrrolidone affords I as an initial condensation product (Scheme I). Compound I is subject to cyclization and yields IV when heated at 188°. Compounds II and III were isolated on treating I in acetic anhydride–pyridine under milder conditions. Cyclization of II to give IV was accomplished by heating at 260° or refluxing in acetic anhydride–pyridine. When heated at 260°, III rearranges to IV. The alternative isoimide formulation II′ for the imide II seems inconsistent with the infrared



II′

spectrum of the compound, which shows carbonyl absorption at 1780, 1720, and 721 cm^{-1} (normal imide). The spectrum of II′ would be expected to have two strong infrared absorptions at 1800 and 1710 cm^{-1}, attributed to stretching frequencies of the strained >C=O and >C=N– structure, respectively, and have no absorption at 721 cm^{-1}.[7]

The formation of compound IV from II was shown by ultraviolet and nmr methods to proceed in the sequence II → III → IV. This type of rearrangement is notable because bisanthranil, 5H-indazolo[2,3-*a*]-[3,1]benzoxazin-5-one (V), similarly rearranges to VI on heating,[8] and 1-methyl-2-phenyl-4(1H)-quinazolinone (VII) is converted on heating into 3-methyl-2-phenyl-4(3H)-quinazolinone (VIII).[1] Anthranilamide, upon strong heating with phthalic anhydride without solvent, affords IV, whereas Crippa[2] and Gaudemaris[3] reported the product as II but provided no spectral data to support their conclusions. These authors also reported that a product, mp 242°, prepared by thermal cyclization of II at 250° or refluxing II in acetic anhydride–pyridine was III. In a previous paper,[1] we have shown that, in the 4-quinazolinone system, the most thermally stable structure is that with a >C=N– bond fixed at a β,γ position to the carbonyl group.



V VI

VII VIII

Compound III had carbonyl absorption peaks at 1760 (five-membered carbonyl) and 1680 cm^{-1} (six-membered carbonyl), and a >C=N– absorption peak at 1620 cm^{-1}, whereas IV had carbonyl peaks at 1780 (five-membered carbonyl) and 1700 cm^{-1} (six-membered carbonyl), and >C=N– absorption peak

(1) For the preceding paper of this series, see Y. Hagiwara, M. Kurihara, and Y. Yoda, *Tetrahedron*, **25**, 783 (1969).

(2) G. B. Crippa and R. Caracci, *Gazz. Chim. Ital.*, **68**, 109 (1938).

(3) G. Rabilloud, B. Sillion, and G. de Gaudemaris, *Makromol. Chem.*, **108**, 18 (1967).

(4) M. Kurihara and Y. Yoda, *J. Polym. Sci., Part B*, **6**, 875 (1968).

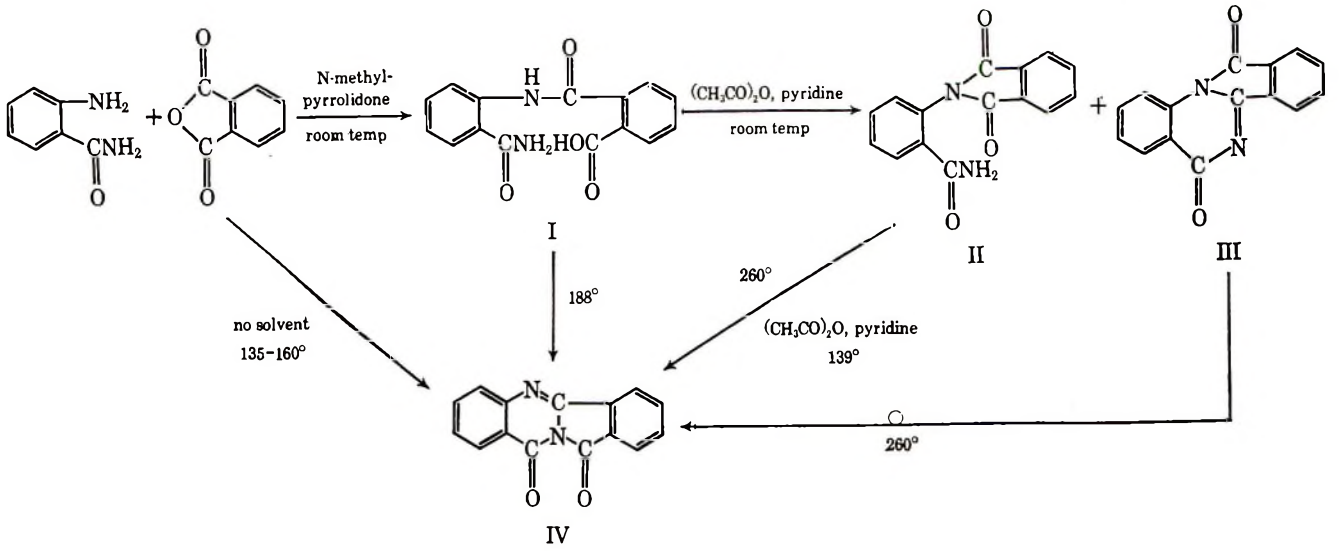
(5) (a) C. S. Bell, P. H. L. Wei, and S. T. Childress, *J. Org. Chem.*, **29**, 3206 (1964); (b) S. C. Bell, and G. Conklin, *J. Heterocycl. Chem.*, **5**, 183 (1968).

(6) K. Kratzl and H. Ruis, *Monatsh. Chem.*, **96**, 1596 (1965); *ibid.*, **96**, 1586 (1965).

(7) (a) R. A. Dine-Hart and W. W. Wright, *J. Polym. Sci., Part A-1*, **11**, 609 (1967); (b) A. L. Laszlo, U. S. Patent 3,179,633 (1965); (c) R. J. Angelo, U. S. Patent 3,282,898 (1966).

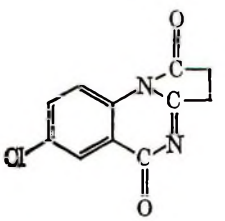
(8) (a) G. Heller, *Chem. Ber.*, **49**, 523 (1916); (b) W. L. Mosby, *Chem. Ind.* (London), 17 (1967); (c) G. K. J. Gibson and A. S. Lindsey, *J. Chem. Soc., C*, 1792 (1967).

SCHEME I

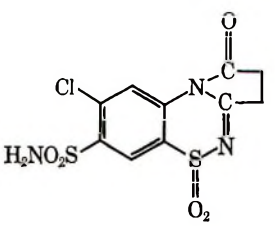


at 1640 cm^{-1}, the shift to a higher wave number being attributed to the CONCO grouping. This result is in good agreement with the previous data.[1] Carbonyl groups with an α,β-conjugated –N=C< double bond absorb at lower wave numbers than those with a β,γ-unsaturated carbonyl group. These results are also observed in the absorption band of a >C=N– double bond in the 4-quinazolinone system. The difference in absorption bands dissociated with the six-membered carbonyl group and >C=N– double bond of III and IV is 20 cm^{-1}. From these infrared measurements, it is concluded that compounds III and IV are isoindolo[2,1-*a*]quinazoline-5,11-dione (III) and isoindolo[1,2-*b*]quinazoline-10,12-dione (IV), respectively. This conclusion is also supported by the comparison of uv spectra. Compound III has λ_{max} at 255 mμ (ε 19,400), 310 (4340), whereas IV has λ_{max} at 275 mμ (ε 10,170). We have reported[1] that the spectrum of β,γ-unsaturated 4(3H)-quinazolinone derivatives had a distinct absorption at 277–280 mμ, whereas that of α,β-conjugated 4(1H)-quinazolinone at about 255 and 310 mμ.

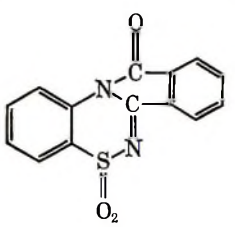
Furthermore, a comparison of the nmr spectra of III and IV revealed a considerable difference in the aromatic region. In IV, the aromatic proton adjacent to the 5-nitrogen had a normal value of δ 7.65, whereas in III the corresponding *ortho* proton was shifted downfield to δ 8.77. Analogous 7-chloro-2,3-dihydro-



IX



X



XI

pyrrolo[1,2-*a*]quinazoline-1,5-dione (IX),[5b] pyrrolo[2,1-*c*][1,2,4]benzothiadiazine (X),[5b] and 11-oxo-11H-isoindolo[1,2-*c*][1,2,4]benzothiadiazine 5,5-dioxide (XI)[6] also had a large downfield shift (δ 8.90, 8.95) for the corresponding *ortho* proton.

This downfield shift of an *ortho* proton due to the orientation of a carbonyl group toward the benzene ring has recently been reported.[5] Thus the large downfield shift in III, produced by the deshielding from the adjacent carbonyl group, verified that III is isoindolo[2,1-*a*]quinazoline-5,11-dione.

Experimental Section[9]

2′-Carbamoylphthalanilic Acid (I). Method A.—A mixture of 1.36 g (0.01 mol) of anthranilamide and 1.48 g (0.01 mol) of phthalic anhydride was added to 20 ml of N-methylpyrrolidone at 10° and stirred for 5 hr at 10°. After disappearance of the carbonyl absorption of phthalic anhydride at 1880 cm^{-1}, 1780 cm^{-1} in the infrared spectrum of the solution, N-methylpyrrolidone was removed under reduced pressure (10^{-1} mm) at 70° to yield white crystals melting at 140°. The yield was 3.8 g (theoretical amount was 2.84 g). This compound was presumed to be a 2′-carbamoylphthalanilic acid–N-methylpyrrolidone complex. Recrystallization from ethanol yielded I as white crystals: mp 186 (lit.[3] mp 212°); ir 1705, 1690, 1665 cm^{-1} (C=O); uv_{max} 253 mμ (ε 13,760), 303 (5480).

Anal. Calcd for $C_{15}H_{21}O_4N_2$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.13; H, 4.42; N, 9.80.

Method B.—Products prepared in a mixed solvent system of chloroform, benzene, and methanol were identical with those obtained by method A in 90% yield with mp 186°.

o-Phthalimidobenzamide (II).—A 200-mg portion of 2′-carbamoylphthalanilic acid (I) was dissolved in a mixture (1:1) of 80 ml of acetic anhydride and pyridine and the solution was kept for 12 hr at room temperature. The solvent was removed under reduced pressure (10^{-4} mm at 25°) and the residue was washed with ether. The yield was 140 mg (75.2%), mp 237°. One recrystallization from ethanol then raised the melting point to 239° (lit. mp 225,[2] 239[3]): ir 1780, 1700, 1650 cm^{-1} (C=O); uv_{max} 218 mμ (ε 35,700), 282 (5190).

Anal. Calcd for $C_{15}H_{10}O_3N_2$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.44; H, 3.56; N, 10.80.

(9) All melting points were taken on a Büchi melting point apparatus and were uncorrected. The microanalyses were carried out by the Microanalytical Section of these laboratories. The infrared spectra were recorded with a Hitachi Model EPI-S recording spectrophotometer, using a potassium bromide disk. The ultraviolet spectra were recorded with a Cary Model 14 recording spectrophotometer in 99.5% ethanol. The nmr spectra were obtained on a Varian A-60 spectrometer using 15% dimethyl sulfoxide-d_6 solutions; chemical shifts are given in parts per million downfield from tetramethylsilane.

Isoindolo[2,1-*a*]quinazoline-5,11-dione (III).—To a mixture (1:1) of 40 ml of acetic anhydride and pyridine was added 2.0 g of 2′-carbamoylphthalanilic acid (I). The solution was stirred slowly for 23 hr at room temperature, during which time yellow solids separated out. The crystals were collected: yield 0.25 g (14.3%); mp 246°. Recrystallization from ethanol gave III: mp 247°; ir (KBr) 1760, 1680 (C=O), 1620 cm^{-1} (C=N); uv_{max} 230 mμ (ε 26,500), 245 (18,690), 255 (19,400), 265 (15,500), 283 (9060), 310 (4,340); nmr δ 8.78 (d) 8.20 (m), 7.64.

Anal. Calcd for $C_{15}H_8O_2N_2$: C, 72.57; H, 3.25; N, 11.27. Found: C, 72.37; H, 3.12; N, 11.39.

From the filtrate, on addition of ethyl ether, there was obtained 1.40 g (74.8%) of *o*-phthalimidobenzamide (II), mp 220°. Recrystallization from ethanol yielded pure II, mp 239°.

Isoindolo[1,2-*b*]quinazoline-10,12-dione (IV). Method A. Cyclization of 2′-Carbamoylphthalanilic Acid (I).—A 2.84-g portion of 2′-carbamoylphthalanilic acid (I) was heated at 188° for 20 min to obtain white crystals. Sublimation at 260° yielded white crystals melting at 233°. The yield was 2.50 g (99%): ir (KBr) 1780, 1700 (C=O), 1640 cm^{-1} (C=N); uv_{max} 275 mμ (ε 10,170), 303 (7690), 315 (5750); nmr δ 8.16 (d) 7.20, 8.00 (m).

Anal. Calcd for $C_{15}H_8O_2N_2$: C, 72.57; H, 3.25; N, 11.27. Found: C, 72.58, H, 3.29; N, 11.45.

Method B. Cyclization of *o*-phthalimidobenzamide (II). a.—By the treatment of *o*-phthalimidobenzamide (II) at 260° for 1 hr, isoindolo[1,2-*b*]quinazoline-10,12-dione (IV) was obtained quantitatively, mp 233°. The structure was confirmed by the comparison of its infrared spectrum with those of an authentic sample of IV prepared directly from 2′-carbamoylphthalanilic acid by the thermal cyclization.

b.—To a mixture (1:1) of 10 ml of acetic anhydride and pyridine was added for 200 mg of *o*-phthalimidobenzamide (II). The solution was refluxed for 2 hr. By removal of the solvent under vacuum, there was obtained 180 mg of IV, mp 225°, recrystallization from ethanol yielded III as pure yellow crystals, mp 233°.

Method C. Intramolecular Acyl Rearrangement of Isoindolo[2,1-a]quinazoline-5,11-dione (III) to Isoindolo[1,2-b]quinazoline-10,12-dione (IV) by Heating.—Isoindolo[2,1-*a*]quinazoline-5,11-dione (III, 200 mg) was heated in a test tube at 260° for 30 min and cooled, affording 188 g of a precipitate, mp 225°. One sublimation raised the melting point to 232°. The infrared, ultraviolet, and nmr spectra are in good agreement with those of an authentic sample.

Anal. Calcd for $C_{15}H_8O_2N_2$: C, 72.57; H, 3.25; N, 11.27. Found: C, 72.38; H, 3.19; N, 11.25.

Method D. Reaction of Anthranilamide with Phthalic Anhydride without Solvent.[3]—A mixture of 2.72 g (0.02 mol) of anthranilamide and 2.96 g (0.02 mol) of phthalic anhydride was heated at 135–160° for 2.5 hr by the method of Crippa and Caracci,[2] cooled, and 4.5 g of the product (90.8% yield, mp 225°) was obtained. Recrystallization from ethanol gave pure IV, mp 234°. A previous paper[2] reported that this product was II. The infrared, ultraviolet, and nmr data are identical with those of pure IV.

Registry No.—I, 18257-54-0; II, 18257-55-1; III, 18257-78-8; IV, 19910-55-5.

Acknowledgments.—The author gratefully acknowledges the interest and encouragement of Drs. T. Hoshino, R. Nakanishi, and N. Yoda of Basic Research Laboratories, Toyo Rayon Co., Ltd. The author is indebted to Mr. Y. Ebata and his staff for microanalyses, and Dr. K. Nukada for helpful discussion of the nmr data.

Equilibration Studies. 2-Methylthiopyridine–N-Methyl-2-thiopyridone

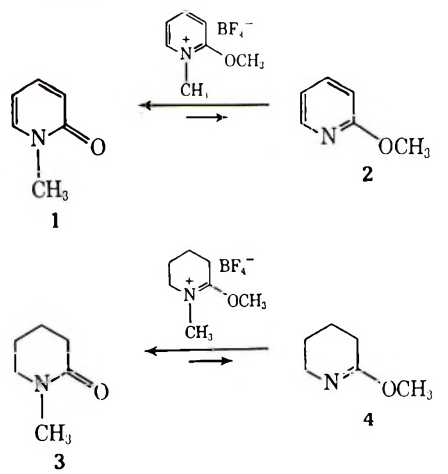
PETER BEAK AND JAMES T. LEE, JR.

Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois 61801

Received January 2, 1969

Equilibration of N-methyl-2-thiopyridone (**7**) with 2-methylthiopyridine (**9**) through the catalytic action of N-methyl-2-methylthiopyridinium fluoroborate at 145–188° indicates that **9** is favored in the liquid phase by an enthalpy of 2.6 ± 1.3 kcal/mol. Conversion of this enthalpy difference to the gas phase with correction for differences in kinetic and zero-point energies gives a difference in chemical binding energy between **7** and **9** of 7.6 ± 4.3 kcal/mole in favor of **9**. This order of stabilities is contrasted with those observed for the analogous protomeric and oxygen-substituted systems.

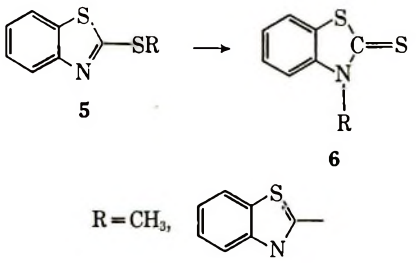
Relative chemical binding energies have been obtained for amide–imidate isomer pairs by measurements of liquid-phase enthalpies, extrapolations to the gas phase, and estimates of differences in kinetic and zero-point energies.[1] For the pairs N-methyl-2-pyridone (**1**)–2-methoxypyridine (**2**) and N-methyl-2-piperidone (**3**)–O-methylvalerolactim (**4**) the amides are the more stable isomers in chemical binding energies by 8.0 ± 3.5 and 14.1 ± 3.5 kcal/mol, respectively. Extension of the equilibration procedure and estimates of differences in binding energies to the corresponding thioamides–thioimidates is of interest for determination of the relative stabilities of these isomeric functionalities, comparison of the chemical-binding abilities of sulfur and oxygen, and insight into the relative stabilization energies of pyridine–pyridone isomer pairs.



Few thioamide–thioimidate equilibrations have been reported. However, at least one system which has a formal resemblance to a simple thioamide–thioimidate pair has been equilibrated; 2-thiobenzothiazoles (**5**) may be transformed to the isomeric 2,3-dihydro-3-thiobenzothiazoles (**6**) under equilibrating conditions.[2]

(1) P. Beak, J. Bonham, and J. T. Lee, Jr., *J. Am. Chem. Soc.*, **90**, 1569 (1968).

(2) D. J. Fry and J. D. Kendall, *J. Chem. Soc.*, 1716 (1951); J. J. D'Amico, S. T. Webster, R. H. Campbell, and C. E. Twine, *J. Org. Chem.*, **30**, 3628 (1965).

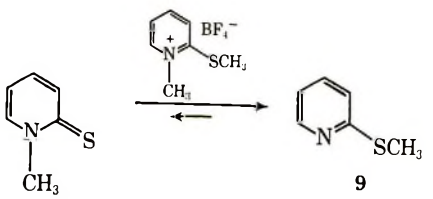


5 6

R = CH_3,

Results

When separate mixtures of N-methyl-2-thiopyridone (**7**) and N-methyl-2-methylthiopyridinium fluoroborate (**8**) and of 2-methylthiopyridine (**9**) and **8** are heated at 190° for 20 hr, an equilibrium mixture consisting of *ca.* 10% **7** and 90% **9** is produced, as shown by the relative areas of the methyl resonances of each isomer in the nmr spectra of the mixtures. Competing reactions involving either isomer or the catalyst cannot be detected by infrared or nmr spectroscopy or by thin layer chromatography. However, attempts to measure accurately the equilibrium constant at 150 and 190° by ultraviolet spectroscopy, the method of choice, gave poor results. The values obtained starting with each isomer, **7** or **9**,



7 9

are (K = [**9**]/[**7**]) 12.9 ± 2.9 (190°, five runs) and 9.1 ± 1.7 (150°, four runs). This low precision is attributed to the formation of side products which escape detection by the alternate methods of analysis. In an effort to minimize this source of scatter, a series of equilibrations was carried out at 145 and 188° for *ca.* one half-life with mixtures of **9** and **7** which were chosen to narrowly bracket the expected equilibrium values.[3] Equilibrium constants (K = [**9**]/[**7**]) of 14.4 ± 1.0 (188°, four runs) and 10.7 ± 0.8 (145°, three runs) are obtained. These values give a plot of log K *vs.* $1/T$ which reveals a liquid-phase enthalpy difference ($\Delta H_l°_{190°}$) between **7** and **9** of −2.3 ± 1.3 kcal/mol in favor of **9**. The heats of vaporization ($\Delta H_{vap}°_{190°,\ 1\ atm}$) of **7** and **9** were estimated as previously described[1] with nonreduced Cox–Antoine vapor pressure data at 189 and 191° and the Clasius–Clapeyron equation. The values of $\Delta H_{vap}°_{190°}$ obtained are 16.1 ± 0.75 kcal/mol for N-methyl-2-thiopyridone (**7**) and 11.1 ± 0.75 kcal/mol for 2-methylthiopyridine (**9**). Combination of the difference in these values and the liquid-phase enthalpy difference for isomers **7** and **9** gives a gas-phase standard enthalpy difference of −7.6 ± 2.8 kcal/mol. On the basis of previous arguments[1] the kinetic energy difference between these isomers may be presumed to be negligible and the difference in zero-point energies no greater than ±1.5 kcal/mol. This correction gives a difference in chemical binding energy between **7** and **9** of −7.6 ± 4.3 kcal/mol in favor of **9**.

(3) G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Am. Chem. Soc.*, **86**, 3197 (1964).

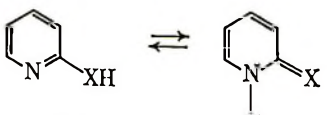
Attempts to equilibrate N-methyl-2-thiopiperidone (**10**) and 2-methylthio-3,4,5,6-tetrahydropyridine (**11**) by the catalytic action of N-methyl-2-methylthiopiperidinium fluoroborate (**12**) at 170° starting from **10** and **12** gave only **10**, but a mixture of **11** and **12** gives an 80% loss of **11** and formation of only 10% of **12**. Of incidental interest is our observation of an unusual long-range coupling between the N-methyl protons and the methylene groups at C-3 (J = <1 Hz) and C-6 (J = 1.5 Hz) in the nmr spectrum of **12**.

Discussion

Comparison of the chemical binding energy differences for members of the structurally related isomer pairs **1–2** and **7–9** shows that there is a reversal in the relative stabilities of the 2-pyridone–2-substituted pyridine systems with the change of sulfur for oxygen. Amide **1** is more stable than the imidate **2** by 8.0 ± 3.5 kcal/mol, but thioamide **7** is less stable than the thioimidate **9** by 7.6 ± 4.3 kcal/mol.

This difference in relative stabilities could be attributed to differences in localized bond energies and/or the relative π-delocalization energies of the functional groups. Although the models and assumptions are controvertible, it appears that both effects would predict the observed result. Differences in localized bond energies suggest that a carbonyl group is favored relative to an ether group (amide–imidate) by several kilocalories per mol more than a thiocarbonyl group is favored relative to a thioether (thioamide–thioimidate).[4] Hückel calculations, with the parameters suggested by Streitwieser,[5] show the thioimidate to have a larger π-delocalization energy than the thioamide by 0.48 β. The same method shows the imidate function to have a 0.13 β smaller π-delocalization energy than the amide.

Tautomeric equilibrium constants have been determined from ionization constants for the protomeric isomer pairs corresponding to **7–9** and **1–2**. In both cases, in aqueous solution at 20°, the amide isomer is heavily favored. The energy differences are 6.3 kcal/mol[6]



13, X = S **14**, X = S

15, X = O **16**, X = O

between **13** and **14**, in favor of **14**, and 4.1 kcal/mol between **15** and **16**, in favor of **16**.[7] The contrast between these equilibria and those of the alkylated isomers **1–2** and **7–9** is striking and clearly demonstrates that tautomeric equilibria in protomeric systems cannot reliably serve as a predictive guide for the corresponding alkyl-

(4) (a) T. L. Cottrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworth and Co. Ltd., London, 1958, Chapter 10: >C=O, 162; ⩾CO, 77; >C=S, 121; ⩾CS, 59 kcal/mol; (b) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, pp 53, 131: >C=O, 142; ⩾CO, 70; >C=S, 103; ⩾CS, 55 kcal/mol.

(5) A. Streitwieser, Jr., "Molecular Orbital Theory," John Wiley and Sons, Inc., New York, N. Y., 1961, p 135.

(6) (a) A. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959); (b) R. A. Jones and A. R. Katritzky, *ibid.*, 3610 (1958).

(7) (a) A. Albert and J. N. Phillips, *ibid.*, 1294 (1956); (b) S. F. Mason, *ibid.*, 674 (1958).

ated isomers. The latter are the models of choice for discussions of relative chemical binding energies.[1]

The failure of equilibration of the isomers **10** and **11** with the salt **12** suggests a limitation on the equilibration procedure.[1] Resolution of this difficulty might be achieved by the use of a nucleophilic anion which could act as the alkyl transfer agent[8] or by measurement of the heats of methylation of **10** and **11**.

Experimental Section[9]

Materials.—Commercially available, reagent grade solvents were used without additional purification. The following reagents were obtained from the indicated suppliers and were used without further purification: silver fluoroborate, Ozark-Mahoning Company; iodomethane, N-methyl-2-piperidone, and 2-piperidone, Aldrich Chemical Co.; phosphorus pentasulfide, Eastman Organic Chemicals; 2-pyridone, J. T. Baker Chemical Co.; iodomethane-d_3, Stohler Isotope Chemicals.

Pyrex tubes were charged and sealed as previously described. Sealed tubes were placed in an electrically heated, stirred bath whose temperature was regulated (±1.5°) with a proportional controller.[10]

N-Methyl-2-thiopyridone (7) was prepared in 60% yield from N-methyl-2-pyridone[1] and phosphorus pentasulfide according to the method of Renault[11] and purified by sublimation at 75° (0.1 mm), mp 88–90° (lit.[11] 89–90°). The infrared spectrum (chloroform) showed absorptions at 2950, 1620, 1530, 1485, 1470, 1410, 1305, 1140, 1110, and 1020 cm^{-1}. The nmr spectrum (chloroform-d) showed resonances centered at δ 4.00 (3 H, singlet, N-methyl), 6.68 and 7.25, (1 H each, apparent triplet of doublets with line spacings of 1 and 6 Hz, protons at C-4 and C-5), and 7.70 (2 H, complex multiplet, ring protons at C-3 and C-6).

2-Methylthiopyridine (9) was prepared in 65% yield by methylation–deprotonation of 2-thiopyridone[11] according to the method of Renault,[12] bp 82–83° (17 mm) [lit.[12] 91° (22 mm)]. The infrared spectrum (neat) showed prominent absorptions at 2950, 2900, 1580, 1450, 1430, 1410, 1320, 1280, 1170, 1150, 1125, 1090, and 1045 cm^{-1}. The nmr spectrum (chloroform-d) displayed resonances centered at δ 2.53 (3 H, singlet, S-methyl), 6.60–7.50 (3 H, complex multiplet, ring protons at C-3, C-4, and C-5), and 8.29 (1 H, broadened doublet, line spacing 5 Hz, ring proton at C-6).

N-Methyl-2-methylthiopyridinium iodide was prepared in 70% yield from N-methyl-2-thiopyridone and iodomethane according to the procedure of Renault,[12] mp 155–157° (lit.[12] 156°). The infrared spectrum (chloroform) showed absorptions at 2830, 1615, 1560, 1490, 1450, 1430, 1330, 1160, 1120, and 1020 cm^{-1}. The nmr spectrum (dimethyl sulfoxide-d_6) showed resonances centered at δ 2.91 (3 H, singlet, S-methyl), 4.20 (3 H, singlet, N-methyl), 7.65–8.20 (2 H, complex multiplet, ring protons at C-4 and C-5), 8.42 (1 H, apparent triplet of doublets, line spacings 8, 2 Hz, ring proton at C-3), and 9.15 (1 H, broadened doublet, line spacing of 7 Hz, ring proton at C-6).

The same compound was obtained when 2-methylthiopyridine was treated with iodomethane. Identity was established by melting point (155–157°), mixture melting point (153–155°), and the nmr spectrum.

N-Methyl-2-methyl-d_3-thiopyridinium Iodide.—A mixture of 0.817 g (6.5 mmol) of N-methyl-2-thiopyridone and 1.14 g (7.7 mmol) of iodomethane-d_3 in 10 ml of acetone was stirred at ambient temperature for 3 hr. The crystalline precipitate was isolated by suction filtration and dried at reduced pressure. The yield of N-methyl-2-methyl-d_3-thiopyridinium iodide was 1.73 g (98%), mp 153–154°.

Anal. Calcd for $C_7H_7D_3NSI$: C, 31.10; H, 3.73; N, 5.19. Found: C, 31.31; H, 3.80; N, 5.02.

The infrared and nmr spectra were consistent with the assigned structure. The nmr spectrum displayed resonances corresponding to those of the isotopically normal material except for the absence of a signal at δ 2.8–3.0.

N-Methyl-2-methylthiopyridinium Fluoroborate (8).—A mixture of 2.11 g (0.02 mol) of N-methyl-2-thiopyridone, 3.22 g (0.02 mol) of silver fluoroborate, and 9.0 g (0.06 mol) of iodomethane in 60 ml of 1,2-dichloroethane was stirred at ambient temperature for 26 hr. After filtration the silver iodide paste was leached with 550 ml of boiling methanol and the filtrate and washings were combined and concentrated at reduced pressure to give a crystalline residue. Clarification of a 60-ml ethanol solution of this material with activated carbon followed by cooling gave 2.45 g (65%) of N-methyl-2-methylthiopyridinium fluoroborate as colorless prisms, mp 119–121°.

Anal. Calcd for $C_7H_{10}NSBF_4$: C, 37.02; H, 4.45; N, 6.17; S, 14.07. Found: C, 37.12; H, 4.55; N, 6.07; S, 14.12.

The infrared spectrum (potassium bromide) showed absorptions at 2970, 2900, 1605, 1555, 1475, 1430, 1300, 1265, 1165, 1180, 1020 (broad), 780, and 705 cm^{-1}. The nmr spectrum (dimethyl sulfoxide-d_6) was identical with that of N-methyl-2-methylthiopyridinium iodide.

This material was alternately prepared in 78% yield by treating N-methyl-2-methylthiopyridinium iodide with 1 equiv of silver fluoroborate in 1,2-dichloroethane. Identity was established by melting point (118–120°), mixture melting point (118.5–121°) and the nmr spectrum.

Thermal Stability of 7, 8, and 9 at 190°.—Separate sealed tubes containing these materials were heated at 190° for 19.3 hr, cooled to ambient temperature, and opened. The infrared and nmr spectra were indistinguishable from those of authentic samples. The recovered N-methyl-2-thiopyridone had mp 87–89° and mmp 87.5–90° with authentic material. The recovered N-methyl-2-methylthiopyridinium fluoroborate had mp 118.5–121.5° and mmp 118.5–121.5° with authentic material.

Equilibration of N-Methyl-2-thiopyridone (7) and 2-Methylthiopyridine (9) at 190°.—A sealed tube containing 0.150 g of 2-methylthiopyridine and 0.024 g of N-methyl-2-methylthiopyridinium fluoroborate was heated at 190° for 19.5 hr, cooled to ambient temperature, and opened. The contents were triturated with 1.0 ml of chloroform and the resultant slurry was filtered. The nmr spectrum of the filtrate indicated the presence of *ca.* 10% of N-methyl-2-thiopyridone and *ca.* 90% of 2-methylthiopyridine. The residue (0.023 g, 90%) was identified as N-methyl-2-methylthiopyridinium fluoroborate by melting point (120–121.5°), mixture melting point with an authentic sample (119–121.5°), and infrared analysis. Parallel runs with N-methyl-2-thiopyridone and N-methyl-2-methylthiopyridinium fluoroborate at 190° for 19.5 hr gave 85% recovery of N-methyl-2-methylthiopyridinium fluoroborate and a mixture identified by nmr as *ca.* 10% N-methyl-2-thiopyridone and *ca.* 90% 2-methylthiopyridine. Competing reactions involving either isomer or the catalyst could not be detected by infrared or nmr spectroscopy or by tlc.

Direct Determination of the N-Methyl-2-thiopyridone (7)–2-Methylthiopyridine (9) Liquid-Phase Equilibrium Constant.—The multicomponent spectral technique of Dewar and Urch[13] was employed for direct determinations of the equilibrium isomer ratios at several temperatures. Catalyst **8** was isolated by diethyl ether precipitation prior to measurement. The spectral measurements were made with anhydrous ethanol as solvent and absorbance data were taken at six wavelengths (2925, 2900, 2875, 2850, 2825, and 2800 Å) centered about the N-methyl-2-thiopyridone maximum at 2860 Å to maximize the sensitivity of the mixture spectra to low concentrations of this isomer. Absorbance data were processed with an IBM 1800 digital computer using a modified version of a least-squares plotting program provided by S. G. Smith. Control experiments established that ethanol solutions of each isomer obey Beer's law over the concentration

(8) H. J. Teague and W. P. Tucker, *J. Org. Chem.*, **32**, 3144 (1967).

(9) Melting points were determined on a Reichert block equipped with thermometers accurate to ±1°, as determined by melting point measurements for appropriate standards. Boiling points are uncorrected. Infrared spectra were measured on Perkin-Elmer Models 521 and 137 instruments with sodium chloride plates or cells. Ultraviolet spectra were measured with a Cary Model 14 spectrophotometer and 1.0-cm matched silica cells. The proton magnetic resonance spectra were measured with Varian Associates A-60, A-60A, and A-56/60 spectrometers with chloroform-d solutions unless otherwise noted. Chemical shifts are reported in δ, parts per million relative to the internal standard tetramethylsilane. Spin decoupling experiments were conducted using a Varian Associates HA-100 instrument. Molecular weight mass spectra at *ca.* 15-eV ionizing potential were determined on an Atlas Model CH4 instrument equipped with a vacuum lock inlet system. Microanalyses were performed by J. Nemeth and associates. Aerograph Models A-600-B and A-90-P gas chromatographs were used for analytical and preparative glpc.

(10) R. W. Anderson, *J. Chem. Educ.*, **44**, 569 (1967).

(11) J. Renault, *Bull. Soc. Chim. France*, **20**, 1001 (1953).

(12) J. Renault, *Ann. Chim.* (Paris), **10**, 135 (1955).

(13) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957).

and wavelength ranges employed in the analyses. The equilibrium constants obtained from this analysis were $K_{190°} = 12.9 \pm 2.9$ (reaction time 19.5 hr) and $K_{150°} = 9.1 \pm 1.7$ (reaction time 174 hr).

It was found in preliminary experiments that unless the catalyst, N-methyl-2-methylthiopyridinium fluoroborate, is removed prior to spectral measurement, spurious results are obtained. Separation of the pyridinium salt was achieved by its precipitation from the reaction mixture with diethyl ether.

The products of equilibration reactions at 188 and 145° were analyzed after partial reaction by the techniques described above.

2-Methylthio-3,4,5,6-tetrahydropyridine.—A solution of 5.25 g (0.02 mol) of 2-methylthio-3,4,5,6-tetrahydropyridinium iodide[14] in 160 ml of pH 10 buffer (*ca.* 0.20 *M*) was vigorously stirred at ambient temperature for 60 sec, then rapidly extracted with two 100-ml portions of ethyl ether. The ether extracts were combined, dried (anhydrous magnesium sulfate), and concentrated at reduced pressure with minimal heating to provide 2.39 g of yellow residue. Glpc analysis (20% Apiezon L on Firebrick, 120°) of this material indicated the presence of one major component and at least two minor components. The major component was collected and identified as 2-methylthio-3,4,5,6-tetrahydropyridine.

Anal. Calcd for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 56.10; H, 8.74; N, 10.71.

The infrared spectrum (neat) showed prominent absorptions at 2910, 2850, 1640, 1440, 1420, 1340, 1325, 1310, 1270, and 1250 cm^{-1}. The nmr spectrum (chloroform-*d*) displayed resonances centered at δ 1.77 (4 H, complex multiplet, ring protons at C-4 and C-5), 2.27 (2 H, complex multiplet, ring protons at C-3), 2.27 (3 H, singlet, S-methyl), and 3.63 (2 H, complex multiplet, ring protons at C-6).

N-Methyl-2-thiopiperidone was prepared in 50% yield from N-methyl-2-piperidone and phosphorus pentasulfide according to the procedure of Renault,[11] and purified by recrystallization from ligroin–ethyl ether (50:50) at −20°, mp 37–38° (lit.[11] 37–38°).

Anal. Calcd for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 56.03; H, 8.71; N, 10.78.

The infrared spectrum (chloroform) included prominent absorptions at 2875, 1540, 1530, 1450, 1420, 1350, and 1330 cm^{-1}. The nmr spectrum (chloroform-*d*) displayed resonances centered at δ 1.82 (4 H, complex multiplet, ring protons at C-4 and C-5), 2.98 (2 H, complex multiplet, ring protons at C-3), 3.44 (2 H, complex multiplet, ring protons at C-6), and 3.46 (3 H, singlet, N-methyl).

N-Methyl-2-methylthio-3,4,5,6-tetrahydropyridinium Fluoroborate.—A mixture of 0.628 g (2.0 mmol) of N-methyl-2-methylthio-3,4,5,6-tetrahydropyridinium iodide[12] and 0.421 g (2.0 mmol) of silver fluoroborate in 35 ml of 1,2-dichloroethane was stirred at ambient temperature for 19 hr. After silver iodide had been removed by gravity filtration, 30 ml of ethyl ether was added to the filtrate and the resultant clear solution was allowed to stand at −20° for 2 hr. The colorless crystals which formed were isolated and dried at reduced pressure. The yield of N-methyl-2-methylthio-3,4,5,6-tetrahydropyridinium fluoroborate was 0.191 g (36%), mp 95–96°.

Anal. Calcd for $C_7H_{14}NSBF_4$: C, 36.39; H, 6.11; N, 6.06; S, 13.88. Found: C, 36.45; H, 6.08; N, 5.72; S, 13.97.

The infrared spectrum (Nujol) showed prominent absorptions at 2950, 1590, 1340, 1320, 1275, 1225, 1175, 1020 (broad), 950, and 910 cm^{-1}. The nmr spectrum (acetone-d_6) displayed resonances centered at δ 1.95 (4 H, complex multiplet, ring protons at C-4 and C-5), 2.80 (3 H, singlet), 3.04 (2 H, complex multiplet, ring protons at C-3), 3.52 (3 H, complex multiplet), and 3.90 (2 H, complex multiplet, ring protons at C-6). Spin decoupling experiments (100 MHz) provided clarification of the 60 MHz spectrum. The complex pattern at δ 3.52 collapsed to a triplet (J = 1.5 Hz) upon irradiation at 3.90 and to a broad singlet ($J < 1$ Hz) upon irradiation at 3.04. Irradiation at δ 3.52 resulted in perceptible simplifications of the multiplets at 3.90 and 3.04. These results indicate that one of the methyl groups, probably that bound to nitrogen on the basis of its chemical shift, and two sets of ring protons are coupled.

Attempted Equilibration of N-Methyl-2-thiopiperidone (14) and 2-Methylthio-3,4,5,6-tetrahydropyridine (15) at 170°.—Sealed tube experiments, analogous to those described above, established that N-methyl-2-thiopiperidone, 2-methylthio-3,4,5,6-tetrahydropyridine, and N-methyl-2-methylthio-3,4,5,6-tetrahydropyridinium fluoroborate are thermally stable at 170° for at least 20 hr.

A sealed tube containing 0.080 g of N-methyl-2-thiopiperidone and 0.011 g of N-methyl-2-methylthio-3,4,5,6-tetrahydropyridinium fluoroborate was heated at 170° for 21.3 hr, cooled to ambient temperature, and opened. After trituration of the orange product mixture with ethyl ether, tlc and gas chromatographic (20% Apiezon L on Firebrick, 120°) analyses of the ether solution indicated the presence of one component, N-methyl-2-thiopiperidone. It was established that at least 2% of 2-methylthio-3,4,5,6-tetrahydropyridine would have been detected. Concentration of the ether solution under a dry nitrogen jet gave 0.078 g (98%) of N-methyl-2-thiopiperidone, as shown by infrared and nmr spectra. An infrared spectrum of the material insoluble in ether was essentially indistinguishable from that of authentic N-methyl-2-methylthio-3,4,5,6-tetrahydropyridinium fluoroborate.

A tube containing 0.046 g of 2-methylthio-3,4,5,6-tetrahydropyridine and 0.014 g of N-methyl-2-methylthio-3,4,5,6-tetrahydropyridinium fluoroborate was heated at 170° for 20 hr, cooled to ambient temperature, and opened. The orange product mixture was triturated with ethyl ether. Although tlc of the ether solution indicated the presence of 2-methylthio-3,4,5,6-tetrahydropyridine, N-methyl-2-thiopiperidone and at least two other components were present. A glpc analysis (20% Apiezon L on Firebrick, 120°) of this solution showed the presence of only 2-methylthio-3,4,5,6-tetrahydropyridine under conditions allowing detection of at least 9% of N-methyl-2-thiopiperidone.

The orange, ether-insoluble material, which remained an intractable gum after extensive evacuation at 0.01 mm, was highly impure, as shown by its four-component thin layer chromatogram, its weight (0.032 g, 230%), and its infrared spectrum, which resembled that of authentic N-methyl-2-methylthio-3,4,5,6-tetrahydropyridinium fluoroborate, but displayed several substantial absorptions not observed in the authentic spectrum.

A second tube, containing 0.033 g of 2-methylthio-3,4,5,6-tetrahydropyridine and 0.009 g of N-methyl-2-methylthio-3,4,5,6-tetrahydropyridinium fluoroborate, was heated at 170° for 20 hr, cooled to ambient temperature, and opened. The contents were triturated with 1.0 ml of ethyl ether. A glpc analysis of the solution showed the presence of only *ca.* 18% of the original 2-methylthio-3,4,5,6-tetrahydropyridine charge.

Registry No.—**7**, 2044-27-1; **8**, 19766-06-4; **9**, 18438-38-5-; N-methyl-2-methyl-d_3-thiopyridinium iodide, 19766-28-0; 2-methylthio-3,4,5,6-tetrahydropyridine, 19766-29-1; N-methyl-2-methylthio-3,4,5,6-tetrahydropyridinium fluoroborate, 19795-94-9.

Acknowledgment.—We are grateful to the Alfred P. Sloan Foundation and to the Public Health Service (Grant GM-12595) for partial support of this work and to the University of Illinois for a fellowship to James T. Lee, Jr.

(14) J. V. Kostir and Z. Padr, *Chem. Listy*, **40**, 276 (1946).

The Reaction of Amines with 1-Phenacyl-2-bromopyridinium Salts. A New Route to Imidazo[1,2-*a*]pyridinium, Oxazolo[3,2-*a*]pyridinium, and Dihydropyrido[2,1-*c*]-*as*-triazinium Salts[1]

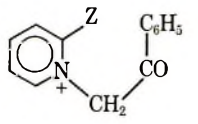
C. K. BRADSHER, R. D. BRANDAU, J. E. BOLIEK, AND T. L. HOUGH

Department of Chemistry, Duke University, Durham, North Carolina 27706

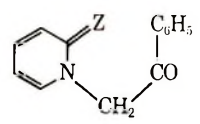
Received October 29, 1968

The reaction of 2-bromo-1-phenacylpyridmium bromide (1) with arylamines, acethydrazide, or butylamine leads to 1-substituted imidazo[1,2-*a*]pyridinium salts (10). If the reaction with butylamine was interrupted, two intermediates, 1-butyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium (7, R = Bu) bromide and a 2-phenyloxazolo[3,2-*a*]pyridinium salt (9) were isolated. With tertiary amines the latter (9) became the major product. With hydrazine or methylhydrazine, 3-phenyl-1,4-dihydropyrido[2,1-*c*]*as*-triazinium ion (13) or its 1-methyl homolog (15) were obtained, while with 1,2-dimethylhydrazine the product was the 1,2-dimethyl-3-phenyl-1,2-dihydropyrido[2,1-*c*]triazinium ion (19). In boiling acid 19 loses a methyl group from the nitrogen at the 2 position affording 15. In boiling acid 3-phenyl-1,4-dihydro[2,1-*c*]-*as*-triazinium ion (13) undergoes ring contraction to 1-amino-2-phenylimidazo[1,2-*a*]pyridinium ion (22).

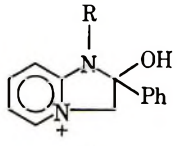
In a recent paper[2] it was shown that 2-bromo-1-phenacylpyridinium salts (1) and certain analogs are convenient starting materials for the synthesis of 2-substituted thiazolo[3,2-*a*]pyridinium salts (8) *via* cyclization of the intermediate 1-phenacyl-2-pyridinethiones (5). Since it is known that 1-phenacyl-2-pyridone (6)



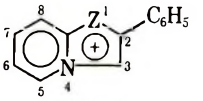
1, Z = Br
2, Z = NHR
3, Z = H
4, Z = Cl



5, Z = S
6, Z = O



7

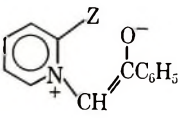


8, Z = S
9, Z = O
10, Z = NR

and its analogs may be cyclized to oxazolo[3,2-*a*]pyridinium salts (*e.g.*, 9),[3] and since 2-alkylamino-1-phenacylpyridinium salts (2 or 7) must be converted readily to imidazo[1,2-*a*]pyridinium salts (10),[4] it seemed reasonable to expect that 1·Br might serve also as a convenient starting material for the preparation of both the oxazolo- (9) and imidazopyridinium (10) systems. The present research, dealing with the reaction of 1 with amines, was directed toward the synthesis of imidazo-[1,2-*a*]pyridinium salts (10).

When 2 equiv of *n*-butylamine was added to a suspension of 2-bromo-1-phenacylpyridmium bromide (1) in anhydrous acetonitrile, the solution turned yellow and the reaction proceeded with sufficient vigor to cause boiling of the solvent. It was also evident from the ultraviolet absorption spectra that a change had occurred. After the mixture had been refluxed for 14 hr, 1-butyl-2-phenylimidazo[1,2-*a*]pyridinium cation (10, R = Bu) was obtained in 66% yield. If the reaction was interrupted after only 10 min of refluxing, two products were isolated. The first of these, obtained in smaller yield, was identified as 2-phenyloxazolo[3,2-*a*]-pyridinium ion (9), while the second product, isolated in 47% yield, had the properties expected for 1-butyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium (7, R = Bu) bromide, the ring tautomer of 2-(butylamino)-1-phenacylpyridinium bromide (2, R = Bu). The butyl derivative (7 or 2, R = Bu) readily underwent dehydration to yield 1-butyl-2-phenylimidazo[1,2-*a*]pyridinium cation.

The isolation of 2-phenyloxazolo[3,2-*a*]pyridinium perchlorate (9), even though in a yield of only 11%, was very interesting in that strictly anhydrous conditions had been used, making it clear that the oxygen atom of the new heterocyclic ring originated from the carbonyl function of the phenacylpyridinium salt (1). Kröhnke[5] has shown that when phenacylpyridinium bromide (3) and suitable analogs are treated with weak bases such as sodium carbonate, orange-red betaines (*e.g.*, 12) are



11, Z = Br
12, Z = H

formed and can actually be isolated and purified. It has been reported[6] that a cautious attempt to extend the reaction to 2-chloro-1-phenacylpyridinium ion led to the formation of 1-phenacyl-2-pyridone (6). Compound 9 is probably formed by the nucleophilic attack of the enolate oxygen of 11 on the carbon at position 2. The failure to isolate any of the oxazolo[3,2-*a*]pyridinium salt when the reaction was allowed to proceed for 14 hr is understandable since 2-phenyloxazolo[3,2-*a*]-pyridinium ion (9) apparently undergoes ring opening when heated with butylamine. Better yields of the oxazolopyridinium salt (9) were obtained when tertiary amines were substituted for butylamine, triethylamine (68% yield of 9) proving superior to the less basic dimethylaniline (51% yield of 9).

(1) This research was supported by Public Health Service Grants No. HE-2170 of the National Heart Institute and No. CA-05509 of the National Cancer Institute.

(2) C. K. Bradsher and J. E. Boliek, *J. Org. Chem.*, **32**, 2409 (1967).

(3) (a) C. K. Bradsher and M. F. Zinn, *J. Heterocyclic Chem.*, **1**, 219 (1964); (b) *ibid.*, **4**, 66 (1967).

(4) C. K. Bradsher, E. F. Litzinger, Jr., and M. F. Zinn, *ibid.*, **2**, 331 (1965).

(5) F. Kröhnke, *Ber.*, **68**, 1177 (1935).

(6) F. Kröhnke and W. Heffe, *ibid.*, **70B**, 864 (1937).

TABLE I

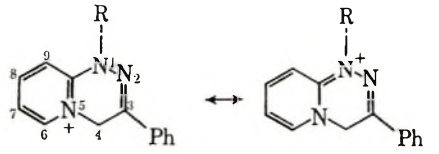
1-ARYL-2-PHENYLIMIDAZO[1,2-*a*]PYRIDINIUM (10, R = ARYL) PERCHLORATES

10, R[a]	Reflux time, hr	Yield, %	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
C_6H_5	9	75	226–228[b–d]	$C_{19}H_{15}ClN_2O_4$	61.54	61.42	4.07	4.18	7.55	7.55
p-$NO_2C_6H_4$	7	58	208–210[e,f]	$C_{19}H_{14}ClN_3O_6$	54.88	54.54	3.39	3.62	10.11	10.18
p-HOC_6H_4	18	62	201–202[c,f]	$C_{19}H_{15}ClN_2O_5$	59.00	58.85	3.91	3.93	7.24	7.36
p-$EtOOCC_6H_4$	4.5	64	213–215[c,f]	$C_{22}H_{19}ClN_2O_6$	59.66	59.66	4.32	4.47	6.33	6.50
α-$C_{10}H_7$	4	66	196–227[f,g]	$C_{23}H_{17}ClN_2O_4$	65.64	65.22	4.07	4.12	6.66	6.42

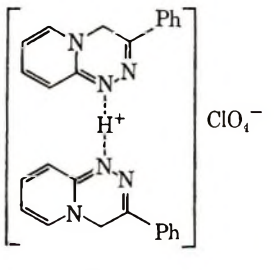
[a] See structure **10**. [b] The nmr spectrum in heavy water showed no resonance below δ 7.78 ppm. [c] Colorless prisms. [d] From methanol–ethyl acetate. [e] Pale yellow prisms. [f] From methanol. [g] Light purple prisms.

The reaction of aniline with **1** bromide is much less vigorous than that of butylamine, and the reaction mixture lacks the color to be expected of the enolate salt **11**. If the reaction mixture was refluxed for 4 hr, 1,2-diphenylimidazo[1,2-*a*]pyridinium (**10**) ion (as the perchlorate) was obtained in 75% yield. It is believed significant that no 2-phenyloxazolo[2,3-*a*]pyridinium salt (**9**) has been isolated from the reaction of aniline and its derivatives with **1**·Br, especially since it was demonstrated that the oxazolopyridinium salt **9** is recovered unchanged after heating with aniline under the usual reaction conditions. The reaction shown by aniline appears general for arylamines and, as may be seen in Table I, the yields are not greatly different whether electron-releasing or electron-attracting groups are present.

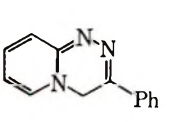
It would be anticipated that hydrazine could lead to the formation of either a new five-membered or six-membered ring. It was found that reaction of hydrazine or methylhydrazine with **1**·Br gave products which, on the basis of spectral evidence, must be six-ring compounds, 3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (**13**) perchlorate, or its 1-methyl homolog (**15**), respectively.



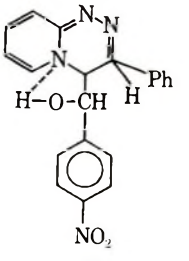
13, R = H
14, R = $COCH_3$
15, R = CH_3



16



17



18

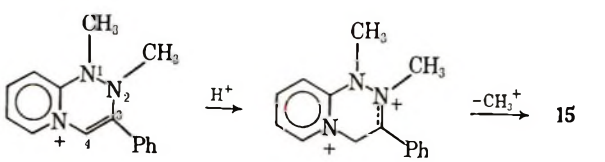
For the hydrazine derivative **13** the only nmr signal outside the aromatic region was a two-proton singlet at δ 5.52 ppm (CH_2). The positive charge of the new system is shared principally by the nitrogen atoms at positions 1 and 5, and it is not surprising that the proton on the nitrogen at position 1 is acidic. When **13** was treated with sodium bicarbonate, the yellow compound which precipitated was not the expected base **17**, but a compound having the composition of 1 mole of the base **17** plus 1 mole of the salt **13**. Acidification of the compound salt gave back the original simple salt **13**. It is proposed that in the compound salt 1 mole of the base **17** is hydrogen bonded to 1 mole of the salt **13**, the arrangement being symmetrical with respect to the 1 position, the unit positive charge being spread over both of the moities **16**. Similar structures have been discussed in a recent publication.[7]

If sodium hydroxide was added to an aqueous solution of the simple salt **13**, the product was the free base, 3-phenyl-4H-pyrido[2,1-*c*]-*as*-triazine (**17**). The nmr spectrum of the base exhibited a two-proton singlet at δ 4.81 and a total of nine protons in the aromatic region. Significantly, equimolecular quantities of the base **17** and the simple salt **13** unite to form the compound salt **16**.

The base **17** underwent acetylation or methylation with ease, presumably at position 1. The products, **14** and **15** when treated with bicarbonate did not afford a precipitate, and both exhibited nmr spectra with the characteristic downfield signals due to the presence of methylene groups. The methyl derivative was identical with the product **15** prepared by the reaction of methylhydrazine with **1**·Br.

In addition to the methylation and acetylation reactions at position 1, the base **17** reacted at position 4 with *p*-nitrobenzaldehyde. The nmr spectrum of the product **18** had a pair of one-proton doublets centered at δ 5.90 and 5.10. A broad absorption band at 2400–2750 cm^{-1} in the infrared spectrum of **18** suggested hydrogen bonding between the bridgehead nitrogen atom and the hydroxylic hydrogen.

With 1,2-dimethylhydrazine, **1**·Br gave a derivative of the 1,2-dihydro system, 1,2-dimethyl-3-phenyl-1,2-dihydropyrido[2,1-*c*]-*as*-triazinium ion (**19**). The system was easily protonated at the 4 position, for although nmr in dimethyl sulfoxide shows signals for ten hydrogen atoms in the aromatic region (with methyl signals as singlets at δ 3.51 and 2.80 ppm), the nmr in trifluoroacetic acid showed signals for only nine hydrogen atoms



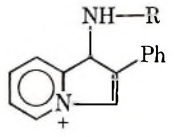
19 **20** **15**

(7) H. F. Andrew and C. K. Bradsher, *J. Heterocyclic Chem.*, **3**, 282 (1966). Crystallographic evidence for the existence of such symmetrical hydrogen bonds in potassium hydrogen malonate has been published recently: C. Ferguson, J. G. Sime, J. C. Speakman, and R. Young, *Chem. Commun.*, 162 (1968).

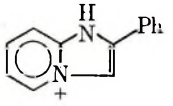
in the aromatic region plus a new two-proton singlet at δ 5.69 ppm. On heating **19** with 16% hydrobromic acid, a methyl group was lost, affording **15** isolated as the perchlorate.

The loss of a methyl group from a nitrogen atom, uncommon except with some quaternary salts, is at least partially explicable in that the protonated species **20** is essentially a bis quaternary salt.

1,1-Dimethylhydrazine reacted as a tertiary amine with **1**·Br, affording the oxazolopyridinium salt **9** as the only product isolated.



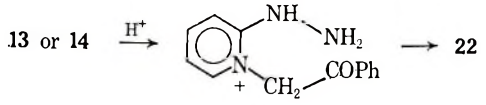
21, R = CH_3CO
22, R = H



23

Of the hydrazine derivatives studied only acetylhydrazide afforded an imidazopyridinium derivative (**21**) directly. Hydrolysis of the amide linkage afforded 1-amino-2-phenyl-imidazopyridinium bromide (**22**). The nmr of the amine **22** in trifluoroacetic acid showed signals in the aromatic region only and reaction of the amine with nitrous acid afforded the deamination product, 2-phenylimidazo[1,2-*a*]pyridinium ion (**23**), isolated as the perchlorate. The identity of the corresponding base was established by comparison with an authentic sample.[8]

It is worthy of note that **22** could also be made by ring contraction of **13**, brought about by heating it in hydrobromic acid.



24

Experimental Section

Elemental analyses were carried out by the Janssen Pharmaceutica, Beerse, Belgium, and by Galbraith Laboratories, Knoxville, Tenn. All melting points have been corrected. Ultraviolet absorption spectra were measured in 95% ethanol using 1-cm matched quartz cells in a Cary Model 14 spectrophotometer. Infrared data were determined in potassium bromide pellets using a Model 137 or Model 237 Perkin-Elmer spectrophotometer. Nmr data was determined with a Varian A-60 spectrometer using tetramethylsilane as the standard.

1-Butyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium (7, R = Bu) Bromide.—To a suspension of 3.57 g of 2-bromo-1-phenacylpyridinium bromide[9] (**1**) in about 70 ml of anhydrous acetonitrile (distilled from P_2O_5) 2.02 g (2 equiv) of *n*-butylamine was added (exothermic reaction).

After refluxing the yellow solution for 10 min, concentration under vacuum gave a viscous red gum which was partitioned between methylene chloride and water. Addition of sodium perchlorate solution to the aqueous layer produced a colorless precipitate which, on crystallization from methanol–ethyl acetate, afforded 0.32 g (11%) of 2-phenyloxazolo[3,2-*a*]pyridinium (**9**),[3] mp 216–218°. The methylene chloride layer was dried ($MgSO_4$) and concentrated and the residue was crystallized from methanol–ethyl acetate yielding in two crops 1.65 g (47%) of colorless plates, mp 149–150°, with a strong blue fluorescence under uv light. The ir showed no strong band in the 1660–1800-cm^{-1} region (carbonyl stretching);[10] λ_{max} [mμ (log ϵ)] 333 (3.70), 241 (4.19), and 203 (4.46).

Anal. Calcd for $C_{17}H_{21}BrN_2O$: C, 58.42; H, 6.06; N, 8.02. Found: C, 58.23; H, 6.04; N, 8.13.

If the oxazolo compound **9** was heated for 2.75 hr with 5 equiv of butylamine, the product was impure **7** (ir spectra).

1-Butyl-2-phenylimidazo[1,2-*a*]pyridinium Perchlorate (10, R = Bu). A. By Dehydration of 1-Butyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium (7, R = Bu) Bromide.—A mixture of 0.25 g of the carbinolamine bromide (**7**, R = Bu) and 10 g of polyphosphoric acid was heated with stirring on a steam bath. The mixture was cooled and diluted with ice water and excess 35% perchloric acid solution was added. The resulting precipitate was crystallized from methanol–ethyl acetate giving 0.19 g (76%) of colorless crystals, mp 93–96°. The analytical sample had mp 98.5–100°.

B. From 2-Bromo-1-phenacylpyridinium Bromide (1).—If the reaction of 7.14 g of the title compound **1** with butylamine was carried out as in the preparation of the carbinolamine **7** bromide except that refluxing was continued for 14 hr, 4.4 g (66%) of 1-butyl-2-phenylimidazo[1,2-*a*]pyridinium ion was isolated as the perchlorate, mp 99–101°. This was identical in infrared spectrum and in mixture melting point with the product obtained in A; ν_{max} 2800–3000 cm^{-1} (aliphatic C–H stretch); nmr (trifluoroacetic acid), δ 4.01 (t, 2, CH_2, J = 7 cps), 0.2–1.6 (seven remaining Bu protons), 6.9–8.3 (10 aromatic H); λ_{max} 288 mμ (log ϵ 4.15), 228 (4.32), 204 (4.51).

Anal. Calcd for $C_{17}H_{19}ClN_2O_4$: C, 58.20; H, 5.46; N, 7.98. Found: C, 58.44; H, 5.57; N, 7.83.

2-Phenyloxazolo[3,2-*a*]pyridinium (9) Perchlorate by Action of Tertiary Amines on 1.—The addition of 1.01 g of triethylamine to a suspension of 1.79 g of **1** in 50 ml of dry acetonitrile produced an orange-red solution which was refluxed for about 3 hr, the mixture being protected from contact with moisture. Addition of the cool solution to 250 ml of anhydrous ether yielded a pink precipitate which was collected and dissolved in water. Addition of 35% perchloric acid to the aqueous solution afforded **9** which was crystallized from ethanol–ethyl acetate as colorless needles, mp 216–218°, yield 1.0 g (68%).

When the above procedure was repeated using N,N-dimethylaniline in the place of triethylamine and continuing refluxing for 6 hr, 0.75 g (51%) of **9**, mp 216–218°, was obtained.

1-Aryl-2-phenylimidazo[1,2-*a*]pyridinium (10, R = Aryl) Perchlorates.—There was no color change or exothermic reaction when **1**·Br was added to an acetonitrile solution of an arylamine (2 equiv). After a 14-hr reflux, the cooled mixture was poured into ether and the resulting precipitate was dissolved in water and reprecipitated ($HClO_4$) as the perchlorate (see Table I).

3-Phenyl-1,4-dihydropyrido[2,1-*c*]*as*-triazinium (13) Bromide.—Hydrazine hydrate (2 equiv) was refluxed for 14 hr in acetonitrile with **1**·Br. When the mixture reached room temperature it was filtered to remove a small quantity of by-product and solution was concentrated *in vacuo*. The residue crystallized from ethanol–ethyl acetate as hydrated yellow needles, mp 214–215°.

Anal. Calcd for $C_{13}H_{12}BrN_3 \cdot 0.5H_2O$: C, 52.17; H, 4.40; N, 14.04. Found: C, 51.77; H, 4.45; N, 14.37.

A sample of the salt, crystallized from water as yellow needles, appeared to be the **monohydrate**, mp 125–126°.

Anal. Calcd for $C_{13}H_{12}BrN_3 \cdot H_2O$: C, 50.66; H, 4.58; N, 13.63. Found: C, 50.82; H, 4.73; N, 13.41.

Recrystallization of the hydrate from ethanol afforded the higher melting hemihydrate salt as needles, mp 214–215°.

Addition of sodium perchlorate solution to a hot solution of the bromide precipitated the **perchlorate** which crystallized from methanol–ethyl acetate as colorless needles: mp 199–200°; nmr (trifluoroacetic acid), δ 5.52 (s, 2, CH_2), 7.38–8.39 (ten protons); uv max, 360 mμ (log ϵ 3.99), 293 (4.02), 243 sh (3.96), 223 sh (4.08), 202 (4.36); ν_{max} 2600–3600 cm^{-1} (acidic H bonded to N).

Anal. Calcd for $C_{13}H_{12}ClN_3O_4$: C, 50.41; H, 3.91; N, 13.57. Found: C, 50.35; H, 3.91; N, 13.85.

3-Phenyl-4H-pyrido[2,1-c]-*as*-triazine (17).—To a hot solution of 2.0 g of 3-phenyl-1,4-dihydropyrido[2,1-c]-*as*-triazinium (**13**) perchlorate in 20 ml of water, 3 ml of 50% aqueous sodium hy-

(8) A. E. Tschitschibabin, *Ber.*, **59**, 2048 (1926).

(9) C. Djerassi and G. R. Pettit, *J. Amer. Chem. Soc.*, **76**, 4470 (1954).

(10) Although there is a possibility that the molecule exists in the open-chain form (**2**, R = Bu), and that hydrogen bonding has shifted the absorption due to the carbonyl group to a frequency low enough for it to merge with the band due to the C=N linkage, it is felt that the cyclic carbinolamine structure **7** is more probable.

droxide solution was added with stirring. The dark oil which separated solidified on cooling and was crystallized from a 10% aqueous solution of methanol as yellow needles. When dried at 80°, 1.2 g (92%) of orange-red needles was obtained; mp 222–223°; nmr ($CDCl_3$), δ 4.81 (s, 2, CH_2), 6.15–7.9 (nine protons).

Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.59; H, 5.49; N, 19.94.

Compound Salt 16. A. By Action of Bicarbonate Ion on 3-Phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (13) Perchlorate.—To a hot solution of 0.5 g of the triazinium salt **13** in water, 10 ml of saturated sodium bicarbonate solution was added. On cooling, yellow needles separated and were collected and recrystallized from methanol–ethyl acetate. The product, 0.25 g (56%), had mp 197–199° dec; ν_{max} 3400 cm^{-1} (N–H bonding); λ_{max} 360 mμ (log ε 4.25), 302 (4.16), 252 (4.28), and 206 (4.58).

B. By Addition of an Equimolecular Quantity of the Triazine Base 17 to the Triazinium Salt 13.—To a solution of 0.20 g of the triazinium salt **13** in 20 ml of methanol 0.13 g of the base **17** in 20 ml of methanol was added. Upon concentration to approximately 15 ml followed by cooling, 0.30 g (91%) of the compound salt, mp 197–199° crystallized. This material was shown by mixture melting point and ir spectra to be identical with the preparation A.

Anal. Calcd for $C_{26}H_{23}N_6ClO_4$: C, 60.17; H, 4.47; N, 16.20. Found: C, 60.42; H, 4.72; N, 16.20.

Addition of a few drops of perchloric acid to a methanol solution of the compound salt **16** followed by precipitation with ether gave back 3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (**13**) perchlorate in 84% yield.

1-Aceto-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (14) Perchlorate. A. By Acetylation of the Bromide Salt (13).—A suspension of 4.5 g of 3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (**13**) bromide in 100 ml of acetic anhydride was refluxed for 5 hr then the anhydride was removed under reduced pressure. The residual gum was crystallized from methanol–ethyl acetate as colorless needles: mp 206–208°; nmr (D_2O), δ 2.48 (s, 3, CH_3), 5.37 (s, 2, CH_2), 7.17–8.60 (nine aromatic H).

Anal. Calcd for $C_{15}H_{14}N_3OBr$: C, 54.23; H, 4.25; N, 12.65. Found: C, 53.91; H, 4.28; N, 12.40.

The **perchlorate** crystallized from ethanol–ethyl acetate as colorless needles: mp 228–230°; uv max 203.5 mμ (log ε 4.23), 223 sh (4.02), 245.5 sh (3.87), 255.5 sh (3.83), 292 (4.01), 360 (3.99).

B. By Acetylation of the Triazine Base 17.—To a sample of the base in anhydrous chloroform a few drops of acetyl chloride was added. The mixture was refluxed for 15 min and then concentrated. Addition of perchloric acid to an aqueous solution of the residue afforded a product identical in ir spectrum and melting point with the perchlorate salt prepared by method A.

Anal. Calcd for $C_{15}H_{14}ClN_3O_5$: C, 51.22; H, 4.01; N, 11.95. Found: C, 51.35; H, 4.05; N, 11.47.

Deacetylation of 1-Aceto-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (14) Bromide.—A solution of **14** in 50 ml of 5% hydrobromic acid was allowed to stand for 8 hr at room temperature. The yellow monohydrate of **13**·Br, mp 125–126° crystallized from the solution. Recrystallization of the hydrate from ethanol afforded the higher melting hemihydrate as needles, mp 214–215°, yield 0.5 g (72%).

3-Phenyl-4-(α-hydroxy-4′-nitrobenzyl)pyrido[2,1-*c*]-*as*-triazine (18).—A mixture containing 0.8 g of the triazine base **17** and 0.6 g of *p*-nitrobenzaldehyde in 20 ml of chloroform was refluxed for 24 hr. The filtered solution was concentrated and the residue was crystallized from methanol as golden needles: mp 184–185°; yield 1.2 g (85%); nmr (trifluoroacetic acid), δ 5.80 (d, 1, J = 2.5 Hz, CH) 6.60 (d, 1, J = 2.0 Hz, CH), plus aromatic protons; ν_{max} 2400–2750 cm^{-1} (H bonding to N).

Anal. Calcd for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55. Found: C, 66.31; H, 4.49; N, 15.26.

1-Methyl-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (15) Perchlorate. A. By Methylation of the Triazine Base 17.—Excess methyl iodide was added to a chloroform solution of the triazine base **17** and the mixture refluxed for 10 min. The precipitate was collected and crystallized from methanol–ethyl acetate. The product (0.6 g) was dissolved in water and 70% perchloric acid was added. The resulting perchlorate crystallized from ethanol as yellow needles: mp 188°; nmr (DMSO-d_6), δ 3.72 (s, 3, CH_3), 5.48 (s, 2, CH_2), 7.33–8.42 (complex, 9); nmr (trifluoroacetic acid), δ 3.37 (s, 3, CH_3), 4.86 (s, 2, CH_2), 6.75–8.15 (complex 9).

B. From Methylhydrazine.—Following the general procedure used for the preparation of 1-arylimidazopyridinium salts (**10**) but using methylhydrazine instead of arylamine, the product **15**, obtained in 90% yield, was identical in melting point and ir spectrum with that prepared by procedure A.

Anal. Calcd for $C_{14}H_{14}N_3ClO_4$: C, 51.94; H, 4.36; N, 12.98. Found: C, 51.86; H, 4.29; N, 12.99.

1,2-Dimethyl-3-phenyl-1,2-dihydropyrido[2,1-*c*]-*as*-triazinium (19) Perchlorate.—To a suspension of 1.79 g of **1** in 50 ml of dry acetonitrile 1.33 g of 1,2-dimethylhydrazine dihydrochloride and 1.01 g of triethylamine was added and the mixture refluxed for 14 hr. The solution was concentrated to 20 ml and the salts were removed by filtration. Concentration of the filtrate under vacuum and reprecipitation of the residue from water as the perchlorate produced an orange solid which, crystallized from ethanol, had mp 210–211°; yield 1.1 g (69%); nmr (DMSO-d_6), δ 2.80 (s, 3, CH_3), 3.51 (s, 3, CH_3), 7.38–8.53 (complex 10); nmr (CF_3COOH), 3.80 (s, 3, CH_3), 3.99 (s, 3, CH_3), 5.69 (s, 2, CH_2), 7.3–8.5 (complex 9).

Anal. Calcd for $C_{15}H_{16}ClN_3O_4$: C, 53.33; H, 4.77; N, 12.44. Found: C, 53.25; H, 4.76; N, 12.54.

Loss of a Methyl Group from 1,2-Dimethyl-3-phenyl-1,2-dihydropyrido[2,1-*c*]-*as*-triazinium (19) Perchlorate.—A suspension of 0.20 g of the title compound **19** in 10 ml of 16% hydrobromic acid was heated at 100° for 12 hr, then 70% perchloric acid was added to the cooled solution. The resulting precipitate crystallized from ethanol as yellow needles, mp 188°, yield 0.18 g (94%). The product was shown to be 1-methyl-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium perchlorate (ir, mixture melting point).

Reaction of 1,1-Dimethylhydrazine with 2-Bromo-1-phenylpyridinium Bromide.—When the title reagents were allowed to react in refluxing acetonitrile under essentially the same conditions used with hydrazine to produce **13**, the product, isolated in 41% yield, was 9 perchlorate, mp 216–218°.

1-Acetamido-2-phenylimidazo[1,2-*a*]pyridinium (21) Bromide.—A solution containing 1.79 g of **1**·Br and 0.74 g of acetylhydrazide in 50 ml of acetonitrile was refluxed for 15 hr, and the salt precipitated with ether and was recrystallized from methanol–ethyl acetate as colorless needles; mp 303° dec; yield 1.45 g (87%); nmr (D_2O), δ 3.08 (s, 3, CH_3CO), 8.39–9.73 (ten, aromatic).

Anal. Calcd for $C_{15}H_{14}BrN_3O$: C, 54.23; H, 4.25; N, 12.65. Found: C, 53.98; H, 4.37; N, 12.61.

The **perchlorate** crystallized from ethanol–ethyl acetate as colorless needles: mp 178–180°; uv max (95% EtOH), 204 mμ (log ε 4.47), 233.5 (4.37), 294.5 (4.01).

Anal. Calcd for $C_{15}H_{14}ClN_3O_5$: C, 51.22; H, 4.01; N, 11.95. Found: C, 50.94; H, 4.16; N, 11.61.

1-Amino-2-phenylimidazo[1,2-*a*]pyridinium (22) Perchlorate. A. By Hydrolysis of 1-Acetamido-2-phenylimidazo[1,2-*a*]pyridium (21) Bromide.—The aceto derivative **21** (1.45 g) was heated for 20 hr on a steam bath with 25 ml of 16% hydrobromic acid. The product was precipitated by addition of 35% perchloric acid and recrystallized from ethanol–ethyl acetate as colorless needles, mp 193–194°, yield 0.94 g (61%).

B. By Hydrolysis and Rearrangement of 1-Aceto-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (14) Bromide.—If **14** (1.45 g) was subjected to the same conditions used in the hydrolysis of the isomer **21**, 1.06 g (68%) of colorless needles was obtained mp 193–194°.

C. By Rearrangement of 3-Phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (13) Bromide.—The title compound (1.50 g) was heated in acid under conditions used in the hydrolysis of the aceto derivatives **14** and **21**; yield 0.83 g (52%) of colorless needles: mp 193–194°; uv max (95% ethanol), 205 mμ (log ε 4.49), 234.5 (4.35), 293 (4.12); nmr (CF_3COOH), δ 7.23–8.74 (ten, vinyl and aromatic). Products obtained by methods A, B, and C were shown to be identical by ir and mixture melting points.

Anal. Calcd for $C_{13}H_{12}ClN_3O_4$: C, 50.41; H, 3.91; N, 13.57. Found: C, 50.43; H, 4.05; N, 13.60.

Action of Nitrous Acid on 1-Amino-2-Phenylimidazo[1,2-*a*]-pyridinium (22) Perchlorate.—To a solution of 1 g of **22** in 12 ml of 8 *N* sulfuric acid at 0° a sodium nitrite solution was added dropwise until there was a positive test for nitrous acid, then 70% perchloric acid was added to the cold solution until precipitation was complete. The precipitate crystallized from acetone–water as colorless needles, mp 169–170°, yield 0.7 g 77%. The composition was approximately that expected for **2-phenylimidazo[1,2-*a*]pyridinium perchlorate.**

Anal. Calcd for $C_{13}H_{11}ClN_2O_4$: C, 52.99; H, 3.76; N, 9.51. Found: C, 53.45; H, 3.92; N, 9.47.

Addition of sodium hydroxide to an aqueous solution of the product afforded a fluorescent colorless crystalline compound, mp 134–135°, which by ir spectra and mixture melting point was shown to be identical with an authentic sample[8] of 2-phenylimidazopyridine.

Registry No.—**7** (R = Bu) bromide, 19770-05-9; **9** perchlorate, 13794-84-8; **10** (R = Bu) perchlorate, 19770-06-0; **10** (R = Ph) perchlorate, 19770-07-1; **10** (R = *p*-$NO_2C_6H_4$) perchlorate, 19789-58-3; **10** (R = *p*-HOC_6H_4) perchlorate, 19770-08-2; **10** (R = $EtOOCC_6H_4$) perchlorate, 19770-09-3; **10** (R = α-$C_{10}H_7$) perchlorate, 19770-10-6; **13** bromide, 19770-11-7; **13** perchlorate, 19770-12-8; **14** bromide, 19770-13-9; **14** perchlorate, 19770-14-0; **15** perchlorate, 19770-15-1; **16**, 19770-16-2; **17**, 19770-17-3; **18**, 19770-18-4; **19** perchlorate, 19770-19-5; **21** bromide, 19770-20-8; **21** perchlorate, 19770-21-9; **22** perchlorate, 19770-22-0; **23**, 19770-23-1.

The Synthesis of Oxiranes from Aqueous Solutions of Simple Alkyl, Allyl, and Benzylsulfonium Salts[1a]

MELVIN J. HATCH[1b]

Physical Research Laboratory, Dow Chemical Company, Midland, Michigan

Received December 3, 1968

The reaction of simple sulfonium salts with warm aqueous NaOH and carbonyl compounds yields various oxiranes (epoxides). Previously, oxirane syntheses from such sulfonium salts has been achieved only in nonaqueous solutions of much stronger bases. The present work shows that often sufficient sulfonium ylide is formed in aqueous bases to permit trapping reactions. Trimethyl- or triethylsulfonium chlorides gave oxiranes with benzaldehyde (*ca.* 70%). No oxiranes were formed with formaldehyde nor acetaldehyde, since Cannizzaro or aldol condensation reactions apparently intervened. Allyldimethylsulfonium chloride reacted well with benzaldehyde (*ca.* 70% oxirane), poorly with formaldehyde (8%), and not at all with acetaldehyde. A side reaction, leading to propylene oxide, also occurred. Benzyldimethylfonium chloride gave oxiranes with both benzaldehyde and formaldehyde (85 and 87%) and, under conditions of minimal exposure to NaOH, with acetaldehyde also (48%).

Previous workers have described the formation of ylides from alkyl- or benzylsulfonium ions in *nonaqueous* solutions of very strong bases, *e.g.*, methylsulfinyl carbanion in dimethyl sulfoxide,[2] and the reaction of the unstable ylides with aldehydes or ketones to yield oxiranes.[2-5] However, the prospects appeared to be questionable for using *aqueous* solutions in this synthetic reaction of simple[6] sulfonium salts. Thus, the reaction in water of unsubstituted benzyldimethylsulfonium ion and hydroxide ion was known to give only a high yield of benzyl alcohol by an apparent SN2 mechanism.[7] This result indicated that even with the extra ylide stabilization conveyed by the phenyl group, the aqueous ylide concentration was very small, too small at least to yield any carbene and resulting olefin.[8]

The present investigation originated from the following idea. Although in aqueous NaOH, simple sulfonium ylides could be present only in concentrations so small that no olefin-producing carbene intermediate would be produced, *the ylide concentration still might be sufficient for "trapping" reactions to occur with reactive carbonyl compounds.* Preliminary experimental results

$$RCH_2\overset{+}{S}(CH_3)_2\ \bar{O}H \rightleftharpoons \bar{R}\overset{-}{C}H\overset{+}{S}(CH_3)_2 + H_2O$$

$$\bar{R}\overset{-}{C}H\overset{+}{S}(CH_3)_2 + R'COR'' \longrightarrow RCH(O)CR'R'' + S(CH_3)_2$$

indeed demonstrated that such trapping reactions are possible, and that synthetically useful yields of oxiranes might be achieved. Studies therefore were made to explore the scope and limitations of the reactions.

The experimental conditions generally were similar. Excess aqueous NaOH (50% solids) was added to a warm, stirred mixture of aqueous sulfonium salt, carbonyl compound, and (usually) an immiscible solvent. After reaction times which ranged from a few minutes to several hours at 70–80°, the immiscible solvent (or distillate) was analyzed for oxirane content by use of a pyridine–pyridine–hydrochloride mixture,[9] and product epoxide was then further isolated and/or characterized.

Reaction of Trialkylsulfonium Salts.—Even trialkylsulfonium salts were sufficiently acidic to react in

(1) (a) This work was reported at the 22nd Annual Southwest Regional Meeting of the American Chemical Society, Albuquerque, N. M., Nov 1966. (b) Chemistry Department, New Mexico Institute of Mining and Technology, Socorro, N. M. 87801.

(2) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(3) E. J. Corey and W. O. Oppolzer, *ibid.*, **86**, 1899 (1964). One may note that this oxirane synthesis bears obvious analogy to the classical Darzen glycidic ester synthesis.

(4) A. W. Johnson, V. J. Hruby, and J. L. Williams, *ibid.*, **86**, 918 (1964).

(5) (a) V. Franzen and H. E. Fruessen, *Chem. Ber.*, **96**, 1881 (1963). (b) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 328–337, gives a review of the reaction. This author (p 2) also suggests the term "ylid," rather than "ylide."

(6) In this article, simple sulfonium salts are considered to be those containing only alkyl, allyl, or benzyl groups which have no substituents or at least have no strongly electron-withdrawing substituents.

(7) C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **83**, 4033 (1961).

(8) Previously known to exist in water were sulfonium ylides in which the carbanionic center is stabilized considerably by conjugation to electron-withdrawing groups in *addition* to the adjacent sulfonium center. (These, then, were nonsimple sulfonium ylides.) Thus, dimethylsulfonium fluorenylide was prepared in aqueous solution by C. K. Ingold and J. A. Jessop, *J. Chem. Soc.*, 713 (1930), and this stabilized ylide could react with certain carbonyl compounds, at least in nonaqueous solution, to yield epoxides, as shown by A. W. Johnson and R. B. LaCount, *J. Amer. Chem., Soc.*, **83**, 417 (1961). Dimethylsulfonium *p*-nitrobenzylide in aqueous solution was suggested as a reaction intermediate which led to the carbene and corresponding stilbene in the work of Swain and Thornton.[7] This contrasted with their above-cited results from unsubstituted benzylsulfonium ion. The phenyl group would provide far less stabilization of a carbanionic center than would the *p*-nitrophenyl group, of course.

(9) F. E. Critchfield, "Organic Functional Group Analysis," Pergamon Press, Inc., New York, N. Y., 1963, pp 133–136. This method is only semiquantitative with some disubstituted oxiranes. It will give 10–15% low results often in such cases, as indicated by studies in this laboratory with purified *trans*-stilbene oxide (*trans*-2,3-diphenyloxirane). With styrene oxide, the method gave results that were reproducible to ±5%, and averaged about 5% lower than theory.

aqueous bases with *some* carbonyl compounds. Thus, trimethylsulfonium chloride, sodium hydroxide, and benzaldehyde yielded styrene oxide (68%). Triethylsulfonium bromide, sodium hydroxide, and benzaldehyde readily formed 2-methyl-3-phenyloxirane (*cis* and *trans* mixture, *trans* predominant, 80% yield). This latter experiment showed that even in sulfonium salts containing β-hydrogen atoms, ylide formation and reaction could compete very well with any anticipated complications[3,4] of E2 elimination.

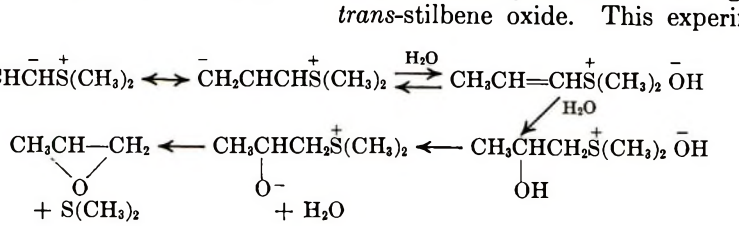
A rough kinetic study was made of the effect of the presence of benzaldehyde on the rate of reaction of trimethylsulfonium or triethylsulfonium ions with NaOH (stirred, aqueous–alcoholic systems, containing benzene extractant). When benzaldehyde was present, the initial rates of NaOH consumption were increased at least fivefold in both cases. (See the Experimental Section for details.) These results indicated that the benzaldehyde was diverting the normal SN2 or E2 reaction courses of the sulfonium ions by addition reaction with very small concentrations present of rapidly, reversibly formed ylide.

Reaction of aqueous trimethylsulfonium chloride with NaOH and formaldehyde or acetone yielded no detectable oxirane. The rapid Cannizzaro reaction of formaldehyde with hot NaOH probably prevented ethylene oxide formation. Similarly, condensation reactions of acetone may have prevented isobutylene oxide formation.

Reactions of Allylsulfonium Salts.—The allylic ylide from allyldimethylsulfonium ion should have increased stability, relative to ylides from trialkylsulfonium ions, due to some conjugation of the carbanionic center with the adjacent vinyl group. The resulting higher ylide concentration could lead to improved reaction with carbonyl compounds.

Indeed, about 8% yield of butadiene monoepoxide (2-vinyloxirane) was achieved with formaldehyde (15-min reaction). With benzaldehyde, 60% or better yields of phenylbutadiene monoepoxide (2-phenyl-3-vinyloxirane, *cis* and *trans* mixture, predominately *trans*) resulted. However, only trace amounts or none of the desired oxiranes formed in the reaction of aqueous allyldimethylsulfonium chloride, NaOH, and acetaldehyde, heptaldehyde, acrolein, or acetone.

Besides competing Cannizzaro and aldol condensation reactions of the carbonyl compounds, possible side reactions of allylsulfonium salts and bases[10] also limited the possibilities of obtaining the desired epoxide products.



One side reaction, surprisingly, led to the formation of propylene oxide (2-methyloxirane), generally in yields from 10 to 40%. The carbonyl compound was not involved in this side reaction, since allyldimethylsulfonium chloride and sodium hydroxide when allowed to react directly together gave about 50% yield of propylene oxide product. Its origin could be rationalized as follows. Hydroxide ion catalyzed isomerization of the allylsulfonium ion to a propenylsulfonium ion was followed by Michael addition of water, deprotonation of the hydroxypropyl group, and ring closure to propylene oxide and dimethyl sulfide. The isomerization of analogous allyl and propenyl phosphonium ylides is known.[11]

In the reaction of allyldimethylsulfonium ion, hydroxide ion, and benzaldehyde to yield phenylbutadiene monoepoxide, the propylene oxide by-product essentially could be eliminated by conducting the reaction at room temperature, or by using an alcohol cosolvent. (The adduct epoxide is not very labile to base.) See Table I for details.

Reactions of Benzylsulfonium Salts.—Due to conjugation of the carbanionic center with the benzene ring, one expects greater stability in the benzylic ylide derived from benzyldimethylsulfonium ion than would be present in an allylic ylide; one might therefore expect improved reactivity with carbonyl compounds. Indeed, benzylic sulfonium salts proved to be better reaction intermediates than those with allylic conjugation. High yields of styrene oxide resulted by reaction of benzyldimethylsulfonium chloride, formaldehyde, and NaOH. Within a few minutes after this very fast reaction was over, the Cannizzaro reaction consumed all residual formaldehyde.

Benzyldimethylsulfonium chloride also reacted well with benzaldehyde and NaOH to yield stilbene oxide (as expected since favorable results were obtained even with formaldehyde, which undergoes the competitive Cannizarro reaction more readily). In contrast, only self-condensation and polymerization reactions of acetaldehyde or acrolein were evident under the usual reaction conditions. The slow addition of benzene-diluted acetaldehyde or acrolein to preheated mixture of benzyldimethylsulfonium chloride and NaOH ("inverse addition") did give modest yields of the desired epoxide products (1,2-epoxypropylbenzene and 2-phenyl-3-vinyloxirane, respectively). Inverse addition of aqueous glyoxal to the basic sulfonium salt solution yielded no detectable epoxide, however. With acetone or acetophenone, fair yields of the corresponding epoxides were produced (2,2-dimethyl-3-phenyloxirane and 2,3-diphenyl-2-methyloxirane).

Benzylbis(2-hydroxyethyl)sulfonium chloride reacted with benzaldehyde and NaOH to give a modest yield of *trans*-stilbene oxide. This experiment indicated that benzylic ylide formation and reaction successfully competed with proton removal from the alcoholic OH groups followed by neighboring-group displacement reaction at the sulfonium center, which would have yielded ethylene oxide.

An empirical study was made of the synthesis of sty-

(10) For example, see the communication of J. E. Baldwin, R. E. Hackler, and D. P. Kelley, *J. Amer. Chem. Soc.*, **90**, 4758 (1968), and the work cited therein.

(11) E. E. Schweizer, E. T. Shaffer, C. T. Hughes, and C. S. Berninger, *J. Org. Chem.*, **31**, 2907 (1966).

TABLE I
PHENYLBUTADIENE MONOEPOXIDE PREPARATIONS

Initial sulfonium molarity[a]	Reactant ratios[b] Benzaldehyde	Hydroxide	Solvent[g]	Temp, °C Initial	Temp, °C Max	Reaction time, min	Yield (%) of epoxide products[c] Total	Propylene oxide	Phenylbutadiene monoepoxide
2.8	3.0	1.4	Benzene	40	72	60	70	13	57
3.4	1.0	1.6	Benzene	37	62	15	58	21	37
3.0	1.0	2.5	Benzene	35	65	10	65	18	48
2.8	1.0	3.0	Toluene	55	83	90	15	4	11
3.4	1.0	1.6	Toluene	35	60	15	65	18	48
3.4	1.0	1.6	Toluene	5	25	1000[d]	60	<1	60
1.2[f]	1.0	1.3	Methanol[f]	25	50	120	65	<2	63[e]
1.6[f]	1.0	1.6	Isopropyl alcohol[f]	35	68	150	73	<1	73

[a] Total moles of allyldimethylsulfonium chloride was 0.150. Concentration based on volume of aqueous phase of reaction mixture (after addition of aqueous NaOH). [b] Initial moles per mole of sulfonium salt. The hydroxide used was NaOH in all cases. [c] Total epoxide yield by pyridine hydrochloride analysis[9] of product solution. Propylene oxide yield by gas chromatographic comparison with authenic standards, and by pyridine hydrochloride analysis of all products distilling under 65°. Phenylbutadiene monoepoxide yield by pyridine hydrochloride analysis of 65° distillation residue. [d] Approximate; reaction held under 15° for 60 min, then let stand overnight at room temperature. [e] Value by difference. [f] With these compatibilizing solvents, concentration was based on total volume of the system. [g] Approximately 75 ml of water-immiscible solvents were used. Approximately 70 ml of methanol and 45 ml of isopropyl alcohol was used.

TABLE II
STYRENE OXIDE PREPARATIONS

Initial sulfonium molarity[a]	Reactant ratios[b] Formaldehyde	Hydroxide	Solvent[f]	Temp, °C Initial	Temp, °C Max	Reaction time, min	Yield (%)[c] of styrene oxide
1.48*	2.8	1.42	*n*-Hexane	25	30	4000	14
1.48*	2.8	1.42	Benzene	40	67	60[d]	48
1.58	2.8	1.42	Toluene	80	88	5	48
1.28	2.8	4.25	Benzene	27	60	2	61
1.28	2.8	4.25	Toluene	55	84	2	86
1.28	2.8	4.25	Toluene	55	84	10	84
1.25	2.8	4.25	Ethylbenzene	55	87	2	88
1.28	2.8	4.25	Heptane[e]	75	84	2	66
1.51	1.41	4.25	Toluene	55	84	2	70
1.13	1.41	8.0	Toluene	55	84	2	34

[a] Total moles of benzyldimethylsulfonium chloride was 0.330 in starred runs and 0.165 in all others. Concentration based on volume of aqueous phase of reaction mixture, after addition of aqueous CH_2O and aqueous NaOH. [b] Initial moles per mole of sulfonium salt. The hydroxide used was NaOH in all cases. [c] Yield, by pyridine hydrochloride analysis of product solution, based on sulfonium salt. [d] Yield was 41% when this reaction was run 6 min. [e] With toluene under these conditions, the reaction boiled over (recovered yield, 80%) and slower addition of NaOH reduced the yield (65%). [f] Approximately 75 ml of solvent was used.

rene oxide from benzyldimethylsulfonium chloride, formaldehyde, and NaOH (see Table II).

The product yield increased at higher temperatures and higher formaldehyde and NaOH loadings, using solvents like benzene or preferably toluene or ethyl benzene. The following describes a typical good run. With a solution of 1.28 *M* sulfonium chloride, 3.6 *M* formaldehyde, stirred well with about 1 vol of toluene and preheated to 55°, rapid addition of 4.25 mol of 50% NaOH/mol of sulfonium chloride gave immediate exotherm to 84° (reflux). After 2 min, the reaction was terminated with ice and an 86% yield of styrene oxide was present in the toluene. A study of the mechanism of this reaction by means of deuterium labeling has been reported elsewhere.[12]

One might expect the reaction of negatively substituted benzylic sulfonium salts with carbonyl compounds and NaOH should be more facile than the reaction of unsubstituted benzylic sulfonium salts. (Actually, *p*-nitrobenzyl chloride itself is known to undergo a Darzens reaction with various aromatic aldehydes.[13,14]) However, if the sulfonium ylides are too stabilized and/or sterically hindered, their reactivities with carbonyl compounds may drop off again. Thus, sulfonium fluorenylides are known to be limited in the types of carbonyl compounds with which they will form epoxides.[4,15] Also, *p*-nitrobenzylsulfonium salts might give the corresponding stilbene instead of epoxides, since the carbene forms readily.[7]

Conclusions.—The present work demonstrates that a sulfonium substituent is in the same class in ability to make α-methylene groups acidic and thereby "activate" them for carbonyl condensation reactions as are the well-known "activating" groups, such as keto groups. Consequently, in order to perform such condensation reactions with sulfonium salts, one need not always resort to the previously used low-temperature preparations of ylides in extremely basic, nonaqueous systems. Direct reactions in basic aqueous or alcoholic media, with resulting advantages of convenience and economy, often will serve. The scope of synthetically useful reactions of aqueous sulfonium salts, carbonyl compounds, and NaOH to produce oxiranes is quite broad, but is subject to structural factors and reaction conditions. Within limits, increasing acidity of the sulfonium salts, and decreasing base-catalyzed self-reactivity of the carbonyl compounds will favor the formation of

(12) M. Yoshimine and M. J. Hatch, *J. Amer. Chem. Soc.*, **89**, 5831 (1967).
(13) E. Kleucker, *Chem. Ber.*, **55B**, 1634 (1922).
(14) E. Bergmann, and J. Hervey, *ibid.*, **62B**, 893 (1929).
(15) Johnson and LaCount, ref 8.

the desired epoxy products. Many side reactions are possible, especially with the benzylic and *allylic* sulfonium salts.

Experimental Section[16]

Trimethylsulfonium Chloride.—Crystalline trimethylsulfonium iodide was prepared similarly to the method of Emeleus and Heal[17] by the reaction of methyl iodide and dimethyl sulfide. The sulfonium iodide (430 g), dissolved in water (*ca.* 900 ml), was converted to trimethylsulfonium chloride by passage through a bed (3.2 l.) of chloride-form anion-exchange resin (Dowex 1, 8% cross-linked 50–100 mesh[18]). The elutate fractions were monitored by potentiometric titrations for ionic chloride and iodide ($AgNO_3$), and the iodide-free fractions (83% yield) were concentrated (to *ca.* 5 *M*) *in vacuo* at room temperature, by use of a rotary evaporator.

Triethylsulfonium bromide was prepared in aqueous solution by refluxing a stirred mixture of ethyl sulfide (100 g, 1.11 mol), ethyl bromide (123 g, 1.11 mol), ethanol (120 ml), and water (35 ml) for 20 hr. The final aqueous phase (120 ml), separated and washed with benzene, contained the sulfonium bromide (2.78 mol) in 30% conversion, and HBr (hydrolysis product) in 2.3% conversion, as shown by ionic bromide and acidity titrations ($AgNO_3$ and NaOH, respectively).

Allyldimethylsulfonium chloride was prepared in aqueous solution by stirring at room temperature a mixture of allyl chloride (282 g, 3.8 mol), dimethyl sulfide (255 g, 4.1 mol), and water (300 ml). After 8 days the separated, nitrogen-blown aqueous solution contained 89% yield of the product (4.7 *M*), as shown by analysis for ionic chloride. (Hydrolysis was less than 5%.)

Benzyldimethylsulfonium chloride was prepared in aqueous solution by stirring at reflux (35–40°) a mixture of benzyl chloride (2000 g, 15.8 mol), dimethyl sulfide (1080 g, 17.4 mol), and water (2.4 l.). After 20 hr, the separated, nitrogen-blown solution contained the product (3.4 *M*) in essentially quantitative yield, as shown by analysis for ionic chloride. (Hydrolysis was less than 1%.)

Benzylbis(2-hydroxyethyl)sulfonium chloride was prepared in aqueous solution by heating a stirred mixture of benzyl chloride (690 g, 5.5 mol), bis(2-hydroxyethyl) sulfide (665 g, 5.5 mol), and water (550 ml) at about 70° for 2 hr. The mixture was allowed to stir overnight without heating to give a single-phase, aqueous solution of the sulfonium salt. Ionic chloride analyses indicated 95% conversion to sulfonium salt and 5% hydrolysis.

Styrene Oxide from Trimethylsulfonium Chloride.—The reaction was run (hood) in a three-neck flask, equipped with heating mantle, mechanical stirrer, and reflux condensor. To a stirred mixture of the sulfonium salt (50 ml, aqueous, 0.28 mol), benzaldehyde (28 ml, 0.28 mol), benzene (200 ml), *n*-propyl alcohol (100 ml), and water (12 ml) at 50°, aqueous NaOH (21 ml, 0.39 mol) was added rapidly. There was little or no heat evolution. The mixture was heated at reflux (*ca.* 70°) for 1 hr and cooled, and the separated oil layer was washed with water and dried ($MgSO_4$). Gas chromatographic analysis comparing known styrene oxide (Aldrich Chemical Co.,) indicated styrene oxide (68% yield) was present in the product oil. Vacuum distillation (seven-plate Vigreux column) yielded styrene oxide (22 g, 69–73°, 10 mm) which contained about 7% benzaldehyde, as shown by comparison of the infrared spectra with known standards.

1,2-Epoxypropylbenzene from Triethylsulfonium Bromide.—To a stirred mixture of the sulfonium salt (100 ml, aqueous, 0.28 mol), benzaldehyde (30 ml, 0.30 mol), benzene (200 ml), ethanol (80 ml), and water (15 ml) at 50°, was added rapidly aqueous NaOH (22 ml, 0.42 mol). There was a little heat evolution. The mixture was heated at reflux (*ca.* 70°) for 2 hr and cooled, and the oil phase was separated. Semiquantitative chemical analysis[9] indicated that product oxirane was present (over 70% yield). Distillation (as above) yielded a mixture of *cis*- and *trans*-2-methyl-3-phenyloxirane (26 g, 47–50°, 2 mm) which contained about 10% benzaldehyde, as shown by infrared analysis. Reported for racemic *cis*- and *trans*-2-methyl-3-phenyloxiranes, respectively, are *cis*, bp 83–84° (13 mm); *trans*, bp 88° (13 mm).[19] Benzaldehyde could be extracted from the product oxirane mixture by use of aqueous Girard's reagent, $NH_2NHCOCH_2{}^+N(CH_3)_3\ Cl^-$. Comparison of the infrared spectra with reported spectra[20] identified the oxirane products. The *trans* product appeared to be dominant, based on the spectra.

Reaction of Sulfonium Salts with NaOH in the Absence and Presence of Benzaldehyde.—The following systems were studied: (A) triethylsulfonium bromide (aqueous, 5.0 ml, 17 mmol), NaOH (aqueous, 1.20 ml, 23.5 mmol), water (1.0 ml), ethanol (4.0 ml), benzene (10.0 ml), NaCl (2.5 g); (B) like A, minus NaCl and plus benzaldehyde (1.7 ml, 17 mmol); (C) trimethylsulfonium chloride (aqueous, 2.5 ml, 13.7 mmol), NaOH (aqueous 1.00 ml, 19.7 mmol), water (1.0 ml), *n*-propyl alcohol (5.0 ml), benzene (10.0 ml), NaCl (2.5 g); (D) like C minus NaCl and plus benzaldehyde (1.7 ml, 17 mmol). Each system, minus NaOH, was heated to 50° with stirring. Then the NaOH solution was added and the system was heated at reflux for the appropriate time, quenched in water, and analyzed for residual NaOH by titration with acid. The results follow: (A) in 15, 30, and 60 min, 15, 24, and 30% NaOH was consumed, respectively; (B) in 5, 15, and 30 min, 42, 58, and 65% NaOH was consumed, respectively; (C) in 15, 30, and 60 min, 28, 31, and 34% NaOH was consumed, respectively; (D) in 5, 15, and 30 min, 60, 65, and 80% NaOH was consumed, respectively.

2-Vinyloxirane and By-product from Allyldimethylsulfonium Chloride.—A mixture of the sulfonium salt (75 ml, aqueous, 0.33 mol), CH_2O (75 ml, aqueous 1.00 mol, CH_3OH inhibitor), and benzene (100 ml) was stirred at 45°. Then aqueous NaOH (23 ml, 0.45 mol) was added in three portions during 3 min, and the temperature rose to 68°. The reaction was allowed to proceed without additional heating until the temperature dropped to 40°; then the separated oil phase was washed with water. The washed oil contained 2-vinyloxirane (7% yield) as shown by gas chromatography, using an authentic sample for comparison. In related experiments at higher temperatures, using toluene instead of benzene, the unwashed product oil was distilled (seven-plate Vigreux column). The distillate (37–40°) contained both 2-methoxyoxirane (12% yield) and 2-vinyloxirane (8% yield), as shown by comparison of infrared spectra of distillate cuts with the spectra of known samples.

2-Phenyl-3-vinyloxirane and By-products from Allyldimethylsulfonium Chloride.—To a stirred mixture of the sulfonium salt (63 ml, aqueous, 0.30 mol), benzaldehyde (30 ml, 0.30 mol), and toluene (100 ml) which was heated to 35°, was added aqueous NaOH (25 ml, 0.47 mol) over a period of 1 min. The temperature rose to 63°, and after 15 min at slightly above 55°, the oil layer (143 g) was separated. The reaction was repeated five times on the same scale, and once using threefold quantities; then the oil layers were combined (958 g out of 1140) and distilled (20-plate Podbelniak column). The cold trap cut (27–47.5°, 100 mm) contained considerable propylene oxide (24 g, 21% yield). Benzaldehyde (58–60, 10 mm) was recovered (89 g, 42%). A product, which apparently was 3-butenyl methyl sulfide (61–63.5°, 100 mm, equals[21] approx 122°, 760 mm; lit.[22] for the analogous butyl methyl sulfide, 123°, at 760 mm), was isolated (26 g, 12% yield). The infrared spectrum showed vinyl absorption (6.10 and 10.95 μ) and the nmr spectrum was consistent with this structure. Peaks were obtained at δ 2.03 (singlet, 3 H), 2.1–2.8 (multiplet, 4 H), 5.4–6.2 (multiplet, 1 H), and 4.8–5.2 ppm (multiplet, 2 H). Product of this structure could arise by a known type of ylide rearrangement.[10]

2-Phenyl-3-vinyloxirane (49–50.5°, 0.7 mm, equals[21] ~220°, 760 mm; lit.[23] 99–101°, 16 mm, equals[21] ~218°, 760 mm) was obtained as a mixture of *cis* and *trans* isomers (77 g, 27% yield). Analysis[9] for epoxide groups gave 84% of the theoretical value, but the method used is expected[9] to give low results. The oxirane (69 g) was redistilled (seven-plate Vigreux column), yielding

(16) When dimethyl sulfide was a reactant or product, a good hood was used. All melting points are uncorrected. Infrared spectra were obtained on a Beckman IR-5 instrument, nmr spectra on a Varian A-60 instrument. Extensive assistance in conducting the experimental work was provided by Mr. Hugh B. Smith and Mr. John A. Dillon of this laboratory. The nmr analyses were provided by the Chemical Physics Laboratory (The Dow Chemical Co.); combustion microanalyses were provided by the Dow Special Services Laboratory. Purity analyses by freezing point curves were provided by the Dow Analytical Laboratory.

(17) H. J. Emeleus and H. G. Heal, *J. Chem. Soc.*, 1126 (1946).

(18) Product of The Dow Chemical Co., Midland, Mich.

(19) F. Fisher, *Chem. Ber.*, **89**, 2438 (1956).

(20) C. M. Froltz and B. Witkop, *J. Amer. Chem. Soc.*, **79**, 203 (1957).

(21) F. J. Zuiderweg, "Laboratory Manual of Batch Distillation," Interscience Publishers, Inc., New York, N. Y., 1957, p 120.

(22) "Handbook of Chemistry and Physics," 46th ed, The Chemical Rubber Publishing Co., Cleveland, Ohio, 1965, p C-552.

(23) D. Abragam and Y. Deux, *Compt. Rend.*, **205**, 285 (1937).

four cuts at 0.5 mm: (1) 46°, 3.8 g; (2) 46–50°, 10.8 g; (3) 50–52°, 25.0 g; (4) 52°, 29 g (residue, 0.5 g). Gas chromatography (9.5 ft × 3/16 in., diethylene glycol succinate on acid-washed silanized Chromosorb, on-column injection, 95°) showed two main peaks in all the cuts, at ratios of 48:48, 34:66, 34:65, 24:76, 10:90, respectively. Gas chromatography at 125° apparently produced isomerization. *Anal.* Calcd for $C_{10}H_{10}O$: C, 82.2; H, 6.90. Found for cut 3: C, 82.6; H, 7.1.

Propylene Oxide from Allydimethylsulfonium Chloride and Sodium Hydroxide.—To a mixture of the sulfonium salt (138 ml, 0.69 mol) and NaOH (70 ml, 0.69 mol) stirred and rapidly heated to 60°, benzene (~250 ml) was added during a period of 20 min. After another 30 min at about 70°, the oil phase was separated, washed twice with equal volumes of water, dried and analyzed[9] for epoxide content: found 48% yield. Distillation (seven-plate Vigreux column) gave product (35–38°, 743 mm) which was shown to be a mixture (about 50:50) of propylene oxide and dimethyl sulfide (25.2 g, oxide yield 35%). The analysis was made by comparison of the infrared spectra with spectra of known mixtures of the two compounds.

Styrene Oxide from Benzyldimethylsulfonium Chloride.—To a well-stirred mixture of the sulfonium salt (59.6 ml, aqueous, 0.165 mol), CH_2O (37.5 ml, aqueous, 0.465 mol, CH_3OH inhibitor), and ethylbenzene (75 ml) at 55°, NaOH solution was added rapidly (36.0 ml, aqueous, 0.70 mol). The temperature rose quickly to 87° (reflux). After 2 min, ice was added to cool the mixture, and the oil phase (92 g) was separated. By analysis[9] it contained 87% yield of styrene oxide, based on starting sulfonium salt. Most of the oil phase (71 g) was distilled (seven-plate Vigreux column). Styrene oxide (71–73°, 10 mm) which was 94% pure, based on epoxide analysis,[9] was obtained (15 g). By freezing-point analysis (fp −38.14°) the mole per cent purity was 96.8. Thus the isolated yield was over 90% if the impurities had about the same molecular weight as styrene oxide itself.

Stilbene Oxide from Benzyldimethylsulfonium Chloride.—The sulfonium salt (100 ml, aqueous, 0.33 mol), ethanol (200 ml), and benzaldehyde formed a clear solution on mixing. NaOH (50 ml, 0.05 mol) was added, the mixture was heated to 65°, and more NaOH was added (35 ml, 0.435 mol). The solution clouded immediately and cleared on addition of more ethanol (75 ml). After heating at reflux (70°) for about 1 hr, the mixture was diluted with water (1000 ml) and extracted with CH_2Cl_2 (300 ml). Evaporation of the CH_2Cl_2 layer gave a heavy oil which crystallized. The white solid was slurried in a small amount of methanol, filtered, washed with methanol, and dried, (mp 67–70°, 28 g, 45% yield, lit.[7] 68° for *trans*-stilbene oxide). The infrared spectrum was identical with that of authentic *trans*-stilbene oxide.

A similar reaction of benzylbis(hydroxyethyl)sulfonium chloride, NaOH, and benzaldehyde gave a 19% yield of *trans*-stilbene oxide.

Large-scale preparations, using benzyldimethylsulfonium chloride (1000 ml, 3.4 mol), excess benzaldehyde (686 ml, 6.86 mol), excess NaOH (284 ml, aqueous, 5.6 mol), and toluene (1500 ml) and heating at reflux (*ca.* 80° for 30 min) gave 85% corrected[9] analytical yield of stilbene oxide. Pure *trans* isomer easily was isolated (57% yield) by evaporating (vac) most of the toluene and cooling the concentrate.

1,2-Epoxypropylbenzene from Benzyldimethylsulfonium Chloride.—The sulfonium salt (150 ml, aqueous 0.54 mol) and NaOH (55 ml, 0.54 mol) were stirred and heated to 60°, and a solution of CH_3CHO (32 ml, 0.54 mol, in 150 ml of benzene) was added over a period of 10 min. The temperature rose gradually to about 64° during the addition. Heating the mixture at reflux for another 20 min gave a slightly dark oil phase. The aqueous phase (160 ml) contained 0.136 equiv of base, so 76% of the theoretical amount of NaOH had reacted. The separated oil phase (200 g) contained 0.27 equiv of epoxide[9] (67% yield, based on NaOH reacted). Distillation of the oil phase (seven-plate Vigreux column) yielded 1,2-epoxypropylbenzene (40–44°, 0.5 mm, 26 g, 48% yield based on NaOH reacted). Its infrared spectrum was very similar to the spectrum of 1,2-epoxypropylbenzene, prepared by reaction of triethylsulfonium chloride, benzaldehyde, and NaOH (see above), and indicated that the *trans* product was dominant.

2-Phenyl-3-vinyloxirane from Benzyldimethylsulfonium Chloride.—Acrolein (25 ml, 0.44 mol) in benzene (150 ml) was added over a period of 10 min to a well-stirred mixture of the sulfonium salt (160 ml, aqueous, 0.44 mol) and NaOH (50 ml, aqueous, 0.47 mol), which had been rapidly preheated to 60°. The mixture was heated at reflux (68–70°) for an additional 15 min, then the oil phase was separated (148 g) and analyzed[9] for epoxide content (16% yield). Distillation (seven-plate Vigreux column) of the oil layer gave a fraction (13 g, 50–53°, 0.9–0.8 mm) whose infrared spectrum, on comparison with that of known 34/65 *cis/trans* mixture of 2-phenyl-3-vinyloxirane,[24] showed the fraction was about 50% 2-phenyl-3-vinyloxirane. The quantitative estimation was made from the comparative intensities of the vinyl (10.13 and 10.8 μ) and epoxide ring (8.00 and 11.43 μ) infrared absorption peaks. Chemical analysis[9] of the fraction for epoxide functionality also indicated about 50% 2-phenyl-3-vinyloxirane content.

2,2-Dimethyl-3-phenyloxirane from Benzyldimethylsulfonium Chloride.—The sulfonium salt (100 ml, 0.30 mol), acetone (60 ml, 0.83 mol), and *n*-hexane (150 ml) were mixed and stirred at 24°. Then NaOH (38 ml, aqueous, 0.47 mol) was added. The temperature rose slightly to 27°. The mixture was heated at reflux (50°), and NaOH consumption was found by titration of samples with acid. After 20 min, NaOH consumed was about 0.26 equiv; after 45 and 60 min, about 0.33 equiv. The oil phase was separated (208 ml) and filtered, and the volatile solvent was evaporated.

Chemical analysis[9] of the final oil (26 g) for epoxide content indicated that it contained at least 40% yield. Part (12 g) of the oil was distilled (seven-plate Vigreux column) to give 2,2-dimethyl-3-phenyloxirane (10.5 g, 57% yield, 77°, 10 mm, equals[21] ~200°, 760 mm; lit.[25] 87–90°, 15 mm, equals[21] ~200–204°, 760 mm). *Anal.* Calcd for $C_{10}H_{12}O$: C, 81.0; H, 8.1. Found: C, 80.8; H, 7.9.

2,3-Diphenyl-2-methyloxirane from Benzyldimethylsulfonium Chloride.—To a stirred mixture of the sulfonium salt (100 ml, aqueous, 0.30 mol), acetophenone (120 ml, 1.03 mol), and hexane (150 ml) at room temperature was added NaOH (38 ml, aqueous, 0.46 mol). The temperature rose 2°. The mixture was heated at reflux (50–60°) for about 2 hr. The oil layer then was separated and the solvent was evaporated. Chemical analysis[9] of the residue (141 g) for epoxide content indicated at least 45% yield. The oil was filtered and part (94 g) was distilled at 0.7 mm (seven-plate Vigreux column). Decomposition was evident in the pot material as the product began to distill and only a small amount was collected (3.6 g, 97–115°, 0.7–1.5 mm). The distillate formed a white solid, mp 45–47° (lit.[26] 45–47° for 2,3-diphenyl-2-methyloxirane).

Registry No.—Trimethylsulfonium chloride, 3086-29-1; triethylsulfonium bromide, 3378-18-5; allyldimethylsulfonium chloride, 19766-51-9; benzyldimethylsulfonium chloride, 14182-14-0; benzylbis(2-hydroxyethyl)sulfonium chloride, 19766-53-1.

(24) Redistilled product, cut 3, from the reaction of allyldimethylsulfonium chloride, benzaldehyde, and NaOH (see above).

(25) J. Levy and A. Tabart, *Bull. Soc. Chim. Fr.*, **49**, 1776 (1931).

(26) F. Kayser, *Ann. Chim.*, **11**, 236 (1936).

Diazocine Chemistry. V. Synthesis and Rearrangement of Dibenzo(*b*,*f*)(1,4)diazocine-6,11(5H,12H)-dione

WILLIAM W. PAUDLER AND ANDREW G. ZEILER

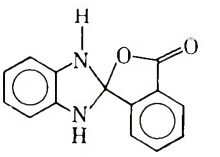
Department of Chemistry, Cippinger Laboratories, Ohio University, Athens, Ohio 45701

Received November 20, 1968

It has been shown that the condensation of *o*-phenylenediamine with diethyl phthalate, in the presence of sodium hydride, yields the dibenzo-1,4-diazocine derivative **6**. Contrary to reports in the literature, this compound has never been prepared. Diazocine **6**, when heated at its melting point, forms the dehydrated and ring-contracted compound **5**. Base hydrolysis of **6** yields the benzimidazole derivative **2**. A similar ring-contracted compound **13** (isolated as ester**14**) is obtained when **6** is treated with phosphorus pentachloride. The N,N′-dimethyl derivative of **6** (compound **10**), when treated with base, yields the zwitterionic ring-contracted compound **15**, which, upon heating, is converted into the methyl *o*-2-(3-methylbenzimidazoyl)benzoate (**16**). Monobenzo-1,4-diazocine (**18**) was prepared from diethy succinate and *o*-phenylenediamine and was thermally rearranged to the ring-contracted compound **19**.

The condensation of *o*-phenylenediamine with various derivatives of phthalic acid has been the subject of numerous publications.[1] The use of phthalic anhydride and *o*-phenylenediamine affords, depending upon the reaction conditions, compounds **1**–**5** (Scheme I). Stetter and coworkers[2] have reported that the condensation of *o*-phenylenediamine with phthaloyl chloride, under high-dilution conditions, affords the dibenzodiazocine derivative **6**. Compounds **1**, **2**, and **6** are clearly isomeric, while substances **3** and **4** are formed from the condensation of 2 mol of the diamine with 1 mol of phthalic anhydride and *vice versa*, respectively. Imidazopyrrole **5** can be envisioned to be formed from the dehydration of compounds **1** and/or **2**.

There remains the possibility of the existence of yet a fourth compound that is isomeric with the one to one condensation products **1**, **2**, and **6**. This substance would be lactone **7**.



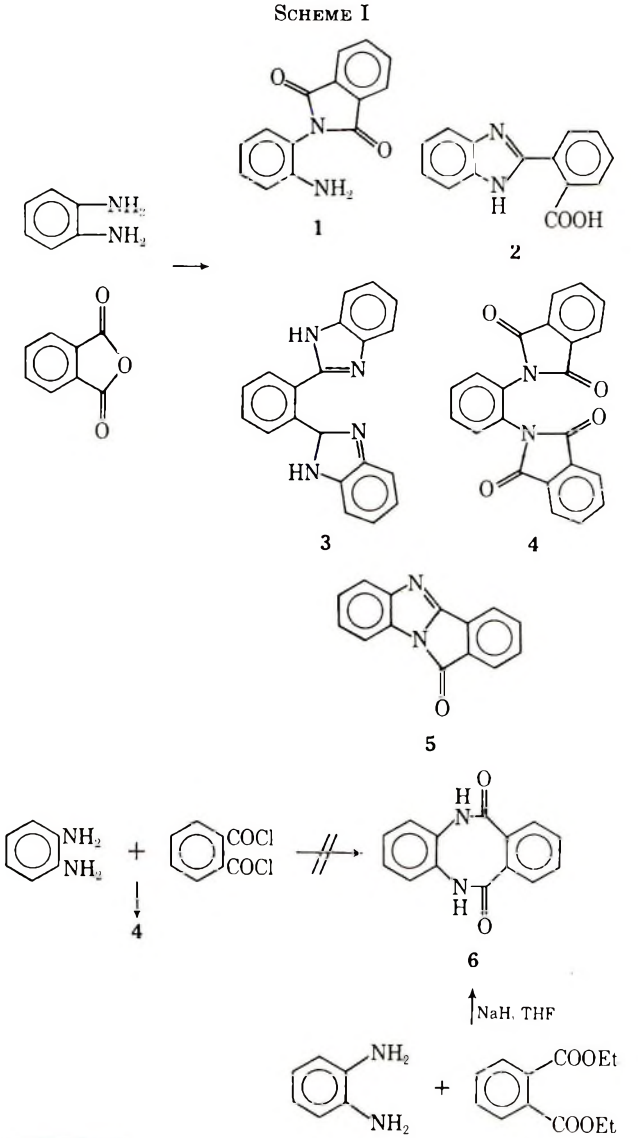
7

Stetter's compound (presumably **6**) was described as melting at 300° and as being readily soluble in benzene and ethanol. The appropriate elemental analysis and molecular weight of this compound were also reported.

In view of our interest in diazocine chemistry, this substance became of some interest to us as a potential precursor for other 1,4-diazocine derivatives. Repetition of the reported condensation procedure afforded a compound which melts at 298° and has the reported solubility characteristics. The mass spectrum of this compound is, however, *not in agreement* with the assigned structure, since the mass spectrometric molecular weight (*m*/*e*) is 368 and not the expected 238 mass units. This molecular weight is in agreement with that expected if the compound is in fact the phthalimide derivative **4**. In fact, the melting point and solubility properties of "Stetter's compound" are also in agreement with the phthalimide structure **4**.[1d] This rather disappointing result made it necessary to consider the development of a new synthetic approach to the preparation of the desired diazocine **6**.

In a preliminary communication[3] we have described the synthesis of dibenzo(*b*,*f*)(1,5)diazocine (**9**) from

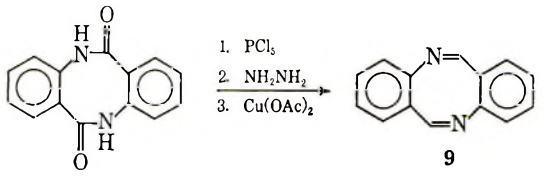
SCHEME I



(1) (a) J. Arient and J. Marhan, *Collect. Czech. Chem. Commun.*, **26**, 98 (1961); (b) L. Guglialmelli, P. Chanussot, and C. L. Ruiz, *Bull. Soc. Chim. Fr.*, **51**, 80 (1932); (c) R. Meyer and H. Luders, *Ann.*, **415**, 29 (1918); (d) B. A. Porai-Koshits and M. M. Antoshul'skaya, *J. Gen. Chem. USSR*, **13**, 339 (1943), *Chem. Abstr.*, **38**, 1234 (1944).

(2) H. Stetter, L. Marx-Moll, and H. Rutzen, *Chem. Ber.*, **91**, 1775 (1958).

(3) W. W. Paudler and A. G. Zeiler, *Chem. Commun.*, 1077 (1967).



8 9

diamide **8**. The latter compound was prepared by condensing ethyl anthranilate with itself in the presence of sodium hydride. The application of this condensation to the preparation of the 1,4-diazocine **6** represents a logical extension. In fact, when *o*-phenylenediamine was condensed with diethyl phthalate, there was obtained a 71% yield of a compound which analyzed correctly for diamide **6**. The mass spectrometric molecular weight of this compound, 238, is also in agreement with the diamide structure. The alternate lactone structure **7** can be eliminated from consideration since the condensation product is insoluble in acid and its infrared spectrum is void of a lactone carbonyl absorption peak. The carbonyl absorption in the infrared region (1695 cm^{-1}) of compound **6** is the same as that observed for the 1,5-diazocine derivative **8**. These data confirm the assigned structure (**6**) for the condensation product of *o*-phenylenediamine and diethyl phthalate in the presence of sodium hydride.

The conversion of diamide **6** into dichloro derivative **11** was attempted in a fashion similar to that described for the preparation of 6,12-dichlorodibenzo(*b*,*f*)(1,5)-diazocine.[4] However, the product resulting from the action of phosphorus pentachloride on diamide **6** had a mass spectrometric molecular weight of 256 and showed the typical "doublet" due to the presence of one chlorine atom.

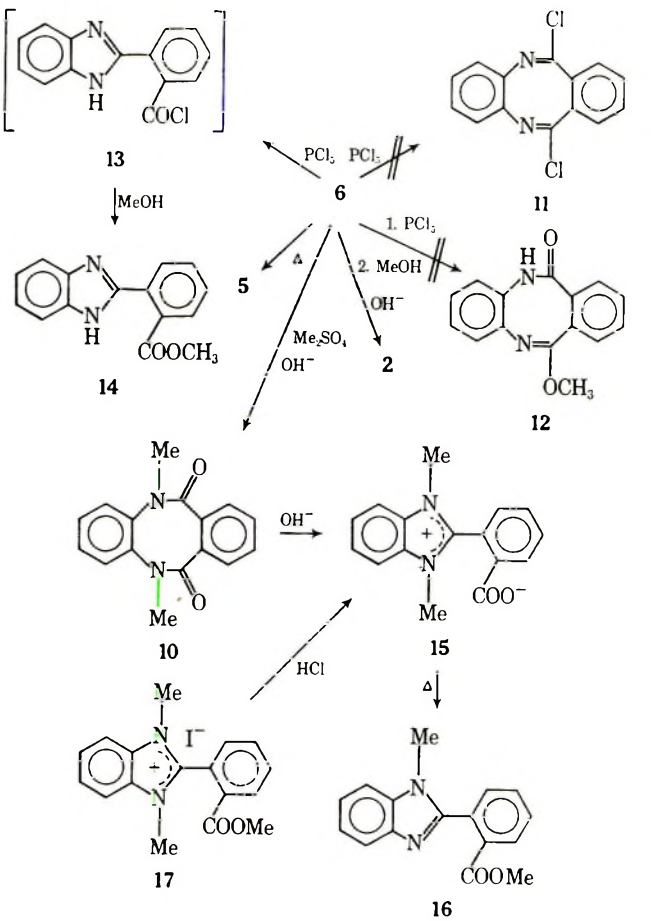
Treatment of this unstable compound with methanol gave a monomethyl derivative whose pmr spectrum is considerably different from that expected for a structure such as **12**. The aromatic protons, which appear as two peaks in the parent compound and in its dimethyl derivative (**10**) (*cf.* Experimental Section), appeared as a rather complex multiplet with a one-proton deshielded multiplet as a distinct feature suggesting rearrangement of the ring skeleton during the halogenation reaction.

Consideration of the possible rearrangement paths open to diazocine **6** and the established ring contractions observed in diazepine derivatives[5] indicate that the chloro compound and the methyl derivative might be compounds **13** and **14**, respectively. Ester **14** is a known compound and can be prepared[6] from the imidazopyrrole derivative **5**. The identity of the methyl ester was readily established by a comparison of the melting point and infrared and pmr spectra.

Since an analysis of the mass spectrum of diazocine **6** revealed the curious fact that it loses 18 mass units with great facility, we decided to study its thermal stability. When compound **6** was heated at 300°, the yellow crystalline material which sublimed was shown to be identical with an authentic sample of compound **5**.[1a] Thus, a facile thermal ring contraction takes place in analogy with the ring contraction that occurs upon treatment of compound **6** with phosphorus pentachloride.

The base hydrolysis of diazocine **6** also reveals its tendency toward ring contraction, since the only product that is obtained is the known *o*-2-benzimidazoylbenzoic acid **2** (*cf.* Scheme II).[1a]

SCHEME II



The N,N′-dimethyl derivative **10**, when treated with sodium hydroxide, yields a compound that is isomeric with the starting material (**10**). The pmr spectrum of this substance reveals two identical methyl groups and the complex aromatic proton system typical of the various ring-contracted products described earlier. The infrared spectrum of the new compound shows absorption peaks typical for the carboxylate anion. Thus structure **15** is suggested as the most likely one for this hydrolysis product and is confirmed by an unequivocal synthesis of this zwitterionic compound from the known[7] ester **17**.

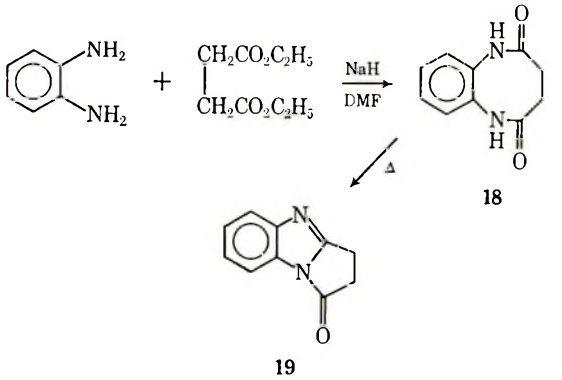
Finally, compound **15** can be thermally rearranged to methyl ester **16** whose structure proof rests upon a comparison of its pmr and infrared spectra with that of compound **14** (*cf.* Experimental Section).

An extension of the condensation reaction which, ultimately, could have some bearing upon a better understanding of the stability of these ring systems, involves the condensation of diethyl succinate with *o*-phenylenediamine under the conditions which afford dibenzo compound **6** in such excellent yield. When this reaction was investigated, there was obtained a compound which analyzed correctly for the expected

(4) G. Schroeter, *Chem. Ber.*, **52**, 2224 (1919).
(5) M. Israel, L. C. Jones, and E. J. Modest, *Tetrahedron Lett.*, 4811 (1968).
(6) J. Arient, L. Havlickova, and J. Slosar, *Collect. Czech. Chem. Commun.*, **29**, 3115 (1964).
(7) H. Rupe and K. G. Thiess, *Ber.*, **42**, 4287 (1909).

benzodiazocine **18**. The pmr spectrum of this substance shows the presence of a four-proton singlet (based upon the molecular formula) at δ 2.92 typical of slightly deshielded methylene protons. In addition to this singlet there appears a typical A_2B_2 aromatic proton multiplet centered at δ 7.54. These data clearly confirm the assigned structure **18** (*cf.* Scheme III).

SCHEME III



That this compound, in analogy with the dibenzo derivative **6**, is also subject to facile ring contraction was shown by the observation that it is readily transformed into the known imidazopyrrole **19**[1c] when it is heated at its melting point.

Experimental Section[8]

Dibenzo(*b*,*f*)(1,4)diazocine-6,11(5H,12H)-dione (6).—To a stirred solution of 32.4 g (0.3 mol) of *o*-phenylenediamine and 66.6 g (0.3 mol) of diethyl phthalate in 600 ml of dry tetrahydrofuran in a 2-l. flask was added 29 g (0.6 mol) of a 50% oil dispersion of sodium hydride. The reaction mixture was stirred at room temperature until a vigorous reaction began. The mixture was then cooled in ice and stirred for 12 hr, followed by stirring at room temperature. The resulting dark solution was diluted with 500 ml of water and acidified with aqueous HCl. The white solid that precipitated was filtered and washed with ethanol and benzene to afford 50.8 g (71%) of compound **6**. An analytical sample was obtained by recrystallization from dimethylformamide: mp 301–302.5°; ir (KBr) 3180 cm^{-1} (N–H), 1695 (C=O); pmr (CF_3COOH) δ 7.59 (s), 7.35 (s); mol wt, 238 (mass spectrum).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.22; N, 11.76. Found: C, 70.71; H, 4.39; N, 11.72.

5,12-Dimethyldibenzo(*b*,*f*)(1,4)diazocine-6,11-dione 10.—To a cooled, stirred suspension of 10 g (0.042 mol) of diamide **6** in 100 ml of 20% NaOH was added 10 ml of dimethyl sulfate. The reaction mixture was stirred for 2 hr at room temperature and the resulting precipitate was filtered and recrystallized from ethanol to afford 6.8 g (60%) of compound **10**: mp 262–265°; ir (KBr) 1695 cm^{-1} (C=O); pmr ($CDCl_3$) δ 7.25 (d, 8), 3.45 (s, 6); mol wt, 266 (mass spectrum).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.23; N, 10.52. Found: C, 72.08; H, 5.44; N, 10.55.

Reaction of Compound 6 with Phosphorous Pentachloride.—A suspension of 3 g (0.012 mol) of **6** and 6 g (0.029 mol) of PCl_5 in 100 ml of $CHCl_3$ was refluxed for 0.5 hr. Removal of the solvent gave a pale yellow residue. A small portion of this material was washed with tetrahydrofuran to afford a white solid (**13**) which rapidly turns yellow on standing: mp 211–212° dec; mass spectrum *m/e* (per cent of P) 256 (100), 258 (25).

The remaining solid was warmed with 100 ml of methanol and the resulting solution was diluted with 100 ml of water and 10 ml of aqueous ammonia. The white solid that precipitated was collected and afforded 2.7 g (86%) of methyl *o*-2-benzimidazoyl benzoate (**14**): mp 193°; ir (KBr) 1718 cm^{-1} (C=O); pmr ($CDCl_3$) δ 8.28 (m, 1), 7.45 (m, 7), 3.83 (s, 3). This material was identical with an authentic sample prepared by the method of Arient, Havlickova and Slosar.[6]

Thermal Dehydration of Compound 6.—A 1-g sample of diamide **6** was heated at 300° (0.1 mm), affording 0.75 g (85%) of isoindolo(2,1-*a*)benzimidazol-11-one (**5**) as a yellow sublimate. This material (mp 213–214°) was identical in every respect (mp 213–214°, ir, pmr) with a sample prepared by the method of Arient and Marhan.[1a]

Base Hydrolysis of Compound 6.—A solution of 3 g (0.012 mol) of **6** in 30 ml of 10% NaOH was refluxed for 48 hr. After cooling, the solution was neutralized with acetic acid and the resulting precipitate of *o*-2-benzimidazoylbenzoic acid was collected (2.2 g, 73%). This material (**2**) (mp 271–272°) was identical (mp 271–272°, ir, pmr) with a sample prepared by the method of Arient and Marhan.[1a]

Base Hydrolysis of the Dimethyl Compound 10.—A suspension of 3 g (0.011 mol) of compound **10** in a solution of 1 g of NaOH in 20 ml of water and 10 ml of dioxane was refluxed for 12 hr. The mixture was cooled, acidified with acetic acid, and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave a heavy oil which, when boiled with tetrahydrofuran, yielded 1.85 g (61%) of *o*-2-(1,3-dimethylbenzimidazolium) benzoate (**15**). An analytical sample was obtained by recrystallization from a mixture of dioxane and water (20:1, v/v): mp 294–295°; ir (KBr) 1618 and 1580 cm^{-1} (COO^-); pmr (D_2O) δ 7.35 (m, 1), 7.00 (m, 7), 2.95 (s, 6); mol wt, 266 (mass spectrum).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.23; N, 10.52. Found: C, 72.08; H, 5.44; N, 10.44.

***o*-2-(1,3-Dimethylbenzimidazolium) Benzoate (15).**—Methyl *o*-2-(1-methylbenzimidazoyl)benzoate methiodide (**17**) was prepared by the method of Rupe and Thiess.[7] This material (1.5 g, 3.7 mmol) was dissolved in 50 ml of 4 *N* HCl and refluxed for 12 hr. The solution was basicified with NaOH, neutralized with acetic acid, and exhaustively extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated to yield 0.73 g (75%) of **15** as white crystals. This compound was identical in every respect (melting point, ir, pmr, mass spectra) with that obtained from the hydrolysis of compound **10**.

Thermal Rearrangement of Compound 15.—A 1-g sample of **15** was heated at 320° (0.1 mm) for 12 hr. The resulting oily sublimate was recrystallized from a mixture of acetone and water (1/1, v/v) to afford 0.6 g (60%) of methyl *o*-2-(3-methylbenzimidazoyl)benzoate: mp 132–133°; ir (KBr) 1718 cm^{-1} (C=O); pmr ($CDCl_3$) δ 8.2–7.20 (m, 8), 3.64 (s, 3), 3.53 (s, 3).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.23; N, 10.52. Found: C, 71.88; H, 5.38; N, 10.59.

3,4-Dihydro-1,6-benzodiazocine-2,5(1H,6H)-dione 18.—To a solution of 10.8 g (0.1 mol) of o-phenylenediamine and 17.4 g (0.1 mol) of diethyl succinate in 50 ml of dimethylformamide was added 10 g of a 50% oil dispersion of NaH. After a few minutes and exothermic reaction began and the reaction mixture was cooled in an ice bath. After the initial reaction had subsided, the mixture was heated on a steam bath for 1 hr. Water (200 ml) and concentrated HCl (50 ml) were added and the resulting precipitate was collected and washed with benzene. Recrystallization from dimethylformamide gave 4.7 g (25%) of pure **18**: mp 264–265.5° dec; ir (KBr) 3180 cm^{-1} (N–H), 1700 (C=O); pmr (CF_3COOH) δ 7.94 (A_2B_2, 4), 2.92 (s, 4); mol wt, 190 (mass spectrum).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H. 5.30; N, 14.73. Found: C, 63.23; H, 5.44; N, 14.76.

Thermal Dehydration of Compound 18.—When a 0.5-g sample of compound **18** was heated for 5 min at 270° there sublimed 0.28 g (62%) of compound **19**, mp 171–172°. This material is identical with a sample prepared by the method of Meyer and Luders.[1c]

Registry No.—**6**, 4482-14-8; **10**, 19799-45-4; **13**, 19766-46-2; **14**, 1780-94-5; **15**, 19779-46-5; **18**, 19766-48-4; methyl *o*-2-(3-methylbenzimidazoyl)benzoate, 19766-49-5.

Acknowledgment.—This investigation was supported in part by a research grant (CA-07917-03) from the National Cancer Institute, U. S. Public Health Service.

(8) Nmr spectra were obtained with a Varian A-60 spectrometer. Mass spectra were obtained with a Hitachi-Perkin Elmer RMU-6E instrument equipped with a solid sample injector. The ionizing voltage employed was 80 V. Elemental analyses were done by Mrs. K. Decker of this department.

Synthesis and Reactions of Isoquinuclidone Diesters[1]

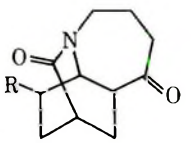
ROBERT L. AUGUSTINE AND RUSSELL F. BELLINA[2]

Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079

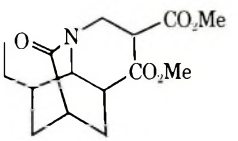
Received October 21, 1968

3-Oxo-6-carbomethoxy-2-azabicyclo[2.2.2]octane (**13**) and its 7-ethyl derivative **15** were prepared by heating the amino diesters **8** and **9** in the presence of 1 equiv of sodium methoxide. Treating the isoquinuclidones with methyl acrylate in the presence of sodium gave the N-substituted diesters **17** and **18**. All attempts at Dieckmann cyclization of **17** were unsuccessful. On attempted acyloin condensation of **18** the major product formed was that resulting from retro-Michael reaction and reduction of the 6-carbomethoxy group. This material was isolated as its acetate, **21**.

As part of a program leading to a general synthesis of the iboga alkaloids several routes to the preparation of the tricyclic ketone **1a** and its desethyl counterpart **1b** were investigated. One approach which has recently been described[3] led to **1b** and thus, to desethylibogamine. It was felt, however, that the diester **2**, an oxidative degradation product of ibogaine,[4] would also be a useful intermediate in the synthesis of **1a** since either Dieckmann cyclization followed by ring expansion or acyloin condensation and reduction could be envisioned as reasonable routes for this conversion. Thus, efforts were expended on developing a synthesis of **2** and investigating its cyclization reactions.

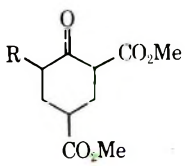


1a, R = Et
b, R = H

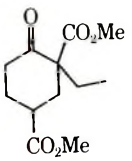


2

Alkylation of 2,4-dicarbomethoxycyclohexanone[5] (**3**) with ethyl iodide and potassium *t*-butoxide[6] followed by refluxing the alkylated material **4** with sodium methoxide in toluene[7] gave a very good yield of the 2,4,6-trisubstituted cyclohexanone **5**. The nmr spectrum



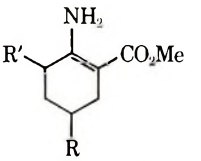
3, R = H
5, R = Et



4

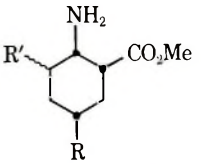
of **5** indicated that both ethyl epimers (ethyl group *cis* and *trans* to the 4-carbomethoxy group) were present in about equal amounts.

Both **3** and **5** were converted to their respective enamines **6** and **7** by passing a vigorous stream of ammonia through the β-keto ester at elevated temperatures in the presence of a trace of ammonium nitrate.[8] Hydrogenation of these enamines over palladium[9] gave the aminocyclohexane diesters **8** and **9**. Hydrogenation of the



6, R = CO_2Me; R′ = H
7, R = CO_2Me; R′ = Et
10, R = R′ = H

tetrahydroanthranilic ester **10**[10] over rhodium has been reported to give the *cis*-2-aminocyclohexanecarboxylate **11**.[11] This same product is obtained from palladium-catalyzed hydrogenation of **10**.[9] Thus, in both **8** and **9** it can be assumed that the amino group and the ester at C-2 are *cis* to each other.



8, R = CO_2Me; R′ = H
9, R = CO_2Me; R′ = Et
11, R = R′ = H

The stereochemistry of the ester group at C-4, however, remains to be established. It was previously shown that the presence of the 4-carbomethoxy group makes the hydrogenation of **6** considerably more difficult than the saturation of the double bond in **10**.[9] A comparison of the spectra obtained from **6** and **10** also revealed some interesting data. The ultraviolet spectrum of **6** exhibited a maximum at 284 mμ with an extinction coefficient of 20,000; **10** also absorbed at 283 mμ, but had an extinction coefficient of only 15,000. The nmr spectrum of **6** displayed a broad singlet at δ 6.3 (378 Hz) for the N–H protons, but the peak for the analogous set of protons from **10** was observed at δ 6.0 (361 Hz). The unreactive ring double bond, enhanced extinction coefficient, and deshielded N–H protons of **6** can be interpreted as the result of a special type of field effect known as a supraannular effect.[12] With this

(1) Supported by Grant MH-10107 from the National Institutes of Health. Grateful acknowledgement is made of this support.

(2) (a) NDEA Fellow 1965–1968. (b) Taken from the dissertation submitted by R. F. B. to Seton Hall University in partial fulfillment of the requirements for the Ph.D. degree, 1968.

(3) R. L. Augustine and W. G. Pierson, *J. Org. Chem.*, **34**, 1070 (1969).

(4) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Amer. Chem. Soc.*, **80**, 126 (1958).

(5) H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 912 (1946).

(6) G. Stork and S. M. McElvain, *J. Amer. Chem. Soc.*, **68**, 1053 (1946).

(7) W. L. Meyer, A. P. Lobo, and E. T. Marquis, *J. Org. Chem.*, **30**, 181 (1965); L. Nicole and L. Berlinguet, *Can. J. Chem.*, **40**, 353 (1962).

(8) H. G. Becker, *J. Prakt. Chem.*, **12**, 294 (1961).

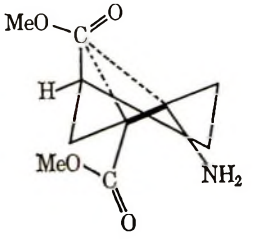
(9) R. L. Augustine, R. F. Bellina, and A. J. Gustavsen, *J. Org. Chem.*, **33**, 1287 (1968).

(10) V. Prelog and U. Geyer, *Helv. Chim. Acta*, **28**, 1677 (1945).

(11) K. J. Liska, *J. Pharm. Sci.*, **53**, 1427 (1964).

(12) G. P. Kugatova-Shemyakina and Yu. A. Ovchinnikov, *Tetrahedron*, **18**, 697 (1962); G. P. Kugatova-Shemyakina, G. M. Nikolaev, and V. M. Andreev, *ibid.*, **23**, 2721 (1967); G. P. Kugatova-Shemyakina and G. M. Nikolaev, *ibid.*, **23**, 2987 (1967).

effect in operation the vinylogous urethan **6**, contrary to expectation, would exist preferentially in the conformation **12**, in which the 4-carbomethoxy group is in an

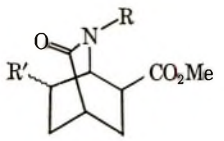


12

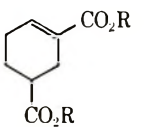
axial position and is near enough to the ring double bond to give rise to an intramolecular interaction between the π electrons of the latter and the electrophilic carbon of the former. Thus, hydrogenation of the double bond of **6** would be expected to give the all-*cis* product **8**. Products resulting from a similar type of *trans* attack have also been obtained from epoxidation[13] and hydroboration[14] of a number of carbonyl-substituted cyclohexenes.

This stereochemical assignment is strengthened by the ease of deamination of **8** and **9** as compared to that of **11**. The preferred conformation for the all-*cis* isomer **8** would have the amine group in an axial configuration,[15] and, thus, it would be expected to be readily eliminated. The preferred arrangement of stereoisomers of **8** having either or both of the ester groups *trans* to amine function would have the amino group predominantly or exclusively in the equatorial conformation and, therefore, less easily involved in an elimination reaction.

Because of this ease of deamination the cyclization of **8** to the isoquinuclidone **13** proved troublesome. Heating a dilute solution of **8** gave, as the major isolable material, the unsaturated diester **14a**, which was identified by hydrolysis to the known[16] tetrahydroisophthalic acid **14b**. However, cyclization could be effected in



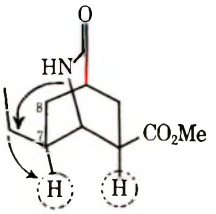
13, R = R′ = H
15, R = H; R′ = Et
17, R = $CH_2CH_2CO_2Me$; R′ = H
18, R = $CH_2CH_2CO_2Me$; R′ = Et



14a, R = Me
b, R = H

reasonably good yield by heating a methanol solution of **8** at 185° for 8 min in a sealed bomb in the presence of 1 equiv of sodium methoxide. The use of less base and/or longer reaction times resulted in the formation of less isoquinuclidone. The nmr spectrum of **13** exhibited two closely spaced singlets in a 3:2 ratio which have been assigned to the protons of the *exo* and *endo*[17] methyl ester groups, respectively.

Cyclization of **9** gave the substituted isoquinuclidone **15** as a nearly equal mixture of *exo* and *endo*[17] ethyl epimers. In contrast to what was observed with **13** the nmr spectrum of **15** showed only one clean singlet for the carbomethoxy protons indicating that only one ester epimer was present. Clearly, the isomer of **15** possessing an *endo* ethyl group would exist preferentially with the epimerizable carbomethoxy group in an *exo* configuration. The reasons why the carbomethoxy group preferred the *exo* position when the ethyl group was *exo* were not apparent. However, if the steric repulsion between the heterocyclic bridge and the *exo* ethyl group were great it would force rotation about the 7,8 carbon–carbon bond resulting in the 7-hydrogen being thrust toward the 6-*endo* group as depicted in **16**.

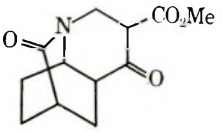


16

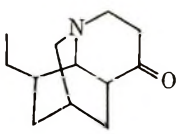
Since the 6-carbomethoxy group has a greater steric requirement than the 6-hydrogen, the carbomethoxy entity would prefer the *exo* position.

The isoquinuclidones **13** and **15** were treated with methyl acrylate in the presence of sodium metal to give the diesters **17** and **18**, respectively. Compound **18** had infrared spectral characteristics identical with those reported for 2[4] but was, obviously, a mixture of ethyl epimers. The presence of two three-proton singlets in the nmr spectrum of **18** indicated that the 6-ester group was still in the *exo* configuration. With **17**, however, four carbomethoxy singlets were observed showing that this material was still a mixture of 6-carbomethoxy isomers.

The Dieckmann cyclization was attempted originally on **17** since it was felt that under the basic reaction conditions used ester epimerization would occur and, thus, the stereochemistry at C-6 was not important. All attempts to cyclize **17** under a wide variety of reaction conditions failed to give the desired β-keto ester, **19**. However, when the addition of methyl acrylate to **13** was run in the presence of a small amount of methanol a very small quantity (~1% yield) of **19** was obtained. It is



19



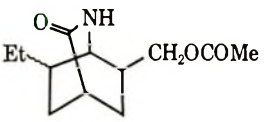
20

probable that the trigonal nature of the lactam nitrogen imparts considerable strain to a tricyclic system such as **19**, and, thus, cyclization does not take place for steric reasons. On the other hand the tricyclic amino ketone **20**, which is readily obtained by degradation of ibogaine, is relatively strain free.

Attention was then turned to the acyloin condensation of these isoquinuclidone diesters. Because of competitive Dieckmann cyclization the acyloin condensation is normally not very useful for the formation of seven-membered rings.[18,19] However, in the present

(13) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 221 (1959).
(14) J. Klein, E. Dunkelblum, and A. Avrahami, *J. Org. Chem.*, **32**, 935 (1967).
(15) J. Hirsch, "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, 199.
(16) W. H. Perkin and S. S. Pickles, *J. Chem. Soc.*, 87 (1905).
(17) An *exo* substituent is defined as one which is *cis* to the lactam bridge of the isoquinuclidone, and an *endo* substituent is *trans* to this bridge.
(18) P. D. Gardner, G. R. Haynes, and R. L. Brandon, *J. Org. Chem.*, **22**, 1206 (1957).
(19) K. T. Finley, *Chem. Rev.*, **64**, 573 (1964).

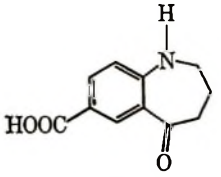
instance this competitive reaction does not take place and, therefore, the acyloin condensation was expected to occur readily. The diester **18** was used in these reactions since this material had the 6-carbomethoxy group in the proper configuration. The condensation of **18**, using a liquid ammonia–tetrahydrofuran solvent system, gave a product which failed to exhibit an ester carbonyl band in the infrared spectrum. The crude product was acetylated and chromatographed on silicic acid. The major component, which was present in about 60–70% yield, exhibited bands in the infrared spectrum at 3425 (*NH*CO), 1680 (lactam carbonyl), 1735 (acetate carbonyl), and 1250–1230 cm^{-1} (acetate C–O stretching frequency). The nmr spectrum of this compound displayed a three-proton singlet at δ 2.05 anticipated for an acetate methyl, a two-proton doublet (J = 7.5 Hz) at δ 3.94 corresponding to an entity such as CHCH_2OAc, and a broad singlet at about δ 7.4 for the lactam proton. These data, coupled with the elemental analysis, lead to the conclusion that this compound was the isoquinuclidone acetate **21**. Thus un-



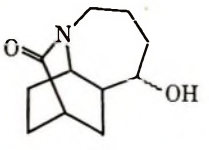
21

expected product apparently arises from retro-Michael reaction of the N-alkyl ester and reduction of the 6-carbomethoxy group, followed by acetylation of the resulting alcohol. The proton required for this unusual reduction is thought to originate from the α position of the N-alkyl ester. The formation of a small quantity of an alcohol under acyloin conditions has been previously reported.[18] A thin layer chromatographic and infrared spectral study of all of the fractions from the column chromatography failed to indicate the presence of any acyloin product. In addition to the acetate **21** a small quantity of a crystalline material was isolated which displayed a very intense band at 1705 cm^{-1} in the infrared spectrum. The structure of this compound has not been ascertained.

The failure of **18** to cyclize is probably due primarily to the action of the facile retro-Michael reaction and not to any steric factors since the tricyclic material **23** has been previously obtained in very good yield on hydrogenative cyclization of the amino acid **22**.[20]



22



23

It is apparent, then, that these cyclizations cannot be used to synthesize **1** as desired and that other approaches to this problem need to be developed.[21,22]

(20) Y. Ban, T. Wakamatsu, Y. Fujimoto, and T. Oishi, *Tetrahedron Letters*, 3383 (1968).

(21) Two syntheses of the amine analog of **1** have recently been reported.[20,22]

(22) S. I. Sallay, *J. Amer. Chem. Soc.*, **89**, 6762 (1967).

Experimental Section[23]

1,3,3,5-Tetracarbomethoxypentane (24).—To a mixture of 200 g (1.52 moles) of dimethyl malonate and 5.0 g (0.22 g-atom) of sodium in 250 ml of dry benzene was added, with stirring, 312.7 g (3.64 moles) of methyl acrylate in 300 ml of dry benzene over a 3-hr period. After addition the mixture was stirred an additional 3 hr and refrigerated overnight. The benzene solution was washed with cold 10% hydrochloric acid and water, dried, filtered, and evaporated to give 475 g of a colorless oil which crystallized while cooling. Two recrystallizations from methanol gave large colorless crystals, mp 54–57°.

Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62. Found: C, 51.00; H, 6.72.

1,3,5-Pentanetricarboxylic Acid (25).—The tetraester **24** (220 g, 0.72 mole) was refluxed for 14 hr in 1100 ml of concentrated hydrochloric acid. The residue obtained on evaporation was heated at 200° for 2.5 hr. Recrystallization of this residue from acetone–chloroform gave 145.5 g (95%) of product, mp 109–111°. A second recrystallization from acetone furnished crystals, mp 111–113° (lit.[6] mp 113–114°).

1,3,5-Tricarbomethoxypentane (26).—A mixture of 125.2 g (0.61 mole) of **25**, 180 g (5.53 mole) of absolute methanol, 60 ml of concentrated sulfuric acid, and 300 ml of dry benzene was refluxed for 18 hr. The benzene layer was separated and replaced by 300 ml of fresh dry benzene and 20 ml of concentrated sulfuric acid. After the mixture was refluxed an additional 4 hr, the benzene phase was separated and combined with the first benzene solution. The combined solution was washed with cold saturated aqueous sodium bicarbonate solution, dried, filtered, and evaporated to give 145.6 g of the triester. The sulfuric acid phase was neutralized with potassium carbonate and extracted twice with ether to yield an additional 5.0 g of product. Distillation of 270 g of this material gave 250.2 g (93%) of a colorless oil, bp 119° (0.5 mm) [lit.[5] bp 162° (12 mm)].

2-Ethyl-2,4-dicarbomethoxycyclohexanone (4).—To a solution of potassium *t*-butoxide (prepared from 7.86 g (0.20 g-atom) of potassium metal and 200 ml of dry *t*-butyl alcohol) was added 43.1 g (0.20 mole) of the β-keto ester **3**[5] in 200 ml of dry *t*-butyl alcohol. The mixture was refluxed for 45 min and allowed to cool to room temperature. Ethyl iodide [62.4 g (0.40 mole)] was added in one portion and the mixture refluxed with stirring for 24 hr. Most of the alcohol was removed by evaporation under reduced pressure. The supernatant alcohol was decanted and the residue was washed three times with ether. The ethereal washings were combined with the supernatant alcohol, and the combined solution was washed with ice-cold 10% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and saturated brine. Evaporation of the solvent after drying left 46.1 g (95%) of a colorless oil which did not give a color reaction with ferric chloride. Distillation of 50 g gave 47.3 g (90%) of product: bp 135.5–138° (0.7 mm); $n^{20}D$ 1.4696; infrared spectrum (film), 1740 strong shoulder (2-**C**OOMe), 1735 strong (4-**C**OOMe), and 1715 cm^{-1} (six-membered ring CO); nmr spectrum, 3 H triplet at δ 0.90 (J = 7.0 Hz) (CH_2CH_3) and 6 H singlet at 3.83 (both CO_2Me).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.33; H, 7.38.

The 2,4-dinitrophenylhydrazone was recrystallized from methanol, mp 148–149°.

Anal. Calcd for $C_{18}H_{22}N_4O_8$: C, 51.18; H, 5.25; N, 13.26. Found: C, 50.99; H, 5.19; N, 13.21.

6-Ethyl-2,4-dicarbomethoxycyclohexanone (5).—Dry toluene (150 ml) was added to 5.94 (0.11 mole) of sodium methoxide. To this rapidly stirred slurry was added 24.0 g (0.099 mole) of the β-keto ester **4** in 150 ml of dry toluene over a 1-hr period. The mixture was refluxed for 8 hr after which the solvent was distilled until its boiling point rose to 110° (about 30 min). After cooling, the reaction mixture was diluted with 100 ml of benzene, and washed with ice-cold 10% hydrochloric acid. The acidic

(23) All melting points were determined in open capillary tubes using a Mel-Temp apparatus and are uncorrected. All boiling points are uncorrected. The infrared spectra were recorded on a Beckman Model IR-10 recording spectrophotometer in chloroform solution unless otherwise indicated. The ultraviolet spectra were recorded in absolute methanol on a Beckman Model DK-2 ratio recording spectrophotometer. The nuclear magnetic resonance were determined on a Varian Associates Model A-60A recording spectrometer in deuteriochloroform unless otherwise specified. Tetramethylsilane (TMS) was used as the internal standard and all signals are given in parts per million (δ) relative to TMS at δ 0.

washings were saturated with sodium chloride and extracted twice with benzene. The combined benzene solution was washed with 4 ml of saturated aqueous sodium bicarbonate solution and three times with 6 ml of saturated brine, dried, and evaporated to give a pale orange oil. Distillation of the crude product gave 14.6 g (61%) of product, bp 125–134° (0.07–0.1 mm), which gave a very intense ferric chloride test. A fraction of the colorless oil which had bp 128–130° (0.07 mm) and n^{20}D 1.4764 served as the analytical sample; infrared spectrum ($HCCl_3$), 1740 (2-**COO**Me), 1735 (4-**COO**Me), 1660 (-HOC=C**OCO**Me), and 1620 cm^{-1} (enolic C=C); nmr spectrum, overlapping 3 H triplets at *ca.* δ 1.0 (J = 6.0 Hz) (epimric $CH_2\mathbf{CH_3}$), 3 H singlet at 3.72 (4-COO**Me**), 3 H singlet at 3.78 (2-COO**Me**), and 0.6 H singlets of approximately equal intensities at 12.21 and 12.37 (indicative of enolic OH protons in different chemical environments).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.45; H, 7.40.

Methyl 4-carbomethoxy-6-ethyl-3,4,5,6-tetrahydroanthranilate (7) was prepared following the procedure used to synthesize the desethyl analog 6[9] except that the required reaction temperature was 115–125°. The product, which was obtained in quantitative yield, did not react with ferric chloride reagent. The viscous oil resisted all attempts at crystallization. An attempt to distil this material led to extensive decomposition. The infrared spectrum (film) of the crude material showed bands at 3460 (nonbonded N–H), 3330 (bonded N–H), 1730 (4-**COO**Me), 1670 (2-**COO**Me), and 1615 cm^{-1} (C=C); the nmr spectrum had overlapping 3 H triplets of approximately equal intensities centered at *ca.* δ 1.10 (J = 6.5 Hz) (epimeric $CH_2\mathbf{CH_3}$), 3 H singlet at 3.68 (4-**COO**Me), 3 H singlet (2-**COO**Me), and overlapping broad singlets centered at *ca.* 6.50 which integrated for 2 H ($\mathbf{NH_2}$).

2,4-Dicarbomethoxy-6-ethylcyclohexylamine (9) was prepared by the hydrogenation of 7 by the previously described procedure.[9] The amino diester 9 was obtained as a thick, viscous oil which resisted crystallization and decomposed on distillation. All attempts to derivatize 9 as the hydrochloride salt, the *p*-nitrobenzamide, or the 3,5-dinitrobenzamide led only to extensive deamination. This material showed infrared absorption (film) at 3350 (N–H) and 1735 cm^{-1} (both -**COO**Me), but no absorption at 1655 (NH_2C=C**COO**Me) or at 1618 cm^{-1} (C=C).

3-Oxo-6-carbomethoxy-2-azabicyclo[2.2.2]octane (13).—Into a 35-ml stainless steel bomb was placed 4.0 g (0.19 mole) of the amino diester 8 in 15 ml of dry methanol and 1.0 g (0.19 mole) of sodium methoxide in 15 ml of dry methanol. The vessel was sealed, vigorously shaken, and immersed in an oil bath at 185 ± 5° for 7–10 min. The bomb was removed from the oil bath, allowed to cool for 15 min at room temperature, and subsequently placed in a freezing mixture until very cold at which time the reaction vessel was opened.

Small pieces of Dry Ice and 10 ml of water were added to a flask containing the methanolic reaction mixtures from two runs. The solution was acidified to pH 4–6 by the dropwise addition of concentrated hydrochloric acid and the acidified reaction mixture was extracted thoroughly with chloroform which was dried, filtered, and evaporated to furnish an orange oil. This residue was taken up in methanol and filtered through a pad of Norit, and the solvent was evaporated to give 6.5 g of a pale yellow oil. Infrared analysis indicated that the oil contained the desired isoquinuclidone and some unsaturated side product which resulted from deamination of the starting material.

This crude product (6.5 g) was taken up in 25 ml of water. The aqueous solution was extracted twice with 10-ml portions of ether. The combined ethereal solution was back extracted with two 10-ml portions of water. The ethereal solution (A) was set aside for further study. The aqueous extracts were combined with the original aqueous solution. This combined solution was saturated with sodium chloride and extracted four times with 25-ml portions of methylene chloride. The combined methylene chloride extract was dried, filtered, passed through a Norit pad, and evaporated to give 4.0 g (56%) of nearly colorless product. All attempts to induce this oil to crystallize failed.

This oil was placed on a small silica gel column and eluted with ether to remove the trace impurity. The isoquinuclidone product was removed from the column with methanol. The methanol was evaporated and the residue was distilled from a metal block distillation apparatus at 175–225° *in vacuo*. Thin layer chromatographic studies (silica gel) of the distillate using chloroform, ether, and methanol as eluents indicated the presence of only one component: infrared spectrum ($HCCl_3$), 3425 (**NH**CO), 3230 broad (clathrated H_2O), 1735 (**COO**Me), and 1685 cm^{-1} strong (NH**CO**); nmr spectrum, broad 4 H singlet at δ 1.78 (CH_2CH_2), singlets at 3.73 and 3.76 integrating for a total of 3 H (epimeric COO**Me**), 0.8 H broad singlet centered at 4.0 (clathrated H_2O), and a broad 1 H singlet centered at 7.65 (NHCO).

Anal. Calcd for $C_9H_{13}NO_3 \cdot 0.6H_2O$: C, 55.69; H, 7.38; N, 7.22. Found: C, 55.68; H, 7.38; N, 7.09.

Identification of the Major Side Product from the Isoquinuclidone Synthesis.—The ethereal solution (A) from the previous reaction was filtered through Norit, dried, and evaporated to yield 1.88 g of pale yellow oil which rapidly decolorized a bromine–carbon tetrachloride solution and had infrared absorption (film) at 1735 (CH**COO**Me), 1715 (C=C**COO**Me), and 1650 cm^{-1} (C=C). A small quantity of this compound was hydrolyzed by refluxing in 15% hydrochloric acid for 8 hr. White crystals, mp 237–241°, formed while the acidic solution was cooling. The Δ^3-tetrahydroisophthalic acid **14b** so obtained was recrystallized from water, mp 245.5–248° (lit.[16] mp 243–244°). Running the cyclization of 8 for longer times on in the presence of smaller amounts of base gave more **14a** and considerably less of the desired **13**.

3-Oxo-6-*exo*-carbomethoxy-7-ethyl-2-azabicyclo[2.2.2]octane (15). (1) **Sodium Methoxide Method.**—The procedure used to synthesize **15** was the same as that which was employed for the preparation of the desethyl analog **13**. Twelve grams of the amino diester 9 were cyclized in four portions to furnish the isoquinuclidone product in 53% yield (5.4 g). All attempts to induce the product to crystallize failed. A sample of the isoquinuclidone was distilled nearly quantitatively from a metal block distillation apparatus to give a viscous, colorless oil; infrared spectrum ($HCCl_3$), 3425 (**NH**CO), 1730 (**COO**Me), and 1680 cm^{-1} (NH**CO**); nmr spectrum, 3 H overlapping triplets centered *ca.* δ 0.97 (J = 6.0 Hz) (epimeric $CH_2\mathbf{CH_3}$), 3 H singlet at 3.73 (COO**Me**), and a broad 1 H singlet at *ca.* 7.47 (NHCO).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.29; H, 8.23; N, 6.52.

(2) **Hydrogenation–Cyclization Method.**—To 1.6 g of 5% ruthenium-on-charcoal catalyst which was thoroughly moistened with dry dioxane, was added, with caution, a solution of 1.5 g (0.0062 mole) of the vinylogous urethan 7 in 60 ml of absolute methanol. This mixture was hydrogenated at 1800 psig and 120° for 24 hr and then at 1900 psig and 175° for an additional 12 hr and the catalyst was removed by filtration. Evaporation of the solvent under reduced pressure afforded an oil which was taken up in ether and filtered through a sintered-glass funnel. The ethereal filtrate was thoroughly extracted with small portions of water and the aqueous extracts combined. The combined aqueous solution was thoroughly extracted with methylene chloride, the methylene chloride extracts were combined, dried, filtered, and evaporated under reduced pressure to furnish 0.25 g (19%) of the isoquinuclidone **15**, which was identical with that prepared by method 1.

N-(β-Methyl propionate)-3-oxo-6-carbomethoxy-2-azabicyclo-[2.2.2]octane (17).—A mixture of 1.58 g (0.0087 mole) of the isoquinuclidone **13**, 0.05 g (0.0022 g-atom) of sodium (cut into small pieces), and 7 ml of dry benzene was stirred at room temperature for 10 min. The mixture was chilled in an ice bath and 0.86 g (0.01 mole) of methyl acrylate was added in one portion with stirring. The solution was cooled for 15 min after the addition, and then the reaction was allowed to stir at room temperature for 24 hr. The solution was decanted from the unreacted sodium and the reaction flask was rinsed several times with a few milliliters of benzene. The combined benzene solution was washed with a small volume of 10% hydrochloric acid. The acidic washings were saturated with sodium chloride and extracted twice with 10-ml portions of benzene. The benzene extracts were added to the original benzene solution and the combined solution was washed with saturated aqueous sodium bicarbonate solution and saturated brine, dried, filtered, and evaporated to give 2.1 g (92%) of product as a colorless cloudy oil which was further purified by filtering a methanolic solution of it through a Norit pad. The analytical sample was prepared by distillation from a metal block distillation apparatus at 125–160° *in vacuo*; infrared spectrum ($HCCl_3$), 1735 (**COO**Me) and 1660 cm^{-1} (**NCO**); the nmr spectrum showed a 4 H broad singlet at δ 1.76 ($CH\mathbf{CH_2CH_2}CH$), and four very close singlets at 3.67–3.76 which integrate for a total of 6 H (*exo* and *endo* COO**Me**, *cis* and *trans* $-N(CH_2)_2\mathbf{COOMe}$).

Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.24; N, 5.07.

N-(β-Methyl propionate)-3-oxo-*exo*-6-carbomethoxy-7-ethyl-2-azabicyclo[2.2.2]octane (18) was prepared by using the same procedure as employed for the preparation of the desethyl analog **17**. Alkylation of 1.9 g (0.0090 mole) of **15**, with 0.95 g (0.011 mole) of methyl acrylate, afforded 2.21 g (83%) of nearly pure product as a colorless oil. The analytical sample distilled cleanly from a metal block distillation apparatus at 180–230° *in vacuo*; infrared spectrum (film), 1740 (ester CO) and 1678 cm^{-1} (lactam CO) [lit.[4] 1742 (ester CO) and 1678 cm^{-1} (lactam CO) for **2**]; nmr spectrum, poorly resolved triplet at δ 0.97 (J = 6.0 Hz) (epimeric CH_2CH_3), 3 H singlet at 3.70 (CH_2CH_2COOMe), and a 3 H singlet at 3.73 (CHCOO**Me**).

Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.46; H, 7.61; N, 4.87.

Preparation of the Tricyclic Ketolactam 19.—A mixture of 0.50 g (0.0027 mole) of the isoquinuclidone **13**, 0.06 g (0.0027 g-atom) of sodium, 0.24 g (0.0028 mole) of methyl acrylate, 2 drops of absolute methanol, and 10 ml of dry benzene was stirred for 30 min at room temperature. The yellow solution was then refluxed with stirring for 7 hr under dry nitrogen. The solvent was distilled until the boiling point of the distillate reached 80° (about 30 min) and the cooled reaction mixture was diluted with 40 ml of benzene. The reaction mixture was washed with a small portion of ice-cold 10% hydrochloric acid. The acidic wash was extracted twice with 5-ml portions of methylene chloride. All organic phases were combined, washed with saturated aqueous sodium bicarbonate solution, dried, and evaporated to give 0.48 g of a viscous orange oil. The crude product was taken up in methanol, filtered through a Norit pad, and evaporated under reduced pressure to furnish 0.37 g of a pale yellow oil which gave a positive ferric chloride test.

The oil[24] was chromatographed on 15 g of silicic acid and eluted with absolute ether. The ether eluent afforded about 9 mg of a crystalline material. Chloroform ws used to recover starting material and the alkylated, but uncyclized isoquinuclidone, **17**. The crystalline solid was sublimed at 70–90° (1 mm); mp 80–120°; infrared spectrum ($HCCl_3$), 3370 (enolic OH), 1730 (COCH**COO**Me), 1710 (COCHCOOMe), 1680 shoulder (–HOC=COCOMe), 1670 (**NCO**), and 1614 cm^{-1} (C=C); ultraviolet spectrum, λ_{max}^{MeOH} 250 mμ, λ_{max} (methanol plus a trace of sodium hydroxide) 280 mμ.

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37. Found: C, 60.40; H, 6.63.

Attempted Acyloin Cyclization of the Lactam Diester 18.—The lactam diester **18** was placed on a hot-water bath under high vacuum for 10 hr prior to use to remove any trace of water or methanol which may have been present. A 1-l. three-neck flask equipped with a Dry Ice condenser, mechanical stirrer, addition funnel, and a dry nitrogen system was thoroughly flamed-out before being used. All incoming predried gases were passed through potassium hydroxide drying towers as a precautionary step. The exit port of the system was similarly protected from moisture. A positive nitrogen pressure was maintained at all times, and all additions to the reaction flask were made against the stream of nitrogen.

(24) A similar oil was obtained by treating **17** with 1 equiv of sodium methoxide in refluxing toluene after which the solvent was distilled until its boiling point rose to 110°. Both of these oils displayed a minor, but identical ferric chloride active spot on tlc (silica gel) using several solvents of varying polarity as eluents.

To the reaction flask was added 350 ml of anhydrous liquid ammonia and 220 ml of freshly distilled anhydrous tetrahydrofuran. In this solvent system was dissolved 1.36 g (0.059 g-atom) of freshly cut sodium. A solution of the diester [2.50 g (0.0084 mole)] in 220 ml of anhydrous tetrahydrofuran was added with stirring over 90 min. The stirring was continued as the reaction slowly warmed to room temperature. The reaction was allowed to stand overnight under a slow stream of nitrogen.

The unreacted sodium was destroyed by the addition of 8 ml of methanol followed by 30 min of stirring. Two 10-ml portions of cold 10% hydrochloric acid were added and the mixture was vigorously shaken. The tetrahydrofuran was removed under reduced pressure at 25°. The remaining aqueous phase was saturated with sodium chloride and extracted four times with 40-ml portions of methylene chloride. The extracts were dried, filtered, and evaporated to give 1.60 g of a viscous yellow oil.

This crude product was dissolved in a solution of 9.5 ml of acetic anhydride and 15.8 ml of pyridine and allowed to stand at room temperature for 40 hr. The dark red residue obtained on evaporation of the reaction mixture was taken up in methylene chloride, washed twice with 5-ml portions of 5% hydrochloric acid, dried, filtered, and evaporated to give a red oil. The crude acetate was chromatographed on 20 g of silicic acid as a preliminary purification step. Only two fractions, which were eluted with chloroform–methanol (10:1), contained material which exhibited infrared spectral characteristics which were in accord with the anticipated acetylated product. These fractions were combined and evaporated to furnish 0.78 g of an oil which was then rechromatographed on 100 g of silicic acid.

From the chloroform eluent was obtained 171 mg of a crystalline solid. With considerable material loss, the solid was recrystallized from ether–hexane; mp 96–98°; infrared spectrum ($HCCl_3$), 1755 cm^{-1} (ketone?); mol wt (cryoscopic) 116.

Anal. Found: C, 57.04; H, 7.30.

A reasonable structure to account for these data has not been ascertained.

From the ether eluent was obtained 130 mg of a cloudy oil which was taken up in methanol and filtered through a Norit pad. Evaporation of the solvent left a clear oil which was distilled from a metal block distillation apparatus at 150–200° *in vacuo*. This compound was assigned structure **21** from the following data: infrared spectrum ($HCCl_3$), 3425 (**NH**CO), 1735 (**OCO**Me), 1680 (NH**CO**), and 1250–1210 cm^{-1} (acetate C–O stretch); nmr spectrum, 3 H singlet at δ 2.05 (OCO**Me**), 2 H doublet at 3.94 (CH**CH₂**OCOMe), and a 1 H broad singlet at *ca.* 7.36.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50. Found: C, 63.73; H, 8.48.

A thin layer and vapor phase chromatographic estimate of all of the fractions from both column chromatographies indicated that 60–70% of the crude reaction mixture consisted of this compound.

This experiment was repeated several times varying the conditions including the solvent system (ether–ammonia); however, none of the desired acyloin product was detected at any time.

Registry No.—**4**, 19766-30-4; **4** (2,4-dinitrophenylhydrazone), 19766-31-5; **5**, 19766-32-6; **13**, 19795-95-0; **15**, 19766-07-5; **17**, 19766-33-7; **18**, 19766-08-6; **19**, 19766-34-8; **21**, 19766-35-9; **24**, 19766-36-0.

Tetracyanoethylene Oxide. IV. Nucleophilic Ring Opening

W. J. LINN AND E. CIGANEK

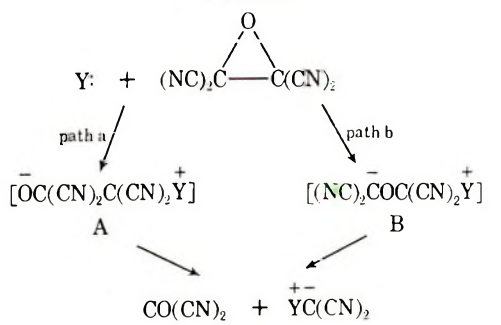
Contribution No. 1473 from the Central Research Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware

Received June 28, 1968

Most reactions of nucleophiles with tetracyanoethylene oxide (TCNEO) involve fragmentation of the ring. Examples are given of reactions with amines, thiocarbonyl compounds, benzylideneaniline, and benzophenone azine. The amine reaction gives the same products as the reaction of the amines with carbonyl cyanide. The products from TCNEO and thiocarbonyl compounds depend on the substituents attached to the thiocarbonyl group. Thus, thiourea gives a stable thiouronium ylide whereas with thiobenzophenone, sulfur is eliminated with the formation of a dicyanoethylene. The reaction of TCNEO with benzylideneaniline takes two pathways. One gives an addition product with loss of hydrogen cyanide. The second involves ring scission to form a 1,3 dipole that adds a second molecule of benzylideneaniline. The benzophenone azine reaction, however, takes a different course and gives nitrogen, 1,1-dicyano-2,2-diphenylethylene, and the epoxide of this olefin. Acetic anhydride and acetyl chloride add to TCNEO to give ring-opened products without fragmentation. Benzaldehyde and TCNEO form a 1:1 addition product believed to be a cyclic acetal.

The oxirane ring of tetracyanoethylene oxide (TCNEO) is extremely susceptible to nucleophilic attack. A common result is cleavage into the elements of carbonyl cyanide and dicyanomethylene. Examples of reactions with pyridines and alkyl sulfides have been given.[1] These reactions may be concerted, *i.e.*, both bonds may break simultaneously. However, if the process is stepwise, an initial attack on carbon can be followed by one of two different reaction sequences, either of which could lead to the same ultimate products (Scheme I). The two paths differ in the order in which the C–C and C–O bonds break. These paths can only be distinguished if it is possible to intercept either A or B.

SCHEME I



We have now observed additional examples of nucleophilic ring-opening reactions of TCNEO. Although some of these are similar to the earlier reported reactions and involve rupture of two bonds, there are two clear-cut instances that follow path a. There are cases also suggesting that path b ring opening can occur, but these are ambiguous. Negative charge is stabilized in both A and B, and a delicate balance may be swung in either direction depending upon the attacking reagent.

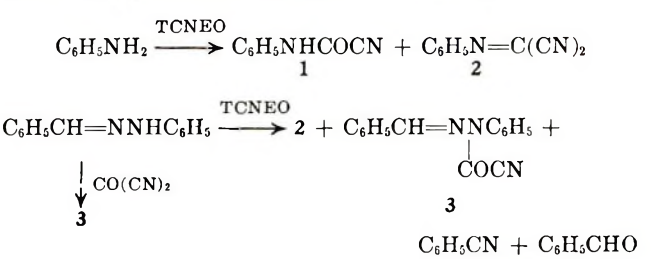
Another difficulty is the possibility of nucleophilic attack on oxygen. Brown and Cookson[2] isolated an unsymmetrical adduct of TCNEO to the 9,10 positions of anthracene. This was attributed to initial attack on oxygen, but it is not possible to distinguish this from a path a reaction.

Reaction with Amines.—Nothing can be inferred about the direction of ring opening of TCNEO by amines. Both a C–C and a C–O bond are broken. Whereas the previously reported reaction with pyridine derivatives is fairly clean, reaction with simple primary, secondary, and tertiary amines is more complex. Yields of products are generally low and it is often not possible to account for all the molecular fragments.

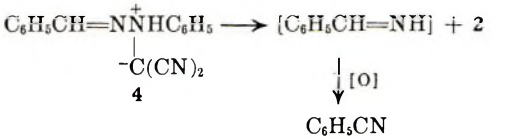
One of the reaction products of TCNEO and aniline is N-(cyanoformyl)aniline (**1**). This is also obtained from reaction of carbonyl cyanide and aniline,[3] and it is likely that the TCNEO reaction also involves the intermediacy of carbonyl cyanide. The complexity of the reaction is indicated by the isolation, in small yields, of the anil of carbonyl cyanide (**2**). An oxidation must be involved to explain this product.

Closely related to this reaction is that of TCNEO with benzaldehyde phenylhydrazone. The anil **2** is also a product of this reaction along with 1-cyanoformyl-1-phenyl-2-benzylidenehydrazine (**3**) and small amounts of benzonitrile and benzaldehyde. The structure of **3** was established by an independent synthesis from the hydrazone with carbonyl cyanide and the anil **2** was prepared from malononitrile and nitrosobenzene.

The initial reaction presumably results in the scission of TCNEO into carbonyl cyanide and the unstable zwitterion **4**. The carbonyl cyanide produced in this first step is undoubtedly the source of **3**, whereas the



breakdown of **4** may be responsible for formation of carbonyl cyanide anil and benzonitrile. The complications in such a process are indicated by the low yields of all the products.

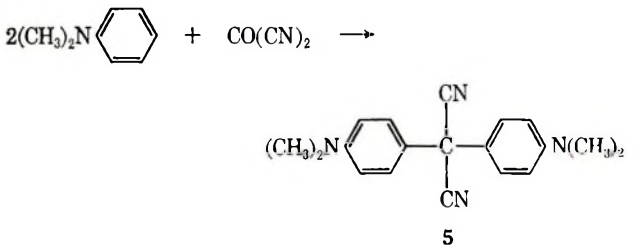


(1) W. J. Linn, O. W. Webster, and R. E. Benson, *J. Am. Chem. Soc.*, **87**, 3651 (1965).

(2) P. Brown and R. C. Cookson, *Tetrahedron*, **24**, 2551 (1968).

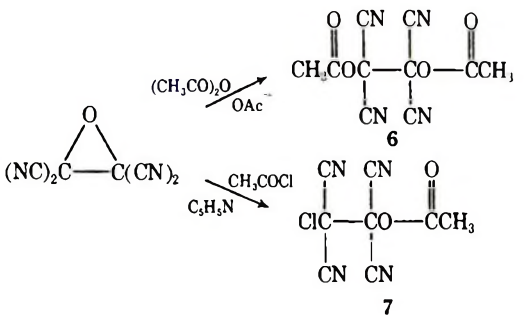
(3) R. Malachowski and J. Jankiewicz-Wasowska, *Roczniki Chem.*, **25**, 34 (1951).

Products of the reaction of a tertiary aliphatic amine, *e.g.*, triethylamine, with TCNEO are unstable and decompose on attempted purification. It was expected, however, that from dimethylaniline one might obtain bis(*p*-dimethylaminophenyl)dicyanomethane (**5**), the product of condensation of the amine and carbonyl cyanide.[3] This is the case although the yields from TCNEO are small and no products were isolated to account for the remainder of the molecule.



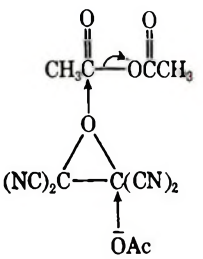
5

Reaction with Acetic Anhydride and Acetyl Chloride.—These reactions afforded the first example of nucleophilic ring opening of TCNEO proceeding *via* path a, the C–C bond remaining intact. Addition of a catalytic amount of acetate ion to a solution of TCNEO in acetic anhydride results in the precipitation of the diacetate of tetracyanoethylene glycol (**6**), identified on the basis of elemental analysis and spectra. Similarly, **7** is obtained when a drop of pyridine is added to a suspension of TCNEO in acetyl chloride.



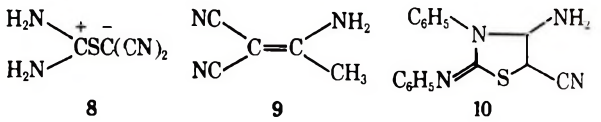
6 **7**

The preservation of the carbon–carbon bond of the epoxide ring is probably due to solvation by large amounts of the anhydride or acetyl chloride which can trap the anion as soon as it develops.



Reaction with Unsaturated Nucleophiles.—The ability of TCNEO to add to double and triple bonds[4] led to the investigation of molecules containing other types of unsaturation. Some preliminary work of this kind has been reported.[5] However, each system behaves differently and there are interesting aspects to each.

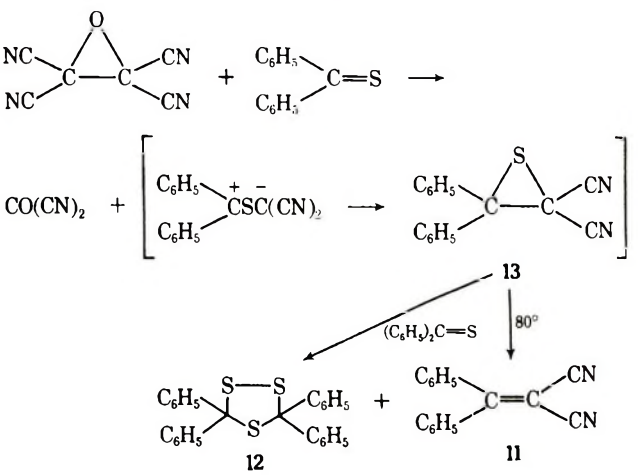
(4) W. J. Linn and R. E. Benson, *J. Am. Chem. Soc.*, **87**, 3657 (1965).
(5) E. Ciganek, *J. Org. Chem.*, **30**, 4198 (1965).



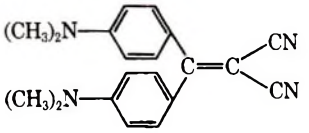
8 **9** **10**

Middleton has described the reaction of 2,2-dicyano-3,3-bis(trifluoromethyl)ethylene oxide with thiocarbonyl compounds.[6] Tetracyanoethylene oxide reacts similarly with thiourea, thioacetamide, and N,N′-diphenylthiourea to give compounds **8**–**10**, respectively. Side reactions involving carbonyl cyanide were avoided by using ethanol as a solvent, which reacts with carbonyl cyanide to yield ethyl cyanoformate and hydrogen cyanide. TCNEO also reacts rapidly with thiobenzophenone in boiling benzene giving 1,1-diphenyl-2,2-dicyanoethylene (**11**) in 68% yield. The reaction occurs more slowly at room temperature in acetonitrile or in ethanol. In the latter instance 3,3,5,5,-tetraphenyl-1,2,4-trithiolane (**12**) can be isolated in substantial yield. This compound has been reported[7] as a minor product in the autoxidation of thiobenzophenone. At elevated temperatures the trithiolane decomposes into thiobenzophenone and sulfur; thus it was not isolated in the reaction at 80°.

SCHEME II



A possible mechanism for these reactions involves an unstable dicyano episulfide **13** (Scheme II). Reaction between 4,4′-bis(dimethylamino)thiobenzophenone (**14**) and TCNEO occurs even at −50° yielding the corresponding dicyanoethylene derivative **15** in 79% yield; elemental sulfur was also isolated.

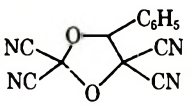


15

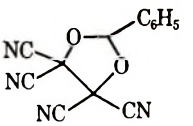
Reaction with Carbonyl Groups.—Unlike the thiocarbonyl compounds, benzaldehyde reacts with TCNEO only at elevated temperature. A 1:1 adduct could be isolated in about 10% yield. Because of the reaction conditions, it was first assumed that the mechanism of the reaction was similar to that observed for the addi-

(6) W. J. Middleton, *ibid.*, **31**, 3731 (1966).
(7) A. Schönberg, O. Schütz, and S. Nickel, *Chem. Ber.*, **61**,2175 (1928); H. Staudinger and H. Freudenberger, *ibid.*, **61**, 1838 (1928).

tion of TCNEO to olefins.[8] Therefore the expected product was the dioxolane **16**. However, mild hydrolysis of the adduct with dilute hydrochloric acid gives benzaldehyde in good yield.[9] It is conceivable that hydrolysis of **16** could give benzaldehyde, although this does not seem probable in view of the mild conditions employed. Therefore the hydrolysis experiment favors the alternative structure **17**. Spectral characterization



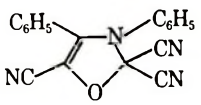
16



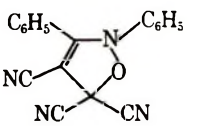
17

does not distinguish between **16** and **17**. The single proton on the five-membered ring shows a sharp resonance peak at τ 3.08. This may be contrasted with the hydrogen in the ethylene acetal of benzaldehyde which has its resonance at τ 4.50.[10] Although this downfield shift could be interpreted in favor of structure **16**, the chemical evidence that points to **17** is stronger. This reaction, therefore, is evidently a second example of ring opening of TCNEO *via* path a in which the carbon–oxygen bond is preferentially broken.

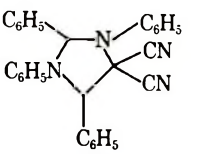
Reaction with Schiff Bases.—Two crystalline products are isolated from the reaction of TCNEO with benzylideneaniline in benzene at reflux temperature. The major product (25% yield) has the composition of a 1:1 adduct which has lost one molecule of hydrogen cyanide. It is unlikely that this product arises from addition of benzylideneaniline to a species derived from predissociation of the carbon–carbon bond of the epoxide. This mechanism has been shown to operate in addition of TCNEO to olefins,[8] but at an appreciable rate only above 100°. In this case, nucleophilic attack on carbon followed by ring closure and loss of HCN could only occur with opening of the carbon–carbon bond of the epoxide ring which would give **18**. Opening of the carbon–oxygen bond would give rise to a five-membered ring that could not eliminate HCN. We cannot, however, rule out a structure (**18a**) in which the ring has opened unsymmetrically by nucleophilic attack on oxygen. However, the longer wavelength



18

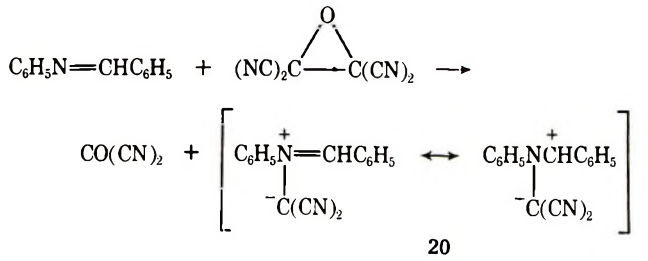


18a



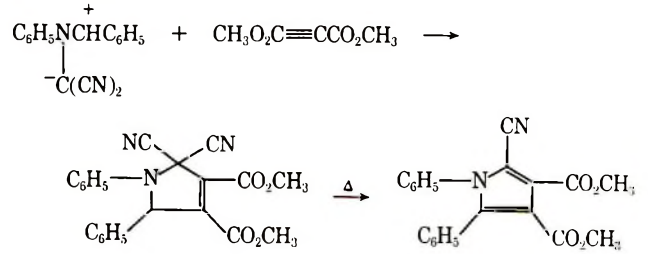
19

absorption of the product (λ_{max} 332 mμ) favors structure **18** which has the ring oxygen in conjugation with the double bond and nitrile group. The alternative structure should have an ultraviolet spectrum similar to that of *cis*-cinnamonitrile (λ_{max} 273 mμ) or 2-phenyl-1-cyclohexenecarbonitrile (λ_{max} 251 mμ).[11] Neither of these has a longer wavelength absorption. The second product, found in only 8% yield, is 1,2,3,4-tetraphenyl-5,5-dicyanoimidazolidine (**19**). The latter assignment is based on analysis, spectral evidence, and acid hydrolysis to aniline and benzaldehyde. A reasonable mechanism for the formation of the minor product **19** is *via* a 1,3-dipolar intermediate **20** which can add another molecule of the Schiff base. Evidence for this inter-



20

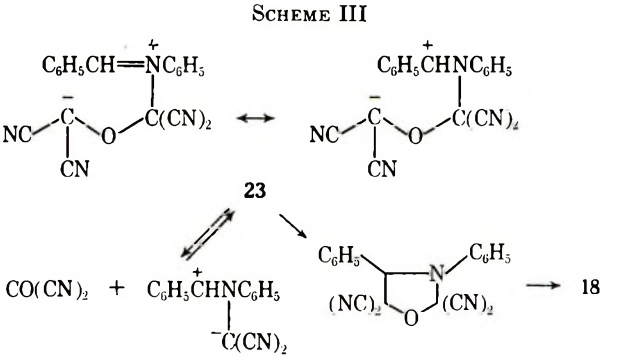
mediate is furnished by carrying out the reaction of TCNEO and benzylideneaniline in the presence of dimethyl acetylenedicarboxylate. The *only* product isolated (in 62% yield) is a colorless, crystalline compound to which structure **21** is assigned on the basis of analytical and spectral data. The product loses hydrogen cyanide readily on heating to form the pyrrole **22** in 72% yield.



21 **22**

This experiment provides strong evidence for the dipole **20** as an intermediate in the reaction, but it is of interest that the adduct **18** is *not* formed in the presence of the added acetylenic dipolarophile. The fragmentation reaction which leads to the intermediate 1,3 dipole may be reversible (Scheme III). When the acetylenic ester is present, the dipolar addition reaction is faster than ring closure. In the absence of the acetylene, ring closure competes with the addition of benzylideneaniline, a poorer dipolarophile. Another possible explanation of the results could involve addition of dimethyl acetylenedicarboxylate to **23** followed by elimination of carbonyl cyanide to give **21**.

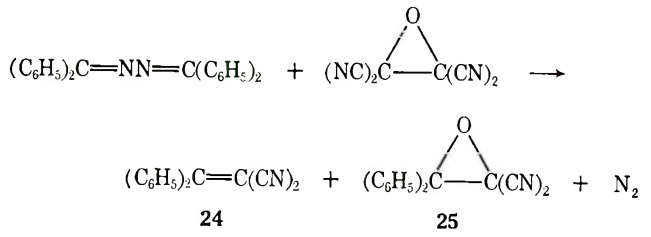
SCHEME III



(8) W. J. Linn, *J. Am. Chem. Soc.*, **87**, 3665 (1965).
(9) A referee suggested the hydrolysis experiment.
(10) B. A. Arbuzov, Yu. Yu. Samitov, and L. K. Yieldasheva, *Izv. Akad. Nauk, SSSR Ser. Fiz.*, **27**, 89 (1963) (for the English translation, see *Bull. Acad. Sci. USSR, Phys. Ser.*, **27**, 95 (1963)).
(11) W. E. Parham, W. N. Moulton, and A. Zuckerbraun, *J. Org. Chem.*, **21**, 72 (1956).

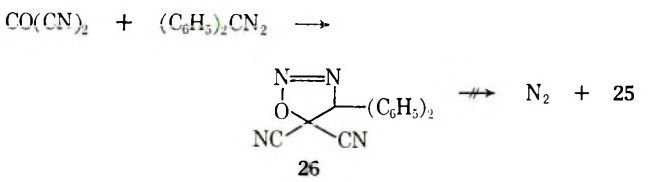
A somewhat related reaction is that of TCNEO and benzophenone azine. The reaction occurs smoothly in boiling benzene. Nitrogen is evolved nearly quantitatively (91%), and two crystalline products are formed.

One was identified as 1,1-dicyano-2,2-diphenylethylene (**24**) by an independent synthesis from benzophenone and malononitrile. The other product was believed to be 1,1-diphenyl-2,2-dicyanoethylene oxide (**25**), but attempts to synthesize it by direct oxidation of the olefin were unsuccessful. This was not unexpected because alkaline epoxidation of 1,1-dicyanoethylenes invariably gives the epoxyamide.[12]



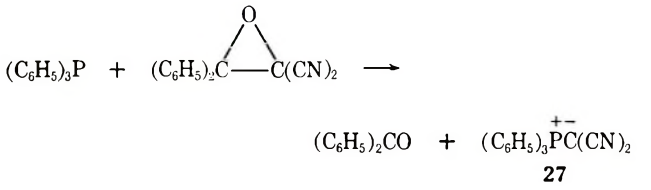
24 **25**

This same product is obtained from reaction of diphenyldiazomethane and TCNEO. One might suspect that **25** was formed from diphenyldiazomethane and carbonyl cyanide in this latter reaction. However, it has been shown in this laboratory that carbonyl cyanide adds to diphenyldiazomethane giving **26** which is thermally stable and does not decompose to **25** and nitrogen on heating.[13] The structure of the product **25** was established by elemental analysis and spectra combined



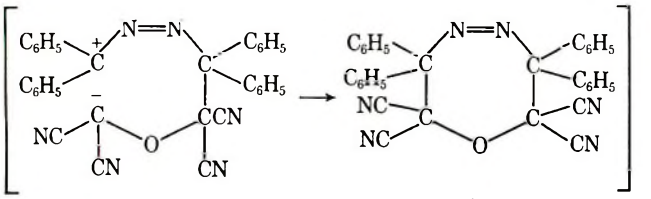
26

with the observation that reaction with triphenylphosphine gives benzophenone and triphenylphosphonium dicyanomethylide (**27**).



27

The mechanism of formation of **25** in the reaction of diphenyldiazomethane and TCNEO is unknown. Possibly, the active reactant is benzophenone azine (the decomposition product of diphenyldiazomethane), although the olefin **24** was not actually identified as the other reaction product. No evidence is at hand that bears on the mechanism of the azine reaction, but the seven-membered ring **28** is a possible method of combining the fragments in the proper order to give the observed products.



28

(12) G. B. Payne, *J. Org. Chem.*, **26**, 662 (1961).
(13) We are indebted to Dr. E. L. Martin for this experiment.

Experimental Section

Reaction of TCNEO and Aniline.—A solution of 1.86 g (0.02 mole) of freshly distilled aniline in 15 ml of ether was cooled in an ice bath, and 1.44 g (0.01 mole) of TCNEO was added all at once. The reaction mixture was stirred for 1.5 hr, and the resulting yellow solution was evaporated to leave 2.78 g of light orange solid. This product was dissolved in hot benzene and the solution was cooled. The precipitated solid was collected by filtration. The light-colored product, mp 123–126°, weighed 0.92 g (63%). The reported melting point of N-(cyanoformyl)-aniline is 123–126°.[2] The infrared spectrum of the product was identical with that of N-(cyanoformyl)aniline prepared by the reaction of carbonyl cyanide and aniline. Attempts to purify the product by repeated recrystallization led to a gradual lowering of the melting point. Malachowski[2] reports neither further purification nor analysis of N-(cyanoformyl)aniline, but does report reaction with ammonia to give phenylurea. Our product also reacts with ammonia to give phenylurea, identical with an authentic sample.

In another experiment a solution of 1.31 g (0.0141 mole) of aniline in 5 ml of tetrahydrofuran was added, all at once, to a cold (−30°) solution of 2.03 g (0.0141 mole) of TCNEO in 15 ml of tetrahydrofuran. The mixture was stirred at −20° for 5 min and at room temperature for 3 hr. The solvent was removed at room temperature leaving 3.88 g of a pale yellow semisolid. Immediate chromatography of 1.80 g of this product over Florisil gave 0.12 g of yellow crystals (eluted with benzene–hexane, 3:2) having an infrared spectrum identical with that of carbonyl cyanide anil (see below). The yield was 12%. When this reaction was carried out in the presence of yellow mercuric oxide under otherwise identical conditions, the yield of carbonyl cyanide anil was 15%.

Reaction of TCNEO with Benzaldehyde Phenylhydrazone.—To a boiling solution of 3.60 g (0.025 mole) of TCNEO in 50 ml of benzene was added, over 1.5 hr, a solution of 3.90 g (0.025 mole) of benzaldehyde phenylhydrazone in 50 ml of benzene and 20 ml of tetrahydrofuran. The reaction mixture was then heated at reflux for 1 hr. The cooled mixture was concentrated (rotary evaporator) leaving a dark semisolid. Chromatography on Florisil (elution with benzene–methylene chloride, 3:1) gave 1.01 g (52% crude yield) of a partially crystalline yellow compound and 1.97 g (63% crude yield) of a pale yellow solid. The former, on crystallization from cyclohexane, gave bright yellow plates of carbonyl cyanide anil: mp 63–64° (sealed tube); ultraviolet spectrum (in cyclohexane), λ_{max} 367 mμ (ε 4900), 281 (5300), and 235 sh (5600); infrared spectrum ($CHCl_3$), 2225 (m), 1550 (s), 1160 cm^{-1} (vs).

Anal. Calcd for $C_9H_5N_3$: C, 69.67; H, 3.27; N, 27.08; mol wt, 155. Found: C, 69.70; H, 3.43; N, 27.28; mol wt, 160 (boiling point elevation in benzene).

The second product was recrystallized from benzene–cyclohexane to give pale yellow needles of 1-(cyanoformyl)-1-phenyl-2-benzylidenehydrazine: mp 154–154.5°; ultraviolet spectrum (in cyclohexane), λ_{max} 289 mμ (ε 21,500); infrared spectrum (KBr), 2240 (w), 1690 cm^{-1} (s).

Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.95. Found: C, 72.27; H, 4.34.

The reaction was repeated by heating 1.57 g of TCNEO and 2.00 g of benzaldehyde phenylhydrazone in 8 ml of benzene under reflux for 30 min. The flask was then connected to a cold trap, and the volatile products were distilled at 0.4-mm pressure, first at room temperature and then at elevated temperature. The distillate was transferred to a volumetric flask and diluted to 10.0 ml with benzene. Gas chromatographic analysis of this solution was carried out using a 30% silicone oil coumn at 150°. It was shown to contain about 130 mg of a mixture of benzonitrile and benzaldehyde (ratio 4.9:1). A small amount of this mixture was collected and the components were identified by mass spectroscopy.

Carbonyl Cyanide Anil from Malononitrile and Nitrosobenzene.—A mixture of 2.3 g of potassium cyanide, 16 ml of *t*-butyl alcohol, 4 ml of water, 20 ml of ether, and 20 ml of benzene was cooled to −5°, and a solution of 3.1 g (0.047 mole) of malononitrile and 5.0 g (0.047 mole) of nitrosobenzene in 15 ml of benzene and 15 ml of ether was added. The temperature was kept below −5° during the addition, which took 15 min. Stirring at −5° was then continued for 5 min, and a 15% aqueous sodium chloride solution (100 ml) was added. The layers were separated, and the aqueous phase was extracted with 15 ml of

ether followed by 15 ml of benzene. The combined organic phases were washed with water, 10% potassium carbonate solution, and concentrated sodium chloride solution and dried over $MgSO_4$. Removal of the solvents left 4.84 g of a dark liquid which was chromatographed on 130 g of Florisil. The first 600 ml of *n*-hexane–benzene (4:1) eluted 1.79 g of carbonyl cyanide anil containing 3% nitrosobenzene as shown by gas chromatography on a 30% silicone grease column at 155°. An additional 0.41 g of an 80:20 mixture of the anil and nitrosobenzene was eluted with the next 300 ml of the same solvent mixture. The total yield of the anil in both fractions was 2.07 g (29%). Crystallization of the first fraction from cyclohexane gave 1.29 g of the pure anil, mp 63–64°. Another 0.44 g was obtained from the mother liquor and second fraction. The total weight of purified product was 1.73 g (24%). The product was identical with the carbonyl cyanide anil obtained from aniline and TCNEO and from benzaldehyde phenylhydrazone and TCNEO as shown by comparison of the infrared spectra and by mixture melting point determinations.

1-Cyanoformyl-1-phenyl-2-benzylidenehydrazine from Benzaldehyde Phenylhydrazone and Carbonyl Cyanide.—To a vigorously stirred solution of 8.50 g (0.043 mole) of benzaldehyde phenylhydrazone in 25 ml of glacial acetic acid, 25 ml of benzene, and 40 ml of tetrahydrofuran was added, over 15 min, a solution of 3.68 g (0.046 mole) of carbonyl cyanide in 20 ml of benzene. The temperature was kept below −3° during the addition. The yellow solution was then stirred at 0° for 20 min; the solvent was removed and the residue was dried under high vacuum over solid potassium hydroxide. Crystallization from 250 ml of ethanol gave 8.93 g (83%) of 1-(cyanoformyl)-1-phenyl-2-benzylidenehydrazine, mp 153–154°, identical with the product obtained from TCNEO and benzaldehyde phenylhydrazone (see above).

Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.86; mol wt, 249. Found: C, 72.33; H, 4.49; N, 16.71; mol wt, 267.

Bis(*p*-dimethylaminophenyl)dicyanomethane from TCNEO and Dimethylaniline.—A solution of 2.53 g (0.021 mole) of dimethylaniline in 5 ml of glacial acetic acid was cooled in an ice bath. To this solution 1.00 g (0.007 mole) of TCNEO was added in small portions. The reaction mixture first turned light green, then a very dark green, and finally reddish brown. After a short time a yellow solid began to precipitate. After 1 hr this yellow solid was collected by filtration and dried to give 0.45 g of crude product. In a similar preparation which had been allowed to stand for only 10 min, the crude product weighed 0.23 g. These two solids were combined, boiled with ethanol, and filtered. The insoluble portion, 0.37 g, was recrystallized from *n*-butyl alcohol to give light yellow crystals of bis(*p*-dimethylaminophenyl)dicyanomethane, mp 195–196°. This material was identified by comparison of its infrared spectrum with that of an authentic sample.[3]

Bis(*p*-dimethylaminophenyl)dicyanomethane from Carbonyl Cyanide and Dimethylaniline.—The addition of N,N-dimethylaniline to a solution of carbonyl cyanide in acetic acid results in a strongly exothermic reaction and the production of deep yellow solutions from which greenish yellow crystals separate. Recrystallization of the crystals does not remove the color but passage of a methylene chloride solution of the compound over neutral alumina removes a small amount of an intensely yellow impurity. Colorless crystals, mp 192–193°, can be obtained from the colorless solution obtained by chromatography.[14]

Anal. Calcd for $C_{19}H_{20}N_4$: C, 74.97; H, 6.62; N, 18.41. Found: C, 74.93; H, 6.71; N, 18.35.

Tetracyanoethylene Glycol Diacetate.—To a solution of 2.88 g (0.02 mole) of TCNEO and 10 ml of acetic anhydride was added two small drops of pyridine in 1.0 ml of glacial acetic acid. A precipitate began to form after approximately 15 min. The reaction mixture was stirred overnight at room temperature and then filtered. The solid was washed with water and air dried to give 3.52 g of crude product which was recrystallized from ethylene dichloride to give 3.24 g (66%) of colorless crystals of tetracyanoethylene glycol diacetate, mp 194.5–195°.

Anal. Calcd for $C_{10}H_6N_4O_4$: C, 48.78; H, 2.45; N, 22.76. Found: 48.94; H, 2.57; N, 23.15.

The proton magnetic resonance spectrum in deuterioacetone shows only a single peak at τ 7.38.

(14) We are indebted to Dr. E. L. Martin for this experiment. Malachowski[3] reports that this product melts at 192–193°.

2-Chlorotetracyanoethyl Acetate.—A suspension of 2.88 g (0.02 mole) of TCNEO in 15 ml of acetyl chloride was cooled in an ice bath and stirred. One drop of pyridine was added. After approximately 5 min all the TCNEO had gone into solution. The pale yellow reaction mixture was allowed to stand in the ice bath for 1 hr and then poured onto cracked ice to hydrolyze the excess acid chloride. The solid was collected by filtration, air dried, and recrystallized from carbon tetrachloride to give 2.03 g of tan needles, mp 85.5–90°. Repeated recrystallization gave an analytical sample, mp 90–91°.

Anal. Calcd for $C_8H_3ClN_4O_2$: C, 43.16; H, 1.81; Cl, 15.93. Found: C, 43.48; H, 1.58; Cl, 15.68.

The proton resonance spectrum in CD_3Cl shows only a single peak at τ 7.54.

S-Thiouroniodicyanomethanide (8).—A solution of 5.79 g (0.0402 mole) of TCNEO in 50 ml of ethanol was cooled to −10°; thiourea (3.05 g, 0.0402 mole) was added, with stirring, the temperature being kept below −5°. The resulting faintly yellow solution was concentrated to dryness (rotary evaporator) and the residue was dried under high vacuum. The yield of crude S-thiouroniodicyanomethanide was 5.51 g (98%). The infrared spectrum was identical with that of an authentic sample.[6]

2-Amino-1,1-dicyanopropene (9).—To a cold stirred solution of 1.91 g (0.0133 mole) of TCNEO in 15 ml of ethanol was added, over a period of 20 min, 1.00 g (0.0133 mole) of thioacetamide. The temperature was kept below 0°; after *ca.* 10 min, a yellow precipitate formed. The mixture was stirred at 0° for another 10 min and then filtered to give 0.83 g of a yellow solid, and from the filtrate, 0.88 g of an ill-smelling semisolid. Both products had similar infrared spectra. A small sample of the solid was heated in ethanol and the solution was decanted from the rubber-like insoluble material (presumably sulfur). On cooling, 2-amino-1,1-dicyanopropene deposited as colorless needles. Its infrared spectrum was identical with an authentic sample prepared by Middleton.[6]

4-Amino-5-cyano-3-phenyl-2-phenylimino-2,3-dihydrothiazole (10).—To a stirred solution of 3.00 g (0.0208 mole) of TCNEO in 50 ml of ethanol was added, over 20 min, 4.75 g (0.0208 mole) of finely powdered N,N′-diphenylthiourea. The temperature was kept below 30° during the addition. The mixture was stirred at room temperature for 1 hr, and the yellow precipitate was collected by filtration. The yield of 4-amino-5-cyano-3-phenyl-2-phenylimino-2,3-dihydrothiazole was 4.57 g (75%). Its infrared spectrum was identical with that of a sample prepared by Middleton.[6]

Reaction of TCNEO with Thiobenzophenone in Benzene at 80°.—The reaction was carried out in a 100-ml three-necked flask fitted with pressure-equalizing dropping funnel and a 15-cm Vigreux column set up for distillation. To a boiling solution of 3.50 g (0.0243 mole) of TCNEO in 50 ml of benzene was added with stirring, over 10 min, a solution of 4.30 g (0.0218 mole) of thiobenzophenone in 50 ml of benzene. Nitrogen was passed through the reaction mixture, and solvent was distilled continuously during and for about 15 min after the addition. A total of 60 ml of a yellow distillate was collected. The reaction mixture was concentrated to dryness (rotary evaporator), the distillate being caught in a solid carbon dioxide–acetone trap. The two distillates were combined and diluted to 100 ml with benzene. Analysis by gas chromatography (30% Triton X-305 on 60–80-mesh acid-washed Firebrick at 52°) showed this solution to contain *ca.* 0.2 g (10%) of carbonyl cyanide (identification by retention time only). The brown semisolid residue, on chromatography over Florisil, gave 3.40 g (68% yield) of 1,1-dicyano-2,2-diphenylethylene (elution with benzene), the infrared spectrum of which was identical with that of an authentic sample (see below). A small amount (0.21 g) of 3,3,5,5-tetraphenyl-1,2,4-trithiolane was also obtained (see below).

Reaction of TCNEO with Thiobenzophenone in Acetonitrile at Room Temperature.—A solution of 2.95 g (0.0149 mole) of thiobenzophenone and 2.50 g (0.0173 mole) of TCNEO in 30 ml of purified acetonitrile was stirred at room temperature under nitrogen for 24 hr. The yellow precipitate which had formed in the dark green solution was collected by filtration. The yield of crude 3,3,5,5-tetraphenyl-1,2,4-trithiolane so obtained was 1.08 g (51%). It was purified by chromatography over Florisil (elution with benzene–methylene chloride, 7:3) and crystallization from methylene chloride–petroleum ether (30–60°) to give colorless crystals, mp 122–124° dec, lit.[7] mp 124°.

Anal. Calcd for $C_{26}H_{20}S_3$: C, 72.85; H, 4.71; S, 22.44. Found: C, 72.72; H, 4.62; S, 22.45.

The filtrate was concentrated to dryness (rotary evaporator) and part of the residue was chromatographed over Florisil, yielding 165 mg (extrapolated yield: 48%) of 1,1-dicyano-2,2-diphenylethylene, identified by its infrared spectrum (see below). TCNEO was recovered in 54% yield by sublimation of the other part of the residue.

A similar run, using ethanol instead of acetonitrile as the solvent, gave 1,1-dicyano-2,2-diphenylethylene in 47% yield and 3,3,5,5-tetraphenyl-1,2,4-trithiolane in 53% yield; the latter had to be isolated by chromatography; it did not precipitate from the ethanol solution.

1,1-Dicyano-2,2-diphenylethylene.—Dry ammonia was passed into a solution of 54 g of benzophenone (0.31 mole) and 20 g of malononitrile (0.30 mole) in 180 ml of anhydrous ethanol for 1 hr. The mixture was left standing at room temperature for 4 days, but no 1,1-dicyano-2,2-diphenylethylene crystallized as claimed by previous workers.[15] The solution was poured into 400 ml of water and the mixture was extracted with three 150-ml portions of benzene; the combined extracts were washed with 10% potassium hydroxide solution, water, and concentrated sodium chloride solution, and dried over magnesium sulfate. Removal of the solvent left 62 g of a pale yellow liquid to which 50 ml of ethanol was added. After standing at room temperature for 20 hr, the colorless crystals of 1,1-dicyano-2,2-diphenylethylene, mp 140–141.5° (lit.[15] mp 136°), were collected by filtration. A further crop was obtained by adding 50 ml of petroleum ether (30–60°) to the mother liquor and keeping the mixture in a cold room for 20 hr; total yield: 8.91 g (12%). An analytical sample, mp 141–142°, was obtained by two crystallizations from ethanol: ultraviolet spectrum (in cyclohexane), λ_{max} 315 mμ (ε 15,800), 275 sh (10,500), and 228 (10,400).

Anal. Calcd for $C_{16}H_{10}N_2$: C, 83.46; H, 4.38; N, 12.17. Found: C, 83.97; H, 4.46; N, 12.09.

1,1-Dicyano-2,2-bis(4-dimethylaminophenyl)ethylene (15).—A mixture of 10.0 g (0.035 mole) of 4,4′-bis(dimethylamino)-thiobenzophenone, 10.0 g of malononitrile, 5.0 g (0.036 mole) of anhydrous potassium carbonate, and 100 ml of *n*-propyl alcohol was stirred under reflux for 1 hr. The reaction mixture was cooled with ice, 100 ml of water was added, and the precipitate was collected by filtration, washed with cold water and methanol, and dried. The 1,1-dicyano-2,2-bis(4-dimethylaminophenyl)ethylene so obtained (10.80 g, 97%) had mp 254–257°; it was 97% pure as indicated by its ultraviolet spectrum. Recrystallization from glacial acetic acid (40 ml/g) gave purple crystals of the pure product, mp 259–260°, in 82% yield (overall); ultraviolet spectrum (in acetonitrile), λ_{max} 430 mμ (ε 48,550), 320 (4000), 310 (3700), 265 (22,900).

Anal. Calcd for $C_{20}H_{20}H_4$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.85; H, 6.42; N, 17.68.

Reaction of TCNEO with 4,4′-Bis(dimethylamino)thiobenzophenone.—A solution of 0.92 g (0.0064 mole) of TCNEO in 5 ml of tetrahydrofuran and 10 ml of ethanol was cooled to around −50°, and a solution of 1.53 g (0.0054 mole) of 4,4′-bis(dimethylamino)thiobenzophenone in 30 ml of chloroform was added with vigorous stirring over 25 min. The red color of the thioketone changed to green immediately. The mixture was allowed to warm to room temperature (1 hr); it was then stirred at room temperature for 30 min. The solvents were removed leaving 1.95 g of a brown semisolid. A small amount (46 mg) of this solid was dissolved in 50 ml of acetonitrile; the insoluble portion (3.7 mg of a rubber-like material) contained 88.8% sulfur as shown by microanalysis; total yield of elemental sulfur: 140 mg (81%). The acetonitrile solution had an ultraviolet spectrum identical with that of 1,1-dicyano-2,2-bis(4-dimethylaminophenyl)ethylene: the *k* value of the 430-mμ band was 120, indicating that the product contained 1.52 g (89% yield) of the ethylene derivative. Recrystallization of 1.31 g of the crude product from 40 ml of glacial acetic acid gave 0.90 g (79%) of 1,1-dicyano-2,2-bis(4-dimethylaminophenyl)ethylene as purple crystals, mp 256–258°. The infrared spectrum was identical with that of an authentic sample prepared as described in the preceding experiment.

4,4,5,5-Tetracyano-2-phenyl-1,3-dioxolane (17).—A reaction vessel containing 3.00 g (0.0208 mole) of TCNEO in 25 ml of freshly distilled benzaldehyde was alternately evacuated and flushed with nitrogen. It was heated at 100–110° for 18 hr. Most of the benzaldehyde was evaporated at reduced pressure, and the residual solid was dried on a porous plate. The dried residue was sublimed at 80–90° (0.1 mm) until sublimation ceased. This first fraction was mainly recovered TCNEO as indicated by the infrared spectrum. However, some of the desired adduct was present. The sublimation was continued at 110°. The second fraction contained essentially no TCNEO. This product was recrystallized once from 2-propanol to give 0.62 g of brown needles which were sublimed at 190° (0.1 mm) to give 0.53 g (10%) of colorless crystals, mp 140–142°. Further recrystallization from 2-propanol raised the melting point to 141–142°.

Anal. Calcd for $C_{13}H_6N_4O_2$: C, 62.40; H, 2.42; N, 22.39; mol wt, 250. Found: C, 62.15; H, 2.48; N, 22.11; mol wt, 238–240.

Acid Hydrolysis of Benzaldehyde–TCNEO Adduct.—A suspension of 0.101 g of the 1:1 adduct of TCNEO and benzaldehyde in 5 ml of 5% hydrochloric acid was warmed overnight on a steam bath in a nitrogen atmosphere. The solid disappeared and was replaced by small drops of oil immiscible in the aqueous phase. The mixture smelled strongly of benzaldehyde. The reaction mixture was extracted with methylene chloride and the extract was dried with Drierite. Gas chromatography of the extract on a 6 ft × 0.25 in. column of XE-60 on Gas Chrom RA at 145° and a helium flow of 100 ml/min showed, besides the methylene chloride peak, a component eluting at 4.4 min. An authentic sample of benzaldehyde in methylene chloride also eluted at 4.4 min. Removal of the solvent with a rotary evaporator left a small residue which was dissolved in 6 ml of 50% aqueous ethanol. The solution was heated to boiling for 0.5 min after the addition of two drops of phenylhydrazine. Cooling the solution caused the precipitation of pale yellow needles which weighed 0.050 g (63%) and melted at 153–155°. Recrystallization from 50% aqueous ethanol raised the melting point to 155–156.5°. An authentic sample of benzaldehyde phenylhydrazone had the same melting point and the infrared spectra of the two samples were identical.

Reaction of TCNEO and Benzylideneaniline.—The reaction was carried out in a 500-ml, three-necked flask fitted with gas-inlet tube, two 125-ml dropping funnels, and a 20-cm Vigreux column connected to a 1000-ml receiving flask, the contents of which (45 g of dimethylaniline in 100 ml of glacial acetic acid) was cooled with ice and stirred. To 500 ml of boiling benzene in the three-necked flask were added separately and with stirring, solutions of 25.5 g (0.18 mole) of TCNEO in 75 ml of tetrahydrofuran and of 46.5 g (0.26 mole) of benzylideneaniline (Eastman White Label, mp 53–54°) in 200 ml of benzene. Nitrogen was passed through the reaction mixture, and solvent was distilled out continuously. Addition of the two solutions was complete after 50 min. Benzene (100 ml) was added and solvent distillation was continued for 25 min, when the volume of the dark green reaction mixture was *ca.* 200 ml. It was cooled with ice and the yellow precipitate was collected by filtration. It weighed 13.3 g (25%). Crystallization from 85 ml of acetonitrile gave 9.05 g of yellow needles of 2,2,4-tricyano-1,5-diphenyl-Δ^4-oxazoline (18), mp 232.5–234° (sealed tube). Further recrystallization did not increase the melting point. The infrared spectrum (KBr) showed bands at 2230, 1685, and 955 cm^{-1}; ultraviolet spectrum (in acetonitrile), λ_{max} 252 mμ (ε 21,600) and 332 (6500); nmr spectrum, two peaks (each split at least into a doublet) at τ 2.29 and 2.50 (ratio of areas 1:1).

Anal. Calcd for $C_{18}H_{10}N_4O$: C, 72.47; H, 3.38; N, 18.78; mol wt, 298. Found: C, 72.62; H, 3.30; N, 18.79; mol wt, 319 (ebullioscopically in benzene).

The mother liquor was concentrated, using a rotary evaporator, and to the residue (56.78 g of a black oil) was added, with stirring with a glass rod, 200 ml of boiling ethanol. The cooled mixture was filtered to give 21.16 g of a light tan solid, which was chromatographed on 300 g of Florisil. A pale yellow solid (8.47 g) was eluted with benzene. It was crystallized from acetonitrile, giving 6.48 g (8.5% yield) of 1,2,3,4-tetraphenyl-5,5-imidazolidinedicarbonitrile (19) as almost colorless plates, mp 209–211° (sealed tube). The analytical sample melted at 210–211°; ultraviolet spectrum (in acetonitrile), λ_{max} 237 mμ (ε 19,300) and 287 sh (1900); infrared spectrum, weak CN band at 2240 cm^{-1} (in KBr); nmr spectrum (in acetonitrile), singlets at τ 3.92 and 3.34 (area ~1 each) and a very complex spectrum from 2.4 to 3.2 (area ~20).

Anal. Calcd for $C_{29}H_{22}N_4$: C, 81.66; H, 5.20; N, 13.14; mol wt, 426. Found: C, 81.89; H, 5.29; N, 13.17; mol wt, 451 (ebullioscopically in benzene).

(15) R. Schenck and H. Finken, *Ann. Chem.*, **462**, 27 (1928).

The contents of the receiving flask (containing the reaction product of dimethylaniline with carbonyl cyanide) were concentrated to dryness using a rotary evaporator. The residual yellow crystals were heated with 30 ml of ethanol and collected by filtration to give 5.73 g (11%) of bis(*p*-dimethylaminophenyl)-dicyanomethane identified by comparison of its infrared spectrum with that of an authentic sample (see above).

Reaction of TCNEO with Benzylideneaniline and Dimethyl Acetylenedicarboxylate.—The apparatus used was a 100-ml, three-necked flask fitted with magnetic stirrer, gas-inlet tube, 100-ml dropping funnel, and a 15-cm glass spiral column set for distillation. To a stirred boiling solution of 3.24 g (0.0225 mole) of TCNEO and 6.40 g (0.045 mole) of dimethyl acetylenedicarboxylate in 50 ml of benzene was added, over 70 min, a solution of 4.10 g (0.0225 mole) of benzylideneaniline in 50 ml of benzene. Nitrogen was passed through the reaction mixture, and solvent was distilled into a receiving flask (containing 8 g of dimethylaniline in 15 ml of glacial acetic acid) at about the same rate as benzylideneaniline solution was added. Thirty milliliters of benzene was then added, and distillation of solvent was continued for 30 min. The reaction mixture, on cooling with ice, deposited 4.67 g of light tan crystals of dimethyl 2,2-dicyano-1,5-diphenyl-Δ^3-3,4-pyrrolinedicarboxylate (**21**), mp 174–176° dec. From the filtrate, on evaporation to dryness and chromatography on Florisil, an additional 0.73 g of the diester was obtained. The analytical sample, prepared by two recrystallizations from benzene, melted at 175° dec; ultraviolet spectrum (in acetonitrile), λ_{max} 230 mμ (ε 16,000), shoulders at 265 (2800) and 272 (2500); infrared spectrum (KBr), 2240 (w), 1750, 1730 (s) cm^{-1}.

Anal. Calcd for $C_{22}H_{17}N_3O_4$: C, 68.21; H, 4.43; N, 10.85; mol wt, 387. Found: C, 68.48; H, 4.56; N, 10.71; mol wt, 429.

The yield of bis(*p*-dimethylaminophenyl)dicyanomethane, isolated from the contents of the receiving flask as described for the reaction of TCNEO with benzylideneaniline, was 1.60 g (23%).

No **19** was obtained in the chromatography, nor was any **18** isolated by sublimation of a small sample of the evaporated filtrate (before chromatography) at 180° and 0.3 mm.

Thermal Decomposition of 21.—A sample of 0.61 g of the pyrroline **21** in a 10-ml flask was evacuated to 120 Torr and slowly heated in an oil bath. Smooth evolution of hydrogen cyanide started at 171° (bath temperature). After 20 min a temperature of 185° had been reached and no gas was being evolved. On cooling, 0.53 g of a colorless solid was obtained. This was recrystallized from 4 ml of benzene–cyclohexane (3:1) to give 0.40 g (71%) of dimethyl 1,2-diphenyl-5-cyano-3,4-pyrroledicarboxylate (**22**): mp 151–152°; ultraviolet spectrum (in acetonitrile); λ_{max} 285 mμ (ε 10,000), 235 (22,000); infrared spectrum (KBr), 2240, 1740, and 1725 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77; mol wt, 360. Found: C, 70.56; H, 4.43; N, 7.86; mol wt (ebullioscopic in benzene), 370, 371.

Reaction of TCNEO with Diphenyldiazomethane.—To a stirred boiling solution of 1.35 g (0.0094 mole) of TCNEO in 40 ml of benzene was added, over 30 min, a solution of 1.81 g (0.0093 mole) of diphenyldiazomethane in 30 ml of benzene. The mixture was then heated under reflux for 10 min. A total of 200 ml (88%) of nitrogen was evolved. In a second experiment, solvent was distilled continuously during the addition; no carbonyl cyanide was detected in the distillate. The solvent was removed at reduced pressure to give 3.19 g of a dark semisolid, part of which (1.66 g) was chromatographed over Florisil (45 g). In the first 200 ml of benzene, 0.40 g (17%) of 1,1-dicyano-2,2-diphenylethylene oxide was eluted. Two recrystallizations from benzene gave an analytical sample: mp 166–167°; ultraviolet spectrum (in cyclohexane), λ_{max} 269 mμ (ε 685), 262 (850), 258 (750), 256 (755), 226 (11,900); infrared spectrum (KBr), 2245, 1590, 1500, 1240, 1230, 1225, 910, and 885 cm^{-1}.

Anal. Calcd for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.10; N, 11.38; mol wt, 246. Found: C, 78.13; H, 4.12; N, 11.28; mol wt, 261.

An unstable yellow oil was obtained by further elution with benzene and benzene–methylene chloride.

Reaction of 1,1-Dicyano-2,2-diphenylethylene Oxide (25) with Triphenylphosphine.—A mixture of 0.22 g (0.00093 mole) of 1,1-dicyano-2,2-diphenylethylene oxide, 0.44 g (0.0015 mole) of triphenylphosphine, and 3 ml of 1,2-dichloroethane was heated under reflux for 1 hr. Removal of the solvent (rotary evaporator) gave a dark oil, which was dissolved in 2 ml of hot benzene. Addition of 2 ml of hot cyclohexane and cooling gave 0.20 g of triphenylphosphonium dicyanomethylide.[16] The mother liquor was concentrated to dryness and the residue was chromatographed over Florisil. Triphenylphosphine (0.19 g) was eluted with the first 36 ml of benzene–*n*-hexane (1:1). Another 60 ml of the same solvent mixture eluted 0.15 g (92% yield) of benzophenone, identified by its infrared spectrum. A small quantity (*ca.* 0.03 g) of triphenylphosphonium dicyanomethylide (**27**) was eluted with methylene chloride–tetrahydrofuran (4:1). The total yield of **27** was 0.23 g (79%).

Reaction of TCNEO with Benzophenone Azine.—The reaction was carried out in a 100-ml three-necked flask fitted with a pressure-equalizing dropping funnel and a reflux condenser, the top of which was attached, through a drying tube, to a 100-ml gas buret. To a boiling solution of 1.68 g (0.0117 mole) of TCNEO in 15 ml of benzene was added, over 8 min, a solution of 1.40 g (0.00389 mole) of benzophenone azine in 20 ml of benzene, and the mixture was then heated under reflux until gas evolution ceased (3 hr). A total of 86 ml (at 24°, 91% of the theoretical amount) of nitrogen was evolved. The solvent was removed (rotary evaporator), leaving 2.99 g of a tan solid. Chromatography over Florisil gave 0.73 g (76%) of 1,1-dicyano-2,2-diphenylethylene oxide (eluted with benzene–hexane, 2:3) and 0.79 g (88%) of 1,1-dicyano-2,2-diphenylethylene (eluted with benzene). The two products were identified by comparison of their infrared spectra with those of samples prepared previously (see above).

Registry No.—TCNEO, 3189-43-3; **2**, 19769-98-3; **3**, 19769-99-4; **6**, 19770-00-4; **7**, 19770-01-5; **14**, 1226-46-6; **15**, 19770-02-6; **17**, 19770-03-7; **18**, 19770-04-8; **19**, 19769-85-8; **21**, 19769-86-9; **22**, 19769-87-0; **25**, 19769-88-1; aniline, 62-53-3; benzaldehyde phenylhydrazone, 588-64-7; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5; thiobenzophenone, 1,450-31-3; benzylideneaniline, 538-51-2; diphenyldiazomethane, 883-40-9; benzophenone azine, 983-79-9.

Acknowledgment.—We are indebted to Dr. R. E. Benson for many helpful discussions in connection with this work.

(16) L. Hoerner and H. Oediger, *Chem., Ber.*, **91**, 437 (1958).

Purine N-Oxides. XXV. 3-N-Oxides of Adenine and Hypoxanthine[1]

I. SCHEINFELD, JAMES C. PARHAM, SARAH MURPHY, AND GEORGE BOSWORTH BROWN

Division of Biological Chemistry, Sloan-Kettering Institute for Cancer Research, and Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University Medical College, New York, New York 10021

Received December 3, 1968

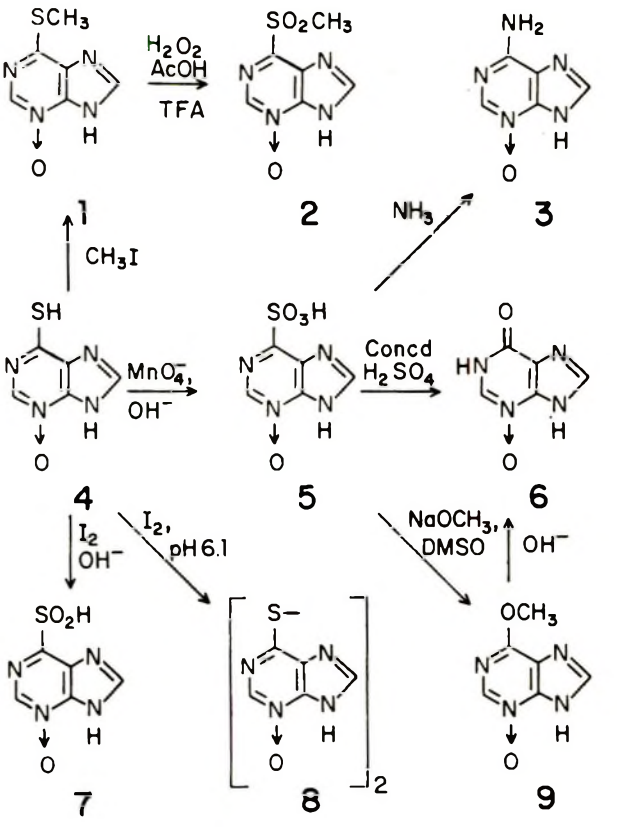
The 3-N-oxides of adenine, hypoxanthine, and 6-methoxypurine are synthesized by displacements of the sulfonyl group of 6-sulfonylpurine 3-oxides. The latter is obtained from 6-mercaptopurine 3-oxide, as are the corresponding sulfinyl-, methylsulfonyl-, and disulfide derivatives. An oxidation product of 6-methoxypurine is shown to be the 3-N-oxide.

Adenine 1-oxide,[2,3] and what is now known to be guanine 3-oxide,[4-6] each obtained by direct oxidation, and 3-hydroxyxanthine prepared from the latter, have been shown[5,7,8] to be chemical oncogens.[9] The isomeric 1-hydroxyxanthine, obtained by chemical modification of adenine 1-oxide,[10] is a far weaker oncogenic agent[8] than 3-hydroxyxanthine; that pair of isomers offered the first major indication of considerable structural specificity with respect to oncogenicity.

A variety of purine N-oxides must be evaluated before a correlation can be established between structure and oncogenicity. Most will be obtainable only by total synthesis since direct oxidation fails to introduce oxygen into positions where it is desired. We now report total syntheses of adenine 3-oxide, (**3**) and hypoxanthine 3-oxide (**6**).

Oxidation of 7-aminothiazolo[5,4-*d*]pyrimidine to its 6-oxide, and rearrangement, had provided a synthesis[11,12] of 6-mercaptopurine 3-oxide (**4**). A series of oxidation products of **4**, the sulfinate **7**, sulfonate **5**, and disulfide **8**, and the methylsulfonyl **2** from its S-methyl derivative **1** were prepared (Scheme I) for studies of the ease of displacement of the 6 substituents. The methods were analogous to those used for the corresponding derivatives from 6-mercaptopurine;[13] there was no undue influence of the 3-N-oxide function on the oxidation of the 6 substituents.

The methylmercapto group of 6-methylmercaptopurines can be readily displaced by amines.[14] Attempted displacement of the methylmercapto group of 6-methylmercaptopurine 3-oxide (**1**) with liquid ammonia at room temperature or in ethanolic ammonia at elevated temperatures produced adenine. Similar treatment of 6-chloropurine 3-oxide[15] also resulted in deoxygenation as well as displacement of the chloro group.



Successful displacement with retention of the N-oxide function was accomplished, on a preparative scale, by the reaction of the potassium salt of purine-6-sulfonate 3-oxide (**5**) with concentrated aqueous ammonia at 100° for 18 hr. The adenine 3-oxide (**3**) was isolated either as the hemihydrate or as a complex with 1 mole of ammonium sulfate.

Purine-6-sulfonate 3-oxide, like purine-6-sulfonate, is alkali stable and acid labile. Although purine-6-sulfonate is readily hydrolyzed to hypoxanthine by hydrochloric acid,[13] no analogous product could be isolated from the hydrolysis of purine-6-sulfonate 3-oxide (**5**) under similar conditions. However, when **5** was dissolved in concentrated sulfuric acid, immediate evolution of sulfur dioxide occurred, and a single product could be isolated. It was hypoxanthine 3-oxide (**6**) which is stable in the solid state and in alkaline solution, but somewhat unstable in aqueous acid.[4]

(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748) and from the Atomic Energy Commission (Contract No. AT(30-1)-910).

(2) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Amer. Chem. Soc.*, **80**, 2755 (1958).

(3) M. A. Stevens and G. B. Brown, *ibid.*, **80**, 2759 (1958).

(4) U. Wölcke and G. B. Brown, *J. Org. Chem.*, **34**, 978 (1969).

(5) G. B. Brown, K. Sugiura, and R. M. Cresswell, *Cancer Res.*, **25**, 986 (1965).

(6) T. J. Delia and G. B. Brown, *J. Org. Chem.*, **31**, 178 (1966).

(7) K. Sugiura and G. B. Brown, *Cancer Res.*, **27**, 925 (1967).

(8) M. Teller, K. Sugiura, J. C. Parham, and G. B. Brown, *Proc. Am. Assoc. Cancer Res.*, **9**, 70 (1968).

(9) The more common term "chemical carcinogen" should logically be restricted to agents that induce carcinomas. Oncogenic is an inclusive term for agents that induce any form of neoplasia.

(10) J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, **32**, 1151 (1967).

(11) G. Levin and G. B. Brown, *J. Med. Chem.*, **6**, 825 (1963).

(12) G. B. Brown, G. Levin, S. Murphy, A. Sele, H. C. Reilly, G. S. Tarnowski, F. A. Schmid, M. N. Teller, and C. C. Stock, *ibid.*, **8**, 190 (1965).

(13) I. L. Doerr, I. Wempen, D. A. Clarke, and J. J. Fox, *J. Org. Chem.*, **26**, 3401 (1961).

(14) D. J. Brown, P. W. Ford, and K. M. Tratt, *J. Chem. Soc., C*, 1445 (1967).

(15) A. Giner-Sorolla, C. Gryte, A. Bendich, and G. B. Brown, *J. Org. Chem.*, **34**, 2157 (1969), following paper.

TABLE I
CHEMICAL SHIFTS (τ)

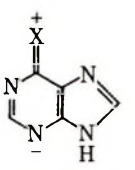
Protons	6-XCH_3 S	6-XCH_3 SO	6-XCH_3 SO_2	H-2 S	H-2 SO	H-2 SO_2	H-8 S	H-8 SO	H-8 SO_2
Purine 6-XCH_3[a,c]	7.29	6.88	6.43	1.23	0.95	0.81	1.52	1.25	1.05
Purine 3-oxide 6-XCH_3[a]	7.30		6.58	1.12		0.81	1.52		1.20
9-Methylpurine XCH_3[b,d]	7.29	6.86	6.52	1.26	0.91	0.91	2.08	1.85	1.65

[a] Solvent DMSO-d_6 (TMS). [b] Solvent $DCCl_3$ (TMS): P. W. Ford, Thesis, Australian National University, Canberra, 1968. [c] Registry numbers: X = S, 50-66-8; X = SO, 19769-31-4; X = SO_2, 19769-32-5. [d] Registry numbers: X = S, 1127-75-9; X = SO, 19769-34-7; X = SO_2, 19769-35-8.

A synthesis of hypoxanthine 3-oxide recently reported in the patent literature[16] was accomplished by oxidation of 6-methoxypurine to an N-oxide **9**, followed by alkaline hydrolysis of the methoxyl group. We have long had an N-oxidation product from 6-methoxypurine,[17] but until now have been unable to assign the position of oxidation. The 3-N-oxide of 6-methoxypurine (**9**) has now been synthesized by heating purine-6-sulfonate 3-oxide (**5**) with sodium methoxide in dimethyl sulfoxide. A comparison of the 6-methoxypurine 3-oxide prepared by oxidation with that prepared by the displacement reaction showed them to be identical, and demonstrated that oxidation had occurred at the 3 position. We, too, have obtained hypoxanthine 3-N-oxide from 6-methoxypurine 3-oxide,[16] and find it identical with that obtained by the hydrolysis of purine 6-sulfonate 3-oxide and different from 1-hydroxyhypoxanthine,[18] a substantiation of the assignment of 3-N-oxide structures to **6** and **9**. Further confirmation is afforded by the conversion, in this laboratory, of 6-chloropurine 3-oxide to the 6-methoxy and 6-hydroxy derivatives.[15]

Conversions of **4** to the methyl sulfoxide and methyl sulfone were also undertaken but only the latter was obtained. 6-Methylmercaptopurine 3-oxide (**1**) was inert to oxidation by peroxyacetic acid even at 60°; oxidation in peroxytrifluoroacetic acid did not yield reproducible results and numerous by-products were detectable by paper chromatography. The addition of acetic acid to trifluoroacetic acid and the use of limited amounts of hydrogen peroxide moderated the reaction; a product precipitated and no further oxidation occurred. The product was shown to be the sulfone, 6-methylsulfonylpurine 3-oxide (**2**) by its strong absorption bands in the regions of 1120–1160 and 1310–1350 cm^{-1} in the infrared, which are characteristic of sulfones.[19] The absence of an absorption band in the region 1040–1060 cm^{-1} eliminated the possibility that it was a sulfoxide.[19] The assignment of the sulfone structure was further supported by a comparison of the nmr methyl chemical shifts of the purine N-oxides to those of 6-SCH_3, 6-$SOCH_3$, and 6-SO_2CH_3 purines. Table I shows that as the oxidation state of the sulfur increases there is a progressive downfield shift of the position of the methyl signal. The value of τ 6.58 is in agreement with that of other sulfone methyl groups at τ 6.43 and 6.53, and distinctly different from the sulfoxide methyl values found at about τ 6.9. The proximity of τ values for the methyl groups of 6-methylmercaptopurine and its 3-oxide indicates that the N-oxide function in the 3 position exerts little influence on the S-methyl shift.

Of the 6-substituted purines, the amino-[2,3] and methylpurines[20] are oxidized on the nitrogen adjacent to the substituent and yield 1-oxides, while the methoxy- and chloropurines[15] are oxidized at the nitrogen *"para"* to the substituent and yield 3-oxides. These offer the first assessment of directive influence by these groups on N-oxidation in the purine ring. The 4-alkoxyquinazolines are oxidized on the nitrogen *"para"* to the substituent.[21] The oxidation of 4-alkoxypyrimidines[22] and 4-phenylpyrimidines[23] is also reported to occur on the *"para"* nitrogen. Oxidation of 4-methylpyrimidine, however, produces a mixture of N-oxides in which the N-oxide adjacent to the substituent predominates by a factor of 3.5:1.[24] The effect of a substituent on the electron density at the ring nitrogens should be the primary influence that determines the position of oxidation, although steric influence, solvent effects, or both, may contribute. The amino and methyl groups appear to provide strong activation for N-oxidation at the adjacent position. The chloro and methoxy groups, however, would tend to deactivate the adjacent position by inductive electron withdrawal, but could provide activation elsewhere in the ring by resonance. Thus, a mesomeric contribution by **10** could explain N-oxidation *"para"* to the substituent in 6-chloro- and 6-methoxypurines.



10, X = Cl, CH_3O

The ultraviolet spectra for several pH's, and the p*K*'s, are given in Table II. From them it is deduced that the neutral molecules of **3**, **6**, and **9** exist primarily as the N-oxide tautomers, since the strong absorption at 220–230 mμ is associated with the neutral molecules

(16) Ajinomoto Co., Brevet d'Invention P. V. no. 83,853, French Patent 1,500,662 (1967).

(17) 6-Methoxypurine was first oxidized by R. M. Cresswell. The method described here is a modification of that of T. J. Delia.

(18) J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, **31**, 966 (1966).

(19) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 54.

(20) M. A. Stevens, A. Giner-Sorolla, H. W. Smith, and G. B. Brown, *J. Org. Chem.*, **27**, 567 (1962).

(21) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **7**, 152 (1959).

(22) H. Yamanaka, *ibid.*, **6**, 633 (1952).

(23) T. Kato, H. Yamanaka, and T. Shibata, *Yakugaku Zasshi*, **87**, 1096 (1967).

(24) M. Ogata, H. Watanabe, K. Tori, and H. Kano, *Tetrahedron Lett.*, 19 (1964).

TABLE II

SPECTRAL DATA AND pK_aS

pH	Charge	λ_{max}, mμ ($\epsilon \times 10^{-3}$)	pK_a
		Adenine 3-Oxide (**3**)	
0	(+)	224[a] (5.8), 277 (8.5)	
5	(0)	229 (9.0), 293 (7.0)	2.87 (±0.06)
10	(−)	231 (11.7), 278[a] (5.7), 290 (6.3)	E[b] 6.91 (±0.07)
		Hypoxanthine 3-Oxide (**6**)	
−1	(+)	212 (14.4), 275 (8.0)	
3	(0)	223 (17.2), 271 (9.4)	1.2 (±0.1)
8	(−)	218 (19.5), 286 (12.1)	5.08 (±0.1)
12	(−2)	224 (22.0), 275[a] (10.1), 285 (10.3)	9.3 (±0.1)
		6-Methoxypurine 3-Oxide (**9**)	
0	(+)	263 (6.9)	
4	(0)	224 (24.1), 283 (10.1)	1.47 (±0.05)
9	(−)	227 (28.2), 276 (9.1)	E[b] 6.75 (±0.02)
		Purine-6-sulfonate 3-Oxide (**5**)	
3	(−)	229 (22.8), 311 (12.2)	E[b] 6.60 (±0.05)
12	(−2)	230 (28.6), 316 (8.5)	
		6-Methylmercaptopurine 3-Oxide (**1**)	
−1	(+)	236 (8.1), 317 (21)	
3	(0)	236 (7.3), 254 (8.2), 319 (18.9)	1.00 (±0.02)
12	(−)	214 (16.0), 245 (16.1), 312 (17.0), 322[a] (15.4)	6.02 (±0.02)
		Disulfide of 6-Mercaptopurine 3-Oxide (**8**)	
6	(0)	238 (26.2), 323 (20.5)	
		6-Methylsulfonylpurine 3-Oxide (**2**)	
3	(0)	232 (36), 299[a] (14), 322 (23)	
9	(−)	233 (43), 258[a] (9.0), 302 (13), 332 (15)	E[b] 5.10 (0.08)

[a] Shoulder. [b] Determined electrometrically with 0.01 *M* solutions.

and is suppressed in the protonated species.[25] With **1**, the spectrum is shifted bathochromically, as is usual with sulfur derivatives, and no well-defined change can definitely be associated with the N-oxide function. By analogy to the sulfur-containing derivatives **2** and **5** and to the O-methyl derivative **9**, the S-methyl derivative **1** is named as the N-oxide.

Experimental Section

Analyses were performed by the Spang Microanalytical Laboratories, Ann Arbor, Mich., and Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were obtained on a Mel-Temp apparatus and are corrected. Chromatograms were developed, ascending, on Whatman No. 1 paper; R_f values are given in Table III.

TABLE III

R_f VALUES

Compd	Solvents[a] A	B	C
6-Methoxypurine 3-oxide (**9**)	0.50	0.63	0.52
Purine-6-sulfonate 3-oxide (**5**)	0.07	0.80	0.26[b]
Purine-6-sulfinate 3-oxide (**7**)	0.07	0.80	
Disulfide of 6-mercaptopurine 3-oxide (**8**)	0.32	0.44	0.40[b]
6-Methylsulfonylpurine 3-oxide (**2**)	0.36	0.70	0.50
Adenine 3-oxide (**3**)	0.36[b]	0.40	0.40
Hypoxanthine 3-oxide (**6**)	0.30[b]	0.68	0.18
6-Mercaptopurine 3-oxide (**4**)	0.30	0.52	0.17

[a] A, BuOH–HAc–H_2O (60:15:25 v/v); B, 5% disodium phosphate–isoamyl alcohol (3:2 v/v) [C. E. Carter, *J. Am. Chem. Soc.*, **72**, 1466 (1950)]; C, *i*-PrOH–NH_4OH–H_2O (7:1:2 v/v). [b] Trailing.

The p*K* values were determined spectrophotometrically by methods described,[26] with 0.01 *M* buffers[27] at 20–22° or electrometrically with 0.01 *M* solutions. The infrared data were obtained using a Perkin-Elmer Model 137B Infracord spectrophotometer (KBr pellet). The uv spectra were determined with Beckman DU and Unicam SP 800A spectrophotometers. The nmr data were obtained on a Varian A-60 spectrometer.

Purine-6-sulfinate 3-Oxide (**7**).—To a stirred solution of 6-mercaptopurine 3-oxide (0.56 g, 3 mmol), dissolved in 30 ml of 1 *N* NaOH, was added 22.5 ml (5.4 mmol) of 0.5 *N* I_2 dropwise over a period of 15 min. The pH was adjusted to 5 by addition of AcOH, and the volume was reduced to *ca.* 20 ml under reduced pressure. EtOH (70 ml) was added to precipitate the product, the flask was chilled, and the product was collected and dried over P_2O_5 to yield 0.54 g (80%). The sample was recrystallized from H_2O and EtOH to yield a fine yellow powder, 400 mg. The analytical sample was dried at 110°.

Anal. Calcd for $C_5H_3N_4SO_3Na_2$: C, 24.50; H, 1.22; N, 22.90; S, 13.10; Na, 18.76. Found: C, 24.51; H, 1.00; N, 23.20; S, 13.21; Na, 18.47.

Purine-6-sulfonate 3-Oxide (**5**).—A solution of 6-mercaptopurine 3-oxide (7.81 g, 0.042 mol) in 130 ml 0.05 *N* KOH was cooled in an ice–water bath and stirred. A solution of 13.3 g of potassium permanganate in 250 ml of H_2O was added slowly. The addition completed, the resulting suspension was stirred cold for an additional 15 min and at room temperature for 4 hr. The suspension was filtered through a Celite pad, and *i*-PrOH (100 ml) was added to ensure complete reduction of the permanganate. The pH was adjusted to *ca.* 7 with glacial AcOH, and, after evaporation *in vacuo* to *ca.* 200 ml, was brought to pH ≈4 with glacial AcOH, and kept overnight at *ca.* 5°. The product was collected, washed with anhydrous EtOH followed by Et_2O, and air dried to yield 8.30 g (90.5%). For analysis it was recrystallized from 70% EtOH, mp >400°.

Anal. Calcd for $C_5H_3N_4SO_4K$: C, 23.62; H, 1.19; N, 22.03; S, 12.61. Found: C, 23.54; H, 1.27; N, 21.84; S, 12.79.

This product is identical with that prepared from 6-chloropurine 3-oxide, which had in turn been prepared from 6-mercaptopurine 3-oxide.[15]

Electrophoretic Separation.—The 6-sulfonate and 6-sulfinate 3-oxides showed very similar R_f values by paper chromatography, but could be separated by ionophoretic migration on Whatman 3 MM paper in a buffer of pH 7.7 (0.032 *M* Na_2HPO_4 and 0.004 NaH_2PO_4), 2 hr, at about 750 V and 30 mA. A single spot, anodic migration 15.2 cm, was shown by **7**, and a single one at 17.0 cm by **5**.

Disulfide of 6-Mercaptopurine 3-Oxide (**8**).—A sample of 6-mercaptopurine 3-oxide (0.93 g, 5 mmol) was dissolved in 300

(25) G. B. Brown, *Progr. Nucleic Acid Res. Mol. Biol.*, **8**, 209 (1968).

(26) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, N. Y., 1962.

(27) D. D. Perrin, *Australian J. Chem.*, **16**, 572 (1963).

ml of NaH_2PO_4 buffer (pH 6.1) by warming to 40°. After the solution had cooled to room temperature, 10 ml of 0.5 *N* iodine solution was added dropwise, which reacted rapidly. The product precipitating during addition of I_2 was collected after the mixture had been chilled. It was washed thoroughly with H_2O, EtOH, and finally Et_2O, to yield 635 mg (68%). The analytical sample was dried overnight at 80° over P_2O_5 and was found to darken above 250°.

Anal. Calcd for $C_{10}H_6N_8S_2O_2 \cdot 0.5H_2O$: C, 34.98; H, 2.05; N, 32.63; S, 18.67. Found: C, 35.20; H, 2.27; N, 32.72; S, 18.20.

It was identical spectrally and chromatographically with an anhydrous sample, prepared by oxidation with butyl nitrite, and for which an explosion point is described.[15]

6-Methoxypurine 3-Oxide (9).[17]—A solution of 6-methoxypurine (2 g, 13 mmol), dissolved in 10 ml of trifluoroacetic acid and 4 ml of 30% H_2O_2, was stirred at room temperature for *ca.* 20 hr; from it, a yellow oil separated upon addition of Et_2O. The reaction flask was chilled, and the Et_2O layer was decanted and promptly discarded. Crystallization of the oily residue was induced by warming on a steam bath with 20 ml of MeOH. The suspension was cooled, 50 ml of Et_2O was added, and the solvents were decanted and discarded. The remaining white granular solid, after being warmed on a water bath with 20 ml of *n*-PrOH to remove unreacted 6-methoxypurine, was washed with Et_2O and air dried; yield 1.43 g (66%). Paper chromatography proved the sample to be homogeneous. The analytical sample was obtained as colorless needles from H_2O and *n*-PrOH and dried overnight at 110°, mp 216–218°.

Anal. Calcd for $C_6H_6N_4O_2$: C, 43.38; H, 3.64; N, 33.72. Found: C, 43.59; H, 3.89; N, 33.43.

It was identical chromatographically and by uv spectra with material prepared from 6-chloropurine 3-oxide.[15]

6-Methylsulfonylpurine 3-Oxide (2).—6-Methylmercaptopurine 3-oxide (1)[12] (220 mg, 1.2 mmol) was suspended in a mixture composed of 0.35 ml (9.5 mmol) of trifluoroacetic acid, 2.1 ml of AcOH, and 0.4 ml of H_2O_2. After a few minutes of stirring, a clear solution resulted from which, about 1 hr later, precipitation of a white solid, began; stirring was continued at room temperature for an additional 1 hr. The product was collected, washed with anhydrous EtOH and Et_2O, and air dried to yield 115 mg (44%) of a light yellow chromatographically pure material, mp 192–193° dec.

Anal. Calcd for $C_6H_6N_4SO_3$: C, 33.64; H, 2.82; N, 26.15; S, 14.96. Found: C, 33.78; H, 2.85; N, 26.07; S, 14.94.

The infrared spectrum shows strong absorption in two band groups in the two regions characteristic of sulfone absorption.[19] In the region between 1310 and 1350 cm^{-1}, the bands are found at 1300, 1315, and 1330 cm^{-1}; in the 1120–1160-cm^{-1} region they are observed at 1125, 1140, and 1150 cm^{-1}.

Adenine 3-Oxide (3) Hemihydrate.—Purine-6-sulfonate 3-oxide (2.0 g, 9.25 mmol) was dissolved in *ca.* 40 ml of concentrated NH_4OH and placed in a glass-lined, high-pressure reaction vessel. The reaction vessel was heated at 100° for 18 hr, and cooled to 0°. The solution was evaporated on a rotary evaporator to *ca.* 15 ml. Concentrated NH_4OH was added to a pH of *ca.* 11, and water to a final volume of about 35 ml, when all the solids had dissolved. The solution was neutralized with glacial AcOH and cooled at 5° overnight. The precipitate was collected, redissolved in dilute NH_4OH, reprecipitated by the addition of glacial AcOH, and again cooled overnight at *ca.* 5°. The product was collected, washed with anhydrous EtOH and then Et_2O, and air dried, yielding 0.920 g of a white material (62%), dec pt >350°.

Anal. Calcd for $C_5H_5N_5O \cdot 0.5H_2O$: C, 37.50; H, 3.77; N, 43.73. Found: C, 37.77; H, 3.39; N, 43.72.

Adenine 3-Oxide–Ammonium Sulfate Complex.—If after evaporation and before the reprecipitation, 6 *N* H_2SO_4 is utilized instead of glacial AcOH, the resulting product contains 1 mol of $(NH_4)_2SO_4$.

Anal. Calcd for $C_5H_5N_5O \cdot (NH_4)_2SO_4$: C, 21.20; H, 4.63; N, 34.61; S, 11.31. Found: C, 21.41; H, 4.53; N, 34.32; S, 10.90.

Hypoxanthine 3-Oxide (6).—Purine-6-sulfonate 3-oxide (5) (3.44 g, 16 mmol) in 50 ml of concentrated H_2SO_4 was stirred until solution was complete, when it was added dropwise to 1 lb of anhydrous Et_2O and the mixture was refrigerated overnight. The Et_2O was decanted, and the solid was dissolved in 100 ml H_2O, stirred with Darco at room temperature, and filtered through a Celite pad. EtOH was then added until a permanent cloudiness resulted and the solution was again refrigerated overnight. The precipitate was collected and washed with anhydrous EtOH and then Et_2O to yield 3.32 g (undried). The filtrate, after evaporation *in vacuo* to *ca.* 50 ml and the addition of 50 ml of EtOH, was cooled at *ca.* −10° overnight. The additional precipitate was collected and washed with EtOH and Et_2O. The 2.20 g obtained was combined with that previously obtained and suspended in 25 ml of H_2O, and 1 *N* NaOH was added slowly with cooling in an ice bath until it dissolved (the pH was *ca.* 7), when it was stirred with Darco and filtered through a Celite pad. Glacial AcOH was then added until precipitation commenced (pH *ca.* 4); the reaction mixture was cooled at 5° overnight, and the precipitate was collected and washed with anhydrous EtOH and Et_2O to yield 1.54 g (62.5%). For analysis it was dried at 80° *in vacuo*.

Anal. Calcd for $C_5H_4O_2$: C, 39.48; H, 2.65; N, 36.83. Found: C, 39.28; H, 2.72; N, 36.81.

Column chromatography with Dowex-50, 200–400 mesh, convex gradient of 0.05 *N* plus 3 *N* HCl, which separates hypoxanthine 3-oxide, 1-hydroxyhypoxanthine, and hypoxanthine in that sequence, was used to demonstrate homogeneity of the product.

Reduction of Hypoxanthine 3-Oxide.—A mixture of Raney nickel (*ca.* 100 mg), 10 ml of 5% NH_4OH, and 4.79 mg (3.15×10^{-2} mmol) of **6** was heated under reflux for 2 hr, filtered, and found, spectrophotometrically, to contain 47.3% of the theoretical amount of hypoxanthine. The solid residue, dissolved in 2 *N* HCl, contained 57.8% of the calculated amount of hypoxanthine, a total recovery of 105%. Column chromatography on Dowex-50, 200–400 mesh, with a convex gradient starting with 0.05 *N* HCl showed only hypoxanthine.

Reduction of Adenine 3-Oxide.—Adenine 3-oxide (2.3 mg, 1.48×10^{-2} mmol) was treated as above and refluxed for 1.5 hr. The filtrate contained 28.5% of the calculated amount of adenine, whereas the solution obtained by dissolving the residue with 2 *N* HCl contained 74.1%, a total recovery of 102.7%.

Registry No.—**1**, 2846-86-8; **2**, 19769-23-4; **3**, 19769-24-5; **5**, 19765-63-0; **6**, 19769-26-7; **7**, 19769-27-8; **8**, 19765-66-3; **9**, 19765-64-1.

Acknowledgments.—We wish to acknowledge the capable assistance of Mr. Marvin Olsen with the nmr spectra and of Mr. Thomas Winn and Mr. John Schwarz with the p*K* determinations, and helpful discussions with Dr. A. Giner-Sorolla and Dr. J. D. Fissekis. A sample of 6-methylsulfinylpurine was kindly furnished by Dr. G. H. Hitchings of the Wellcome Research Laboratories, Tuckahoe, N. Y.

Purine N-Oxides. XXVI. The Synthesis and Properties of 6-Halogenopurine 3-N-Oxides[1]

ALFREDO GINER-SOROLLA, CAROL GRYTE, AARON BENDICH, AND GEORGE BOSWORTH BROWN

Division of Biological Chemistry, Sloan-Kettering Institute for Cancer Research and Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University Medical College, New York, New York 10021

Received December 3, 1968

The 3-N-oxides of 6-chloro- and 6-bromopurine were prepared by halogenation of 6-mercaptopurine 3-oxide and 6-iodopurine 3-oxide from the chloro derivative and HI. Displacement of chloride from 6-chloropurine 3-oxide gave purine-6-sulfonate 3-oxide and 6-methoxypurine 3-oxide. Ethanolic hydroxylamine and 6-methylmercaptopurine 3-oxide led to hypoxanthine 3-oxide. Treatment of 6-chloropurine 3-oxide with NH_3, NH_2NH_2, NH_2OH, and morpholine resulted in substitution and simultaneous loss of oxygen to yield adenine and 6-hydrazino-, 6-hydroxylamino-, and 6-morpholinopurine, respectively. Oxidation of 6-mercaptopurine 3-oxide with butyl nitrite afforded its disulfide. 6-Iodopurine 3-oxide inhibited slightly the growth of carcinoma EO771 in mice; the other compounds were inactive.

N-Oxides of chemotherapeutically effective purines offer[2] a possible improvement of the chemotherapeutic index since they are often less toxic than the parent purine, as in the case of the 6-methylpurine[3] and its 1-oxide[4] and 6-mercaptopurine and its 3-oxide.[5] The halogenopurines such as 6-chloro-[6] and 6-bromopurines[7] have shown encouraging antitumor activity in experimental animals[8] and 6-chloropurine reached clinical trial for the treatment of leukemia.[9] We now report syntheses, some chemical behaviors, and biological testing of several 6-halogenopurine 3-oxides.

Direct oxidation of purines in acetic or trifluoroacetic acids, the usual method for the preparation of purine N-oxides,[10] was not applicable to 6-chloropurine because of its instability in acidic solutions,[6] although a low yield may be obtained with *m*-chloroperoxybenzoic acid under anhydrous conditions.[11] The halogenopurine 3-N-oxides have now been obtained by substitution of the mercapto group of 6-mercaptopurine 3-oxide[5] by the corresponding halogen.

Treatment of 6-mercaptopurine 3-oxide[5] (**1**) with chlorine in methanolic HCl at $-10°$ gave an 89% yield of 6-chloropurine 3-oxide (**2**) (Scheme I). Replacement of the mercapto group by chlorine in the purine series has been previously reported.[12] A synthesis of **2** by another method has recently appeared.[13] Conversion of 6-mercaptopurine 3-oxide (**1**) to 6-bromopurine 3-oxide (**3**) was effected with HBr and Br_2. Treatment of 6-chloropurine 3-oxide (**2**) with concentrated HI afforded 6-iodopurine 3-oxide (**4**). The structure of 6-chloropurine 3-oxide (**2**) was established by its conversion to the starting 6-mercaptopurine 3-oxide (**1**) with thiourea[6] and its reduction to 6-chloropurine[6] (**5**) with Raney nickel. 6-Bromo- and 6-iodopurine 3-oxides (**3** and **4**) were also reduced to the respective 6-bromo- and 6-iodopurines[7a] (**6** and **7**) with Raney nickel.

Equimolar amounts of **2** and sodium sulfite[14] gave purine 6-sulfonate 3-oxide (**8**) which was identical with the product obtained by $KMnO_4$ oxidation of 6-mercaptopurine 3-oxide[15] (**1**). Reaction of 6-chloropurine 3-oxide (**2**) with an excess of sodium methoxide resulted in the formation of 6-methoxypurine 3-oxide (**9**) which was converted to 6-methoxypurine[16] with Raney nickel. On prolonged treatment with aqueous ammonia, 6-chloropurine 3-oxide (**2**) gave adenine **11**. Treatment of **2** with hydrazine resulted in the simultaneous and rapid reduction and hydrazinolysis to 6-hydrazinopurine[17] (**12**). Compound **2**, which reacted more slowly than its parent with ethanolic hydroxylamine, yielded 6-hydroxylaminopurine[18] (**13**). Treatment of 6-chloropurine 3-oxide (**2**) with morpholine afforded 6-morpholinopurine[19] (**14**).

Hypoxanthine 3-oxide (**16**) resulted from the treatment of 6-methylmercaptopurine 3-oxide[5] (**15**) with

(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748), the Atomic Energy Commission (Contract No. AT(30-1)-910), and the American Cancer Society (Grant No. T-128F).

(2) G. B. Brown, 4th International Congress of Biochemistry, Vienna, 1958, Vol. XIII-Colloquia, Pergamon Press, London, 1958, p 111.

(3) D. A. Clarke, F. S. Philips, S. S. Sternberg, and C. C. Stock, *Ann. N. Y. Acad. Sci.*, **60**, 235 (1954).

(4) M. A. Stevens, A. Giner-Sorolla, H. W. Smith, and G. B. Brown, *J. Org. Chem.*, **27**, 567 (1962).

(5) (a) G. Levin and G. B. Brown, *J. Med. Chem.*, **6**, 825 (1963); (b) G. B. Brown, G. Levin, S. Murphy, A. Sele, H. C. Reilly, G. S. Tarnowski, F. A. Schmid, M. N. Teller, and C. C. Stock, *ibid.*, **8**, 190 (1965).

(6) A. Bendich, P. J. Russell, and J. J. Fox, *J. Amer. Chem. Soc.*, **76**, 6073 (1954).

(7) (a) G. B. Elion and G. H. Hitchings, *ibid.*, **78**, 3508 (1956); (b) A. G. Beaman, J. F. Gerster, and R. K. Robins, *J. Org. Chem.*, **27**, 986 (1962).

(8) (a) C. C. Stock and K. Sugiura, *Ann. N. Y. Acad. Sci.*, **68**, 834 (1958); (b) A. C. Sartorelli and B. A. Booth, *Cancer Res.*, **20**, 198 (1960); (c) A. C. Sartorelli, E. J. Schoolar, Jr., and P. F. Kruse, Jr., *Proc. Soc. Exp. Biol. Med.*, **104**, 266 (1960); (d) A. C. Sartorelli, B. A. Booth, and R. K. Robins, *Biochem. Pharmacol.*, **11**, 1017 (1962); (e) R. K. Robins, *J. Med. Chem.*, **7**, 186 (1964); (f) G. B. Elion, S. Callahan, H. Nathan, S. Bieber, R. W. Rundles, and G. H. Hitchings, *Biochem. Pharmacol.*, **12**, 85 (1963).

(9) (a) M. L. Murphy, T. C. Tan, R. R. Ellison, D. A. Karnofsky, and J. H. Burchenal, *Proc. Am. Assoc. Cancer Res.*, **2**, 36 (1955); (b) R. R. Ellison, D. A. Karnofsky, and J. H. Burchenal, *Blood*, **13**, 705 (1958); (c) R. R. Ellison, R. T. Silver, and R. L. Engle, Jr., *Ann. Internal Med.*, **51**, 322 (1959); (d) L. R. Duvall, *Cancer Chemotherapy Repts.*, **11**, 178 (1961); (e) R. M. Whittington, S. L. Rivers, R. T. Doyle, and D. Kodlin, *ibid.*, **18**, 73 (1962).

(10) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Amer. Chem. Soc.*, **80**, 2755 (1958).

(11) T. J. Delia, M. J. Olsen, and G. B. Brown, *J. Org. Chem.*, **30**, 2766 (1965), report the oxidation of cytosine and cytidine to their 3-N-oxides in 21 and 41% yields with *m*-chloroperoxybenzoic acid; and T. Kato, H. Yamanaka, and H. Hiranuma, *Chem. Pharm. Bull.* (Tokyo), **16**, 1337 (1968), report the preparation of chloropyrimidine N-oxides with monopermaleic acid.

(12) (a) Wellcome Foundation Ltd., British Patent 767,216 (1957); *Chem. Abstr.*, **51**, 14796 (1957); (b) C. W. Noell and R. K. Robins, *J. Amer. Chem. Soc.*, **81**, 5997 (1959); (c) R. K. Robins, *ibid.*, **82**, 2654 (1960); (d) A. G. Beaman and R. K. Robins, *J. Appl. Chem.*, **12**, 432 (1962); (e) G. B. Brown, *Biochem. Prepn.*, **10**, 145 (1963).

(13) Ajinomoto Co., Brevet d'Invention, P. V. no. 83,853, French Patent 1,500,662 (1967).

(14) This reaction was adapted from the similar conversion of 6-chloropurine to purine 6-sulfonate (I. L. Doerr, I. Wempen, D. A. Clarke, and J. J. Fox, *J. Org. Chem.*, **26**, 3401 (1961)).

(15) I. Scheinfeld, J. C. Parham, S. Murphy, and G. B. Brown, *ibid.*, **34**, 2153 (1969), preceding paper.

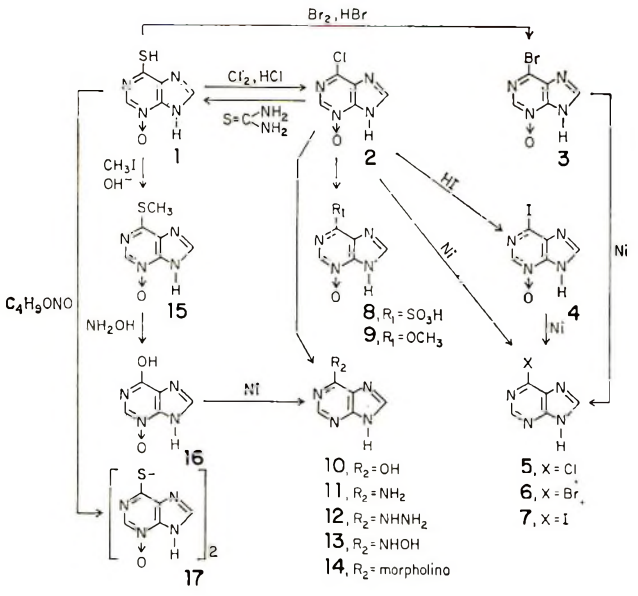
(16) G. Huber, *Chem. Ber.*, **90**, 698 (1957).

(17) J. A. Montgomery and L. B. Holum, *J. Amer. Chem. Soc.*, **79**, 2185 (1957).

(18) A. Giner-Sorolla and A. Bendich, *ibid.*, **80**, 3932 (1958).

(19) G. B. Elion, E. Burgi, and G. H. Hitchings, *ibid.*, **74**, 411 (1952); *cf.* also ref 5.

SCHEME I



methanolic hydroxylamine. This compound was identical with the product obtained in this laboratory from purine-6-sulfonate 3-oxide[15] (**8**). 6-Mercaptopurine 3-oxide (**1**) was oxidized to the disulfide **17** with butyl nitrite. Reaction of **2** with molten cyanamide resulted in its conversion to 6-chloro-9-cyanaminopurine 3-oxide.

Biological Activity.—The new purine 3-N-oxides have been tested in the Divisions of Drug Resistance and Experimental Chemotherapy for their effects against several mouse leukemias and Sarcoma 180.

The toxicity of 6-chloropurine 3-oxide toward mice bearing Sarcoma 183 was but slightly less than that of 6-chloropurine, as measured by lack of weight gain. Dosages of 6-chloropurine 3-oxide (**2**) of 125–500 mg/kg/day for 7 days gave the same modest tumorinh ibition as 62.5–250-mg doses of 6-chloropurine (**5**).

Preliminary studies revealed that 6-chloro-, 6-iodo-, and 6-bromopurine 3-oxides were ineffective when tested against mouse leukemia L1210 and Ridgway osteogenic sarcoma. Some slight inhibitory action against carcinoma E0771 in mice was observed with 6-iodopurine 3-oxide (15 days administration, 250 mg/kg/day).

Experimental Section

Ultraviolet absorption spectra were determined with a Cary recording spectrophotometer, Model 11. Paper chromatograms were run by the ascending method on Whatman No. 1 paper in the following solvent systems: H_2O saturated with *n*-BuOH, *n*-BuOH saturated with H_2O (with or without 10% NH_3); *n*-BuOH–HCOOH–H_2O (77:10:13, v/v). Melting points were taken in a Thomas–Hoover Unimelt apparatus and were corrected. The microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. In all cases, the criteria for the identity of known compounds or the new ones prepared by different methods were based on mixture melting point, uv spectra, and paper chromatography in the solvent systems described above. Th p*K* values were determined electrometrically by methods described.[20] Spectra were determined in 0.01 *M* buffers.[21] Spectral data are shown in Table I.

6-Chloropurine 3-Oxide (2).—Chlorine was bubbled through a suspension of 6-mercaptopurine 3-oxide hydrate[5] (**1**, 15 g, 0.081 mmol) in MeOH (15 ml) and concentrated aqueous HCl (45 ml) previously saturated at −10° with HCl. The solid dissolved and later a yellow crystalline product appeared, which redissolved. The addition of chlorine was continued until a sample of the solution permanently bleached a piece of pH indicator paper (~2.5 hr). Crushed ice (100 g) was poured onto the solution and concentrated aqueous NH_3 was added dropwise with stirring to pH 5 while the temperature was maintained below 0°. The thick white crystalline precipitate was kept at 5° overnight, collected, washed with a little cold water, and dried *in vacuo* over P_2O_5; yield 7.8 g of thin needles, mp 160° (explodes when inserted at 150°). Upon concentration of the mother liquors *in vacuo*, a second crop was obtained (5.8 g), mp 160° (explodes when inserted at 150°); total yield 13.6 g (89%). An analytical sample was prepared by repeated washing with 90% aqueous MeOH at 25°.

Anal. Calcd for $C_5H_3N_4OCl$: C, 35.21; H, 1.77; N, 32.85; Cl, 20.80. Found: C, 35.01; H, 1.93; N, 33.76; Cl, 20.71.

Treatment of **2** with mineral acids (HCl, HF) at 80° for 1 hr gave hypoxanthine (**10**).

Preparation of 6-Chloropurine 3-Oxide by Oxidation.[11]—6-Chlorpurine (**5**, 250 mg, 1.6 mmol) was dissolved in ether (400 ml) and *m*-chloroperoxybenzoic acid (85% pure) (0.6 g, 3.2 mmol) was added. The solution was stirred at 25° for 1 week. The resulting crystalline precipitate was collected, washed with ether, and yielded 30 mg (11%). This product was identical with the material prepared above. The residue obtained from the filtrate upon evaporation was washed with C_6H_6 to yield 6-chloropurine containing a small proportion of its 3-N-oxide.

An ether solution of 6-bromopurine (100 mg, 0.5 mmol, in 400 ml ether) and *m*-chloroperoxybenzoic acid (85%) (200 mg, 1 mmol) was stirred at room temperature for 1 week. The starting material was recovered unchanged.

6-Iodopurine was also recovered unchanged from a similar treatment with *m*-chloroperoxybenzoic acid.

Reactions of 6-Chloropurine 3-Oxide (2).—Treatment of **2** (100 mg) with aqueous concentrated NH_3 at 70° for 12 hr gave a product which was identified as adenine (**11**). Adenine was also obtained from **2** with saturated EtOH NH_3 at 100° for 18 hr.[15]

Refluxing of **2** (100 mg) with 20% EtOH hydrazine (5 ml) for 30 min gave a 54% yield of 6-hydrazinopurine[17] (**12**).

A solution of 6-chloropurine 3-oxide (**2**) (0.50 g) in 1 *M* EtOH hydroxylamine (250 ml, pH 6.8) was refluxed for 18 hr in the dark. The solution was evaporated to dryness *in vacuo* and the residue was washed with cold MeOH to yield 0.27 g (61%) of a substance which was identified as 6-hydroxylaminopurine[18] (**13**). The rate of transformation of **2** into 6-hydroxylaminopurine (as measured by uv spectral changes and by the time required to show a positive $FeCl_3$ test) was much slower than the rate of reaction of 6-chloropurine with hydroxylamine.[18]

6-Mercaptopurine 3-Oxide (1) from 6-Chloropurine 3-Oxide (2).—6-Chloropurine 3-oxide (**2**) (10 mg, 0.06 mmol) and thiourea (9 mg, 0.12 mmol) in EtOH (3 ml) were refluxed for 5 min. The colorless solution turned yellow after 1 min and exhibited uv spectra (at pH 1, 6.9, and 12) and R_f values (in the three solvent systems), identical with those of 6-mercaptopurine 3-oxide (**1**).[5]

TABLE I

SPECTRAL DATA AND p*K*'S

pH	Charge	λ_{max}, mμ ($\epsilon \times 10^{-3}$)	p*K*
		6-Chloropurine 3-Oxide (**2**)	
2	(0)	229 (22.4), 302 (9.1)	
			5.37 ± 0.07
8	(−)	230 (27.8), 305 (7.8)	
		6-Bromopurine 3-Oxide (**3**)	
2	(0)	233 (22.1), 290[a] (9.2), 303 (11.2)	
			5.28 ± 0.04
8	(−)	233 (29.1), 293[a] (7.3), 306 (8.4)	
		6-Iodopurine 3-Oxide (**4**)	
2	(0)	217 (14.0), 231 (13.9) 293[a] (9.5), 311 (14.1)	
			5.35 ± 0.06
8	(−)	238 (20), 295[a] (9.3) 311 (10.9), 322[a] (8.6)	

[a] Shoulder.

(20) A. Albert and E. P. Serjeant "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, N. Y., 1962.

(21) D. D. Perrin, *Australian J. Chem.*, **16**, 572 (1963).

6-Bromopurine 3-Oxide (**3**).—6-Mercaptopurine 3-oxide hydrate (**1**) (2.0 g, 12 mmol) was added slowly to a mixture of concentrated HBr (20 ml) and MeOH (15 ml) at −12°. When the addition was complete, bromine (5 ml) was added dropwise with stirring at the same temperature. The temperature was maintained between −10° and −5° and after 1 hr the suspension was adjusted with 50% KOH to pH 7. The yellow precipitate was collected, washed with a little cold H_2O, and dried *in vacuo* over P_2O_5; yield 1.3 g (57%), short yellow needles, mp 178° (explodes when inserted at 170°). An analytical sample was prepared by thorough washing of the product with H_2O and EtOH at 25°.

Anal. Calcd for $C_5H_3N_4BrO$: C, 27.93; H, 1.41; N, 26.06; Br, 37.17. Found: C, 27.79; H, 1.74; N, 25.97; Br, 37.08.

6-Bromopurine 3-oxide (**3**) (100 mg) was recovered unchanged after refluxing with concentrated aqueous NH_3 (50 ml) for 12 hr. Similar treatment with 1 *M* hydroxylamine led to 6-hydroxylaminopurine[18] **13**.

6-Iodopurine 3-Oxide (**4**).—Finely pulverized 6-chloropurine 3-oxide (**2**) (5.0 g, 29.3 mmol) was poured at −15° with stirring into 40 ml of HI (*d* 1.7). Solution occurred and, after a few minutes, an abundant yellow crystalline precipitate appeared. The reaction mixture was kept at −15° for 3 hr. The precipitate was collected and poured into crushed ice (40 g) and the pH carefully was adjusted to 5 with concentrated aqueous NH_3. Colorless needles, mp 175° (explodes when inserted at 165°), 6.2 g (81%), were obtained. When this product was heated slowly, decomposition with evolution of I_2 occurred. An analytical sample was prepared by thorough washing of a sample with H_2O and EtOH.

Anal. Calcd for $C_5H_3N_4IO$: C, 22.92; H, 1.15; H, 21.38; I, 48.44. Found: C, 22.91; H, 1.20; N, 21.37; I, 48.25.

A sample of 6-iodopurine 3-oxide (**4**) gave hypoxanthine (**10**) and iodine when treated with aqueous HF at 80°. When **4** (100 mg) was refluxed with concentrated aqueous NH_3 (50 ml) for 12 hr, no change in the uv spectrum was observed. Upon similar treatment with 1 *M* EtOH, hydroxylamine **4** was converted to 6-hydroxylaminopurine (**13**).

Purine-6-Sulfonate 3-Oxide (**8**).—6-Chloropurine 3-oxide **2** (170 mg, 1 mmol) was suspended in H_2O (5 ml), Na_2SO_3 (126 mg, 1 mmol) was added, and the mixture was heated to 80° for 1 hr.[14] After cooling, EtOH (15 ml) was added, the crystalline precipitate was collected and dissolved in H_2O (2 ml), and the solution was acidified to pH 5 with glacial AcOH. A precipitate, colorless prisms (78 mg, 36%), mp >350°, was obtained. This substance was identical with the product obtained from **1** by $KMnO_4$ oxidation.[15]

6-Methoxypurine 3-Oxide (**9**).—Sodium (1.15 g, 50 mg-atoms) was dissolved in MeOH (100 ml) and finely powdered 6-chloropurine 3-oxide (**2**) (2.5 g, 14.7 mmol) was slowly added with stirring. The mixture was refluxed for 3 hr, cooled, and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue was dissolved in H_2O (20 ml) and neutralized with 20% aqueous AcOH. The precipitate was thoroughly washed with H_2O and EtOH to yield 1.36 g (56%) of a crystalline product, mp 230° (explodes when inserted at 220°). An analytical sample of 6-methoxypurine 3-oxide (**9**) was prepared by solution in a minimum amount of H_2O, charcoal treatment, and precipitation by excess *n*-PrOH; long thin needles, mp 232° (explodes when inserted at 220°).

Anal. Calcd for $C_6H_6N_4O_2 \cdot 0.33H_2O$: C, 41.86; H, 3.90; N, 32.60. Found: C, 41.63; H, 3.80; N, 32.57.

Hypoxanthine 3-Oxide (**16**).—6-Methylmercaptopurine 3-oxide[5] (**15**) (1.0 g, 5.5 mmol) was dissolved in 2 *M* anhydrous hydroxylamine solution in MeOH (200 ml) and refluxed for 18 hr. The precipitate was collected and dissolved in H_2O (10 ml), and the pH was adjusted to 5.5 with 20% aqueous AcOH. The crystalline product was collected and washed thoroughly with H_2O and EtOH; yield 0.55 g (66%) of colorless prisms, mp 330° (explodes when inserted at 320°).

Anal. Calcd for $C_5H_4N_4 \cdot 0.5H_2O$: C, 37.27; H, 3.13; N, 34.78. Found: C, 37.68; H, 3.77; N, 33.68.

This substance was identical with that obtained from purine-6-sulfonate 3-oxide (**8**) by acid hydrolysis.[15]

Disulfide of 6-Mercaptopurine 3-Oxide (**17**).—6-Mercaptopurine 3-oxide hydrate (**1**) (0.30 g, 1.9 mmol) was suspended in EtOH (30 ml) and butyl nitrite (2 ml) was added slowly while stirring. The mixture was refluxed and stirred for 4 hr, and the yellow precipitate was filtered and washed with EtOH giving yellow crystals (0.20 g, 63%) which darkened when inserted at 265° and exploded at 270°. An analytical sample was prepared by repeated washing with 95% EtOH.

Anal. Calcd for $C_{10}H_6N_6O_2S_2$: C, 35.92; H, 1.81; N, 33.52; S, 19.18. Found: C, 35.96; H, 1.81; N, 33.52; S, 19.19.

This product was identical with that obtained by iodine oxidation of **1**.[15]

6-Chloro-9-cyanaminopurine 3-Oxide.—6-Chloropurine 3-oxide (**2**) (0.05 g, 2.9 mmol) was dissolved in molten cyanamide (2.5 g, 0.06 mmol) at 50°. The solution was heated at 80–85° for 30 min and then cooled. The mixture was washed with MeOH to afford 0.46 g (69%) of thin colorless needles, mp >350°. An analytical sample was obtained by recrystallization from EtOH.

Anal. Calcd for $C_6H_3N_6OCl \cdot H_2O$: C, 31.52; H, 2.20; N, 36.76; Cl, 15.51. Found: C, 31.36; H, 3.09; N, 36.52; Cl, 15.37.

In a similar experiment 6-chloropurine (**5**) did not react with cyanamide.

Reduction of 6-Substituted Purine 3-Oxides.—The 3-oxides of 6-chloro- (**2**), 6-bromo-, (**3**), and 6-iodopurine (**4**), purine-6-sulfonate (**8**), 6-methoxypurine (**9**), and hypoxanthine (**16**) were dissolved (10 mg each) in 5% aqueous NH_3 (10 ml) suspension of Raney nickel (100 mg) and boiled for 1 hr (except for **2** which required 72 hr to complete conversion to **5**). After evaporation of the filtrate to 0.5 ml, the reaction products were found to be identical[20] with 6-chloro- (**5**),[6] 6-bromo- (**6**),[7] and 6-iodopurine (**7**)[7a] purine-6-sulfonate,[14] 6-methoxypurine,[16] and hypoxanthine (**10**), respectively.

Registry No.—**2**, 19765-60-7; **3**, 19765-61-8; **4**, 19765-62-9; **8**, 19765-63-0; **9**, 19765-64-1; **16**, 19675-65-2; **17**, 19765-66-3; 6-chloro-9-cyanaminopurine 3-oxide, 19765-67-4.

Acknowledgments.—The authors wish to thank Dr. J. H. Burchenal, Dr. M. R. Dollinger, and Dr. G. Tarnowski for the screening tests and Mr. T. Winn for technical assistance. The continued interest of and valuable discussions with Dr. J. C. Parham and Dr. I. Scheinfeld are gratefully acknowledged.

Purine Nucleosides. XXIV. A New Method for the Synthesis of Guanine Nucleosides. The Preparation of 2′-Deoxy-α- and -β-guanosines and the Corresponding N^2-Methyl Derivatives[1]

MORRIS J. ROBINS AND ROLAND K. ROBINS

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

Received January 7, 1969

Diazotization of 2-amino-6-benzyloxypurine in fluoroboric acid produced 2-fluoro-6-benzyloxypurine (**1**). Acid-catalyzed fusion of **1** with 1,3,5-tri-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranose (**2**) gave the anomeric 2-fluoro-6-benzyloxy-9-(3,5-di-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranosyl)purines (**3**). Treatment of this mixture with alcoholic ammonia (or methylamine) provided the 2-amino- (or 2-methylamino-) 6-benzyloxy-9-(2-deoxy-α- and -β-D-*erythro*-pentofuranosyl)purines which were resolved into pure anomers by chromatography on Dowex 1-X2. Palladium–carbon-catalyzed hydrogenation of these benzyloxy derivatives gave the desired guanine 2′-deoxynucleosides, which obey Hudson's isorotation rules. The nmr spectra of these 2′-deoxy-D-*erythro*-pentofuranosides had a peak corresponding to an A_2X system which appeared as a "triplet" with $J_{H_1'} = 7$ Hz for the β anomer and a "quartet" with $J_{H_1'} \cong 3.5$ and 7.5 Hz for the α anomer. A facile synthesis of 2-amino-6-benzyloxypurine from 2,4,5-triamino-6-benzyloxypyrimidine is described. Alternative binding mechanisms of actinomycin D to DNA are considered with respect to N^2-methyl-2′-deoxyguanosine.

Interest in the preparation and biological evaluation of certain anomeric purine 2′-deoxynucleosides has been stimulated by the report[2] that 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-thione (α-2′-deoxythioguanosine) is incorporated *per se* into DNA. Since N^2-methylguanosine is a naturally occurring "minor component" nucleoside in RNA,[3] it is of interest to consider N^2-methyl-2′-deoxyguanosine for incorporation into DNA in order to determine physical changes[4] in the macromolecule as well as biological effects. In addition, N^2-methyl-2′-deoxyguanosine (**9**) is a valuable molecule for evaluation of the two suggested models for the binding of actinomycin D to DNA. According to the model of Müller and Crothers,[5] the actinomycin D chromophore is intercalated between the base pairs in the DNA complex adjacent to any guanine–cytosine base pair. The guanine specificity is attributed to electronic interactions in the intercalated π complex. In contrast, a free 2-amino group of guanine is required for hydrogen bonding in the actinomycin D–DNA complex model of Reich and coworkers.[6] Therefore a synthetically polymerized DNA with N^2-methyl-2′-deoxyguanosine (**9**) in place of 2′-deoxyguanosine (**8**) could not bind actinomycin D by the Reich mechanism[6] but should bind to some extent (uv spectra of **8** and **9** are qualitatively and quantitatively similar) by the π-complex[5] mechanism.

Several approaches have been employed in the synthesis of nucleosides of the guanine ring system.[7] However, certain of these procedures involve high-temperature amination and/or acidic deamination steps and are somewhat unsuited for the preparation of deoxyguanosines. Indeed, 2′-deoxyguanosine (**8**) has been prepared previously in 1.5%[7b] and 4.4%[7e] over-all yields based on purine starting materials.

Success in the fusion procedure[8] of deoxynucleoside synthesis[9] suggested a new approach to the problem. The synthesis of 2′-deoxyguanosine (**8**) and its α anomer **10** (obtained for the first time) has now been accomplished in 14 and 16% yields, respectively, from starting purine **1** *via* the fusion method (Scheme I). This procedure also precluded any toxic mercury ion contamination.[10]

The starting material base chosen for the fusion procedure was 2-fluoro-6-benzyloxypurine which has a group at the 2 position readily susceptible to nucleophilic displacement[11,12] and the benzyloxy function at the 6 position which can be readily converted to keto oxygen by hydrogenation at neutral pH. Ring closure of 2,4,5-triamino-6-benzyloxypyrimidine[13] with diethoxymethyl acetate[14] gives a convenient alternative synthesis of 2-amino-6-benzyloxypurine.[15] Treatment of 2-amino-6-benzyloxypurine with sodium nitrite in aqueous fluoroboric acid according to the general procedure of Montgomery and Hewson[16] gave 2-fluoro-6-benzyloxypurine (**1**), the desired base for fusion coupling in 48% yield.

Acid-catalyzed fusion of **1** and 1,3,5-tri-*O*-acetyl-2-deoxy-D-*erthro*-pentofuranose[9] (**2**) gave 2-fluoro-6-benzyloxy-9-(3,5-di-*O*-acetyl-2-deoxy-α- and -β-D-*erythro*-pentofuranosyl)purines (**3**) in at least 40% yield as a syrupy mixture. Treatment of this product with methanolic ammonia at 80° gave 2-amino-6-benzyloxy-9-(2-deoxy-α- and -β-D-*erythro*-pentofuranosyl)purines

(1) This work was supported by Research Grant CA 08109 from the National Cancer Institute of the National Institutes of Health.

(2) G. A. LePage and I. G. Junga, *Mol. Pharmacol.*, **3**, 37 (1967).

(3) R. H. Hall, *Biochemistry*, **4**, 661 (1965), and references therein.

(4) See, for example, P. R. Srinivasan and E. Borek, *Science*, **145**, 548 (1964); A. D. Broom, M. P. Schweizer, and P. O. P. Ts'o, *J. Amer. Chem. Soc.*, **89**, 3612 (1967).

(5) W. Müller and D. M. Crothers, *J. Mol. Biol.*, **35**, 251 (1968).

(6) E. Reich and I. H. Goldberg, *Prog. Nucleic Acid Res. Mol. Biol.*, **3**, 183 (1964); A. Cerami, E. Reich, D. C. Ward, and I. H. Goldberg, *Proc. Natl. Acad. Sci. U. S.*, **57**, 1036 (1967).

(7) See, for example, (a) S. R. Jenkins, F. W. Holly, and E. Walton, *J. Org. Chem.*, **30**, 2851 (1965); (b) H. Venner, *Chem. Ber.*, **93**, 140 (1960); (c) J. Davoll and B. A. Lowy, *J. Amer. Chem. Soc.*, **74**, 1563 (1952); (d) E. J. Reist and L. Goodman, *Biochemistry*, **3**, 15 (1964); (e) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963); (f) Y. Furukawa and M. Honjo, *Chem. Pharm. Bull.* (Tokyo), **16**, 1076 (1968).

(8) T. Sato, T. Simadate, and Y. Ishido, *Nippon Kagaku Zasshi*, **81**, 1440 (1960).

(9) M. J. Robins and R. K. Robins, *J. Amer. Chem. Soc.*, **87**, 4934 (1965).

(10) J. Škoda, I. Bartošek, and F. Šorm, *Collect. Czech. Chem. Commun.*, **27**, 906 (1962); E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *J. Med. Chem.*, **8**, 659 (1965); G. L. Tong, W. W. Lee, and L. Goodman, *J. Org. Chem.*, **32**, 1984 (1967).

(11) J. F. Gerster and R. K. Robins, *J. Amer. Chem. Soc.*, **87**, 3752 (1965).

(12) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **11**, 48 (1968).

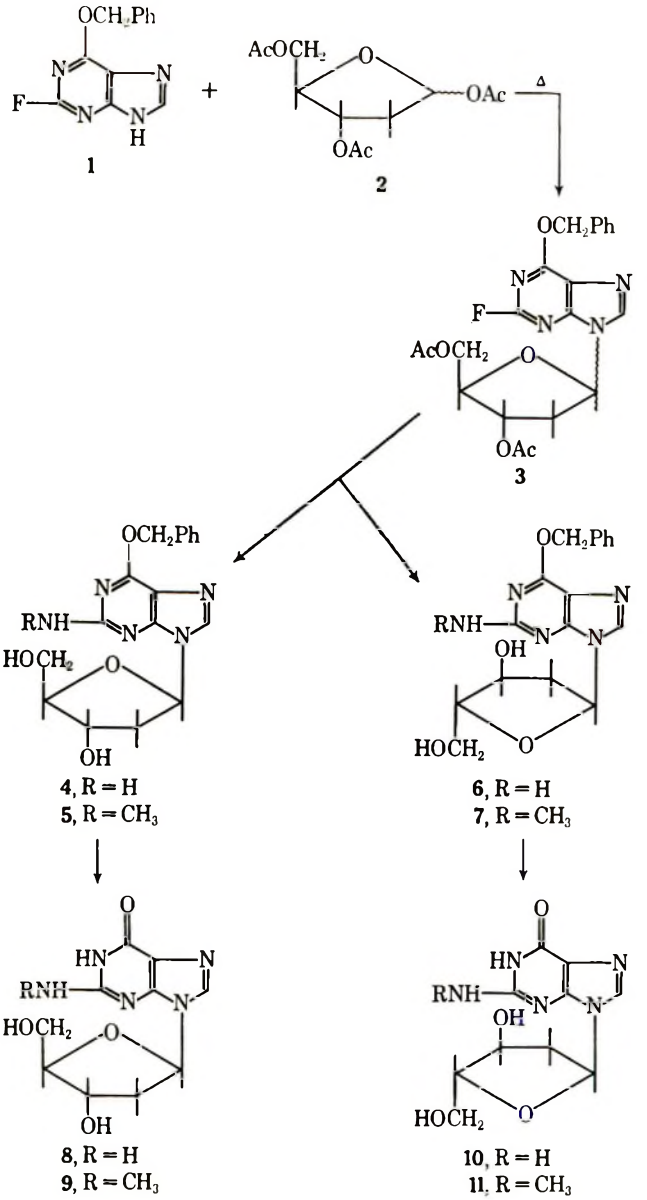
(13) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, **73**, 2869 (1951).

(14) H. W. Post and E. R. Erickson, *J. Org. Chem.*, **2**, 260 (1937). An improved preparation of diethoxymethyl acetate has been developed: private communication from Dr. J. A. Montgomery, Southern Research Institute.

(15) W. A. Bowles, F. H. Schneider, L. R. Lewis, and R. K. Robins, *J. Med. Chem.*, **6**, 471 (1963).

(16) J. A. Montgomery and K. Hewson, *J. Amer. Chem. Soc.*, **82**, 463 (1960).

SCHEME I



(6 and 4) in contrast to results reported with analogous treatment of 2-chloro-6-methoxy-9-β-D-ribofuranosylpurine.[17] In the latter case the 6-alkoxy function was selectively replaced by ammonia and thus the successful choice of the 2-fluoro leaving group is suggested. The anomers **4** and **6** were resolved on a Dowex 1-X2 (OH^-) column.[18] The α anomer was crystallized and characterized by elemental analysis and uv spectroscopic comparison with the β-D-ribofuranose analog.[11] The β anomer **4** was compared with **6** spectroscopically and by thin layer chromatography (tlc) and was converted directly to 2′-deoxyguanosine (**8**) by palladium-catalyzed hydrogenation without further purification. The properties of synthetic and naturally occurring **8** were rigorously compared and found to be identical. This confirms the position of attachment and configuration of synthetic **8** and the other nucleosides obtained from the intermediate **3**. Compound **6** was similarly hydrogenated to give the first reported synthesis of 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purin-6-one (α-2′-deoxyguanosine) (**10**).

(17) H. J. Schaeffer and H. J. Thomas, *J. Amer. Chem. Soc.*, **80**, 3738 (1958).

(18) C. A. Dekker, *ibid.*, **87**, 4027 (1965).

For the synthesis of the N^2-methyl-2′-deoxyguanosines, the syrupy mixture containing the anomeric 2-fluoro-6-benzyloxy-9-(3,5-di-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranosyl)purines (**3**) was treated with methanolic methylamine at room temperature to give 2-methylamino-6-benzyloxy-9-(2-deoxy-α- and -β-D-*erythro*-pentofuranosyl)purines (**7** and **5**). Anomeric resolution of **5** and **7** was accomplished on Dowex 1-X2 (OH^-). These anomers had tlc behavior similar to **4** and **6** and had uv absorption comparable to the riboside analog.[11] Compound **5** was catalytically hydrogenated to the desired 2-methylamino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-one (**9**) without further purification. Compound **7** was transformed to 2-methylamino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)-purin-6-one (**11**) by the same procedure. The anomers **9** and **11**, obtained in 17 and 21% over-all yield, respectively, exhibit uv spectra almost identical with those of N^2-methylguanosine.[11] The tlc migrations of **9** and **11** are identical with those of 2′-deoxyguanosine (**8**) and α-2′-deoxyguanosine (**10**), respectively (see Experimental Section). Examination of the nmr spectra of the 2′-deoxynucleosides **6** and **8**–**11** demonstrated results in accord with A_2X splitting patterns previously observed for purine 2′-deoxy-*erythro*-pentofuranosides.[9] These anomeric 2′-deoxynucleosides **8**–**11** were found to obey Hudson's isorotation rule[19] in dimethylformamide.

Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Nmr spectra were determined on a Varian A-60 instrument with sodium 5,5-dimethyl-5-silapentanesulfonate as internal standard. Uv spectra were determined on a Beckman DK-2 instrument. Hydrogenations were effected using a Parr hydrogenation apparatus at specified hydrogen gas pressure. Evaporations were accomplished using a Büchler rotating evaporater under reduced pressure unless otherwise specified. Thin layer chromatography (tlc) was run on glass plates coated with SilicAR-7GF (Mallinckrodt Chemical Works) using the upper phase of ethyl acetate–*n*-propyl alcohol–water (4:1:2) unless specified otherwise.

2,4,5-Triamino-6-benzyloxypyrimidine.[13]—A solution of 50 g (0.20 mol) of 2,4-diamino-5-nitroso-6-benzyloxypyrimidine[13] in 1500 ml of 95% EtOH was reduced as previously described. The resulting solution was evaporated to dryness under a nitrogen stream. The brown residue was added to boiling EtOH–H_2O and this mixture was treated with Norit and filtered. The filtrate was cooled at 0° for 18 hr and the resulting yellow crystals (40 g, 85%) which separated were filtered. A small sample for analysis was recrystallized from EtOH–H_2O to give crystals: mp 149–151°; uv $\lambda_{max}^{pH\ 1}$ 277 mμ (ε 12,500), $\lambda_{Sh}^{pH\ 1}$ 224 mμ (ε 8900), $\lambda_{max}^{pH\ 11}$ 283, 243 mμ (ε 7870, 8660), λ_{max}^{EtOH} 285, 245 mμ (ε 7230, 8660).

Anal. Calcd for $C_{11}H_{13}N_5O \cdot 0.5H_2O$: C, 55.00; H, 5.87; N, 29.16. Found: C, 55.00; H, 5.92; N, 29.14.

2-Amino-6-benzyloxypurine.[15]—To 15 g (0.093 mol) of diethoxymethyl acetate[14] was added 4.62 g (0.02 mol) of crude 2,4,5-triamino-6-benzyloxypyrimidine while stirring magnetically. The resulting red-brown solution was placed in an oil bath preheated to 185°. Vigorous boiling was moderated by raising the flask periodically. After heating for 25 min, the flask was removed from the oil bath and the thick pasty mass was allowed to cool to about 100° and then was evaporated to dryness. Water (20 ml) was added to the brown residue and NaOH pellets were added slowly until all solid material dissolved. This solution (pH >12) was refluxed for 15 min, treated with Norit, refluxed 5 min, and filtered through a Norit–Celite pad. The hot filtrate was acidified to pH ~6 with HOAc and the resulting mixture was cooled at 0° for 18 hr. The orange crystalline solid

(19) C. S. Hudson, *ibid.*, **31**, 66 (1909); *Advan. Carbohydrate Chem.*, **3**, 1 (1948).

(3.90 g, 81%) was filtered and recrystallized from EtOH–H_2O (using Norit) to yield 3.0 g (62%) of crystals, mp 197–200°, chromatographically homogeneous (tlc) and identical with authentic 2-amino-6-benzyloxypurine.[15] A small sample was recrystallized from EtOH–H_2O to give needles: mp 204–206°; uv $\lambda_{max}^{pH\ 1}$ 286 mμ (ε 12,100), $\lambda_{max}^{pH\ 11}$ 282 mμ (ε 9400), λ_{max}^{MeOH} 282, 241 mμ (ε 9200, 7500); lit.[15] mp 202–204°, mmp 203–205°.

Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.59; H, 4.36; N, 29.13.

2-Fluoro-6-benzyloxypurine (1).—To 90 ml of 48% fluoroboric acid precooled to −25° in an *i*-PrOH–Dry Ice bath was added 7.3 g (0.03 mol) of 2-amino-6-benzyloxypurine with vigorous stirring. A solution of 3.5 g (0.05 mol) of $NaNO_2$ in 4.5 ml of H_2O was added dropwise over a period of 20 min to the vigorously stirred mixture and the reaction temperature was carefully maintained at −20 to −25°. The mixture was allowed to stir an additional 20 min at −25 to −18° and then was carefully neutralized to pH ~6 with 50% aqueous NaOH solution while keeping the inside temperature −15 to −10°. The mixture was allowed to stand at 0° for 15 hr and then was filtered to give 6.3 g of solid after air drying. This solid was finely powdered and continuously extracted with absolute Et_2O for 10 days (while protected from moisture). The ether was evaporated to yield 4.4 g of yellow solid which was recrystallized from absolute EtOH to yield 3.54 g (48%) of 2-fluoro-6-benzyloxypurine (1): mp 184–185°; uv $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 13,400), $\lambda_{max}^{pH\ 11}$ 263 mμ (ε 12,900), λ_{max}^{MeOH} 256 mμ (ε 12,700), λ_{Sh}^{MeOH} 270.5, 260.5, 239 mμ (ε 3540, 11,400, 7600).

Anal. Calcd for $C_{12}H_9FN_4O$: C, 59.01; H, 3.71; F, 7.78; N, 22.94. Found: C, 58.84; H, 3.78; F, 7.95; N, 22.73.

Acid-Catalyzed Fusion of 2-Fluoro-6-benzyloxypurine (1) and 1,3,5-Tri-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranose (2).—To 3.50 g (0.0135 mol) of 1,3,5-tri-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranose (1,3,5-tri-*O*-acetyl-2-deoxy-D-ribose)[9] (2) in a 25-ml round-bottom flask was added 2.0 g (0.0082 mol) of finely powdered 2-fluoro-6-benzyloxypurine (1). This mixture was stirred well and placed in an oil bath preheated to 145°. The mixture was stirred several minutes and then 5 drops of dichloracetic acid was added with vigorous stirring. Stirring was continued until a clear amber melt formed. An oil pump was then attached to the reaction flask and fusion was continued at 145° (*in vacuo*) for 25 min. The melt was removed from the oil bath and allowed to cool to about 100° and then was dissolved in 50 ml of EtOAc. This solution was cooled in ice–H_2O and then extracted with two 30-ml portions of ice-cold saturated aqueous Na_2CO_3 solution, ice–H_2O to pH ~6, and dried over Na_2SO_4. The mixture was filtered using a Norit–Celite bed and the filtrate was evaporated to a viscous oil. The uv spectra of this syrup had λ_{max} 255.5 mμ with no shift from acidic to basic solution in EtOH. Tlc (SilicAR-7GF $CHCl_3$–Me_2CO, 9:1) showed the presence of one major uv quenching spot and several minor products. This syrup containing the anomeric mixture **3** did not crystallize and was used directly for amine displacements.

2-Amino-6-benzyloxy-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-purine (4) and 2-Amino-6-benzyloxy-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine (6).—The above syrup containing **3** was dissolved in 20 ml of MeOH, and 130 ml of MeOH presaturated with NH_3 at −10° was added. This solution was heated at 80° in a stainless steel bomb for 4.5 hr. To the cooled ammoniacal solution was added 8 ml (0.008 mol) of 1 *N* NaOH and this solution was evaporated to dryness. The residue was partitioned between 75 ml of EtOAc and 25 ml of H_2O. The aqueous phase was extracted with two 30-ml portions of EtOAc and the combined organic phase was washed with 40 ml of H_2O and 40 ml of saturated aqueous NaCl solution. The EtOAc layer was dried over Na_2SO_4, filtered, and evaporated to yield an off-white solid foam. This material was dissolved in 9 ml of glyme and 11 ml of H_2O was added. This solution was applied to a column (1 × 35 in., 500 ml) of Dowex 1-X2 (OH^-), 200–400 mesh resin packed in glyme–water (45:55). The column was eluted with the same solvent mixture and 10-ml fractions were collected. Fractions 1–74 were discarded. Fractions 75 to 87 were pooled and evaporated to dryness to yield 0.67 g (23%) of crude **6**. This product was dissolved in hot *i*-PrOH and cooled at 0° for several days to yield 0.4 g (14%) of **6** as white needle clusters. A small sample was recrystallized from *i*-PrOH to give needles of **6**: mp 158–160°, uv $\lambda_{max}^{pH\ 1}$ 287 mμ (ε 12,500), $\lambda_{max}^{pH\ 11}$ 280, 249 mμ (ε 12,000, 10,000), λ_{max}^{MeOH} 282, 249 mμ (ε 12,500, 10,900); the nmr spectrum in DMSO-d_6 was consistent with the assigned structure with an A_2X "quartet" with $J_{H_1'-H_2',H_2''}$ = 3.0 and 7.5 Hz (peak width 10.5 Hz) at δ 6.37 corresponding to the anomeric proton of a 2′-deoxy-α-*erythro*-pentofuranoside.[9]

Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 56.91; H, 5.38; N, 19.67.

Fractions 88–97 from the above column separation were pooled and evaporated to dryness to yield 0.22 g (7.5 %) of solid which was found by tlc and nmr to consist of an approximately 65:35 mixture of the α and β anomers **6** and **4**, respectively. Fractions 98–128 were pooled and evaporated to dryness to yield 0.65 g (22%) of solid **4**. The uv spectrum of this product in alcohol was essentially the same as recorded for **6**. The nmr spectrum was similar with an A_2X "pseudotriplet" corresponding to the peak for the anomeric proton.[9] The tlc R_4/R_6 = 1.1. Crude **4** was hydrogenated to give 2′-deoxyguanosine (**8**) which conclusively confirmed structure **4**.

2-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-one (2′-Deoxyguanosine) (8).—To a solution of 0.60 g (0.0017 mol) of crude **4** in 30 ml of EtOH and 60 ml of H_2O was added 0.3 g of 5% palladium on charcoal and the mixture was hydrogenated at 48 psi for 7.5 hr. The catalyst was removed by filtration using a Norit–Celite bed and the filtrate was evaporated to dryness. The crystalline solid was recrystallized from 10 ml of H_2O to yield 0.33 g (69% based on crude **4**, 14% based on starting **1**) of **8** monohydrate: $[\alpha]^{26}D$ −20.3° (*c* 1.2, DMF); uv $\lambda_{max}^{pH\ 1}$ 255 mμ (ε 12,100), $\lambda_{sh}^{pH\ 1}$ 272 mμ (ε 8460), $\lambda_{max}^{pH\ 11}$ 258–266 mμ (broad) (ε 12,000), λ_{max}^{MeOH} 253 mμ (ε 14,500), λ_{Sh}^{MeOH} 267 mμ (ε 10,600); nmr (DMSO-d_6, D_2O) δ 6.28 (t, 1, $J_{H_1'-H_2',H_2''}$ = 7 Hz, H_1') plus the remainder of a usual 2′-deoxy-β-*erythro*-pentofuranoside spectrum.[9] These physical characteristics were essentially identical with those determined on a similarly recrystallized commercial sample of 2′-deoxyguanosine; tlc R_8(synthetic)/R_8(natural) = 1.0.

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.90; H, 5.25; N, 24.65.

2-Amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purin-6-one (10).—To a solution of 0.40 g (0.0011 mol) of crude **6** in 25 ml of EtOH and 50 ml of H_2O was added 0.2 g of 5% palladium on charcoal and the mixture was hydrogenated at 48 psi for 15 hr. The mixture was treated as in the preparation of **8** above to yield 0.22 g (71% based on crude **6**, 16% based on starting **1**) of crystalline **10** hemihydrate: $[\alpha]^{26}D$ +102.4° (*c* 0.99, DMF); uv $\lambda_{max}^{pH\ 1}$ 254.5 mμ (ε 10,700), $\lambda_{Sh}^{pH\ 1}$ 274 mμ (ε 7710), $\lambda_{max}^{pH\ 11}$ 259–267 mμ (broad) (ε 9960), λ_{max}^{MeOH} 253 mμ (ε 12,000), λ_{Sh}^{MeOH} 268 mμ (ε 8830); nmr (DMSO-d_6, D_2O) δ 6.24 (q, 1, $J_{H_1'-H_2',H_2''}$ = 3.5 and 7.5 Hz, H_1'); tlc R_8/R_{10} = 1.2.

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot 0.5H_2O$: C, 43.47; H, 5.11; N, 25.35. Found: C, 43.24; H, 5.07; N, 25.57.

Reaction of Methylamine with Syrupy 2-Fluoro-6-benzyloxy-9-(3,5-di-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranosyl)purine.—A fusion of 2-fluoro-6-benzyloxypurine and 1,3,5-tri-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranose was effected in a manner identical with that described above. The syrupy product containing **3** obtained after the extraction procedure was dissolved in a minimum volume of MeOH and treated with a solution of 30 ml of liquid $MeNH_2$ in 70 ml of MeOH. The resulting yellow solution was allowed to stir at room temperature for 2 hr and 8 ml (0.008 mol) of 1 *N* NaOH was added. This solution was evaporated to dryness and the residue was partitioned between EtOAc and H_2O as described above for the preparation of the 2-amino analogs **4** and **6**. The off-white solid foam obtained by evaporating the combined, dried EtOAc phase was dissolved in 9 ml of glyme, and 11 ml of H_2O was added. This solution was applied to a column (1 × 35 in., 500 ml) of Dowex 1-X2 (OH^-) (200–400 mesh) resin packed in glyme–H_2O (45:55). Elution of the column with the same solvent mixture was begun and 10-ml fractions were collected. Fractions 1–57 were discarded. Fractions 58–82 were pooled and evaporated to dryness to yield crude 2-methylamino-6-benzyloxy-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)-purine (**7**). This product had similar uv absorption spectra to those reported[11] for 2-methylamino-6-benzyloxy-9-β-D-*ribo*-pentofuranosylpurine. The tlc migration and nmr (of the carbohydrate portion) spectrum of this product were similar to those of **6**. Fractions 83–86 contained essentially no product and were discarded. Fractions 87–130 were pooled and evaporated to dryness to yield crude 2-methylamino-6-benzyloxy-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (**5**). Again the uv spectra were similar to those reported for the riboside analog[11] and tlc migration and nmr (sugar portion) were comparable to those of **4**. These chromatographically homogeneous intermediates were

hydrogenated directly to the desired guanine-type nucleosides without further purification.

2-Methylamino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-one (9).—A solution of 0.90 g (0.0024 mol) of crude **5** in 35 ml of EtOH and 70 ml of H_2O was hydrogenated at 47 psi for 6.5 hr with 0.5 g of 5% palladium on charcoal. This mixture was treated as in the preparation of **8** above to yield 0.41 g [55% based on crude **5**, 17% based on starting 2-fluoro-6-benzyloxypurine (**1**)] of crystalline **9** hemihydrate: $[\alpha]^{26}D$ −15.2° (*c* 1.64, DMF); uv $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 13,400), $\lambda_{Sh}^{pH\ 1}$ 281 mμ (ε 7370), $\lambda_{max}^{pH\ 11}$ 258 mμ (ε 11,200), $\lambda_{Sh}^{pH\ 11}$ 270 mμ (ε 10,200), λ_{max}^{MeOH} 254 mμ (ε 14,500), λ_{Sh}^{MeOH} 273 mμ (ε 9150); nmr (DMSO-d_6, D_2O) δ 6.28 (t, 1, $J_{H_1'-H_2',H_2''}$ = 7 Hz, H_1'), 2.92 (s, 3, 2-NHC**H**$_3$); tlc R_9/R_8 (natural) = 1.0.

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot 0.5H_2O$: C, 45.51; H, 5.56; N, 24.13. Found: C, 45.32; H, 5.58; N, 24.38.

2-Methylamino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purin-6-one (11).—A solution of 1.0 g (0.0027 mol) of crude **7** in 40 ml of EtOH and 80 ml of H_2O was hydrogenated at 48 psi for 15 hr with 0.5 g of 5% palladium on charcoal. This mixture was treated as in the preparation of **8** above to yield 0.50 g (64% based on crude **7**, 21% based on starting **1**) of crystalline **11** hemihydrate: $[\alpha]^{26}D$ +94.1° (c 1.55, DMF); uv $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 11,400), $\lambda_{Sh}^{pH\ 1}$ 279.5 mμ (ε 6380), $\lambda_{max}^{pH\ 11}$ 257 mμ (ε 10,200), $\lambda_{Sh}^{pH\ 11}$ 269 mμ (ε 8980), λ_{max}^{MeOH} 254 mμ (ε 13,100), λ_{Sh}^{MeOH} 273 mμ (ε 8260); nmr (DMSO-d_6, D_2O) δ 6.27 (q, 1, $J_{H_1'-H_2',H_2''}$ = 3.5 and 8.0 Hz, H_1'), 2.91 (s, 3, 2-NHC**H**$_3$); tlc R_9/R_{11} = 1.2.

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot 0.5CH_3$: C, 45.51; H, 5.56; N, 24.13. Found: C, 45.38; H, 5.44; N, 24.17.

Registry No.—2,4,5-Triamino-6-benzyloxypyrimidine, 19916-72-4; 2-amino-6-benzyloxypurine, 19916-73-5; **1**, 19916-74-6; **6**, 19916-75-7; **8**, 961-07-9; **9**, 19916-77-9; **10**, 19916-78-0; **11**, 19916-79-1.

Reactions of Carbohydrates with (Halomethylene)dimethyliminium Halides and Related Reagents. Synthesis of Some Chlorodeoxy Sugars[1]

STEPHEN HANESSIAN[2] AND NIKE R. PLESSAS

Department of Chemistry, University of Montreal, Montreal, Quebec, Canada, and Research Laboratories, Parke, Davis and Co., Ann Arbor, Michigan 48106

Received November 13, 1968

The reaction of (chloromethylene)- and (chloroethylidene)dimethyliminium chloride with selected carbohydrate derivatives containing hydroxyl, epoxide, and unsaturated functions has been investigated. Primary hydroxyl groups are converted into formate esters or are replaced by a chlorine atom, depending on the reaction conditions. Acetal and ketal groups migrate in certain cases, especially when the hydroxyl group is secondary. The reagent reacts with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside to give the *trans*-2-chlorodeoxy-3-formate derivative, as a result of nucleophilic attack of chloride ion on the epoxide function. At elevated temperature a second chlorine atom is incorporated into the molecule with acetal migration to give methyl 3,4-*O*-benzylidene-2,6-dichloro-2,6-dideoxy-α-D-altropyranoside. The mechanism of the reaction is discussed.

Relatively few methods are available for the direct replacement of a hydroxyl group (except at C-1) in a sugar derivative by a halogen atom.[3,4] Among the methods that are considered to be of synthetic utility are the reactions of suitably blocked sugars with sulfuryl chloride,[5,6] and with triphenyl phosphite halides.[7,8] In both of these methods the halogen atom is incorporated by SN2-type reactions leading to inversion of configuration in those cases where secondary hydroxyl groups are involved. Selective chlorination of the primary hydroxyl group in some methyl hexopyranosides has been accomplished with reagents such as sulfur monochloride[9] and *N*,*N*-dimethylformamide–methanesulfonyl chloride adducts.[10]

In a preliminary communication[11] we reported on the utility of halomethyleneiminium halide reagents[12] in the preparation of certain chlorodeoxy sugars. We now wish to disclose details of this work and to comment on some synthetic and mechanistic aspects of the reaction.

The strongly electrophilic character of amide halide reagents such as (chloromethylene)dimethyliminium chloride[13,14] **2** has been exploited in a wide variety of reactions.[12−15] Some applications which are pertinent to synthetic carbohydrate chemistry include the reaction of **2** with various alcohols to give formate esters[13,14a] and chlorodeoxy sugar derivatives.[11] The sequence of reactions leading to formylation and chlorination of alcohols is illustrated in Scheme I. The precise nature of the addition product from an alcohol and **2** cannot be readily established since an equilibrium such as A ⇌ B is possible. Only one case[13] is known where the primary adduct (type B) of *t*-butyl alcohol was actually isolated as the perchlorate salt. When solutions of the adducts of simple alcohols are heated in chlorinated hydrocarbons, the corresponding alkyl halides and presumably *N*,*N*-dimethylformamide are formed.[15] Although the reaction is of preparative significance, its application has not been extended to more complex systems. Furthermore, the stereochemical course of the reaction has not been established. Some analogy can be drawn from the pyrolysis of simple imino ester hydrochlorides to the corresponding alkyl halides, which has been shown[16] to proceed by a bimolecular mechanism. The conversion of optically

(1) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, D 16.

(2) To whom correspondence should be addressed at the University of Montreal.

(3) J. E. G. Barnett, *Advan. Carbohydrate Chem.*, **22**, 177 (1967).

(4) S. Hanessian, Advances in Chemistry Series, No. 74, American Chemical Society, Washington, D. C., 1968, p 159.

(5) B. Helferich, *Ber.*, **54**, 1082 (1921).

(6) H. J. Jennings and J. K. N. Jones, *Can. J. Chem.*, **43**, 2372 (1965), and previous papers.

(7) N. K. Kochetkov and A. I. Usov, *Tetrahedron*, **19**, 973 (1963).

(8) N. K. Kochetkov and A. I. Usov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 492 (1965); *Chem. Abstr.*, **63**, 1857 (1965).

(9) H. B. Sinclair, *J. Org. Chem.*, **30**, 1283 (1965).

(10) M. E. Evans, L. Long, Jr., and F. W. Parrish, *ibid.*, **33**, 1074 (1968).

(11) S. Hanessian and N. R. Plessas, *Chem. Commun.*, 1152 (1967).

(12) For a review, see, H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

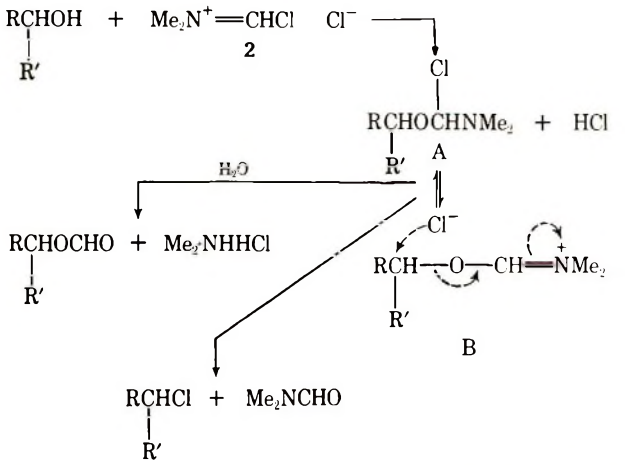
(13) Z. Arnold, *Collection Czech. Chem. Commun.*, **24**, 4048 (1959).

(14) (a) K. Morita, S. Noguchi, and M. Nishikawa, *Chem. Pharm. Bull.* (Tokyo), **7**, 896 (1959); (b) N. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

(15) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **96**, 2671 (1963).

(16) S. M. McElvain and B. E. Tate, *J. Amer. Chem. Soc.*, **73**, 2233 (1951).

SCHEME I

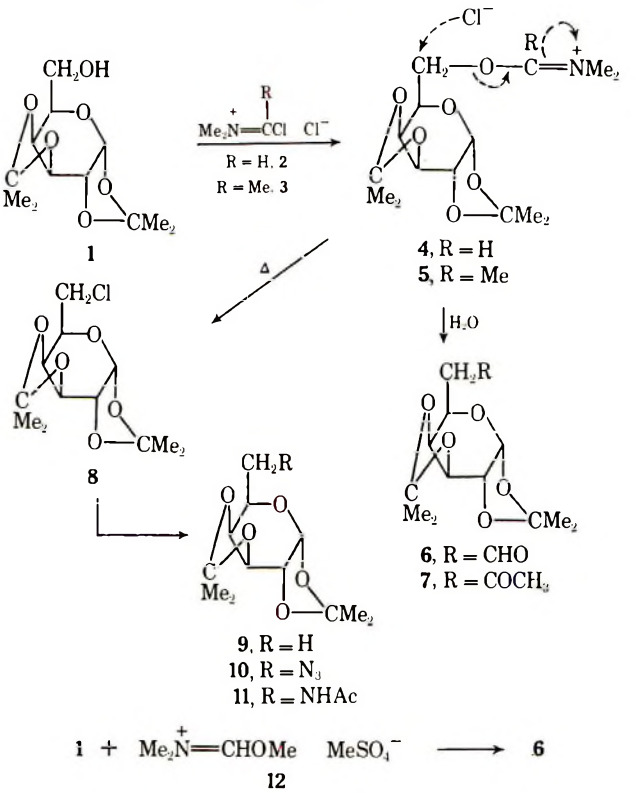


active *sec*-butyl alcohol to the corresponding halide with inversion of configuration *via* the pyrolysis of the intermediate imino ester hydrochloride has also been reported.[17] Certain derivatives of carbohydrates containing an isolated hydroxyl group are converted into chlorodeoxy derivatives in good yield, by reaction with reagents of type **2**.[11] Recent observations in these laboratories indicate, however, that the replacement of a secondary hydroxyl group in derivatives containing cyclic acetals and ketals may be accompanied by a rearrangement of these groups to give chlorodeoxy derivatives which are different from those expected on the basis of simple replacement of the hydroxyl group.

Treatment of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1**) with **2** in 1,1,2-trichloroethylene or a similar solvent resulted in almost complete conversion of **1** into the imino ester intermediate **4**[18] (Scheme II).

Treatment of the reaction mixture with aqueous bicarbonate afforded the formate ester **6**, in addition to small amounts of the 6-chlorodeoxy derivative **8**. The formation of the latter, even under mild conditions, reflects on the activated character of the imino ester group in the adduct **6**. Heating the reaction mixture afforded 6-chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**8**), in yields ranging from 85–98%. Compound **8** has been previously prepared in varying yields by other methods,[19–22] which require at least two steps starting with **1**. By conventional methods, **8** was converted into the known 6-deoxy[23,24] **9**, 6-azido[25] **10**, and 6-acetamido[25] **11** derivatives. Treatment of **1** with an excess of (chloroethylidene)dimethyliminium chloride[26] (**3**) followed by quenching of an aliquot with aqueous bicarbonate and examination by tlc, revealed the presence of the 6-*O*-acetate **7** as a preponderant product, in addition to small amounts of **1** and **8**. The reagent **3** could therefore be used as an acetylating agent in certain cases. Heating a solution containing the primary adduct **5** afforded the acetate **7** (tlc, ir) and

SCHEME II



the 6-chlorodeoxy derivative **8** in low yield (*ca.* 25%). While these results can be rationalized to some extent on the basis of steric hindrance to the attack of chloride ion at C-6, another factor which should be considered is the electronic effect exerted by the methyl group of the dimethylaminoethylidene group which would tend to stablize an intermediate such as **5**. The reaction of (methoxymethylene)dimethylimmium methylsulfate[27] (**12**) with **1** was found to be much slower than that of **2**; the formate ester **6** and unchanged **1** were the only products detectable on tlc.

As a model of a sugar derivative containing an isolated secondary hydroxyl group, we selected 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[28] (**13**).

When **13** was allowed to react with **2** at room temperature in 1,1,2,2-tetrachloroethane, the major product obtained was the 3-*O*-formate ester of **13**. Refluxing a solution containing **13** and **2** afforded a syrupy product which had spectral properties and an elemental analysis consistent with a product resulting from the loss of the hydroxyl group and the incorporation of a chlorine atom. However, the product was not the expected 3-chlorodeoxy derivative, which would have been formed by simple replacement[29] of the C-3 hydroxyl group in **13**, but rather, 6-chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose[30–32] (**14**) (Scheme III).

The structure of **14** was firmly established by comparison of optical rotation data and by appropriate

(17) C. L. Stevens, D. F. Morrow, and J. Lawson, *J. Amer. Chem. Soc.*, **77**, 2341 (1955).

(18) For simplicity, these primary adducts are represented as imino ester salts. It should be pointed out, however, that structures such as **4** could be part of an equilibrium involving related species.

(19) K. A. Petrov, E. E. Nifant'ev, A. A. Shchegolov, and V. G. Tevekhov, *J. Gen. Chem. USSR*, **34**, 1463 (1964).

(20) K. W. Buck and A. B. Foster, *J. Chem. Soc.*, 2217 (1963).

(21) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).

(22) K. R. Wood, D. Fisher, and P. W. Kent, *J. Chem. Soc.*, 1994 (1966).

(23) K. Freudenberg and K. Raschig, *Ber.*, **60**, 1633 (1927).

(24) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).

(25) W. A. Szarek and J. K. N. Jones, *Can. J. Chem.*, **43**, 2345 (1965).

(26) H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, **42**, 1659 (1959).

(27) H. Bredereck, F. Effenberger, and G. Simchen, *Chem. Ber.*, **96**, 1350 (1963).

(28) O. Th. Schmidt, *Methods Carbohydrate Chem.*, **2**, 318 (1963).

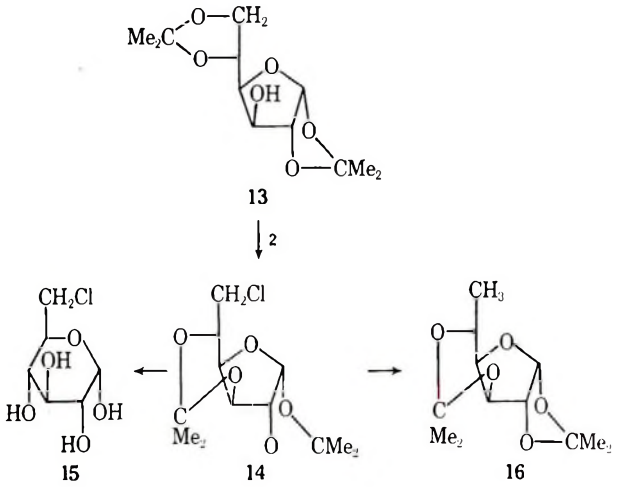
(29) It should be noted that the only example of a successful configurational inversion at C-3 in **13** involves treatment of the corresponding tosylate with refluxing hydrazine: M. L. Wolfrom, J. Bernsmann, and D. Horton, *J. Org. Chem.*, **27**, 4505 (1962), and references cited therein.

(30) J. B. Allison and R. M. Hixon, *J. Amer. Chem. Soc.*, **48**, 406 (1926).

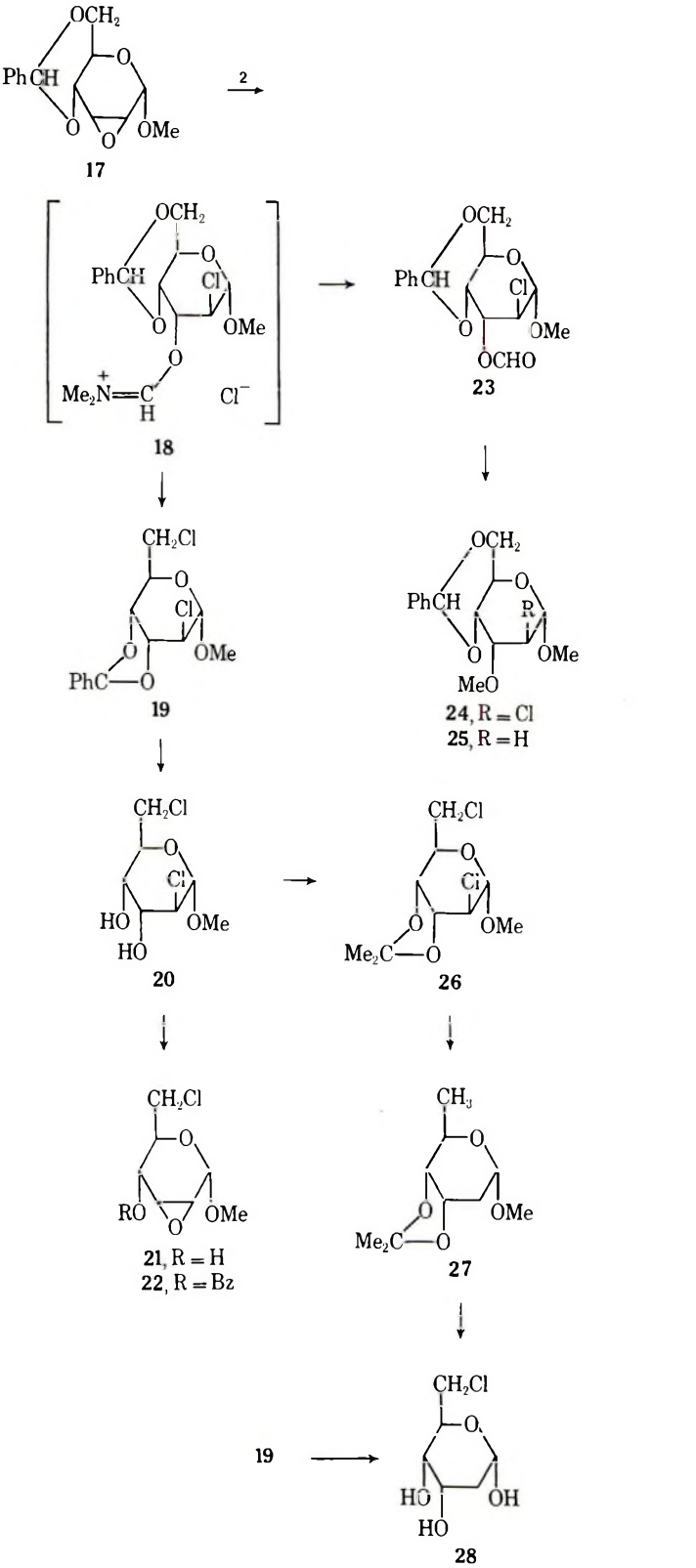
(31) D. C. C. Smith, *J. Chem. Soc.*, 1244 (1956).

(32) E. Hardegger, G. Zanetti, and K. Steiner, *Helv. Chim. Acta*, **46**, 282 (1963).

SCHEME III



SCHEME IV



conversions into the 6-deoxy derivative **16** and the crystalline free sugar, 6-chloro-6-deoxy-α-D-glucose[31] (**15**). The one-step conversion of **13** into **14** in yields exceeding 70% is particularly noteworthy, since previous preparations[30-32] utilizing phosphorus pentachloride as the chlorination agent have been accomplished at best in less than 15% yield.

Migration of the 5,6-*O*-isopropylidene group has also been observed[30-33] during the reaction of **13** with phosphorus pentachloride and with triphenyl phosphite dihalides[7] which afford the 6-halodeoxy derivatives corresponding to **14**. A possible pathway for the transformation of **13** to **14** by the method described herein has been suggested[4] and invokes the formation of an orthoester intermediate.

The reagent **2** reacts with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside[34] (**17**) to give monochlorodeoxy or dichlorodideoxy derivatives depending upon the reaction conditions.[11] At room temperature, the major product of the reaction is methyl 4,6-*O*-benzylidene-2-chloro-2-deoxy-3-*O*-formyl-α-D-altropyranoside (**23**) (Scheme IV). The latter is presumably formed by nucleophilic attack of chloride ion on the epoxide **17** or an activated form, in which the epoxide oxygen coordinated with the reagent, thus rendering it a good leaving group. Intermediate **18** which can be considered as the primary reaction product affords upon hydrolysis, the 2-chloro 3-formate derivative **23**. That the chlorine atom was situated at C-2 in the product isolated after chromatography was proved by conversion of **23** into the crystalline 3-*O*-methyl ether **24** and reduction of the latter to the known crystalline methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-*ribo*-hexopyranoside[35] (**25**). The conversion of the epoxide function in **17** into a vicinal *trans*-chloro formate system such as in **23**, under very mild conditions, demonstrates a further utility of halomethyleneiminium halide reagents in carbohydrate chemistry. Heating a solution of **17** and **2** in 1,1,2-trichloroethane afforded a methyl *O*-benzylidenedichlorodideoxyhexopyranoside in high yield. The incorporation of the second chlorine atom was originally assumed[11] to have taken place at C-3, according to mechanistic considerations,[16,17] to give a 2,3-dichlorodideoxy derivative. We have now found that the incorporation of the second chlorine atom is accompanied by a rearrangement of the benzylidene acetal, and the actual product is methyl 3,4-*O*-benzylidene-2,6-dichloro-2,6-dideoxy-α-D-altropyranoside (**19**). A direct proof in support of this is the conversion of **19** into 2,6-dideoxy-D-*ribo*-hexose (digitoxose)[36] (**28**). Mild

(33) J. Baddiley, J. G. Buchanan, and F. E. Hardy, *J. Chem. Soc.*, 2180 (1961).

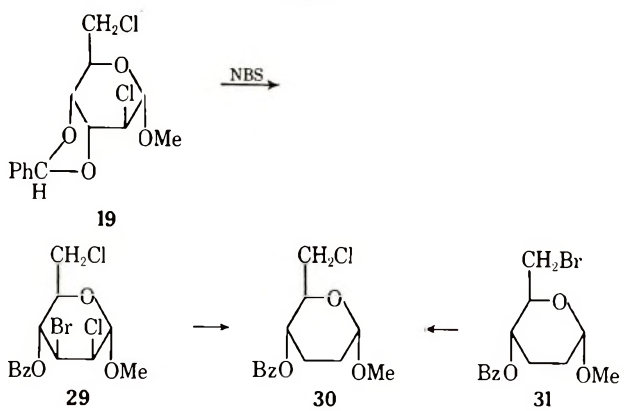
(34) G. J. Robertson and C. F. Griffith, *ibid.*, 1193 (1935); N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.*, **63**, 1727 (1941).

(35) R. W. Jeanloz, D. A. Prins, and T. Reichstein, *Helv. Chim. Acta*, **29**, 371 (1946).

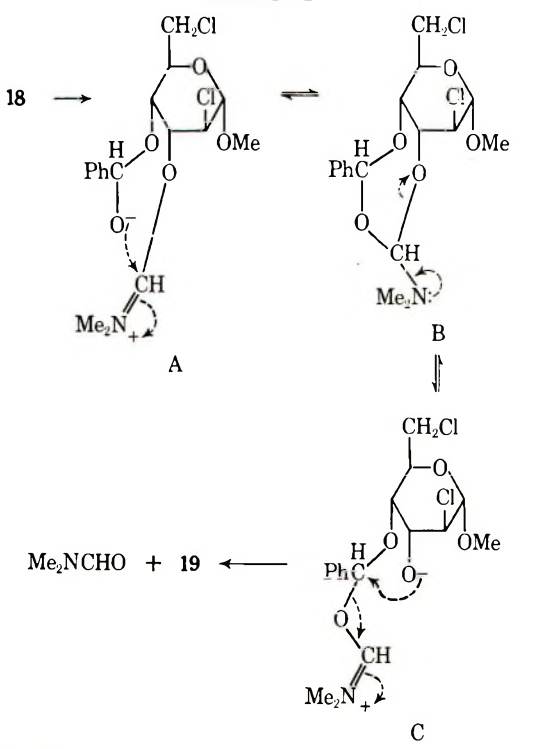
(36) H. R. Bolliger and P. Ulrich, *ibid.*, **35**, 93 (1952), and references cited therein.

acid hydrolysis or catalytic hydrogenation removed the benzylidene group from **19** to give crystalline methyl 2,6-dichloro-2,6-dideoxy-α-D-altropyranoside (**20**). This substance was attacked by periodate, but the oxidation in unbuffered solutions proceeded slowly. Treatment of **20** with base afforded a crystalline epoxide **21** which on benzoylation gave the monobenzoate **22** as a homogeneous syrup. That the benzoate group was attached to a secondary carbon atom was evident from the nmr spectrum of the product which showed a quartet at low field corresponding to the C-4 proton in **22**. Compound **20** readily formed a crystalline acetonide **26**, which, when reduced with lithium aluminum hydride, afforded the 2,6-dideoxy derivative **27** as the major product. Mild acid hydrolysis of the latter gave crystalline digitoxose[36] (**28**). Although the vapor phase chromatograms of compounds **20**, **21**, and **26** indicated single peaks for the respective substances, the chromatogram of **19** showed two peaks in the approximate ratio of 1.3:1. Furthermore, the nmr spectrum of **19** showed two singlets for the benzylidene acetal proton, as well as two signals each for the anomeric proton and the methoxyl protons. From the integrated areas of these peaks it appeared that the product **19** was a mixture of diastereoisomers, differing in the configuration of the benzylidene acetal carbon atom. The nmr spectrum of methyl 2-*O*-benzoyl-3,4-*O*-benzylidene-β-D-arabinopyranoside[37,38] shows two singlets of the same relative frequency as in **19**, due to the presence of two diastereoisomers. Treatment of **20** with benzaldehyde and zinc chloride afforded a product which showed two peaks having the same retention time as those found in the chromatogram of the original product **19**. That the ratio of diastereoisomers obtained from the acetalation of **20** was changed (1.8:1) compared to **19** is not unexpected, since the mechanism of acetalation differs from the rearrangement reaction.[39] The structure of the rearranged product **19** was proved in a different manner (Scheme V). Treatment of **19** with *N*-bromosuccinimide[4,40] opened the acetal ring to give after chromatography a product which, based on its subsequent tranformations, can be designated as methyl-4-*O*-benzoyl-3-bromo-2,6-dichloro-2,3,6-trideoxy-α-D-mannopyranoside (**29**). Catalytic reduction of **29** gave a syrupy product, which was purified by chromatography and was obtained as a homogeneous syrup (purity >96% by vpc). The nmr spectrum of this product indicated the presence of a four-proton multiplet corresponding to two methylene groups and the absence of a C-methyl group. Since the ring-opening reaction with NBS is not expected[4,40] to be accompanied by rearrangement in this case, the absence of a C-methyl group in the reduced product is a clear indication that a 4,6-*O*-benzylidene acetal was not present in the starting material **29**. The preponderant incorporation of the bromine atom at C-3 in **29** can be explained on the basis of a stereoselectivity in the ring opening of the 3,4-*O*-benzylidene acetal in **19**. Similar results have been obtained with related acetals.[38] It is interesting to note that whereas the two chlorine atoms in **19** were inert to catalytic hydrogenation, the incorporation of a bromine atom at C-3 led to a selective reduction of the C-2 and C-3 halogen atoms, in preference to the C-6 chlorine atom. The identity of the reduced product **30** was further established by comparison of its nmr spectrum with that of **31**[41] and by converting the latter compound into **30** by reaction with lithium chloride in *N*,*N*-dimethylformamide. The sequence of reactions outlined in Scheme V thus provides additional proof for the location of the second chlorine atom at C-6, and also establishes the pyranose ring structure of the rearranged product **19**. A possible mechanism for the formation of **19** is outlined in Scheme VI. It invokes the formation of an orthoester-type intermediate by a reversible reaction (A ⇄ B) and an irreversible acetal formation (C → **19**). The latter step explains the formation of diastereoisomeric benzylidene acetals.

SCHEME V



SCHEME VI



(37) N. Baggett, K. W. Buck, A. B. Foster, and J. M. Webber, *J. Chem. Soc.*, 3401 (1965).

(38) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1053 (1969), paper IV in a series.

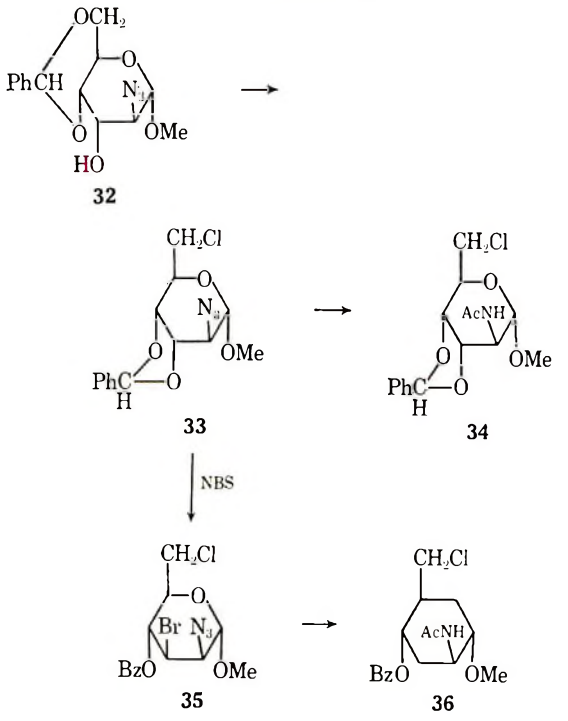
(39) The possibility of anomerization was also considered in an attempt to explain the chromatographic and nmr spectral behavior of **19**. The available data, and the transformations of **19** seem to favor the presence of diastereoisomers.

(40) S. Hanessian, *Carbohydrate Res.*, **2**, 86 (1966); S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1035 (1969), paper II in a series.

(41) S. Hanessian and N. R. Plessas, *ibid.*, **34**, 1045 (1969), paper III in a series.

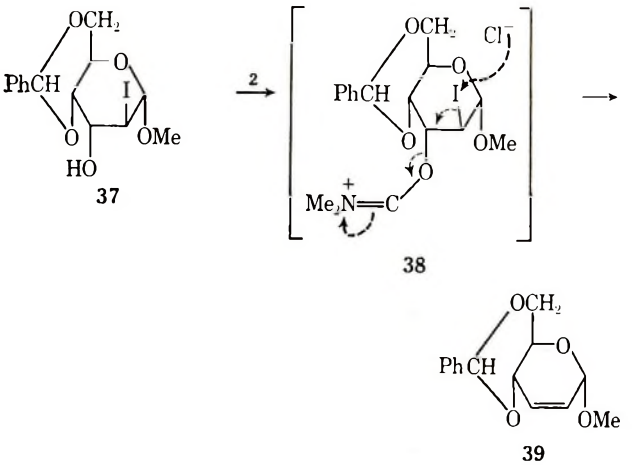
The reaction of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[42] (**32**) with **2** in refluxing 1,1,2,2-tetrachloroethane afforded a product whose analysis corresponded to the loss of a hydroxyl group and the incorporation of a chlorine atom in the molecule. On the basis of the transformations illustrated in Scheme VII this product is designated as methyl 2-azido-3,4-*O*-benzylidene-6-chloro-2,6-dideoxy-α-D-altropyranoside (**33**).[43] The nmr spectrum of **33**, like that of **19**, showed evidence for the presence of two diastereoisomers differing in the configuration of the benzylic carbon atom. Treatment of **33** with *N*-bromosuccinimide[40] afforded a product, presumably **35**, which was catalytically reduced and N-acetylated. The nmr spectrum of the product contained a two-proton multiplet corresponding to a methylene group, but no signal for a C-methyl group. In analogy with the results obtained with **19** (Scheme IV), this reduced and N-acetylated product is designated as methyl 2-acetamido-4-*O*-benzoyl-6-chloro-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (**36**). Selective reduction of the azido group in **33** and subsequent N-acetylation afforded crystalline methyl 2-acetamido-3,4-*O*-benzylidene-6-chloro-2,6-dideoxy-α-D-altropyranoside (**34**). The nmr spectrum of this product in pyridine-d_5 exhibited only one singlet for the benzylidene acetal proton, and it is not unlikely that, in the crystallization process, only one of the diastereoisomers was isolated.[37,38]

SCHEME VII



Whereas the chlorination of **17** and **32** (*via* the intermediate 3-imino ester) proceeded with rearrangement, but with no accompanying side reactions, the reaction of **2** with methyl 4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside[44] (**37**) led to a complex mixture of products. One of these products was isolated and identified as methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[44,45] (**39**). The formation of **39** can be explained by attack of chloride ion on the iodine atom as in intermediate **38**, with concomitant elimination of the C-3 substituent (Scheme VIII). It is of interest to note that a preparative route[44] to **39** consists of treating the 3-*O*-tosyl derivative of **37** with pyridine hydrochloride, which follows an analogous pathway, with expulsion of the tosyloxy function. Since the product **39** reacts with the reagent **2**, the sequence shown in Scheme VIII is not of preparative significance at this time.

SCHEME VIII



Experimental Section

Melting points are uncorrected. Nmr spectra were obtained in chloroform-*d* unless otherwise stated on a 60-MHz spectrometer using tetramethylsilane as reference. Optical rotations were measured with a Perkin-Elmer photoelectric polarimeter at 25°. Thin layer chromatography was performed on silica gel HF plates and the spots were detected with a spray containing 5% each of ammonium molybdate, sulfuric acid, and phosphoric acid after heating the plate for 10 min at 110°, and with a 1% potassium permanganate solution in 0.1 *N* sulfuric acid. Solvent systems and mobilities (slow, medium, fast) are given. Chlorinated hydrocarbons were dried by passage over neutral alumina (Woelm) prior to use. Processed solutions of chloroform and ether were dried over anhydrous sodium sulfate. Vapor phase chromatography was done on columns containing 5% SE-30 (Analabs, Inc.) or 3% OV-17 (Applied Science Labs, Inc.) depending on the derivative.

6-Chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (8).—To a solution containing 0.77 g (6 mmoles) of (chloromethylene)dimethyliminium chloride[14] (**2**) in 6 ml of 1,1,2-trichloroethane was added a solution of **1** (1.3 g, 5 mmoles) in 12 ml of the same solvent. After stirring for 1–2 hr an aliquot (1 ml) was taken from the yellow solution and treated with aqueous bicarbonate. Examination of the organic layer by tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:1) revealed the presence of the 6-formate ester **6**, in addition to a small amount of **8**. The reaction mixture was refluxed with stirring for 3 hr and the dark solution was cooled and treated with aqueous sodium bicarbonate solution. Processing in the usual way afforded a pale yellow solution which was decolorized and evaporated to dryness to give the product **8**, as a colorless chromatographically homogeneous syrup; yield 1.32 g, 95%. The yield varied between 85 and 98%. A portion was distilled 95–100° (bath temperature) (0.1 mm), and showed $[\alpha]_D$ −66° (*c* 0.78, chloroform); nmr data, τ 4.55 (center of a doublet, J_{12} = 5 Hz, C-1 proton), 5.36 (center of a quartet, C-2 proton), 8.45, 8.58, 8.66 (ketal methyl protons), etc.; vpc, singlet peak, >98% pure.

(42) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 5288 (1963); Y. Ali and A. C. Richardson, *Carbohydrate Res.*, **5**, 441 (1967).

(43) Based on mechanistic considerations,[16,17] this product was previously assumed[11] to be methyl 2-acetamido-4,6-*O*-benzylidene-3-chloro-2,3-dideoxy-α-D-mannopyranoside.

(44) R. U. Lemieux, E. Fraga, and K. A. Watanabe, *Can. J. Chem.*, **46**, 61 (1968).

(45) E. Albano, D. Horton, and T. Tsuchiya, *Carbohydrate Res.*, **2**, 349 (1966), and references cited therein.

Anal. Calcd for $C_{12}H_{19}O_5Cl$: C, 51.70; H, 6.87; Cl, 12.72. Found: C, 51.82; H, 6.73; Cl, 12.54.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (9).—A solution of **8** (0.45 g) in 30 ml of ether was added dropwise to a suspension of lithium aluminum hydride (0.5 g) in 50 ml of tetrahydrofuran. After stirring under reflux overnight, excess reagent was decomposed by cautious addition of water and the salts were removed by filtration. Evaporation of the filtrate gave a syrup which was dissolved in ether, and the solution was washed once with a small volume of water and dried. Evaporation gave a colorless syrup which was homogeneous on tlc and had a mobility slightly slower than **8**. It gave a characteristic green color with the molybdate spray. A portion of the syrup was distilled at 68–70° (0.5 mm) to give the product as a pure liquid: $[\alpha]_D$ −47.5° (*c* 2.67, chloroform), lit.[23,24] $[\alpha]_D$ −47.1° (chloroform); nmr data, τ 4.45 (center of a doublet, J_{12} = 5 Hz, C-1 proton), 5.40 (center of a quartet, C-2 proton), 8.62 (center of a 15-proton multiplet, ketal and C-6 methyl protons), etc.

6-Azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (10).—To a solution of **8** (0.46 g) in 15 ml of *N*,*N*-dimethylformamide was added sodium azide (0.46 g) and the mixture was refluxed with stirring during 36 hr. The solution was evaporated to dryness in the presence of butyl alcohol and the residue was suspended in ether and filtered. This was repeated several times to give finally a yellow syrup which was homogeneous on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.5, medium); ir data, 2100 cm^{-1} (azide). A portion was purified by preparative tlc; $[\alpha]_D$ −91° (*c* 0.97, chloroform), lit.[25] $[\alpha]_D$ −92.1° (chloroform) as a syrup.

A portion of the syrup was dissolved in methanol and treated with acetic anhydride and excess Raney nickel. After stirring overnight at room temperature the mixture was filtered and the filtrate was processed to give 6-acetamido-6-deoxy-1,2:3,4-*O*-isopropylidene-α-D-galactopyranose as a chromatographically homogeneous syrup: ir data, 1660 (amide I), 1550 cm^{-1} (amide II); $[\alpha]_D$ −5.4° (*c* 1.425, chloroform containing 1% ethanol), lit.[26] $[\alpha]_D$ −8.3° (chloroform–ethanol) as a syrup.

6-Chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (14).—To a solution of **13** (4.4 g) in 30 ml of 1,1,2,2-tetrachloroethane was added **2** (6.5 g) in 60 ml of the same solvent. After 2–3 hr at room temperature an aliquot (2 ml) was withdrawn from the solution and treated with aqueous sodium bicarbonate. Investigation of the organic layer by tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.4, medium) revealed the presence of the formate ester as the major product. The reaction mixture was refluxed for 3.5 hr with stirring, and the dark solution was cooled and treated with cold aqueous sodium bicarbonate. Processing of the organic layer in the usual way afforded 5.1 g (70%) of a pale yellow syrup which was homogeneous by tlc. A portion was distilled at 84–85° (0.05 mm); $[\alpha]_D$ +36° (*c* 2.64, chloroform); nmr data, τ 4.0 (center of a doublet, J_{12} = 3.5 Hz, C-1 proton), 5.42 (center of a doublet J_{21} = 3.5 Hz, C-2 proton), etc.; vpc analysis, >98% pure.

Anal. Calcd for $C_{12}H_{19}O_5Cl$: C, 51.70; H, 6.87; Cl, 12.72. Found: C, 51.44; H, 6.80; Cl, 13.22.

A portion of **14** was hydrolyzed essentially according to Smith[31] to give crystalline **6-chloro-6-deoxy-α-D-glucopyranose (15)**, mp 135–136°, $[\alpha]_D$ +95.8° → +51.1° (18 hr, in water); lit.[31] mp 135–136°, $[\alpha]_D$ +92.5° → +46.6° (at equilibrium, in water).

A portion of **14** (0.2 g) was reduced with lithium aluminum hydride in ether in the usual way. Processing of the reaction mixture gave **6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (16)**, as a pale yellow syrup (0.1 g): nmr data, τ 4.0 (center of a doublet, J_{12} = 3.5 Hz, C-1 proton), 5.42 (center of a doublet J_{21} = 3.5 Hz, C-2 proton), 8.60 (center of a 15-proton multiplet, ketal and C-6 methyl protons), etc.

Methyl 3,4-*O*-Benzylidene-2,6-dichloro-2,6-dideoxy-α-D-altropyranoside (19).—To a solution containing 0.64 g of **2** in 15 ml of 1,1,2,2-tetrachloroethane was added dropwise a solution of **17** (1.32 g) in 25 ml of the same solvent. After stirring overnight at room temperature, an aliquot treated with aqueous bicarbonate and examined by tlc showed the virtual absence of starting material (see below). The pale yellow solution was heated at 110° for 2–2.5 hr, the resulting dark-colored solution was cooled and treated with aqueous bicarbonate, and the processed organic layer was evaporated in the presence of butyl alcohol. The resulting tan-colored syrup was dissolved in chloroform and decolorized, and the processed solution was evaporated to an almost colorless syrup, 1.55 g (97%). The product showed essentially a fast-moving major double spot in addition to one or two slower moving components of minor intensity (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.5). In the case of larger runs, the yield varied between 75 and 95% depending on the purity of the reagent and the quantitative formation of the chloro ester **18**. A portion was further purified by distillation: bp 157–160° (0.25 mm); $[\alpha]_D$ +41.5° (*c* 1.47, chloroform); vpc analysis showed two major closely spaced peaks in an approximate ratio of 1.3:1; nmr data, τ 2.58 (aromatic protons, apparent singlet), 3.84, 4.10 (benzylic protons, 1:1.25 approximate ratio, integrate for one proton), 5.15, 5.21 (anomeric proton, 1:1.25 approximate ratio, integrate for one proton), 6.5, 6.51 (C-1 methoxyl protons, integrate for three protons).

Anal. Calcd for $C_{14}H_{16}O_4Cl_2$: C, 52.67; H, 5.05; Cl, 22.21. Found: C, 53.18; H, 5.12; Cl, 22.38.

An aliquot from the reaction of **17** with **2** taken after 18–24 hr showed essentially a major component on tlc which gave a postive test with the hydroxylamine spray. Purification of this product by preparative tlc gave **methyl 4,6-*O*-benzylidene-2-chloro-2-deoxy-3-*O*-formyl-α-D-altropyranoside (23)** as a colorless syrup: $[\alpha]_D$ 51.1° (*c* 3.94, chloroform); ir data, 1730 cm^{-1} (ester). Attempted purification of **23** by chromatography over neutral alumina (Merck) or storage at room temperature resulted in partial deformylation.

Methyl 2,6-Dichloro-2,6-dideoxy-α-D-altropyranoside (20). A. By Hydrogenolysis of 19.—A solution of **19** (3 g) in 100 ml of methanol was stirred in the presence of 20% palladium on carbon (1 g) and hydrogen during 5.5 hr. Filtration and evaporation afforded a colorless syrup which was homogeneous on tlc (benzene–methanol, 10:1.5) and showed a single peak by vpc analysis. The syrup crystallized in a few hours and the crystals were triturated with a mixture of ether and petroleum ether (bp 30–60°) to give 0.55 g of colorless crystals, mp 70–72°. Recrystallization from the same solvent gave colorless crystals showing a purity of over 99% by vpc analysis: mp 78–80°; $[\alpha]_D$ +118° (*c* 1, methanol); nmr data, τ 5.15 (C-1 anomeric proton, apparent singlet), 6.54 (C-1 methoxyl protons, singlet), etc. The mother liquors remaining after the filtration of the crystalline product were evaporated to a syrup which showed essentially one spot on tlc corresponding to **20**; yield 1.38 g (combined yield, 94%). A portion of this product was purified by preparative tlc to give a crystalline product which was identical (nmr, tlc, vpc) with material obtained from the first crop, mp 78–80°.

Anal. Calcd for $C_7H_{12}O_4Cl_2$: C, 36.59; H, 5.22; Cl, 30.68. Found: C, 36.81; H, 5.68; Cl, 30.78.

A portion of the product was treated with benzaldehyde and zinc chloride and the mixture was stirred for 5 hr. Processing of the reaction mixture in the usual way afforded a syrup which was indistinguishable from the original **19** by tlc, ir, and nmr. Vpc analysis revealed the presence of the same two components found in the original mixture; however, the ratio of the faster to the slower components was now about 1.8:1 respectively.

B. By Acid Hydrolysis of 19.—An amount of **19** (0.8 g) was dissolved in 10 ml of methanol and the solution was treated with 10 ml of 0.1 *N* sulfuric acid. After stirring at 45–50° overnight the solution was neutralized with barium carbonate and processed to give a syrup which showed a major component corresponding to **20** on tlc, in addition to some minor more slowly moving components. A portion of the syrup was purified by preparative tlc to give a crystalline product, identical (nmr, vpc) with **20** obtained by procedure A; mp 70–72°, $[\alpha]_D$ +118° (*c* 1, methanol)

Methyl 2,3-Anhydro-6-chloro-6-deoxy-α-D-allopyranoside (21).—To a solution of **20** (0.24 g) in 7 ml of ethanol was added 1.2 ml of 1 *N* sodium hydroxide and the resulting solution was refluxed for 20 min. Neutralization of the solution with dilute acetic acid, extraction with ether, and processing of the ethereal extract in the usual way afforded a colorless syrup which exhibited a single spot on tlc with a mobility very slightly slower than **20** (chloroform–methanol, 10:0.7, fast). The syrup was taken up in acetone, filtered, and evaporated to a syrup which crystallized. Trituration with ether–petroleum ether and filtration gave 0.1 g (50%) of **21**, mp 90–92°. Two recrystallizations from the same solvent mixture gave pure material: mp 93–94°; $[\alpha]_D$ +155° (*c* 0.59, chloroform); vpc, >99% pure. Investigation of the mother liquors from the crystallization of **21** by vpc and tlc indicated the presence of the epoxide mainly.

Anal. Calcd for $C_7H_{11}O_4Cl$: C, 43.19; H, 5.69; Cl, 18.22. Found: C, 43.04; H, 5.52; Cl, 18.60.

A portion of crude **21** (90 mg) was benzoylated in pyridine in the usual way to give **methyl 2,3-anhydro-4-*O*-benzoyl-6-chloro-6-deoxy-α-D-allopyranoside (22)** as a syrup. This product was

purified by preparative tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:1); nmr data, τ 4.68, 4.74 (centers of two doublets, J_{45} = 9.5 Hz, J_{43} = 1.5 Hz), 5.68 (center of a multiplet, C-3 proton), 6.35 (center of a four-proton multiplet, C-2, C-5, C-6 protons), 6.45 (C-1 methoxyl protons), etc. Treatment of **22** with a dilute solution of sodium methoxide in methanol, either at room temperature or at reflux for 30 min, gave the epoxide **21** as the sole product.

Methyl 4,6-*O*-Benzylidene-2-chloro-2-deoxy-3-*O*-methyl-α-D-altropyranoside (24).—A portion (1 g) of the crude formate ester **23** was dissolved in chloroform and passed through a chilled column containing neutral alumina. The column was washed with chloroform and the fractions were examined by tlc. It appeared that extensive deformylation had taken place. The first eluates containing mostly the deformylated product were combined and processed to a colorless syrup (0.5 g). The latter was dissolved in 50 ml of methyl iodide and 2 g of silver oxide was added in portions to the refluxing solution. After refluxing overnight, the suspension was filtered and the filtrate was evaporated to dryness. The resulting crystalline solid was triturated with cold ether and filtered to give the product in two crops, yield 0.35 g, mp 120–122°. Recrystallization from a mixture of acetone–ether and petroleum ether gave an analytical sample: mp 121–122°; $[\alpha]_D$ +68° (*c* 0.82, chloroform); nmr data, τ 4.42 (benzylic proton, singlet), 5.26 (C-1 proton, singlet), 6.45 (C-1 methoxyl proton, singlet), 6.60 (C-3 methoxyl protons).

Anal. Calcd for $C_{15}H_{19}O_5Cl$: C, 57.23; H, 6.08; Cl, 11.26. Found: C, 57.03; H, 6.10; Cl, 11.04.

Methyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-methyl-α-D-*ribo*-hexopyranoside (25).—A solution of **24** (0.1 g) in 30 ml of ether was added dropwise to a suspension of lithium aluminum hydride (1 g) in ether and the mixture was refluxed for 3 days with stirring. After the addition of water to the cooled reaction mixture, and processing in the usual way, the ethereal solution was dried and evaporated to dryness. The crystalline residue consisted of three products which were separated by preparative tlc. The component with medium mobility (25 mg) was crystallized from a mixture of ether and petroleum ether, mp 95–97°, $[\alpha]_D$ 136° (*c* 0.28, chloroform), and was found to be identical (ir, vpc) with the title compound; lit.[35] mp 100°, $[\alpha]_D$ +127° (chloroform). The faster (15 mg) and slower (12 mg) components were isolated as syrups which were oxidized by aqueous permanganate and exhibited signals for vinyl-type protons in their respective nmr spectra, but no signals for methylene protons indicating that they were unsaturated by-products.

Methyl 2,6-Dichloro-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-altropyranoside (26).—An amount of **20** (0.3 g) was dissolved in 50 ml of acetone containing 0.01 ml of concentrated sulfuric acid. The solution was stirred at room temperature overnight after which another 0.01 ml of acid was added. After a total time of 36 hr tlc showed the virtual absence of starting material. The acid was neutralized with barium carbonate, the salts were filtered and the filtrate was evaporated to dryness. The mobile liquid containing acetone condensation products was subjected to repeated evaporation from an aqueous solution and the final syrup was dissolved in petroleum ether, dried, and evaporated to a syrup which crystallized. Trituration with cold petroleum ether and filtration gave 0.22 g of product, mp 63–65°, >99% pure by vpc analysis. Recrystallization from the same solvent afforded material with mp 65–66°; $[\alpha]_D$ +63° (c 0.5, chloroform); nmr data, τ 5.22 (center of a doublet, J_{12} = 4.5 Hz, C-1 proton), 5.72 (center of a two-proton multiplet, C-3, C-4 protons), 6.51 (singlet, methoxyl protons), 8.54 (center of a doublet, ketal methyl protons).

Anal. Calcd for $C_{10}H_{16}O_4Cl_2$: C, 44.50; H, 5.94. Found: C, 44.54; H, 5.87.

Reduction of 26 with Lithium Aluminum Hydride and Isolation of D-Digitoxose.—A solution of **26** (0.1 g) in 10 ml of tetrahydrofuran was added to a suspension of lithium aluminum hydride (35 mg) in 15 ml of the same solvent. The mixture was refluxed for 48 hr and excess reagent was decomposed by cautious addition of water. Filtration of the salts and evaporation of the filtrate gave a syrup which showed a major spot and another spot of minor intensity corresponding to unreacted **26** (chloroform–2,2,4-trimethylpentane–methanol, 100:40:0.1). The major component, **methyl 2,6-dideoxy-3,4-*O*-isopropylidene-α-D-*ribo*-hexopyranoside**, was separated by preparative tlc and was obtained as a syrup (35 mg): nmr data, τ 5.22 (center of a triplet, J = 4.5 Hz, C-1 proton), 7.92 (center of a two-proton multiplet, C-2 protons), 8.62 (center of a nine-proton triplet, ketal and C-6 methyl protons).

The product was hydrolyzed with 0.02 *N* aqueous sulfuric acid at 60° during 20 min and the solution was neutralized with barium carbonate. Filtration and evaporation of the filtrate gave a syrup which showed essentially one spot corresponding to digitoxose on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:20). Purification by preparative tlc gave 8 mg of crystalline D-digitoxose (**2,6-dideoxy-D-*ribo*-hexose**) which was identical (melting point, ir) with an authentic sample.[36,46]

A similar sequence of reactions was performed starting with **19**, and digitoxose was the major product identified by tlc. In this case the hydride reduction led, in addition to the expected 2,6-dideoxy derivative, to a mixture of products. The nmr spectra of these products lacked the benzylidene acetal proton, and they could presumably be benzyl ethers.

Reaction of 19 with N-Bromosuccinimide.—To a solution of **19** (3.0 g) in 150 ml of carbon tetrachloride were added 5 g of barium carbonate and 2 g of NBS, and the mixture was refluxed with stirring for 2.5 hr. Filtration, evaporation of the filtrate, and processing of the resulting syrup afforded a dark yellow syrup (3.9 g) which contained some starting material (tlc, chloroform–2,2,4-trimethylpentane–methanol, 100:40:0.1) in addition to the expected ring-opening product (major product). A portion (0.38 g) of this syrup was purified by preparative tlc to give a syrupy product which, based on subsequent transformations, consisted mainly of **methyl 4-*O*-benzoyl-3-bromo-2,6-dichloro-2,3,6-trideoxy-α-D-mannopyranoside (29)** (0.2 g): ir data, 1720 cm^{-1} (ester).

Anal. Calcd for $C_{14}H_{15}O_4BrCl_2$: C, 42.23; H, 3.79; Br, 20.07; Cl, 17.81. Found: C, 42.75; H, 4.24; Br, 19.49; Cl, 17.70.

Methyl 4-*O*-Benzoyl-6-chloro-2,3-*O*-dideoxy-α-D-*erythro*-hexopyranoside (30). A. From 29.—A mixture of **29** (0.19 g), 20% palladium on carbon (0.2 g), and barium carbonate in 70 ml of methanol was hydrogenated during 8 hr. The suspension was filtered, and the filtrate was evaporated to a syrup which showed a major spot on tlc, in addition to traces of **29**. Purification by preparative tlc gave the product (80 mg) as a chromatographically homogeneous syrup: ir data, 1730 cm^{-1} (ester); vpc, >94% pure; nmr data, τ 5.04 (centr of a multiplet, C-4 proton), 5.20 (center of a broad triplet, C-1 proton), 6.65 (singlet, methoxyl protons), 8.05 (center of a two-proton multiplet, C-3, C-4 protons).

Anal. Calcd for $C_{14}H_{17}O_4Cl$: Cl, 12.40. Found: Cl, 12.59.

B. From Methyl 4-*O*-Benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (31).—An amount of **31**[41] (75 mg) was dissolved in 5 ml of *N*,*N*-dimethylformamide containing 0.1 g of lithium chloride. After refluxing the solution for 1 hr, it was evaporated to dryness, the residue was dissolved in water, and the solution was extracted with ether. Processing the organic phase afforded a pure yellow syrup which was purified by preparative tlc to give **30** as a colorless syrup. This product was found to be >99% pure by vpc analysis and it had the same retention time as **30** obtained above and had emerged from the column before **31**.

Methyl 2-Azido-3,4-*O*-benzylidene-6-chloro-2,6-dideoxy-α-D-altropyranoside (33).—A solution of **32** (0.96 g) in 20 ml of 1,1,2,2-tetrachloroethane was added to **2** (0.45 g) in 10 ml of the same solvent. After stirring for 1 hr at room temperature, the pale yellow solution was refluxed for 3 hr. The dark solution was cooled and poured into aqueous sodium bicarbonate and the organic layer was processed as usual. Evaporation gave a light brown syrup which was decolorized from chloroform and evaporated to a dark yellow syrup which showed essentially one major component on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.2, fast); yield 0.95 g. This product was dissolved in ether and passed through a column containing neutral alumina. Evaporation of the first few fractions after the holdup volume gave **33** as a colorless syrup (0.44 g, 47% over-all). Another portion purified further by preparative tlc showed $[\alpha]_D$ + 38.8° (*c* 0.216, chloroform); ir data, 2100 cm^{-1} (azide), no hydroxyl absorption; nmr data, τ 3.82, 4.11 (benzylic protons, approximate ratio, 1:1, integrate for one proton), 5.38, 5.47 (centers of two doublets, J_{12} = 1 and 1.5 Hz, respectively, integrate for one proton, C-1 proton), 6.51 (singlet, methoxyl

(46) We thank Professor T. Reichstein for a generous sample of D-digitoxose.

protons), etc. The product decomposed on attempted vpc analysis.

Anal. Calcd for $C_{12}H_{16}N_3O_4Cl$: Cl, 10.88. Found: Cl, 11.25.

A mixture of this product (0.3 g) in 20 ml of carbon tetrachloride containing 0.18 g of NBS and 0.2 g of barium carbonate was refluxed for 2 hr. The suspension was filtered, and the filtrate was evaporated to a syrup which exhibited a major spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.2). The product (0.3 g) was separated by preparative tlc and the zone corresponding to the major product was isolated and processed to give **methyl 2-azido-4-*O*-benzoyl-3-bromo-6-chloro-2,3,6-trideoxy-α-D-mannopyranoside (35)** as a syrup. Catalytic hydrogenation of this product in the presence of palladium on carbon and barium carbonate in methanol afforded a syrup which was dissolved in methanol and treated with acetic anhydride. Evaporation of the solution and purification of the syrupy product by preparative tlc gave **methyl 2-acetamido-4-*O*-benzoyl-6-chloro-2,6-dideoxy-α-D-*arabino*-hexopyranoside (36)** (49 mg): ir data, 1718 (ester), 1660 (amide I), 1560 cm^{-1} (amide II); nmr data, τ 5.40 (singlet, C-1 proton), 7.85 (center of a two-proton multiplet, C-3 proton), 7.96 (singlet, N-acetyl protons), etc.

Anal. Calcd for $C_{16}H_{20}ClNO_5$: N, 4.42. Found: N, 4.21.

Methyl 2-Acetamido-3,4-*O*-benzylidene-6-chloro-2,6-dideoxy-α-D-altropyranoside (34).—To a solution of **33** (0.4 g) in 50 ml of methanol were added excess Raney nickel (previously washed with methanol by decantation) and 5 ml of acetic anhydride. After stirring overnight at room temperature, the catalyst was filtered, the filtrate was evaporated to dryness, the residue was taken up in ether, and some insoluble matter was removed by filtration. Evaporation of the filtrate gave the crystalline product **34**, contaminated with some inorganic salts which were removed by washing the solid with cold 0.1 *N* acetic acid, followed by water. The insoluble crystalline product was homogeneous by tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.4, medium); yield 0.11 g; mp 209–210°; ir data, 1660 (amide I), 1560 cm^{-1} (amide II). Recrystallization of a portion from a small volume of methanol gave an analytical sample; mp 211–212° dec, $[\alpha]_D$ +95° (c 0.26, chloroform). This compound was previously reported[11] to have mp 179°, $[\alpha]_D$ + 72° (chloroform).

Anal. Calcd for $C_{16}H_{20}NO_5Cl$: C, 56.22; H, 5.89; N, 4.09; Cl, 10.37. Found: C, 55.93; H, 5.83; N, 3.81; Cl, 10.28.

Attempted Reaction of 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose with (Chloroethylidene)dimethyliminium Chloride.—A solution of **1** (1.3 g) in 15 ml of 1,1,2,2-tetrachloroethane was added to a cooled suspension of **3** (1 g) in 5 ml of the same solvent. After stirring for 1 hr at room temperature 1 g of **3** was added and the yellow solution was stirred for an additional 24 hr. A 2-ml aliquot was treated with aqueous bicarbonate and the organic layer was processed to give a syrup which exhibited essentially one spot on tlc (hydroxylamine positive) corresponding to the 6-*O*-acetyl derivative **7**: ir data, 1742 cm^{-1} (ester). A small amount of the 6-chloro derivative **8** was also present. The remainder of the reaction mixture was heated under reflux during 3 hr and the dark solution was processed as described for **8**. A syrup was obtained which was identical in all respects with **8** obtained *via* reaction with **2**; yield 0.36 g (25%).

Attempted Reaction of 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose with (Methoxymethylene)dimethyliminium Methylsulfate.—A solution of **1** (1.3 g) in 15 ml of chloroform was added to a solution of **12** (5 g) in 5 ml of chloroform. After stirring at room temperature for 4 hr, a portion was treated with aqueous sodium bicarbonate and the organic layer was processed to a colorless syrup which consisted of a mixture of starting material (preponderant) and the 6-*O*-formate ester **6**, as evidenced by tlc. Refluxing the remaining solution for 4 hr, followed by processing in the usual manner, gave a syrup which also consisted mostly of starting material and a small amount of the ester **6** (tlc, ir data).

Attempted Reaction of Methyl 4,6-*O*-Benzylidene-2-deoxy-2-iodo-α-D-altropyranoside with (Chloromethylene)dimethyliminium Chloride.—To a solution of **2** (0.39 g) in 6 ml of 1,1,2-trichloroethane was added 0.15 g of **37** in portions at 0°. An aliquot was processed after stirring at room temperature for 3 hr. Examination by tlc revealed the presence of the unsaturated derivative **39**, and two slow-moving components, in addition to some starting material, (chloroform–2,2,4-trimethylpentane–methanol 100:30:1). Prolonged reaction periods led to extensive decomposition (tlc) and no definite products could be isolated. The unsaturated derivative **39**, mp 116–118° (lit.[44,45] 119–129°), could be isolated in about 10–15% yield by preparative tlc of the product after a reaction time of 3–4 hr. The ir spectrum and vpc characteristics of **39** were identical with those of an authentic sample.

Treatment of **39** with stoichiometric amounts of **2** even at temperatures as low as −10° led to the formation of several products and eventual decomposition as evidenced by tlc. At −70°, compound **39** remained mostly unchanged during a few hours in the presence of an equimolar amount of **2**.

Registry No.—**8**, 13454-63-2; **14**, 19685-14-4; **19**, 19685-15-5; **20**, 19685-16-6; **21**, 19685-17-7; **24**, 19685-18-8; **26**, 19684-26-5; **29**, 19684-27-6; **30**, 19684-28-7; **33**, 19684-23-2; **34**, 19684-24-3; **36**, 19684-25-4.

Bile Acids. XXVII. Mechanism of Allomerization of Steroids with Raney Nickel[1]

M. N. MITRA AND WILLIAM H. ELLIOTT

Department of Biochemistry, St. Louis University School of Medicine, St. Louis, Missouri 63104

Received October 3, 1968

The transformation of 3-hydroxy 5β-steroids to 5α compounds by heating with Raney nickel in boiling *p*-cymene proceeds by dehydrogenation to the 3-keto 5β derivative and desaturation to the 3-keto Δ⁴-steroids. An equilibrium is established between the 3-keto 5β-, 3-keto Δ⁴-, and 3-keto 5α-steroid with the latter predominating. The 4α hydrogen of the steroid is transferred to the *p*-cymene. *p*-Cymene can be replaced with similar aromatic or cycloalkyl hydrocarbons.

Previously[2] it was reported that 3-hydroxy steroids and steroidal sapogenins with *cis*-A/B configuration (5β) undergo epimerization at the 5 position to provide 3-keto-*trans*-A/B (5α) compounds on heating under reflux with freshly prepared Raney nickel in a solvent such as *p*-cymene. This procedure has been successfully applied to normal (5β) cholanoates with various substituents for the preparation of allo-(5α) cholanoates like allodeoxycholic acid,[3] allochenodeoxycholic acid,[4] 3β,7α,12α-trihydroxy-5α-cholanoic acid,[5,6] and allo-

(1) (a) This investigation was supported in part by N.I.H. Grant HE-07878 and AM-09992. (b) The following abbreviations have been used: tlc, thin layer chromatography; glpc, gas–liquid partition chromatography; plc, preparative layer chromatography; ORD, optical rotatory dispersion; unless otherwise mentioned, R_t, retention time relative to methyl deoxycholate (methyl 3α,12α-dihydroxy-5β-cholanoate; absolute time, 30 min on QF-1, 36 min on OV-17). R_f and R_t values of different compounds reported in this manuscript have been compared with those of authentic samples and found to be identical.

(2) D. Chakravarti, R. N. Chakravarti, and M. N. Mitra, *Nature*, **193**, 1071 (1962).

(3) H. Danielsson, A. Kallner, and J. Sjövall, *J. Biol. Chem.*, **238**, 3846 (1963).

(4) S. A. Ziller, Jr., M. N. Mitra, and W. H. Elliott, *Chem. Ind.* (London), **24**, 999 (1967).

(5) I. G. Anderson and G. A. D. Haslewood, *Biochem. J.*, **93**, 34 (1964).

(6) M. N. Mitra and W. H. Elliott, *J. Org. Chem.*, **33**, 175 (1968).

cholic acid.[6] Although this method of transformation of 5β-steroids to 5α-steroids had been substantiated by tlc, glpc, ord, mass spectrometry, and chemical degradation in many cases,[3,4,6,7] no work was carried out on the mechanism by which this transformation takes place. In this paper investigations with a mechanistic approach are reported.

When methyl lithocholate (**1**) or methyl 3-dehydrolithocholate (**2**) is heated in boiling *p*-cymene in the presence of freshly prepared W-2 Raney nickel catalyst for 10 hr, analysis of the reaction mixture by glpc showed the presence of about 70% methyl 3-keto-5α-cholanoate (**3**), R_t 0.71; 20% methyl 3-keto-5β-cholanoate (**2**); R_t 0.61; and a third substance as a small peak, R_t 0.93, subsequently identified as methyl 3-keto-Δ⁴-cholenoate[8] (**4**) by comparison with an authentic sample obtained by Oppenauer oxidation of methyl 3β-hydroxy-Δ⁵-cholenoate. Isolation of **4** from the reaction mixture by plc, preparative layer chromatograpy, permitted characterization by uv, ir, and mass spectrometry.

The mass spectrum of **4** showed the molecular ion, *m/e* 386, as base peak, and the characteristic fragments of methyl esters of bile acids (*m/e* 371, M − 15; *m/e* 355, M − 31; *m/e* 271, M − 115) as well as those fragments derived from 3-keto Δ⁴-steroids (*m/e* 344, M − 42; *m/e* 329, M − (42 + 15); *m/e* 301, M − 85; *m/e* 263, M − 123; *m/e* 229, M − (115 + 42); *m/e* 124). Shapiro and Djerassi[9] found similar fragmentation in the mass spectrum of 3-keto-Δ⁴-androstene. The mass spectra of **2** and **3** showed the expected fragments *m/e* 373 (M − 15), *m/e* 318 (M − 70) and *m/e* (M − 115). The ratio of the relative intensities of the fragments *m/e* 318 (M − 70) from **2** and **3** was approximately 7:1 in accord with the observations of Budzikiewicz and Djerassi[10] on the more favorable loss of ring A from 3-keto 5β-steroids than the corresponding 5α derivatives.

Similar treatment of methyl deoxycholate (**5**) with Raney nickel in boiling *p*-cymene and analysis of the products by glpc showed the presence of about 20% methyl 3-keto-12α-hydroxy-5β-cholanoate (**6**), 60% methyl 3-keto-12α-hydroxy-5α-cholanoate[7] (**7**), and a small amount of 3-keto-12α-hydroxy-Δ⁴-cholenoate (**8**). An attempt was made to prepare the reference compound **8** by the action of 2,3-dichloro-5,6-dicyanobenzoquinone on methyl 3-keto-12α-hydroxy-5β-cholanoate **6**, but the product was found to be a mixture of a small amount of **8** with a number of other compounds of very close polarity in tlc. A similar observation was recently reported by Turner and Ringold.[11] Consequently, **8** was prepared by the procedure of Riegel and McIntosh[12] from **6** by bromination at C_4 followed by dehydrobromination.

Since **8** is a 12-hydroxy derivative of **4**, the mass spectrum should exhibit certain similarities. The M − 15 fragment of **4** is replaced in **8** by the M − 18 fragment (*m/e* 384), and the M − 31 fragment common to both spectra is joined in **8** by an M − 32 fragment (*m/e* 370). Loss of a molecule of water from **8** results in the formation of a sequence of fragments, M − (42 + 18), M − (123 + 18) and M − (115 + 42 + 18), comparable to those fragments of **4**. The base peak of **8**, *m/e* 269, M − (115 + 18), contrasts to the molecular ion of **4**. Fragmentation *via* M − 85 is weak in **4** and insignificant in **8**; the fragment, *m/e* 124, of considerable intensity in **4** is very weak in **8**. The fragments, *m/e* 147 and 145, of **8** probably represent stabilized fragments from *m/e* 261 by loss of the C_{17} side chain and addition or loss of a proton.

Reversible Nature of the Reaction.—With sufficient quantities of **4** and **8** available each of these was refluxed with Raney nickel in boiling *p*-cymene and the products were analyzed by glpc. From **4**, both **2** and **3** were obtained in about 20 and 70% yield, respectively; from **8**, about 20% **6** and 60% **7** were obtained. In a similar experiment with 5α-cholestan-3β-ol (**9**) glpc analysis showed the presence of 74% 5α-cholestan-3-one (**10**), 11% 5β-cholestan-3-one (coprostanone) (**11**), and 15% Δ⁴-cholestenone (**12**). Previous experiments[2] with several 3β-hydroxy Δ⁵ derivatives showed the presence of 3-keto Δ⁴-steroids and 5α-3-ketones but no quantitative experiments were conducted. These data suggest that Raney nickel promotes the formation of an equilibrium mixture of 5α- and 5β-steroids and that the 3-keto Δ⁴ derivative is an intermediate in this transformation.

Role of the Solvent.—In order to ascertain whether the solvent, *p*-cymene, plays a significant role in this reaction, glpc–mass spectrometric analysis of the solvent was undertaken after the reaction. Small quantities of the menthanes (*cis* and *trans*), *p*-xylene, ethyl toluene, and toluene were characterized. However, these materials were found in about the same quantities after boiling *p*-cymene and Raney nickel without steroid, suggesting that they represent minor products of action of the catalyst on the solvent. In subsequent experiments substantial quantities of di-*p*-cymene[13] were identified in the hexane eluent from column chromatography of the reaction mixture.

In order to define more clearly the role of the solvent in the reaction, methyl lithocholate (**1**) was treated with Raney nickel in boiling aromatic solvents (xylene, cumene, diisopropylbenzene) or nonaromatic solvents (1,4-dimethylcyclohexane, diisopropylcyclohexane, *n*-butylcyclohexane). The steroid residue obtained after separation of solvent and catalyst was analyzed by glpc on a column of 3% OV-17 on Gas Chrom Q (Table I). These results show that the alkyl cyclohexanes function as well or better than their corresponding aromatic analogs for the preparation of the 5α derivatives and suggest that a higher temperature of the reaction medium favors the formation of the latter. This behavior of the solvent may be due to a tendency of adsorbed hydrogen of Raney nickel to saturate the aromatic ring at the temperature of the reaction medium. This is supported by the observation that aromatic solvents recovered from Raney nickel with or without sterol invariably contain small amounts of the corresponding cyclohexanes as detected by glpc on Bentone 34. When the reaction was carried out in the presence of readily

(7) M. N. Mitra and W. H. Elliott, *J. Org. Chem.*, **33**, 2814 (1968).
(8) M. J. Haddadin and C. H. Issidorides, *ibid.*, **25**, 403 (1960).
(9) R. H. Shapiro and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2825 (1964).
(10) H. Budzikiewicz and C. Djerassi, *ibid.*, **84**, 1430 (1962).
(11) A. B. Turner and H. J. Ringold, *J. Chem. Soc., C*, 1720 (1967).
(12) B. Riegel and A. V. McIntosh, Jr., *J. Amer. Chem. Soc.*, **66**, 1099 (1944).

(13) H. Pines, B. Kvetinskas, and V. N. Ipatieff [*ibid.*, **77**, 343 (1955)] reported mp 156° for di-*p*-cymene; R. Pappo, B. M. Bloom, and W. S. Johnson [*ibid.*, **78**, 6354 (1956)] reported mp 157–159°. The product obtained in these experiments showed mp 158° after crystallization from acetone; the structure was supported by uv, ir, and mass spectrometry.

TABLE I

REACTION OF METHYL LITHOCHOLATE AND RANEY NICKEL IN DIFFERENT SOLVENTS[a]

Exptl no.	Solvent	Bp, °C	Source[b]	R_t[c]	Methyl 3-keto-cholanoates, 5α	5β	Δ⁴
	Alkyl Benzene						
1	1,4-Dimethyl-	138	B	0.31	34	56	1
2	Isopropyl-	152–153	A	0.46	43	50	4
3	1-Methyl-4-isopropyl-	177	B	1.00	70	20	10
4	1,4-Diisopropyl-	210	A	3.23	73	15	12
	Alkyl Cyclohexane						
5	1,4-Dimethyl-	120–124	A	0.07 0.09	65	31	1
6	Isopropyl-	154–155	A	0.27	78	18	4
7	*n*-Butyl-	178–180	A	0.71	74	21	5
8	1,4-Diisopropyl-	201–203	C	2.49	77	16	7
9	Menthone	207	D		2	60	
10	80% *p*-Cymene–20% cyclohexene		B		5	45	

[a] Recovered methyl lithocholate: 1, 10%; 2, 3%; 5, 4%; 9, 38%; 10, 50%. [b] Source: A, Aldrich Chemical Co., Inc., Milwaukee, Wis.; B, Fisher Scientific Co., St. Louis, Mo.; C, Chemical Samples Co., Columbus, Ohio; D, Matheson Coleman and Bell, Norwood, Ohio. [c] R_t = retention time relative to *p*-cymene (absolute time = 20 min) on 5% Bentone 34–5% diisodecylphthalate. S. F. Spencer, *Anal. Chem.*, **35**, 592 (1963).

reducible solvents such as cyclohexene or menthone, very little transformation from 5β- to 5α-steroid occurred as measured by glpc (Table I) in confirmation of the above conclusions.

Role of the Steroid. A. Structure.—The structural requirements of the participating steroid were investigated initially with methyl 5β-cholanoate. After treatment with the reagents in the usual way, no methyl 5α-cholanoate[7] could be detected by glpc. In order to ascertain whether an oxygen function at position 7 instead of 3 could promote the transformation at 5, the following methyl esters were treated individually with Raney nickel in boiling *p*-cymene: 7α-hydroxy-5β- and -5α-cholanoates[6,14] and 7α,12α-dihydroxy-5β- and -5α-cholanoates.[6,15] In each case about 25% of the starting material was dehydrogenated to the corresponding 7-keto derivative, but no transformation at position 5 could be detected on QF-1 by glpc, since the major portion of the steroid was recovered unchanged.[6,7] These observations confirm earlier studies[6,7] in which 7-dehydro derivatives of the 5α and 5β series were identified, and demonstrate the importance of functional oxygen at position 3 for a favorable reaction.

B. Abstraction of Hydrogen.—Studies with **1**, and **5**, methyl cholate,[6] and methyl chenodeoxycholate[7] have shown that the reaction proceeds equally well with the corresponding 3-dehydro derivatives (*e.g.*, **2** or **6**). Thus, Raney nickel dehydrogenates the secondary steroidal alcohol to a ketone similar to that reported by Paul[16] for the preparation of hexanone-3 in 80% yield from hexanol-3.

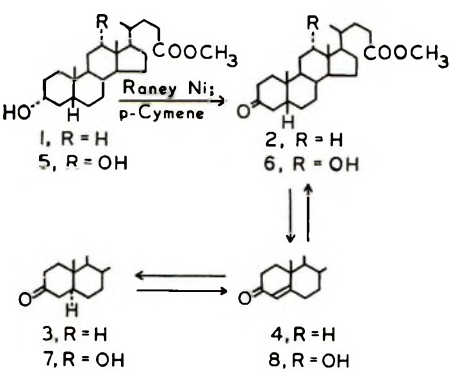
To gain insight into the mechanism of dehydrogenation of the 3-keto steroid this material was labeled at position 4. Methyl 3-keto-4β-bromo-5β-cholanoate was prepared from **2** and debrominated with zinc and tritiated acetic acid according to Corey and Sneen[17] to provide methyl 3-keto-4α-^{3}H-5β-cholanoate (**13**). Treatment of **13** with Raney nickel provided the expected yield of **3**, but the product contained less than 2% of the tritium. After separation of the recovered solvent into menthanes (R_t 0.45 and 0.50) and *p*-cymene (R_t 1.00) by preparative glpc on Bentone 34 and assay for radioactivity in these components, the tritium was found exclusively in *p*-cymene. Upon oxidation[18] of this material to *p*-toluic acid, approximately one-half of the tritium was retained in this moiety. These data suggest that the tritium was lost from the steroid preferentially to the solvent with approximately equal distribution between the toluic acid moiety and the isopropyl group of *p*-cymene.

Time of the Reaction.—Although these studies were carried out in accordance with earlier observations[2] regarding a reaction period of 10 hr, subsequent experiments have been conducted with **1**, **5**, and methyl cholate in *p*-cymene and Raney nickel in which aliquots of the reaction mixture were removed at various intervals and analyzed by glpc. These studies show that the reaction is complete within 1 hr, and that longer periods of heating provide no improvement in yield of the 5α-steroids.

Discussion

On the experimental evidence presented the course of the stereoisomerism of steroids at position 5 in the presence of W-2 Raney nickel[19] at the reflux temperature of various high-boiling solvents is represented in Chart I.

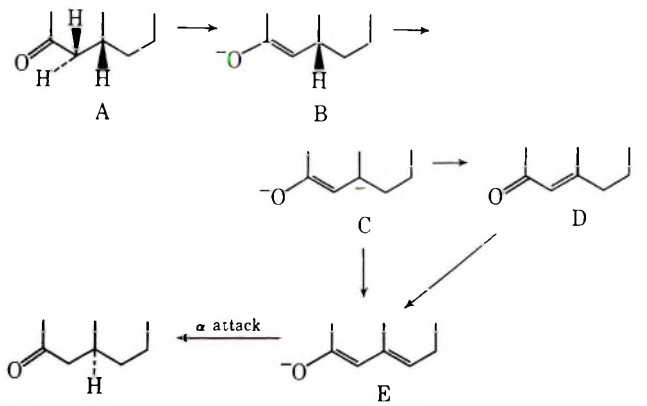
CHART I



Raney nickel enjoys three functions in this sequence: dehydrogenation of the C_3 hydroxyl, and dehydrogenation and rehydrogenation at C_4–C_5. The dehydrogenation at C_3 is not unexpected, since the formation of aldehydes and ketones from primary and secondary alcohols over finely divided metal at high temperature has been reported extensively.[16,20,21] To study the mechanism of the dehydrogenation of **2** to **4**, tritiated **2** was pre-

(14) H. B. Kagan and J. Jacques, *Bull. Soc. Chim. Fr.*, 871 (1960).
(15) A. S. Jones, M. Webb, and F. Smith, *J. Chem. Soc.*, 2164 (1949).
(16) R. Paul, *C. R. Acad. Sci., Paris*, **208**, 1319 (1939).
(17) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956).
(18) W. F. Tuley and C. S. Marvel, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 822.
(19) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 181.
(20) R. P. A. Sneeden and R. B. Turner, *J. Amer. Chem. Soc.*, **77**, 190 (1955), and references cited therein.
(21) E. Lieber and F. L. Morritz, *Advan. Catal.*, **5**, 417 (1953).

pared and formulated as the 4α-tritio derivative in accord with the arguments of Corey and Sneen.[17,22] If dehydrogenation of this 4α-^{3}H-3-keto ester occurred solely *via cis* elimination of the 4β and 5β hydrogen atoms, the steroid should retain the tritium; if a *trans* diaxial elimination occurred, the steroid should be devoid of tritium. Since the steroid did in fact contain very little tritium, *cis* elimination need not be considered. Elimination of the 4α,5β-diaxial protons by direct combination with the catalyst is difficult to visualize. However, if polarization or enolization of **2** occurred in the reaction medium to form the enolate (B), the axial tritium would be removed from the steroid and could appear in the solvent by exchange, in a manner analogous to that reported by Horner and Mayer[23] between deuterium and the hydrogens of alkyl benzenes. The tertiary allylic proton at C_5 of the enol (B) could be abstracted by the catalyst from the β side of



the molecule to form the dianion (C), which then proceeds to the α,β-unsaturated ketone (D). This mechanism is essentially the reverse of that suggested by Barton and Robinson[24] for the reduction of α,β-unsaturated ketones by metals in liquid ammonia, and in effect supports a *trans*-diaxial elimination.[25] Support for the involvement of the 3-oxo group in the above is found in the inability to detect isomerization of methyl 5β-cholanoate under comparable conditions. Additional studies to clarify this subject are now in progress.

The course of hydrogenation of 3-keto Δ^4-steroids has been reviewed by Fieser and Fieser,[26] Shoppee,[27] and McQuillin,[28] and reinvestigated by Augustine[29-31] McQuillin, *et al.*,[32] Nishimura, *et al.*,[33] and Combe, *et al.*[34] Reduction in the presence of palladium under nonequilibrating conditions provides varying amounts of the 5β or 5α isomers, and is dependent on the acidity, alkalinity, or polarity of the solvent. McQuillin, *et al.*,[32] point out that polarization of the 3-keto Δ^4-steroid will assist deformation and permit the absorbed molecule to assume the preferred *trans*-decalin type configuration. Whereas the β face of the α,β-unsaturated ketone is less hindered than the α side, inspection of Dreiding models of the enolate or polarized form reveals axial interaction on the α side of the molecule only at positions 2 and 9, as opposed to hinderance at positions 1, 7, and 10 on the β side. Inhoffen and coworkers[35] showed in 1950 that cholestenone enol ether was reduced on the α side by palladium and hydrogen. 4-Methyl-3-keto Δ^4-steroids provide the more stable 4α-methyl 5α derivatives on catalytic reduction in the presence of palladium.[28,36] Nishimura, *et al.*,[33] have projected structures for enolic derivatives of 3-keto Δ^4-steroids in which fixation of the metallic catalyst at the 5β position enables ring A to assume a conformation almost at right angles to the remainder of the structure and assures β attack; a similar structure with the catalyst affixed on the α side assures a more planar configuration and α attack. Each of these cases is concerned with reduction in a nonequilibrating system. Although the experiments reported here were generally conducted for a period of 10 hr, equilibration is reached within 1 hr. Since conditions for catalytic reduction (*i.e.*, room temperature and generally cessation after uptake of 1 mol of hydrogen) differ appreciably from these experiments, the mechanistic interpretations of the former cases may not apply *in toto* here.

In reduction of substituted naphthalenes[37] under equilibrating conditions several *trans*-decalins were obtained. Siegel[38] earlier interpreted the formation of *trans*-dimethylcyclohexanes as *cis* addition to a newly migrated double bond generated by the "half-hydrogenated" state. Whether the interpretations of Siegel and Weitkamp need to be invoked in this case (*e.g.*, intermediate E above) awaits results of additional experiments. However, these interpretations offer an explanation for the formation of 20–30% **7** or **3** by the action of Raney nickel in boiling *p*-cymene on methyl cholate or methyl chenodeoxycholate,[7] respectively. After the 7α-hydroxy analog of **8** or **4** has been formed, the allylic hydroxyl is eliminated to form the conjugated 3-keto $\Delta^{4,6}$ system, which is then reduced to **7** or **3**. Although small quantities of 12-keto derivatives have been noted in these reactions, in no case has a 12-deoxy derivative been detected from **5** or methyl cholate.

The failure of the 7-keto-5β-cholanoates to undergo dehydrogenation at position **5** from the β side may be

(22) It should be noted that the specific activity of the tritiated steroid was lower than that of the tritiated acetic acid by a factor of 11, in support of the assignment of structure. If inversion did not take place in the formation of the tritiated steroid and the product was indeed the 4β derivative, tritium should be eliminated from the steroid whether or not enolization occurred. Further studies on this inversion are in progress.

(23) L. Horner and D. Mayer, *Ann. Chem.*, **680**, 1 (1964), cited from *Chem. Abstr.*, **63**, 9765 (1965).

(24) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(25) Concerning the composition of the catalyst, V. N. Ipatieff and H. Pines [*J. Amer. Chem. Soc.*, **72**, 5320 (1950)] reported an analysis of W-6 catalyst as 21% alumina, 1.4% metallic aluminum, 0.5% sodium aluminate, and 77% nickel. No comparable analysis has been reported for W-2 catalyst. However, the latter is prepared over a longer period of time than the W-6 catalyst, and is washed copiously with water *after* it has been washed to neutrality; the catalyst is finally washed several times with *p*-cymene before use. It should be noted that the allomerization proceeds equally well with catalyst which is 3 months old, but fails with the triacetate of methyl cholate (unpublished observations).

(26) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 272.

(27) C. W. Shoppee, "Chemistry of the Steroids," Butterworth and Co., Ltd., London, 1964, p 50.

(28) F. J. McQuillin in "Elucidation of Structures by Physical and Chemical Methods," A. Weissberger, Ed., Part I, Interscience Publishers, New York, N. Y., 1963, p 498.

(29) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958).

(30) R. L. Augustine and A. D. Broom, *ibid.*, **26**, 802 (1960).

(31) R. L. Augustine, *ibid.*, **28**, 152 (1963).

(32) F. C. McQuillin, W. O. Ord, and P. L. Simpson, *J. Chem. Soc.*, 5996 (1963).

(33) S. Nishimura, M. Shimahara, and M. Shiota, *J. Org. Chem.*, **31**, 2394 (1966).

(34) M. G. Combe, H. B. Henbest, and W. R. Jackson, *J. Chem. Soc.*, 2467 (1967).

(35) H. H. Inhoffen, G. Stoeck, G. Koelling, and U. Stoeck, *Ann.*, **568**, 52 (1950).

(36) H. B. Henbest, W. R. Jackson, and I. Malunowicz, *J. Chem. Soc.*, 2469 (1967).

(37) A. W. Weitkamp, *Advan. Catal.*, **18**, 1 (1968).

(38) S. Siegel, *ibid.*, **16**, 123 (1966).

attributed to axial hindrance by the C_{10} methyl group and the C_8 hydrogen. On the other hand, dehydrogenation of the more planar 7-keto 5α-steroid is hindered by axial interaction of hydrogen at C_9, C_1, and C_{14}. Reduction of Δ^5-7-keto steroids is reported to proceed primarily by α attack,[39,40] although both 5β and 5α derivatives are formed.[41] Evidently the catalyst reached the axial 7α-hydroxy group to a limited extent, since about 25% of the 7-keto derivative was formed in each case.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. Infrared spectra were recorded on a Model 21 Perkin-Elmer double-beam spectrophotometer as Nujol mulls. The ultraviolet absorption spectrum was obtained with a Hitachi Perkin-Elmer uv spectrophotometer, Model 139.

Analytical tlc was carried out on 20 × 20 cm plates coated with 0.25 mm of silica gel G (Brinkmann Instruments Inc., Westbury, N. Y.); the different steroids were located on the plate after development in specified mixtures of acetone and benzene by spraying with 10% phosphomolybdic acid in 95% ethanol. Preparative layer chromatography (plc) was carried out with plates coated with 0.5 mm of silica gel H; the steroids were located on the plate after development by spraying with water.

Gas chromatography of steroids was carried out on an F & M Model 402 gas chromatograph with a U-shaped glass column (6 ft × 0.25 in. o.d.) packed with 3% OV-17 on Gas Chrom Q (Applied Science Laboratories, State College, Pa.) under the following conditions: flash heater, 280°; column, 260°; detector, 280°; helium, 40 psi at a flow rate of 80 cc/min. Quantitation of the steroids by glpc was carried out by multiplying the height of the peak by the width at half-height. Glpc of the hydrocarbons (Table I) was carried out in the same apparatus with a column of 5% Bentone 34–5% diisodecylphthalate on Gas Chrom Q (100–120 mesh) prepared according to Spencer;[42] flash heater, 100°; column, 60°; detector, 75°; helium, 40 psi at a flow rate of 65 cc/min. Glpc analysis of *p*-cymene was carried out on a column of 3% OV-1 on Gas Chrom Q (100–120 mesh); flash heater, 100°; column, 70°; detector, 105°; helium, 40 psi at a flow rate of 25 cc/min.

Mass spectrometry was carried out with an LKB Model 9000 single-focusing gas chromatograph mass spectrometer fitted with molecule separators of the Becker–Ryhage type. For the analysis of *p*-cymene and companions a coiled glass column (8 ft × 0.25 in. o.d.) packed with 3% OV-1 on Gas Chrom Q (100–120 mesh) was used with the following conditions: flash heater, 85°; column, 54°; molecule separator, 104°; ion source, 250°; accelerating voltage, 3.5 kV; ionizing energy 70 eV; trap current, 60 μA. Mass spectra of bile acids were determined with the direct inlet probe.

Radioactivity was measured in a Model 3314 Tricarb liquid scintillation spectrometer. Aqueous scintillator[43] was used as the medium for assay of tritium. The effluent from glpc was passed directly into the aqueous scintillator; the flame jet of the detector was replaced with a heated tube 18 in. × 1/16 in. o.d.

Raney Nickel Catalyst.—W-2 catalyst was prepared from Raney catalyst powder (No. 2813, W. R. Grace and Co., Chattanooga, Tenn.) according to the method of Mozingo.[19]

Action of Raney Nickel on Methyl Lithocholate.—The procedure described here is typical and can be applied to other steroids referred to earlier. *p*-Cymene used in this experiment can be replaced by other solvents described earlier. Methyl lithocholate (1.5 g, mp 128–129°) was mixed with freshly prepared Raney nickel catalyst (*ca.* 3.0 g) and freshly distilled *p*-cymene (15 ml). The Raney nickel was washed with *p*-cymene just before addition to remove adherent liquid. After the mixture was refluxed for 10 hr, the product was filtered and the filtrate was distilled in steam. From the distillate *p*-cymene was separated from water, dried over anhydrous sodium sulfate, and analyzed by glpc. The solid residue (1.39 g) in the distillation flask was taken up in ether and the ether layer dried. After evaporation of the ether, the product was purified by plc with 5% acetone in benzene and crystallized from aqueous methanol. An aliquot of the solid residue (500 mg) by this procedure yielded (i) methyl 3-keto-5α-cholanoate[7] (**3**) [280 mg, mp 113–114°, R_t 0.71, R_f 0.60 (5% acetone in benzene)]; (ii) methyl 3-keto-5β-cholanoate[44] (**2**) (90 mg, mp 119–120°, R_t 0.61, R_f 0.62); and (iii) methyl 3-keto-Δ^4-cholenoate[8] (**4**) [40 mg, mp 125–126°, R_t 0.93, R_f 0.41, uv max (C_2H_5OH) 241.5 mμ (log ε = 4.22), ir 1730, 1666, 1607, 1207, 1184, 1165, 1040, 869 cm^{-1}].

Oppenauer Oxidation of Methyl 3β-Hydroxy-Δ^5-cholenoate.—Methyl 3β-hydroxy-Δ^5-cholenate,[8] mp 143–144° (1.7 g), was oxidized by the Oppenauer method.[45] The crude oxidation product (1.65 g) was purified by chromatography on a column of silica gel followed by crystallization from aqueous methanol. Methyl 3-keto-Δ^4-cholenoate thus obtained had mp 125–126°; R_t 0.93; R_f 0.41 (5% acetone in benzene).

Action of Raney Nickel on Methyl Deoxycholate.—Methyl deoxycholate (1.0 g, mp 82°) on treatment with Raney nickel (*ca.* 2 g) in *p*-cymene (12 ml) in the usual way yielded a product (890 mg) which was purified by plc using 20% acetone in benzene followed by crystallization from acetone–hexane. An aliquot of this product (500 mg) by this procedure yielded (i) methyl 3-keto-12α-hydroxy-5α-cholanoate[7] (**7**) [270 mg, mp 145°, R_t 1.41, R_f 0.49 (20% acetone in benzene)]; (ii) methyl 3-keto-12α-hydroxy-5β-cholanoate[15] (**6**) (84 mg, mp 141–142°, R_t 1.17, R_f 0.40); and (iii) methyl 3-keto-12α-hydroxy-Δ^4-cholenoate[12] (**8**) (18 mg, mp 151–152°, R_t 1.87, R_f 0.33).

Action of 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) on Methyl 3-Keto-12α-hydroxy-5β-cholanoate (6).—A mixture of **6** (600 mg) and DDQ (350 mg) dissolved in 60 ml of dioxane was refluxed for 6 hr.[46] The solution was cooled and the dark brown residue left after evaporation of solvent was treated with benzene. The benzene solution was passed through a column of neutral Woelm alumina deactivated with 12% water. The residue from the benzene eluate (520 mg) containing a number of compounds was separated by plc into four fractions of different polarity. The fraction (107 mg) with a mobility just less than that of **6** was purified by repeated plc followed by crystallization from acetone–hexane to provide shining needles, mp 170–171°. On glpc two distinct peaks appeared, one amounting to about 70% of the mixture corresponded to methyl 3-keto-12α-hydroxy-Δ^4-cholenoate, R_t 1.86.

Methyl 3-Keto-12α-hydroxy-Δ^4-cholenoate. A.—Methyl 3-keto-12α-hydroxy-5β-cholanoate (**6**, 1.79 g) in 20 ml of acetic acid was brominated with a solution of 0.257 ml of bromine in 12 ml of acetic acid according to the procedure of Riegel and McIntosh.[12] Purification of the crude brominated product by plc in 15% acetone in benzene provided a residue, 1.55 g, which, however, failed to crystallize from acetone–hexane or benzene–hexane.

B. The brominated residue (1.55 g) was dried and refluxed in 20 ml of dry pyridine for 4 hr. The solution was poured into dilute hydrochloric acid. The resulting precipitate was extracted with ether–benzene and the extract washed with dilute hydrochloric acid, sodium bicarbonate solution, and finally with water. After evaporation of the solvent, the residue (0.97 g) was purified by plc in 25% acetone in benzene. The major compound thus obtained (470 mg) on crystallization from acetone–hexane yielded stout needles of methyl 3-keto-12α-hydroxy-Δ^4-cholenoate: mp 151–152°; R_t 1.87; R_f 0.33 (20% acetone in benzene); ir 3472, 1721, 1669, 1612, 1453, 1208, 1179, 1160, 1096, 1055, 866 cm^{-1}; uv max (C_2H_5OH) 241 mμ (log ε = 4.2).

Methyl 3-Keto-4β-bromo-5β-cholanoate.—Methyl 3-keto-5β-cholanoate[44] **2**, mp 121–122°; 1.0 g) in 15 ml of acetic acid was mixed with 0.16 ml of bromine in 1.5 ml of acetic acid. The mixture was allowed to stand 4 hr and then poured on ice. The resulting solid was filtered and purified by plc using 3% acetone in benzene and crystallized from acetone–methanol. This afforded methyl 3-keto-4β-bromo-5β-cholanoate[47] (820 mg):

(39) O. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.*, **65**, 1503 (1943).
(40) H. J. Ringold, *ibid.*, **82**, 961 (1960).
(41) I. G. Anderson and G. A. D. Haslewood, *Biochem. J.*, **74**, 37p (1960).
(42) See Table I, footnote *c*.
(43) P. D. Ray, E. A. Doisy, Jr., J. T. Matschiner, S. L. Hsia, W. H. Elliott, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, **236**, 3158 (1961).
(44) L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, **72**, 5530 (1950).
(45) R. V. Oppenauer, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., p 207.
(46) H. J. Ringold and A. B. Turner, *Chem. Ind.* (London), 211 (1962).
(47) L. F. Fieser and R. Ettorre, *ibid.*, **75**, 1700 (1953).

mp 99–100°; R_f 0.61 (3% acetone in benzene; R_f of methyl 3-keto-5β-cholanoate, 0.37, and methyl lithocholate, 0.16).

Acetic Acid-t[48,49].—Acetic anhydride (3.5 g), water (0.5 g), and tritiated water (0.1 g) with an original activity of 10 mC were mixed together and refluxed for 1 hr. The product was cooled, left overnight at room temperature, and distilled. After rejecting the first fraction, the second fraction was collected as tritiated acetic acid.

Methyl 3-Keto-4α-^{3}H-5β-cholanoate (13).—Methyl 3-keto-4β-bromocholanoate (300 mg) was dissolved in 10 ml of dry ether which was added directly into the reaction flask by distillation from lithium aluminum hydride. Tritiated acetic acid (0.3 ml) and zinc dust (0.6 g), previously dried *in vacuo*, were added to the ether solution which was maintained at 15° and magnetically stirred for 1 hr in an atmosphere of nitrogen. Ether was added and the mixture was filtered. The ethereal filtrate was washed with sodium bicarbonate solution and then with water, and finally dried over anhydrous sodium sulfate. On evaporation of ether a residue of 249.4 mg was obtained which on tlc had the same mobility as methyl 3-keto-5β-cholanoate,[7] R_f 0.62 (5% acetone in benzene). On crystallization of the residue from acetone–hexane short needles of methyl 3-keto-4α-^{3}H-5β-cholanoate,[17] mp 121–122°, were obtained: specific activity, 2.36×10^4, 2.38×10^4 dpm/mg.

Action of Raney Nickel on Methyl 3-Keto-4α-^{3}H-5β-cholanoate.—A mixture of compound **13** (152 mg), Raney nickel catalyst (*ca.* 400 mg), and *p*-cymene (10 ml) was refluxed in the usual way. After separation of the catalyst and the solvent, the product (120 mg) was purified by plc in 3% acetone in benzene. The major compound (96 mg) on crystallization from aqueous methanol yielded shining plates of methyl 3-keto-5α-cholanoate: mp 115–116°; specific activity 4.3×10^2, 4.6×10^2 dpm/mg.

***p*-Toluic Acid-^{3}H.**—*p*-Cymene-^{3}H (specific activity 1.24×10^2 dpm/mg, 5 ml), obtained by steam distillation of the product from the previous reaction, was oxidized by dilute nitric acid by the procedure of Tuley and Marvel.[18] The crude *p*-toluic acid-^{3}H (1.5 g, mp 173–174°) was purified by extraction with toluene in a Soxhlet and chilling the product. *p*-Toluic acid-^{3}H was separated, dissolved in sodium hydroxide solution, precipitated by hot dilute hydrochloric acid, and crystallized from toluene: mp 177–178°; specific activity 0.57×10,[2] 0.59×10^2 dpm/mg after two crystallizations.

Action of Raney Nickel on Cholestanol.—A mixture of cholestanol (510 mg), 20 ml of *p*-cymene, and Raney nickel catalyst (*ca.* 1.2 g) was heated for 10 hr under reflux in the usual way. After separation of the catalyst and the solvent, the product (440 mg) was separated by plc in 5% acetone in benzene into the following compounds: (a) 5α-cholestan-3-one [270 mg, mp 128°, R_f 0.80 (R_f of cholestanol 0.30, methyl 3-keto-5α-cholanoate 0.60), R_t 0.41 (R_t of cholestanol 0.35)]; (b) 5β-cholestan-3-one [32 mg, mp 62°, R_f 0.84, R_t 0.35]; (c) Δ^4-cholestenone [36 mg, mp 82°, R_f 0.56 (R_f of methyl 3-keto-Δ^4-cholenoate 0.41), R_t 0.53]. No cholestanol was detected in the above reaction product.

(48) E. J. Corey and G. A. Gregoriou, *Chem. Ind.* (London), **81**, 3127 (1959).
(49) J. D. Roberts, C. M. Regan, and I. Allen, *ibid.*, **74**, 3679 (1952).

Registry No.—**2**, 1173-32-6; methyl 3-keto-12α-hydroxy-Δ^4-cholenoate, 19684-72-1; *p*-toluic acid-^{3}H, 19689-62-4; 5β-cholestan-3-one, 601-53-6; Δ^4-cholestenone, 601-57-0.

Acknowledgment.—We are grateful for the expert assistance of Mr. Michael Thorne in gas chromatography and Mr. Howard Robinson and Miss Abby Braxton in mass spectrometry. Deoxycholic acid was a generous gift of the Wilson Laboratories, Chicago, Ill.

Neighboring Group Participation in Reactions of Alcohols with Lead Tetraacetate

PETER MORAND AND M. KAUFMAN

Department of Chemistry, University of Ottawa, Ottawa, Canada

Received October 16, 1968

The participation of the neighboring group in two related steroidal α-methoxy alcohols has been studied. 3β-Acetoxy-5α-methoxycholestan-6β-ol, **2a**, and 3β-acetoxy-6β-methoxycholestan-5α-ol, **5a**, were prepared by cleavage of the corresponding 5β,6β- and 5α,6α-epoxides, **1a** and **1b**, in methanol in the presence of acetic acid or boron trifluoride. The course of the lead tetraacetate oxidation of these alcohols was strongly influenced by the adjacent methoxyl group. The structures of the products isolated have been established and mechanisms for their formation are discussed.

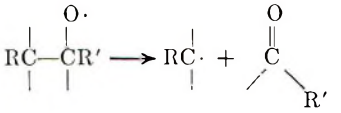
Since the discovery, in 1959, that CH_3, CH_2, and CH groups δ, and sometimes ε, to a secondary alcohol group could be oxidized by lead tetraacetate[1] to give rise to cyclic ethers, reactions of this type have been extensively studied.[2] Much of this work has been done with steroids[3] which are convenient models on which to study the geometrical factors involved in this interesting reaction. However, alcohols in diterpene,[4] bridged bicyclic,[5] and aliphatic[6–8] systems have also been shown to form cyclic ethers as well as other products. Conditions for this reaction vary; in the work described here the alcohol was treated with lead tetraacetate and irradiated in refluxing cyclohexane or benzene in the presence of iodine.[9]

Certain correlations have been made[2b] regarding the favorable internuclear distance between the oxyradical and the carbon atom carrying hydrogen atoms which can be abstracted intramolecularly. When a molecule has more than one alkyl group appropriately situated for hydrogen atom abstraction, other factors may influence the preferential abstraction of one hydrogen

(1) G. Cainelli, M. Lj. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959).
(2) For excellent reviews, see (a) R. Criegee in "Oxidation in Organic Chemistry," Part A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, p 321; (b) K. Heusler and J. Kalvoda, *Angew. Chem.*, **76**, 518 (1964).
(3) For example, see (a) J. F. Bagli, P. Morand, and R. Gaudry, *J. Org. Chem.*, **28**, 1207 (1963); (b) K. Heusler and J. Kalvoda, *Helv. Chim. Acta.*, **46**, 2020, 2732 (1963); (c) A. Bowers, E. Denot, L. C. Ibáñez, E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962); (d) H. Immer, M. Lj. Mihailović, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta.*, **45**, 7-3 (1962); (e) K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *ibid.*, **45**, 2575 (1962); (f) L. Velluz, G. Müller, R. Bardoneschi, and A. Poittevin, *C. R. Acad. Sci., Paris*, **250**, 725 (1960); (g) A. Bowers and E. Denot, *J. Amer. Chem. Soc.*, **82**, 4956 (1960).
(4) U. Scheidegger, K. Schaffner, and O. Jeger, *Helv. Chim. Acta.*, **45**, 400 (1962).
(5) K. Kitahonoki and A. Matsuura, *Tetrahedron Lett.*, 2263 (1964).
(6) V. M. Mićović, R. J. Mamuzić, D. Jeremić, and M. Lj. Mihailović, *ibid.*, 2091 (1963); *Tetrahedron*, **20**, 2279 (1964).
(7) V. M. Mićović, S. Stojčić, S. Mladenovic, and M. Stefanović, *Tetrahedron Lett.*, 1559 (1965).
(8) W. H. Starnes Jr., *J. Org. Chem.*, **33**, 2767 (1968).
(9) Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 1317 (1962).

atom over another. For example, hydrogen atoms attached to an oxygen-bearing carbon atom are more reactive[10] than the hydrogen atoms of a methyl group and, as expected, the reactivity of hydrogen atoms decreases[11] in the order tertiary > secondary > primary.

In addition to intramolecular abstraction of suitably situated hydrogen atoms, oxy radicals produced by oxidation with lead tetraacetate are also known to undergo fragmentation, as shown. The amount of



cleavage which occurs increases with the stability[12,13] of the product, $R\dot{C}<$. The stability of the ketone formed, the decrease in strain by the loss of bulky groups, entropy factors in the resonance stabilization of the radical formed by cleavage, and, in cyclic compounds (particularly small rings), the decrease in strain as a result of ring opening are also factors which determine the outcome of the competition between intramolecular hydrogen abstraction and fragmentation.

Results

Lead Tetraacetate Oxidation of 3β-Acetoxy-5α-methoxycholestan-6β-ol (2a).—Epimerization at the carbon atom bearing the hydroxyl group and at a carbon atom further removed has been shown to occur in the lead tetraacetate oxidation of 4β-hydroxy steroids[14] and of 6α-methyl-6β-hydroxy steroids.[15] A reversible fragmentation reaction was postulated by the authors in both cases to explain the formation of the products isolated. Intermediates in which bond cleavage had occurred at C-4, C-5 and at C-5, C-6, respectively, were invoked.

In steroids having a secondary hydroxyl group at C-6, apart from small quantities of C-6 ketone, only the 6β,19-oxide[16] has been isolated.[17] It was therefore decided to introduce a 5α-methoxy group in a suitable 6β-hydroxy steroid to investigate what influence it would have on the course of the lead tetraacetate oxidation of the alcohol.

3β-Acetoxy-5α-methoxycholestan-6β-ol, **2a**, was prepared[18] by heating 3β-acetoxy-5β,6β-oxidocholestane, **1a**, in methanol in the presence of acetic acid (Scheme I). The relative positions of the hydroxyl and methoxyl groups were confirmed by oxidation of **2a** to a ketone identified as 3β-acetoxy-5α-methoxycholestan-6-one, **6**. The ORD curve of this compound had a negative Cotton effect curve with a trough at 327 mμ, consistent with a C-6 ketone[19] in a *trans* A/B ring system.

Treatment of 3β-acetoxy-5α-methoxycholestan-6β-ol, **2a**, with excess lead tetraacetate and irradiation in refluxing cyclohexane in the presence of iodine gave a crude product from which three pure substances were isolated by column chromatography. The first compound to be eluted from the column was the methylenedioxy compound **3b** in a yield of 36%. On further elution, 3β-acetoxy-5α-methoxy-6β,19-oxidocholestane, **4** (27%), and 3β-acetoxy-5α-methoxycholestan-6-one, **6** (4%), were isolated.

The structure of **4** was deduced from its analysis and by examination of its ir and nmr spectra. The infrared spectrum showed a low intensity band at 1497 cm^{-1} which has been assigned[3a] to the C–H scissoring of the protons of the C-19 methylene group of the 6β,19-oxide. The nmr spectrum confirmed the presence of an acetate group, a methoxyl group, and a C-19 methylene group.[3a] A broad signal at 4.75 ppm for the hydrogen atom at C-3 indicated an equatorial configuration[20] for the C-3 acetate group which would be expected if the A/B ring was *trans*.

Examination of the nmr spectrum of compound **3b** showed that the acetate group at C-3 and the C-19 methyl group were intact. The presence of a five-membered methylenedioxy group was suggested[21] by the appearance of a singlet at 5.1 ppm which integrated for two protons. When the spectrum was determined in benzene instead of CD_3Cl an unresolved quartet was observed.

Examination of Drieding models shows that three isomeric methylenedioxy compounds are possible (Figure 1). Since the proton attached to C-6 would not be

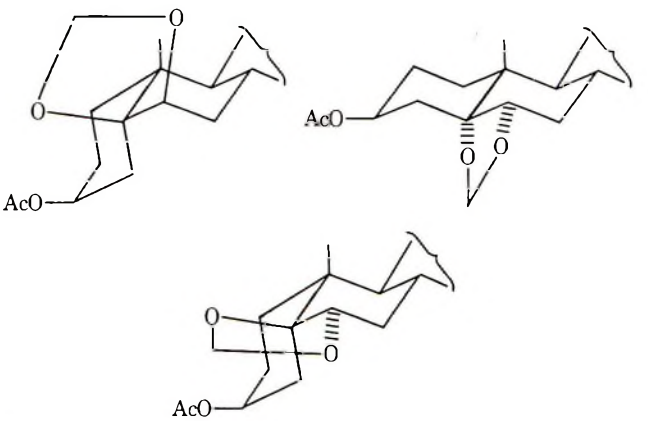


Figure 1.—Possible isomers of the methylenedioxy compound.

expected to be in too different an environment in any of these compounds the triplet centered at 3.86 ppm in the nmr spectrum and attributed to the C-6 proton did not enable one to establish configurations with any degree of certainty. Furthermore, since the band attributed to the 3α-H coincided with the signal of the methylenedioxy group, examination of the half-band width of the former was not possible.

(10) P. F. Beal and J. E. Pike, *Chem. Ind.* (London), 1505 (1960).

(11) J. Kalvoda, G. Anner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, M. Lj. Mihailović, K. Schaffner, and A. Wettstein, *Helv. Chim. Acta*, **44**, 186 (1961); D. Bertin and J. Perronet, *C. R. Acad. Sci., Paris*, **257**, 1946 (1963).

(12) J. Kocki, *J. Amer. Chem. Soc.*, **84**, 1193 (1962).

(13) Ch. Walling and A. Padwa, *ibid.*, **85**, 1593 (1963).

(14) K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963).

(15) K. Heusler and J. Kalvoda, *Tetrahedron Lett.*, 1001 (1963); *Helv. Chim. Acta*, **46**, 2732 (1963).

(16) A. Bowers, L. C. Ibáñez, E. Cabezas, and H. J. Ringold, *Chem. Ind.* (London), 1299 (1960); A. Bowers, E. Denot, L. C. Ibáñez, E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

(17) When a 5α-bromine atom is present, varying amounts of 5β,6β-epoxide are formed, depending on the reaction conditions (P. Morand and M. Kaufman, unpublished observation).

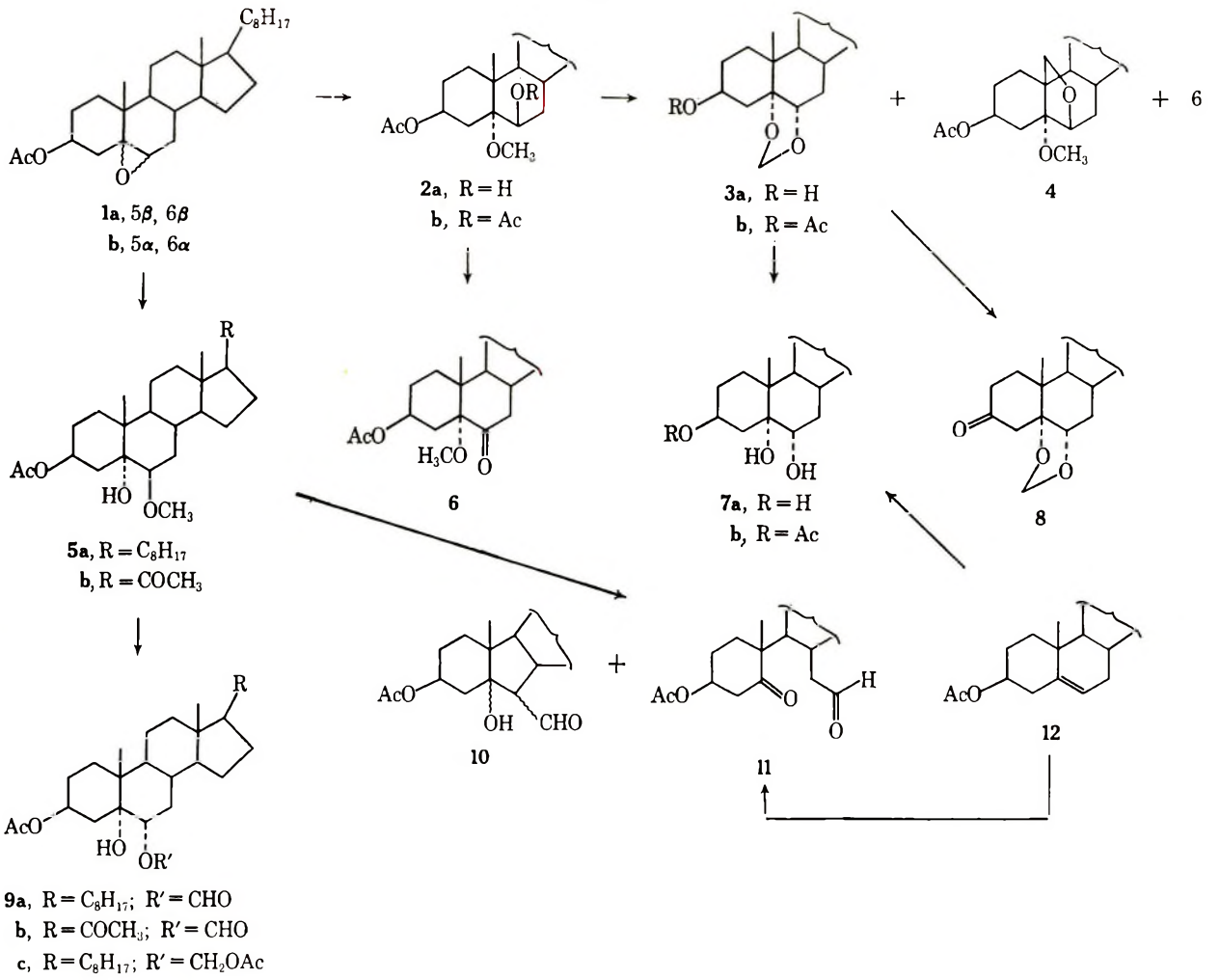
(18) *Cf.* R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 613 (1943).

(19) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp 42, 43.

(20) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 79.

(21) T. A. Crabb and R. C. Cookson, *Tetrahedron Lett.*, 679 (1964).

SCHEME I



Hydrolysis of compound **3b** under basic conditions gave the 3β-hydroxy compound **3a** which was subsequently oxidized with chromic acid in pyridine to ketone **8**. The ORD curve of this compound showed a positive Cotton effect as would be expected with a C-3 ketone in a *trans* A/B ring system.[22]

Treatment of **3b** with hydrogen chloride gas in ether–methanol cleaved the methylenedioxy group and hydrolyzed the C-3 acetate group giving a triol. The structure of this triol was identical with 3β,5α,6α-trihydroxycholestane, **7a**, obtained by hydroxylation of cholesterol acetate, **12**, with osmium tetroxide[23] and subsequent hydrolysis. The configuration at C-5 and C-6 of the methylenedioxy compound must therefore be as indicated in **3b**.

Lead Tetraacetate Oxidation of 3β-Acetoxy-6β-methoxycholestan-5α-ol (5a).—The lead tetraacetate oxidation of 5α- and 5β-hydroxy steroids has been shown[24] to yield products in which the C-5, C-10 bond is cleaved. The introduction of a methoxyl group at C-6 in steroids having a 5α-hydroxy group has a strong influence on the course of the lead tetraacetate oxidation of such compounds and a discussion of these results follows.

The mixture of the epimeric epoxides, **1a** and **1b**, obtained by treatment of cholesterol acetate, **12**, with perphthalic acid was treated with boron trifluoride etherate[25] in methanol and the product isolated was subsequently acetylated. By chromatography it was possible to isolate 5α-methoxycholestane-3β,6β-diol diacetate, **2b**, and 3β-acetoxy-6β-methoxycholestan-5α-ol, **5a**, in a ratio of 1:2.

When 3β-acetoxy-6β-methoxycholestan-5α-ol, **5a**, was oxidized with lead tetraacetate under the same conditions used for the reaction with **2a**, two products were isolated from the reaction mixture by chromatography on silica gel. The major product was the keto aldehyde **11** in which cleavage of the C-5, C-6 bond had occurred. The structure of this substance was confirmed by direct comparison with the same substance obtained by ozonolysis[26] of cholesterol acetate. The other product isolated was assigned the structure **10** on the basis of its elemental analysis and spectral properties. It was also shown that when the pure keto aldehyde **11** was eluted over silica gel it was partially converted into the hydroxy aldehyde **10**.

Under slightly different conditions and using less of an excess of lead tetraacetate, Lunn[27] has reported the isolation of the formate ester **9b** from 3β-acetoxy-5α-

(22) C. Djerassi, L. A. Mitscher, and B. J. Mitscher, *J. Amer. Chem. Soc.*, **81**, 947 (1959).
(23) V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1867 (1944).
(24) M. Lj. Mihailović, M. Stefanović, Lj. Lorenc, and M. Gašić, *Tetrahedron Lett.*, 1865 (1964); M. Lj. Mihailović, Lj. Lorenc, M. Gašić, M. Rogić, A. Melera, and M. Stefanović, *Tetrahedron*, **22**, 2345 (1966).
(25) S. Julia, B. Decouvelaere, and F. Englemann, *Bull. Soc. Chim. Fr.*, 2277 (1966).
(26) J. W. Cornforth, G. D. Hunter, and G. Popjak, *Biochem. J.*, **54**, 590 (1953).
(27) W. H. W. Lunn, *J. Org. Chem.*, **30**, 1649 (1965).

hydroxy-6β-methoxypregnan-20-one, **5b**. We have confirmed these results by isolation of the analogous formate ester **9a** (30%) from 3β-acetoxy-6β-methoxycholestan-5α-ol, **5a**, under the conditions described by Lunn. The structure of **9a** was assigned on the basis of its elemental analysis, its nmr and ir spectra, and the fact that triol **7a** was obtained on hydrolysis of this substance in base.

A small quantity (8%) of a second product, identified as acetyl 3β-acetoxy-5α-hydroxy-6α-cholestanyl formal, **9c**, was also isolated in this experiment. The empirical formula ($C_{32}H_{54}O_6$) of this compound was confirmed by its mass spectrum and by elemental analysis. Examination of the nmr spectrum of this substance indicated the presence of two acetate groups and an AB quartet centered at 5.22 ppm was attributed to a methylene group flanked by two oxygen atoms. The group at C-6 was assigned the α-configuration on the basis of the half-band width (20 Hz) of the signal attributed to the 6β-H.

Discussion

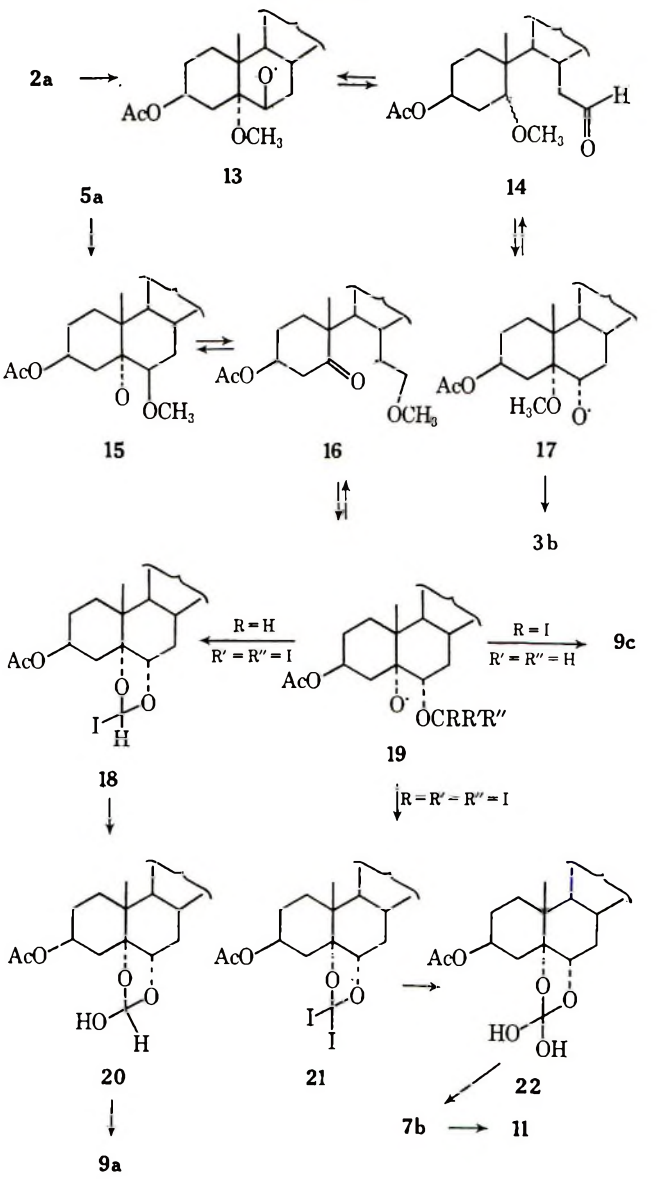
As already mentioned, epimerizations have been observed in the lead tetraacetate reaction of certain steroidal alcohols and these results have been explained[14,15] by assuming a reversible fragmentation reaction. Bearing this in mind an attempt will now be made to correlate the results obtained from the oxidation of both methoxy alcohols. For the sake of simplicity, it is assumed in the mechanisms discussed below that decomposition of the lead(IV) alkoxide intermediates formed in these reactions occurs homolytically.

Looking at Scheme II, it is seen that homolysis of the lead(IV) alkoxide of **2a** leads to the formation of an oxy radical (**13**) which can give rise to the intermediate **14** in which cleavage of the C-5, C-6 bond has occurred. This intermediate can then undergo cyclization with epimerization of the substituent at C-6 to give the oxy radical **17** in which the substituents at C-5 and C-6 are geometrically disposed to allow for abstraction of a hydrogen atom from the methoxyl group, resulting in the formation of 3β-acetoxy-5α,6α-methylenedioxycholestane, **3b**.

Lead tetraacetate oxidation of 3β-acetoxy-6β-methoxycholestan-5α-ol, **5a**, using a 2 molar excess of reagent, can proceed in an analogous manner. Cleavage of the C-5, C-6 bond (**16**), followed by cyclization with epimerization at C-6, leads to the formation of the intermediate **19** (R = R′ = R″ = H). From this intermediate it is possible to explain the formation of acetyl 3β-acetoxy-5α-hydroxy-6α-cholestanyl formal, **9c**, by the abstraction of a proton from the methoxyl group and concomitant addition of an acetoxyl radical. Alternatively, abstraction of two hydrogen atoms from the methoxyl group followed by the addition of two atoms of iodine would give the intermediate **19** (R = H, R′ = R″ = I). Upon displacement of one atom of iodine by the oxy radical the monoiodomethylenedioxy intermediate **18** could be formed which, under the reaction conditions, could decompose to give 3β-acetoxycholestane-5α,6α-diol 6-formate, **9a**.

With an excess of lead tetraacetate present the hydrogen atoms of the methoxyl group in **19** (R = R′ = R″ = H) can be substituted by three atoms of iodine.

SCHEME II



Displacement of one of these atoms by the oxy radical may lead to intermediate **21** which could then decompose to *cis* glycol **7b**. Further reaction with lead tetraacetate would cleave this glycol in the usual manner giving ketoaldehyde **11** as the final product.

The difference in behavior of the two methoxy alcohols toward lead tetraacetate can be rationalized on the basis of steric hindrance. By using Dreiding models it is revealed that the methoxyl group in **17** is restricted in its rotation about the C–O bond at C-5. The least hindered position for this group appears to be just under the oxy radical. Abstraction of more than one hydrogen atom with concomitant addition of iodine is therefore not favored and even if excess lead tetraacetate is used the only other products that can be isolated are the 6,19-oxide **4** (formed *via* intermediate **13**) and methoxy ketone **6**.

In the case of the intermediate **19** (R = R′ = R″ = H) rotation about the C–O bond at C-6 does not involve any serious steric interactions. Abstraction of more than one hydrogen atom with concomitant addition of iodine is therefore possible, leading to the formation of formate ester **9a** when 2 molar excess reagent was used

and to ketoaldehyde **11** when a larger excess of the reagent was used.

Experimental Section[28]

3β-Acetoxy-5α-methoxycholestan-6β-ol (2a).—3β-Acetoxy-5β,6β-oxidocholestane[29] (**1a**, 0.25 g) was dissolved in 9:1 methanol–acetic acid (30 ml) and the solution was stirred at 60° until no starting material remained (tlc). Usual work-up gave a crude product (0.24 g) which, upon crystallization from MeOH, gave a substance identified as 3β-acetoxy-5α-methoxycholestan-6β-ol, **2a**: mp 152.5–154°; $[\phi]_D$ −119° (c 0.6, $CHCl_3$); nmr ($CDCl_3$) δ 4.8 (m, 1, $w/2$ = 20 Hz, CHOAc), 3.9 (m, 1, $w/2$ = 9 Hz, CHOH), 3.2 (s, 3, OCH_3), 2.0 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{30}H_{52}O_4$: C, 75.58; H, 11.00. Found: C, 75.83; H, 10.84.

Oxidation of 3β-acetoxy-5α-methoxycholestan-6β-ol (**2a**, 0.15 g) with Jones reagent[30] led to the isolation of a crude product (0.12 g) after working up the reaction mixture in the usual manner. Crystallization of this material from methanol gave an analytical sample of a substance identified as **3β-acetoxy-5α-methoxycholestan-6-one, 6**: mp 149–150°; $[\phi]_D$ −206° (c 0.6, $CHCl_3$); ORD (dioxane) $[\phi]_{600}$ −280°, $[\phi]_{327}$ −5680°, $[\phi]_{315}$ −1860°, $[\phi]_{285}$ +2620°; nmr ($CDCl_3$) δ 4.8 (m, 1, $w/2$ = 25 Hz, CHOAc), 3.14 (s, 3, OCH_3), 2.0 (s, 3, $OCOCH_3$); ir ($CHCl_3$) 1725 (acetate C=O), 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 75.68; H, 10.55.

Lead Tetraacetate Oxidation of 3β-Acetoxy-5α-methoxycholestan-6β-ol (2a).—Lead tetraacetate (6.5 g), previously dried over P_2O_5, and anhydrous calcium carbonate (3.5 g) were added to benzene (150 ml) and the system was refluxed for 40 min by means of a 500-W lamp.[9] Freshly sublimed I_2 (2.0 g) and 3β-acetoxy-5α-methoxycholestan-6β-ol (**2a**, 0.50 g) were then added and the reaction mixture was refluxed for 1 additional hr. The insoluble white residue was removed by filtration over Celite and the filtrate was washed with an aqueous 30% $Na_2S_2O_3$ solution (200 ml). After working up in the usual manner, a crude product (0.48 g) consisting of three major components (tlc) was isolated.

Chromatography of this material over silica gel (500 g) and elution with benzene separated the first component (19 mg) which, after crystallization from methanol, was found to be identical in all respects with an authentic sample of **3β-acetoxy-5α-methoxycholestan-6-one, 6**.

The second substance (182 mg) to be eluted from the column was identified as **3β-acetoxy-5α,6α-methylenedioxycholestane, 3b**, on the basis of its spectral properties and of its subsequent chemical reactions. An analytical sample of this substance was obtained by crystallization from methanol: mp 150–152°; $[\phi]_D$ −137° (c 0.7, $CHCl_3$); nmr ($CDCl_3$) δ 5.1 (m, 1, CHOAc), 5.1 (s, 2, OCH_2O), 3.86 (t, 1, CHOC), 2.0 (s, 3, $OCOCH_3$), 1.0 (s, 3, CCH_3); nmr (benzene) δ 4.29, 4.19 (m, 2, OCH_2O).

Anal. Calcd for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 75.78; H, 10.42.

Further elution with benzene led to the isolation of a third substance (136 mg) which could be purified by crystallization from methanol–acetone–water. It was identified as **3β-acetoxy-5α-methoxy-6β,19-oxidocholestane, 4**: mp 110.5–112°; $[\phi]_D$ +32° (c 0.9, $CHCl_3$); ir ($CHCl_3$) 1720 (acetate C=O), 1497 cm^{-1} (CH_2OC); nmr ($CDCl_3$) δ 4.8 (s, 1, $w/2$ = 26 Hz, CHOAc), 3.8 (m, 3, CH_2OC and CHOC), 3.27 (s, 3, OCH_3), 2.0 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 75.60; H, 10.62.

Hydrolysis and Oxidation of 3β-Acetoxy-5α,6α-methylenedioxycholestane (3b).—Treatment of **3b** (0.13 g) with a solution of potassium hydroxide (0.10 g) in 9:1 methanol–water (10.0 ml) for 12 hr at room temperature gave, after usual work-up, a crude product (0.10 g) which could be purified by crystallization from acetone. The pure substance was identified as **3β-hydroxy-5α,6α-methylenedioxycholestane, 3a**: mp 153–155°, $[\phi]_D$ −80.8°.

Sarett[31] oxidation of **3a** (25 mg) led to the isolation of a crude product which, on crystallization from methanol, afforded a pure sample of **5α,6α-methylenedioxycholestan-3-one, 8**: mp 167–169°; ir ($CHCl_3$) 1710 cm^{-1} (C=O); ORD (dioxane) $[\phi]_{600}$ −117°, $[\phi]_{350}$ +292°, $[\phi]_{308}$ +2250°, $[\phi]_{264}$ −3600°.

Acid Hydrolysis of 3β-Acetoxy-5α,6α-methylenedioxycholestane (3b).—Treatment of **3b** (180 mg) in a dry methanolic solution of HCl gave, on usual work-up, a crude product which afforded an analytical sample of **3β,5α,6α-trihydroxycholestane, 7a**, on crystallization from acetone: mp 236–237° (lit.[23] mp 236–238°).

Osmium tetroxide oxidation of 3β-acetoxycholest-5-ene,[23] **12**, and subsequent hydrolysis of the product gave an authentic sample of **3β,5α,6α-trihydroxycholestane, 7a**, which was identical in all respects with the substance obtained above by treatment of **3b** in a dry methanolic solution of HCl.

3β-Acetoxy-6β-methoxycholestan-5α-ol (5a).—Epoxidation of 3β-acetoxycholest-5-ene (**12**, 10.0 g) was effected by treatment of the latter in an ethereal solution containing an excess of monoperphthalic acid for 12 hr at room temperature. The reaction solution was then washed with an aqueous 20% solution of Na_2SO_3. Phthalic acid formed in the reaction was removed by filtering the dried ethereal solution through a column of alumina (500 g). The crude product (10.6 g) which was isolated was found (by tlc) to consist of two major components.

Part of the product (5.0 g) obtained by epoxidation of **12** was treated with distilled boron trifluoride etherate (5.0 ml) in dry MeOH (40 ml) for 4 hr at room temperature.[25] Usual work-up gave a crude product (4.56 g), part (2.5 g) of which was acetylated with acetic anhydride and pyridine for 18 hr at room temperature. Ice–water was added to the reaction solution and the solid material (2.4 g) which precipitated was collected by filtration. The crude product was found to consist of two major components (tlc) which were subsequently separated by chromatography on silica gel (600 g).

The first fraction obtained by elution with benzene consisted of an oil (0.60 g) which consisted mostly of **3β,6β-diacetoxy-5α-methoxycholestane, 2b**: nmr ($CDCl_3$) δ 5.0 (m, 1, $w/2$ = 6 Hz, 6α-H), 4.82 (m, 1, $w/2$ = 25 Hz, 3α-H), 3.38 (s, 3, OCH_3), 2.0 (s, 3, $OCOCH_3$), 1.95 (s, 3, $OCOCH_3$).

Further elution with benzene gave a solid (1.26 g) which was purified by crystallization from methanol and subsequently identified as 3β-acetoxy-6β-methoxycholestan-5α-ol, **5a**: mp 139–141° (lit. mp 139.5–140.5°,[32] 138–139°,[25] 124–125°[33]); nmr ($CDCl_3$) δ 5.1 (m, 1, 3α-H), 3.3. (s, 3, OCH_3), 2.99 (s, 1, $w/2$ = 5 Hz, 6α-H), 2.05 (s, 3, $OCOCH_3$).

Oxidation of 3β-Acetoxy-6β-methoxycholestan-5α-ol (5a) with Excess Lead Tetraacetate.—3β-Acetoxy-6β-methoxycholestan-5α-ol (**5a**, 0.50 g) was treated with lead tetraacetate (7.0 g) under conditions identical with those previously described for the oxidation of **2a**. The crude product isolated appeared to consist of at least two major components (tlc) and these were separated by chromatography over silica gel (300 g).

On elution with benzene an oil (148 mg) was isolated which was identified as **3β-acetoxy-5,6-secocholestan-5-on-6-al, 11**: ir ($CHCl_3$) 2715 (CHO), 1735 (acetate C=O), 1725 (aldehyde C=O), 1700 cm^{-1} (C=O), ORD (dioxane) $[\phi]_{600}$ +318°, $[\phi]_{316}$ +7600°, $[\phi]_{309}$ +5400°, $[\phi]_{305}$ +6000°, $[\phi]_{295}$ +1600°, $[\phi]_{265}$ +5500°; nmr ($CDCl_3$) δ 9.35 (m, 1, CHO), 5.35 (m, 1, 3α-H), 2 (s, 3, $OCOCH_3$).

A second substance was obtained as a solid (36 mg) on further elution with benzene. Crystallization from ethyl acetate gave

(28) Melting points were determined on a Hoover Uni-Melt apparatus and are uncorrected. Infrared and nmr spectra were recorded on a Beckman IR-8 infrared spectrophotometer and on a Varian V-4302 60 Mc spectrometer, respectively. A Durrum-Jasco automatic spectropolarimeter, Model ORD-5, and a Perkin-Elmer 141 recording polarimeter were used to determine optical rotatory dispersion curves and optical rotations, respectively. Microanalyses were performed in the Microanalytical Laboratory of Dr. A. Bernhardt, Max Planck Institute, West Germany. SilicaR (200–300 mesh) and neutral alumina (Woelm, activity I) were used as adsorbants for column chromatography. Silica gel G (according to Stahl) was used as adsorbant for thin layer chromatography and sulfuric acid was used as spraying agent. In working up the products of reactions the organic extracts were washed with dilute HCl solution and/or $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and evaporated to dryness under reduced pressure.

(29) J. Hattori, *J. Pharm. Soc. Jap.*, **60**, 125 (1940); *Chem. Abstr.*, **34**, 7294 (1940).

(30) K. Bouden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2555 (1953).

(31) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(32) J. Hattori, *Chem. Abstr.*, **33**, 8622 (1939).

(33) J. W. Blunt, A. Fischer, M. P. Hartshorn, F. W. Jones, D. N. Kirk, and S. W. Young, *Tetrahedron*, **21**, 1567 (1965).

an analytical sample of a substance identified as **3β-acetoxy-B-nor-6ζ-formylcholestan-5ζ-ol, 10**: mp 91–92°; ir ($CHCl_3$) 3600 (OH), 2720 (CHO), 1725 (acetate C=O), 1710 cm^{-1} (aldehyde C=O); ORD (dioxane) $[\phi]_{600}$ −74°, $[\phi]_{316}$ −277°, $[\phi]_{280}$ +166°; nmr ($CDCl_3$) δ 9.35 (m, 1, CHO), 5.1 (m, 1, 3α-H), 2.05 s, 3, $OCOCH_3$).

Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.34; H, 10.53.

Preparation of 11 by Ozonolysis of 3β-Acetoxycholest-5-ene (12).—Ozonized oxygen was passed through a saturated solution of 3β-acetoxycholest-5-ene (**12**, 5.0 g) in hexane (100 ml) for 24 hr.[25] The solvent was removed under vacuum and the product was washed with petroleum ether and dried under vacuum at room temperature.

The ozonide was reduced by shaking with zinc powder (7.5 g) in acetic acid (50 ml) for 60 hr at room temperature. The zinc was removed by filtration over Celite and ether (50 ml) was added to the filtrate which was washed repeatedly with an aqueous 60% solution of $NaHCO_3$. After usual work-up part (2.7 g) of the crude product was chromatographed over silica gel (300 g). Elution with benzene gave pure **3β-acetoxy-5,6-secocholestan-5-on-6-al (11**, 1.0 g, oil) which was identical in all respects with the substance produced in the lead tetraacetate oxidation of 5a.

Oxidation of 3β-Acetoxy-6β-methoxycholestan-5α-ol (5a) with 2 Mol of Lead Tetraacetate.—A solution of 3β-acetoxy-6β-methoxycholestan-5α-ol (**5a**, 0.50 g), lead tetraacetate (0.89 g, previously dried over P_2O_5), and iodine (1.0 g) in dry benzene (50 ml) was refluxed for 2.75 hr. The reaction mixture was cooled and water (0.5 ml) was added with rapid stirring, followed 15 min later by the addition of an aqueous 10% solution of sodium bisulfite (30 ml). Usual work-up gave a crude product (474 mg) which was chromatographed over silica gel (300 g).

Elution with benzene afforded a fraction (144 mg) of a solid substance which was crystallized from methanol and identified as **3β-acetoxycholestane-5α,6α-diol 6-formate, 9a**: mp 141.5–143°; nmr ($CDCl_3$) δ 8.05 (m, 1, OCHO), 5.05 (m, 2, 3α-H, 6β-H), 2.0 (s, 3, $OCOCH_3$), 1.03 (s, 3, CH_3 at C-10).

Anal. Calcd for $C_{30}H_{50}O_5$: C, 73.43; H, 10.27. Found: C, 73.73; H, 10.47.

A second substance (40 mg) was isolated on further elution with benzene. Crystallization from methanol gave an analytical sample identified as **acetyl 3β-acetoxy-5α-hydroxy-6α-cholestanyl formal, 9c**: mp 156.5–157.5°; nmr ($CDCl_3$) δ 5.31, 5.25, 5.20, 5.15 (m, 2, J_{AB} = 6 Hz, OCH_2O), 5.2 (m, 1, 3α-H), 3.5 (m, 1, $w/2$ = 20 Hz, 6β-H), 2.06 (s, 3, $OCOCH_3$), 2.0 (s, 3, $OCOCH_3$), 0.94 (s, 3, CH_3 at C-10); mass spectrum (70 eV) *m/e* (relative intensity) 456 (48), 444 (49), 426 (40), 414 (60), 396 (61), 384 (99), 368 (100), 360 (86).

Anal. Calcd for $C_{32}H_{54}O_6$: C, 71.87; H, 10.18. Found: C, 71.72; H, 10.13.

Hydrolysis of 9a to 3β,6α,6α-Trihydroxycholestane (7a).—3β-Acetoxycholestane-5a,6a-diol 6-formate (**9a**, 20 mg) was treated with a 0.5 *N* methanolic potassium hydroxide solution (5 ml) for 12 hr at room temperature. The product which was obtained by working up in the usual manner was identical in all respects with the 3β,5α,6α-trihydroxycholestane, **7a**, prepared by the osmium tetroxide oxidation of 3β-acetoxycholest-5-ene, **12**, and subsequent hydrolysis.

Registry No.—**2a**, 19317-73-8; **2b**, 2515-24-4; **3a**, 19289-39-5; **3b**, 19289-40-8; **4**, 19289-41-9; **5a**, 2515-20-0; **6**, 19289-48-6; **8**, 19289-49-7; **9a**, 19289-50-0; **9c**, 19289-51-1; **10**, 19289-52-2; **11**, 19289-53-3; lead tetraacetate, 546-67-8.

Acknowledgment.—The authors express their thanks to Professor R. R. Fraser for helpful discussions concerning the nmr spectra of some of the compounds described in this paper. Financial assistance from the National Research Council of Canada and from Bristol Laboratories is gratefully acknowledged.

Chemical Identification of the Trail-Following Pheromone for a Southern Subterranean Termite[1]

AKIRA TAI, F. MATSUMURA, AND H. C. COPPEL

Department of Entomology, University of Wisconsin, Madison, Wisconsin

Received October 10, 1963

The synthetic procedures for the three isomers of a trail-following pheromone of a southern subterranean termite were described. Two of the isomers had identical spectroscopic properties as the natural pheromone. Only one of the isomers, *cis*-3,*cis*-6,*trans*-8-dodecatrien-1-ol, showed, however, an outstanding biological activity comparable to the natural product: less than 1 pg of the synthesized pheromone (like the natural pheromone) stimulated worker termites to follow artificially laid trails on ground-glass surfaces.

The presence of insect pheromones that chemically control the behavior of highly specialized social insect species has been well documented.[2] One such pheromone, "termite trail-following substance," is secreted by the sternal gland of various species of termite workers to mark the source of suitable wood to other workers of the same species.[3,4] The substance, when streaked across the surface of a solid object, creates a trail-following response in termite workers allowing them to follow the exact streak. Esenther, *et al.*,[5] discovered that woods decayed by the fungus *Lenzites trabea* Pers. ex Fr. also produced a substance attractive to the eastern subterranean termite, *Reticulitermes flavipes*. This substance was later found to work also as a "trail-following substance" against *R. flavipes* and a southern subterranean termite, *Reticulitermes virginicus*.[6] The active principle was purified and analyzed spectroscopically.[7] We now report the synthetic aspects of the pheromone leading to its identification.

Synthesis of Candidate Compounds and Bioassay.—As a result of various spectroscopic analyses of the purified termite pheromone,[7] two candidate compounds were considered to have spectroscopic properties identical with the natural product: *i.e.*, *cis*-3,*cis*-6,*trans*-

(1) Supported in part by U. S. Department of Agriculture Forest Service, Contract No. 12-11-012-560(5), and in part by Hatch Project 822, Wisconsin Agricultural Experiment Station. Approved for publication by the Director of the Wisconsin Agricultural Experiment Station. We thank Drs. H. R. Johnston and G. R. Esenther, Forest Service, U. S. Department of Agriculture, Gulfport, Miss., and Madison, Wis., respectively, for their cooperation in supplying the biological materials; and Dr. P. Bender, Mr. L. D. Sims, and Dr. B. M. Trost, Department of Chemistry, University of Wisconsin, Madison, for nmr and ir spectroscopic analyses.

(2) M. Jacobson, "Natural Pest Control Agents," Advances in Chemistry Series, No. 53, American Chemical Society, Washington, D. C., 1966, p 17.

(3) A. M. Stuart, *Nature*, **189**, 419 (1961).

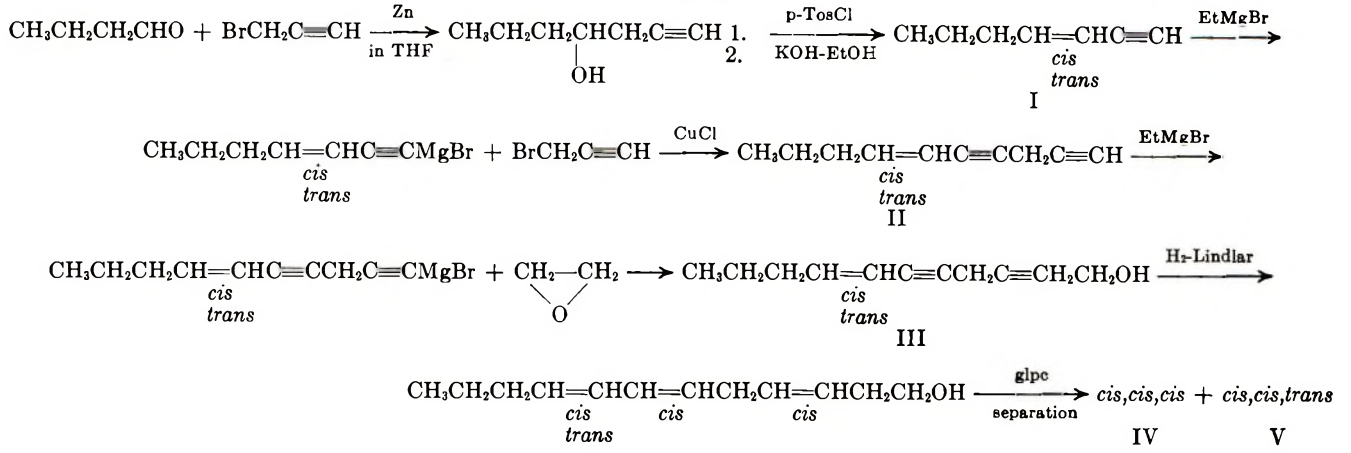
(4) R. V. Smythe and H. C. Coppel, *Ann. Entomol. Soc. Amer.*, **59**, 1008 (1966).

(5) G. R. Esenther, T. C. Allen, J. E Casida, and R. D. Shenefelt, *Science*, **134**, 50 (1961).

(6) R. V. Smythe, H. C. Coppel, S. H. Lipton, and F. M. Strong, *J. Econ. Entomol.*, **60**, 228 (1967).

(7) F. Matsumura, H. C. Coppel, and A. Tai, *Nature*, **219**, 963 (1968).

SCHEME I



8- and *cis*-3,*trans*-6,*cis*-8-dodecatrien-1-ol. The total synthesis of these two compounds and the comparison of their biological potencies appeared to be the only means to positively identify the chemical structure of the termite pheromone. The synthetic route to obtain the above compounds and *cis*-3,*cis*-6,*cis*-8-dodecatrien-1-ol are shown in Schemes I and II.

Altogether 15 mg of *cis,cis,cis* IV, 12 mg of *cis,cis, trans* V, and 35 mg of *cis,trans,cis* XI isomers of 3,6,8-dodecatrien-1-ol were obtained. They were dissolved in ether to make 1 mg/ml of stock solution from which samples of various dilution series were made. A 10-μl portion of the diluted sample solution was used for each bioassay.

The minimum amounts required to stimulate the worker termites to follow artificially laid 10-cm paths along a 120° arc on ground-glass surfaces were 100 pg for *cis,cis,cis*, 10 pg for *cis,trans,cis*, and 0.01 pg for *cis, cis,trans* as compared to the natural termite trail-following pheromone, 0.05 pg. The manner in which the worker termites followed the trails of compound V was identical with that with the natural product.

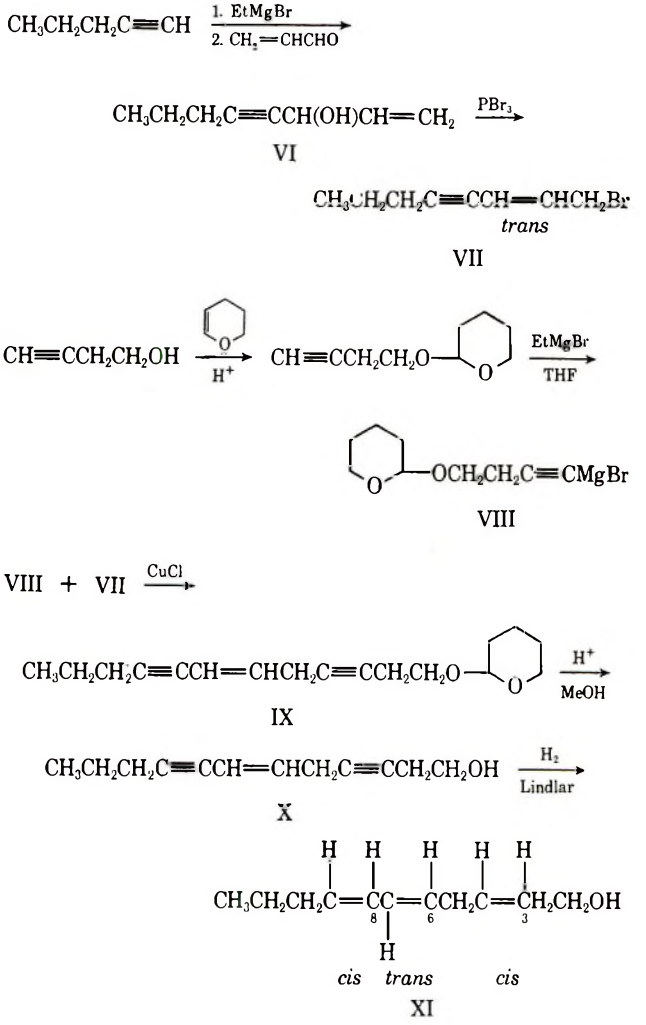
The result clearly indicated that *cis*-3,*cis*-6,*trans*-8-dodecatrien-1-ol was the termite trail-following pheromone.

Experimental Section

The instrument used for the chromatographic analyses was a Beckman GC4 with a dual hydrogen-flame detector. A post-column (and predetector) splitter was used to divert nine-tenths of the sample to the *n*-pentane trap at −60°. In all cases, 0.25 in. by 6 ft stainless steel columns were used with the carrier (He) speed at 40 ml/min. One tenth of the sample was used for detecting the sample peaks.

cis-**3**,*cis*-**6**,*cis*(*trans*)-**8-Dodecatrien-1-ol (Scheme I). 3-Hepten-1-yne (I).**—Thirty-five grams of propargyl bromide was treated with 26 g (0.36 mol) of *n*-butyraldehyde[8] (Reformatski reaction); 36 g of crude 1-heptyn-4-ol (*ca.* 0.3 mol) was obtained. It was directly converted to *p*-toluenesulfonyl ester by adding the above product into a solution of 54 g of *p*-toluenesulfonyl chloride in 68 ml of pyridine. The product was transferred into 300 ml of 10% aqueous NaOH solution at 0°. The ester was extracted with ether and the solvent was removed. It was refluxed in 250 ml of 18% ethanolic KOH for 8 hr. The product was extracted with 100 ml of Skelly B, washed with 10% aqueous sulfuric acid, distilled water, 5% of sodium bicarbonate, and distilled water, and dried over sodium sulfate. Removal of solvent and distillation of the residual oil gave 7 g (23.4%) of I, bp 48–55° (135 mm). The catalytic hydrogenation product (with PtO_2), heptane, was checked by a gas chromatographic system; ir (CS_2), 3300 (C≡CH) and 2100 (C≡C), 1600 (C=C), 952 (HC=CH *trans*) and 720 cm^{-1} (HC=CH *cis*). Gas chromatographic analysis indicated the ratio between *trans* and *cis* isomers was approximately 1:1.

SCHEME II



6-Decen-1,4-diyne (II).—A 6-g (0.064 mol) portion of 3-hepten-1-yne (*cis,trans* mixture) was added dropwise to a Grignard reagent, prepared by reacting 8 g of ethyl bromide and 1.8 g of magnesium in 30 ml of ether, and the system was refluxed until evolution of ethane gas ceased. Cuprous chloride (0.5 g) was added to the mixture and the system was stirred for additional 30 min. Propargyl bromide (8.8 g) with ether (26 ml) was added dropwise over a period of 4 hr and the system was refluxed for additional 24 hr.[9] The product in ether was washed

(8) L. Crombie and A. G. Jacklin, *J. Chem. Soc.*, 1740 (1955).

(9) W. J. Gensler, A. P. Mahadevan, Jr., and J. Casella, *J. Amer. Chem. Soc.*, **78**, 163 (1956).

with 15% sulfuric acid, water, 5% sodium bicarbonate, and water, and dried over sodium sulfate. Removal of solvent and distillation of residue gave 3.6 g (42.5%) of decene-1,4-diyne, bp 55–60° (10 mm). Gas chromatographic analyses showed two substances, *cis* and *trans* isomers, one with ir (CS_2) peak at 720 cm^{-1} and the other with 950 cm^{-1}. Both gave *n*-decane upon catalytic hydrogenation with PtO_2; uv, λ_{max} 226 mμ.

8-Dodecene-3,6-diyn-1-ol (III).—A 1.83-g (0.014 mol) portion of 6-decen-1,4-diyne (*cis,trans* mixture) was added to a Grignard reagent, prepared by reacting 1.69 g of ethyl bromide and 0.38 g of magnesium in 25 ml of ether, and the system was refluxed for 1 hr. After cooling the system to 0° ethylene oxide (0.7 g) in 2 ml of ether was added dropwise. Extraction, washing, and distillation steps were repeated as above to obtain 1.42 g (58%) of III: bp 125–135° (1 mm) (*Anal.* Calcd for $C_{12}H_{16}O$: C, 81.82; H, 9.09. Found C, 82.46; H, 10.53.); ir (CS_2) of gas chromatographic peak 1, 3400 (broad) for OH, 3000 for CH=CH, 2200 for C≡C, 1670 for CH=CH, 1040 for C–O, and 720 cm^{-1} for *cis* CH=CH; ir (CS_2) for the peak 2 closely resembled that of the peak 1 except for the absence of absorption at 720 cm^{-1} and the appearance of a new absorption peak at 945 cm^{-1} for *trans* CH=CH. Both compounds gave dodecanol upon catalytic hydrogenation.

3,6,8-Dodecatrien-1-ol (IV and V).—The above product (*i.e.*, the mixture of *cis*-8- and *trans*-dodecen-3,6-diyn-1-ol) was further purified on a Florisil column (1 × 30 m) with ether as a mobile phase. A 0.8-g (4.7 mmol) portion of the column purified product was dissolved in 30 ml of methanol containing 4 drops of quinoline. To hydrogenate selectively the triple bonds only, 0.2 g of Lindlar catalyst[10] was used under 1 atm of H_2 at room temperature. The product was extracted, washed, and dried over sodium sulfate, and the solvent was partially removed as before. The *cis* and *trans* isomers were separated and purified twice on gas chromatographic systems (SE52 and NGA columns). Only one-tenth of the final product was purified in this manner to yield 15 mg of IV and 12 mg of V (IV and V combined yield: 32.0%).

Both compounds were unstable in the concentrated state: they polymerized even under nitrogen at 0°. Elemental analysis was conducted upon their precursor, 8-dodecene-3,6-diyn-1-ol only.

Compound V showed the following spectral properties: ir (CS_2) 3600–3260 (OH), 3000 (=CH), 1055 (C–O), 925 and 980 (CH=CH, *trans-cis* conjugated), 728 cm^{-1} (CH=CH *cis*); uv (*n*-pentane) λ_{max} 234 mμ; nmr (CCl_4) δ 0.92 (t, 3 H, J = 6.5 Hz, CH_3CH_2), 1.25–1.51 (m, 2 H, CH_3CH_2), 1.99–2.32 (m, 5 H, $=CHCH_2CH_2$ and OH), 2.76–2.99 (m, 2 H, $=CHCH_2CH=$), 3.55 (t, 2 H, J = 6.5 Hz, CH_2CH_2OH), 5.0–6.1 (m, 6 H olefinic proton). Compound IV showed the following spectral properties: ir (CS_2) 3600–3260 (OH), 3000 (=CH), 1055 (C–O), 720 cm^{-1} (CH=CH *cis*, prominent); nmr same as V except 1.90–2.35 ($=CHCH_2CH_2$); uv (*n*-pentane) λ_{max} 235 mμ. Both isomers gave dodecan-1-ol by a catalytic hydrogenation with platinum oxide. V behaved in a manner identical with the natural product in all chromatographic tests.

***cis*-3,*trans*-6,*cis*-8-Dodecatrien-1-ol (Scheme II). 1-Octen-4-yn-3-ol (VI).**—To a Grignard reagent (36 g of EtBr and 8 g of Mg in 100 ml of ether) was added dropwise 20 g (0.3 mol) of 1-pentyne, and the mixture was refluxed for 1 hr. After cooling to 10°, 16.8 g of acrolein was added dropwise. The mixture was stirred for an additional 1 hr at 10°, and was then refluxed for 1 hr. After cooling, a 100-ml aliquot of ice–water was added to the reaction vessel and the reaction product was extracted three times with 50 ml each of ether. The solution was dried over sodium sulfate, freed of solvent, and distilled to give 20 g (54.9%) of VI: bp 79–81° (1 mm); ir (CS_2) 3350 (OH), 3010 (CH vinyl), 2225 (C≡C), 1640 (C=C), 920 cm^{-1} (C=CH_2).

1-Bromo-*trans*-2-octen-4-yne (VII).—To a cooled solution of 1-octen-4-yn-3-ol (16 g or 0.13 mol in 100 ml ether containing 2.4 g of dry pyridine) was added dropwise a solution of 11.8 g of phosphorus tribromide in 30 ml of dry ether over a 20-min period with continuous stirring. The reaction mixture was then gently heated to reflux for 20 min. Upon cooling, the product was poured over ice. The ether phase was washed successively with 100 ml each of water, 5% of aqueous sodium carbonate, and water and dried over sodium sulfate. Removal of the solvent and distillation of the residue gave 18 g (77.6%) of VII; bp 56–62° (1 mm); ir (CS_2) 2200 (C≡C), 1610 (C=C), 945 cm^{-1} (HC=CH, *trans*).

***trans*-6-Dodecene-3,8-diyn-1-ol (X).**—To a 100 ml of tetrahydrofuran solution with Grignard reagents (6.1 g of EtBr and 1.33 g of Mg) was added dropwise 8.5 g of 1-(tetrahydro-2-pyranoxy)-3-butyne, and the mixture was refluxed for 1 hr with stirring. Cuprous chloride (0.5 g) and then 9 g of VII was added to the reaction mixture at 60°, the latter over a period of 4 hr. The reaction continued overnight, and the product was purified as before to give 1-(tetrahydro-2-pyranoxy)-6-dodecene-3,8-diyne (IX). The product was dissolved in 100 ml of MeOH. Concentrated sulfuric acid (16 ml) was added to the solution, and the system was kept for 24 hr at room temperature. The reaction mixture was poured into 1 l. of 5% sulfuric acid, and the product was extracted three times with 100 ml each of Skellysolve B. Removal of the solvent and distillation of the residue gave 7.5 g (46.0%) of pearl yellow oil, *trans*-6-dodecene-3,8-diyn-1-ol (X), bp 120–125° (0.8 mm). Gas chromatography on NGA (170°) gave a single peak; ir (CS_2) 3300 (OH), 3005 (CH=CH), 2200 (C≡C), 1660 and 1610 (C=C), 1040 (C–O), 950 (CH=CH, *trans*). Catalytic hydrogenation with PtO_2 gave an identical peak as *n*-dodecanol by two glpc systems (SE52 and NGA).

***cis*-3,*trans*-6,*cis*-8-Dodecatrien-1-ol (XI).**—The above product (X) was further purified on a Florisil column (2.5 × 30 cm) with ether. A 1-g (5.9 mmol) portion of the purified material was dissolved in 30 ml of MeOH containing 4 drops of quinoline and was hydrogenated[10] with 0.2 g of Lindlar catalyst at room temperature. Glpc purification of one-twentieth of the reaction product gave 35 mg (66%) of pure *cis*-3,*trans*-6,*cis*-8-dodecatrien-1-ol (XI). Uv, nmr, and ir spectra were identical with those of *cis*-3,*cis*-6,*trans*-8-dodecatrien-1-ol (V). Catalytic hydrogenation gave a compound identical with dodecanol in two glpc systems.

Registry No.—I(*cis*), 764-57-8; I(*trans*), 764-58-9; II(*cis*), 19926-59-1; II(*trans*), 19926-60-4; III(*cis*), 19926-61-5; III(*trans*), 19926-62-6; IV, 19926-63-7; V, 19926-64-8; VI, 19926-65-9; VII, 19926-66-0; X, 19926-67-1.

(10) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

Reactions of Some Acylquinolones with Diazomethane[1]

J. W. HUFFMAN AND J. H. CECIL[2]

Department of Chemistry and Geology, Clemson University, Clemson, South Carolina 29631

Received November 19, 1968

Several acylquinolones have been treated with diazomethane and the products characterized principally by spectroscopic means. 3-Isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) gave 3-isobutyryl-4,8-dimethoxy-2-quinolone (**4a**), 1-methyl-2-isobutyryl-4,8-dimethoxy-2-quinolone (**9**), and 3-isopropyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone (**6a**). 3-Isovaleryl-4-hydroxy-8-methoxy-2-quinolone (**2b**) gave 3-(2-oxo-3-methylpentyl)-4,8-dimethoxy-2-quinolone (**3b**), 3-(2-oxo-3-methylpentyl)-2,4,8-trimethoxyquinoline (**11**), and 3-isobutyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone (**6b**). 3-Isobutyryl-4-hydroxy-2-quinolone (**2d**) gave 3-(2-oxo-3-methylbutyl)-4-ethoxy-2-quinolone (**3c**), 3-isobutyryl-4-methoxy-2-quinolone (**4b**), 3-isopropyl-9-methylfuro[2,3-*b*]-4-quinolone (**6c**), and 3-isopropyl-3-hydroxy-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline (**13**). Treatment with hydrochloric acid gave 3-isopropylfuro[2,3-*b*]-4-quinolone (**14**) from **13**, and **3b** from **11**.

In previous work directed toward a general synthesis of furoquinoline alkaloids such as lunacrine (**1**), the reactions of the 3-acylquinolones **2a** and **2b** with diazomethane have been reported to give **3a** and **3b** (Chart I), the result of insertion into the side chain in addition to O methylation.[1] Reduction of these quinolones and cyclization leads to isobutyl furoquinolines rather than the desired isopropyl derivatives. In an attempt to take advantage of this homologation reaction, the 3-isobutyryl-4-hydroxy-2-quinolones **2c** and **2d** were treated with diazomethane, in the expectation that suitable precursors to the lunacrine alkaloids could be obtained.

Treatment of 3-isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) with ethereal diazomethane gave a mixture from which two compounds, A and B, were isolated. Compound A, $C_{15}H_{17}NO_4$, shows a split carbonyl band in the infrared with absorption at 5.98 and 6.20 μ. The 6.20-μ absorption is at somewhat longer wavelength than that generally associated with 2-quinolones[3] (6.02–6.10 μ), however, the nmr spectrum is lacking the resonances due to the deshielded C-5 proton in a 4-quinolone.[4,5] This spectrum is essentially the same as that of the starting quinolone (**2c**), with a barely resolved pair of singlets centered about 4.01 ppm in place of the methoxyl singlet at 4.00 ppm. On the basis of these data, A must be 3-isobutyryl-4,8-dimethoxy-2-quinolone (**4a**), the result of simple O methylation.

Compound B has an empirical formula of $C_{16}H_{17}NO_3$ and the infrared spectrum shows carbonyl absorption at 6.11 μ, at somewhat lower wavelength than that generally associated with 4-quinolones (6.13–6.17 μ),[3] however the nmr spectrum has the highly deshielded C-5 proton resonance at 8.10 ppm indicative of a 4-quinolone.[4,5] This C-5 proton is the X portion of the ABX multiplet, (J_{ortho} = 8 Hz and J_{meta} = 2 Hz) and in addition to the AB multiplet at 6.95–7.30 ppm, the balance of the nmr spectrum of B shows a vinyl doublet (J = 1 Hz) at 6.95 ppm, a methoxyl singlet, an N-methyl singlet, the typical isopropyl pattern with a methyl doublet (J = 7 Hz) at 1.35 ppm, and a rather deshielded methine multiplet centered about 3.32 ppm. Irradiation of the methine multiplet collapsed the doublet at 6.95 to a singlet, indicating that the isopropyl group is adjacent to the vinyl proton. The ultraviolet spectrum of B is virtually identical with that reported for anhydrobalfouridine; which has been shown to have the assigned structure (**5**) by its reduction to lunacrine (**1**).[6] Although the melting points of B and anhydrobalfouridine only differ by 1°, the mixture melting point[7] of the two is depressed, the infrared spectra are not identical and on the basis of these data B is assigned the structure 3-isopropyl-8-methoxy-9-methylfuro-[2,3-*b*]-4-quinolone (**6a**). It was originally thought that **6a** may have been anhydrobalfouridine on the basis of the chemical shift (6.95 ppm) of the furyl proton. It has been suggested that α protons of furoquinolones of general structure **7** have a chemical shift of 7.20–7.24 ppm while the β protons are in the range 6.98–7.01 ppm. The synthesis of the furoquinolone (**6a**) with α-proton resonance at 6.95 ppm indicates that these assignments are probably reversed. Apparently, in these 4-quinolone systems, the β protons are deshielded very strongly by the 4-carbonyl, while the α protons are in the normal range for those in simple furans.

House, *et al.*,[8] have reported the use of both methanol and boron trifluoride as catalysts for the diazomethane homologation of ketones. These catalysts were therefore employed in the reaction of 3-isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) with diazomethane. Large volumes of methanol gave a mixture, from which, after repeated chromatography on alumina, were isolated two compounds. One of these was 3-isopropyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone (**6a**), while the second compound, $C_{16}H_{19}NO_4$, shows carbonyl absorption in the infrared at 5.95 and 6.20 μ. The ultraviolet spectrum of this compound is similar to that of 3-isobutyryl-4,8-dimethoxy-2-quinolone (**4a**); however, the spectrum shifts in neither acid or base, while that of **4a** shifts in base (Scheme I). The nmr spectrum has a pair of singlets at 3.92 ppm with an area corresponding to nine protons, whereas **4a** has a pair of singlets at 4.01 ppm with an area corresponding to six protons. This methanol catalyzed product must therefore be 1-

(1) This work was supported in part by Grant GM-08731 and Research Career Program Award 1-K3-GM-5433 from the National Institute of General Medical Sciences. and should be considered as paper IV in a series "The Furanoquinoline Alkaloids." Previous paper: J. W. Huffman, S. P. Garg, and J. H. Cecil, *J. Org. Chem.*, **31**, 1276 (1966).

(2) Abstracted in part from a dissertation presented by J. H. Cecil in partial fulfillment of the requirements for the Ph.D. degree, Clemson University, Dec 1968.

(3) (a) M. F. Grundon, N. J. McCorkindale, and M. N. Rodgers, *J. Chem. Soc.*, 4282 (1955); (b) M. F. Grundon and N. J. McCorkindale, *ibid.*, 2177 (1957).

(4) S. Goodwin, J. H. Shoolery, and L. F. Johnson, *J. Amer. Chem. Soc.*, **81**, 3065 (1959).

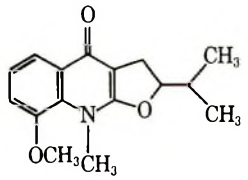
(5) A. V. Robertson, *Aust. J. Chem.*, **16**, 451 (1963).

(6) H. Rapoport and K. G. Holden, *J. Amer. Chem. Soc.*, **82**, 4395 (1960).

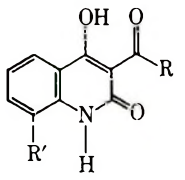
(7) Appreciation is expressed to Dr. Henry Rapoport for a sample of anhydrobalfouridine.

(8) H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, **82**, 4099 (1960).

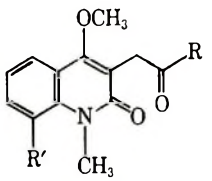
CHART I



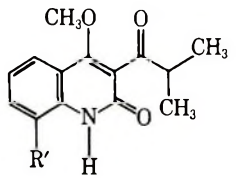
1



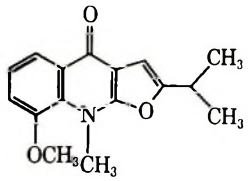
2a, R = *i*-Bu; R¹ = H
b, R = *i*-Bu; R¹ = OCH_3
c, R = *i*-Pr; R¹ = OCH_3
d, R = *i*-Pr; R¹ = H



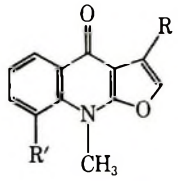
3a, R = *i*-Bu; R¹ = H
b, R = *i*-Bu; R¹ = OCH_3
c, R = *i*-Pr; R¹ = H



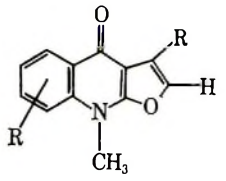
4a, R = OCH_3
b, R = H



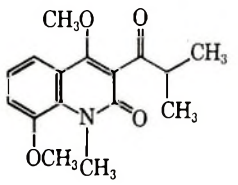
5



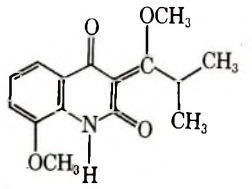
6a, R = *i*-Pr; R¹ = OCH_3
b, R = *i*-Bu; R¹ = OCH_3
c, R = *i*-Pr; R¹ = H



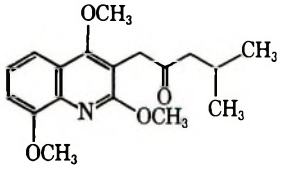
7



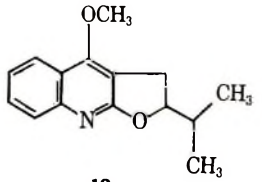
9



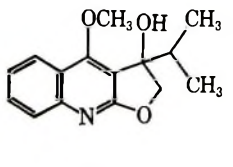
10



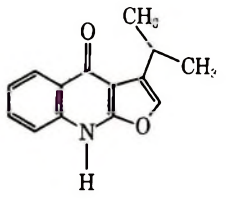
11



12



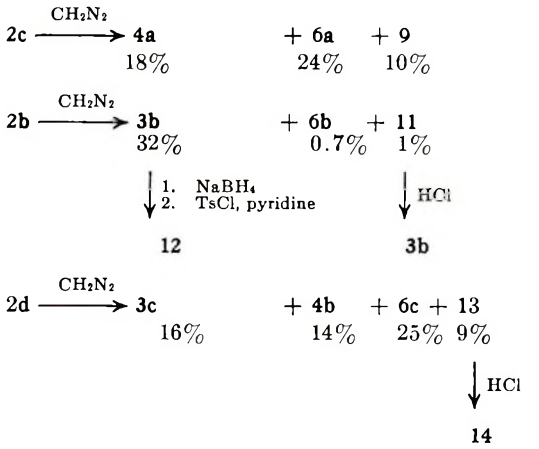
13



14

methyl-2-isobutyryl-4,8-dimethoxy-2-quinolone (**9**), the result of N,O dialkylation.

SCHEME I



The use of boron trifluoride as a catalyst for the reaction of 3-isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) with diazomethane gave a bright yellow solid, which, when dissolved in methanol, gave a yellow solution that turned colorless as it was warmed. From this colorless solution, only the starting quinolone (**2c**) could be obtained. Moreover, while the ultraviolet spectra in methanol of **2c** and the diazomethane product were identical, the infrared spectra were not. Owing to the instability of this material it could not be characterized completely; however, it appears that this compound is the enol ether (**10**).

Since the isobutyrylquinolones did not give homologation to any appreciable extent, it was felt that a repetition of the reaction of 3-isovaleryl-4-hydroxy-8-methoxy-2-quinolone (**2b**) with diazomethane might lead to the simple O-alkylated acylquinolone. However, the major product of the treatment of **2b** with ethereal diazomethane was the inserted quinolone (**3b**), identical with that previously reported.[1]

Two other compounds, C and D, were also isolated in small quantity from this reaction. Compound C has an empirical formula of $C_{17}H_{19}NO_3$ and its infrared, ultraviolet, and nmr spectra were quite similar to those of the furoquinolone (**6a**). Compound C is thus assigned the structure 3-isobutyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone (**6b**). The nmr spectrum of C is in complete agreement with this assignment, showing in addition to a vinyl proton multiplet at 7.02 ppm, the typical isobutyl pattern of a broadened doublet at 2.71 ppm, a multiplet at 1.8–2.5 ppm, and a doublet at 0.97 ppm. These are assigned, respectively, to the methylene, methine, and methyl protons of the isobutyl group.

The infrared spectrum of D has absorption at 5.87 μ assigned to the side chain carbonyl, and medium intensity absorption at 6.15 μ which is probably due to aromatic absorption, since the nmr spectrum shows no evidence supporting a 4-quinolone structure. The ultraviolet spectrum of D has much the same shape as that of the 2-quinolone (**3b**), but is altered on acidification and does not shift in basic solution. The nmr spectrum of D shows singlets at 3.82, 3.93, 4.05, and 4.10 ppm with an area ratio equivalent to eleven protons. These data, particularly the shift of the ultraviolet spectrum in acidic solution, suggests that D is a trimethoxyquinoline. Treatment of D with hydrochloric acid gives the 2-quinolone (**3b**), and consequently D must be 3-(2-oxo-3-methylpentyl)-2,4,8-trimethoxyquinoline (**11**).

In order to explore further the nature of these reactions of 3-acylquinolones, 3-isobutyryl-4-hydroxy-2-quinolone (**2d**) was also treated with diazomethane to give a mixture from which two compounds, E and F, were isolated. Compound E has an empirical formula of $C_{15}H_{15}NO_2$, and the infrared spectrum has the medium intensity carbonyl absorption at 6.15 μ typical of a 4-quinolone. The nmr spectrum of E is the same as that of furoquinoline (**6a**), however the methoxyl singlet is absent. Compound E is therefore 3-isopropyl-9-methylfuro[2,3-*b*]-4-quinolone (**6c**).

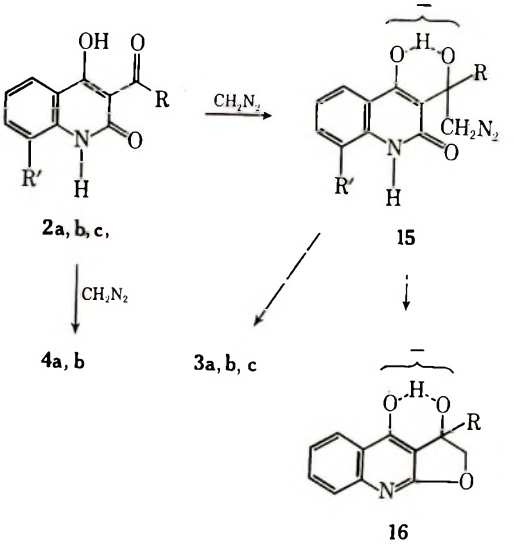
Compound F has the empirical formula $C_{15}H_{17}NO_3$, corresponding to the addition of two methylene units. The infrared spectrum shows strong 2-quinolone carbonyl absorption at 6.0 μ and nonconjugated carbonyl absorption at 5.85 μ. The nmr spectrum has a three-proton methoxy singlet at 3.92 ppm and a two-proton methylene singlet at 3.88 ppm in addition to aromatic and isopropyl signals. On the basis of these data F is assigned the structure 3-(2-oxo-methylbutyl)-4-methoxy-2-quinolone (**3c**), the result of both homologation and O methylation. Reduction of **3c** with sodium borohydride afforded the corresponding alcohol which on treatment with *p*-toluensulfonyl chloride–pyridine gave 2-isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]-quinolone (**12**), by analogy with the synthesis of the isobutyl analog.[1] The spectral data for both these compounds (see Experimental Section) were in agreement with the assigned structures. There was insufficient material to complete the synthesis of demethoxylunacrine, and attempts to repeat this sequence gave variable results (*vide infra*).

When, however, the diazomethane reaction with 3-isobutyryl-4-hydroxy-2-quinolone (**2c**) was repeated under apparently identical conditions, the inserted quinolone (**3c**) could not be isolated although both thin layer chromatography and spectral measurements indicated that it was present. However, a third compound, G, was obtained. The empirical formula of G is $C_{14}H_{15}NO_3$, corresponding to the addition of one methylene group, and the infrared spectrum is almost identical with that of quinolone (**3c**), having peaks at 5.87 and 6.1 μ. The nmr spectrum, however, shows only one singlet at 4.04 ppm with an area corresponding to three protons plus aromatic and isopropyl resonances, and compound G is therefore 3-isobutyryl-4-methoxy-2-quinolone (**4b**), the result of simple O methylation.

In other reactions of **2c** with diazomethane, again under apparently identical conditions, neither the inserted nor the noninserted quinolones were isolated; however, the furoquinolone (**6c**) and another new compound, H, could be obtained. Compound H has an empirical formula of $C_{15}H_{17}NO_3$, indicating addition of two methylene units, and the infrared spectrum has strong hydroxyl absorption at 3.13 μ. The ultraviolet spectrum of H shifts in acid, but not in base, and the nmr spectrum does not have the deshielded C-5 proton multiplet, ruling out a 4-quinolone structure and suggesting that H is a quinoline. There is also present in the nmr a broadened singlet due to the hydroxyl proton at 5.45 ppm, which is removed by shaking with D_2O. The presence of a one-proton multiplet at 2.7 ppm and two doublets (J = 7 Hz) at 1.10 and 0.76 ppm indicates the presence of an isopropyl group attached to an asymmetric center. A simple AB quartet (J = 13 Hz) at 4.33 ppm with a superimposed methoxyl singlet at 4.22 ppm suggests that H is 3-hydroxy-3-isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline (**13**). Confirmation of this structural assignment was accomplished by the conversion of **13** by treatment with dilute hydrochloric acid into 3-isopropylfuro[2,3-*b*]-4-quinolone (**13**).[9] The nmr spectrum of **13** is identical with that of 3-isopropyl-9-methylfuro[2,3-*b*]-4-quinolone **6c**, with the exception of the absence of the N-methyl singlet.

The product distributions obtained in these reactions of 3-acyl-4-hydroxy-2-quinolones are summarized in Scheme I, and although the above data indicate that their course is quite complex, the observed products may all be explained in terms of the generally accepted mechanism for the reaction of diazomethane with aryl alkyl ketones.[8] In Scheme II the over-all course of

SCHEME II



these reactions is summarized and several generalizations may be made concerning the interaction of these quinolones with diazomethane. First, direct O methylation is competitive with the addition of diazomethane to the carbonyl group in the case of the 3-isobutyryl compounds (**2c, d**). However, in the reactions of the 3-isovaleryl ketones (**2a, b**),[1] only the homologated ketones could be isolated. This is easily explained in terms of steric hindrance in the vicinity of the carbonyl group caused by the α-isopropyl group in **2a** and **b**, as opposed to the methylene group in **2c** and **d**.[10]

In the intermediate (**15**) arising from the addition of diazomethane to the carbonyl group, hydrogen bonding between the C-4 hydroxyl and the alkoxide moiety in the side chain must be invoked in order to explain the exclusive formation of linear furoquinolones in these reactions since it has been observed that nucleophilic displacement reactions of this type normally give the angular isomer.[11] Intermediate **15** may decompose by one of two paths, either migration of the aryl residue to give the homologated ketone[8] or cyclization to afford an intermediate (**16**) which may then give rise to the

(9) E. A. Clarke and M. F. Grundon [*J. Chem. Soc.*, 438 (1964)] have carried out similar reactions in this series.

(10) The possibility that O methylation precedes addition to the carbonyl group seems remote in view of the work of M. E. C. Biffin, L. Crombie, and J. A. Eldridge. *J. Chem. Soc.*, 7500 (1965).

(11) J. W. Huffman and L. E. Browder, *J. Org. Chem.*, **29**, 2598 (1964).

various furoquinolones obtained from these reactions. The former path appears to be favored when R = isobutyl and the latter when R = isopropyl, and these differences must be caused by subtle differences in the conformation of intermediate **15** caused in turn by differences in the bulk of the isopropyl and isobutyl groups.

Experimental Section[12]

3-Isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**) was prepared by the method reported earlier for the synthesis of 3-isovaleryl-8-methoxy-2-quinolone[1] (**2b**). From 12.0 g of 4-hydroxy-8-methoxy-2-quinolone and 25.0 ml of isobutyryl chloride was obtained 12.33 g (75.2%) of 3-isobutyryl-4-hydroxy-8-methoxy-2-quinolone (**2c**). Recrystallization from methylene chloride–hexane gave white needles: mp 166–167°; ir 6.05 μ; uv max, neutral and acid, 248 mμ (log ε = 4.30), 308 (4.12), 316 (4.13), base, 242 (4.49), 267 sh (4.03), 310 (3.96); nmr δ 7.0–7.9 m (Aryl H), *ca.* 4.3 m (CH), 4.00 s (OCH_3), 1.22 d (*J* = 7 Hz, isopropyl). The analytical sample was recrystallized from methylene chloride–hexane, mp 169–170°.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.53; H, 5.67; N, 5.28.

Reaction of 3-Isobutyryl-4-hydroxy-8-methoxy-2-quinolone with Diazomethane. A.—To a slurry of 5.00 g of the above quinolone (**2c**) in 100 ml of absolute ether was added 100 ml of a solution of diazomethane in dry ether made from 8.00 g of nitrosomethylurea. A trace of methanol was added and the slurry stirred overnight at room temperature. Reducing the volume of solution gave 1.31 g of recovered starting material. Boiling the solution to dryness gave a red glass which was chromatographed on Merck acid-washed alumina.

Elution with methylene chloride–hexane 1:1 gave 0.93 g (24.3%) of **3-isopropyl-8-methoxy-9-methylfuro[2,3-*b*]-4-quinolone** (**6a**), recrystallized from methylene chloride–hexane as colorless needles: mp 130–131°, a mixture melting point with anhydrobalfouridine[7] was 110–120°; ir 6.11 μ (C=O); uv max, neutral and base, 235 mμ (log ε = 4.40), 241 sh (4.45), 247 (4.53), 262 sh (3.86), 295 sh (3.66), 303 (3.73), 327 sh (3.80), 339 (3.98), 354 (3.93), acid, 248 (4.59), 303 (3.60), 328 sh (3.71), 340 (3.88), 354 (3.88); nmr δ 8.10 q (J_{ortho} = 8 Hz, J_{meta} = 2 Hz, C-5 H), 6.95–7.30 (Ar H), 6.95 d (*J* = 1 Hz =CH),4.01 s (OCH_3), 3.83 s (NCH_3), *ca.* 3.3 m (CH), 1.35 d (*J* = 7 Hz, isopropyl). Irradiation of the multiplet at 3.3 collapsed the doublet at 6.95 to a singlet. The analytical sample was recrystallized from methylene chloride–hexane, mp 130.0–130.5°.

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.66; H, 6.21; N, 5.07.

Elution with methylene chloride gave 0.68 g (17.5%) of **3-isobutyryl-4,8-dimethoxy-2-quinolone** (**4a**), crystallized from methylene chloride–hexane: mp 183–186°; ir 5.98 (C=O) and 6.20 μ (amide C=O); uv max, neutral and acid, 225 mμ (log ε = 4.10), 253 (4.22), 287 (3.69), base 253 (4.36), 275 sh (3.84); nmr δ 7.0–7.8 (Ar H), 4.01 (OCH_3, six protons), 3.50 m (CH), 1.27 d (*J* = 7 Hz, isopropyl). The analytical sample was recrystallized from methylene chloride–hexane as colorless plates, mp 189–191°.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.31; H, 6.23; N, 5.08.

B.—The diazomethane reaction was repeated with 7.00 g of quinolone (**2c**) in 100 ml of methanol and 100 ml of an ether solution of diazomethane from 20.0 g of nitrosomethylurea. Boiling the solution to dryness gave a red glass which, after being chromatographed three times on Merck acid-washed alumina, gave 0.77 g (10.0%) of **1-methyl-3-isobutyryl-4,8-dimethoxy-2-quinolone** (**9**). Crystallization from hexane gave white needles: mp 61–63°; ir 5.95 (C=O) and 6.20 μ (amide C=O); uv max neutral, acid, base, 232 mμ (log ε = 4.55), 258 (4.41), 291 (3.93); nmr δ 7.1–7.6 (Ar H), 3.92, 3.92 s (NCH_3, OCH_3, nine protons), 3.28 m (CH), 1.22 d (*J* = 7 Hz, isopropyl). The analytical sample was recrystallized from hexane as colorless plates, mp 68–69°.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.24; H, 6.72; N, 4.82.

C.—The diazomethane reaction was repeated with a solution of 2.00 g of the quinolone (**2c**) and 1 ml of boron trifluoride etherate in 50 ml of methylene chloride. To this solution was added diazomethane from 4.0 g of nitrosomethylurea in 40 ml of dry ether. The solution was allowed to stir overnight, washed with sodium bicarbonate and water, dried, and boiled to dryness, giving 1.97 g (93.6%) of the cross-conjugated *enol ether* (**10**). attempted recrystallization of this yellow compound from methanol gave colorless solutions on warming, from which only the starting quinolone (**2c**) could be obtained. All other attempts to purify this compound gave only **2c**: ir 6.10 μ (C=O); nmr δ 7.1–7.3 m (Ar H), 4.00, 4.10 (OCH_3), 1.34 d (*J* = 6 Hz, isopropyl).

Reaction of 3-Isovaleryl-4-hydroxy-8-methoxy-2-quinolone with Diazomethane.—To a solution of 4.00 g of the above quinolone (**2b**) in 100 ml of absolute ether was added a trace of methanol and 150 ml of an ether solution of diazomethane from 8.00 g of nitrosomethylurea. The solution was allowed to stir overnight. Filtration gave 0.42 g of **3-(2-oxo-4-methylpentyl)-4,8-dimethoxy-2-quinolone** (**3b**), identical with an authentic sample.[1] Boiling the solution to dryness gave a red glass which was chromatographed on Merck acid-washed alumina.

Elution with methylene chloride gave 0.17 g of solid material. Dissolving this material in hexane and cooling to 5° gave 0.025 g (0.6%) of 9-methyl-8-methoxy-3-isobutylfuro[2,3-*b*]-4-quinolone (**6b**): mp 125–127°; ir 6.15 μ (C=O); uv max, neutral and base, 235 mμ (log = ε 4.40), 241 sh (4.45), 247 (4.53), 262 sh (3.86), 295 sh (3.66), 303 (3.73), 327 sh (3.80), 339 (3.98), 354 (3.93), acid, 248 (4.59), 303 (3.60), 328 sh (3.71), 340 (3.88), 354 (3.88); nmr 8.16 m (C-5 H), 7.1–7.4 m (Ar H), 7.02 m (=CH), 4.12 s (OCH_3), 3.90 s (NCH_3), 2.71 d (*J* = 7 Hz, CH_2), 1.8–2.5 m (CH), 0.97 d (*J* = 6 Hz, isopropyl). The analytical sample recrystallized from hexane as colorless needles, mp 126–127°.

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.61; H, 6.84; N, 4.85.

Cooling the hexane mother liquors from the above crystallizations to −15°, followed by immediate filtration, gave 0.045 g (1.0%) of **3-(2-oxo-4-methylpentyl)-2,4,8-trimethoxyquinoline** (**11**): mp 62–64; uv max, neutral and base, 246 mμ (log ε = 4.66), 247 sh (3.73), 280 (3.73), 290 (3.65), 315 (3.35), 328 (3.28), acid 247 (4.58), 257 sh (4.29), 283 (3.70), 315 (3.62), 333 (3.46); nmr 6.9–7.7 m (Ar H), 4.10, 4.05, 3.93 s (OCH_3), 3.82 s (=CCH_2CO), 1.8–2.5 m (CH_2CH), 0.95 d (*J* = 7 Hz, isopropyl). The analytical sample recrystallized from hexane as colorless needles, mp 62–63°.

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.95; H, 7.18; N, 4.34.

Heating this 2-methoxyquinoline (**11**) on a steam bath with 10% hydrochloric acid gave **3-(2-oxo-4-methylpentyl)-4,8-dimethoxy-2-quinolone** (**3b**).

Further repeated chromatography of the remaining material from the diazomethane reaction gave only an additional 0.97 g (31.6% total) of **3-(2-oxo-4-methylpentyl)-4,8-dimethoxy-2-quinolone** (**3b**).

3-Isobutyryl-4-hydroxy-2-quinolone (**2d**) was prepared in the same manner as the 8-methoxy analog (**2c**). From 15.0 g of 4-hydroxy-2-quinolone and 35.0 ml of isobutyryl chloride there was obtained 12.7 g (59%) of a white solid, mp 198–201°. Recrystallization from ethyl acetate–cyclohexane gave light yellow needles: mp 221–224° (lit.[13] mp 222–224°); ir 6.0 μ; uv max, neutral and acid, 220 mμ (log ε 4.25), 237 (4.44), 306 (4.04).

Reaction of 3-Isobutyryl-4-hydroxy-2-quinolone with Diazomethane. A.—To a slurry of 4.72 g of the above quinolone (**2d**) in 75 ml of absolute ether at 0–5° was added 100 ml of a solution of diazomethane in dry ether made from 8.00 g of nitrosomethylurea. A trace of methanol was added and the slurry stirred overnight at room temperature. Reducing the volume of solution gave 1.15 g of recovered starting material. Boiling the solution to dryness gave a red glass which was chromatographed on 80 g of Merck acid-washed alumina.

(12) Melting points were determined on a Kofler hot stage or a Hershberg melting point apparatus and are uncorrected. Infrared spectra were taken as potassium bromide disks using a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were taken in methanol, using a Perkin-Elmer Model 202 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 nuclear magnetic resonance spectrometer using deuteriochloroform as a solvent unless otherwise noted, and tetramethylsilane as an internal reference. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(13) N. S. Vul'fsan and R. B. Zhurin, *Zh. Vses. Khim. Obshch. im D. I. Mendeleeva*, **5**, 352 (1960); *Chem. Abstr.*, **54**, 24733 (1960).

Elution with absolute ether yielded 0.96 g (25.0%) of **9-methyl-3-isopropylfuro[2,3-*b*]-4-quinolone** (**6c**), recrystallized from methylene chloride–hexane as colorless needles: mp 139.0–139.7°; ir 6.15 μ (C=O); uv max, neutral and base, 240 mμ (log ϵ = 4.23), 252 (4.20), 260 (4.23), 285 (3.23), 295 (3.23), 328 sh (3.67), 339 (3.79), 353 sh (3.71), acid *ca.* 243 (4.57), 257 sh (3.88), 305 (3.47), 318 (3.69), 333 sh (3.74), 343 (3.82), 355 sh (3.77); nmr ($CDCl_3$), δ 8.45 m (C-5 H), 7.1–7.75 (Ar-H), 6.98 d (J = 1 Hz, =CH), 3.72 s (NCH_3), 3.34 *m* (CH), 1.38 d (*J* = 7 Hz, isopropyl); nmr (d_6-DMSO) δ 8.28 m, 7.2–7.8 m, 7.41 s, 3.85 s, 3.25 m, 1.31 d (*J* = 6.5 Hz). The analytical sample was recrystallized from methylene chloride–hexane, mp 140.0–140.5°.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.49; H, 6.40; N, 5.83.

Elution with methylene chloride–isopropyl alcohol 20:1 gave 0.65 g (16.2%) of **3-(2-oxo-3-methylbutyl)-4-methoxy-2-quinolone** (**3c**). Crystallization from methylene chloride–hexane gave white needles: ir 5.85 μ (C=O) and 6.0 μ (amide C=O); uv max, neutral and acid, 231 mμ (log ϵ = 4.28), 245 sh (3.80), 264 (3.59), 271 (3.70), 279 (3.65), 314 (3.44), 324 (3.61), 336 (3.55); nmr δ 7.2–7.9 m (Ar H), 3.92 s (OCH_3), 3.88 s (Ar CH_2), 2.89 m (CH), 1.25 d (*J* = 7 Hz, isopropyl). Recrystallization from methylene chloride–hexane gave the analytical sample, mp 182–183°.

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.18; H, 6.39; N, 5.68.

B.—The diazomethane reaction was repeated with 10.00 g of the quinolone (**2d**) and diazomethane from 20.00 g of nitrosomethylurea. Reducing the volume of solution gave 3.80 g of recovered starting material and a red glass which was chromatographed on Merck acid-washed alumina. Elution with methylene chloride gave 0.59 g (9.9%) of the furoquinolone (**6c**). Elution with methylene chloride–isopropyl alcohol 20:1 gave 1.50 g of a white solid which by tlc was a mixture of the inserted and noninserted acylquinolones. Several recrystallizations from methylene chloride–hexane gave 0.91 g (13.8%) of **3-isobutyryl-4-methoxy-2-quinolone** (**4b**): ir 5.87 μ (C=O) and 6.1 μ (amide C=O); uv max, neutral and acid, 228 mμ (log ϵ = 4.40), 273 (3.70), 278 (3.71), 328 (3.63), base 236 (4.41), 273 sh (3.69), 338 (3.50); nmr δ 7.1–8.1 m (Ar H), 4.04 s (OCH_3), 3.40 m (CH), 1.31 d (*J* = 7 Hz, isopropyl). The analytical sample was recrystallized from methylene chloride–hexane, mp 158–160°.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71: Found: C, 68.79; H, 6.18; N, 5.65.

C.—The diazomethane reaction was repeated with 3.00 g of the quinolone (**2d**) and diazomethane from 6.00 g of nitrosomethylurea, followed by chromatography on Merck acid-washed alumina. Elution with benzene gave 0.56 g (17.9%) of the furoquinolone (**6c**). Elution with benzene–isopropyl alcohol 100:1 gave 0.31 g (9.2%) of **3-hydroxy-3-isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline** (**13**). Crystallization from methylene chloride–hexane gave a white amorphous solid: mp 157–159°; ir 3.13 μ (OH); uv max, neutral and base, 228 mμ (log ϵ = 4.52), 239 sh (4.45), 264 (3.67), 274 (3.73), 285 (3.67), 305 sh (3.41), 314 (3.63), 328 (3.67), acid 238 (4.49), 293 (3.87), 314 sh (3.77); nmr δ 7.2–8.1 m (Ar H), 5.45 s (OH), 4.33 AB (*J* = 13 Hz, OCH_2), 4.22 s (OCH_3), 2.7 m (CH), 1.10 d (*J* = 7 Hz, isopropyl), 0.76 d (*J* = 7 Hz, isopropyl). Recrystallization from methylene chloride–hexane gave the analytical sample, mp 158–159°.

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.77; H, 6.68; N, 5.32.

3-Isopropylfuro[2,3-*b*]-4-quinolone (**14**).—To 0.140 g of 3-hydroxy-3-isopropyl-4-methoxy-2, 3-dihydrofuro [2,3-*b*] quinoline (**13**) was added 20 ml of 10% hydrochloric acid. After 1.5 hr of heating on a steam bath, the solution was cooled, filtered, and the solid recrystallized from methanol–water yielding 0.050 g (41.0%) of colorless cubes: mp 245–258°; ir 6.12 μ; uv max, neutral, 238 mμ (log ϵ = 4.42), 249 (4.36), 257 (4.39), 282 (3.40), 294 (3.40), 320 sh (3.80), 332 (3.92), 340 sh (3.84), acid, 241 (4.68), 257 sh (4.10), 286 (3.33), 299 sh (3.57), 318 sh (3.78), 334 (3.88), 342 sh (3.80), base 232 (4.29), 255 sh (4.52), 262 (4.59), 307 sh (3.53), 320 sh (3.70), 331 sh (3.82), 342 (3.93), 355 (3.85); nmr (d_6-DMSO) δ 8.33 m (C-5 H), 7.2–7.8 m (Ar H), 7.41 d (*J* = 1 Hz, =CH), 3.28 m (CH), 1.33 d (*J* = 6 Hz, isopropyl). The analytical sample was recrystallized from methanol–water, mp 245–247°.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.09; H, 5.90; N, 6.02.

3-(2-Hydroxy-3-methylbutyl)-4-methoxy-2-quinolone.—To a solution of 0.22 g of **3c** in 50 ml of 95% ethanol was added 2.00 g of sodium borohydride. The solution was heated at reflux 5 hr, concentrated to about one-half its volume, and diluted with water. The aqueous suspension was extracted with four portions of methylene chloride, the extracts were combined and dried, and the solvent was removed. Crystallization from hexane–ethyl acetate gave 0.14 g (63%) of colorless needles: mp 156–157°; ir 6.10 μ (C=O); uv max, neutral acid, base and 231 mμ (log ϵ = 4.39), 245 sh (3.98), 272 (3.82), 280 (3.77), 311 sh (3.63), 324 (3.76), 336 sh (3.63); nmr δ 7.2–7.9 (ArH), 4.02 s (OH), 4.00 s (OCH_3), 3.90 t (CH_2), 3.69 (CHOH), *ca.* 1.8 m (CH-$(CH_3)_2$), 1.05 d (*J* = 7 Hz, isopropyl). The analytical sample, mp 166–167°, was crystallized from hexane–ethyl acetate.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.35; N, 5.36. Found: C, 69.24; H, 7.50; N, 5.20.

2-Isopropyl-4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline (**12**).—To a solution of 0.170 g of 3-(2-hydroxy-3-methylbutyl)-4-methoxy-2-quinolone in 3 ml of dry pyridine was added 0.70 g of *p*-toluenesulfonyl chloride. The reaction mixture stood at room temperature 72 hr, was diluted with water, and the precipitated solid collected. The filtrates were made strongly basic with 10% sodium hydroxide and extracted with four portions of methylene chloride. The organic extracts were dried and the solvents removed at reduced pressure leaving a brown oil which was combined with original precipitate, dissolved in 1:1 hexane–methylene chloride and chromatographed on Merck acid-washed alumina. Elution with the same solvents gave 0.050 g (32%) of **12**; uv, neutral and base, 229 mμ (log ϵ = 4.56), 232 sh (4.44), 252 (3.74), 262 (3.75), 272 (3.78), 283 (3.70), 309 (3.48), 323 (3.51), acid 216 (4.44), 234 (4.47), 239 sh (4.45), 293 (3.93), 304 (3.88), 317 (3.76); nmr δ 7.1–8.1 (ArH), 4.40 m (OCH), 4.10 (OCH_3), 3.35 m (CH_2), 195 m $(CH_3)_2$, 0.98 d (*J* = 7 Hz, isopropyl). Recrystallization from hexane–methylene chloride gave the analytical sample, mp 125–126°.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.85; H, 7.21; N, 5.93.

Registry No.—Diazomethane, 334-88-3; **2c**, 19765-48-1; **3c**, 19765-49-2; **4a**, 19779-44-3; **4b**, 19765-50-5; **6a**, 19765-51-6; **6b**, 19765-52-7; **6c**, 19765-53-8; **9**, 19765-54-9; **11**, 19765-55-0; **12**, 19765-56-1; **13**, 19765-57-2; **14**, 19765-58-3; 3-(2-hydroxy-3-methylbutyl)-4-methoxy-2-quinolone, 19765-59-4.

Diels–Alder Reactions of 2-Pyrones. Direction of the Addition Reaction with Acetylenes[1a]

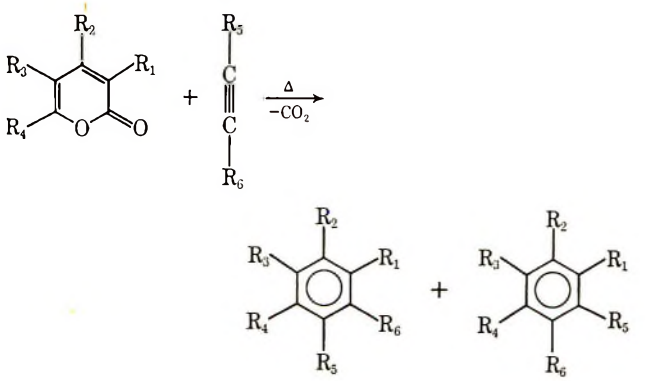
JOE A. REED, CURTIS L. SCHILLING, JR., R. F. TARVIN, T. A. RETTIG, AND J. K. STILLE[1b]

Department of Chemistry, University of Iowa, Iowa City, Iowa 52240

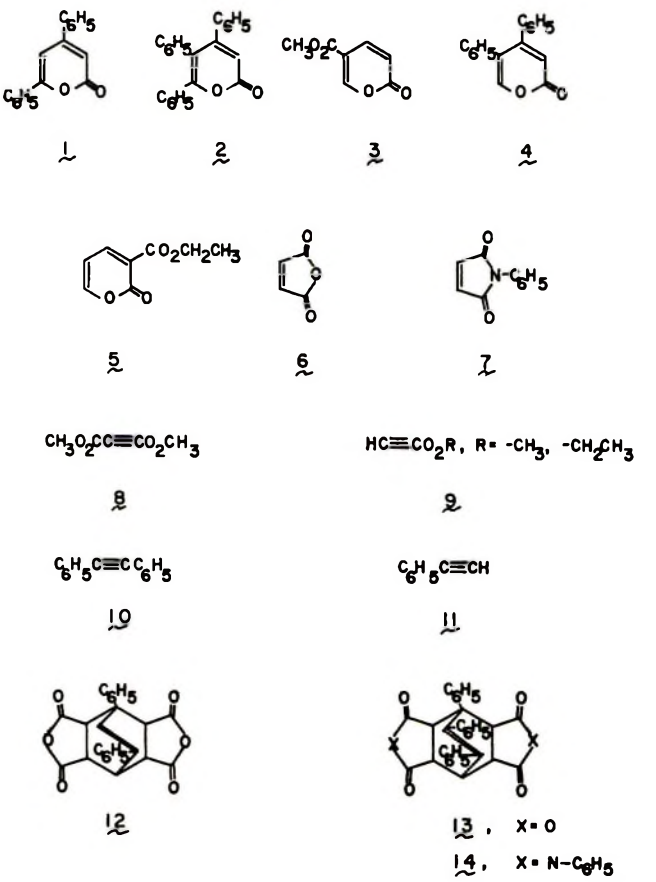
Received December 3, 1968

The Diels–Alder reactions of unsymmetrically substituted acetylenes with 2-pyrones containing unsymmetrically substituted diene fragments reveal varying degrees of stereoselectivity with regard to the direction of addition, depending on the positions and types of substituents. Extended Hückel MO calculations of the net charge distribution on the reactants can be used to predict the direction of addition when phenylacetylene is the dienophile, but the method is not general when methyl propiolate is the dienophile.

Diels–Alder reactions of 2-pyrones with acetylenes produce benzene derivatives by loss of carbon dioxide from the intermediate adduct.[2] Alder and Rickert initially reported the reactions of 5-carbomethoxy-2-pyrone, 4,6-dimethyl-5-carbomethoxy-2-pyrone, and 4-hydroxy-6-methyl-2-pyrone with diethyl acetylenedicarboxylate.[2] The methyl or ethyl diesters of acetylenedicarboxylic acid have also been employed as dienophiles in reactions with 4-methoxy-6-methyl-,[3] 6-carbomethoxy-,[4] 4,5-diphenyl-,[5] 3-methyl-4-ethyl-,[6] 3-methyl-4-propyl-,[6] 3-methyl-4-*n*-butyl-,[6] and 3,5,6-trimethyl-2-pyrones.[7] 5-Carbomethoxy-2-pyrone, 5-methyl-2-pyrone, and 2-pyrone itself undergo this reaction with bis(trimethylstannyl)acetylene.[8] 2-Pyrone also reacts with phenyltrimethylstannylacetylene and bis(trimethylsilyl)acetylene,[8] with an unusual rearrangement occurring in the latter case. With this last exception, the Diels–Alder reaction in each of these examples has given rise to a single benzene derivative since either the acetylene or the diene fragment of the 2-pyrone was symmetrically substituted. When the acetylene and the diene fragment are both unsymmetrically substituted, however, the possibility of forming two isomeric benzene derivatives exists. One such reaction has been reported,[9] but only one isomer was formed.



In the interest of preparing phenylated polyphenylenes from bis-2-pyrones and diethynylbenzenes, model reactions of phenylated and unphenylated 2-pyrones with acetylenic dienphiles were studied to examine relative reactivities and stereochemical preferences. Accordingly, 4,6-diphenyl-[10] (**1**), 4,5,6-triphenyl-[11] (**2**), 5-carbomethoxy-[12] (**3**), 4,5-diphenyl-[5] (**4**), and 3-carboethoxy-2-pyrone[13] (**5**) were prepared. Their reactions with one or more of the following dienophiles: maleic anhydride (**6**), N-phenylmaleimide (**7**), dimethyl acetylenedicarboxylate (**8**), methyl or ethyl propiolate (**9**), diphenylacetylene (**10**), and phenylacetylene (**11**), were carried out.



Results

Pyrones **1** and **2** react with **6**, and **2** with **7** in refluxing xylene, to form the crystalline double adducts **12–14**, respectively. Dimethyl 3,4,5-triphenylphthalate (**15**)

(1) (a) Supported in part by the U. S. Army Research Office, Durham, N. C. (b) To whom communications regarding this paper should be sent.

(2) K. Alder and H. Rickert, *Ber.*, **70**, 1354 (1937).

(3) J. Bu'Lock and H. Smith, *J. Chem. Soc.*, 502 (1960).

(4) E. Wenkert, D. Johnston, and K. Dave, *J. Org. Chem.*, **29**, 2534 (1964).

(5) A. Padwa and R. Hartman, *J. Amer. Chem. Soc.*, **88**, 1518 (1966).

(6) N. Shusherina, R. Levina, and V. Shostakovskii, *Zh. Obshch. Khim.*, **29**, 3237 (1959); *Chem. Abstr.*, **54**, 13057*g* (1960).

(7) N. Dmitrieva, A. Shil'nikova, N. Shusherina, and R. Levina, *Zh. Obshch. Khim.*, **34**, 2835 (1964); *Chem. Abstr.*, **61**, 16042*f* (1964).

(8) A. Evnin and D. Seyferth, *J. Amer. Chem. Soc.*, **89**, 952, 4793 (1967).

(9) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, and A. Eschenmoser, *Helv. Chim. Acta*, **44**, 540 (1961).

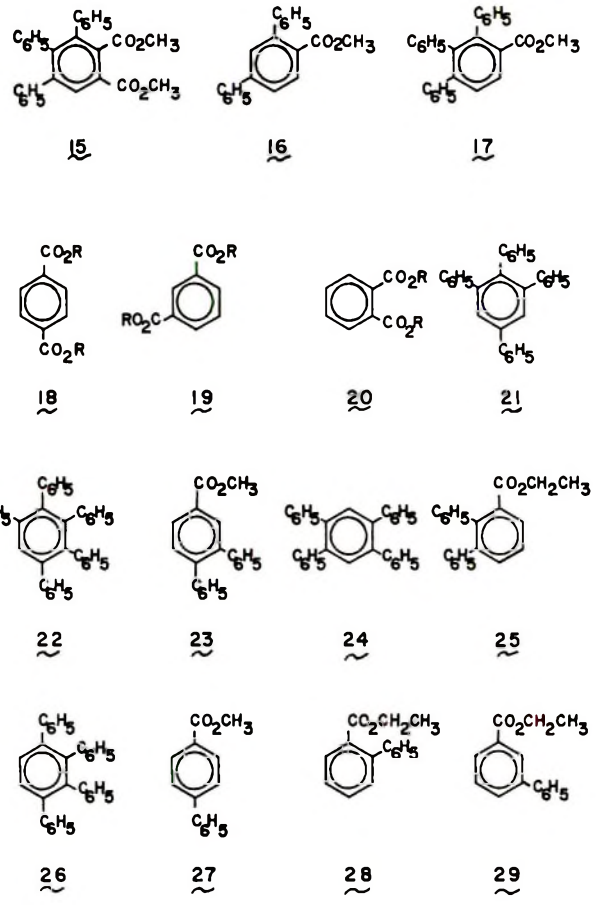
(10) F. Feist, H. Pauschardt, and H. Dibbern, *Ber.*, **58B**, 2311 (1925).

(11) S. Ruhemann, *J. Chem. Soc.*, **97**, 459 (1910).

(12) J. Boyer and W. Schoen, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 532.

(13) T. Windholz, L. Peterson, and G. Kent, *J. Org. Chem.*, **28**, 1443 (1963).

is produced from **2** and **8**, also in refluxing xylene. The reactions of **3**[2] and **4**[5] with **8** have been reported. Pyrones **1** and **2** react in refluxing xylene with **9** (R = CH_3) to form methyl 2,4-diphenylbenzoate (**16**) and methyl 2,3,4-triphenylbenzoate (**17**), respectively, while **3** and **9** (R = CH_3) yield a 3:2 mixture of dimethyl terephthalate (**18**, R = CH_3) and dimethyl isophthalate (**19**, R = CH_3) under the same conditions.



The dienophiles **10** and **11** require stronger conditions (200–300°, sealed tube) for reaction. Under these conditions, **1**–**5** react with **10** to form 1,2,3,5-tetraphenylbenzene (**21**), pentaphenylbenzene (**22**), methyl 3,4-diphenylbenzoate (**23**), 1,2,4,5-tetraphenylbenzene (**24**), and ethyl 2,3-diphenylbenzoate (**25**), respectively. Pyrone **2** and **11** yield both **21** and 1,2,3,4-tetraphenylbenzene (**26**) in an approximately 1:5 ratio, while **3** and **11** yield methyl 4-phenylbenzoate (**27**). The reaction of **5** and **11** yields a 2:1 mixture of ethyl 2-phenylbenzoate (**28**) and ethyl 3-phenylbenzoate (**29**), while **5** and **9** (R = CH_3CH_2) yield a 4:1 mixture of diethyl isophthalate (**19**, R = CH_3CH_2) and diethyl phthalate (**20**, R = CH_3CH_2).

The reactions of **5** are in contrast to an earlier report that electron-withdrawing substituents such as nitro, sulfo, or carboxyl groups in the 3 position of the 2-pyrone ring completely deactivate the diene system, making it inert to the diene synthesis.[14] Compound **5** and its 6-methyl and 6-phenyl derivatives have also been shown to undergo diene syntheses with ethylene, to yield double adducts.[15]

(14) N. Shusherina, N. Dmitrieva, E. Luk'yanets, and R. Levina, *Usp. Khim.*, **36**, 436 (1967).

(15) F. Baker and L. Stock, *J. Org. Chem.*, **32**, 3344 (1967).

Discussion

The olefin dienophiles maleic anhydride (**6**), N-phenylmaleimide (**7**), and the acetylenes (**8**, **9**) containing carboxylic acid functions react with pyrones under much less vigorous conditions than those required for phenyl-substituted acetylenes. The results summarized in Table I indicate that the direction of addition in these reactions, where a choice is available, is similar to that observed for unsymmetrically substituted butadienes.[16] The relative energies of activation with respect to the direction of addition may be a result of polar attraction between the diene and the dienophile, steric effects, or a combination of these. The fact that dienophiles substituted with highly polar groups react more readily suggests that polar attraction is an important factor in determining the direction of addition.

In order to assess the influence of the polar nature of the reactants, charge distributions on 2-pyrone (**30**), 5-carbomethoxy-2-pyrone (**3**), 3-carbomethoxy-2-pyrone (**5**), methyl propiolate (**9**), and phenylacetylene (**11**) were calculated with an iterative extended Hückel computer program.[17] Coulomb integrals H_{ii} were obtained from the valence-state ionization potentials[18] and were adjusted for charge with Cusachs' B term in the equation $H_{ii} = H^0_{ii} - Bq_i$, where H_{ii} is the adjusted Coulomb integral, q_i the charge, and B the parameter for each particular orbital of each element.[19] The resonance integrals were calculated according to the Wolfsberg–Helmholz geometric mean[20] with K = 1.75.[17] Orbital exponents were taken from tables by Clementi and Raimondi[21] and were not adjusted for charge. The hydrogen exponent was set at 1.20. In order to correct excessive charge buildup at the more electronegative oxygen atoms, the Hamiltonian matrix elements were iterated using a damping technique to a set of self-consistent matrix elements and charges. Through the equation $q_i = (\lambda q_{i-1} + C_i)/(1 + \lambda)$ (λ = 9.0), the newly calculated charges C_i are damped and q_i is used to calculate the new H_{ii}. This is repeated until the charge distribution no longer changes more than 0.05 on iteration. Where the bond distances and angles for the compounds had not been experimentally determined, they were obtained from the angles and distances listed for similar compounds and/or functional groups.[22] The following electron densities were obtained.

The net atomic charge has been successfully used as a reactivity index in aromatic substitution.[23–25] The close agreement between the experimental dipole moment and that calculated from the extended Hückel program lends support to the use of the net atomic charges as representative isolated molecule reactivity

(16) A. S. Onishchenko, "Diene Synthesis," Israel Program for Scientific Translations, Ltd., Jerusalem, 1964, pp 22–34.

(17) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963); **40**, 2745 (1964).

(18) H. A. Skinner and H. O. Pritchard, *Trans. Faraday Soc.*, **49**, 1254 (1953); H. O. Pritchard and H. A. Skinner, *Chem. Rev.*, **55**, 745 (1955).

(19) L. C. Cusachs and J. W. Reynolds, *J. Chem. Phys.*, **43**, s160 (1965).

(20) M. Wolfsberg and L. Helmholz, *ibid.*, **20**, 837 (1952).

(21) E. Clementi and D. L. Raimondi, *ibid.*, **38**, 2686 (1963).

(22) L. E. Sulton, Sci. Ed., "Tables of Interatomic Distances and Configurations in Molecules and Ions," The Chemical Society, London, 1958; Suppl, 1965.

(23) A. Streitweiser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, pp 328–334.

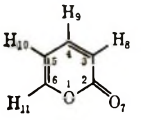
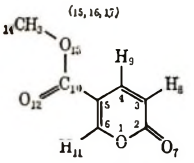
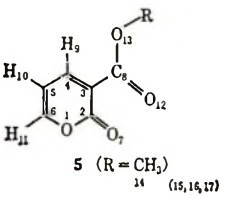
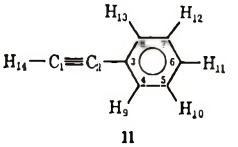
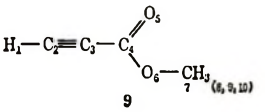
(24) H. H. Greenwood and R. McWeeney, *Advan. Phys. Org. Chem.*, **4**, 73 (1966).

(25) L. Salem, "The Molecular Orbital Theory of Conjugated Systems," W. A. Benjamin, Inc., New York, N. Y., 1966, pp 288–297.

TABLE I
DIELS–ALDER REACTIONS BETWEEN ASYMMETRICALLY SUBSTITUTED 2-PYRONES AND ACETYLENES

Diene	Dienophiles	Product(s) (yield, %, and ratio)
1	9, R = CH_3	Methyl 2,4-diphenylbenzoate (16) (70)
2	9, R = CH_3	Methyl 2,3,4-triphenylbenzoate (17) (55)
2	11	1,2,3,4- and 1,2,3,5-tetraphenylbenzenes (26 and 21) (38.9, 5:1)
3	9, R = CH_3	Dimethyl isophthalate and dimethyl terephthalate, (19 and 18) (40, 2:3)
3	11	Methyl 4-phenylbenzoate (27) (60)
5	9, R = CH_3CH_2	Diethyl phthalate and diethyl isophthalate (20 and 19) (50, 1:4)
5	11	Ethyl 2- and 3-phenylbenzoates (28 and 29) (60, 2:1)

TABLE II
NET ATOMIC CHARGES

Compd	Atom, charge		
 30	1, −0.275	5, 0.041	9, 0.050
	2, 0.183	6, 0.104	10, 0.056
	3, 0.048	7, −0.398	11, 0.087
	4, 0.043	8, 0.060	
	Total charge −0.001		
 3	1, −0.233	7, −0.359	13, −0.256
	2, 0.231	8, 0.045	14, 0.108
	3, 0.048	9, 0.040	15, 0.059
	4, 0.048	10, 0.230	16, 0.060
	5, 0.082	11, 0.068	17, 0.060
	6, 0.125	12, −0.360	
	Total charge −0.004		
 5 (R = CH_3)	1, −0.256	7, −0.380	13, −0.295
	2, 0.212	8, 0.200	14, 0.101
	3, 0.110	9, 0.064	15, 0.072
	4, 0.074	10, 0.062	16, 0.075
	5, 0.055	11, 0.094	17, 0.075
	6, 0.120	12, −0.387	
	Total charge −0.004		
 11	1, −0.079	6, −0.020	11, 0.027
	2, −0.052	7, −0.017	12, 0.027
	3, 0.008	8, −0.011	13, 0.030
	4, −0.011	9, 0.030	14, 0.056
	5, −0.017	10, 0.027	
	Total charge −0.002		
	μ(calcd) 0.90 D μ(obsd) 0.72–0.84 D[a]		
 9	1, 0.080	6, −0.298	
	2, 0.008	7, 0.104	
	3, 0.033	8, 0.070	
	4, 0.207	9, 0.072	
	5, −0.350	10, 0.073	
	Total charge −0.001		

[a] A. L. McClellan, "Tables of Experimental Dipole Moments," Freeman and Co., San Francisco , Calif., 1963.

indices. The net atomic charges calculated (Table II) can be used to correctly predict the direction of addition of phenylacetylene to **2**, **3**, and **5**. Alignment of the reactants, so that the most electronegative (terminal) carbon in phenylacetylene and the most electropositive carbon in the corresponding pyrone form the new bond, predicts the product and allows the greatest dissipation of charge in the formation of the new bond. In the calculation, pyrone itself was taken as a model for both the phenyl-substituted pyrones **1** and **2** on the assumption that the phenyl groups would not alter the net atomic charges on the pyrone ring.

In the case of the reaction of **2** with **11**, however, product **26** is predicted while in fact a mixture of **26** and **21** is obtained (5:1). In the reaction of **5** with **11**, there is a slight difference in the charges on atoms 3 and 6 of **5**, but product **28**, which is formed in the greatest amount, is that which is predicted. The reaction of **3** with **9** yields mostly **18**, and the reaction of **5** with **9** affords two isomers. However, isomers obtained from the reactions of **1** and **2** with **9** are not those which would be expected from a consideration of charges.

The extended Hückel method neglects steric factors, so that this contribution cannot be evaluated easily. For the reactions of methyl propiolate with dienes, calculation of the energies of activation of the transition state leading to the two isomers would probably provide a more suitable answer.

Experimental Section

Reactants.—Pyrones 1,[10] 2,[11] 3,[12] 4,[5] and 5[13] were synthesized according to published procedures, as was diphenylacetylene (10).[26] The dienophiles 6–9 and 11 were obtained commercially. Reagent grade xylene and toluene were used as solvents. Nmr spectra were run on a Varian A60A spectrometer; microanalyses were peroformed by Micro-Tech Laboratories, Inc., of Skokie, Ill. Melting points are uncorrected.

1,3-Diphenyl-2-bicyclo[2.2.2]octene-5,6,7,8-tetracarboxylic Dianhydride (12).—A solution of 1.5 g (6.0 mmoles) of 4,6-diphenyl-2-pyrone[10] and 1.2 g (12 mmoles) of maleic anhydride in 20 ml of xylene was heated at reflux for 8 hr. After cooling, the solid product was collected and recrystallized from toluene. The yield of the product, mp 322–325°, was 0.83 g (35%). *Anal.* Calcd for $C_{24}H_{16}O_6$: C, 72.00; H, 4.00. Found: C, 71.75; H, 4.05.

1,2,3-Triphenyl-2-bicyclo[2.2.2]octene-5,6,7,8-tetracarboxylic Dianhydride (13).—4,5,6-Triphenyl-2-pyrone[11] (3.0 g, 9.0 mmoles), maleic anhydride (1.9 g, 20 mmoles), and 55 ml of xylene were heated at reflux for 24 hr. The solid product was recrystallized from toluene to yield 1.9 g (44%) of product, mp 333–334°. *Anal.* Calcd for $C_{30}H_{20}O_6$: C, 75.63; H, 4.20. Found: C, 75.63; H, 4.37.

1,2,3-Triphenyl-2-bicyclo[2.2.2]octene-5,6,7,8-tetracarboxylic Di(N-phenyl)imide (14).—A solution of 2.0 g (6.0 mmoles) of 4,5,6-triphenyl-2-pyrone[11] and 2.1 g (12 mmoles) of N-phenylmaleimide in 50 ml of xylene was heated at reflux for 14 hr. The solid product, 2.2 g (60%) after recrystallization from toluene, had mp 330–332°. *Anal.* Calcd for $C_{42}H_{30}O_4N_2$: C, 80.51; H, 4.79. Found: C, 80.80; H, 5.03.

Dimethyl 3,4,5-Triphenylphthalate (15).—Dimethyl acetylenedicarboxylate (2.0 g, 14 mmoles) and 4,5,6-triphenyl-2-pyrone (2.0 g, 6.0 mmoles) were heated at reflux in 50 ml of xylene for 46 hr. Removal of solvent under vacuum left dimethyl 3,4,5-triphenylphthalate, which, after recrystallization from methanol, yielded 1.8 g (75%), mp 174–176° (lit.[27] mp 174–175°).

Methyl 2,4-Diphenylbenzoate (16).—A solution of 0.52 g (2.1 mmoles) of 4,6-diphenyl-2-pyrone[10] and 0.4 g (4.2 mmoles) of methyl propiolate in 10 ml of xylene was heated at reflux for 60 hr. Removal of solvent left a gummy solid. On several extractions with small portions of Skellysolve BX and after recrystallization from Skellysolve BX 0.43 g (70%) of methyl 2,4-diphenylbenzoate, mp 76–78° (lit.[28] mp 75.5–76°), was obtained.

Methyl 2,3,4-Triphenylbenzoate (17).—4,5,6-Triphenyl-2-pyrone[11] (1.5 g, 4.6 mmoles) and methyl propiolate (0.50 g, 6.0 mmoles) were heated at reflux for 22 hr. Cooling precipitated 0.6 g of starting pyrone. Concentration of the mother liquor yielded 0.56 g (55%) of methyl 2,3,4-triphenylbenzoate, mp 147–149°, after recrystallization from methanol (lit.[27] mp 141.5–142.5° for methyl 3,4,5-triphenylbenzoate). The nmr spectrum showed an AB quartet centered at δ 7.7 in accordance with the assigned structure of methyl 2,3,4-triphenylbenzoate. *Anal.* Calcd for $C_{26}H_{20}O_2$: C, 85.71; H, 5.49. Found: C, 85.47; H, 5.62.

Dimethyl Terephthalate (18) and Dimethyl Isophthalate (19).—A solution of 0.79 g (5.0 mmoles) of 5-carbomethoxy-2-pyrone[12] and 0.84 g (10 mmoles) of methyl propiolate in 10 ml of xylene was heated at reflux for 90 hr. Removal of solvent and recrystallization from Skellysolve B yielded 0.37 g (40%) of product, mp 65–90°. Two recrystallizations of this material from a minimum amount of 95% ethanol yielded 0.15 g of dimethyl terephthalate, mp 139–140°.[29] Evaporation of the combined Skellysolve B and ethanol mother liquors, and recrystallization of the residue once from 95% ethanol and twice from Skellysolve B yielded 0.10 g of dimethy isophthalate, mp 67–68° (lit.[29] mp 68°). Both isomers were further identified by their nmr spectra. The terephthalate:isophthalate ratio was 3:2.

Diethyl Isophthalate (19) and Diethyl Phthalate (20).—3-Carboethoxy-2-pyrone[13] (0.84 g, 5.0 mmoles), ethyl propiolate (0.70 g, 7.0 mmoles), and 5 ml of xylene were heated at reflux for 30 hr. Removal of solvent and vacuum distillation of the residual oil yielded one cut, bp 95–100° (0.3 mm), 0.56 g (50%), identified as a 4:1 mixture of diethyl isophthalate and diethyl phthalate by nmr and glpc comparisons with authentic samples.

Reactions of 4,6-diphenyl-, 4,5,6-triphenyl-, 5-carbomethoxy-, 4,5-diphenyl-, and 3-carboethoxy-2-pyrones with diphenylacetylene or phenylacetylene were run in 20-ml lyophilization tubes using 10 ml of toluene as solvent. After filling, each tube was subjected to three freeze–thaw cycles in liquid nitrogen under reduced pressure and was sealed under reduced pressure. The tubes were heated at 250° for 24 hr for the 5-carbomethoxy- and 3-carboethoxy-2-pyrones and at 300° (unless otherwise noted) for 24 hr for the others, in a 476-ml Parr bomb containing 75–100 ml of toluene. Heat was applied by electric mantle, the temperature being controlled by a Jelrus automatic controller connected to a thermocouple in the bomb head. Tubes were cooled in a Dry Ice–acetone bath before opening and products were isolated by removal of solvent and recrystallization or vacuum distillation.

1,2,3,5-Tetraphenylbenzene (21).—4,6-Diphenyl-2-pyrone[10] (1.3 g, 5.0 mmoles) and diphenylacetylene (0.97 g, 5.5 mmoles) yielded, after recrystallization from 6:1 benzene–methanol, 1.4 g (74%) 1,2,3,5-tetraphenylbenzene, mp 222–224° (lit.[30] mp 224–226°).

Pentaphenylbenzene (22).—4,5,6-Triphenyl-2-pyrone (1.62 g, 5.00 mmoles) and diphenylacetylene (0.97 g, 5.50 mmoles) yielded, after recrystallization from 1:1 benzene–methanol, 1.24 g (54%) of pentaphenylbenzene, mp 247–250° (lit.[31] mp 251°).

Methyl 3,4-Diphenylbenzoate (23).—5-Carbomethoxy-2-pyrone[12] (1.1 g, 8.0 mmoles) and diphenylacetylene (1.4 g, 8.0 mmoles) yielded, after recrystallization from methanol, 0.99 g (43%) of methyl 3,4-diphenylbenzoate, mp 130–131° (lit.[32] mp 127°).

1,2,4,5-Tetraphenylbenzene (24).—4,5-Diphenyl-2-pyrone[5] (0.76 g, 3.0 mmoles) and diphenylacetylene (0.55 g, 3.0 mmoles) yielded, after recrystallization from toluene, 0.78 g (68%) of 1,2,4,5-tetraphenylbenzene, mp 263–265° (lit.[31] mp 262–263°).

Ethyl 2,3-Diphenylbenzoate (25).—3-Carboethoxy-2-pyrone[13] (1.0 g, 6.0 mmoles) and diphenylacetylene (1.2 g, 6.0 mmoles) yielded an oily product. Vacuum distillation yielded recovered diphenylacetylene and an oil, bp 14–180° (0.3 mm), which crystallized from 95% ethanol giving 0.38 g (21%) of product. After three recrystallizations from 95% ethanol, the analytical sample melted at 90–91.5°. *Anal.* Calcd for $C_{21}H_{18}O_2$: C, 83.44; H, 5.96. Found: C, 83.25; H, 5.96.

1,2,3,5- and 1,2,3,4-Tetraphenylbenzenes (21 and 26).—4,5,6-Triphenyl-2-pyrone[11] (3.51 g, 10.9 mmoles) and 1.11 g (10.9 mmoles) of phenylacetylene were combined as above in a 50-ml lyophilization tube with 30 ml of toluene. The tube was heated at 200° for 90 hr, followed by 225° for 24 hr. Cooling, opening the tube, and allowing it to stand for 2 days caused the crystallization of 0.753 g (21.4%) of starting 2-pyrone. Addition of a few milliliters of methanol to the mother liquor crystllized two successive crops of 1,2,3,4-tetraphenylbenzene (0.727 g, 17.4%), mp 190–192° (lit.[31] mp 190–191°). Evaporation of the mother liquor and extraction of the residue with 50 ml of methanol left a mixture of products, 1.797 g (43.2%), from which 1,2,3,4-tetraphenylbenzene (0.625 g, 15.1%) and 1,2,3,5-tetraphenylbenzene (0.268 g, 6.98%) were isolated by numerous fractional recrystallizations.

The same reaction, run at 300° for 24 hr, yielded no recovered 2-pyrone, and gave compounds **21** and **26** in yields of 12 and 14%, respectively, from an 80% yield of crude products.

Methyl 4-Phenylbenzoate (27).—5-Carbomethoxy-2-pyrone[12] (1.1 g, 8.0 mmoles) and phenylacetylene (0.82 g, 8.0 mmoles) yielded, after recrystallization from methanol, 1.0 g (60%) of methyl 4-phenylbenzoate, mp 118–120° (lit.[32] mp 118°).

Ethyl 2-Phenylbenzoate (28) and Ethyl 3-Phenylbenzoate (29).—3-Carboethoxy-2-pyrone (2.2 g, 13 mmoles) and phenylacetylene (1.8 g, 19 mmoles) yielded 1.7 g (60%) of oil, bp 115–140° (0.3 mm), consisting of ethyl 2-phenylbenzoate and ethyl 3-phenylbenzoate in a ratio of 2:1, as shown by nmr.

Registry No.—**12**, 19926-51-3; **13**, 19926-52-4; **14**, 19926-53-5; **17**, 19926-47-7; **25**, 19926-48-8; **28**, 19926-49-9; **29**, 19926-50-2.

(26) A. C. Cope, D. S. Smith, and R. J. Cotter, ref 12, p 377.

(27) W. Polaczkowa, O. Achmatowicz, Jr., and J. Böhm, *Roczniki Chem.*, **31**, 115 (1957); *Chem. Abstr.*, **51**, 14630*d* (1957).

(28) C. K. Bradsher and I. Swerlick, *J. Amer. Chem. Soc.*, **72**, 4189 (1950).

(29) "Handbook of Chemistry and Physics," 41st ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1959, pp 1062, 1234.

(30) G. F. Woods, J. E. Swenarton, and R. B. Isaacson, *J. Org. Chem.*, **26**, 309 (1961).

(31) W. Dilthey and G. Hurtig, *Ber.*, **67**, 2004 (1934).

(32) K. Alder and J. Haydn, *Ann.*, **570**, 201 (1950).

Acknowledgment.—This research was supported in part by the U. S. Army Research Office, Durham, N. C. We wish to thank the Graduate College, University of Iowa, for providing the computer time and Mr. Burton Gearhart of the University of Iowa Computer Center for mathematical assistance.

Molecular Rearrangements. An Interannular Acylation of Enol Esters

J. CORREA AND R. M. MAINERO

Department of Chemistry, Universidad Ibero Americana, Mexico, D. F.

Received October 9, 1968

Several enol esters of 2-benzylcyclohexane-1,3-diones (**5**) were treated with polyphosphoric acid (PPA). The reaction products were the aryl alkyl ketones (**6**). This constitutes a new acylation at aromatic carbon using enol esters as acylating agents, and also a novel molecular rearrangement comprising an interannular migration of the acyl group. The chemical and spectroscopic properties of these compounds, as well as that of other new compounds prepared in the synthetic sequence, are described. When **2b** was treated with cyclohexane-1,3-dione enol acetate in the presence of PPA, **6b** was obtained. Stereochemical considerations suggest the reaction mechanism as intermolecular.

Two of the most well-known organic reactions are the Friedel–Crafts acylation[1] and alkylation and its familiar Fries modification.[2] Acid catalysts are used in both reactions, polyphosphoric acid (PPA) being one that is gaining more adepts.[3] In the Fries rearrangement,[4] treatment of phenol esters with acid catalysts gives rise to 1,3 or 1,5 shifts of the acyl group, producing the *o*- or *p*-acylphenols.

In the present paper we wish to report the results obtained when some enol esters of 2-benzylcyclohexane-1,3-diones are treated with PPA. A rapid, general method for the preparation of enol esters was developed; it consists in the heating of the 1,3-diketone with excess anhydride and a catalytic amount of *p*-toluenesulfonic acid on the steam bath, followed by the high-vacuum distillation of the mixture. This allowed the recovery of the excess anhydride and avoided the hydrolysis of the labile enol esters.

In the cases under study the products obtained from the treatment of the esters with PPA resulted from the migration of the acyl group to the C-4 position of the aromatic ring (Scheme I: **5a** → **6a**, **5b** → **6b**, etc.).

The mentioned sequences appear to be the first reported on acylations of aromatic hydrocarbons by the action of aliphatic enol esters. At the same time they constitute the interesting case of an interannular 1,8 migration of the acyl group. Chemical and spectroscopic evidence of the mentioned structures is given below.

The simplest example of the sequence is the one starting with 2-benzylcyclohexane-1,3-dione (**2a**) which was obtained by the general method of Stetter and Klauke.[5]

A small amount of the 2,2-dibenzyl derivative (**3**) was also obtained in this experiment. It possesses a peculiar nmr spectrum, in which, for example, the C-5 methylene protons are found at a higher field δ 0.83) than the usual for such protons (δ 2); this must be due to the shielding by the phenyl rings, as a result of the geometry in the molecule.[6]

The enol acetate of **2a** was prepared by its treatment with acetic anhydride and *p*-toluenesulfonic acid. The product **5a** shows in its ir spectrum the characteristic absorption bands for the vinyl ester (1750 cm^{-1}), the α,β-unsaturated carbonyl (1665 and 1645 cm^{-1}), and the monosubstituted benzene (690 cm^{-1}). In its nmr spectrum three singlets are observed at δ 2.06 (3 H), 3.48 (2 H), and 7.15 (5 H), corresponding successively to the acetate, the benzylic methylene, and the aromatic protons; the annular methylene groups exhibit a multiplet centered at δ 2.31 (6 H).

A crystalline product ($C_{15}H_{18}O_3$) could be isolated when this acetate (**5a**) was heated in the presence of PPA, and the reaction mixture was purified by chromatography. The acidic character of this substance, its positive ferric chloride test, and its ir spectrum (which shows bands at 3150 (broad), 1620 and 1630 cm^{-1}) indicated that this product is an isomer of **5a** containing the free enol grouping.

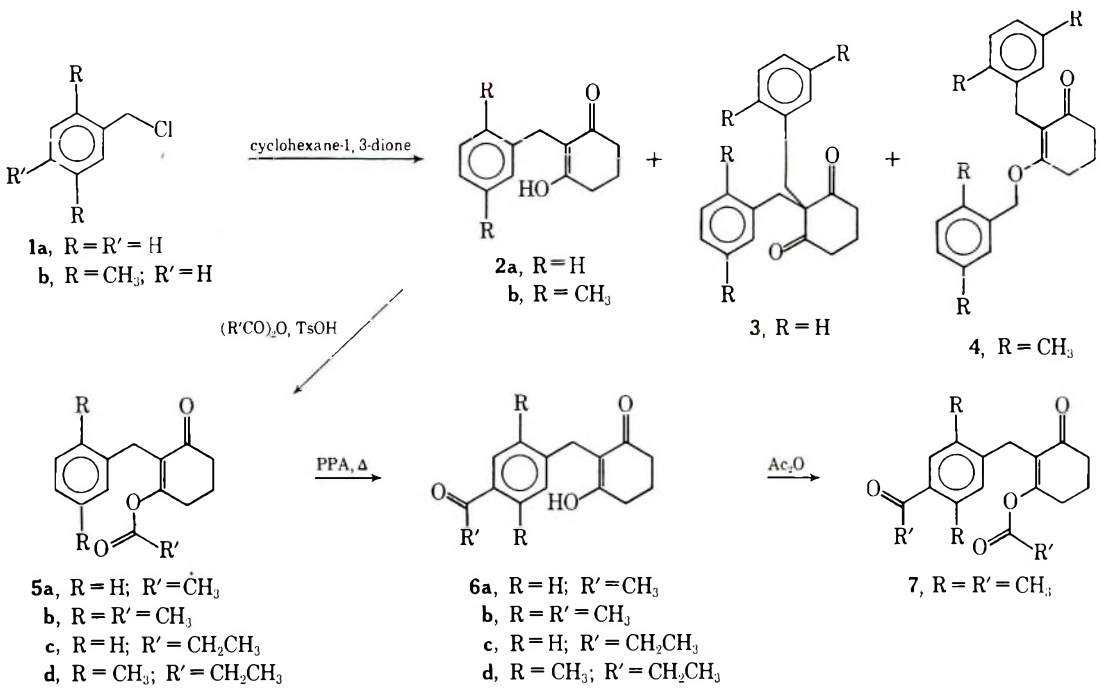
The fact that the acetyl group had migrated to the aromatic ring in this compound was deduced from its ir spectrum which exhibits a strong peak at 1670 cm^{-1} (Ar–CO) and lacks the band in the 700-cm^{-1} region. This group was assigned to C-4 position in the aromatic ring, based on the nmr spectrum which has a singlet at δ 2.54 (3 H) (due to the CH_3COAr) and two doublets at 7.33 (2 H, J = 8 cps) and 7.72 (2 H, J = 8 cps) (due to the aromatic protons); the shape and position of the doublets are in full agreement with the ABA′B′ aromatic system of a *p*-alkylacetophenone.[7] The other bands in the nmr spectrum, those due to the methylene protons of this compound (**6a**), appear as a quintet at δ 1.96 (2 H, J = 5.5 cps) (C-5), a triplet at 2.45 (4 H, J = 5.5 cps) (C-4 and C-6), and a singlet at 3.70 (benzylic methylene).

The propionic enol ester (**5c**) of the 2-benzylcyclohexane-1,3-dione was also prepared; all of these spectra are also in accord with its structure.

Transposition of the propionyl group by heating the ester with PPA gave the 2-(4-propionylbenzyl)cyclohexane-1,3-dione. Its spectroscopic behavior is very similar to that of the acetylbenzyl derivative (**6a**) and fully supports the proposed structure (**6c**).

(1) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 282.
(2) Reference 1, p 292.
(3) F. Uhlig and H. R. Snyder, *Advan. Org. Chem.*, **1**, 35 (1960).
(4) P. de Mayo, "Molecular Rearrangements," Vol. I, Interscience Publishers, New York, N. Y., 1967, p 318.
(5) H. Stetter and E. Klauke, *Chem. Ber.*, **85**, 1065 (1952).
(6) E. Cortés and F. Walls, *Bol. Inst. Quim. Univ. Nacl. Auton. Mex.*, **17**, 165 (1965); H. A. P. de Jongh and H. Wynberg, *Tetrahedron*, **21**, 515 (1965).
(7) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "Varian High Resolution NMR Spectra Catalog," No. 188, Varian Associates, Palo Alto, Calif.; D. H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 121.

SCHEME I



1a, R = R′ = H
b, R = CH_3; R′ = H

2a, R = H
b, R = CH_3

3, R = H

4, R = CH_3

5a, R = H; R′ = CH_3
b, R = R′ = CH_3
c, R = H; R′ = CH_2CH_3
d, R = CH_3; R′ = CH_2CH_3

6a, R = H; R′ = CH_3
b, R = R′ = CH_3
c, R = H; R′ = CH_2CH_3
d, R = CH_3; R′ = CH_2CH_3

7, R = R′ = CH_3

In this transposition experiment (from **5c**) as in the former one (from **5a**) no other product was obtained on treatment with PPA, but the yields were very low and a large amount of substrate was recovered (in the form of **2a** and not of the esters **5c** or **5a**, probably because of the hydrolytic conditions of the isolation procedure).

Based on the consideration that this acylation is an electrophilic substitution on the aromatic ring and so electron-donor groups must facilitate it, another series was found which gives much better yields. The series starts with the 2-(2,5-dimethylbenzyl)cyclohexane-1,3-dione (**2b**). It was prepared through the condensation of 2,5-dimethylbenzyl chloride (**1b**) with cyclohexane-1,3-dione.

A small amount of the 2,O-dibenzyl derivative **4** was produced in the reaction. The structure of this compound was easily deduced from the examination of its nmr spectrum; it resembles that of the monobenzyl derivative **2b** (see Table I) and indeed **4** may be transformed into **2b** by heating with diluted acid, as corresponds to the behavior of an enol ether.

The enol acetate of **2b** (**5b**) was prepared by the usual method. The strong, characteristic, enol-ester band appears in its ir spectrum at 1750 cm^{-1}. Its nmr spectrum exhibits in the aromatic region (δ 6.96) a signal with the familiar shape of the 1,2,4-trisubstituted benzene.

When **5b** was treated with PPA it was rearranged in a quantitative manner to **6b**, which has an acid character and gives a positive ferric chloride test.

The ir spectrum for **6b** confirms the proposed structure showing bands for its enolic 1,3-diketone at 3150 (broad), 1710 and 1600 cm^{-1}, for the aryl ketone at 1665 cm^{-1}, and for the 1,2,4,5-tetrasubstituted benzene at 870 cm^{-1}. In its nmr spectrum the aromatic methyl, acetyl, and benzylic methylene protons appear as singlets, respectively, at δ 2.33, 2.42, 2.53, and 3.56; the annular methylene protons are shown as a complex signal centered at δ 2.28. The peaks corresponding to the aromatic protons are seen as two well-separated singlets at δ 6.87 and 7.47, as is expected for two isolated protons in different electronic environments. This evidence permits an assignment of the 4 position in the aromatic ring to the migrated acyl group. The compound **6b** gives an enol acetate (**7**) and a 2,4-dinitrophenylhydrazone.

In a similar way the enol propionate of **2b** (**5d**) was obtained. It underwent the aforementioned rearrangement to give the 4-acetyl derivative **6d** whose structure was derived from its chemical and spectroscopic properties. Its nmr, for example, is very similar to that of the 4-acetyl derivative **6b** (see Table I).

The examination of models permits one to see that in the conformations of **5** the acyl carbon atom lies near the C-2 aromatic carbon and not as near the C-3 or C-4 positions. If the reaction mechanism were intramolecular, the C-2 acyl derivatives should have been obtained. The fact that we obtained only the C-4 acyl compounds led us to think that the mechanism here is intermolecular. A further experiment was carried out in connection with this; the nonacetylated compound **2b** was treated with cyclohexane-1,3-dione enol acetate in the presence of PPA, giving a good yield of **6b**; this result also suggests the mechanism of the reaction as being intermolecular, although it does not exclude the possibility of the production of **6b** intramolecularly through an initial ester-exchange reaction before the final acylation.

Further studies on mechanistic aspects of the reaction are in progress.

Experimental Section

Melting points are uncorrected. Ir spectra were run in chloroform solution on a Beckman IR-8 spectrophotometer. Uv spectra were determined in ethanol solution on a Unicam SP-800 spectrophotometer. Nmr (Table I) and mass spectra were determined, respectively, on a Varian A-60A spectrometer and on a double-focusing Hitachi–Perkin-Elmer RMU-6D spectrometer. The microanalyses were performed by Dr. Franz Pascher, Bonn, Germany, and by Schwarzkopf Microanalytical Labs, Woodside,

TABLE I
NMR SPECTRA OF BENZYLCYCLOHEXANEDIONE DERIVATIVES[a]

Compd	δ, ppm					
	CH_2–Ar	Cyclic CH_2	R'COO	R'CO–Ar	Benzyl CH_2	H–Ar
2a[b]		2.04 (qn, 2, *J* 6), 2.42 (t, 4, *J* 6)			3.60 (s, 2)	7.18 (s, 5)
2b	2.30 (s, 6)	2.23 (m, 6)			3.64 (s, 2)	6.93 (m, 3)
3		0.83 (qn, 2, *J* 6), 1.87 (t, 4, *J* 6)			3.25 (s, 4)	7.15 (m, 10)
4	2.18 (s, 6), 2.24 (s, 6)	2.15 (m, 6)			3.61 (s, 2), 5.02 (s, 2)	7.00 (m, 6)
5a		2.31 (m, 6)	2.06 (s, 3)		3.48 (s, 2)	7.15 (s, 5)
5b	2.24 (s, 6)	2.34 (m, 6)	1.98 (s, 3)		3.52 (s, 2)	6.96 (m, 3)
5c		2.26 (m, 6)	1.12 (t, 3, *J* 7), 2.41 (q, 2, *J* 7)		3.53 (s, 2)	7.18 (s, 5)
5d	2.23 (s, 6)	2.31 (m, 6)	1.99 (t, 3, *J* 7), 2.17 (q, 2, *J* 7)		3.43 (s, 2)	6.48 (m, 3)
6a		1.93 (qn, 2, *J* 6), 2.45 (t, 4, *J* 6)		2.54 (s, 3)	3.70 (s, 2)	7.33 (d, 2, *J* 8), 7.72 (d, 2, *J* 8)
6b	2.33 (s, 3), 2.42 (s, 3)	2.28 (m, 6)		2.53 (s, 3)	3.56 (s, 2)	6.87 (s, 1), 7.47 (s, 1)
6c		1.97 (qn, 2, *J* 6), 2.50 (t, 4, *J* 6)		1.23 (t, 3, *J* 7), 2.98 (q, 2, *J* 7)	3.75 (s, 2)	7.34 (d, 2, *J* 8), 7.87 (d, 2, *J* 8)
6d[b]	2.33 (s, 3), 2.36 (s, 3)	2.25 (m, 6)		1.10 (t, 3, *J* 7), 2.90 (q, 2, *J* 7)	3.57 (s, 2)	6.93 (s, 1), 7.50 (s, 1)
7	2.34 (s, 3), 2.48 (s, 3)	2.42 (m, 6)	2.17 (s, 3)	2.56 (s, 3)	3.57 (s, 2)	6.90 (s, 1), 7.52 (s, 1)

[a] TMS was the internal standard. Coupling constants (*J*) are given in Hz; s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet; chloroform solutions were used unless otherwise specified. The signal of the hydroxylic proton suffers variation in its form and position and sometimes is lost in the noise. [b] In acetone solution.

N. Y. Aluminum oxide standarized Merck (Brockmann grade I–II), was used for chromatographic columns.

2-Benzylcyclohexane-1,3-dione (2a) and 2,2-Dibenzylcyclohexane-1,3-dione (3).—Using the method of Stetter and Klauke,[5] and starting with 11.5 g of cyclohexane-1,3-dione, 14 g of **2a** (mp 185°) was obtained; ir, 3200 broad (enol OH), 1700 (keto form C=O), 1610 (conj C=O and C=C), 695 cm^{-1} (monosubstituted benzene).

The neutral product on the above reaction was extracted with ether from the alkaline aqueous solution. The residue after drying (Na_2SO_4) and evaporation of the ether extracts was recrystallized from ethanol giving 5 g of **3**: mp 141–142°; ir, 1708 and 1682 (keto form C=O), 1600, 1572, 1490, 1450, and 695 cm^{-1} (monosubstituted benzene); uv max, 204 mμ (ε 11,403), 260 (269), and 295 (116).

2-Benzylcyclohex-2-en-3-ol-1-one Acetate (5a).—A solution of 4 g of 2-benzylcyclohexane-1,3-dione (**2a**) and 280 mg of *p*-toluenesulfonic acid in acetic anhydride (36 ml) was heated for 1 hr. Vacuum distillation afforded 3 g of the acetate (**5a**): bp 178–183° (7 mm); ir, 1750 (ester C=O), 1665 and 1645 (conj C=O and C=C), 690 cm^{-1} (monosubstituted benzene); uv max, 207 (ε 9549), 217 infl (8661), 238 (7440).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; O, 19.65. Found: C, 73.78; H, 6.89; O, 19.95.

2-(4-Acetylbenzyl)cyclohexane-1,3-dione (6a).—The general method used for the rearrangement reaction was as follows.[3] An intimate mixture of the enol ester with an excess of PPA[8] (ten times its weight) was heated in a closed vessel, with ocassional stirring, on the steam bath, until a deep red color was developed. An excess of ice and water, ten times the weight of PPA, was added with stirring to allow the hydrolysis of the excess acid. A precipitate appeared which was worked up as indicated.

A mixture of 2 g of the acetate (5a) and PPA was heated for 45 min. The precipitate which appeared after the hydrolysis of the acid was extracted with chloroform. The chloroform solution was dried (Na_2SO_4), concentrated (to approximately 100 ml) and chromatographed on a column of alumina (40 g). The first fractions, eluted with chloroform, contained the recovered benzyl derivative **2a**, 1.5 g. The 4-acetyl derivative **6a** was collected on the remaining fractions, eluted with acetone. It was recrystallized from acetone–ether, acetone–cyclohexane, and then from methanol–water (0.15 g, mp 178°); ir, 3150 broad (enol OH), 1700 sh (keto form C=O), 1670 (aryl ketone C=O), 1620 sh and 1600 cm^{-1} (conj C=O and C=C); uv max, 205 mμ (ε 39,080), 260 (53,740); uv min, 225 mμ (ε 11,327).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; O, 19.65. Found: C, 73.85; H, 6.44; O, 19.79.

2-Benzylcyclohex-2-en-3-ol-1-one Propionate (5c).—To a solution of 20 g of **2a** in 90 ml of warm propionic anhydride, 1.4 g of *p*-toluenesulfonic acid was added. After heating the mixture for 2 hr, vacuum distillation afforded 25 g of the ester **5c**, a pale yellow liquid [bp 168° (7 mm)] which crystallized on cooling to give a colorless solid: mp 35–39°; ir, 1750 (ester C=O), 1665 and 1645 (conj C=O and C=C), 690 and 660 cm^{-1} (monosubstituted benzene); uv max, 207 mμ (ε 12,398), 230 infl (8394), 243 (9169); mass spectrum (70 eV), *m/e* (relative intensity) 258 (1.2), 202 (17.3), 91 (11.8), 57 (100), 29 (58.3).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02; O, 18.58. Found: C, 74.14; H, 7.19; O, 18.47.

2-(4-Propionylbenzyl)cyclohexane-1,3-dione (6c).—A mixture of 5 g of propionate **5c** and PPA was heated for 45 min. After the addition of ice and water the mixture was extracted with chloroform. The organic extracts were washed with water and evaporated to dryness. The solid yellow residue (4 g) was dissolved in benzene (40 g) and chromatographed on alumina (100 g); 2-benzylcyclohexane-1,3-dione (**2a**) (3.5 g) was recovered in the first fractions, eluted with benzene and chloroform. Rearranged product **6c** was collected in the fractions eluted with acetone (evaporated at room temperature). The product was recrystallized from acetone–ether, giving 165 mg; mp 167–172°; ir, 3150 broad (enol OH), 1700 (keto form C=O), 1670 (aryl ketone C=O), 1620 sh and 1600 cm^{-1} (conj C=O and C=C); uv max, 205 mμ (ε 18,855), 260 (25,313); uv min, 225 mμ (ε 5940); mass spectrum (70 eV), *m/e* (relative intensity) 258 (7.4) 229 (34.4), 55 (45.9), 43 (100), 28 (50).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02; O, 18.58. Found: C, 74.13; H, 7.21; O, 18.74.

2-(2,5-Dimethylbenzyl)cyclohexane-1,3-dione (2b).—To a solution of 3.3 g (0.03 mol) of cyclohexane-1,3-dione in 7 ml of 20% aqueous potassium hydroxide, 4.6 ml (0.03 mol) of 2,5-dimethylbenzyl chloride[9] (**1b**) and 0.3 g of potassium iodide were added; the stirred mixture was kept 1 hr on the steam bath and then cooled at room temperature. Potassium hydroxide (10%, 200 ml) was added to dissolve the solid formed. The aqueous solution was extracted with ether and acidified with hydrochloric acid to pH 4. The precipitate was filtered off under vacuum and

(8) Polyphosphoric acid, Matheson Coleman & Bell (approximately $H_8P_4O_{13}$), was used for the majority of the experiments.

(9) J. C. Bardhan and S. C. Sengupta, *J. Chem. Soc.*, 2525 (1932).

recrystallized from methanol–water yielding 3.0 g of the product **2b**: mp 171°; ir, 3400 broad (enol OH), 1740 and 1710 (keto form C=O), 1610 cm^{-1} (conj C=O and C=C); uv max, 204 mμ (ε 18,884), 263 (15,314); uv min, 233 mμ (ε 3799).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88; O, 13.90. Found: C, 77.98; H, 7.80; O, 13.71.

2-(2,5-Dimethylbenzyl)-3-(2,5-dimethylbenzyloxy)cyclohex-2-en-1-one (4).—The ether extracts from the above reaction were washed with water, dried (Na_2SO_4), and evaporated, giving a solid (670 mg, mp 133°) which was recrystallized from ethanol to obtain the analytical sample of **4** (mp 136°): ir, 1630 and 1600 (α,β-unsat C=O), 880 and 805 cm^{-1} (1,2,4-trisubstituted benzene); uv max, 204 mμ (ε 27,183), 269 (18,953); uv min, 234 mμ (ε 3833).

Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10; O, 9.18. Found: C, 82.43; H, 8.40; O, 9.36.

4 (15 mg) was refluxed with 7 ml of 10% hydrochloric acid and then filtered. The reaction product **2b** was purified (extraction with 10% KOH) obtaining 5 mg, mp 170°. Its ir spectrum was superimposable with that of the condensation product.

2-(2,5-Dimethylbenzyl)cyclohex-2-en-3-ol-1-one Acetate (5b).—A solution of 15 g of **2b** and 800 mg of *p*-toluenesulfonic acid in 40 ml of acetic anhydride was heated at the steam bath for 35 min; the solution was allowed to reach the room temperature and poured into 500 ml of water. The white crowded needles (17 g) of the acetate (**5b**), melting at 70°, were filtered and dried under vacuum. Recrystallization from ether–hexane led to the analytical sample: mp 70°; ir, 1750 (ester C=O), 1665 and 1645 (conj C=O and C=C), 900 and 810 cm^{-1} (1,2,4-trisubstituted benzene); uv max, 203 mμ (ε 15,657), 218 infl (11,164), 238 (9122).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40; O, 17.63. Found: C, 75.02; H, 7.03; O, 18.08.

2-(4-Acetyl-2,5-dimethylbenzyl)cyclohexane-1,3-dione (6b).

(a) From 5b.—A mixture of 15 g of the acetate **5b** with PPA was heated for 30 min. After the addition of ice and water a beige precipitate (mp 140°) appeared, which was extracted with chloroform. The organic layer was washed with water, dried ($CaCl_2$), and evaporated to a small volume (70 ml). On cooling, the product **6b** crystallized (quantitative yield, mp 183°). Its analytical sample was prepared by crystallization from chloroform (needles mp 186°); ir, 3250 broad (enol OH), 1700 (keto form C=O), 1665 (aryl ketone C=O), 1610 cm^{-1} (conj C=O and C=C), this band was shifted to 1550 cm^{-1} in the KBr pellet spectrum; uv max, 213 mμ (ε 26,866), 262 (27,593); uv min, 232 mμ (ε 8532).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40; O, 17.62. Found: C, 74.48; H, 7.60; O, 17.59.

(b) From 2b.—Cyclohexane-1,3-dione (mp 105°) was obtained by the Thompson method[10] and transformed into its enol acetate [bp 95° (1 mm)] by the general procedure described above. A mixture of 1.54 g of this acetate, 2.3 g of **2b**, and 50 g of PPA was heated for 1 hr, poured over water, and extracted. The chloroform extracts (dried and concentrated) were chromatographed over 60 g of alumina. In the first fractions eluted with chloroform (2–5), cyclohexane-1,3-dione was recovered (1.1 g, mp 103°). In the latter with the same eluent (8–18) **6b** (1.8 g, mp 171°) was obtained; mixture melting point and ir spectrum were indistinguishable from that of the compound obtained from **5b**. By the usual methods the enol acetate **7** (mp 80°) and the 2,4-dinitrophenylhydrazone (mp 260°) of **6b** were prepared.

2-(2,5-Dimethylbenzyl)cyclohex-2-en-3-ol-1-one Propionate (5d).—A solution of 5 g of 2-(2,5-dimethylbenzyl)cyclohexane-1,3-dione (**2b**) and 500 mg of *p*-toluenesulfonic acid in 50 ml of propionic anhydride was heated for 40 min. On vacuum distillation, 6 g of the propionate **5d** [bp 170° (7 mm)] was obtained; ir, 1750 (ester C=O), 1665 and 1640 (conj C=O and C=C), 880 and 810 cm^{-1} (1,2,4- trisubstituted benzene); uv max, 203 mμ (ε 17,184), 218 infl (12,819), 239 (10,637).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74; O, 16.76. Found: C, 75.66; H, 7.82; O, 16.52.

2-(4-Propionyl-2,5-dimethylbenzyl)cyclohexane-1,3-dione (6d).—A mixture of the propionate **5d** (5 g) with PPA was heated for 1 hr. After the hydrolysis of the excess acid the mixture was extracted with chloroform. The extracts were dried ($CaCl_2$), concentrated, and chromatographed over alumina (60 g). Chloroform eluted from the column the unreacted compound (as **2b**). The propionyl derivative (**6d**, 1 g) was collected in the fractions eluted with acetone (concentrated at room temperature). Recrystallization from acetone–ether gave 350 mg (mp 180–182°); ir, 3200 broad (enol OH), 1700 (keto form C=O), 1665 (aryl ketone C=O), 1610 cm^{-1} (conj C=O and C=C); uv max, 213 mμ (ε 22,339), 261 (22,052); uv min, 232 mμ (ε 6587).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74; O, 16.76. Found: C, 75.26; H, 8.15; O, 16.37.

Registry No.—**2a**, 19755-60-3; **2b**, 19755-61-4; **3**, 739-03-7; **4**, 19755-63-6; **5a**, 19755-64-7; **5b**, 19755-65-8; **5c**, 19755-66-9; **5d**, 19755-67-0; **6a**, 19755-68-1; **6b**, 19755-75-0; **6c**, 19779-36-3; **6d**, 19755-76-1; **7**, 19755-77-2.

Acknowledgments.—This study was carried out with the help of a grant from the Research Corporation to whom we are indebted. We express our gratitude to Dr. J. Romo for its stimulating interest during our whole work. Help received in various aspects from Professor J. Garcilaso is warmly acknowledged. Nmr and mass spectra were determined, respectively, by Mr. E. Díaz and Mr. E. Cortés at the Instituto de Química, Universidad Nacional Autonoma de Mexico; through the courtesy of Dr. A. Sandoval. We want to express our acknowledgement to them.

(10) R. B. Thompson, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 278; the commercial Aldrich product, stabilized with sodium chloride, was also used for the condensations.

Base Cleavage of β,γ-Unsaturated Bicyclic Cyclobutanones

WILLIAM F. ERMAN,[1] ERNEST WENKERT,[2] AND P. W. JEFFS[2]

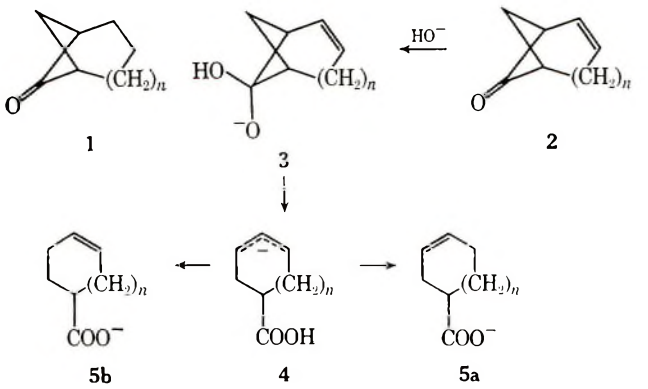
Thr Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239, and the Department of Chemistry, Indiana University, Bloomington, Indiana 47401

Received October 23, 1968

Treatment of chrysanthenone (**13**) with hydroxide ion under a variety of conditions produced as the major product acid **15a** and a smaller but significant quantity of acid **17a**. The ratio of **15a**:**17a** varied from 91:9 to 76:24 depending upon reaction conditions. Treatment of the isomeric ketone **20** with hydroxide ion under the same conditions produced relatively greater quantities of acid **17a**: *i.e.*, the ratio of **15a** to **17a** varied from 72:28 to 43:57. Cleavage of **13** or **20** with potassium methoxide afforded the corresponding esters in approximately the same ratios: 60:40 *vs.* 56:44, respectively. Cleavage of the ketone **14** with hydroxide provided both acids **16a** and **22a** in ratios which again varied with reaction conditions, *i.e.*, 72:28 to 56:44. The mechanistic implications of these contrasting results are discussed.

Whereas saturated four-membered ring ketones contained in a bicyclic ring structure of the type **1** are stable to refluxing methanolic potassium hydroxide, the corresponding β,γ-unsaturated ketones **2** are relatively labile under these conditions.[3-6] The driving force for the cleavage of these ketones results from a combination of ring strain and the stabilization rendered by the π orbitals of the double bond to an incipient carbanion developing in the transition state. Since protonation can occur at either of two sites of the developing allyl anion **4**, cleavage of ketones of type **2** would be expected to yield both possible olefinic carboxylates **5a** and **5b** (Scheme I).

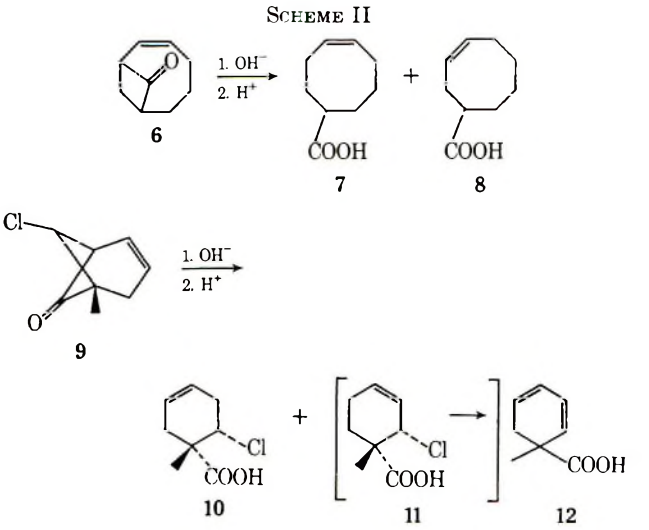
SCHEME I



1 **2** **3** **4** **5a** **5b**

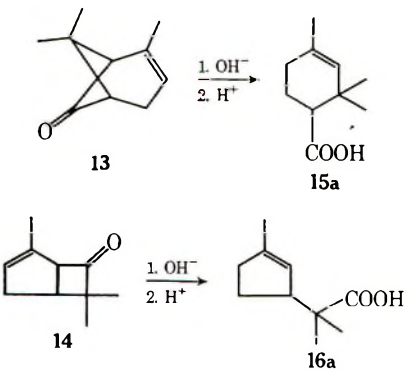
Indeed, bicyclo[5.1.1]non-2-en-8-one (**6**) on treatment with 20% methanolic potassium hydroxide is transformed (after acidification) to a mixture of approximately equimolar quantities of *cis*-4-cyclooctene-1-carboxylic acid (**7**) and *cis*-3-cyclooctene-1-carboxylic acid (**8**)[3] (Scheme II). Similarly the chloro ketone **9** is cleaved to a mixture of 1-methyl-2-*cis*-chloro-4-cyclohexene-1-carboxylic acid (**10**) and 1-methyl-2,4-cyclohexadiene-1-carboxylic acid (**12**) (presumably *via* the intermediate **11**).[6b,c]

SCHEME II



6 **7** **8** **9** **10** **11** **12**

In contrast to the above anticipated reactions, hydroxide ion cleavages of chrysanthenone (**13**) and 2,6,6-trimethylbicyclo[3.2.0]hept-2-en-7-one (**14**) are reputed to yield the single isomeric products 2,2,4-trimethyl-3-cyclohexene-1-carboxylic acid (**15a**)[4] and 2,2-dimethyl-2-(3-methyl-2-cyclopentenyl)acetic acid (**16a**),[7] respectively. A reinvestigation of the base cleavage of these and related cyclobutanones was initiated in order to understand better the mechanism of the cleavage process and explain the exclusive formation of isomers **15a** and **16a**.



13 **15a** **14** **16a**

Results

Cleavage of Chrysanthenone. Initially, the exact procedure of de Pascual Teresa, *et al.*,[4] was followed for the cleavage of chrysanthenone with aqueous meth-

(1) The Procter & Gamble Co.

(2) Indiana University. E. W. and P. W. J. acknowledge gratefully support by the National Science Foundation.

(3) W. F. Erman and H. C. Kretschmar, *J. Amer. Chem. Soc.*, **89**, 3842 (1967).

(4) J. de Pascual Teresa, H. Sanchez Bellido, and I. Sanchez Bellido, *Anales Real Soc. Espan. Fis. Quim.* (Madrid), **B58**, 339 (1962).

(5) A. R. Penfold, G. R. Ramage, and J. L. Simonsen, *J. Chem. Soc.*, 1496 (1939).

(6) (a) R. M. Dodson, J. R. Lewis, W. P. Webb, E. Wenkert, and R. D. Youssefyeh, *J. Amer. Chem. Soc.*, **83**, 938 (1961); (b) C. L. Leicht, Ph.D. Dissertation, Indiana University, 1964; (c) although **10** is slowly converted to **12** under the same conditions, the rate of formation of **12** from **10** is too low to account for the yield of **12** obtained in the base cleavage of **9**: E. Wenkert and P. Bakuzis, unpublished observations.

(7) J. J. Beereboom, *J. Amer. Chem. Soc.*, **85**, 3525 (1963); *J. Org. Chem.*, **30**, 4230 (1965).

Table I

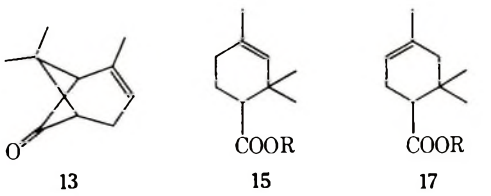
Base Cleavage of Cyclobutanones 13 and 20

Run	Ketone	Base	Base source	Solvent	Base concn, M	Temp, °C	% yield[a] 15b	% yield[a] 17b	% of recd starting ketone	Ratio[b] 15:17	
1	13	KOH	Reagent pellets	Anhy CH_3OH	2	78	41	6		87	13
2	13	KOH	Reagent pellets	Anhy CH_3OH	4	78	32	6	16	85	15
3	13	KOH	Reagent pellets	95% aq CH_3OH	4	78	49	8	17	86	14
4	13	KOH	KH–H_2O (3:1)	THF	[c]	26–27	28	3		91	9
5	13	KOH	$(CH_3)_3CO^-K^+$–H_2O (3:1)	THF	[c]	26–27	49	15	11	76	24
6	13	KOH	$(CH_3)_3CO^-K^+$–H_2O (1:1.4)	THF	c	26–27	45	14	11	76	24
7	13	$CH_3O^-K^+$	CH_3OH, K	CH_3OH	1	78	16	11	9	60	40
8	13	$CH_3O^-K^+$	CH_3OH, K	CH_3OH	4	78	39[d]	24[d]	0	61	39
9	13	$(CH_3)_3CO^-K^+$	$(CH_3)_3COH$, K	$(CH_3)_3COH$	1	82	39[e]	24[e]	0	63	37[f]
10	20	KOH	Reagent pellets	CH_3OH	2	78	20	27		43	57
11	20	KOH	Reagent pellets	CH_3OH	4	78	21	28	20	42	58
12	20	KOH	$(CH_3)_3CO^-K^+$–H_2O (10:3)	THF	[c]	78	31	16	1	66	34
13	20	$CH_3O^-K^+$	CH_3OH, K	CH_3OH	1	26–27	29	22	0	56	44

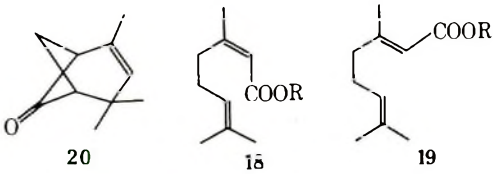
[a] Based upon distilled methyl ester derivatives. [b] Based upon gas chromatographic analysis of the methyl ester derivatives before and after distillation. The product ratios of all runs were duplicated within 3%. [c] Heterogeneous mixture. [d] Based upon combined yield of methyl ester produced directly from the reaction and the methyl ester produced from treatment of the acidic products with diazomethane. [e] Based upon combined yield of *t*-butyl ester produced directly from the reaction and the methyl ester produced from treatment of the acidic products with diazomethane. [f] Based upon the ratio of *t*-butyl esters only.

anolic potassium hydroxide (run 3, Table I). Although both acids **15a** and **17a** were produced under these conditions,[8] the former greatly predominated regardless of the concentration of base or water present in the reaction mixture (compare runs 1–3, Table I). At lower concentrations of base small quantities of neric acid (**18a**) and geranic acid (**19a**) are produced by a competitive thermally induced process[9–12] (see Experimental Section, run 1). When the ketone **13** was treated with a dispersion of anhydrous potassium hydroxide (prepared by adding water to excess potassium hydride)[13] the two acids **15a** and **17a** were produced in a ratio of 91:9. Surprisingly, the ratio of **15a**:**17a** dropped to 76:24 when the hydroxide was generated from potassium *t*-butoxide–water using the general cleavage procedure of Gassman, *et al.*[13] Scission of **13** with potassium methoxide in methanol showed only a slight preference for the production of ester **15b** (runs 7 and 8, Table I).

In contrast to the case of chrysanthenone the isomeric ketone 2,4,4-trimethylbicyclo[3.1.1]hept-2-en-6-one (**20**), when cleaved with methanolic potassium hydroxide, afforded the two acids **15a** and **17a** in almost equimolar quantities with the acid **17a** slightly predominating (runs 10, 11, Table I). However, when potassium hydride–water[13] (run 13, Table I) or potassium butoxide–water[13] (run 12, Table I) was employed for cleavage of **20** the acid **15a** predominated once again. The ratio of **15b** to **17b** from cleavage of **20** with methoxide compared favorably with that obtained from the cleavage of **13** with methoxide (compare run 13 to runs 7 and 8, Table I).



13 15 17



20 18 19

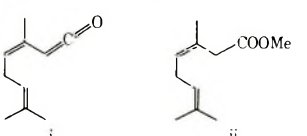
a, R = H; b, R = Me; c, R = *t*-Bu; d, R = Et

The acids **15a**, **17a**, **18a**, and **19a** were identified by comparison of the infrared and nmr spectra and gas chromatography retention times of the corresponding methyl ester derivatives of each with authentic specimens. An authentic specimen of **15b** prepared by diazomethane methylation of the known 2,2,4-trimethyl-3-cyclohexene-1-carboxylic acid,[14a] was converted to the isomer **17b** by heating with boron trifluoride etherate in dichloroethane. That skeletal rearrangement or further migration of the olefin did not occur during the acid treatment was clearly shown by examination of the nmr spectrum of **17b**. Thus, the *gem*-dimethyl protons were apparent as uncoupled superimposed singlets at τ 9.06, the C-4 methyl peak persisted at 8.40, and the single olefinic proton appeared at 4.75.

In view of the possibility of equilibration of **15a** and

(8) The free acids are produced from the carboxylate salt only after acidification of the alkaline solution with hydrochloric acid during work-up.

(9) Conversely, in refluxing 5% aqueous potassium hydroxide the ketone **13** is converted exclusively to geranic acid instead of the acids **15a** and **17a**.[4,5,10] This latter reaction undoubtedly is thermally initiated, however, and probably proceeds *via* the ketene i.[11] In an analogous manner, chrysanthenone undergoes slow cleavage to methyl 3,7-dimethyl-*seq-cis*-3,6-octadienoate (ii) in refluxing methanol in the absence of hydroxide ion.[12]



i ii

(10) M. Kotake and H. Nonaka, *Ann.*, **607**, 153 (1957).

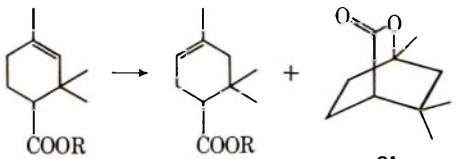
(11) E. P. Blanchard, Jr., *Chem. Ind.* (London), 293 (1958).

(12) W. F. Erman, *J. Amer. Chem. Soc.*, **90**, 779 (1969).

(13) P. G. Gassman, J. T. Lumb, and F. V. Zalar, *ibid.*, **89**, 946 (1967). We should emphasize that maximum yields of acid cleavage products were obtained when the Gassman method was employed. Since ring opening occurs at low temperatures (25–26°) under these conditions, competitive thermal scission is avoided. In contrast to the conditions required for fragmentation of larger ring ketones, the exact 3:1 ratio of potassium *t*-butoxide to water was not required for cleavage of the cyclobutanones. In fact water could be used in excess (*e.g.*, see run 6) without variation in results.

17a during work-up of the product mixtures from each of the above reactions further comment about the acid-catalyzed isomerization of **15a** to **17a** is necessary. The acid **15a** is isomerized slowly to **17a** on storage, but undergoes more rapid conversion to **17a** in ethereal hydrogen chloride Thus treatment of **15a** for 3 hr at room temperature with ethereal hydrogen chloride produced **15a** and **17a** and the lactone **21** in 47, 9, and 3% yields, respectively. Prolonged treatment (16 hr) with ethereal hydrogen chloride afforded the same materials in yields of 33, 16, and 18%, respectively. However, isomerization during work-up of the base cleavage products of **13** and **20** was negligible when they were methylated with diazomethane immediately after acidification and extraction with ether. Thus, the product distribution observed was that resulting directly from base cleavage of the ketones and not from subsequent acid-catalyzed rearrangement.

Product distribution of the free acids at equilibrium was not determined since under more drastic conditions the acids were transformed exclusively to the lactone **21** (see, for example, isomerization with boron trifluoride etherate, Experimental Section). However, acid isomerization of the ester **15b** indicated a thermodynamic preference for the ester **17b** at equilibrium. The ratio of **17b**:**15b** reached a maximum of 70:30 after a 30-min reflux with 10% boron trifluoride etherate in dichloroethane and this ratio did not change on further treatment with acid.

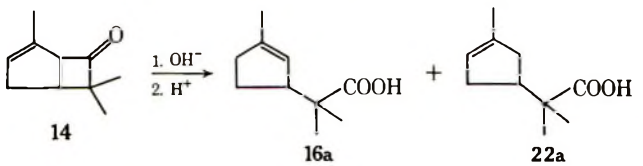


15 17 21

a, R = H; b, R = Me; c, R = *t*-butyl; d, R = Et

Isomerization of an isolated double bond normally requires a base stronger than hydroxide ion.[14b] However, in order to gain some assurance that the initially produced acids **15a** and **17a** are not isomerized under the basic conditions employed for cleavage, the one isomer **15a** was treated with hydroxide ion under the conditions described for base cleavage runs 3 and 5. The acid was recovered unchanged in each instance.

Cleavage of 2,6,6-Trimethylbicyclo[3.2.0]hept-2-en-7-one (14).—Cleavage of the cyclobutanone **14** with base produced both possible isomeric olefinic acids **16a** and **22a** regardless of the conditions employed



14 16a 22a

(see Table II). When the exact conditions of Beereboom[7] were used (run 2, Table II) the isomer **16a** reached a maximum, but, even under these conditions, **22a** was produced in significant quantities. Almost equimolar quantities of the two acids were isolated when the cleavage was performed employing the conditions of Gassman, *et al.*[13]

(14) (a) O. N. Jitkow and M. T. Bogert, *J. Amer. Chem. Soc.*, **63**, 1979 (1941); (b) see A. Schriesheim and C. A. Rowe, Jr., *ibid.*, **84**, 3160 (1962), for a review.

The structure of the acid **16a** was confirmed by comparison of the spectral properties of its methyl ester derivative with those of methyl 2,2-dimethyl-2-(3-methyl-2-cyclopentenyl)acetate (**16b**) reported by Beereboom.[7] The spectral properties of the isomeric ester **22b** are strikingly similar to those of **16b**. However, an exhaustive comparison of the nmr spectra of **16b** and **22b** clearly distinguished the two structures. As expected of an allyl proton the ring C-1 proton in **16b** occurred at 0.48 ppm lower field than the nonallylic C-1 proton in **22b** (see the Experimental Section for details of the nmr spectrum).

Discussion

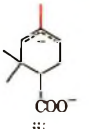
The cleavage of β,γ-unsaturated cyclobutanones may be envisioned as a three-step process: (1) attack of base on the carbonyl function to produce the intermediate anion **3**, (2) bond scission, and (3) protonation of the resulting allyl anion **4** at either of two possible sites. The exact mode of protonation, however, is a point of speculation. Thus, protonation may occur either by an inter- or intramolecular process at a point in the bond scission which resembles more closely the initially produced anion **3** or at a point which approximates the fully developed allyl anion **4**. In the subsequent discussion we propose that protonation is concerted with bond scission but that the mode and timing of the process is dependent upon reaction conditions and structure variations in the cyclobutanones.

The diverse nature of the protonation process may be developed by considering first the cleavage of chrysanthenone with hydroxide ion. Attack of hydroxide on **13** yields the initial anion **23** which would collapse to the allyl anion **25**.

We will consider first that protonation occurs at a point in the bond-scission process which closely resembles the fully developed anion **25**.[15a] It is at once tempting to suggest that production of **15** as the major product is the consequence of inter- or intramolecular protonation at the less hindered C-5 position of the anion **25** (see Scheme III). The relatively small differences in product distribution observed from cleavage of **13** under different solvent conditions could be interpreted as differences in susceptibility of the specific proton source to steric factors.[15b]

Such an argument, however, seems untenable in light of the striking difference in product distribution from cleavage of ketones **13** and **20** in methanolic potassium hydroxide (compare runs 1 and 2 with 10 and 11). Scission of these ketones would lead to the same allyl ion **25** and, consequently, under identical conditions of

(15) (a) Such a mechanism was originally proposed by Cristol for the base cleavage of dehydronorcamphor to 3-cyclopentenyl acetic acid.[15b] Recently, however, Paasivirta has shown that base cleavage of this ketone yields a 1:1 mixture of the 2- and 3-cyclopentylacetic acids.[15c] (b) S. J. Cristol and P. K. Freeman, *ibid.*, **83**, 4427 (1961); (c) J. Paasivirta, *Tetrahedron Letters*, 2867 (1968); *Suomen Kemistilehti*, **B41**, 335 (1968). (d) It is assumed, without qualification, that protonation of the anion occurs before the dianion iii is produced. Cleavages with potassium *t*-butoxide–water or potassium hydride–water, in fact, could proceed *via* the dianion iii. Intermolecular protonation of the dianion iii, however, should proceed with the same stereoselectivity as for the anion **25**.



iii

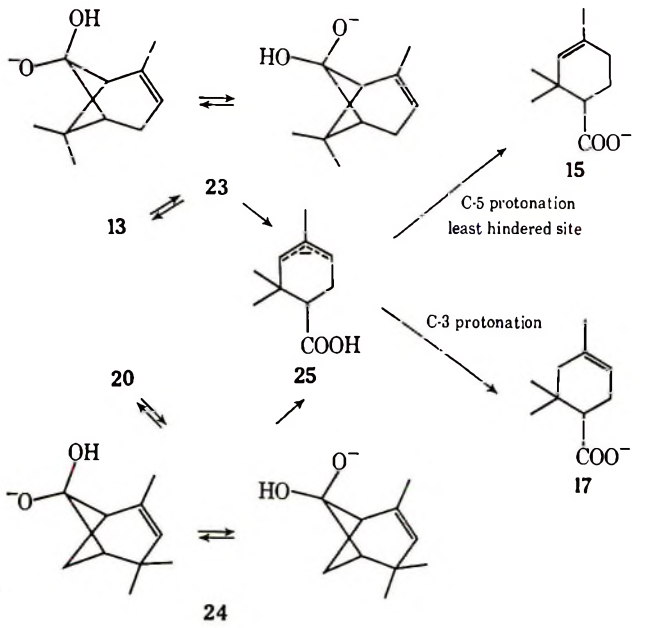
Table II

Base Cleavage of Cyclobutanone 14

Run	Ketone	Base	Base source	Solvent	Base concn, M	Temp, °C	% yield[a] 16b	% yield[a] 22b	% of recd starting material	Ratio[b] 16b	Ratio[b] 22b
1	14	KOH	Reagent pellets	CH_3OH	4	78	4	3	14	62	38
2	14	KOH	Reagent pellets	95% aq CH_3OH	4	78	5	2	9	72	28
3	14	KOH	$(CH_3)_3CO^-K^+-H_2O$ (3:1)	THF	c	26–27	28	22	6	56	44

[a] Based upon distilled methyl ester derivatives. [b] Based upon gas chromatography of the corresponding methyl ester derivatives before and after distillation. The product ratios were reproduced within 3%. [c] Heterogeneous mixture.

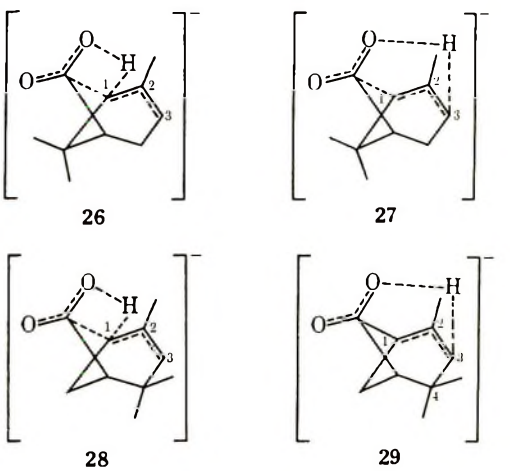
Scheme III



cleavage, should yield products of the same composition regardless of whether protonation is intramolecular or intermolecular. When **13** and **20** are cleaved in methanolic potassium hydroxide, protonation must occur before the completely developed anion **25** is produced, *i.e.*, protonation must occur concerted with ring rupture at a point in the transition state which more closely resembles the anions **23** and **24**, below.[16]

Logical arguments can be presented to explain the observed results if it is assumed that protonation in the presence of an aprotic solvent occurs exclusively by an intramolecular process and in the presence of a protic solvent by competing inter- and intramolecular processes.

Again considering first the cleavage of chrysanthenone (**13**), intramolecular protonation at the C-1 site by what can be envisaged as a 1,3-proton transfer (see structure **26**) would produce **17**; intramolecular protonation at C-3 by a 1,5-proton transfer (see structure **27**) would produce **15**.[17] Examination of a Dreiding model of **23** reveals that the hydroxyl proton is ideally disposed to interact with the π orbitals of the olefin. It is reasonable, therefore, to expect predominant protonation of the C-3 site of **23** if intramolecular protonation is the principal course of reaction. The formation of maximum yields of acid **15a** with hydroxide in the presence of an aprotic solvent (run 4, Table I) is consistent with this proposal. The C-4 *gem*-dimethyl group in **24**, however, might be expected to retard intramolecular protonation (depicted by **29**) at the C-3 site in this isomer and allow competitive intramolecular (depicted by **28**) and intermolecular protonation at C-1. This would explain the fact that significant quantities of both acids **15a** and **17a** are produced from **20** regardless of cleavage conditions. The differences in relative proportions of **15a** and **17a** produced from **20** in the absence and presence of a protic solvent could be explained by the relative contributions of intramolecular and intermolecular protonation with this isomer.

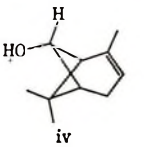


If methoxide ion (or butoxide ion) replaces hydroxide as the attacking nucleophile, intramolecular protonation of the expected intermediate anion **30**[18,19] and **31** (from **13** and **20**, respectively) is impossible and only intermolecular protonation can occur. Approximately equimolar quantities of the two isomeric acids should be, and are, produced from both ketones **13** and **20** under these conditions.

(16) We have already eliminated the possibility that the isomer of greater thermodynamic stability is produced from cleavage of **13** on grounds that the Δ^4 isomer (**17b**) is favored over the Δ^3 isomer (**15b**) on acid equilibration by a factor of at least 7:3. Isolation of different quantities of the two acids **15a** and **17a** from methanolic potassium hydroxide scission of **13** and **20** also precludes the possibility that protonation occurs in such a manner as to produce the most stable olefin.

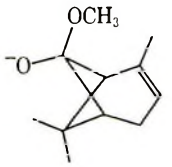
(17) For other examples of base-catalyzed 1,3- and 1,5-hydrogen transfers involving allylic anion systems see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter V, pp 175–210.

(18) Lithium aluminum hydride reduction of chrysanthenone (**13**) leads exclusively to the alcohol iv.[19] In analogy, solvated methoxide should approach from the least hindered side of the molecule to produce the intermediate **30** in exclusion of its epimer.

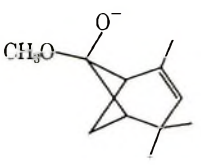


iv

(19) (a) J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 2864 (1960); (b) P. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).



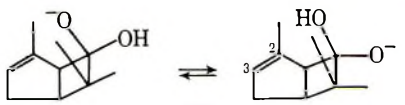
30



31

Thus far in our discussion we have ignored the results obtained from cleavage of ketone **13** and **20** using the potassium *t*-butoxide–H_2O–THF system of Gassman. At least 1 equiv of *t*-butyl alcohol is present in the system but whether the *t*-butyl alcohol is complexed with hydroxide ion or whether a heterogeneous or homogeneous system is present is uncertain. Speculation about these runs therefore must be withheld until the characteristics of this system are better understood. Nonetheless, the results of these cleavages are included to emphasize the synthetic value of Gassman's procedure (see ref 13).

In the case of the cleavage of the five/four fused ketone **14**, regardless of cleavage conditions, both isomeric acids are produced in significant quantities. Examination of molecular models indicates that the hydroxyl proton of the initially produced anion **32** is not ideally suited for a 1,5-proton transfer. In this instance protonation may occur by one of the several other mentioned inter- or intramolecular processes.



32

Experimental Section

General.—Melting points were determined on a Thomas–Hoover capillary melting point apparatus or on a micro hot stage and are corrected; boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 137 or Model 257 spectrophotometers. Nuclear magnetic resonance spectra were run as 10% solutions in carbon tetrachloride on a Varian HA-100 spectrometer using tetramethylsilane as an internal reference. Chemical shifts are recorded as parts per million on the τ scale, coupling constants as hertz. Nuclear magnetic resonance data are recorded in the order: chemical shift (multiplicity, where s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet; coupling constant, interpretation). Gas chromatographic separations were made on one of two columns: column 1, a 10 ft × 0.25 in. stainless steel column packed with 20% GE-SF-96 silicon oil on 70–80 mesh Anakrom ABS; column 2, a 10 ft × 0.25 in. stainless steel column packed with 20% Reoplex 400 on 60–80 mesh Anakrom 300. Microanalyses were performed by T. Atanovich and associates of these laboratories and by Spang Microanalytical Laboratories, Ann Arbor, Mich. Gas chromatographic retention times are recorded relative to air.

Preparation of Chrysanthenone (13).—Chrysanthenone[20] was prepared by a variation[21] of the procedure of Hurst and Whitman.[19a] A solution of 13.332 g of verbenone[22] ($[\alpha]^{26}D$ −256°) in 400 ml of glacial acetic acid was irradiated as previously described[21] with a 450-W Hanovia mercury arc lamp for a period of 2 hr and 35 min. The reaction mixture was diluted with 400 ml of water and extracted with 1 l. of ether. The ethereal layer was separated, washed with three 250-ml portions of water, four 150-ml portions of saturated sodium carbonate, two 250-ml portions of water, and 100 ml of saturated sodium chloride solution, and dried over magnesium sulfate. Evaporation of ether under reduced pressure afforded 13.38 g of yellow liquid. The combined product from two runs was distilled from an 18-in. spinning band column to afford 1.742 g of a mixture of chrysanthenone (**13**) and ketone **20**, bp 70–80° (10.0 mm), 11.864 g of ketone **13**, bp 80–81° (11.2 mm), $[\alpha]^{26}D$ −12.2°, and 3.753 g of a mixture of isopiperitenone and 1,2-dimethyltricyclo[3.3.0.$0^{2,7}$]-octan-6-one, bp 70–80° (7.0–5.25 mm). The ketone **13**, bp 80–81° (11.2 mm), $[\alpha]^{26}D$ −12.2°, was used for the cleavage reactions described below.

Preparation of 2,4,4-Trimethylbicyclo[3.1.1]hept-2-en-6-one (20).—A solution of 7.923 g of chrysanthenone (**13**), $[\alpha]^{26}D$ −12.2°, in 450 ml of cyclohexane was irradiated as previously described[21] for a period of 130 min. Removal of solvent and flash distillation afforded 0.2588 g of liquid, bp 92–106° (44–72 mm), consisting of 2,4,4-trimethylbicyclo[3.1.0]hex-2-ene and 2,6,6-trimethylbicyclo[3.1.0]hex-2-ene and 3.193 g (40%) of liquid, bp 87–89° (10.0 mm), comprised of ketone **13** (39%) and ketone **20** (61%). The two isomers were separated by preparative glpc on an F & M Model 770 instrument using an 8 ft × 0.75 in. stainless steel column packed with 15% Carbowax 20M on 60–70 mesh Anakrom ABS at 100° and 150 ml/min helium flow. There was isolated 997 mg of ketone **20**, bp 89° (10.0 mm), the spectral data of which were consistent with those reported previously.[21] The material as prepared above from several combined runs was employed in the base cleavage reactions.

2,6,6-Trimethylbicyclo[3.2.0]hept-2-en-7-one (14) was prepared by the method of Beereboom[7,23] except that the pure ketone was isolated by fractional distillation as described by Erman.[21] After fractionation there was isolated from 200.0 g of geranic acid 25.78 g of ketone **14**, bp 81° (11.0 mm), containing only traces of *p*-methyl-α-methylstyrene. Redistillation afforded 18.80 g of ketone **14**, bp 88–89° (12.2 mm). Gas chromatographic analysis on column 2 at 100° and 60 ml/min helium flow showed a single peak. The spectral properties (nmr, uv, ir) were consistent with those reported by Beereboom.[7]

Alkaline Cleavage of Chrysanthenone (13). A. With 4.0 *M* 95% Methanolic Potassium Hydroxide (Run 3, Table I).—Essentially the method of de Pascual Teresa, *et al.*,[4] was employed for the cleavage of chrysanthenone with 95% methanolic potassium hydroxide. A solution of 504 mg (0.003 mol) of chrysanthenone, $[\alpha]^{26}D$ −12.2°, in 5 ml of 4.0 *M* 95% methanolic potassium hydroxide solution maintained under a nitrogen atmosphere was heated at reflux for a period of 16 hr. The bulk of the solvent was removed under reduced pressure; the mixture was diluted with 20 ml of water and was washed with 100 ml of ether. The ethereal layer was evaporated to yield 176 mg of residual liquid. Analysis of the liquid by glpc indicated the presence of 50% ketone **13** (17% yield). The aqueous layer was acidified with 9 ml of 2 *N* hydrochloric acid. The precipitated oil was extracted with 100 ml of ether; the ethereal layer was washed with two 10-ml portions of water, dried by swirling over magnesium sulfate for a period of 10 min, and evaporated to afford 519 mg of colorless crystals. The crystalline residue was immediately dissolved in 50 ml of ether and treated with 100 ml of a 2–3% ethereal diazomethane solution. The mixture was stored at 0–5° for 30 min, washed with 6 ml of dilute hydrochloric acid, water, 5 ml of saturated sodium bicarbonate, and water, and dried over magnesium sulfate. Evaporation of ether under reduced pressure and short-path distillation of the residual liquid afforded 343 mg of colorless liquid, bp 80–85° (4.0 mm), which was comprised of methyl 2,2,4-trimethyl-4-cyclohexene-1-carboxylate (**17b**), retention time 75.5 min (14%, 8% yield), and methyl 2,2,4-trimethyl-3-cyclohexene-1-carboxylate (**15b**), retention time 80.8 min (86%, 49% yield) (analyzed by gas chromatography on column 1 at 100° and 60 ml/min helium flow).

Each of the esters **15b** and **17b** was collected by preparative gas chromatography on the same column above. The gas chromatographic retention time and the infrared and nmr spectra of the ester **15b** were identical with the sample of methyl 2,2,4-trimethyl-3-cyclohexene-1-carboxylate (**15b**) prepared by Diels–Alder condensation of acrylic acid and 2,4-dimethyl-2,4-pentadiene and subsequent methylation, below.

The nmr and infrared spectral properties and gas chromatography retention time of the ester **17b** were identical with the ester **17b** obtained by acid-catalyzed rearrangement of the ester **15b**, below.

B. With 4 *M* Methanolic Potassium Hydroxide (Run 2, Table I).—Essentially the same procedure as described above for

(20) A sample of chrysanthenone was kindly furnished by Dr. Sanchez Bellido for initial experiments.

(21) W. F. Erman, *J. Amer. Chem. Soc.*, **89**, 3828 (1967).

(22) We are grateful to The Organic Chemicals Group, Glidden-Durkee Division, SCM Corp., Jacksonville, Fla., for a generous supply of verbenone.

(23) Ch. Balant, Ch. A. Vodoz, H. Kappeler, and H. Schinz, *Helv. Chim. Acta*, **34**, 722 (1951).

cleavage of **13** in 95% methanol was employed. Treatment of 500 mg (0.003 mol) of ketone **13** with 5 ml of 4.0 *M* methanolic potassium hydroxide solution maintained at reflux for 16 hr afforded, after work-up, methylation, and distillation, 230 mg of a mixture of ester **15b** (85%, 32% yield) and **17b** (15%, 6% yield), bp 85–100° (4.25–4.5 mm). The products were isolated and identified as above. From the ethereal washings there was recovered 161 mg of residual liquid. Analysis of the residue by glpc indicated the presence of 48% ketone **13** (16% yield).

C. With 2 *M* Methanolic Potassium Hydroxide (Run 1, Table I).—From 383 mg (2.5×10^{-3} mol) of ketone **13** in 5 ml of 2.0 *M* methanolic potassium hydroxide solution there was isolated after methylation and distillation 234 mg of a mixture, bp 70–80° (2.5 mm), comprised of **17b**, retention time 75.5 min (12%, 6% yield), **15b**, retention time 80.8 min (82%, 41% yield), methyl nerate (**18b**), retention time 111.8 min (2%, 1% yield), and methyl geranate (**19b**), retention time 148 min (4%, 2% yield) (analyzed by glpc as in A).

The esters **15b** and **17b** were isolated and identified as before. The esters **18b** and **19b** were similarly isolated by preparative glpc. Comparison of the glpc retention time and the infrared and nmr spectral properties of the esters **18b** and **19b** with those of authentic specimens of methyl nerate and methyl geranate, prepared below, proved the identity of these two materials.

D. With Potassium Hydride–Water (Run 4, Table I).—Essentially the procedure of Gassman, *et al.*,[13] was followed. To a rapidly stirred suspension of 10.0 g of 40% potassium hydride (4.0 g, 0.10 mol, of potassium hydride in mineral oil) in 12.5 ml of anhydrous tetrahydrofuran maintained under a nitrogen atmosphere at 0–5° was added 540 mg of water. The mixture was allowed to warm to room temperature, 26–27°, when 499 mg (0.003 mol) of chrysanthenone (**13**) in 12.5 ml of tetrahydrofuran was added. The mixture was stirred at 26–27° for 24 hr and cooled to 0–5° and 10 ml of water was added cautiously. The mixture was immediately washed with ether; the water layer was partitioned and acidified with 31 ml of 2 *N* hydrochloric acid. The precipitated acid was extracted with 100 ml of ether; the ethereal layer was washed with water and dried. The solvent was evaporated to yield 742 mg of residual liquid. Esterification with diazomethane afforded 189 mg of distilled liquid, bp 90–100° (4.0–9.0 mm), consisting of **15b** (91%, 28% yield) and **17b** (9%, 3% yield). Products were isolated and identified as above.

E. With Potassium *t*-Butoxide–Water (3:1) (Run 5, Table I).—Essentially the procedure of Gassman, *et al.*,[13] was employed except that tetrahydrofuran was utilized as solvent. To a solution of 4.001 g (0.036 mol) of potassium *t*-butoxide in 12.5 ml of tetrahydrofuran maintained at 26–27° under an atmosphere of argon was added 200 mg of water. To this mixture was added 507 mg (0.003 mol) of **13** in 12.5 ml of tetrahydrofuran. The mixture was stirred at room temperature for 24 hr and worked up as above for the potassium hydride run. Esterification afforded 391 mg of distilled liquid, bp 94–100° (4.2 mm), consisting of **15b** (76%, 49% yield) and **17b** (24%, 15% yield). From the ethereal washings there was isolated 59 mg (11%) of recovered ketone **13**.

F. With Potassium *t*-Butoxide–Water (1:1.4) (Run 6, Table I).—The procedure was the same as above except for the ratio of potassium *t*-butoxide to water.

G. With 4 *M* Methanolic Potassium Methoxide (Run 8, Table I).—A solution of 505 mg (0.003 mol) of **13** in 5.0 ml of 4.0 *M* methanolic potassium methoxide (prepared by addition of 1.55 g of potassium to 10 ml of dry methanol) was heated at reflux under a nitrogen atmosphere for 16 hr. The bulk of the methanol was removed under reduced pressure, and the mixture was diluted with 10 ml of water and extracted with 100 ml of ether. The ethereal layer was washed with five 10-ml portions of water, dried, and distilled to yield 228 mg of a mixture of **15b** (61%, 23% yield) and **17b** (39%, 14% yield). The water layer was acidified and the acid fraction was esterified as in A above to yield 159 mg of ester mixture, bp 68–75° (3.0 mm), consisting of **15b** (61%, 16% yield) and **17b** (39%, 10% yield).[24]

H. With 1 *M* Methanolic Potassium Methoxide (Run 7, Table I).—A solution of 250 mg (1.7×10^{-3} mol) of chrysanthenone (**13**) in 5.0 ml of 1.0 *M* anhydrous methanolic potassium methoxide was heated at reflux under a nitrogen atmosphere for a period of 16 hr. The bulk of the methanol was removed under reduced pressure, and the residue was diluted with 5.0 ml of water and extracted with 50 ml of ether. The ethereal layer was washed with four 10-ml portions of water and dried over magnesium sulfate for 4 hr; the solvent was evaporated and the product was subjected to short-path distillation to afford 157 mg of colorless liquid, bp 70–80° (2.5 mm). Gas chromatography as described in A, above, indicated the presence of five compounds: chrysanthenone (**13**) (14%, 9% yield), ester **17b** (21%, 11% yield), ester **15b** (31%, 16% yield), methyl nerate (**18b**) (12%, 6% yield), and methyl geranate (**19b**) (22%, 12%, yield).

Each of the compounds 1–5 was collected by preparative gas chromatography as described above. The nmr and infrared spectra and gas chromatography retention times of each of the compounds **15b**, **17b**, **18b**, and **19b** were identical with authentic specimens as described above.

I. With Potassium *t*-Butoxide in *t*-Butyl Alcohol (Run 9, Table I).—A solution of 204 mg (1.7×10^{-3} mol) of chrysanthenone (**13**) in 5.0 ml of a solution of 1.0 *M* potassium *t*-butoxide in *t*-butyl alcohol was heated at reflux (80°) under a nitrogen atmosphere for a period of 16 hr. The mixture was cooled to 40° and the bulk of the *t*-butyl alcohol was removed under reduced pressure. The residue was diluted with 10 ml of water and extracted with 100 ml of ether. The ethereal layer was washed with four 10-ml portions of water and dried over magnesium sulfate. Evaporation of solvent and short-path distillation afforded 43 mg of liquid, bp 141° (10.5 mm), comprised of *t*-butyl 2,2,4-trimethyl-4-cyclohexene-1-carboxylate (**17c**) (37%, 5% yield) and *t*-butyl 2,2,4-trimethyl-3-cyclohexene-1-carboxylate (**15c**) (63%, 8% yield) (analyzed on column 1 at 135° and 60 ml/min helium flow). The two peaks were isolated by preparative gas chromatography on the same column and identified by comparison of the infrared and nmr spectrum of each with the authentic specimens prepared below.

The combined water layers from above were acidified by dropwise addition of concentrated hydrochloric acid; the product was extracted with 100 ml of ether; the ethereal layer was washed with two 10-ml portions of water and dried over magnesium sulfate. Evaporation of solvent afforded 150 mg of residual carboxylic acid, infrared λ 3.5–3.9, 5.85–5.9 μ, which was dissolved in 50 ml of ether and treated with 50 ml of 2% diazomethane solution. After storage at 0–5° for 2 hr the excess diazomethane was destroyed by cautious addition of 12 ml of 10% hydrochloric acid; the ethereal solution was washed with three 20-ml portions of water and dried over magnesium sulfate. Evaporation of solvent and short-path distillation afforded 125 mg of colorless liquid, bp 70–75° (2.5 mm), which consisted of methyl ester **17b** (38%, 19% yield) and methyl ester **15b** (62%, 31% yield). Methyl nerate and methyl geranate were not observed in the reaction mixture. The two esters (**17b** and **15b**) were collected and their identities revealed by nmr and infrared spectral comparisons with authentic specimens.

Base Cleavages of 2,4,4-Trimethylbicyclo[3.1.1]hept-2-en-6-one (20) (Runs 10–14, Table I).—Cleavages of the ketone **20** were performed in the same manner as the cleavages of ketone **13**. In each instance 500 ± 5 mg of ketone was treated with base. Yields are based upon distilled ester product. Results are recorded in Table I.

Base Cleavages of 2,6,6-Trimethylbicyclo[3.2.0]hept-2-en-7-one (14).—Alkaline cleavages of ketone **14** were performed as above for ketone **13** using 500 ± 4 mg of ketone **14**. Results are recorded in Table II. Best yields of esters **16b** and **22b** were obtained under conditions of run 3, Table II. Isolation of products from a 1.0-g scale run is described below.

Preparation of Methyl 2-(3-methyl-2-cyclopentenyl-2,2-dimethylacetate (16b) and Methyl 2-(3-methyl-3-cyclopentenyl)-2,2-dimethylacetate (22b).—A solution of 1.005 g (6.8×10^{-3} mol) of ketone **14** was treated as described in E above with potassium *t*-butoxide–water except that double the quantities of reagents were used. After work-up, esterification, and distillation of product, there was isolated 470 mg of colorless liquid, bp 120–126° (4.0–4.5 mm), which was comprised of ester **16b** (56%, 22% yield) and ester **22b** (44%, 17% yield). The two esters were isolated by preparative glpc on column 2 at 100° and 120 ml/min helium flow. Final purification was made by short-path distillation.

The ester **16b**, retention time 26.5 min, was isolated as a colorless liquid: ir (CCl_4) 5.77 (carbonyl), 6.02 μ (olefin); nmr (CCl_4)

(24) The acid products undoubtedly arise *via* an S_N2 displacement by methoxide on the methyl ester carbon: see, for example, J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Amer. Chem. Soc.*, **72**, 2378 (1950); R. A. Sneen and A. M. Rosenberg, *J. Org. Chem.*, **26**, 2099 (1961); and W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **74**, 5683 (1952).

τ 4.91 (m, olefinic proton), 6.46 (s, ester methyl), 7.10 (broad m, C-1), 7.8–8.4 (m, C-4, C-5 protons), 8.31 (m, C-3 methyl protons), 8.98, 9.01 (singlets, *gem*-dimethyls). The nmr spectrum of **16b** in $CDCl_3$ was identical with that reported by Beereboom.[7]

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.50; H, 9.85.

The ester **22b**, retention time 39.5 min, was isolated as a colorless liquid: ir (CCl_4) 5.77, 9.01 μ; nmr (CCl_4) τ 4.90 (m, C-4 proton), 6.46 (s, ester methyl protons), 7.52 (quintet with fine splitting, C-1 proton), 7.8–8.1 (m, C-2 and C-5 protons), 8.39 (s, C-2 methyl protons), 8.96 (s, *gem*-dimethyl protons).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.47; H, 9.90.

Preparation of Methyl Nerate (18b) and Methyl Geranate (19b).—Treatment of 10.00 g (0.06 mol) of commercial geranic acid (Fritzsche Bros., Inc.) with excess diazomethane afforded 7.346 g (68%) of the corresponding methyl ester mixture, bp 95–96° (2.5 mm) [lit.[25] bp 90–92° (3 mm)], comprised of 28% methyl nerate and 72% methyl geranate. The two isomers **18b**, relative retention time 12.3 min, and **19b**, relative retention time 15.0 min, were separated by gas chromatography on column 1 at 150° and 60 ml/min helium flow or on an 8 ft × 0.75 in. column packed with 15% Carbowax 20 M on 60–70 mesh Anakrom ABS at 150° and 100 ml/min helium flow.

Methyl nerate was isolated as a colorless liquid: ir (neat) 5.79 (conj C=O), 6.05 (olefin) 8.58 μ (ester); nmr (CCl_4) τ 4.42 (s, C-2 proton), 4.95 (t with fine splitting, C-6 proton), 6.40 (s, ester methyl), 7.3–7.6 (m, C-4 protons), 7.8–8.1 (m, C-5 protons), 8.15 (s, C-3 methyl), 8.35, 8.40 (s, C-7 methyls).

Methyl geranate was isolated as a colorless liquid: ir (neat) 5.79 (C=O), 6.03 (olefin), 8.1–8.2, 8.63 μ (ester); nmr (CCl_4) τ 4.38 (s, C-2 proton), 4.96 (m, C-6 proton), 6.37 (s, ester methyl), 7.83 (s, with fine splitting, C-3 methyl), 8.32, 8.40 (s, C-7 methyls).

Preparation of 2,2,4-Trimethyl-3-cyclohexene-1-carboxylic Acid (15a).—Essentially the procedure of Jitkow and Bogert[14] was employed with the following exceptions. A mixture of 65.60 g (0.68 mol) of 2,4-dimethyl-1,3-pentadiene and 73.90 g (1.03 mol) of acrylic acid was heated in a glass-lined autoclave under a back pressure of 1500 psi nitrogen at 155–160° for 16 hr. After work-up and distillation from a 12-in. Vigreux column there was isolated 58.118 g (51%) of **15a**, bp 125° (3.1 mm), mp 79–81°. One recrystallization from acetic acid–water afforded **15a** as colorless plates: mp 84.0–85.1° (59% recovery); ir (CCl_4) 3.0–4.0 (carboxyl OH), 5.90 μ (C=O); nmr (CCl_4) τ 4.90 (m, C-3 proton), 7.6–7.8 (m, C-5 proton), 7.8–8.3 (m, C-1 and C-6 protons), 8.32 (broad s, C-4 methyl), 8.82, 9.01 (C-2 *gem*-dimethyls).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.46; H, 9.72.

Methyl 2,2,4-Trimethyl-3-cyclohexene-1-carboxylate (15b) was prepared either by treatment of the acid **15a** with excess diazomethane or by treatment of the corresponding acid chloride with methanol.

From 342 mg (2.2×10^{-3} mol) of acid **15a**, mp 84.0–85.1°, in 50 ml of ether treated with 20 ml of 2% ethereal diazomethane for a period of 1 hr, there was obtained 289 mg (78%) of the ester **15b**: bp 127° (7.5 mm); ir (neat) 5.75 (C=O), 8.25, 8.65, 9.63 μ; nmr (CCl_4) τ 5.00 (s, C-3 proton), 6.45 (s, ester methyl), 7.7–8.0 (m, C-5 allyl), 8.0–8.5 (m, C-1 and C-6 protons), 8.42 (s, C-4 methyl), 8.97, 9.15 (C-2 *gem*-dimethyls).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.51; H, 9.73.

Isomerization of 2,2,4-Trimethyl-3-cyclohexene-1-carboxylic Acid (15a). A. With Ethereal Hydrogen Chloride.—A solution of 158 mg (9.4×10^{-4} mol) of the acid **15a**, mp 84–85°, in 100 ml of anhydrous ether saturated with dry hydrogen chloride was stored at 26–27° for a period of 16 hr. The mixture was washed cautiously with three 20-ml portions of water, dried, and evaporated to afford 149 mg of colorless oil: ir (neat) 3–4 (carboxyl OH), 5.7–5.9 μ broad (lactone C=O and carboxylic acid C=O). The oil was dissolved in 10 ml of ether and treated with 20 ml of 2–3% ethereal diazomethane and this mixture was stored at 0–5° for 20 min. Excess diazomethane was destroyed by addition of 5 ml of 10% hydrochloric acid. The ethereal layer was washed with 10 ml of 10% hydrochloric acid, 5 ml of saturated sodium bicarbonate, and two 10-ml portions of water and dried over magnesium sulfate. Evaporation of solvent and short-path distillation afforded 140 mg of distillate, bp 120–144° (7.75–8.50 mm). Analysis by temperature-programmed gas chromatography on column 2 at 100–150° indicated the presence of three components: ester **17b**, 20% (16% yield); ester **15b**, 40% (33% yield); and lactone **21**, 20% (18% yield).

The two esters **17b** and **15b** were collected by preparative gas chromatography on column 2 at 100° and 60 ml/min helium flow as liquids and identified by spectral comparisons, respectively, with the authentic ester **15b** prepared from the acid **15a** above, and the ester **17b**, prepared by rearrangement of the ester **15b** with boron trifluoride etherate, below.

The lactone **21** was collected on the same column at 150° as colorless crystals, mp 58.5–61.5°, identical with the lactone prepared below, procedure B.

Treatment of 96.2 mg of the acid **15a** in a similar manner with ethereal hydrogen chloride for a period of 3 hr afforded 61 mg of a mixture of **17b**, 16% (9% yield); **15b**, 80% (47% yield); and **21**, 5% (3% yield).

B. With Boron Trifluoride Etherate in 1,2-Dichloroethane. Preparation of 2,2,4-Trimethyl-4-*cis*-hydroxy-3-cyclohexene-1-carboxylic Acid Lactone (21).—A solution of 1.008 g (0.006 mol) of the acid **15a**, mp 81.0–83.1°, in 23 ml of 1,2-dichloroethane containing 8.0 ml of boron trifluoride etherate was heated at reflux for 75 min. The bulk of the dichloroethane was removed under reduced pressure; the residue was dissolved in 100 ml of ether, and the ethereal layer was washed with 25 ml of water, 10 ml of 10% sodium hydroxide, and four 20-ml portions of water and dried over magnesium sulfate. Evaporation of solvent afforded 679 g (70%) of residual oil which, on analysis by gas chromatography as above, indicated the presence only of lactone **21**. Short-path distillation gave 412 mg (42%) of colorless oil, bp 120–130° (4.5 mm). The oil crystallized from petroleum ether afforded 205 mg (21%) of the lactone **21** as colorless prisms: mp 66.8–67.8°; ir (CCl_4) 5.70 μ (bicyclic lactone[26]); nmr (CCl_4) τ 7.91–8.60 (m, methylene and methyne protons), 8.70 (s, C-4 methyl), 8.90, 8.96 (s, C-2 *gem*-dimethyl).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6. Found: C, 71.5; H, 9.5.

Isomerization of Methyl 2,2,4-Trimethyl-3-cyclohexene-1-carboxylate (15b).—A solution of 964 mg (5.3×10^{-4} mol) of the ester **15b**, bp 122° (7.25 mm), in 20 ml of 1,2-dichloroethane containing 6.0 ml of boron trifluoride etherate was heated at reflux for 30 min. The mixture was cooled to room temperature, diluted with 50 ml of ether, and washed with two 15-ml portions of water, 15 ml of saturated sodium bicarbonate, and two 15-ml portions of water, dried, and evaporated to yield 844 mg of colorless liquid. Distillation from a modified Hickman still afforded 425 mg of colorless liquid, bp 120–144° (7.75–8.50 mm), consisting of ester **17b**, 70% (31% yield), and ester **15b**, 30% (13% yield), as analyzed by programmed-temperature gas chromatography on column 2 at 100–150°.

The two esters were isolated by gas chromatography on column 2 at 100° and 60 ml/min helium flow. The ester **15b** was identical in every respect with the ester **15b** prepared directly from acid **15a** above. The ester **17b** was isolated as a colorless liquid: ir (neat) 5.75 (C=O), 8.1–8.9, 8.96, 8.75 μ; nmr (CCl_4) τ 4.75 (m, C-5 proton), 6.46 (s, ester methyl), 7.75–8.3 (m, C-1, C-3, C-6 protons), 8.40 (broad s, C-4 methyl), 9.06 (s, *gem*-dimethyl protons).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.48; H, 9.82.

Treatment of 436 mg (2.4×10^{-4} mol) of the ester **15b**, bp 85–88° (5.25–6.25 mm), in 10.0 ml of dichloroethane containing 3.0 ml (3.357 g) of boron trifluoride etherate at reflux for 1.0 hr afforded 233 mg of liquid, bp 125–140° (7.5 mm), containing ester **17b**, 14% (8% yield); ester **15b**, 6% (2% yield); lactone **21**, 50% (29% yield); and a mixture of ethyl 2,2,4-trimethyl-3-cyclohexene-1-carboxylate (**15d**) and ethyl 2,2,4-trimethyl-4-cyclohexene-1-carboxylate (**17d**), 30% (16% yield).

Preparative gas chromatography on column 2 at 150° and 60 ml/min helium flow separated the esters **17b** and **15b** (relative retention time 9.0 min) from the esters **15d** and **17d** (relative retention time 14.2 min) and the lactone **21** (relative retention time 16.5 min). The two isomers **17b** and **15b** were separated

(25) G. I. Samokhvalov, M. A. Miropal'skaya, L. A. Vakulova, and N. A. Preobrazhenskii, *Dokl. Akad. Nauk, SSSR*, **84**, 1179 (1952); *Chem. Abstr.*, **47**, 3277 (1953).

(26) P. Wilder, Jr., and A. Winston, *J. Amer. Chem. Soc.*, **77**, 5598 (1955).

and collected on the same column at 100° and 60 ml/min helium flow. The lactone was recollected at 150° for final purification.

The ester mixture **15d–17d** could not be separated by glpc. That the latter mixture was indeed composed of **17d** and **15d** was shown by the infrared [5.76 μ (ester C=O)] and nmr spectra. The nmr spectrum indicated the presence of ~70% **17d** and 30% **15d**. Principal peaks of the nmr spectrum of **15d** were assigned as follows: τ 5.0 (s, C-3 proton), 7.9 (q, ester methylene), 7.9–8.3 (m, C-1, C-4, C-5 protons), 8.38 (s, C-4 methyl), 8.75 (t, ester methyl), 8.91, 9.11 (s, C-2 *gem*-dimethyls). Nmr signals of isomer **17d** were assigned as follows: τ 4.72 (m, C-5 proton), 7.9 (q, ester methylene), 7.9–8.3 (m, C-1, C-4, C-5 protons), 8.38 (s, C-4 methyl), 8.75 (t, ester methyl), 9.02, 9.03 (s, C-2 *gem*-dimethyls).

Preparation of *t*-Butyl 2,2,4-Trimethyl-3-cyclohexene-1-carboxylate (15c).—To a solution of 5.587 g (0.050 mol) of potassium *t*-butoxide in 45 ml of *t*-butyl alcohol (freshly distilled over sodium) was added 4.00 g of the acid chloride of **15a** prepared in the same manner as described for preparation of ester **15b** and this mixture was stirred at room temperature under a nitrogen atmosphere for a period of 45 min. After removal of the bulk of the *t*-butyl alcohol under reduced pressure the mixture was diluted with 25 ml of water and extracted with 150 ml of ether. The ethereal layer was washed with four 25-ml portions of water and dried over magnesium sulfate. Evaporation of solvent afforded 1.699 g of residual liquid which on short-path distillation afforded 862 mg (18%) of **15c** as a colorless liquid: bp 141° (10.5 mm); ir (neat) 5.76 μ; nmr (CCl_4) τ 5.12 (broad s, C-3), 8.0 (t, J = 6.1 Hz, C-1), 8.2–8.4 (m, C-5, C-6), 8.5 (s, fine splitting, C-4 olefinic methyl), 8.69 (s, *t*-butyl methyls), 9.02, 9.20 (s, C-2 *gem*-dimethyls).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.09; H, 10.79.

Treatment of 2,2,4-Trimethyl-3-cyclohexene-1-carboxylic Acid (15a) with Base. A. With Potassium *t*-Butoxide–Water (3:1)–THF.—To a solution of 4.011 g (0.036 mol) of potassium *t*-butoxide in 12.5 ml of tetrahydrofuran was added 200 mg of water followed by 500 mg of the acid **15a**, mp 84–85°, as described in cleavage reaction E, above. The mixture was stirred at 26–27° for 24 hr when the bulk of the THF was removed under reduced pressure. The residue was dissolved in 25 ml of water and the water layer was washed with ether. The cold aqueous layer was acidified with 23 ml of 2 N hydrochloric acid and the acid was extracted in the usual fashion to furnish 347 mg (70%) of crystalline acid. Esterification with diazomethane afforded 300 mg of ester, bp 80–105° (0.5–1.0 mm), which on analysis by glpc on two different columns (0.25 in. × 10 ft columns packed with 20% SE-30 silicon oil and with 20% Carbowax 20M TMPA on 60–80 mesh AW DMCS-300) showed a single peak of retention time identical with ester **15b**. (The isomeric ester **17b** was separated cleanly from **15b** under these conditions.) The infrared spectrum of the collected material was identical in every major respect with ester **15b** prepared above.

B. With 4 *M* 95% Methanolic Potassium Hydroxide.—A solution of 503 mg of acid **15a** in 5 ml of 4.0 *M* 95% methanolic potassium hydroxide solution was heated at reflux for 16 hr as in cleavage run 3 above. Removal of solvent, dilution with 20 ml of water, acidification, and ether extraction afforded 419 mg (84%) of recovered acid, mp 79–81°. Esterification with diazomethane afforded 347 mg of ester, bp 90–100° (1.0 mm). Analysis by glpc as described above for the attempted base isomerization with potassium *t*-butoxide–water indicated only ester **15b**.

Acknowledgments.—The authors are indebted to Mr. Logan Stone for his skilled technical assistance and to Mr. Peter Bakuzis for his critical review of the manuscript.

Registry No.—**15a**, 13746-43-5; **15b**, 19766-10-0; **15c**, 19766-11-1; **15d**, 19766-12-2; **16b**, 19766-13-3; **17b**, 19766-14-4; **17d**, 19766-15-5; **18b**, 1862-61-9; **19b**, 1189-09-9; **21**, 19766-16-6; **22b**, 19766-17-7.

Syntheses, Spectra, and Identification of Isomeric, Fused-Ring Paracyclophane Derivatives

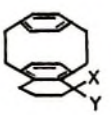
MAURICE J. NUGENT AND TYRONE L. VIGO

Department of Chemistry, Tulane University, New Orleans, Louisiana

Received November 26, 1968

We report the stereoselective syntheses and chemical structure proof of the *exo* (**1a**) and *endo* (**1b**) isomers of 17-hydroxymethyl-4,5-tetramethylene[2.2]paracyclophane. We have also examined the spectral properties of these and related isomeric, fused-ring paracyclophanes, and have discovered an interesting nmr correlation which is indicative of *exo* or *endo* substitution in these systems.

The acetolysis of 2-([2.2]paracyclophenyl)ethyl *p*-toluenesulfonate involves intermediate formation of a phenonium ion.[1] Because of the presence of two aromatic rings in paracyclophanes, several questions arise concerning the stereochemistry of this acetolysis reaction. To examine the stereochemical details of solvolysis reactions of [2.2]paracyclophane derivatives,[2] we have synthesized the *exo* (**1a**) and *endo* (**1b**) isomers of 17-hydroxymethyl-4,5-tetramethylene[2.2]paracyclophane. In this paper we discuss the details of the stereoselective syntheses. We also report an interesting nmr correlation that may be a general method for determining the *exo* or *endo* stereochemistry at the 17 position of 4,5-tetramethylene[2.2]paracyclophanes that have an oxygen atom in the substituent group.

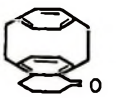


1a, Y = CH_2OH, X = H

1b, Y = H, X = CH_2OH

Results

Synthetic.—The starting material for the syntheses of alcohols **1a** and **1b** is 4,5-tetramethylene-17-oxo-[2.2]paracyclophane (**2**).[3] We were not consistently

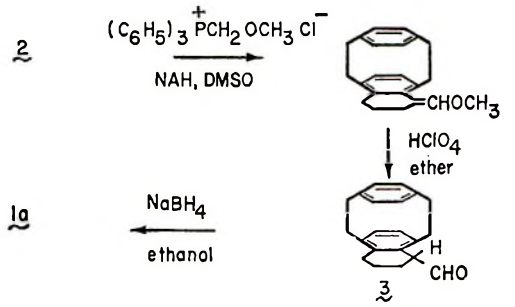


2

(1) D. J. Cram and L. A. Singer, *J. Amer. Chem. Soc.*, **85**, 1075 (1963).
(2) M. J. Nugent and T. L. Vigo, unpublished results.
(3) D. J. Cram, C. K. Dalton, and G. R. Knox, *J. Amer. Chem. Soc.*, **85**, 1088 (1963).

able to obtain satisfactory yields of 2; therefore the modified synthetic sequence described in the Experimental Section was used. The synthesis of **1a** in 60% yield from ketone 2 is shown in Scheme I. The α

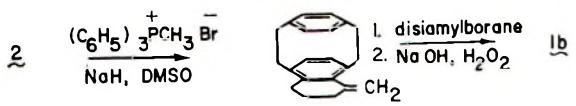
SCHEME I



carbon of **3** completely incorporates deuterium after 68 hr at room temperature in a mixture of sodium–deuterium oxide–tetrahydrofuran[4] as was evidenced by the collapse of the aldehyde proton doublet to a singlet. The starting aldehyde is recovered from sodium–water–tetrahydrofuran reaction mixture in 65% yield after the same period of time. Nearly quantitative reduction of this recovered aldehyde with sodium borohydride shows no contamination by the *endo* isomer **1b**.

The *endo* alcohol **1b** was synthesized *via* 2 using a Wittig reaction followed by hydroboration with disiamylborane[5] as is shown in Scheme II. Alcohol **1b** is

SCHEME II



isomeric with alcohol **1a** and has the same general structure as was determined spectroscopically. The conversion of ketone 2 into alcohol **1b** proceeds in 64% over-all yield.

Spectral.—We have examined the hydroxyl stretching frequency of the alcohols **1a** and **1b** and found at high dilution (0.003 *M*) in carbon tetrachloride that **1a** had its only hydroxyl absorption at 3640 cm^{-1}, while **1b** showed hydroxyl absorption at 3634 cm^{-1}.[6] These frequencies are in the region of free hydroxyl absorptions 3650–3590 cm^{-1},[7] and higher than the π-bonded absorption at 3601 cm^{-1} for 2-phenylethanol.[8]

We have also examined the nmr spectra of various 17-substituted 4,5-tetramethylene[2.2]paracyclophanes. An *exo* or *endo* oxygen-containing substituent at this position, causes two peaks which are more intense than any other peaks to appear between 6 and 7 ppm. As an example, this part of the nmr spectra of **1a** and **1b** are shown in Figure 1. The separation of

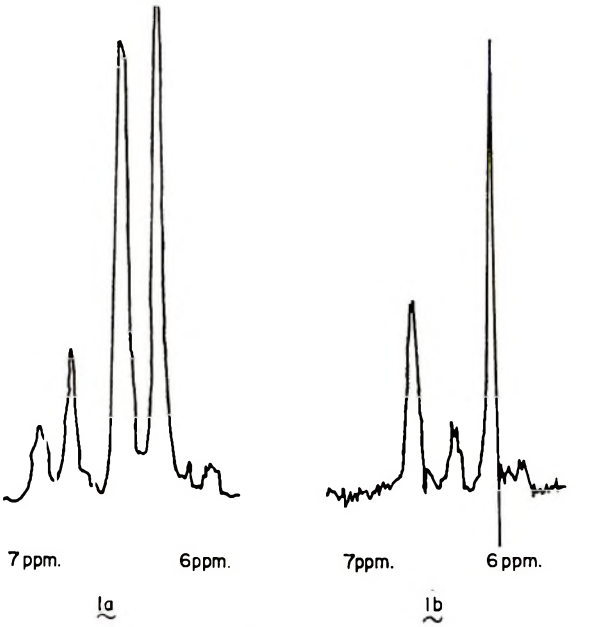


Figure 1.—Partial nmr spectra of **1a** and **1b** in deuteriochloroform.

these intense peaks is smaller for the *exo* isomer than for the *endo* isomer as is shown in Table I. In fused-

TABLE I

STEREOCHEMICAL CORRELATION OF ISOMERIC, FUSED-RING PARACYCLOPHANES WITH NMR SPECTRA

Stereochemistry	17 substituent	Integral of low field peak	Integral of high field peak	Separation, Hz
endo	OH (**5b**)[a]	1.7	1.0	13
endo	OAc[b]	1.4	1.0	17.5
endo	CH_2OH (**1b**)	0.8	1.0	22.5
endo	CH_2OTs[b]	0.9	1.0	19
exo	OH (**5a**)[a]	0.7	1.0	5
exo	CHO	1.5	1.0	4.5
exo	CH_2OH (**1a**)	1.0	1.0	10
exo	CH_2OTs[b]	1.2	1.0	10

[a] M. J. Nugent, *Chem. Commun.*, 1160 (1967). [b] M. J. Nugent and T. L. Vigo, unpublished results.

ring paracyclophane derivatives with no stereochemistry at the 17 position such as 2, the olefin precursor of **1b**, and the methylvinyl ether precursor of **1a**, only one very intense peak is observed in the region between 6 and 7 ppm, or several intense peaks are observed, no two of which can be described as the most intense in this portion of the spectrum.

Discussion

The *exo* stereochemistry of **1a** follows from its aldehyde precursor being the more stable, less hindered *exo* isomer.[9,10] We have demonstrated that the aldehyde obtained from the methylvinyl ether derivative of 2 is recovered in 65% yield under conditions where enolization is complete as was evidenced by complete deuterium exchange in deuterium oxide. Since side products are formed in this reaction, as was demonstrated by tlc, this result does not mean that the reaction mixture at

(4) This procedure is similar to that described by M. Rosenblum and F. W. Abbate, *J. Amer. Chem. Soc.*, **88**, 4178 (1966).

(5) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963), and references cited therein.

(6) These measurements were made on a Beckman IR-7 in silica cells of 10-mm path length (Pyrocell Manufacturing Co. No. S-22-350) which transmit 90% of the light in this region. We are indebted to the chemistry faculty at Louisiana State University of New Orleans for the use of this instrument.

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1964, p 96.

(8) D. S. Trifan, J. C. Weinmann, and L. P. Kuhn, *J. Amer. Chem. Soc.*, **79**, 6566 (1957).

(9) That the *endo*-17-substituted isomer is more sterically hindered has been demonstrated in the case of the *exo*- and *endo*-17-hydroxy-4,5-tetramethylene[2.2]paracyclophanes, **5a** and **5b**, respectively.[10]

(10) Reference *a*, Table I.

equilibrium consists of 65% *exo* aldehyde and 35% *endo* aldehyde. All of our attempts to prepare the *endo* aldehyde or carboxylic acid have been unsuccessful.

The assignment of *endo* stereochemistry to alcohol **1b** is based primarily on the synthetic method. Disiamylborane usually adds to cyclic olefins from the least hindered side.[5] Thus, since the alcohols **1a** and **1b** are isomeric, one is led to the assignment of *endo* stereochemistry to alcohol **1b**.

The ir absorptions of the hydroxyl groups of dilute samples of **1a** and **1b** occur for both isomers in the 3634–3640-cm^{-1} region. In the next lower homologs, *exo*-(**5a**) and *endo*-17-hydroxy-4,5-tetramethyleneparacyclophane (**5b**), hydroxyl absorption occurs at 3617–3618 cm^{-1}.[10] In neither case is there any evidence that the electron cloud above the planes of the aromatic rings in paracyclophane has more affinity for π bonding to hydroxyl hydrogens than the π cloud between the aromatic rings in these fused-ring paracyclophane derivatives.

The data in Table I show that the separation between the most intense peaks in the 6–7-ppm region of the nmr spectra of fused-ring paracyclophane derivatives varies with stereochemistry at the 17 position in a predictable way. We have examined the separation of these intense peaks for the *endo*-substituted derivatives and found that the separation varies from 13 to 22.5 Hz, while for *exo*-substituted derivatives the separation varies from 5 to 10 Hz. The applicability of this correlation in the same way to alcohols **5a** and **5b** as well as to alcohols **1a** and **1b** lends credence to the stereochemical assignments.

Experimental Section

δ-[2.2]Paracyclophanylbutyric Acid Methyl Ester.—β-[2.2]-Paracyclophanoylpropionic acid[3] (18.8 g, 61 mmol) and 9.4 ml (0.18 mol) of 100% hydrazine hydrate were dissolved in 450 ml of diethylene glycol which contained 18.7 g of potassium hydroxide. The conditions of this reaction were essentially those used for reduction of 4,5-tetramethylene-?-(γ-carboxylpropyl)-[2.2]-paracyclophane.[3] The reaction mixture was poured into 3 l. of water, and the aqueous phase was washed three times with ether. The aqueous phase was acidified with concentrated sulfuric acid and the resulting dark gum was dissolved in chloroform. The chloroform solution was washed with water until the washings were neutral, separated, dried over sodium sulfate, and evaporated to dryness. The dark gum thus obtained was dissolved in a mixture of 260 ml of methanol and 3.5 ml of concentrated sulfuric acid and was refluxed for 1 hr. The reaction mixture was then poured into 1 l. of water and extracted four times with ether. The combined ethereal extracts were washed with water, dried over sodium sulfate, and evaporated. The resulting brown oil was chromatographed on silica gel; the ester was eluted with 1:9 ether–petroleum ether (bp 35–80°) (5.5 g, 30% yield); two recrystallizations from ether produced an analytical sample, mp 89.5–91.5°.

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.63; H, 7.87.

4,5-Tetramethylene-17-oxo[2.2]paracyclophane (2).—Equal weights of δ-[2.2]paracyclophanylbutyric acid methyl ester and sodium hydroxide were refluxed for 5 min in 1:1 ethanol–water. Acidification of the cooled (0°) solution with concentrated hydrochloric acid produced δ-[2.2]paracyclophanylbutyric acid in 96% yield, mp 121–124° (lit.[3] mp 123–124°). The dry acid (4.60 g, 15.6 mmol) was dissolved in 42.4 ml of trifluoroacetic anhydride and stirred at room temperature for 2 hr. The reaction mixture was then poured into an ice slush containing excess sodium bicarbonate. Water was added and the mixture was extracted four times with ether. The ethereal extracts were washed with water until neutral, separated, and dried over sodium sulfate. Evaporation of the ether produced an orange oil which was chromatographed on grade III neutral alumina to yield 2.90 g (67%) of the desired crude ketone, mp 108–113° (lit.[3] mp 107–108°). Recrystallization from ether produced material melting from 111 to 113°.

***exo*-17-Formyl-4,5-tetramethylene[2.2]paracyclophane (3).**—The Wittig reagent from (methoxymethyl)triphenylphosphonium chloride (3.43 g, 10.0 mmol) was prepared using the method of Corey, *et al.*[11] Ketone **2** (1.38 g, 5.0 mmol) in 15 ml of warm dimethyl sulfoxide was added at room temperature and the reaction mixture was heated at 65° for 21 hr with stirring. The reaction was quenched by careful addition of water, then extracted with five portions of ether. The combined ethereal extracts were washed seven times with water, dried over sodium sulfate, and evaporated to yield a yellow semisolid. This mixture was dissolved in a small amount of benzene and chromatographed on silica gel. The crude vinyl ether (0.90 g, 62%) was eluted with 1:9 ether–petroleum ether. The melting point of this material was 83–86°. Recrystallization from petroleum ether gave product melting at 90–93°. The methylvinyl ether (1.12 g, 3.8 mmol) was dissolved in 30 ml of ether and the solution was heated on a steam bath. Approximately 10 ml of ether saturated with 72% perchloric acid was added in portions over a 30-min period. The reaction mixture was then cooled and washed with water until neutral. Evaporation of the ether produced the *exo* aldehyde **3** (1.02 g, 97%), mp 130–131°. An analytical sample, mp 132–134°, was obtained after three recrystallizations from ether–petroleum ether.

Anal. Calcd for $C_{21}H_{22}O$: C, 86.85; H, 7.64. Found: C, 86.69; H, 7.60.

***exo*-17-Hydroxymethyl-4,5-tetramethylene[2.2]paracyclophane (1a).**—Sodium borohydride (0.21 g, 5.6 mmol) was added to a solution of pure aldehyde **3** (0.78 g, 2.8 mmol) in 14 ml of 95% ethanol. After 2.5 hr, water was added and the reaction mixture was extracted three times with ether. The ethereal extracts were washed with water and dried over sodium sulfate. Evaporation of the solvent produced a pale yellow oil when mixed with ether–petroleum ether to give a quantitative yield of product of mp 118–121°. An analytical sample, mp 122–123.5°, was obtained by recrystallization from ether–petroleum ether.

Anal. Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.01; H, 8.23.

17-Methylene-4,5-tetramethylene[2.2]paracyclophane was prepared by the Wittig reaction of triphenylmethylphosphonium bromide (4.28 g, 12 mmol) with ketone **2** (2.2 g, 8 mmol) at room temperature; the experimental conditions were essentially the same as those in the Wittig reaction described above. The olefin product was isolated in 86% yield (1.75 g, mp 94–98°). Recrystallization from 1:1 methanol–ether gave an analytical sample, mp 99–101°.

Anal. Calcd for $C_{21}H_{22}$: C, 91.92; H, 8.08. Found: C, 92.16; H, 7.86.

***endo*-17-Hydroxymethyl-4,5-tetramethylene[2.2]paracyclophane (1b)** was prepared by hydroboration of 17-methylene-4,5-tetramethylene[2.2]paracyclophane with disiamylborane, followed by alkaline oxidation with hydrogen peroxide.[5] The disiamylborane was generated by reaction of 3.3 ml (30 mmol) of 2-methyl-2-butene with 0.45 g (12 mmol) of sodium borohydride in 12 ml of diglyme and 2.08 ml (2.24 g, 16 mmol) of boron trifluoride etherate. The disiamylborane thus produced was allowed to react with 1.4 g (5 mmol) of olefin in 12 ml of diglyme at room temperature for 23 hr. The work-up was carried out according to the published procedure,[5] and the resulting oil was chromatographed on silica gel. A solution of 1:3 ether–hexane eluted the desired alcohol (1.1 g) in 75% yield. Recrystallization from ether gave an analytically pure sample, mp 121.5–123.5°. A mixture of this pure alcohol **1b** with its epimer **1a** gave a 20° depression of melting point.

Anal. Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 85.95; H, 8.18.

Isomerization Experiments with *exo*-17-Formyl-4,5-tetramethylene[2.2]paracyclophane (3).—To a solution of tetrahydrofuran which had been redistilled from lithium aluminum hydride and 1 ml of redistilled deuterium oxide was added 3 mg of sodium. After the reaction subsided, 87 mg of aldehyde **3** in 4 ml of redistilled tetrahydrofuran was added and the reaction was allowed to proceed at room temperature for 68 hr. After this period, solvent was removed by vacuum distillation at room temperature; the nmr spectrum of the crude reaction mixture in deuterio-

(11) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 2063 (1963).

chloroform showed a broadened singlet at 9.50 ppm for the aldehyde proton. When this reaction was carried out under identical conditions using water in place of deuterium oxide, the crude reaction mixture showed a doublet for the aldehyde proton with J = 1.5 Hz. Under these conditions the starting aldehyde was recovered after column chromatography in 65% yield.

Registry No.—**1a**, 19916-80-4; **1a** (*p*-toluenesulfonate), 19955-02-3; **1b**, 19916-81-5; **1b** (*p*-toluenesulfonate), 19916-82-6; **3**, 19916-83-7; **5b** (acetate), 19933-74-5; 17-methylene-4,5-tetramethylene[2.2]paracyclophane, 19933-75-6; δ-[2.2]paracyclophanylbutyric acid methyl ester, 19933-76-7.

Acknowledgment.—The authors are indebted to Mr. Paul Kronlage who helped to prepare some of the starting materials. This research was supported by a National Science Foundation Grant to Tulane University. The Varian A-60 instrument used in this work was purchased with National Science Foundation funds. [2.2]Paracyclophane was generously supplied by Union Carbide Corp.

Selective Reductions. XIII. The Reaction of Δ^2-Cyclopentenones with Representative Complex Hydrides. Aluminum Hydride as a Selective Reagent for the Reduction of the Carbonyl Group in Δ^2-Cyclopentenones

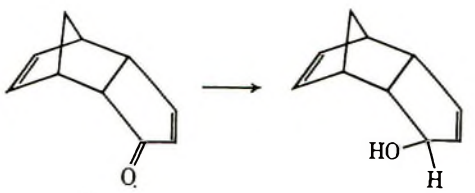
HERBERT C. BROWN AND HENRY M. HESS[1]

Richard B. Wetherill Laboratory of Purdue University, Lafayette, Indiana 47907

Received December 17, 1968

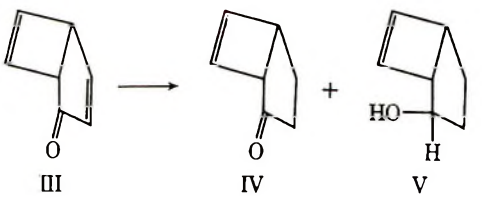
The reduction of 2-cyclopenten-1-one and 5,6-dihydro-*endo*-dicyclopentadien-1-one with metal hydrides takes place with considerable concomitant saturation of the double bond. However, the inverse addition of 0.667 mole equiv of aluminum hydride to 2-cyclopenten-1-one, 3-substituted 2-cyclopenten-1-ones, 5,6-dihydro-*endo*-dicyclopentadien-1-one, and 3-substituted 5,6-dihydro-*endo*-dicyclopentadien-1-ones, produces the unsaturated carbinols in satisfactory purity and yield and thus provides an effective route for the selective reduction of the carbonyl group in Δ^2-cyclopentenones.

The reduction of α,β-unsaturated ketones to the corresponding unsaturated carbinols with metal hydrides has often been reported to occur with varying amounts of concomitant saturation of the double bond, thereby affording saturated ketone and alcohol.[2,3] This mode of behavior is especially enhanced in Δ^2-cyclopentenones. Thus, while Woodward and Katz[4] reported that the reduction of *endo*-dicyclopentadien-1-one (I) with



I II

lithium aluminum hydride afforded the unsaturated alcohol II, Allara[5] and Dilling[6] have been unable to reproduce these results, obtaining substantial amounts of saturated products even at considerably reduced temperatures. Allara[5] has also reported that the reduction of 5,6-dihydro-*endo*-dicyclopentadien-1-one (VII) with lithium aluminum hydride and sodium borohydride produced substantial reduction of the double bond. Cookson[7] has reported that the reduction of *exo*-dicyclopentadien-1-one with lithium aluminum hydride yielded only the saturated alcohol. Story and Fahrenholtz[8] have demonstrated that *cis*-bicyclo[3.2.0]hepta-3,6-dien-2-one (III), when reduced with



III IV V

lithium tri-*t*-butoxyaluminohydride, gave, as the major product, *cis*-bicyclo[3.2.0]-6-hepten-2-one (IV) along with a small amount of the saturated alcohol V.[9-12] Paquette[13] has reported that the reduction of *cis*-bicyclo[3.2.0]hept-3-en-2-one with lithium aluminum hydride, even at −78°, afforded a complex mixture of products accompanying the desired unsaturated alcohol.

In view of these difficulties, and because a number of Δ^2-cyclopentenols were required for other work, a systematic study of the effect of metal hydrides on 2-cyclopenten-1-one (VI) and 5,6-dihydro-*endo*-dicyclopentadien-1-one (VII) was undertaken.

(1) Research assistant on grants (G 19878 and GP 6492 X) provided by the National Science Foundation.

(2) (a) N. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp 180–183; (b) V. M. Micovic and M. L. Mihailovic, "Lithium Aluminum Hydride in Organic Chemistry," Naukna Knjiga, Belgrade, Yugoslavia, 1955.

(3) P. L. Southwick, N. Latif, B. M. Fitzgerald, and N. M. Zaczek, *J. Org. Chem.*, **31**, 1 (1966), and references cited therein.

(4) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(5) D. L. Allara, Ph.D. Thesis, University of California, Los Angeles, 1964.

(6) W. L. Dilling, Britton Laboratory, Dow Chemical Co., private communication.

(7) R. S. Cookson, N. S. Isaacs, and M. Szelke, *Tetrahedron*, **20**, 717 (1964).

(8) P. R. Story and S. R. Fahrenholtz, *J. Amer. Chem. Soc.*, **87**, 1623 (1965).

(9) Lithium tri-*t*-butoxyaluminohydride, in contrast to lithium aluminum hydride and lithium trimethoxyaluminohydride, has previously been reported[10-12] to reduce cinnamaldehyde without attacking the double bond.

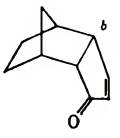
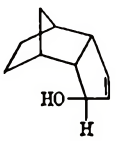
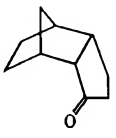
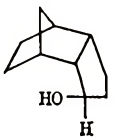
(10) F. A. Hochstein and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3483 (1948).

(11) H. C. Brown and P. M. Weissman, *ibid.*, **87**, 5614 (1965).

(12) H. C. Brown and P. M. Weissman, *Israel J. Chem.*, **1**, 430 (1963).

(13) L. A. Paquette and O. Cox, *J. Amer. Chem. Soc.*, **89**, 5633 (1967).

TABLE I
METAL HYDRIDE REDUCTIONS OF 5,6-DIHYDRO-*endo*-DICYCLOPENTADIEN-1-ONE[a]

Reagent	Solvent	Products, %			
		 [b]			
$LiAlH_4$	Et_2O[c]	31.3	13.8	28.3	26.6
$LiAlH_4$	Et_2O[c,d]	0	67	12.0	21.0
$LiAlH_4$	THF[e]	0	0	100	0
$LiAlH_4$	THF[e,f,m]	0	0	100	0
$LiAlH_4$	THF[g]	0	0	67.2	32.8
$LiAlH(OCH_3)_3$	THF[g]	45.0	42.0	9.6	3.4
$LiAlH(OCH_3)_3$	THF[h]	0	45.0	41.0	14.0
$LiAlH[OC(CH_3)_3]_3$	THF[g]	0	0	84.5	15.5
$NaBH_4$	EtOH[h]	0	0	0	100
AlH_3	THF[g]	0	66.6	14.2	19.2
AlH_3	THF[i]	0	65.8	32.7	1.5
AlH_3	THF[f,j]	0	84.6	7.1	8.3
AlH_3	THF[f,j,k]	0	86.0	10.0	4.0
AlH_3	THF[f,j,l]	27.3	64.3	5.9	2.5

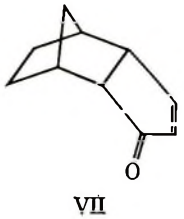
[a] Product analysis by glpc. Unless otherwise specified, the reaction consists of the normal addition of 1 mole of ketone to 1 mole of metal hydride. [b] Starting material. [c] 0.25 hr at 25°. [d] Reference 5. These results could not be reproduced. [e] 0.25 hr, 0°. [f] Inverse addition. [g] 17 hr at 0°. [h] 0.5 hr at 78°. [i] 1 hr at 0°. [j] 0.5 hr at 0°. [k] 0.667 mole equiv of reagent. [l] 0.33 mole equiv of reagent. [m] 0.25 mole equiv of reagent.

TABLE II
METAL HYDRIDE REDUCTIONS OF 2-CYCLOPENTEN-1-ONE[a]

Reagent	Solvent	Products, %			
		 [b]			
$LiAlH_4$	Et_2O[c]	0	85	15	0
$LiAlH_4$	THF[d]	0	14.0	2.5	83.5
$LiAlH(OCH_3)_3$	THF[d]	0	90.5	0	9.5
$LiAlH[OC(CH_3)_3]_3$	THF[d]	0	0	11.2	88.8
$NaBH_4$	EtOH[e]	0	0	0	100
AlH_3	THF[f]	0	83.8	8.7	7.5
AlH_3	THF[f-h]	0	90.0	6.1	3.9

[a] Product analysis by glpc. Unless otherwise specified, the reaction consists of the normal addition of 1 mole of ketone to 1 mole of metal hydride. [b] Starting material. [c] At −10°, ref 5. [d] 17 hr at 0°. [e] 0.5 hr at 78°. [f] 0.5 hr at 0°. [g] Inverse addition. [h] 0.667 mole equiv of reagent.

VI



VII

Results and Discussion

2-Cyclopenten-1-one and 5,6-dihydro-*endo*-dicyclopentadien-1-one were reduced with lithium aluminum hydride, lithium trimethoxyaluminohydride, lithium tri-*t*-butoxyaluminohydride, sodium borohydride, and aluminum hydride. Tables I and II show that, with the exception of lithium trimethoxyaluminohydride and aluminum hydride, nearly exclusive saturation of the double bond resulted from the reaction of metal hydrides with these Δ^2-cyclopentanones under a variety of conditions.[14] The reduction of 3-methyl-2-cyclopenten-1-one with lithium aluminum hydride (inverse addition in THF, 0.5 hr at 0°) afforded 70% of the unsaturated carbinol and 30% of 3-methylcyclopentanol, demonstrating that while the presence of a 3 substituent decreases double bond saturation, such saturation still occurs.

The mechanism of double bond saturation is still uncertain,[2,3,5,8,10,15] but from the results in Table I, it is apparent that the unsaturated alcohol, once formed, is stable to the reaction conditions. Saturated alcohol, however, increases with time, indicating that, depending on the reagent, a metal hydride can add either 1,2 or 1,4 to the unsaturated ketone, the 1,4 attack then being followed by a slower reduction of the initially formed enolate. That similar results for these reductions were obtained with both 2-cyclopenten-1-one and 5,6-dihydro-*endo*-dicyclopentadien-1-one makes questionable the proposal by Story[8] that attack of hydride on the double bond is preferred in hindered cyclopentenones because the salt resulting from 1,2 *exo* attack of the reagent cannot be accommodated in the *endo* position.

(14) It should be noted that the effect of lithium tri-*t*-butoxyaluminohydride and lithium trimethoxyaluminohydride on the double bond of Δ^2-cyclopentenones differs from the effect reported[11,12] for cinnamaldehyde, indicating that the results with cinnamaldehyde, generally regarded as a model for reductions of α,β-unsaturated carbonyls, may not be general.

(15) M. E. Cain, *J. Chem. Soc.*, 3532 (1964).

Aluminum hydride[16,17] was found to be the most generally selective reagent for the selective reduction of the carbonyl group in Δ^2-cyclopentenones. The inverse addition of 0.667 mole equiv of aluminum hydride, prepared by the method previously described,[17] to 2-cyclopenten-1-one, 3-substituted 2-cyclopenten-1-ones, 5,6-dihydro-*endo*-dicyclopentadien-1-one, and 3-substituted 5,6-dihydro-*endo*-dicyclopentadien-1-ones has produced good yields of the corresponding unsaturated carbinols in excellent purity (see Table III). Consequently, this method provides an effective route for the selective 1,2 reduction of Δ^2-cyclopentenones, an important component of many polycyclic molecules.

TABLE III
REDUCTION OF Δ^2-CYCLOPENTENONES WITH ALUMINUM HYDRIDE

Δ^2-Cyclopentenone	Carbinol, % purity	Carbinol, % yield
2-Cyclopenten-1-one	90.0[a]	79.0[a]
3-Methyl-2-cyclopenten-1-one	100[b]	76.2[c]
3-Phenyl-2-cyclopenten-1-one	100[b]	73[c]
5,6-Dihydro-*endo*-dicyclopentadien-1-one	86.0[a]	64.9[a]
3-Methyl-5,6-dihydro-*endo*-dicyclopentadien-1-one	100[b]	89.0[c]
3-Phenyl-5,6-dihydro-*endo*-dicyclopentadien-1-one	100[b]	92.5[c]

[a] Analysis by glpc. [b] Analysis by nmr. [c] Isolated yield.

Experimental Section

Δ^2-Cyclopentenones.—2-Cyclopenten-1-one, bp 150–152°, n^{20}D 1.4795 (lit.[18] bp 151–154°, n^{20}D 1.4810), 3-methyl-2-cyclopenten-1-one, bp 78–82° (20 mm), n^{20}D 1.4842 (lit.[19] bp 74–76° (16 mm), n^{20}D 1.4818), 3-phenyl-2-cyclopenten-1-one, mp 81–82.5° (lit.[20] mp 81–83°), and 5,6-dihydro-*endo*-dicyclopentadien-1-one, mp 49° (lit.[21] mp 50–51°), were prepared by the reported procedures. 3-Methyl-5,6-dihydro-*endo*-dicyclopentadien-1-one, bp 110–112° (3 mm), n^{26}D 1.5262, and 3-phenyl-5,6-dihydro-*endo*-dicyclopentadien-1-one, mp 127.8–128.4, were also prepared[22] and will be reported in a later paper.

General Procedure for the Reductions with Lithium Aluminum Hydride in THF.—Into a dry 50-ml round-bottom flask fitted with a magnetic stirrer and an injection port with a rubber syringe cap, were placed, under nitrogen, 2.1 ml of a 1.27 *M* lithium aluminum hydride solution in tetrahydrofuran (3.5 mmoles of $LiAlH_4$) and 10 ml of dry tetrahydrofuran. To this stirred solution, maintained at 0° in an ice bath, there was slowly added 3.5 mmoles of ketone in 10 ml of dry tetrahydrofuran. The mixture was stirred for the appropriate time, and then a 1:1 aqueous tetrahydrofuran solution was added slowly until no more hydrogen was evolved. After the addition of a standard naphthalene solution (to serve as an internal glpc standard), the reaction mixture was washed in a separatory funnel with a saturated solution of sodium potassium tartrate, and the tetrahydrofuran layer was dried ($MgSO_4$). The solution was concentrated by rotary evaporation and the product was examined by glpc. (For the inverse addition experiment, the procedure was appropriately altered.) For the bicyclic ketone, all analyses were carried out on a Perkin-Elmer 226 temperature-programmed capillary instrument fitted with a 150 ft × 0.01 in. Carbowax 20 M column. The saturated products were identified by comparison of the retention times with authentic samples.[23] For the 2-cyclopenten-1-one reductions, all analyses were carried out on a Perkin-Elmer 154 gas chromatograph fitted with a 3-ft column of Carbowax 20 M on Chromosorb W, HMDS treated.

Reduction of 5,6-Dihydro-*endo*-dicyclopentadien-1-one with Lithium Aluminum Hydride in Ether.—The procedure reported by Allara[5] was used. Ketone, 1 g, in 10 ml of anhydrous diethyl ether was added slowly from a dropping funnel into a stirred solution of 0.12 g of lithium aluminum hydride in 45 ml of dry diethyl ether contained in a 100-ml round-bottom flask previously flushed with nitrogen. After the addition was complete, the reaction was stirred for 15 min more. The mixture was hydrolyzed by adding successively 1 ml of water, 1 ml of 15% sodium hydroxide, and 5 ml of water. After the addition of a standard naphthalene solution, the mixture was filtered, washed once with water, and dried (K_2CO_3). The solution was concentrated by rotary evaporation and the product was examined by glpc.

General Procedure for the Reductions with Lithium Trimethoxyaluminohydride and Lithium Tri-*t*-butoxyaluminohydride.—Into a dry 50-ml round-bottom flask fitted with a magnetic stirrer and an injection port with a rubber syringe cap were placed, under nitrogen, 6.05 ml of a 1.65 *M* lithium aluminum hydride solution in tetrahydrofuran (40 mmoles of hydride) and 10 ml of dry tetrahydrofuran. To this stirred solution, maintained at the appropriate temperature, there was slowly added 30 mmoles of dry methanol (*t*-butyl alcohol). After the solution had reached thermal equilibrium, 2.5 mmoles of ketone in 4 ml of dry tetrahydrofuran was slowly added. The reaction mixture was stirred for the appropriate time and then slowly hydrolyzed with a 1:1 aqueous tetrahydrofuran solution. After the addition of a standard naphthalene solution, the mixture was washed in a separatory funnel with a saturated solution of sodium potassium tartrate, and the tetrahydrofuran layer was dried ($MgSO_4$). The solution was analyzed as before.

TABLE IV
PHYSICAL PROPERTIES OF THE Δ^2-CYCLOPENTENOLS

Δ^2-Cyclopentenols (registry no.)	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3-Methyl-2-cyclopenten-1-ol (*p*-nitrobenzoate) (19926-45-5)	Liquid[a] 91.5–92.5[b]	$C_{13}H_{13}NO_4$	63.15	5.30	5.67	63.24	5.48	5.66
3-Phenyl-2-cyclopenten-1-ol (19926-46-6)	103.3–105.3[c]	$C_{11}H_{12}O$	82.46	7.55		82.28	7.53	
5,6-Dihydro-*endo*-dicyclopentadien-*endo*-1-ol (19926-79-5)	103–105[b,d]	$C_{10}H_{14}O$	79.95	9.39		79.51	9.52	
3-Methyl-5,6-dihydro-*endo*-dicyclopentadien-*endo*-1-ol (19926-80-8)	79.4–79.9[b]	$C_{11}H_{16}O$	80.44	9.83		80.54	10.04	
3-Phenyl-5,6-dihydro-*endo*-dicyclopentadien-*endo*-1-ol (19926-81-9)	96–97[b]	$C_{16}H_{18}O$	84.91	8.02		85.01	8.24	

[a] Bp 70–71° (12 mm), n^{20}D 1.4706. [b] Recrystallized from hexane. [c] Recrystallized from chloroform–hexane. [d] Reduction of 5,6-dihydro-*endo*-dicyclopentadien-1-one with aluminum deuteride, prepared from lithium aluminum deuteride, also produced the corresponding unsaturated deuterated alcohol.

(16) M. J. Jorgenson, *Tetrahedron Letters*, 559 (1962).
(17) H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1464 (1966); N. M. Yoon and H. C. Brown, *ibid.*, **90**, 2927 (1968).
(18) K. Alder and F. H. Flock, *Ber.*, **89**, 1732 (1956).
(19) R. M. Acheson and R. Robinson, *J. Chem. Soc.*, 1127 (1952).
(20) R. Riemschneider and R. Nerin, *Monatsh.*, **91**, 829 (1960).
(21) K. Alder and G. Stein, *Ann.*, **504**, 205 (1935).
(22) H. M. Hess, Ph.D. Thesis, Purdue University, 1969.
(23) H. C. Brown and I. Rothberg, unpublished data.

General Procedure for the Reductions with Sodium Borohydride.—Ketone, 5.0 mmoles, in 10 ml of ethanol was treated at room temperature with 10 mmoles of sodium borohydride in 10 ml of ethanol. After the exothermic reaction had ended (about 20 min), the mixture was heated on a steam bath for 10 min more. The reaction mixture was hydrolyzed with 25 ml of a 3% sodium hydroxide solution. After the addition of a standard naphthalene solution, the solution was extracted several times with ether, and the ether layer was dried ($MgSO_4$). The solution was concentrated by rotary evaporation and analyzed as before.

General Procedure for the Reductions with Aluminum Hydride.—Into a 50-ml round-bottom flask fitted with a magnetic stirrer and an injection port with a rubber syringe cap, were placed, under nitrogen, 2 mmoles of ketone in enough dry tetrahydrofuran to bring the total volume of the final solution to 10 ml. The solution was brought to 0° by means of an ice bath, and the appropriate amount of a standard aluminum hydride solution in tetrahydrofuran, prepared by the method of Brown and Yoon,[17] was added dropwise (for the normal addition experiments, the ketone was added slowly to the aluminum hydride solution). The mixture was stirred for the appropriate time at 0°. The hydrolysis and analysis procedures were the same as for the lithium aluminum hydride experiments.

General Procedure for the Preparative-Scale Reduction of Δ^2-Cyclopentenones.—The reduction of 3-methyl-2-cyclopenten-1-one is typical of the procedure used. Into a 1-l. round-bottom flask fitted with a magnetic stirrer and an injection port with a rubber syringe cap, was placed, under nitrogen, 10 g (104 mmoles) of 3-methyl-2-cyclopenten-1-one in 400 ml of dry tetrahydrofuran. The solution was brought to 0° by means of an ice bath and 90 ml of a 0.77 *M* aluminum hydride solution in tetrahydrofuran (69.3 mmoles of AlH_3) was added dropwise over a 15-min period. After the addition was complete, the reaction mixture was stirred at 0° for 30 min more and then hydrolyzed by adding successively 2.1 ml of water, 2.1 ml of 15% sodium hydroxide, and 6.3 ml of water. The aqueous layer was salted out with sodium carbonate and the aqueous layer was extracted with ether. The combined organic layers were washed with a saturated sodium bicarbonate solution and dried (K_2CO_3). Removal of the solvent by rotary evaporation afforded 8.5 g of liquid. Distillation of the liquid (12 mm) produced 7.8 g (79.5 mmoles, 76.2% yield) of carbinol. The physical properties of 3-methyl-2-cyclopenten-1-ol and the other Δ^3-cyclopentenols prepared by this procedure are recorded in Table IV.

Registry No.—Aluminum hydride, 1302-30-3.

Perhydroindan Derivatives. XI.[1a] The 7-Methoxyhexahydrofluorene System

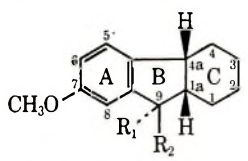
HERBERT O. HOUSE, THOMAS M. BARE,[1b] AND WILLIAM E. HANNERS

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

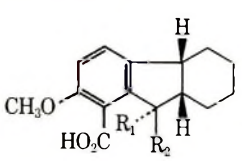
Received November 7, 1968

The known methoxyhexahydrofluorenone **6** has been converted into acids **1**–**4** desired as models for study of transformations in the aromatic ring. Of the various methods used to introduce the carboxyl functions, the selective lithium–hydrogen exchange and subsequent carbonation reactions applied to the olefins **10** and **35** and to alcohol **8** are worthy of special note.

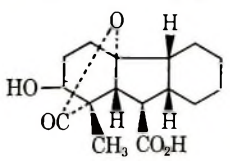
As part of our study of synthetic routes to the gibberellins,[2] we wished to study the acids **1**–**4** as model compounds for the transformation of the aromatic A ring into the nonaromatic system (*e.g.*, **5**) present in the gibberellins. This paper describes the preparation and interrelation of these model acids **1**–**4**.



1, $R_1 = CO_2H$; $R_2 = H$
2, $R_1 = H$; $R_2 = CO_2H$



3, $R_1 = CO_2H$; $R_2 = H$
4, $R_1 = H$; $R_2 = CO_2H$



5

The starting material for these acids was the known ketone **6** (Scheme I) prepared by acid-catalyzed cyclization[3] of the unsaturated ketone **7**. The formation of the ketone **6** under equilibrating conditions ensured the formation of the more stable diastereoisomer in which the B and C rings were *cis* fused.[3b] Reduction of the ketone **6** with $LiAlH_4$ yielded a single alcohol believed to have the stereochemistry indicated in structure **8** as a result of attack of the complex metal hydride anion from the less hindered side.[3c,4] Conversion of this alcohol **8** to the crude methanesulfonate ester followed by reaction with sodium cyanide yielded the olefin **9** rather than the desired nitrile. Olefin formation was more easily effected by brief acid-catalyzed dehydration to form the trisubstituted olefin **10** which was readily isomerized to the tetrasubstituted olefin **9**.

The acids **1** and **2** were most efficiently prepared by conversion of the olefin **10** (or mixtures of **9** and **10**) to the allylic lithium reagent which was carbonated to form the unsaturated acid **11** accompanied by small amounts of the isomeric acid **12**. Hydrogenation of the unsaturated acid **11** yielded the acid **1** as a result of the *cis* addition of hydrogen from the less hindered side of the olefin **11**. The methyl ester **13** of acid **1** could be epimerized and then hydrolyzed to yield the more stable C-9 epimer in which the carboxyl function is *trans* to the methylene groups of ring C.

An alternative route (Scheme II) to the acid **2**, although less efficient, provided evidence that the B–C ring fusion in acids **1** and **2** was *cis*. In this sequence the ketone was converted to olefins **15** and **16** by reaction with the appropriate Wittig reagents. Hydrolysis of the enol ether **15** (mixture of geometrical isomers) afforded the aldehyde **17** which was oxidized to the acid **2**. Hydroboration of the olefin **16** proceeded by attack from the less hindered side to yield, after oxidation, the

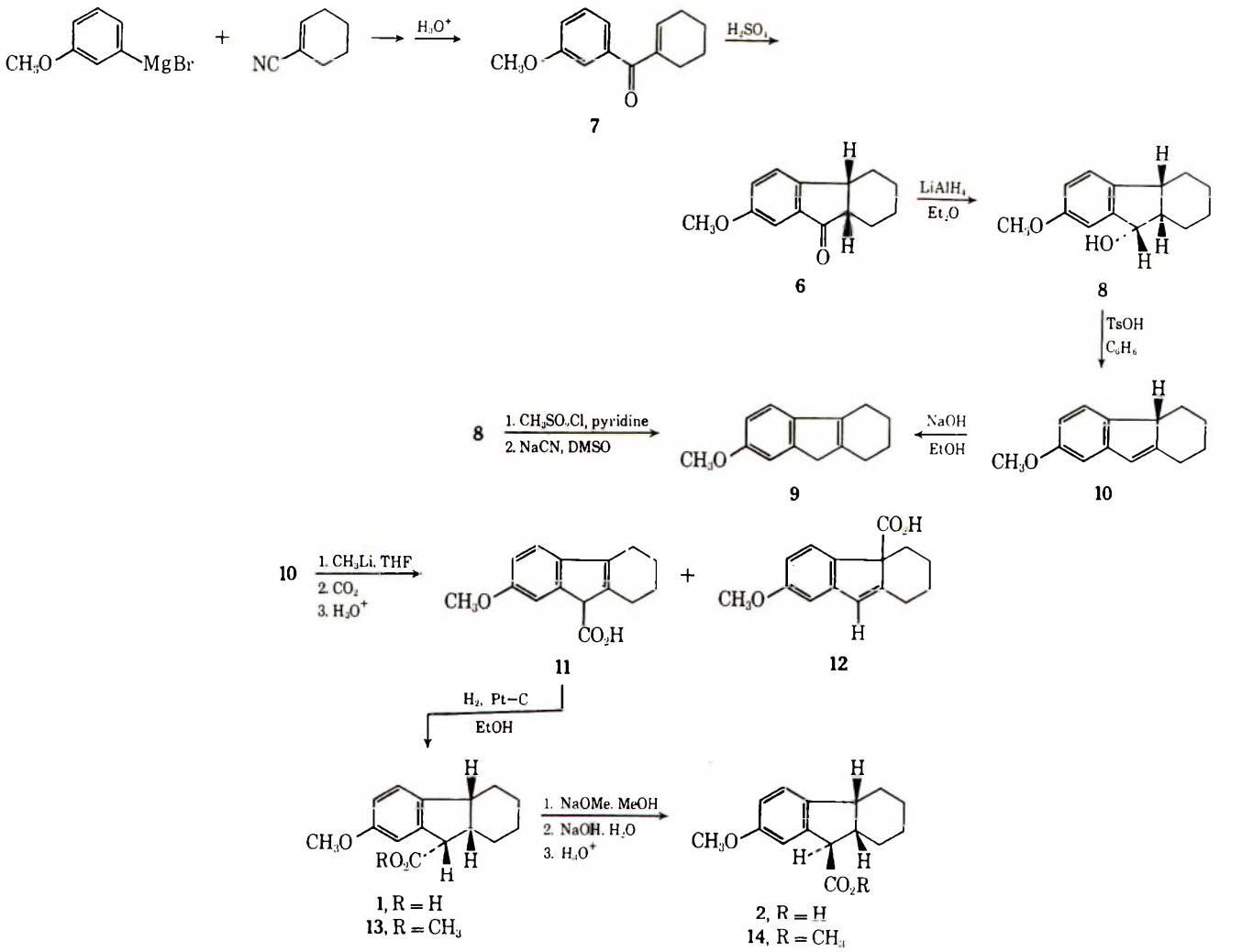
(1) (a) This research has been supported by Research Grant No. GP-5685 from the National Science Foundation and by Public Health Service Grant No. 1-R01-CA10933-01 from the National Cancer Institute. (b) National Institutes of Health Predoctoral Fellow, 1965–1968.

(2) For leading references, see (a) H. O. House, F. J. Sauter, W. G. Kenyon, and J. J. Riehl, *J. Org. Chem.*, **33**, 957 (1968); (b) H. O. House, J. K. Larson, and H. C. Müller, *ibid.*, **33**, 961 (1968).

(3) (a) W. G. Dauben and J. W. Collette, *J. Amer. Chem. Soc.*, **81**, 967 (1959); (b) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *ibid.*, **82**, 1457 (1960); (c) H. O. House, V. Paragamian, and D. J. Wluka, *ibid.*, **82**, 2561 (1960).

(4) H. O. House, R. G. Carlson, H. Müller, A. W. Noltes, and C. D. Slater, *ibid.*, **84**, 2614 (1962).

SCHEME I



hydroxy methyl derivative **18**. This alcohol **18**, also produced from the acid **1**, was the C-9 epimer of the hydroxymethyl derivative **19** formed from the acid **2**. In an attempt to obtain the acid **2** *via* the glycidic ester **20**, the ketone **6** was treated with ethyl chloroacetate under the usual conditions for producing glycidic esters.[5] However, the only material isolated was the C-alkylation product **21** presumed to have the indicated stereochemistry by analogy with earlier studies.[3b,c,4]

To examine the course of electrophilic substitution reactions, the methoxy acid **2** was subjected to the bromination and acetylation reactions summarized in Scheme III. The nmr spectra of the monosubstitution products **22** and **23** and their derivatives **24** and **25** established that substitution had occurred at position C-6 rather than at the desired position C-8. An attempt to acylate the monobromo acid **22** led to acid-catalyzed decarbonylation to yield an olefin. Therefore, these potential routes to C-8 substituted derivatives were abandoned.

We next turned our attention to metallation reactions with the methoxy alcohol **8**. This investigation was prompted by earlier observations that metallation of aromatic hydrocarbons with lithium reagents was accelerated by the presence of *ortho* substituents with unshared electron pairs such as methoxyl, methoxymethyl, and dimethylaminomethyl groups.[6] Presumably the success of these reactions is attributable to reaction of the normally hexameric or tetrameric alkyllithium reagents[7a] to form complexes (*e.g.*, **29**) in which the more reactive monomeric or dimeric form of the lithium reagent is complexed with the *ortho* donor substituents and is in a favorable position for metal–hydrogen exchange.

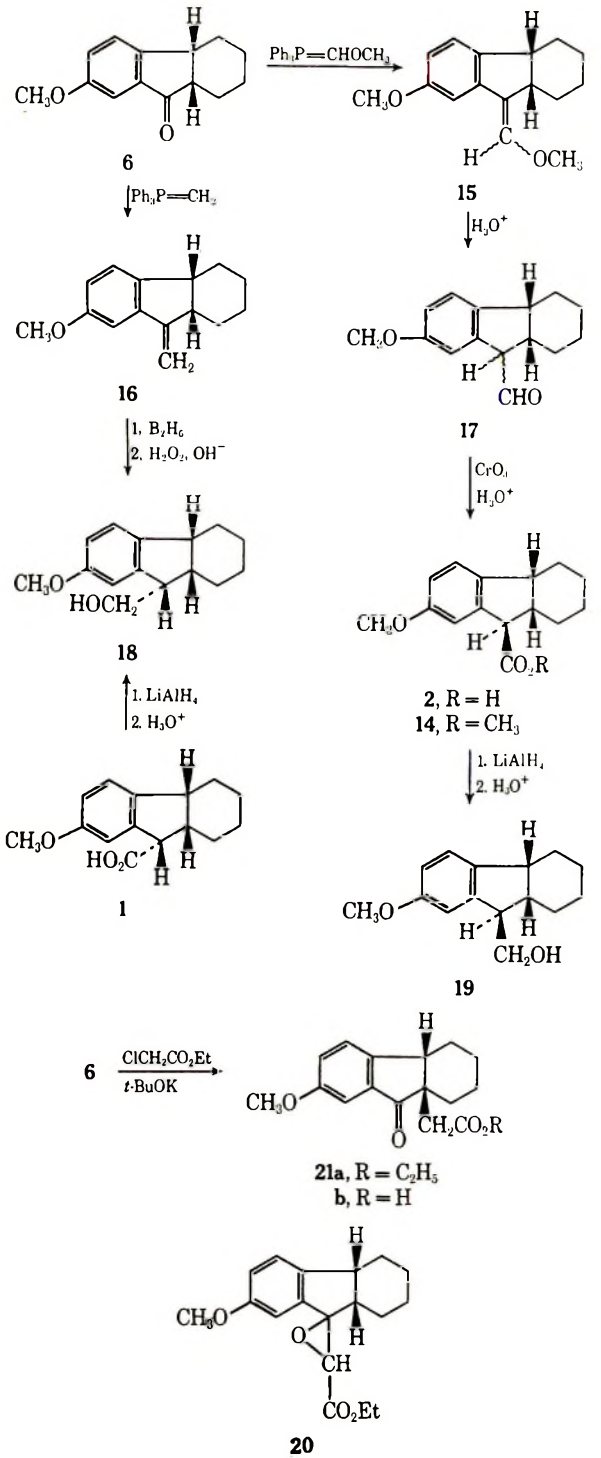
Reaction of the alcohol **8** (Scheme IV) with *n*-butyllithium in a hexane–ether mixture resulted in little if any C metallation and the alcohol **8** was recovered. However, the corresponding reaction with a mixture of *n*-butyllithium and sodium *t*-butoxide in hexane[7b] followed by carbonation produced the desired carboxylic acid **30** in high yield. The structurally specific metallation evidently has rigid requirements for success since the same metallating conditions applied to the homologous alcohol **18** produced a complex mixture of acidic products perhaps caused by competing metallation at the benzylic positions. Activation of the *n*-butyllithium by the addition of N,N,N′,N′-tetramethylethyl-

(5) (a) M. S. Newman and B. J. Magerlein, *Org. Reactions*, **5**, 413 (1949); (b) W. S. Johnson, J. S. Belew, L. J. Chinn, and R. H. Hunt, *J. Amer. Chem. Soc.*, **75**, 4995 (1953).

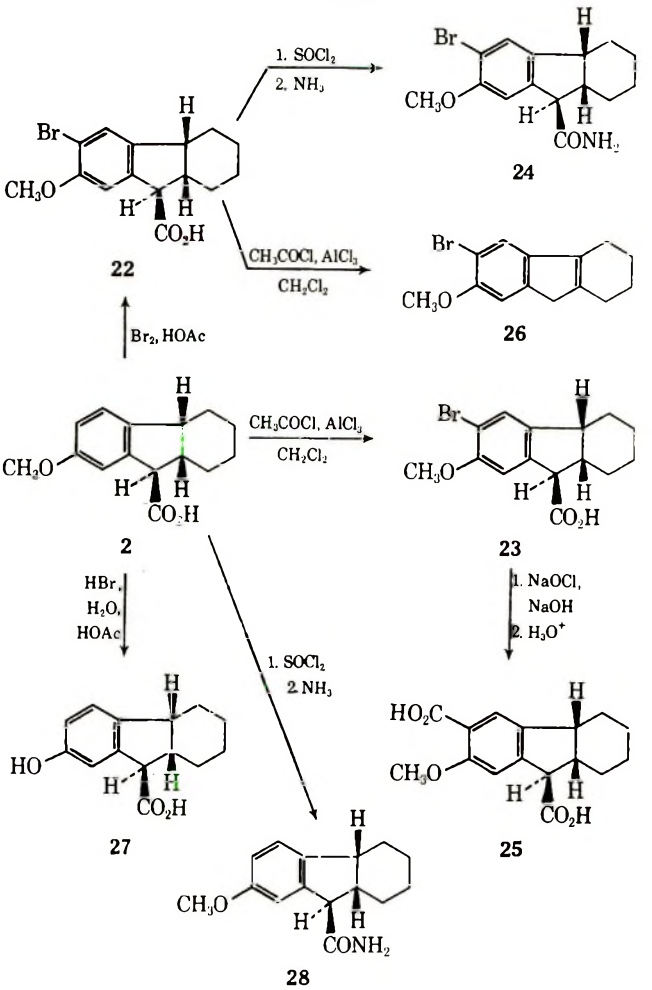
(6) (a) G. Wittig in "Newer Methods of Preparative Organic Chemistry," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1948, pp 571–591; (b) H. Gilman and J. W. Morton, *Org. Reactions*, **8**, 258 (1954); (c) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963); (d) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, **30**, 58 (1965); (e) K. P. Klein and C. R. Hauser, *ibid.*, **32**, 1479 (1967); (f) R. L. Gay and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 2297 (1967).

(7) (a) T. L. Brown, *Accounts Chem. Res.*, **1**, 23 (1968); (b) this mixture of reactants is reported to form *n*-butylsodium: L. Lochmann, J. Pospisil, and D. Lim, *Tetrahedron Letters*, 257 (1966).

SCHEME II



SCHEME III



enediamine[8] prior to metallation resulted in loss of structural specificity. A mixture of the ester **31** and compounds believed to be the ester **32** and lactone **33** was obtained from the alcohol **18** and both acids **30** and **34** were produced from the alcohol **8**. In these latter cases, we presume that the organolithium–diamine complex is more stable than the alternative alkoxide complex such as structure **29** with the result that the structural specificity resulting from a complex of the type **29** is lost.

The further transformation of the hydroxy acid **30** to the mixture of unsaturated acid derivatives **36** and **37** is illustrated in Scheme V. Hydrogenation of the unsaturated acid **37b** afforded the less stable diacid **3** which could be epimerized at C-9 with potassium hydroxide to form the more stable epimer **4**. These stereochemical results are analogous to the aforementioned hydrogenation of acid **11** to produce the less stable saturated epimer **1**. Hydrogenation of the unsaturated ester **37a** produced the less stable diester epimer **38**. However, the conditions required to saponify this ester also epimerized the acid (or ester) to produce the more stable diacid **4**.

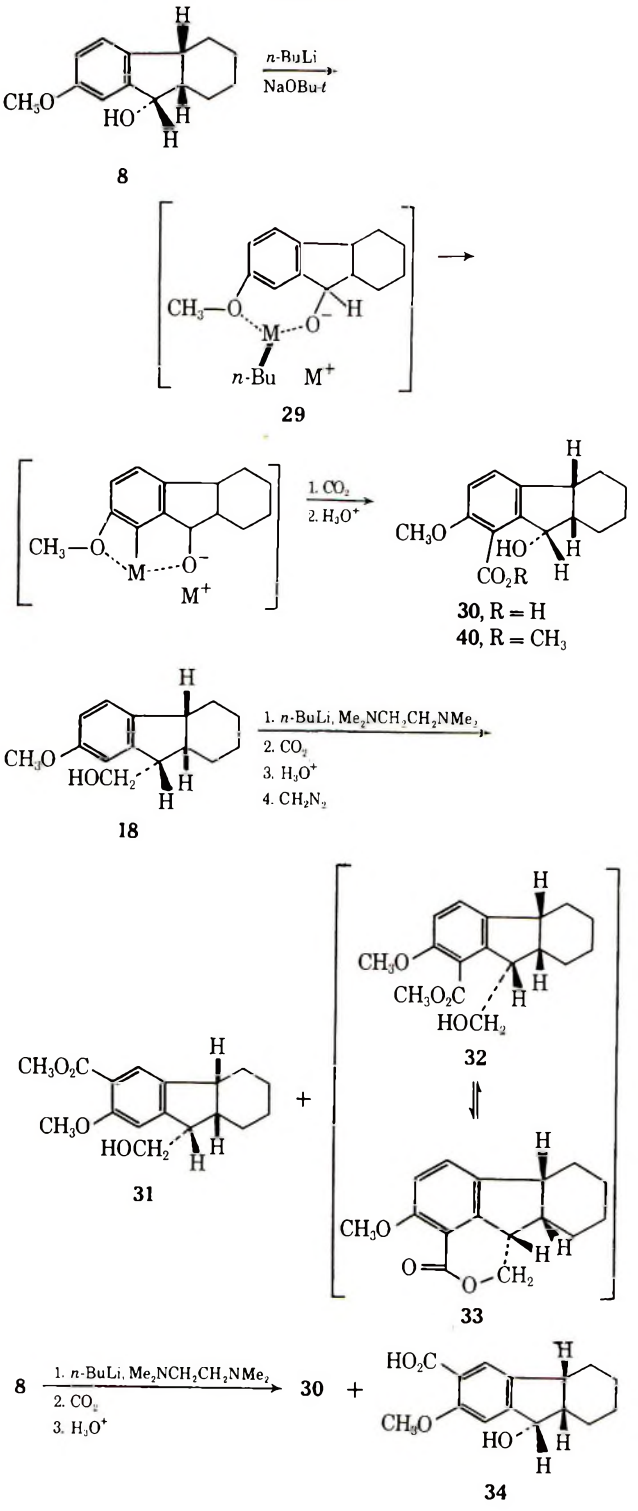
(8) The use of amines to produce reactive monomeric or dimeric complexes with organolithium compounds has been reported by (a) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); (b) C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 3276 (1965).

Experimental Section[9]

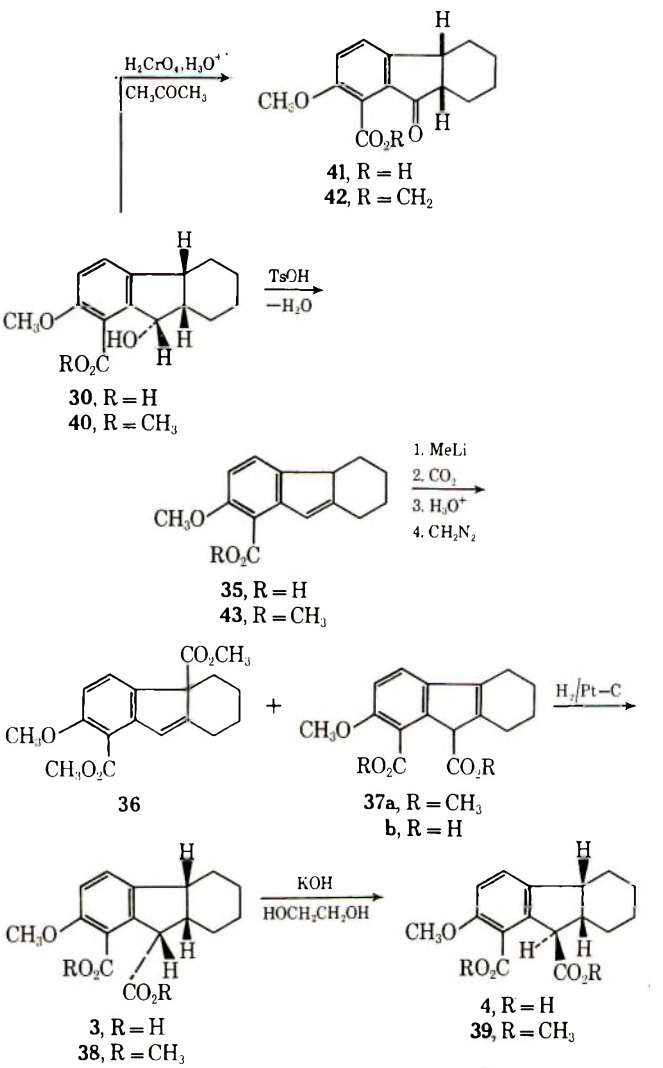
7-Methoxy-*cis*-1,1a,2,3,4,4a-hexahydrofluoren-9-ol (8).—Reaction of 1-cyanocyclohexene with *m*-methoxyphenylmagnesium bromide in Et_2O solution or with *m*-methoxyphenylmagnesium chloride in tetrahydrofuran solution following the general procedures described previously[3b,c,4] produced the unsaturated ketone **7** (52–80% yield) as a pale yellow liquid: bp 129–134° (0.5 mm) [lit.[3a] 164–167° (4 mm)]; ir (CCl_4), 1650 (C=O) and

(9) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined at 60 Mc with a Varian, Model A-60, nmr spectrometer. The chemical shift values are expressed either in cycles per second or δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a CEC, Model 21-130, or with a Hitachi (Perkin-Elmer) mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates. All reactions involving organometallic or strongly basic intermediates were performed under a nitrogen atmosphere.

SCHEME IV



SCHEME V



1640 cm^{-1} (C=C); uv (95% EtOH), 218 mμ (ε 19,600), 247 (11,300), and 301 (2260); nmr (CCl_4), δ 6.7–7.4 (4 H m, aryl CH), 6.43 (1 H br, vinyl CH), 3.76 (3 H s, OCH_3), and 1.4–2.6 (8 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 216, fragments *m/e* 184, 135, 92, 77, 41, 39, and 27. Cyclization of the unsaturated ketone **7** in concentrated H_2SO_4 for 5 min at 60° afforded the ketone **6** as white needles from hexane: mp 99–100°. (lit.[3a] mp 99–100°); yield 69–85%; ir (CCl_4), 1715 cm^{-1} (C=O); uv (95% EtOH), 218 mμ (ε 27,700), 248 (9170), and 319 (3930); nmr ($CDCl_3$), δ 7.0–7.5 (3 H m, aryl CH), 3.81 (3 H s, OCH_3), and 1.0–3.7 (10 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 216, abundant fragments *m/e* 188, 187, 175, 174, 173, 162, and 160.

To a cold (0°) suspension of 3.65 g (96.4 mmol) of $LiAlH_4$ in 100 ml of tetrahydrofuran was added, dropwise with stirring, a solution of 50.0 g (231 mmol) of the ketone **6** in 300 ml of tetrahydrofuran. After the resulting mixture had been stirred at 20–25° for 3.5 hr, it was cooled (ice bath), treated successively with 3.65 ml of H_2O, 3.65 ml of aqueous 15% NaOH, and 10.95 ml of H_2O and the filtered to remove the inorganic salts. The residue was washed with CH_2Cl_2 and the combined organic filtrates were concentrated. Recrystallization of the residual solid (hexane–CH_2Cl_2) separated 47.27 g (93.5%) of the alcohol **8** as colorless needles: mp 147–147.5°; ir ($CHCl_3$), 3590 and 3450 cm^{-1} (free and assoc OH); uv (95% EtOH), 220 mμ sh (ε 7780), 227 sh (7260), 282 (2750), and 288 (2410); nmr [$(CD_3)_2SO$], δ 6.6–7.2 (3 H m, aryl CH), 4.7–5.3 (1 H m, >CHO), 3.72 (3 H s, OCH_3), and 0.8–3.5 (11 H m, OH and aliphatic CH); mass spectrum, molecular ion *m/e* 218, abundant fragments *m/e* 200, 175, 172, and 121.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.05; H, 8.40.

Preparation of the Olefins 9 and 10.—A mixture of 781 mg (3.58 mmol) of the alcohol and 501 mg (4.37 mmol) of CH_3SO_2Cl in 4 ml of pyridine was stirred for 1 hr at 0°, allowed to stand overnight in a refrigerator, and then partitioned between Et_2O and cold H_2O. The Et_2O solution was washed successively with cold, dilute, aqueous HCl and with aqueous $NaHCO_3$ and then dried and concentrated. The residual crude sulfonate (and/or olefin), an orange oil, was treated with a solution of 486 mg (9.92 mmol) of NaCN in 9.5 ml of $(CH_3)_2SO$, and then heated to 40° for 2.5 hr, and partitioned between H_2O and Et_2O. The organic layer was washed with H_2O, dried, and concentrated to leave 0.55 g (77%) of the crude olefin **9** as a pale orange solid, mp 40–50°. A warm MeOH solution of the product was decolorized and cooled to separate the pure olefin **9** as white needles: mp 58–58.5°; ir ($CHCl_3$), 1620 and 1610 cm^{-1} (C=C); uv (95% EtOH), 266 mμ (ε 16,200) and 274 sh (13,600); nmr ($CDCl_3$), δ

6.6–7.2 (3 H m, aryl CH), 3.74 (3 H s, OCH_3), 3.13 (2 H br s, benzylic CH_2), 2.1–2.6 (4 H m, allylic CH_2), and 1.4–2.0 (4 H m, aliphatic CH_2); mass spectrum, molecular ion *m/e* 200, abundant fragments *m/e* 199, 172, 171, 129, 128, and 44.

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.98; H, 8.11.

A solution of 500 mg (2.29 mmol) of the alcohol **8** and 20 mg of TsOH in 20 ml of PhH was refluxed for 5 min and then cooled, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residual yellow oil crystallized from EtOH solution as 409 mg (89.5%) of light yellow solid, mp 30–32°. Recrystallization gave the pure olefin **10** as a white solid: mp 31.7–32.7°; ir (CCl_4), 1620 cm^{-1} (C=C); uv (95% EtOH), 226 mμ (ε 25,900), 264 (7220), 293 (3240), and 303 (3030); nmr (CCl_4), δ 7.06 (1 H d, *J* = 7.7 Hz, C-5 aryl CH), 6.68 (1 H d, *J* = 2.2 Hz, C-8 aryl CH), 6.48 (1 H, d of d, *J* = 2.2 and 7.7 Hz, C-6 aryl CH), 6.19 (1 H br s, vinyl CH), 3.68 (3 H s, OCH_3), and 0.8–3.3 (9 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 200, abundant fragments *m/e* 199, 172, 171, 129, 128, and 105.

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.95; H, 8.21.

The same olefin **10** (mp 31.5–32.5°) was obtained in 28% yield by reaction of the alcohol **8** with CH_3SO_2Cl in pyridine solution for 4 hr at 25–30°. A solution of 516 mg (2.58 mmol) of this olefin **10** and 100 mg (2.5 mmol) of NaOH in 3 ml of EtOH was stirred for 2 hr at 25–30° and then acidified with aqueous HCl and concentrated. An Et_2O solution of the residual oil was washed with H_2O, dried, and concentrated. Recrystallization of the crude product from EtOH separated 349 mg (67.9%) of the olefin **9**, mp 57–58° (identified with the previously described sample by a mixture melting point and by comparison of ir, uv, and nmr spectra).

Preparation of the Unsaturated Acids 11 and 12.—To a cold (−78°) solution of 791 mg (3.96 mmol) of the tetrahydrofluorene **9** and a few milligrams of Ph_3CH in 10 ml of tetrahydrofuran was added 6 ml (*ca.* 6 mmol) of a solution of MeLi in tetrahydrofuran. The initially yellow solution was allowed to warm to room temperature (during which time it assumed the red color of the Ph_3C^-) and then poured, with stirring into a slurry of 20 g of Dry Ice in 20 ml of tetrahydrofuran. The resulting mixture was acidified with dilute aqueous HCl, filtered, and extracted with Et_2O. The Et_2O solution was extracted successively with aqueous NaCl and aqueous $NaHCO_3$. After acidification of the aqueous $NaHCO_3$ extract, the usual manipulations separated 825 mg (84%) of the crude acids **11** and **12**, mp 133–145°. Recrystallization (CCl_4–hexane) separated 540 mg (55.7%) of the acid **11**, mp 153.5–155° dec. Recrystallization (Et_2O) separated the acid **11** as white prisms: mp 156–157° dec; ir ($CHCl_3$), 1710 (carboxyl C=O) and 1615 cm^{-1} (C=C); uv (95% EtOH), 268 mμ (ε 14,600) and 276 sh (13,200); nmr ($CDCl_3$), δ 10.45 (1 H, COOH), 6.6–7.4 (3 H m, aryl CH), 4.17 (1 H br, benzylic CH), 3.82 (3 H s, OCH_3), 2.2–2.7 (4 H m, allylic CH), and 1.5–2.1 (4 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 244, abundant fragments *m/e* 200, 199, 172, 171, and 44.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.54; H, 6.60.

In a subsequent preparation, 50.0 g (0.232 mol) of the ketone **6** was reduced, the crude alcohol **8** was dehydrated, and the crude olefin **9** and/or **10** was metallated and carbonated. The crude acidic product was recrystallized (CH_2Cl_2–hexane) to separate 42.2 g (74.6% over-all) of the crude acid **11**, mp 127–149° dec, which was hydrogenated as subsequently described to yield 22.3 g (39.3% over-all) of the saturated acid **1**, mp 185–187°. The nonvolatile portion of the mother liquor remaining after separation of acid **11** was treated with 0.5 g of TsOH in refluxing MeOH for 12 hr. The acidic fraction separated after this treatment was recrystallized (CH_2Cl_2–hexane) to separate 2.0 g (3.5%) of the isomeric unsaturated acid **12** as white crystals: mp 158–159°; ir ($CHCl_3$), 1740 (sh), 1695 (carboxyl C=O), 1625 and 1605 cm^{-1} (C=C); uv (95% EtOH), 230 mμ (ε 32,800), 265 (5970), 294 (2560), and 305 (2370); nmr ($CDCl_3$), δ 12.0 (1 H br, COOH), 6.5–7.5 (3 H m, aryl CH), 6.45 (1 H s, vinyl CH), 3.77 (3 H s, OCH_3), and 0.8–3.2 (8 H m, aliphatic CH); mass spectrum, abundant fragments *m/e* 200, 172, 171, 157, 141, 129, 128, and 44.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.95; H, 6.67.

Preparation of the Saturated Acid 1.—A solution of 361 mg (1.47 mmol) of the olefinic acid **11** in 8 ml of EtOH was hydrogenated at 25–30° and atmospheric pressure over 36.1 mg of a 5% Pd-C catalyst. After 11 hr the H_2 uptake (37.2 ml or 1.50 mmol) ceased and the mixture was filtered, concentrated, and diluted with water. The crude acidic product (329 mg of pale yellow solid) was recrystallized (Et_2O–hexane) to separate 214 mg (58.8%) of the acid **1** as colorless needles, mp 182–186°. Recrystallization gave the pure acid **1**: mp 186–187°; ir ($CHCl_3$), 1710 cm^{-1} (carboxyl C=O); uv (95% EtOH), 218 mμ (ε 6330), 227 (6780), 281 (2430), and 288 (2140); nmr ($CDCl_3$), δ 10.76 (1 H br, COOH), 6.7–7.4 (3 H m, aryl CH), 4.06 (1 H d, *J* = 6 Hz, $ArCHCO_2R$), 3.85 (3 H s, OCH_3), and 0.9–3.5 (10 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 246, abundant fragments *m/e* 204, 203, 201, 159, and 115.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.35; H, 7.18.

Reaction of 920 mg (3.74 mmol) of the acid **1** with excess ethereal CH_2N_2 followed by recrystallization of the crude neutral product from Et_2O yielded 928 mg (95.5%) of the ester **13** as white needles, mp 77.5–78.2°. Recrystallization (H_2O–MeOH) separated the pure **methyl ester 13**: mp 78–79°; ir ($CHCl_3$), 1740 cm^{-1} (ester C=O); uv (95% EtOH), 227 mμ (ε 8190), 282 (2810), and 288 (2470); nmr ($CDCl_3$), δ 6.5–7.2 (3 H m, aryl CH), 3.87 (1 H d, *J* = 7 Hz, $ArCHCO_2R$), 3.73 (3 H s, OCH_3), 3.69 (3 H s, OCH_3), and 0.8–3.4 (10 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 260, abundant fragments *m/e* 217, 201, 200, 159, and 115.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.89; H, 7.82.

Gas chromatographic analyses[10] established that ester **14** was eluted more rapidly than ester **13** and that neither ester was contaminated with the other epimer. A solution of 490 mg (1.88 mmol) of the ester **13** and 446 mg of NaOMe in 10 ml of MeOH was refluxed for 12 hr and then 2 ml of H_2O was added and refluxing was continued for 5 hr. The resulting suspension was acidified with aqueous HCl and filtered to separate 382 mg of crude product. Recrystallization (Et_2O–hexane) separated 379 mg (82.2%) of the acid **2** as cubic crystals, mp 116–118°. This sample, mp 117–118° after recrystallization, was identified with the subsequently described sample of acid **2** by a mixture melting point and comparison of ir spectra.

Preparation of the Saturated Acid 2.—To the basic solution[11] prepared from 1.85 g (77.2 mmol) of NaH and 36 ml of $(CH_3)_2SO$ was added a solution of 26.48 g (77.2 mmol) of methoxymethyltriphenylphosphonium chloride,[12] mp 196–200° dec (lit.[12] 201–202° dec), to form a red solution of the ylide. A solution of 9.81 g (45.4 mmol) of the ketone **6** in 34 ml of tetrahydrofuran was added to the ylide solution. The resulting mixture was heated to 50° with stirring for 7 hr and then cooled and partitioned between H_2O and pentane. The pentane extract was concentrated, filtered to separate the Ph_3PO, and further concentrated to leave 13.92 g of the crude enol ethers **15** as an orange oil which exhibited no infrared absorption in the 6-μ region attributable to the starting ketone **6**. From a comparable experiment, the crude product was chromatographed on silicic acid. The fractions eluted with Et_2O–hexane mixtures were liquid with spectral characteristics consistent with the **enol ether 15**: ir ($CHCl_3$), 1675 cm^{-1} (enol ether C=C); uv (95% EtOH), 214 mμ (ε 19,800), 267 (12,900), 274 (11,300), and 309 (8250); nmr ($CDCl_3$), δ 6.0–7.5 (4 H m, aryl and vinyl CH), 3.66, 3.70, 3.76, and 3.78 (6 H total, 4 s, OCH_3, of stereoisomeric enol ethers **15**), and 0.8–3.5 (10 H m, aliphatic CH); mass spectrum, weak molecular ion *m/e* 244, abundant fragments *m/e* 74, 59, 57, 56, 45, 43, and 41.

A comparable reaction was run with 256 mg (10.6 mmol) of NaH, 14.5 ml of $(CH_3)_2SO$, 3.753 g (10.5 mmol) of methyltriphenylphosphonium bromide, 1.732 g (8.02 mmol) of the ketone **6**, and 10 ml of tetrahydrofuran employing a reaction time of 26 hr at 55–60°. The crude product was chromatographed on neutral alumina (activity I) and the fractions (1.57 g) eluted with hexane were combined, concentrated, and distilled in a short-path still (0.01 mm and 88–93° bath) to separate 1.49 g (87%) of the **olefin 16** as a colorless liquid: ir ($CHCl_3$), 1640 and 870 cm^{-1} (C=CH_2); uv (95% EtOH), 213 mμ (ε 23,800), 252 (10,900), 306 (5430), and 314 (4780); nmr ($CDCl_3$), δ 6.6–7.3 (3 H m, aryl CH), 5.38 (1 H d, *J* = 2 Hz, vinyl CH), 4.93 (1 H

(10) A gas chromatography column packed with silicone gum, SE-30, suspended on Chromosorb P was employed for this analysis.

(11) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(12) G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961).

d, J = 2 Hz, vinyl CH), 3.77 (3 H s, OCH_3), and 1.0–3.5 (10 H m, aliphatic CH); mass spectrum, molecular ion m/e 214, abundant fragments m/e 199, 186, 185, 160, 128, and 115.

Anal. Calcd for $C_{15}H_{19}O$: C, 84.07; H, 8.47. Found: C, 84.11; H, 8.61.

To a cold (0°) solution of the 13.9 g of the crude enol ether **15** in 480 ml of tetrahydrofuran was added, dropwise and with stirring over a 15-min period, 47 ml of aqueous 70% $HClO_4$. The resulting solution was stirred for 2 hr at 25–30° and made basic with aqueous NaOH and concentrated under reduced pressure. The residue was extracted with Et_2O and the extract was dried and concentrated to leave 13.7 g of the crude aldehyde **17** as an orange oil which contained no enol ether (infrared analysis). From a comparable hydrolysis of 294 mg of the enol ether **15**, the crude product (396 mg) was distilled in a short-path still (0.04 mm and 120–130° bath) to separate 226 mg (81%) of the **aldehyde 17** as a pale yellow liquid: ir ($CHCl_3$), 2720 (aldehyde CH) and 1720 cm^{-1} (C=O); uv (95% EtOH), 281 mμ (ε 2790) and 287 sh (2510); nmr ($CDCl_3$), δ 9.70 (1 H d, J = 3 Hz, CHO, a barely discernible doublet, J = 3 Hz, centered at 9.80 suggests the presence of a small amount of the second aldehyde stereoisomer **17** epimeric at C-9), 6.6–7.3 (3 H m, aryl CH), 3.77 (3 H s, OCH_3), 3.57 (1 H, d of d, J = 3 and 6 Hz, ArCHCO), and 1.0–3.3 (10 H m, aliphatic CH); mass spectrum, molecular ion m/e 230, abundant fragments m/e 201, 159, 121, and 115.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.38; H, 8.07.

To a cold (3°) solution of 13.7 g of the crude aldehyde **17** in 1700 ml of acetone was added, dropwise and with stirring over 7 min, 15.8 ml of aqueous 2.67 M H_2CrO_4.[13] After the resulting solution had been stirred for 4 min, excess i-PrOH was added and the solution was concentrated and then partitioned between H_2O and Et_2O. The Et_2O extract was dried and concentrated to leave a crude product (7.48 g of dark oil) which was crystallized (Et_2O–hexane) to separate 5.333 g (46.7% based on the ketone **6**) of crude acid **2** as tan prisms, mp 113–116°. Decolorization (carbon) and recrystallization afforded 4.20 g of the acid **2** (mp 116–118°) as pale tan prisms: mp 117.5–118.5° after further recrystallization; ir ($CHCl_3$), 1705 cm^{-1} (carboxyl C=O); uv (95% EtOH), 218 mμ sh (ε 8670), 282 (2850), and 287 (2580); nmr ($CDCl_3$), δ 11.15 (1 H, COOH), 6.6–7.4 (3 H m, aryl CH), 3.77 (3 H s, OCH_3, superimposed on a second 1 H signal, $ArCHCO_2R$), and 1.0–3.4 (10 H m, aliphatic CH); mass spectrum, molecular ion m/e 246, abundant fragments m/e 203, 201, 159, 115, 91, and 44.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.23; H, 7.51.

Reaction of 1.05 g (4.27 mmol) of the acid **2** with excess ethereal CH_2N_2 afforded 1.178 g of crude neutral product. Distillation in a short-path still (0.05 mm and 115–117° bath) separated 1.04 g (93.8%) of the **methyl ester 14** as a colorless liquid: ir (CCl_4), 1740 cm^{-1} (ester C=O); uv (95% EtOH), 218 mμ (ε 8120), 282 (2940), and 287 sh (2720); nmr ($CDCl_3$), δ 6.5–7.2 (3 H m, aryl CH), 3.70 (3 H s, OCH_3), 3.64 (3 H s, OCH_3), and 1.0–3.7 (11 H m, aliphatic CH); mass spectrum, molecular ion m/e 260, abundant fragments m/e 217, 201, 200, 157, and 115.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.07; H, 7.91.

After a mixture of 506 mg (2.05 mmol) of the acid **2** and 1.2 ml (17 mmol) of $SOCl_2$ had been stirred at 25–30° for 5 hr, the resulting solution was added to excess aqueous NH_3 and then extracted with CH_2Cl_2. The crude amide (514 mg, mp 176–177.5°) obtained from the organic extract was recrystallized (H_2O–EtOH) to separate 433 mg (86.1%) of the **amide 28** as white needles: mp 178.5–179°; ir ($CHCl_3$), 1670 cm^{-1} (amide C=O); uv (95% EtOH), 218 mμ (ε 8320), 282 (2890), and 287 (2590); nmr [$(CD_3)_2SO$], δ 6.4–7.6 (5 H m, NH and aryl CH), 3.64 (3 H s, OCH_3), and 1.0–3.7 (11 H m, aliphatic CH); mass spectrum, molecular ion m/e 245, abundant fragments m/e 201, 200, 159, and 43.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.30; H, 7.95; N, 5.68.

A mixture of 1.005 g (4.08 mmol) of the methoxy acid **2**, 11.5 ml of aqueous 48% HBr, and 11 ml of HOAc was refluxed for 5 hr and then partitioned between water and CH_2Cl_2. The organic phase was dried, concentrated, and crystallized (CH_2Cl_2–hexane) to separate 787 mg (83%) of the **hydroxy acid 27** as tan needles: mp 177–178°; ir (KBr pellet), 3400 (broad, OH) and 1710 cm^{-1} (carboxyl C=O); uv (95% EtOH), 222 mμ sh (ε 7050) and 283 (3050); nmr [$(CD_3)_2SO$], δ 6.3–7.2 (3 H m, aryl CH), 3.58 (1 H d, J = 7 Hz, $ArCHCO_2R$), and 1.0–3.2 (10 H m, aliphatic CH); mass spectrum, abundant fragments m/e 86, 84, 49, 43, and 40.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.19; H, 6.90.

Reaction of the Ketone 6 with Ethyl Chloroacetate.—To a cold (10°), stirred suspension of 1.998 g (9.24 mmol) of the ketone **6**, 1.131 g (9.23 mmol) of ethyl chloroacetate, and 1.5 ml of t-BuOH was added, dropwise and with stirring, a solution of t-BuOK prepared from 395 mg (10.1 mg-atom) of K and 8 ml of t-BuOH.

The reaction mixture was stirred at 15–20° for 2 hr and then concentrated under reduced pressure and extracted with Et_2O. After the Et_2O solution had been washed successively with H_2O and aqueous NaCl and then dried, concentration left 2.687 g of residual pale yellow oil. The thin layer chromatogram[14] of this material showed two spots corresponding in R_f value to the starting ketone **6** and a component believed to be the ester **21a**. The crude product had infrared absorption (CCl_4) at 1735 (ester C=O) and 1715 cm^{-1} (ketone C=O) with prominent nmr peaks (CCl_4) at δ 3.80 and 2.63 attributable to OCH_3 and CH_2CO_2R functions.

A mixture of 1.106 g of this crude product, 710 mg of NaOH, and 7.1 ml of H_2O was refluxed with stirring for 4 hr and then partitioned between H_2O and Et_2O. Concentration of the Et_2O layer separated 201 mg of crude unchanged starting ketone **6**. After the aqueous phase had been acidified and extracted with CH_2Cl_2, the organic extract was dried and concentrated to leave 768 mg of the crude acid **21b**, mp 145–148°. Recrystallization (EtOAc–hexane) separated 593 mg of the **keto acid 21b** as pale tan plates, mp 151–152°. An additional crystallization raised the melting point to 152–153°; ir ($CHCl_3$), 1715 cm^{-1} (br, C=O of ketone and carboxyl group); uv (95% EtOH), 220 mμ (ε 26,700), 249 (8190), and 320 (3650); nmr ($CDCl_3$), δ 10.75 (1 H, COOH), 6.9–7.7 (3 H m, aryl CH), 3.84 (3 H s, OCH_3), 3.38 (1 H m, benzylic CH), 2.86 (2 H s, CH_2CO_2R), and 0.8–2.4 (8 H m, aliphatic CH); mass spectrum, molecular ion m/e 274, abundant fragments m/e 186, 144, 116, 115, 57, 56, 45, 44, 43, and 41.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.07; H, 6.67.

From a comparable reaction employing 1,2-dimethoxyethane as the reaction solvent, the crude product obtained corresponded closely in ir and nmr absorption to the crude product obtained with t-BuOH as the reaction solvent.

Preparation of the Hydroxymethyl Derivatives 18 and 19.—A mixture obtained from 180 mg (4.75 mmol) of $LiAlH_4$, 958 mg (3.89 mmol) of the acid **2**, and 10 ml of Et_2O was stirred at 25–30° for 5 hr, the excess hydride reagent was destroyed with H_2O, and the resulting mixture was partitioned between Et_2O and aqueous 10% H_2SO_4. After the Et_2O extract had been dried and concentrated, the residual oil (933 mg) was distilled in a short-path still (0.07 mm and 130–135° bath) to separate 840 mg (92.8%) of the **alcohol 19** as a pale yellow viscous liquid: ir ($CHCl_3$), 3600 and 3440 cm^{-1} (free and assoc OH); uv (95% EtOH), 219 mμ (ε 7070), 227 (7320), 281 (2930), and 287 sh (2540); nmr ($CDCl_3$), δ 6.7–7.3 (3 H m, aryl CH), 3.82 (3 H s, OCH_3), an overlapping doublet in the region 3.7–3.9 (2 H, CH_2OR), 2.05 (1 H s, disappears with added D_2O, OH), and 1.0–3.5 (11 H m, aliphatic CH); mass spectrum, molecular ion m/e 232, abundant fragments m/e 201, 196, 139, 112, 57, 43, and 41.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.58; H, 8.71.

A comparable reduction employing 1.022 g (27.0 mmol) of $LiAlH_4$, 5.009 g (20.4 mmol) of the acid **1**, and 140 ml of tetrahydrofuran yielded 4.779 g of neutral product as a white solid. Recrystallization from hexane separated 3.821 g (80.8%) of the epimeric **alcohol 18** as white crystals, mp 94–95°, identified with the subsequently described sample by a mixture melting point and comparison of ir and nmr spectra.

A solution containing 4.701 g (21.9 mmol) of the olefin **16** and 13.9 mmol of B_2H_6 in 20 ml of tetrahydrofuran was stirred at 25–30° for 2 hr and then treated with 2.6 ml of water. The resulting mixture was heated to 45–50°, treated successively with

(13) D. C. Kleinfelter and P. von R. Schleyer, *Org. Syn.*, **42**, 79 (1962).

(14) A plate coated with silicic acid and eluted with a hexane–Et_2O mixture was employed for this analysis.

2.5 ml of aqueous 3 *M* NaOH and 2.7 ml of aqueous 30% H_2O_2 and then stirred at 40° for 1.5 hr. After the resulting mixture had been partitioned between aqueous NaCl and Et_2O, the organic layer was dried and concentrated to leave 5.248 g of the crude alcohol, mp 83.5–88°. Recrystallization (hexane) separated 4.18 g (81.9%) of the **alcohol 18** as white crystals, mp 94–94.5°. Recrystallization raised the melting point to 95–95.5°; ir ($CHCl_3$), 3590 and 3440 cm^{-1} (free and assoc OH); uv (95% EtOH), 228 mμ (ε 7820), 282 (3010), and 288 (2610); nmr ($CDCl_3$), δ 6.4–7.2 (3 H m, aryl CH), 3.6–4.2 (2 H m, CH_2OR), 3.71 (3 H s, OCH_3), and 0.8–3.4 (12 H m, OH and aliphatic CH); mass spectrum, molecular ion *m/e* 232, abundant fragments *m/e* 202, 201, 159, 121, and 115.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.58; H, 8.68.

Bromination of the Acid 2.—A solution of 199 mg (0.81 mmol) of the acid **2** in 2 ml of HOAc was treated with 0.05 ml (*ca.* 1 mmol) of Br_2 and the resulting solution was stirred at 25–30° for 1 hr and then concentrated under reduced pressure. Attempts to recrystallize the residual crude **acid 22** (267 mg of viscous orange oil) were unsuccessful; ir ($CHCl_3$), 1710 cm^{-1} (carboxyl C=O); nmr ($CDCl_3$), δ 7.23 (1 H s, aryl CH), 6.85 (1 H s, aryl CH), 3.80 (3 H s, OCH_3), 3.62 (2 H d, J = 6 Hz, $ArCHCO_2R$), and 0.8–3.5 (*ca.* 11 H m, aliphatic CH). A mixture of 173 mg (0.5 mmol) of the crude acid **22** and 1 ml (14 mmol) of $SOCl_2$ was stirred for 4 hr and the resulting solution was poured into aqueous NH_3 and extracted with CH_2Cl_2. The organic extract was dried and concentrated to leave 198 mg of the crude amide **24**, mp 167–170°. Recrystallization (H_2O–EtOH) separated 135 mg (78.5%) of the **bromo amide 24** as white needles, mp 172–173.5°. After recrystallization the material melted at 173.5–174.5°; ir ($CHCl_3$), 1680 cm^{-1} (amide C=O); uv (95% EtOH), 288 mμ (ε 4620) and 294 (4210); nmr [$(CD_3)_2SO$], δ 7.23 (1 H s, aryl CH), 6.85 (1 H s, aryl CH), 7.42 and 6.87 (2 H, br, NH_2), 3.72 (3 H s, OCH_3), 3.52 (1 H d, J = 6 Hz, $ArCHCONR_2$), and 1.0–3.3 (10 H m, aliphatic CH); mass spectrum, abundant fragments *m/e* 186, 144, 116, and 115.

Anal. Calcd for $C_{15}H_{18}BrNO_2$: C, 55.56; H, 5.59; N, 4.32; Br, 24.65. Found: C, 55.75; H, 5.74; N, 4.33; Br, 24.61.

To a cold (0°) solution prepared from 248 mg (1.86 mmol) of $AlCl_3$, 283 mg (3.61 mmol) of AcCl, and 0.6 ml of CH_2Cl_2 was added, dropwise and with stirring, a solution of 252 mg (*ca.* 0.7 mmol) of the crude bromo acid **22** in 1.2 ml of CH_2Cl_2. Gas evolution was observed during the addition. The resulting mixture was stirred at 0° for 15 min and at 25–30° for 45 min and then partitioned between aqueous HCl and CH_2Cl_2. The organic extract was dried and concentrated and the residual yellow solid (205 mg) was recrystallized (H_2O–EtOH) to separate 90.2 mg (44%) of the **bromo olefin 26** as pale yellow plates, mp 130.5–132°. Recrystallization raised the melting point to 131–133°; ir ($CHCl_3$), 1630 cm^{-1} (C=C); uv (95% EtOH), 217 mμ (ε 27,900), 269 (13,400), 280 sh (10,600), 306 (2750), and 316 sh (1950); nmr ($CDCl_3$), δ 7.17 (1 H s, aryl CH), 6.88 (1 H s, aryl CH), 3.81 (3 H s, OCH_3), 3.09 (2 H, br, benzylic CH_2), 2.1–2.5 (4 H m, allylic CH_2), and 1.5–2.0 (4 H m, aliphatic CH_2); mass spectrum, molecular ion *m/e* 280 (^{81}Br isotope), abundant fragments *m/e* 252, 250, 199, 171, and 128.

Anal. Calcd for $C_{14}H_{15}BrO$: C, 60.23; H, 5.42; Br, 28.59. Found: C, 60.22; H, 5.27; Br, 28.80.

Acetylation of the Acid 2.—To a cold (0°) solution prepared from 752 mg (5.63 mmol) of $AlCl_3$, 773 mg (9.83 mmol) of AcCl, and 1.6 ml of CH_2Cl_2 was added a solution of 492 mg (2.00 mmol) of the acid **2** in 2.6 ml of CH_2Cl_2. The resulting solution was stirred at 0° for 20 min and at 25–30° for 40 min and partitioned between aqueous HCl and CH_2Cl_2. After the CH_2Cl_2 solution had been dried and concentrated, the crude **keto acid 23** was obtained as a viscous oil (634 mg) which could not be induced to crystallize; ir ($CHCl_3$), 1710 (carboxyl C=O) and 1660 cm^{-1} (conjugated ketone C=O); nmr ($CDCl_3$), δ 9.27 (1 H s, COOH), 7.43 (1 H s, aryl CH), 6.93 (1 H s, aryl CH), 3.82 (3 H s, OCH_3), 3.69 (1 H d, J = 6 Hz, $ArCHCO_2R$), 2.55 (3 H s, CH_3CO), and 1.0–3.5 (10 H, aliphatic CH).

A solution of 289 mg (1 mmol) of the crude keto acid **23** and 1.8 ml of an aqueous solution containing 2.7 mmol of NaOCl in 5 ml of aqueous 10% NaOH was stirred at 25–30° for 5 min and at 40° for 30 min. The resulting solution was successively treated with aqueous $NaHSO_3$, extracted with CH_2Cl_2, acidified with aqueous HCl, and extracted with CH_2Cl_2. After the final extract had been dried and concentrated, an Et_2O solution of the residual solid (231 mg) was decolorized (carbon) and diluted with hexane. The **diacid 25** separated as 221 mg (76.3% based on acid **2**) of white needles: mp 211–212°; ir (KBr pellet), 1740 (intramolecularly H-bonded carboxyl C=O) and 1710 cm^{-1} (carboxyl C=O); uv (95% EtOH), 212 mμ (ε 30,400), 243 (8540), and 304 (4480); nmr ($CDCl_3$), δ 10.6 (2 H s, COOH), 7.81 (1 H s, aryl CH), 7.05 (1 H s, aryl CH), 3.98 (3 H s, OCH_3), 3.75 (1 H d, J = 6 Hz, $ArCHCO_2R$), and 1.0–3.5 (10 H m, aliphatic CH); mass spectrum, abundant fragments *m/e* 58, 57, 56, 44, and 43.

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.17; H, 6.28.

Preparation of the Hydroxy Acids 30 and 34.—To a vigorously stirred mixture of 31.73 g (0.330 mol) of sublimed (220–250° at 0.05 mm), powdered *t*-BuONa, 34.7 g (0.159 mol) of the alcohol **8**, and 500 ml hexane was added, dropwise over a 15-min period, 230 ml of a hexane solution containing 0.356 mol of *n*-BuLi, while the reaction mixture was kept at approximately 30°. The resulting dark red solution was stirred at 25–30° for 1 hr and then siphoned, with stirring, into a flask containing powdered Dry Ice. The reaction mixture was diluted with 450 ml of H_2O and then 30 g of Na_2CO_3 was added with stirring and the resulting mixture was allowed to stand overnight. The relatively insoluble sodium salt of acid **30** was collected. From the remaining organic layer, 2.32 g of the crude unchanged alcohol **8** was recovered. The sodium salt of acid **30** was acidified with aqueous HCl and extracted with CH_2Cl_2. After the CH_2Cl_2 extract had been dried and concentrated, the residual acid (36.90 g) was recrystallized (CH_2Cl_2–hexane) to separate 33.8 g (88.0% based on unrecovered alcohol) of the acid **30**, mp 133–137°. The pure **hydroxy acid 30** crystallized (CH_2Cl_2–hexane) as white needles: mp 136–137°; ir ($CHCl_3$), 3240 (broad, OH) and 1725 cm^{-1} (carboxyl C=O); uv (95% EtOH), 291 mμ (ε 2860) with intense end absorption; nmr ($CDCl_3$), δ 7.4–8.8 (2 H br, OH and COOH), an AB pattern with J = 9 Hz and estimated line positions of 7.38 and 6.97 (2 H, aryl CH at C-5 and C-6), 5.35 (1 H d, J = 6.5 Hz, ArCHOR), 4.05 (3 H s, OCH_3), and 1.0–3.1 (10 H m, aliphatic CH); mass spectrum, abundant fragments *m/e* 258, 244, 226, 213, 212, 198, and 184.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.49; H, 6.89.

Reaction of 2.758 g (10.5 mmol) of the acid **30** with excess ethereal CH_2N_2 yielded 2.70 g (92.8%) of the **methyl ester 40** as white needles (mp 120.5–121.5°) from hexane. Recrystallization raised the melting point to 121–122°; ir ($CHCl_3$), 3570, 3400 (OH), 1735, and 1705 cm^{-1} (ester C=O, partial intramolecular H bonding); uv (95% EtOH), 292 mμ (ε 3190); nmr ($CDCl_3$), AB pattern with J = 8.5 Hz and estimated line positions of δ 7.27 and 6.87 (2 H, aryl CH at C-5 and C-6), 5.17 (1 H br t, collapsed to d, J = 6 Hz, upon addition of D_2O, ArCHOR), 3.92 (3 H s, OCH_3), 3.83 (3 H s, OCH_3), and 1.0–3.3 (11 H m, OH and aliphatic CH); mass spectrum, molecular ion *m/e* 276, abundant fragments *m/e* 248, 243, 216, 201, 165, 115, 44, and 41.

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.54; H, 7.34.

To a stirred solution prepared from 2.010 g (9.22 mmol) of the alcohol **8**, 50 ml of hexane, 5.95 ml of a hexane solution containing 9.22 mmol of *n*-BuLi, and 1.12 g (9.62 mmol) of $(Me_2NCH_2-)_2$ was added 6.10 ml of a hexane solution containing 9.45 mmol of *n*-BuLi. The resulting mixture from which a tan precipitate began to separate after 2 min, was refluxed with stirring for 30 min and then siphoned into a stirred mixture of Dry Ice and hexane. The resulting mixture was extracted with aqueous Na_2CO_3 and the remaining hexane solution was concentrated to separate 525 mg of the unchanged alcohol **8**. After the aqueous extract had been acidified and extracted with CH_2Cl_2, the organic layer was dried and concentrated to leave 1.836 g of the crude acidic products as a yellow oil. Fractional crystallization (CH_2Cl_2–hexane and CH_2Cl_2) separated 1.4713 g (82.3%) of crystalline fractions containing various proportions of the acids **30** and **34**. Recrystallization of the more soluble fractions separated a sample of the pure **hydroxy acid 30** as white needles, mp 136–137°, identified with the previously described sample by comparison of ir spectra. From the less soluble fractions, recrystallization (CH_2Cl_2–hexane) separated the pure **hydroxy acid 34** as white needles: mp 154–156°; ir ($CHCl_3$), 3570, 3260 (OH), and 1730 cm^{-1} (carboxyl C=O); uv (95% EtOH), 213 mμ (ε 28,200), 244 (7920), and 304 (4170); nmr (pyridine-d_5), δ 11.2 (2 H br, OH and COOH), 8.07 (1 H s, aryl CH), 7.43 (1 H s, aryl CH), 5.43 (1 H d, J = 6 Hz, ArCHOR), 3.81 (3 H s, OCH_3), and 0.9–3.4 (10 H m, aliphatic CH); mass spectrum,

abundant fragments *m/e* 200, 172, 171, 141, 129, 128, 115, and 44.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.45; H, 6.84.

Preparation of the Keto Acid Derivatives 41 and 42.—After reaction of 1.002 g (3.82 mmol) of the hydroxy acid **30** with 1.2 ml (3.2 mmol) of aqueous 2.67 *M* H_2CrO_4[13] in 100 ml of acetone at 2–4° for 5 min, the excess oxidant was destroyed with *i*-PrOH and the solution was concentrated and partitioned between H_2O and CH_2Cl_2. The organic layer was dried and concentrated to leave 917 mg (92.3%) of the crude keto acid **41** as a tan solid, mp 211–215°. An EtOH solution of the product was decolorized (charcoal) and diluted with hexane. The pure **keto acid 41** crystallized as pale yellow prisms: mp 214–216°; ir ($CHCl_3$), 1715 cm^{-1} (br, carboxyl and ketone C=O); uv (95% EtOH), 218 mμ (ε 23,200), 248 (6490), and 323 (4060); nmr (pyridine-d_5), δ 14.4–15.4 (1 H, COOH), AB pattern with J = 8.5 Hz and line positions estimated to be 7.43 and 7.30 (2 H, aryl CH at C-5 and C-6), 3.79 (3 H s, OCH_3), and 0.8–3.5 (10 H m, aliphatic CH).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.19; H, 6.24.

The same reaction procedure was followed with 989 mg (3.59 mmol) of the hydroxy ester **40** and 1.15 ml (3.07 mmol) of aqueous 2.67 *M* H_2CrO_4[13] in 60 ml of acetone. The crude product (1.177 g of pale yellow oil) was distilled in a short-path still (0.07 mm and 160–170° bath) to separate 966 mg of the **keto ester 42** as a viscous yellow liquid: ir ($CHCl_3$), 1720 cm^{-1} (broad, ester and ketone C=O); uv (95% EtOH), 220 mμ (ε 23,700), 244 (6650), and 323 (4280); nmr ($CDCl_3$), AB pattern with J = 8.5 Hz and estimated line positions of δ 7.48 and 7.20 (2 H, aryl CH at C-5 and C-6), 3.95 (3 H s, OCH_3), 3.85 (3 H s, OCH_3), and 0.9–3.5 (10 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 274, abundant fragments *m/e* 259, 243, 241, 115, 104, 77, 59, 55, 45, 44, 43, 41, and 39.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.92; H, 6.59.

Preparation of the Unsaturated Acid Derivatives 35 and 43.—A solution of 4.857 g (18.6 mmol) of the hydroxy acid **30** and 436 mg of TsOH in 125 ml of PhH was refluxed with continuous separation of H_2O for 1 hr and then washed with H_2O, dried, and concentrated. The residual unsaturated acid **35**, mp 155–157°, amounted to 4.468 g (98.8%). A portion of the material was recrystallized (CH_2Cl_2-hexane) to give the pure **unsaturated acid 35** as pale yellow prisms: mp 161.5–162.5°; ir ($CHCl_3$), 1730 cm^{-1} (ester C=O); uv (95% EtOH), 232 mμ (ε 21,800), 264 (11,500), and 318 (4140); nmr ($CDCl_3$), δ 11.20 (1 H s, COOH), 7.38 (1 H s, vinyl CH), 7.40 (1 H d, J = 8 Hz, aryl CH), 6.73 (1 H d, J = 8 Hz, aryl CH), 4.00 (3 H s, OCH_3), and 0.8–3.2 (9 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 244, abundant fragments *m/e* 226, 212, and 198.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.74; H, 6.55.

A 119-mg (0.487 mmol) sample of the unsaturated acid was esterified with excess ethereal CH_2N_2 and the crude product was recrystallized (hexane) to separate 74.5 mg (59.5%) of the **unsaturated ester 43** as pale yellow plates: mp 95–96°; ir ($CHCl_3$), 1720 (ester C=O) and 1615 cm^{-1} (C=C); uv (95% EtOH), 235 mμ (ε 21,200), 262 (11,300), and 316 (4300); nmr ($CDCl_3$), δ 7.31 (1 H d, J = 8.5 Hz, aryl CH), 6.68 (1 H d, J = 8.5 Hz, aryl CH), 6.60 (1 H s, vinyl CH), 3.92 (3 H s, OCH_3), 3.83 (3 H s, OCH_3), and 0.8–3.2 (9 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 258, abundant fragments *m/e* 227, 226, 199, 198, 141, 128, and 115.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.29; H, 7.05.

Preparation of the Unsaturated Diesters 36 and 37a.—To a solution of 4.051 g (16.6 mmol) of the unsaturated acid **35** in 100 ml of tetrahydrofuran was added, dropwise and with stirring, 23 ml of an Et_2O solution containing 37.3 mmol of MeLi. During the initial phase of the addition a white precipitate separated and then largely redissolved as the addition continued to give a deep red solution. After the solution had been stirred at 35–40° for 15 min it was siphoned onto Dry Ice with thorough mixing. The resulting mixture was diluted with Et_2O and extracted with aqueous Na_2CO_3. The aqueous extract was acidified (HCl) and the crude acid mixture which separated was collected, dissolved in 100 ml of tetrahydrofuran, and esterified with excess ethereal CH_2N_2. The neutral product, a mixture[14] of esters **36** and **37a**, amounted to 5.289 g of a pale orange oil which partially crystallized on standing. The material was chromatographed (SiO_2). The early fractions eluted (1% Et_2O in PhH) were recrystallized (EtOH) to separate 1.60 g (30.5%) of the **diester 36** as white prisms: mp 105.5–106°; ir ($CHCl_3$), 1725 cm^{-1} (ester C=O); uv (95% EtOH), 235 mμ (ε 28,800) and 317 (3850); nmr ($CDCl_3$), δ 7.45 (1 H d, J = 8.5 Hz, aryl CH), 6.73 (1 H s, vinyl CH), 6.69 (1 H d, J = 8.5 Hz, aryl CH), 3.93, 3.85 3.61 (three 3 H s, OCH_3), and 0.8–3.2 (8 H m, aliphatic CH); mass spectrum, molecular ion *m/e* 316, abundant fragments *m/e* 284, 257, 256, 225, 46, 45, 43, and 31.

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.28; H, 6.44.

The later fractions eluted (2–4% Et_2O in PhH) were combined and recrystallized (EtOH) to separate 2.00 g (38%) of the **diester 37a** as white needles: mp 91–91.5°; ir ($CHCl_3$), 1730 cm^{-1} (ester C=O); uv (95% EtOH), 273 mμ (ε 14,000) with intense end absorption (ε 22,900 at 210 mμ); nmr ($CDCl_3$), δ 7.22 (1 H d, J = 8.5 Hz, aryl CH), 6.89 (1 H d, J = 8.5 Hz, aryl CH), 4.44 (1 H br, $ArCHCO_2R$), 3.86 (6 H s, OCH_3), 3.64 (3 H s, OCH_3), 2.1–2.7 (4 H m, allylic CH_2), and 1.5–2.1 (4 H m, aliphatic CH_2); mass spectrum, molecular ion *m/e* 316, abundant fragments *m/e* 257, 256, 225, 44, and 31.

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.49; H, 6.52.

A mixture of 485 mg (1.54 mmol) of the diester **37a**, 156 mg (3.89 mmol) of NaOH, and 7 ml of H_2O was refluxed under N_2 for 45 min. The resulting solution was acidified to separate the crude acidic product which was collected and recrystallized (H_2O–MeOH). The diacid **37b** separated as 329 mg (74%) of white needles, mp 187° dec (dependent on rate of heating). Recrystallization raised the decomposition point of the **diacid 37b** to 200° (dependent on rate of heating); ir (KBr pellet), 1720 (carboxyl C=O) and 1640 cm^{-1} (C=C); uv (95% EtOH), 273 mμ (ε 13,400) and 333 (2220); nmr (pyridine-d_5), AB pattern (J = 8 Hz) with estimated line positions at δ 7.32 and 7.03 (2 H, aryl CH), 5.05 (1 H br s, $ArCHCO_2R$), 3.81 (3 H s, OCH_3), 2.0–3.0 (4 H m, allylic CH_2), and 1.3–2.0 (4 H m, aliphatic CH_2).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.68; H, 5.66.

Hydrogenation of the Diester 37a.—A solution of 324 mg (1.03 mmol) of the diester **37a** in 7.5 ml of MeOH was hydrogenated at 25° and atmospheric pressure over 62.5 mg of a 5% Pt-C catalyst. After 2.75 hr the H_2 uptake (25 ml or 1.0 equiv) ceased and the mixture was filtered and concentrated. The residual crude diester **38** amounted to 339 mg of colorless liquid [ir ($CHCl_3$), 1730 cm^{-1} (ester C=O)] which has three nmr peaks ($CDCl_3$) attributable to methoxyl groups at δ 3.85, 3.77, and 3.68. A mixture of this crude diester with 294 mg (7.35 mmol) of NaOH and 20 ml of H_2O was refluxed for 1.75 hr and the resulting solution was acidified and extracted with CH_2Cl_2.

After the organic extract had been dried and concentrated, a solution of the crude acidic product in PhH–CH_2Cl_2 deposited 258 mg (86.3%) of the crystalline diacid **4**, mp 190–191° dec. Recrystallization (acetone-hexane) afforded the **diacid 4** as white needles: mp 189.5–190.5° dec; ir (KBr pellet), 1735 and 1690 cm^{-1} (carboxyl C=O); uv (95% EtOH), 299 mμ (ε 3280) with intense end absorption; nmr (pyridine-d_5), δ 14.80 (2 H s, carboxyl OH), AB pattern (J = 8.5 Hz) with estimated line positions at 7.29 and 6.93 (2 H, aryl CH), 4.45 (1 H d, J = 4 Hz, $ArCHCO_2R$), 3.73 (3 H s, OCH_3), and 1.0–3.9 (10 H m, aliphatic CH).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.18; H, 6.22.

A 149-mg sample of the diacid **4** was esterified with ethereal CH_2N_2 to yield 170 mg of the crude diester **39** as a pale yellow oil. The crude product was distilled in a short-path still (0.05 mm and 140–150° bath) to separate 143 mg (88%) of the **diester 39** as a pale yellow liquid: ir ($CHCl_3$), 1730 cm^{-1} (ester C=O); uv (95% EtOH), 300 mμ (ε 3470) with intense end absorption (ε 25,500 at 210 mμ); nmr ($CDCl_3$), AB pattern (J = 9 Hz) with estimated line positions at δ 7.27 and 6.88 (2 H, aryl CH), 3.84 (6 H s, OCH_3), 3.65 (3 H s, OCH_3), and 0.9–4.0 (11 H m, aliphatic CH); mass spectrum, weak molecular ion *m/e* 318, abundant fragments *m/e* 258, 220, 206, 205, and 57.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 68.33; H, 7.14.

Hydrogenation of the Diacid 37b.—A solution of 422 mg (1.45 mmol) of the diacid **37b** in a mixture of 20 ml of HOAc and 20 ml of tetrahydrofuran was hydrogenated at 25° and atmospheric pressure over 81.7 mg of a 5% Pt-C catalyst. After 2.75 hr when the H_2 uptake was 37.0 ml (1.04 equiv), the mixture was

filtered and concentrated. The residual solid was recrystallized (acetone–hexane) to separate 343.6 mg (81.2%) of the diacid **3** as white needles, mp 196.5–198.5° dec. Recrystallization raised the decomposition point to 201–203°; ir (KBr pellet), 1705 cm^{-1} (carboxyl C=O); uv (95% EtOH), 300 mμ (ε 3390) with intense end absorption; nmr (pyridine-d_5), δ 12.8–14.2 (2 H br, carboxyl OH), AB pattern (J = 8.5 Hz) with estimated line position at 7.28 and 6.95 (2 H, aryl CH), 4.71 (1 H d, J = 7 Hz, $ArCHCO_2R$), 3.78 (3 H s, OCH_3), and 0.8–3.5 (10 H m, aliphatic CH).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.52; H, 6.44.

A solution of 120 mg (0.415 mmol) of the diacid **3** and 574 mg (8.7 mmol) of KOH in 3.5 ml of $HOCH_2CH_2OH$ was refluxed under N_2 for 2.5 hr and then poured into H_2O, acidified, and extracted with CH_2Cl_2. After the organic extract had been dried and concentrated, the residual crystalline diacid **4** (95.9 mg or 79.8%, mp 184.5–186° dec) was recrystallized (acetone–hexane) to separate the diacid **4**, mp 187–188° dec, identified with the previously described sample by a mixture melting point and comparison of ir spectra.

A 166-mg sample of the diacid **3** was esterified with ethereal CH_2N_2 and the crude neutral product was distilled in a short-path still (0.05 mm and 140–150° bath) to yield 168 mg (92%) of the diester **38** as a colorless liquid: ir ($CHCl_3$), 1735 cm^{-1} (ester C=O); uv (95% EtOH), 302 mμ (ε 3750) with intense end absorption (ε 27,700 at 210 mμ); nmr ($CDCl_3$), AB pattern (J = 8.5 Hz) with estimated line positions at δ 7.27 and 6.90 (2 H, aryl CH), 4.22 (1 H d, J = 6 Hz, $ArCHCO_2R$), 3.86, 3.79, 3.68 (three 3 H s, OCH_3), and 0.8–3.5 (10 H m, aliphatic CH); mass spectrum, molecular ion m/e 318, abundant fragments m/e 220, 206, 205, 126, 84, 83, 55, and 43.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.73; H, 7.06.

Metallation of the Alcohol 18.—A suspension of 2.501 g (10.8 mmol) of the alcohol **18** in 55 ml of hexane was treated with a hexane solution containing 11.9 mmol of *n*-BuLi. A solution was formed from which a new precipitate slowly separated. To this stirred suspension was added 1.443 g (12.4 mmol) of $(Me_2NCH_2-)_2$ and 12.4 mmol of *n*-BuLi in hexane solution. The resulting suspension was refluxed for 45 min and then added to excess Dry Ice with thorough agitation. The usual isolation procedure separated 981 mg of crude starting material in the neutral fraction and 2.077 g of crude acid product as an oil. This acidic product was esterified with ethereal CH_2N_2 to give 2.119 g of orange oil which contained[14] three components. Chromatography on SiO_2 separated an additional 326 mg of the starting alcohol **18** (eluted with Et_2O–PhH) followed by 245 mg of a liquid fraction (eluted with Et_2O–PhH) with ir and nmr absorption suggesting it to be a mixture of the ester **32** and the lactone **33**. Our efforts to obtain either of these components pure were unsuccessful.

Later chromatographic fractions (eluted with Et_2O–PhH) afforded 328 mg of crude ester **31** which was recrystallized (CH_2Cl_2–hexane). The pure **ester 31** separated as 246 mg of white needles: mp 115.5–116°; ir ($CHCl_3$), 3590, 3470 (OH), and 1720 cm^{-1} (ester C=O); uv (95% EtOH), 215 mμ (ε 34,500), 244 (9300), and 304 (4750); nmr ($CDCl_3$), δ 7.58 (1 H br s, aryl CH), 7.05 (1 H br s, aryl CH), 4.05 (2 H d, J = 3.5 Hz, CH_2OR), 3.88 (6 H s, OCH_3), and 0.7–3.5 (12 H m, OH and aliphatic CH); mass spectrum, abundant fragments m/e 57, 45, 44, 43, 41, 31, 29, 28, 18, and 17.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.38; H, 7.64.

Registry No.—**1**, 19765-79-8; **2**, 19765-80-1; **3**, 19765-81-2; **4**, 19765-82-3; **6**, 19765-83-4; **8**, 19765-84-5; **9**, 19766-18-8; **10**, 19765-85-6; **11**, 19766-19-9; **12**, 19766-20-2; **13**, 19765-86-7; **14**, 19765-87-8; **15**, 19765-88-9; **16**, 19765-89-0; **17**, 19765-90-3; **18**, 19765-91-4; **19**, 19765-92-5; **21b**, 19765-93-6; **22**, 19765-94-7; **23**, 19765-95-8; **24**, 19779-41-0; **25**, 19765-96-9; **26**, 19766-21-3; **27**, 19779-42-1; **28**, 19765-97-0; **30**, 19765-98-1; **31**, 19765-99-2; **34**, 19766-00-8; **35**, 19766-22-4; **36**, 19766-23-5; **37a**, 19766-24-6; **37b**, 19766-01-9; **38**, 19779-43-2; **39**, 19766-02-0; **40**, 19766-03-1; **41**, 19766-04-2; **42**, 19766-05-3; **43**, 19766-25-7.

Notes

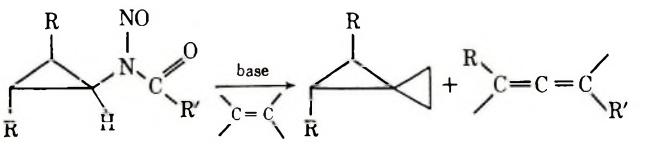
Effects of Solvent on the Cyclopropylidene–Allene Conversion[1]

W. M. JONES[2] AND JOHNNY M. WALBRICK

Department of Chemistry, University of Florida, Gainesville, Florida 32601

Received December 16, 1968

In previous investigations in these laboratories on the chemistry of substituted diazocyclopropanes and cyclopropylidenes, it was found that treatment of the N-nitrosourea or N-nitrosocarbamate of a cyclopropane with base in the presence of an alkene gives a very clean reaction yielding primarily two products, a spiropentane and an allene.[3-5] In an attempt to gain insight into the precursors of these products, the reaction using the 2,2-diphenylcyclopropyl system was studied in some



detail. From a variety of observations, it was concluded that both the spiropentane and the allene have the carbene as a common precursor. However, if this were the sole progenitor to both products, it was reasoned that a plot of the ratio of spiropentane to allene *vs.* the concentration of alkene should be linear. In fact, when such a plot was made (Figure 1), it showed a strong curvature.[5] Furthermore, although it was recognized that the curvature could arise from a solvent effect as a result of the large change in alkene concentration (1.14–11.35 M) the exceptionally good fit to

(1) Based partly upon a dissertation submitted by J. M. Walbrick to the Faculty of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Alfred P. Sloan Fellow, 1963–1967.

(3) W. M. Jones, M. H. Grasley, and D. G. Baarda, *J. Am. Chem. Soc.*, **86**, 912 (1964); D. L. Muck and W. M. Jones, *ibid.*, **88**, 74 (1966); W. M. Jones, D. L. Muck, and T. K. Tandy, Jr., *ibid.*, **88**, 68 (1966); W. M. Jones and D. L. Muck, *ibid.*, **88**, 3798 (1966); for additional work on cyclopropylidenes, see P. S. Skell and R. R. Engel, *ibid.*, **89**, 2912 (1967), and references included therein.

(4) W. M. Jones, *ibid.*, **82**, 6200 (1960); W. M. Jones, M. H. Grasley, and W. S. Brey, Jr., *ibid.*, **85**, 2754 (1963).

(5) W. M. Jones and M. H. Grasley, *Tetrahedron Letters*, 927 (1962).

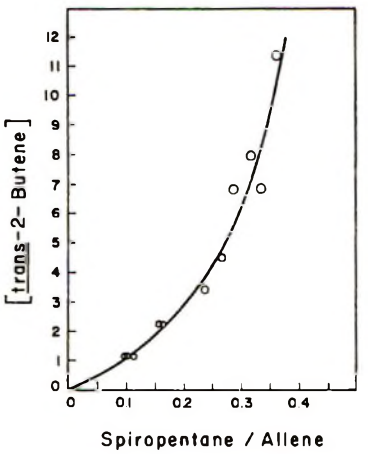
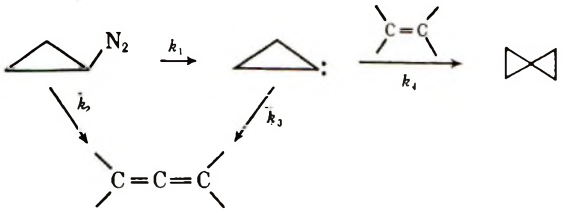


Figure 1.—Dependence of spiropentane/allene ratio on 2-butene concentration (diluted with *n*-heptane).

SCHEME I



the curve calculated from the more complex scheme (Scheme I) involving two different intermediates led us to prefer a reaction scheme in which both the diazocyclopropane and the carbene gave the allene.[5] At this time we report a variety of recent observations that lead us to the conclusion that the curve in Figure 1 does, in fact, result from a medium effect and, as a result, two distinct allene precursors are not required in this reaction.

We were led to this new conclusion in a somewhat circuitous way. During an investigation of the formation of optically active 1,3-diphenylallene from the corresponding optically active ethyl N-nitroso-N-(*trans*-2,3-diphenylcyclopropyl)carbamate[6] it was found that the activity of the allene did not change as the solvent was varied over the range from pure cyclohexane to cyclohexene. The allene was obtained with rotations of 686 ± 30° and 683 ± 30° in cyclohexane and cyclohexene, respectively. If Scheme I were operative, increased cyclohexene concentration would decrease the amount of allene resulting from the carbene. Since it is highly unlikely that the ring opening of both the carbene and the diazocyclopropane, with their different steric circumstances[6] as well as different symmetry-allowed ring-opening modes[7] would lead to allene of the same optical purity, it was necessary to consider the possibility that the allene in fact has only one precursor. To this end a plot of the ratio of spiropentane to allene *vs.* olefin concentration was carried out on the 2,3-diphenylcyclopropyl system in essentially the same manner as that reported for the 2,2-diphenylcyclopropyl system. In fact, when the reaction was carried out in varying mixtures of cyclohexane and cyclohexene, once

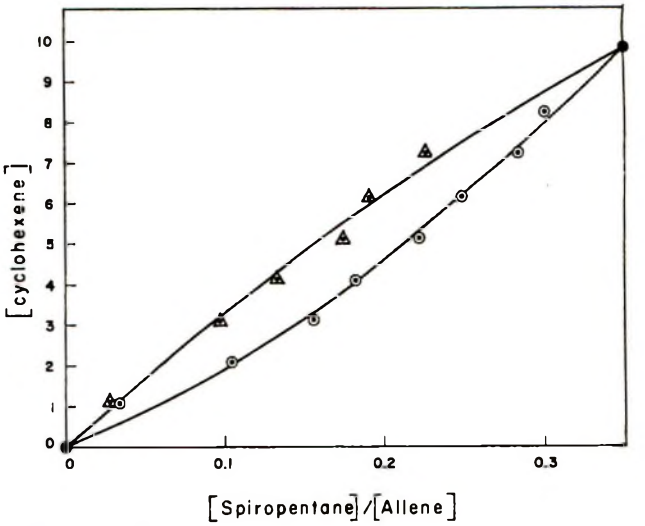


Figure 2.—Dependence of spiropentane/allene ratio on cyclohexene concentration: ⊙ diluted with cyclohexane, Δ diluted with benzene.

again a marked curvature in the plot was observed (Figure 2), albeit less severe.

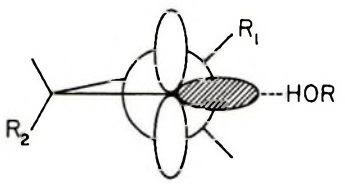
As a possible resolution to the apparent dichotomy created by the optical activity studies which pointed to a single allene precursor and the competition studies which favored a dual mechanism, we looked to a possible solvent effect as the cause of the latter. To test this hypothesis, a solvent was sought which would meet two basic requirements: (1) polarity equal to or greater than cyclohexene and (2) inertness to the intermediate (most certainly the carbene). The solvent that was finally found to meet these requirements was benzene. Polarity was determined for cyclohexane, cyclohexene, and benzene using the Berson Ω criterion.[8] Ω values were found to be 0.595, 0.506, and 0.497, respectively. Inertness of the carbene to benzene was evidenced by the complete absence (<1%) of new products. The results of this investigation using cyclohexene–benzene mixtures are shown in Figure 2. It will be noted that the resulting curve is actually in the opposite direction from the cyclohexane case. For this to be consistent with Scheme I, k_1/k_2 must be negative. Since this is a physical impossibility, it must be concluded that Scheme I is not a proper description of the reaction under consideration. Furthermore, when a few points were taken for an evaluation of the effect of using benzene as the diluting solvent on the previously reported 2,2-diphenylcyclopropyl system, it was found that again the direction of the curvature was reversed. It was also found that, in the 2,3-diphenylcyclopropyl system (the only one studied under the following conditions) the direction of curvature became even more severe as solvent polarity was increased beyond benzene. For example, the spiropentane/allene ratios resulting from the generation of the 2,3-diphenylcyclopropylidene in 1.03 *M* cyclohexene in cyclohexane, benzene, and methylene bromide were found to be 0.034, 0.028, and 0.013, respectively. In other words, the rate of addition of the carbene to olefin relative to its collapse to the allene appears to be sensitive to solvent polarity, the more polar the solvent, the more the

(6) J. M. Walbrick, J. W. Wilson, Jr., and W. M. Jones, *J. Am. Chem. Soc.*, **90**, 2895 (1968); W. M. Jones, J. W. Wilson, Jr., and F. B. Tutwiler, *ibid.*, **85**, 3309 (1963).

(7) Private communication from Professor R. Hoffmann, Cornell University.

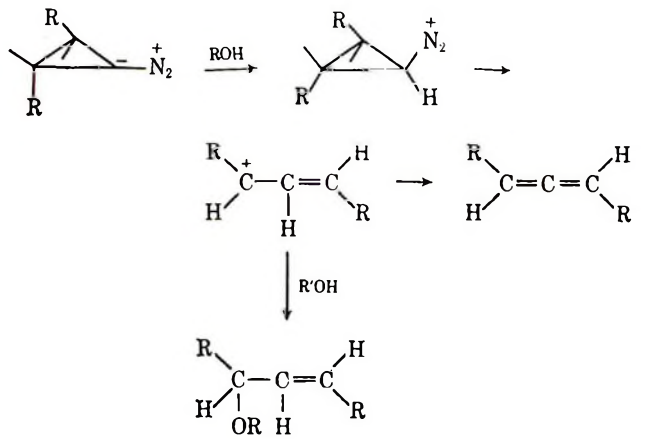
(8) A. Berson, Z. Hamlet, and W. A. Mueller, *J. Am. Chem. Soc.*, **84**, 297 (1962).

ring opening is favored.[9-11] This could arise either from an increase in the rate of ring opening, a decrease in the rate of spiropentane formation, or a combination of both. At this time, these two possibilities cannot be distinguished. However, it should be noted that due to the differences in symmetry of the two cyclopropanes the greater degree of curvature in Figure 1 relative to Figure 2 would be anticipated if the ring-opening transition state were more polar than the carbene. However, it is difficult to understand why the rate of the electrocyclic ring opening of the symmetrical 2,3-diphenylcyclopropylidene would be affected by changes in solvent polarity in view of the observations of both Battiste[12] and Criegee,[13] who have found that the rate of



comparable ring openings of cyclobutenes is insensitive to the nature of the medium.

It was also found that, in contrast to the insensitivity of the stereochemistry of the ring opening to minor variations in solvent polarity (cyclohexane, cyclohexene, and benzene gave nearly identical rotations), protonic solvents showed dramatic effects on this property. Thus, the 1,3-diphenylallene obtained from reactions in benzene, *t*-butyl alcohol, and methanol was found to have rotations of 607 ± 30°, 350 ± 30°, and 197 ± 30°, respectively. Inasmuch as the direction of ring opening is apparently controlled by steric repulsion of the 2,3 substituents, this decrease in activity with increased acid strength may simply reflect an increase in the effective bulkiness at C-1 resulting from solvation. This effect can be seen by using a Newman projection and sighting down the 1,2 bond of I. Factors that promote rotation of R_1 in a clockwise direction should lead to increased activity while any effect that could promote counterclockwise rotation would cause a decrease in activity. Thus, if the alcohol solvates the carbene by hydrogen bonding to the nonbonded pair, the effective bulkiness should be increased in such a way as to promote counterclockwise rotation of R_1 and a net decrease in activity.[14]



Finally it should be noted that these reactions are extremely "clean" reactions and yields are essentially quantitative. Glpc analyses of the reaction products show that in addition to 1,3-diphenylallene the reactions in benzene and methylene bromide yielded no other reaction products (<1% detectable), the reaction in pure cyclohexane yielded only one additional product (2.6%, presumably the corresponding insertion product), the reaction in methanol yielded only one other product, 1-methoxy-*trans*-2,3-diphenylcyclopropane (33%), and the reaction in cyclohexene yielded only one other product, the spiropentane (26%). The optically active spiropentane, $[\alpha]^{25}D$ +135°, isolated from the reaction in cyclohexene is to our knowledge the first optically active spiropentane to be reported.

In conclusion, one final point should be emphasized. Whereas the results presented in this paper eliminate the necessity for two different precursors in this reaction, and, in fact, support a single intermediate, they do not define its structure. However, from the previously reported properties of the spiropentane precursor,[3-5] there can be little doubt but that it is the carbene in the singlet (ground ?) state.

Experimental Section

General.—Melting points were determined in a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Model 1R10 infrared spectrophotometer. Nuclear magnetic resonance spectra were run in dilute carbon tetrachloride solution on a Varian A-60A spectrometer using tetramethylsilane as internal reference. Chemical shifts are recorded as parts per million on the τ scale, coupling constants as cycles per second. Nuclear magnetic resonance data are recorded in the order: chemical shift (multiplicity, where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, coupling constant), integration, and interpretation. Optical rotations were measured in 1-dm tubes with a Perkin-Elmer Model 141 high-precision digital read-out polarimeter. Concentrations are given in g/100 ml. The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Analytical thin layer chromatography was accomplished on 2 × 8 in. plates coated in this laboratory with 0.25-mm layers of Merck silica gel HF_{254} using ultraviolet detection. Gas–liquid partition chromatography (glpc) was performed on two instruments manufactured by Wilkins Instrument and Research, Inc., Walnut Creek, Calif. The analytical glpc was accomplished on a Model 600-D Hi-Fi gas chromatograph, equipped with a hydrogen flame ionization detector and employing nitrogen as a carrier gas. The preparative work was accomplished on a Model A-350-B dual-column, temperature-programming gas chromatograph fitted with a thermistor detector and employing helium as a carrier gas. The instrument was fitted by the manufacturers with accessory parts from a Model A-700 automatic preparative gas chromatograph which allowed automatic injection and collection of samples. Column specifications and operating conditions of these instruments are specified in the individual experiments. Mass spectra were obtained on an Hitachi Perkin-Elmer Model RMU6E mass spectrometer. Ultraviolet determinations were run on a Cary Model 15 double-beam recording spectrophotometer employing silica cells.

(9) The increased rate of ring opening in CH_2Br_2 is particularly striking since spin-orbit coupling[10] between the carbene and the heavy atom solvent would be expected to promote intersystem crossing to the triplet cyclopropylidene which apparently does not open to allene.[11] This observation may reflect a singlet ground state for this carbene or inefficient coupling between the carbene and the heavy atom. Both of these possibilities are under investigation.

(10) *Cf.* N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1967, pp 27–29.

(11) P. S. Skell and R. R. Engle, *J. Am. Chem. Soc.*, **88**, 3749 (1966), and references cited therein; W. T. Borden, *Tetrahedron Letters*, 447 (1967).

(12) Private communication from Professor M. A. Battiste, University of Florida.

(13) R. Criegee, *Angew. Chem. Intern. Ed. Engl.*, **7**, 559 (1968).

(14) Partial reaction involving the following represents an alternative explanation for the decreased optical purity of the allene in the experiments that were run in alcohol as a solvent. Complete absence of the ether and independent demonstration of its stability to reaction conditions argue against this.

Ethyl (−)-N-Nitroso-N-(*trans*-2,3-diphenylcyclopropyl)carbamate.—The procedure as described in an earlier publication[6] was utilized to yield the N-nitrosocarbamate as a yellow oil, $[\alpha]^{25}D$ −251° (c 7.4, ether). This material was homogeneous as shown by tlc (pentane–ether eluent) and had identical ir and nmr spectra with those reported.[3] The racemic material was prepared in an identical manner.

Decomposition of Ethyl (±)-N-Nitroso-N-(*trans*-2,3-diphenylcyclopropyl)carbamate in Cyclohexane–Cyclohexene and Benzene–Cyclohexene Mixtures. Determination of Spiropentane/Allene Ratios.—A 47.8-ml, magnetically stirred, water-jacketed, volumetric reaction flask connected to a pressure-compensated gas buret and a constant-temperature circulator at 30.0° was thoroughly flushed with dry nitrogen. After addition of 0.0620 g (0.20 mmole) of the N-nitrosocarbamate and the appropriate solvent mixture, a 0.38-ml (0.20 mmole) portion of 5.6 *M* sodium methoxide in methanol was added. The reaction was allowed to continue until nitrogen evolution was complete; this normally required 3 hr and gave 80–100% gas evolution. The mixture was then analyzed by glpc using the 600-D instrument with a 1/8 in. × 6 ft column packed with 10% SE 30 on 60–80 mesh Chrom W with DMCS at 156° with temperature programming for elution of the spiropentane. In each case the chromatogram showed no components in addition to the standard, allene, and spiropentane (<1% detectable) with the exception of reactions in which cyclohexane was the solvent. In pure cyclohexane 2.6% of another component was observed, and the amount of this material observed was proportionate to the amount of cyclohexane used in the reactions.

Decomposition of Ethyl (−)-N-Nitroso-N-(*trans*-2,3-diphenylcyclopropyl)carbamate in Various Solvents. Determination of the Optical Rotation of the 1,3-Diphenylallene.—A procedure identical with that for the determination of spiropentane to allene ratios was utilized except that the (−)-N-nitrosocarbamate, $[\alpha]^{25}D$ −251° (*c* 7.4, ether), was used. After the reaction was complete (nitrogen evolution ceased) the reaction mixtures from the cyclohexane and benzene reactions were poured into equal volumes of cyclohexene, and the reaction mixtures from reactions in cyclohexene, methanol, and *t*-butyl alcohol were poured into equal volumes of cyclohexane. These mixtures were evaporated *in vacuo* to an oil, which was immediately chromatographed over 10 g of silica (hexane eluent). The resulting chromatography fractions which were shown to contain only 1,3-diphenylallene by glpc were then used for specific rotation determination. The concentration of the allene in these fractions was determined by glpc by comparison to a standard of approximately equal concentration using the 600-D instrument with a 1/8 in. × 6 ft column packed with 10% SE 30 on 60–80 mesh Chrom W with DMCS at 156°. Using this procedure the specific rotation (+30°) of the (+)-1,3-diphenylallene was obtained for identical reactions in the following solvents: cyclohexene, 683°; cyclohexane, 686°; benzene, 607°; *t*-butyl alcohol, 350°; methanol, 197. Control experiments showed (+)-1,3-diphenylallene to be optically stable when exposed to sodium methoxide in the above solvents at comparable concentrations and exposure times.

Determination of Relative Solvent Polarities.—The procedure of Berson, Hamlet, and Mueller[8] was used. In a nitrogen-flushed, water-jacketed flask kept at 30.0° by use of a constant-temperature circulator was placed 30 ml of the appropriate solvent and 1.3 ml of freshly distilled methyl acrylate. A freshly distilled 1.3-ml portion of cyclopentadiene was then added by use of a syringe through a rubber septum. The reaction mixture was allowed to stir for 24 hr and then evaporated to an oil by use of a rotary evaporator at room temperature. A small portion of ether was added to the oil and again the solvent was removed. Ether was added to the resulting oil and this solution was analyzed by glpc on the 600-D instrument using a 1/8 in. × 10 ft column packed with TCEP on 60–80 mesh Chrom W with DMCS and a nitrogen pressure of 24 psig at 103°. The following *endo*/*exo* ratios (±2%) were obtained for the solvents listed: acetone, 0.414; benzene, 0.497; cyclohexene, 0.506; hexane, 0.577; cyclohexane, 0.595. Control experiments for reaction time and work-up procedure did not alter the observed ratios.

(+)-*trans*-1,2-Diphenyl-1′,2′-tetramethylenespiropentane.—To a solution of 1.54 g (4.98 mmoles) of ethyl (+)-N-nitroso-N-(*trans*-2,3-diphenylcyclopropyl)carbamate, $[\alpha]^{25}D$ +210° (*c* 5.8, ether), in 100 ml of cyclohexene at 22° was added 1.035 ml (5.96 mmoles) of a 5.79 *M* solution of sodium methoxide in methanol. After gas evolution was complete (1 hr), analysis of an aliquot of the reaction mixture by glpc on the 600-D instrument with a 1/8 in. × 5 ft column packed with 6% apiezon L on 60–80 mesh Gas-Chrom Z at 233° and an inlet pressure of 30 psig showed a 26% yield of the spiropentane. After addition of 150 ml of heptane to the reaction mixture and evaporation *in vacuo* to a volume of approximately 60 ml, the mixture was chromatographed over 220 g of silica (hexane eluent). Incomplete separation was obtained as glpc analysis of the chromatography fractions showed elution of the allene, followed by fractions containing both allene and spiropentane, then followed by fractions containing only the spiropentane. These latter fractions were combined and evaporated to an oil. Crystallization of this oil from 95% ethanol at −78° gave 66 mg of the spiropentane: $[\alpha]D^{25}$ +135° (*c* 19.54, hexane); mp 97–97.5°; infrared, λ_{max}^{KBr} 1600, 750, and 700 cm^{-1} (phenyls); nmr, τ 2.85 (m) ten phenyls, 7.67 (pair of doublets, 3.8 cps) two hydrogens of spiropentane adjacent to phenyls, 8.0–9.2 (m) ten remaining protons; mass spectrum, *m/e* 274 (parent peak), 192, 191, 183, 141, 115, and 91; ultraviolet, $\lambda_{max}^{95\%\ EtOH}$ 238 mμ (log ε 4.2), $\lambda_{sh}^{95\%\ EtOH}$ 268 mμ (log ε 3.2), 275 mμ (log ε 3.0).

Anal. Calcd for $C_{21}H_{22}$: C, 91.92; H, 8.08. Found: C, 91.65; H, 8.07.

1-Methoxy-*trans*-2,3-diphenylcyclopropane.—To a solution of 1.65 g (5.32 mmoles) of ethyl (±)-N-nitroso-N-(*trans*-2,3-diphenylcyclopropyl)carbamate in 200 ml of anhydrous methanol was added 1.0 ml (5.6 mmoles) of a 5.6 *M* solution of sodium methoxide in methanol. Gas was rapidly and vigorously evolved. After gas evolution was complete, glpc of the reaction mixture showed the presence of only two components, 1,3-diphenylallene (67%) and 1-methoxy-*trans*-2,3-diphenylcyclopropane (33%). Evaporation of the reaction mixture to a volume of 30 ml and separation of the second component by preparative glpc on the A-350-B instrument with a 0.5 in. × 6 ft column packed with 20% SE 30 on 60–80 mesh Gas-Chrom Z at 190° and an inlet pressure of 50 psig gave the ether as a white solid: mp 60–62°; infrared, λ_{max}^{KBr} 1600, 750, 700 (phenyls), 1110 cm^{-1} (ether); nmr, τ2.83 (m) ten phenyls, 6.42 (q) one hydrogen of cyclopropane adjacent to methoxy group, 6.81 (s) three methyls, 7.57 (m) two hydrogens of cyclopropane adjacent to phenyls; mass spectrum, *m/e* 224 (base and parent peak), 209, 193, 192, 147, and 77.

Anal. Calcd for $C_{16}H_{16}O$: C, 85.67; 7.19. Found: C, 85.58; H, 7.10.

Registry No.—Cyclopropylidene, 2143-70-6; allene, 463-49-0; spiropentane, 157-40-4; (+)-*trans*-1,2-diphenyl-1′,2′-tetramethylenespiropentane, 19817-59-5; 1-methoxy-*trans*-2,3-diphenylcyclopropane, 19817-60-8.

Acknowledgment.—The authors most gratefully acknowledge the support for this work which they received from the National Science Foundation.

Stereoselectivity of Carbene Intermediates. VI. Selectivity of Phenylchlorocarbene[1]

ROBERT A. MOSS, JOANNE R. WHITTLE, AND PHILIP FREIDENREICH[2,3]

Wright Laboratory, School of Chemistry, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08903

Received November 8, 1968

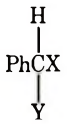
At least formally, phenylhalocarbenes can be generated by the action of base on benzal halides **1**,[4] or by photoinduced elimination of nitrogen from phenyl-

(1) Part V: R. A. Moss and J. R. Przybyla, *Tetrahedron*, **25**, 647 (1969).

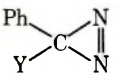
(2) National Science Foundation Summer Undergraduate Research Participant, 1968 (GY-4154).

(3) Henry Rutgers Fellow, 1968–1969.

(4) See R. A. Moss, *J. Org. Chem.*, **27**, 2683 (1962), for example.



1a, X = Br; Y = F
b, X = Y = Cl
c, X = Y = Br



2a, Y = Cl
b, Y = Br

halodiazirines 2.[5] Our recent studies of phenylfluorocarbene (Ph–C–F)[1] and phenylbromocarbene (Ph–C–Br)[5,6] have raised two significant questions which are answerable by a selectivity study of phenylchlorocarbene (Ph–C–Cl). (1) As generated by the action of potassium *t*-butoxide on **1c** or of light on **2b**, "Ph–C–Br" exhibits nonidentical abilities to discriminate between different olefins.[5,6] The discrepancy has been attributed to the intervention of a carbene–base complex (carbenoid) in the butoxide-induced reaction. In view of the supposed superiority of Cl over Br in stabilizing a divalent carbon center,[7] would the butoxide-induced decomposition of **1b** lead to a "free" Ph–C–Cl, identical with that generated by photolysis of **2a**? (2) Ph–C–Br and Ph–C–F, as generated from benzal halides **1c** and **1a**, showed a relatively small difference in their abilities to discriminate between members of a standard set of olefinic substrates.[1] If, however, these base-catalyzed carbene generations both involved carbenoids rather than free carbenes, then the halogen–divalent carbon resonance interaction, which is believed to confer stability (and selectivity) on a carbene,[7] must have been absent or, at best, reduced. Would a selectivity comparison of *photolytically generated* (uncomplexed) phenylhalocarbenes uncover large differences in discrimination between the phenylhalocarbenes as a function of halogen atom identity?

Ph–C–Cl was generated from **1b** by the action of potassium *t*-butoxide[8] at 25°, and added to tetramethylethylene, trimethylethylene, isobutene, *cis*-butene, and *trans*-butene. The product cyclopropanes were identified by comparison of their nmr spectra with reported data.[9] The same product cyclopropanes were obtained in good yield when dilute olefinic solutions of phenylchlorodiazirine[10] were irradiated with a G. E. sunlamp at *ca.* 25° (Pyrex filter).

In all cases, for both generative methods, the alkyl regions of nmr spectra of the crude products were sufficiently clean and compatible so that the nmr spectra of the cyclopropane *mixtures*, formed by generation of Ph–C–Cl in selected binary mixtures of the olefins, could be used to determine quantitatively the cyclopropane mixture compositions. (The nmr analyses were similar to those employed in our Ph–C–Br studies,[5,6] and are detailed in the Experimental Section.) We were thus able to determine the relative rates of addition of base- and light-generated Ph-C-Cl to the several olefins. The *experimental* rates are collected in Table I. Control experiments, using prepared mixtures of pure products, demonstrated the accuracy of the nmr analyses, and also the constancy of product ratios to all experimental conditions. Table II contains the data of Table I, normalized to an isobutene standard. Analogous data for Ph–C–Br and Ph–C–F have also been included in Table II for purposes of comparison. Attempts in this laboratory to prepare a suitable precursor for the photolytic generation of Ph–C–F have met with failure.

TABLE I

EXPERIMENTAL RELATIVE RATES OF ADDITION OF PHENYLCHLOROCARBENE TO SELECTED OLEFINS, *ca.* 25°

Case	Olefin A/olefin B	$(k_A/k_B)_{base}$[a]	$(k_A/k_B)_{light}$[b]
1	Isobutene/ tetramethylethylene	0.38 (3.9$_3$)[c]	0.20 (6.5$_6$)[c]
2	Trimethylethylene[d]/ tetramethylethylene	0.60 (7.9$_3$)	0.62 (12.$_6$)
3	*trans*-Butene/ tetramethylethylene	0.042 (3.6$_3$)	0.039 (10.$_4$)
4	Isobutene/ *cis*-butene[d]	3.2 (3.2$_3$)	2.7 (8.2$_4$)

[a] Ph–C–Cl from benzal chloride and potassium *t*-butoxide. [b] Ph–C–Cl from photolysis of phenylchlorodiazirine. [c] Numbers in parentheses refer to the per cent average deviation of *n* experiments. [d] These rates are composites of both stereochemical modes of addition of Ph–C–Cl to these olefins.

The data of Table I reveal similarity but not identity of the base- and light-generated Ph–C–Cl species. In cases 2 and 3, the experimentally observed relative addition rates of both species are the same, within experimental error. In case 4, the difference lies just outside the combined experimental error. Moreover, as detailed in the Experimental Section, the stereoselectivity of Ph–C–Cl additions to *cis*-butene and trimethylethylene was essentially *independent* of generative method. There can be no question, however, that the experimental difference observed in case 1 is real. It is interesting to note that in the Ph–C–Br studies,[5,6] where *all* olefin pairs examined revealed selectivity differences between the base- and light-produced Ph–C–Br, it was this same tetramethylethylene–isobutene pair which revealed much of the largest difference.

A simple rationale, which is in accord with the facts but not exclusively demanded by them, is that a carbene–base complex (carbenoid) is at least partly involved in the benzal chloride–potassium *t*-butoxide reactions, whereas a free carbene is involved in the phenylchlorodiazirine photolyses.[11] Though one can speculate, it is not yet clear why the selectivity differences show up so dramatically in case 1 (Table I), or whether mechanistic significance can be attached to the substantial identity of all other selectivity measurements we have been able to make on base- and light-generated Ph–C–Cl species.

With regard to the over-all selectivity of the various carbenic species (Table II), the data show (1) Ph–C–X produced from benzal halides and potassium *t*-butoxide show only small variations in selectivity as a function of X; (2) Ph–C–X photogenerated from phenylhalodiazirines show, at most, only a marginally greater selectivity for X = Cl, as opposed to X = Br. Synthetic difficulties attend attempted generation of Ph–C–F by photolytic means. Based on the fore-

(5) R. A. Moss, *Tetrahedron Lett.*, 4905 (1967).
(6) R. A. Moss and R. Gerstl, *Tetrahedron*, **22**, 2637 (1966).
(7) J. Hine, "Divalent Carbon," The Ronald Press Co., New York, N. Y., 1964, pp 36 ff.
(8) Alfa Inorganics, Inc. Other commercially available reagents lead to unacceptably slow reaction at 25°. We thank Professor G. L. Closs for this information.
(9) G. L. Closs and J. J. Coyle, *J. Org. Chem.*, **31**, 2759 (1966).
(10) W. H. Graham, *J. Amer. Chem. Soc.*, **87**, 4396 (1965). We thank Dr. Graham for detailed instructions for this preparation.
(11) Explanations involving different multiplicities for the base- and light-generated Ph–C–Cl species seem precluded, since both add stereospecifically to *cis*- and *trans*-butene.

TABLE II
KINETIC SELECTIVITY OF PHENYLHALOCARBENES, *ca.* 25°

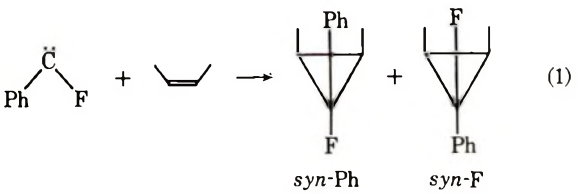
Olefin	Relative rates of addition: Ph-C-Br, Base[a]	Ph-C-Br, Light[b]	Ph-C-Cl, Base[c]	Ph-C-Cl, Light[c]	Ph-C-F, Base[d]
Tetramethylethylene	1.6	4.4	2.6	5.1	2.7
Trimethylethylene[e]	1.3	2.5	1.6	3.2	1.2
Isobutene	1.00	1.00	1.00	1.00	1.00
cis-Butene[e]	0.29	0.53	0.31	0.37	0.12
trans-Butene	0.15	0.25	0.11	0.20	0.10
"Spread"[f]	11	18	24	25	27

[a] Reference 6. [b] Reference 5. [c] This work. [d] Reference 1. [e] These rates are composites of both stereochemical modes of addition of Ph–C–X to these olefins. [f] Ratio of fastest to slowest addition rate.

going, however, it seems likely that the selectivity of this species will be very similar to that of the base-generated Ph–C–F.

As specific answers to the two questions posed above, we conclude (1) photo- and base-generated Ph–C–X do not become wholly identical upon change of X from Br to Cl. The base-induced reactions, in both cases, are probably best regarded as involving carbene–base complexes or carbenoids; (2) the phenylhalocarbenes do not show large selectivity differences as a function of halogen no matter how they are generated. In this respect, they resemble the monohalocarbenes. Only in the case of the dihalocarbenes has it been shown that halogen variation can result in reasonably large selectivity variation.[12]

We also investigated the possibility of predicting the stereoselectivity of a carbene olefin addition reaction. Consider reaction 1, the addition of Ph–C–F to *cis*-butene.[1] Can the observed, kinetically controlled, *syn*-



(1)

F/*syn*-Ph ratio be predicted from an equation such as eq 2, using analogous stereoselectivity data for Ph–C–Cl and F–C–Cl? To answer this question, we re-

$$\left(\frac{syn\text{-F}}{syn\text{-Cl}}\right)_{\text{F-C-Cl}}\left(\frac{syn\text{-Cl}}{syn\text{-Ph}}\right)_{\text{Ph-C-Cl}} = \left(\frac{syn\text{-F}}{syn\text{-Ph}}\right)_{\text{Ph-C-F}} \quad (2)$$

determined stereoselectivity data for F–C–Cl[12] with *cis*-butene and trimethylethylene substrates at 25°. We also redetermined such stereoselectivity data for Ph–C–Cl[9] at 25°. Details appear in the Experimental Section. The data, in the form of eq 2, together with *observed* and *predicted* Ph–C–F stereoselectivity, are summarized in Table III.[13,14]

TABLE III
PREDICTED STEREOSELECTIVITY OF PHENYLFLUOROCARBENE, 25°

Olefin	$\left(\frac{syn\text{-F}}{syn\text{-Cl}}\right)_{\text{F-C-Cl}}$	$\left(\frac{syn\text{-Cl}}{syn\text{-Ph}}\right)_{\text{Ph-C-Cl}}$	$\left(\frac{syn\text{-F}}{syn\text{-Ph}}\right)_{\text{Ph-C-F}}$ Predicted	Observed
cis-Butene	0.42	2.10	0.88	1.23[a]
Trimethylethylene	0.46	1.18	0.54	0.76[a]

[a] Data of ref 1.

Although the predicted *syn*-F/*syn*-Ph ratios change in the proper direction upon change of the olefin from *cis*-butene to trimethylethylene, the predicted ratios are both too small.

Carbene stereoselectivity arises in differential nonbonded interactions between carbene substituents and olefinic substituents. The strength of these interactions and therefore the resultant stereoselectivity will be dependent on the separation and orientation of the carbene and olefin at the transition state for the addition reaction. Therefore eq 2 should hold most closely for carbenes of similar kinetic selectivities, in which, presumably, the addition reaction transition states are similarly located along the reaction coordinate. F–C–Cl is about ten times more selective than either Ph–C–Cl or Ph–C–F,[1] however, and the transition states of its olefin addition reactions are likely to be considerably "tighter" than those of the other two carbenes. It is not unreasonable to suggest that, if the F–C–Cl addition transition states were somewhat "looser," then the effects of the differential polarizabilities of Cl and F (which are believed to determine mainly the stereoselectivity of F–C–Cl[12,15]) would be mitigated; the *syn*-F/*syn*-Cl ratios would increase; and the predicted *syn*-F/*syn*-Ph ratios would more closely approach the observed values.

Experimental Section

1-Phenyl-1-chlorocyclopropanes.—The adducts of phenylchlorocarbene and tetramethylethylene (Chemical Samples Co.), trimethylethylene (Aldrich), isobutene, and *cis*-butene (Matheson) were prepared in the following general way. Benzal chloride (Eastman), 1 equiv, was added to 10 equiv of the indicated olefin in a screw-top Carius tube (Fisher-Porter Co.) at −70°. Potassium *t*-butoxide (Alfa Inorganics), 1.4 equiv, was added. The tube was sealed, secured to a rotary mixer, and agitated for 2 days at *ca.* 25°. The contents of the tube were then washed three times with water, and once with a saturated $NaHCO_3$ solution. The resulting organic phase was dried over $CaCl_2$. Excess olefin was removed with a rotary evaporator and the resultant cyclopropane was purified by vacuum distillation.

(12) R. A. Moss and R. Gerstl, *J. Org. Chem.*, **32**, 2268 (1967); see, also, the discussion in ref 1.

(13) In the light of CCl_2 studies,[14] CFCl may well be a free carbene, even when base generated. It would be best, therefore, to use stereoselectivity data for light-generated (free) Ph–C–X in Table III. Such data are not available for Ph–C–F. In view of the identity (within experimental error) of stereoselectivity data for base- and light-generated Ph–C–Cl (and the great similarity of the analogous Ph-C-Br data[5]) it seems reasonable to use stereoselectivity data for base- and light-generated Ph–C–X interchangeably in eq 2 and Table III.

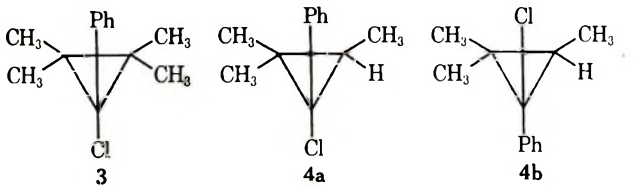
(14) Several thermal α-elimination reactions lead to the same CCl_2 species: D. Seyferth, M. E. Gordon, J. Y-P. Mui, and J. M. Burlitch, *J. Amer. Chem. Soc.*, **89**, 959 (1967); O. M. Nefedov and R. N. Shafran, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **3**, 538 (1965). Photolysis of 1,1-dichloro-2-phenylcyclopropane may lead to the same intermediate: M. Jones, Jr., W. H. Sachs, A. Kulczycki, Jr., and F. J. Waller, *J. Amer. Chem. Soc.*, **88**, 3167 (1966).

(15) R. A. Moss and R. Gerstl, *Tetrahedron*, **23**, 2549 (1967).

Products were identified by comparison of their nmr spectra with the reported data.[9] Yields were somewhat lower than in the literature method, which employed higher reaction temperatures.[9]

1-Phenyl-1-chloro-2,3-*trans*-dimethylcyclopropane was prepared by photolyzing a solution of 0.99 g of phenylchlorodiazirine[10] in 22 g of *trans*-butene (Matheson) in the Carius tube with a G. E. sunlamp for 3 hr at 22°. Removal of olefin, followed by distillation of the residue at 54–56° (0.6 torr), afforded 0.78 g (66%) of product having the correct nmr spectrum.[9]

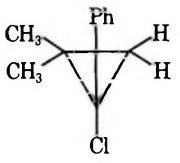
Nmr Analyses.—Binary mixtures of the five products, **3**–**7**, were quantitatively analyzed.



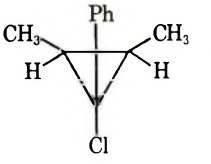
3

4a

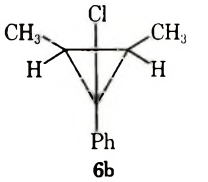
4b



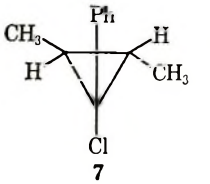
5



6a



6b



7

Case (1), 3 + (4a + 4b).—Cyclopropane **3** shows a singlet at 62.5 cps,[16] worth six protons (methyls *syn* to Ph). Cyclopropanes (**4a + 4b**) show *inter alia* absorptions at 48, 55, and 64 cps. The 48-cps absorption represents the *syn*-Ph methyl group of **4b**. From examination of spectra of synthetic (**4a + 4b**), the integral ratio (55 + 64)/48 was found to be 1.58. The ratio **4b**/**4a** was determined to be 1.18 (see below). With these data, and by integration of the regions 46–50 (area 1) and 52–66 cps (area 2) in the **3 + 4** mixture, it can be deduced that

$$\frac{(4a + 4b)}{3} = \frac{3.72(\text{area } 1)}{(\text{area } 2) - 1.58(\text{area } 1)}$$

Using this expression, four prepared mixtures of **3** and (**4a + 4b**) were analyzed with an average error of 6.7%.

Case (2), 3 + 5.—Cyclopropane **5** shows absorptions at 47 cps (methyl *syn* to Ph) and at 60 and 66 cps (H *syn* to Ph). In the **3 + 5** mixture, the regions 45–49 (area 1) and 58–68 cps (area 2, which includes the six-proton **3** absorption at 62.5 cps) are integrated. With these data and the **5** assignments (above) it can be shown that

$$\frac{5}{3} = \frac{2(\text{area } 1)}{(\text{area } 2) - 0.33(\text{area } 1)}$$

Using this expression, three prepared mixtures of **3** and **5** were analyzed with an average error of 3.8%.

Case (3), 5 + (6a + 6b).—Cyclopropane **5** shows absorptions at 47 cps (methyl *syn* to Ph), and at 60, 66, 74, and 80 cps (ring protons, AB system, value two protons). Cyclopropanes (**6a + 6b**) show absorptions at *ca.* 58 cps (methyls of **6a**) and at *ca.* 76 cps (all protons of **6b**[6,9]). It is known that the area ratio 47/(60 + 66 + 74 + 80) in **5** is 0.67, and that the ratio **6b**/**6a** = 2.10 (see below). With this, and with integration, in the **5** + (**6a + 6b**) mixture, of the regions 45–49 (area 1) and 56–82 cps (area 2), it can be shown that

$$\frac{5}{(6a + 6b)} = \frac{2.45(\text{area } 1)}{(\text{area } 2) - 0.67(\text{area } 1)}$$

Using this expression, three prepared mixtures of **5** + (**6a + 6b**) were analyzed with an average error of 4.1%.

(16) All nmr spectra were determined in CCl_4 solution with a Varian A-60 spectrometer. Chemical shifts are reported in cycles per second downfield from internal TMS. Peaks will be designated by their chemical shift positions.

Case (4), 3 + 7.—The nmr spectrum of pure **7** was divided into two regions, 42.5 – 57 cps (area 2) and 57–69 cps (area 1). The integral ratio (area 1)/(area 2) was found to be 0.37. Area 2 represents the three protons of the methyl *syn* to Ph in **7**. Remembering that **3** exhibits a six-proton singlet at 62.5 cps, determination of the integral ratio of the two regions defined above in the **3 + 7** mixture leads to

$$\frac{7}{3} = \frac{2.0(\text{area } 2)}{(\text{area } 1) - 0.37(\text{area } 2)}$$

Using this expression, six prepared mixtures of **3 + 7** were analyzed with an average error of 8.0%.

Relative Rate Experiments.—The benzal chloride experiments involved 0.5 g (3.11 mmol) of benzal chloride and 0.5 g (4.46 mmol) of potassium *t*-butoxide. These reagents were added to a mixture of olefins A and B (each carefully weighed) in a Carius tube at −70°. The olefins were each present in at least tenfold excess over the benzal chloride. The tube was sealed and warmed to room temperature. The remainder of the procedure was as described above. After removal of excess olefin on the rotary evaporator, the cyclopropane product ratio was determined by nmr. The relatives rates of the carbene addition to olefins A and B were then calculated in the usual manner. Control experiments demonstrated the constancy of products ratios under resubmission of the products to experimental conditions, and also after extended periods on the rotary evaporator.

In phenylchlorodiazirine experiments, weighed amounts of olefins A and B were condensed into the Carius tube and 100 mg of phenylchlorodiazirine was added. The tube was sealed, warmed to room temperature, and irradiated for 1 hr with a G. E. sunlamp (Pyrex filter). A running-water bath maintained the temperature at *ca.* 24–26°. After photolysis, the tube was cooled to −70° and opened. Warming caused excess olefin to evaporate. The residue was stripped (if necessary) of higher boiling olefins, taken up in CCl_4, and analyzed by nmr. Control experiments demonstrated the constancy of product ratios to photolytic and work-up conditions. Data for all relative rate experiments are collected in Table I.

Stereoselectivity of Ph–C–Cl.—Generation of Ph–C–Cl in trimethylethylene led to **4a + 4b**, whereas its generation in *cis*-butene led to **6a + 6b**. These mixtures were analyzed by nmr spectroscopy.[9] For Ph–C–Cl generated by the action of potassium *t*-butoxide on benzal chloride, **4b**/**4a** was 1.27, 1.22, 1.04, and 1.19 in four experiments with trimethylethylene (25°). Over three experiments with *cis*-butene, **6b**/**6a** was 1.96, 2.03, and 2.30. For Ph–C–Cl generated by photolysis of phenylchlorodiazirine (25°) the corresponding data were trimethylethylene, 1.35, 1.26, 1.21, 1.28; *cis*-butene, 1.91, 1.95, and 2.06.

Stereoselectivity of F–C–Cl.—Addition of F–C–Cl, produced by the action of potassium *t*-butoxide on *sym*-difluorotetrachloroacetone, to trimethylethylene and *cis*-butene afforded sets of isomers with the distributions summarized in Table III. Analyses were by ^{19}F nmr spectroscopy.[15] The trimethylethylene experiment was easily carried out at 25° in the manner already described.[15] Results were *syn*-Cl/*syn*-F = 2.22 and 2.18. The addition of F–C–Cl to *cis*-butene at 25° was accomplished as follows. *sym*-Difluorotetrachloroacetone (Allied Chemical Co.) (4.02 g, 0.035 mol) was *sealed* into a small ampoule. The ampoule was placed in an 18-in. Carius tube. The tube was cooled to −70°, and 43 g (0.77 mol) of *cis*-butene was condensed into it. Then, 4.66 g (0.042 mol) of potassium *t*-butoxide was added. The tube was sealed and warmed to 25°. Shaking the pressure tube ruptured the vial contained within it and initiated the reaction, which was then continued by securing the pressure tube to the rotary mixer for 2 hr. Work-up and analysis of the fluorochlorocyclopropane isomers could then be carried out as previously described.[15] Results for two experiments were *syn*-Cl/*syn*-F = 2.34 and 2.45.

Registry No.—Phenylchlorocarbene, 19807-41-1; phenylbromocarbene, 14541-26-5; phenylfluorocarbene, 17825-75-1; **3**, 3141-40-0; **4a**, 13153-95-2; **4b**, 13153-96-3; **5**, 19817-55-1; **6a**, 13153-99-6; **6b**, 13154-00-2; **7**, 19817-58-4.

Acknowledgments.—^{19}F nmr spectra were determined by Dr. L. A. Wilson of Varian Associates, to whom we are most grateful. Financial support by

the National Science Foundation (GP-7817) and the National Institutes of Health (GM-13585) is acknowledged with thanks.

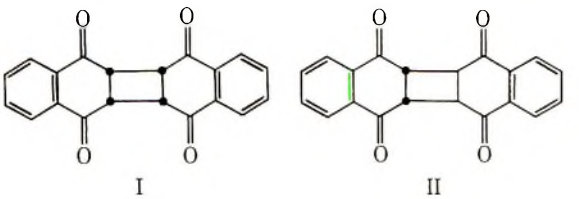
A Study of the Enolization of the *syn* and *anti* Photodimers of 1,4-Naphthoquinone

DANIEL P. VENTER AND JOHANNES DEKKER

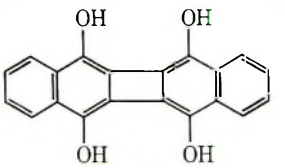
Organic Section, Department of Chemistry, Potchefstroom University for C.H.E., Potchefstroom, South Africa

Received September 4, 1968

The isolation of the *syn* (I) and *anti* (II) photodimers of 1,4-naphthoquinone was reported recently.[1] In the presence of alkali both I and II led to tetraol (III).[1,2]



I II

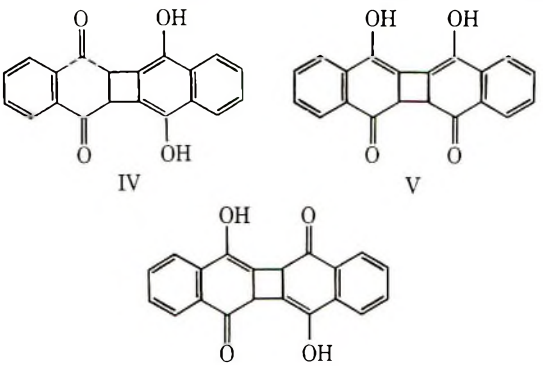


III

If III is treated with concentrated sulfuric acid, complete ketonization occurs, leading quantitatively to II. Similar treatment of I also produces II. The question as to whether the latter reaction proceeds *via* tetraol III or *via* a partially ketonized derivative thereof urged us to investigate the enolization aptitude of I and II in mild and strong acidic media.

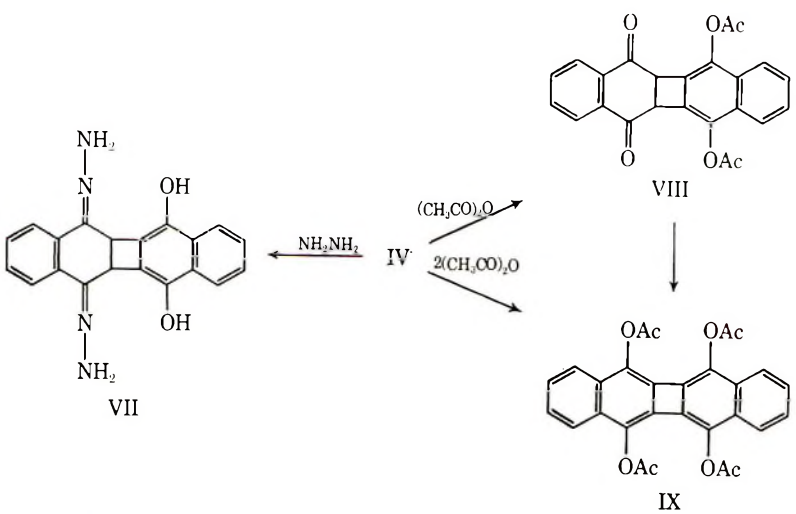
When II was refluxed in acetic acid a yellowish color gradually developed. Concentration of the filtrate, which contained no trace of the monomeric 1,4-naphthoquinone, led to the isolation of orange-red crystals. Molecular weight determination by mass spectrometry[3] (mass 316) and elemental analysis ($C_{20}H_{12}O_4$) indicated that this compound was isomeric with II. The infrared spectrum exhibits a medium peak at 1605 cm^{-1} and a strong peak at 1589 cm^{-1} which may be assigned to two differently environed benzene nuclei, *i.e.*, a naphthalene and a *ortho*-substituted benzene moiety, respectively. A typical olefinic band of medium intensity was observed at 1640 cm^{-1}. A sharp carbonylic absorption appears at 1668 cm^{-1}. A broad absorption band between 3650 and 3100 cm^{-1}, with maximum intensity at 3410 cm^{-1}, indicates the presence of hydroxyl groups. The ultraviolet spectrum of this isomeric compound is very similar to that of II, and the *syn* dimer (I).

On the basis of the spectroscopic data and chemical properties, the three most likely structures for the isomeric orange-red compound are IV, V, and VI. Structures V and VI, however, are unlikely on account of strain, since the sp^3 hybridized carbon atoms in the C_4 ring would prevent the adjacent sp^2 hybridized carbon atoms from attaining planar configuration, required for significant π bonding. This argument is in fact analogous to Bredt's rule.[4] One also has to consider the driving force for the observed enolization of II, which would doubtlessly be aromatization, thus favoring structure IV.



IV V VI

The presence of two carbonyl groups in IV was proved by treatment with excess hydrazine, whereby a dihydrazone (VII) was obtained. When IV was refluxed in dioxane containing 2 mol of acetic anhydride the cor-



VII VIII IX

(1) J. Dekker, P. Janse van Vuuren, and D. P. Venter, *J. Org. Chem.*, **33**, 464 (1968).

(2) J. M. Bruce, *J. Chem. Soc.*, 2782 (1962).

(3) J. Dekker and D. P. Venter, *J. Amer. Chem. Soc.*, **90**, 1225 (1968).

(4) J. Bredt, *Ann. Acad. Sci. Fennicae*, **29A** [2] 000 (1927); *Chem. Abstr.*, **22**, 1152 (1928); D. J. Cram and G. S. Hammond, "Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 398.

responding diacetate (VIII) was obtained. The infrared spectrum of VIII exhibited typical acetate (1768 cm^{-1}), carbonylic (1688 cm^{-1}), and olefinic (1642 cm^{-1}) absorptions. The tetraacetate (IX)[1,2] was obtained by refluxing IV or VIII in acetic anhydride containing sodium acetate.

The enolization of II in strongly acidic medium (dioxane containing concentrated hydrochloric acid) led to a mixture of II and a yellow diol (IVa). The relative amounts of II and IVa depended on the acid strength and reaction time. No complete isomerization of II to IVa could be established by variation of these two factors, indicating that an equilibrium had apparently set in. Under the conditions employed the equilibrium ratio was 3:1 in favor of IVa. The structure of IVa was supported by spectroscopic data and chemical conversion to VII, VIII, and IX. Both elemental analysis ($C_{20}H_{14}O_5$) and mass spectrum (mass 316) were consistent with a hydrate of the orange-red diol (IV), *i.e.*, $C_{20}H_{12}O_4H_2O$.

The hydrated diol (IVa) was converted quantitatively into the anhydrous diol (IV) by refluxing in anhydrous benzene or by heating at 160° for 24 hr. The reverse was accomplished by recrystallization of IV from aqueous ethanol. The infrared spectrum of IVa resembles that of IV with only slight differences in the positions and intensities of the corresponding bands. The associated hydroxyl absorption displayed an upward shift to 3440 cm^{-1}. The most interesting feature of the spectrum of IVa is the splitting of the olefinic absorption into two bands (1639 and 1633 cm^{-1}). The band at 1633 cm^{-1} can only be rationalized by assuming intermolecular hydrogen bonding between a molecule water (water of crystallization) and the olefinic bonds adjacent to the C_4 ring. The π electrons in olefins can act as proton acceptors in inter- and intramolecular hydrogen bonding,[5] resulting in a shift to lower frequency, as was observed.

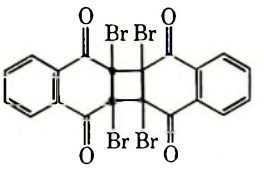
The diol (IV)[6] appeared to be stable in neutral solution and was recovered unchanged after reflux in dioxane. When the solution contained hydrochloric acid, however, a mixture of II and IV was obtained in the same ratio (1:3) as when II was treated similarly, indicating that the following equilibrium should exist in acidic medium: II $\rightleftarrows$ IV.

Owing to its thermal instability, the *syn* dimer (I) isomerized rapidly and completely in dioxane containing hydrochloric acid, leading to a mixture of II and IV (ratio 1:3). This was to be expected, since ketonization of the initially formed IV should preferably lead to the less strained *anti* dimer (II).

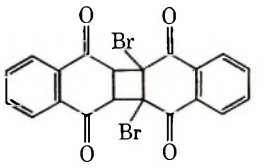
The tetraol (III) behaves like a highly unsaturated compound, decomposing easily in solution. In ethanol III displayed a blue fluorescence, which faded slowly upon standing at room temperature, finally disappearing within 4 hr.[7] Consequent evaporation of the solvent afforded the diol (IV) as sole product. Treatment of III with ethanolic hydrochloric acid produced a mixture of II and IV (ratio 1:3). If, however, a solution of III in cold concentrated sulfuric acid was added to excess water, II was obtained as the sole product.[1] Similar treatment of IV with sulfuric acid led to the same result.[8]

1,4-Diketo-1,2,3,4-tetrahydronaphthalene and its 2-methyl derivative enolize rapidly and completely in acidic media and there is no sign of an equilibrium.[9] In contrast, there is no rapid enolization of the *anti* dimer (II), and a definite equilibrium is established between II and IV. This equilibrium, and the spontaneous ketonization of III to IV in neutral media, may be related to the electron distribution in the region of the central C_4 ring. The data presented obey the generalization formulated by Streitwieser and coworkers,[10] "aryl positions adjacent to a fused strained ring have enhanced acidity and reduced reactivity toward electrophilic substitution," *i.e.*, the atomic orbitals used to construct the fused C_4 ring have higher p character. Hence the 5–5a, 5b–6, 11–11a, and 11b–12 bonds in III should accordingly have higher s character. Further, in order to minimize cyclobutadienoid configuration, these bonds are forced to attain maximum s character, accounting for its spontaneous ketonization to IV in neutral media. The 5–5a and 11b–12 bonds in IV also exhibit high s character, although to a lesser extent.

The typical olefinic nature of these bonds was illustrated amply by (i) the olefinic absorption in the infrared spectra of III (1655 cm^{-1}) and IV (1640 cm^{-1}) and (ii) the facile bromination of III and IV to X and XI, respectively.[11]



X



XI

The influence of the five-membered ring on the different reactivities of the 4 and 5 positions in indan to electrophilic substitution—originally discovered by Mills and Nixon[12]—has been investigated by various authors.[13] Our results, as well as those published by Streitwieser and coworkers,[10] and Cava and coworkers,[14] have established that a four-membered ring, condensed to a naphthalene moiety in the b position, results in a higher bond order of the aryl bonds adjacent to the strained four ring.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 221 spectrophotometer. Mass spectra were obtained on a M.S. 9 mass

(5) L. Joris, P. von R. Schleyer, and R. Gleiter, *J. Amer. Chem. Soc.*, **90**, 327 (1968), and references cited therein. A. W. Baker and A. T. Shulgin, *ibid.*, **81**, 4524 (1959); G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965); I. D. Campbell, G. Eglinton, and R. A. Raphael, *ibid.*, *B*, 338 (1968).

(6) Henceforward IV denotes both IV and IVa, unless explicitly stated otherwise.

(7) The conversion of I into IV proceeds markedly slower in dioxane, owing to its lower polarity.

(8) In some cases a mixture of II and III was obtained.

(9) R. H. Thomson, *J. Chem. Soc.*, 1737 (1950).

(10) A. Streitwieser, Jr., G. R. Ziegler, P. C. Mowery, A. Lewis, and R. G. Lawler, *J. Amer. Chem. Soc.*, **90**, 1357 (1968).

(11) The chemistry of X and XI will be dealt with in a future publication.

(12) W. H. Mills and I. G. Nixon, *J. Chem. Soc.*, 2510 (1930).

(13) W. C. Lothrop, *J. Amer. Chem. Soc.*, **62**, 132 (1940); J. Vaughan and G. J. Wright, *J. Org. Chem.*, **33**, 2580 (1968); H. C. Longuett-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **42**, 756 (1946); F. P. K. de Jong and J. P. Wibaut, *Rec. Trav. Chim. Pays-Bas*, **83** (5), 437 (1964); P. M. Nair and G. Gopakumar, *Tetrahedron Lett.*, 709 (1964); J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron*, 1665 (1965); H. Meier, Eu. Mueller, and H. Shur, *ibid.*, **23**, 3713 (1967); H. Meier, J. Heiss, H. Suhr, and Eu. Mueller, *ibid.*, **24**, 2307 (1968).

(14) M. P. Cava, B. Hwang, and J. P. van Meter, *J. Amer. Chem. Soc.*, **85**, 4032 (1963).

spectrometer. In the case of VII and VIII no mass spectra were obtained. Melting points were determined on a Gallenkamp (design no. 889339) apparatus and are uncorrected.

A. 6,11-Diketo-5,12-dihydroxy-5b,6,11,11a-tetrahydrodibenzo[b,h]biphenylene (IV). 1. From II in Dioxane Containing Hydrochloric Acid.—A mixture of finely powdered II (1 g), dioxane (100 ml), and concentrated HCl (5 ml) was refluxed for 3 hr. The reaction product was precipitated with excess water, filtered, washed with water, and dried at 100°. The enolized product (0.56 g) was separated from unchanged II (0.185 g) by three successive extractions of the dried precipitate with 75-ml portions of boiling ethanol which were cooled to 20° and filtered. (II is practically insoluble in cold ethanol). The separate filtrates were rapidly concentrated until crystals began separating from the hot solution. After cooling, the crystalline product was filtered off.

a. The Anhydrous Diol (IV).—A boiling solution of the crude diol in anhydrous benzene was concentrated rapidly, whereupon IV separated as orange-red needles: mp 235° (blackening commencing at 220°); mass of molecular ion, *m/e* 316; ν_{max}^{KBr} 3410, 1668, 1640, 1589, 1274, 1248, 735 cm^{-1}; λ_{max} (in ethanol) 231 mμ (E 33,700).

Anal. Calcd for $C_{20}H_{12}O_4$: C, 75.95; H, 3.16. Found: C, 75.90; H, 3.20.

b. The Hydrated Diol (IVa).—A concentrated solution of the crude diol in ethanol (20 ml) was treated with water (4 ml). Upon cooling IVa separated as yellow needles: mp 235° (change in color to organge-red at 130–135°, blackening commencing at 220°); mass of molecular ion, *m/e* 316; ν_{max}^{KBr} 3440, 1672, 1639, 1633, 1590, 1275, 1242, 733 cm^{-1}.

Anal. Calcd for $C_{20}H_{12}O_4 \cdot H_2O$: C, 71.86; H, 4.19. Found: C, 71.81; H, 4.12.

2. From II in Acetic Acid.—A solution of II (0.5 g) in acetic acid (200 ml) was refluxed for 24 hr. The yellowish solution was concentrated to a small volume (25 ml) and left for 2 hr at 20°. Unchanged II was filtered off. The filtrate was concentrated to a smaller volume (5 ml), whereupon IV (0.015 g) separated as orange-red crystals.

3. From III in Dioxane Containing Hydrochloric Acid.—A mixture of III (0.1 g), dioxane (10 ml), and concentrated HCl (0.5 ml) was refluxed for 5 hr. The reaction mixture was treated as in procedure A1, yielding II (0.02 g) and IV (0.06 g), respectively.

B. 6,11-Diketo-5,12-dihydroxy-5b,6,11,11a-tetrahydrodibenzo[b,h]-biphenylenedihydrazone (VII).—A boiling solution of IV (0.2 g) in ethanol (40 ml) was treated with 80% hydrazine hydrate (1 ml). The yellow solution darkened rapidly and pale yellow needles of the dihydrazone (VII) separated. Compound VII (0.09 gm) was filtered from the hot reaction mixture and washed with cold ethanol: mp 231° (with violent decomposition); ν_{max}^{KBr} 3340, 1602, 1328, 765, 723 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}O_2N_4$: C, 69.76; H, 4.65; N, 16.28. Found: C, 69.72; H, 4.60; N, 16.20.

C. 5,12-Diacetoxy-6,11-diketo-5b,6,11,11a-tetrahydrodibenzo[b,h]-biphenylene (VIII).—A boiling solution of IV (0.1 g) in dioxane (2 ml) was treated with acetic anhydride (0.065 g) and anhydrous sodium acetate (0.05 g), and the mixture refluxed for 3 min. Dilution with excess water led to the precipitation of VIII (0.064 g). Recrystallization from ethanol afforded colorless needles: mp 192–194°; ν_{max}^{KBr} 1768, 1688, 1356, 1281, 1194,1177 cm^{-1}.

Anal. Calcd for $C_{24}H_{16}O_6$: C, 71.99; H, 4.03. Found: C, 71.94; H, 3.97.

D. 5,6,11,12-Tetraacetoxydibenzo[b,h]biphenylene (IX).—A mixture of IV (0.02 g), acetic anhydride (5 ml), and anhydrous sodium acetate (0.5 g) was refluxed for 2 hr and cooled. The crystalline product was filtered off, and washed successively with acetic acid and water. Recrystallization of the crude IX (0.027 g) from acetic anhydride yielded yellow needles: mp 358–360° (lit.[2] mp 358–360°); the product was identified by ir spectroscopy.

E. Acetylation of VIII.—A mixture of VIII (0.02 g), acetic anhydride (5 ml), and anhydrous sodium acetate (0.5 g) was treated as in procedure D. Recrystallization of the crude product (0.025 g) produced yellow needles, identical with IX.

F. Ketonization of IV (or IVa). 1. In Concentrated Sulfuric Acid.—Compound IV (0.025 g) was dissolved in cold concentrated H_2SO_4 (2 ml), and the solution poured into ice cold water (20 ml). The greyish precipitate was washed with water and recrystallized from acetic acid, yielding colorless plates of II (0.019 g), mp 246–248° (lit.[1] mp 246–248°), identified by ir spectroscopy.

2. In Dioxane Containing Hydrochloric Acid.—A solution of IV (0.05 g) in dioxane (10 ml) was treated with concentrated HCl (1 ml). The mixture was refluxed for 5 hr, cooled, and treated with excess water. The precipitate was treated as in procedure A1, whereby II (0.007 g) and IVa (0.025 g) were obtained.

G. Ketonization of III. 1. In Dioxane Containing Hydrochloric Acid.—A solution of III (0.05 g) in dioxane (20 ml) was treated with concentrated HCl (1 ml). The reaction mixture was treated as in procedure F2, whereby II (0.01 g) and IV (0.026 g) were obtained.

2. In Ethanol.—A solution of III (0.025 g) in ethanol (30 ml) was refluxed until the blue fluorescence disappeared (5 hr). Concentration of the solution yielded crystalline IV (0.021 g). In dilute ethanolic solution (0.002 g/25 ml) complete conversion of III into IV at room temperature (20°) was established within 4 hr. In a similarly concentrated solution of III in dioxane ketonization was completed within 12 hr.

H. 5a,5b,11a,11b-Tetrabromo-5,6,11,12-tetraketo-5,5a,5b,-6,11,11a,11b,12-octahydrodibenzo[b,h]biphenylene (X).—Bromine (0.1165 g, 0.00073 mol) was added to a stirred suspension of III (0.05 g, 0.00015 mol) in benzene (12 ml). The mixture was stirred at room temperature for 1.5 hr. The crystalline product (X) (0.04 g) was filtered off and washed with ether: mp 255–258° dec; ν_{max}^{KBr} 1692, 1591, 1250, 1005 cm^{-1}.

Anal. Calcd for $C_{20}H_8O_4Br_4$: C, 38.01; H, 1.28; Br, 50.59. Found: C, 38.00; H, 1.28; Br, 50.94.

I. 5a,11b-Dibromo-5,6,11,12-tetraketo-5,5a,5b,6,11,11a,-11b,12-octahydrodibenzo[b,h]biphenylene (XI).—Bromine (0.21 g, 0.0013 mol) was added to a solution of IV (0.2 g, 0.00063 mol) in boiling ethanol (20 ml). The colorless crystals of XI (0.2 g) which quickly separated were filtered off, washed with cold ethanol, and recrystallized from ethanol: mp 165–170° dec; ν_{max}^{KBr} 1704, 1686, 1591, 1254, 717 cm^{-1}; mass of molecular ion, *m/e* 472.

Anal. Calcd for $C_{20}H_{10}O_4Br_2$: C, 50.66; H, 2.13. Found: C, 50.63; H, 2.11.

Registry No.—I, 14734-20-4; II, 14734-19-1; IV, 19817-49-3; VII, 19817-50-6; VIII, 19817-51-7; X, 19817-52-8; XI, 19817-53-9.

Acknowledgments.—The authors are indebted to the Council for Scientific and Industrial Research of South Africa for financial support and for a postgraduate grant to D. P. V. A grant by "Afrikaanse Pers Beperk (1962)" to D. P. V. is gratefully acknowledged.

Hydrazine Derivatives. II. Side Reactions in the Preparation of 1,1′-Azobisformamides[1]

CHARLOTTE M. KRAEBEL AND STANLEY M. DAVIS

Exploratory Research Section, Organic Chemicals Division, American Cyanamid Company, Bound Brook, New Jersey 08805

Received July 10, 1968

During the preparation of a series of 1,1′-azobis(N-substituted formamides)[2] from dialkyl azodiformates and amines, 1,6-dialkylbiureas were frequently isolated as by-products. It is the purpose of this note to discuss the competitive and consecutive reactions occurring when dialkyl azodiformates (1) and amines react and to consider the sources of various by-products.

The first two reactions (1 and 2) are a facile lab-

(1) Part I: C. M. Kraebel, S. M. Davis, and M. J. Landon, *Spectrochim. Acta*, **23A**, 2451 (1967).

(2) C. M. Kraebel and S. M. Davis, *J. Chem. Eng. Data*, **14**, 133 (1969).

TABLE I
REDUCTION OF 1,1′-AZOBISFORMAMIDES
RNHCON=NCONHR

R	Solvent	Reducing agent	Molar ratio reducing agent: azobisformamide	Time, hr	Temp, °C	% redn
H	EtOH	EtOH	15	143.5	75	None
H	EtOH	$C_4H_9NH_2$	2	2	75	30
H	$C_4H_9NH_2$	$C_4H_9NH_2$	8	2.5	80	100
c-C_6H_{11}	EtOH	EtOH	25	64	45–50	None
n-C_3H_7	EtOH	EtOH	20	192	25	<2
n-C_3H_7	EtOH	$C_6H_5NH_2$	2	51	25	<2[a]
n-C_3H_7	EtOH	Piperidine	2	28.5	25	4
n-C_3H_7	EtOH	Piperidine	2	95	25	18
n-C_3H_7	EtOH	$C_4H_9NH_2$	2	51	25	20
n-C_3H_7	EtOH	$C_4H_9NH_2$	2	195	25	42
n-C_3H_7	EtOH	Allylamine	2	24	25	28
n-C_3H_7	EtOH	Allylamine	2	72	25	46
n-C_3H_7	EtOH	$(C_4H_9)_2NH$	2	4	25	10
n-C_3H_7	EtOH	$(C_4H_9)_2NH$	2	20	25	66

[a] No Michael addition was observed.

oratory synthesis for 1,1′-azobis(N-substituted formamides), particularly when diethyl azodiformate (**1a**, R′ = C_2H_5) is treated with unhindered aliphatic amines.

$$\underset{\mathbf{1}}{R'OCON{=}NCOOR'} + RNH_2 \longrightarrow R'OCON{=}NCONHR + R'OH \quad (1)$$

$$R'OCON{=}NHCONHR + RNH_2 \longrightarrow \underset{\mathbf{2}}{RNHCON{=}NCONHR} + R'OH \quad (2)$$

The by-product biureas can arise by three possible routes: reduction of 1,1′-azobisformamides (**2**) by the by-product alcohol (reaction 3), reduction by the amine used originally (reaction 4), or aminolysis of a dialkyl bicarbamate (reaction 5). Possible sources of dialkyl bicarbamate (**3**) include reduction of **1** by an alcohol (reaction 6), which has been reported by Yoneda, *et al.*,[3] or by an amine (reaction 7).

$$\mathbf{2} + R'OH \longrightarrow \underset{\mathbf{4}}{RNHCONHNHCONHR} \quad (3)$$

$$\mathbf{2} + RNH_2 \longrightarrow \mathbf{4} \quad (4)$$

$$\underset{\mathbf{3}}{R'OCONHNHCOOR'} + 2RNH_2 \longrightarrow \mathbf{4} + 2R'OH \quad (5)$$

$$\mathbf{1} + R'OH \longrightarrow \mathbf{3} \quad (6)$$

$$\mathbf{1} + RNH_2 \longrightarrow \mathbf{3} \quad (7)$$

Although Witkop, *et al.*,[4] have also cited **1a** as a selective oxidant, the oxidation reactions of **2** have not been studied. The data in Table I show that the amides are less potent dehydrogenating agents than **1a**. The amides are not reduced by ethanol after 192 hr at room temperature [for **2a**, R = n-C_3H_7] or even after 143.5 hr under reflux (for 1,1′-azobisformamide). These conditions are far more rigorous than those which Yoneda reports; thus, reaction 3 is insignificant in this system. However, **2** are reduced with varying degrees of ease by amines (Table I) to give **4** (reaction 4). The order of reducing activity is $(C_4H_9)_2NH$ >> allylamine > $C_4H_9NH_2$ > piperidine >> $C_6H_5NH_2$ ∽ EtOH.

Since reactions 1 and 2 are not quantitative,[2] amine is available for reaction 4 even when initial ratio of **1**: amine is 1:2. Moreover, Yoneda's data[3] indicate that reaction 6 can remove **1** as the amount of alcohol produced by reactions 1 and 2 increases. When **1** is removed by this process, the amine present can react *via* reactions 4, 5, or 7. In view of the relative potency of amines as hydrogen donors, reaction 7 can compete with reactions 1 and 2 and can, in fact, be another reason that compounds **2** are not obtained quantitatively. Although the procedure used to prepare **2** does not allow for the isolation of compounds **3**, which are soluble, we found reaction 5 so sluggish [<20% yield of 1,6-di-n-butylbiurea (**4a**, R = n-C_4H_9) from diethyl bicarbamate (**3a**, R′ = C_2H_5) and n-butylamine after 64 hr under reflux] that it can be excluded as a possible source of **4**. Thus, reaction 4 is the source of **4** in this system.

Dibenzyl azodiformate (**1b**, R′ = $CH_2C_6H_5$), which is about as reactive as **1a** toward amines,[2] is also active as a dehydrogenating agent. In methanol **1b** is rapidly decolorized at room temperature. The color change from orange-red to pale yellow is characteristic of **1a** during its dehydrogenation reactions. Diisopropyl azodiformate (**1c**, R′ = i-C_3H_7), which is less reactive than **1a** or **1b** toward amines, is also less easily hydrogenated. Even after several days of standing at room temperature in methanol, **1c** is incompletely decolorized. Isopropyl alcohol decolorized **1b** less rapidly than methanol; in isopropyl alcohol–heptane at 45°, the purity of **1b** falls from 100 to 97% in 5 hr.[5]

Reactions between secondary amines and azo esters are less predictable than those involving primary amines. Azobisformamides were obtained (Table II) from both dimethylamine and piperidine. However, excess piperidine under reflux gave reduction product. Pyrrolidine gave only the reduction product, whereas dibutylamine gave no azobisformamide, but reduced both **1a** and **1c** to **3**. This result is consistent with the relative position of dibutylamine among the reducing agents used in Table I. Thus, secondary amines can react according to eq 1, 2, 4, and 7. The poor material balances observed suggest that several processes do, in fact, compete.

(3) F. Yoneda, K. Suzuki, and Y. Nitta, *J. Org. Chem.*, **32**, 727 (1967).
(4) R. Axen, M. Chaykovski, and B. Witkop, *ibid.*, **32**, 4117 (1967).
(5) These results were obtained by Dr. E. C. Sabatino.

TABLE II
REACTIONS BETWEEN DIALKYL AZODIFORMATES AND SECONDARY AMINES

Amine	Ester	Molar ratio amine/ester	Solvent	Results
$(CH_3)_2NH$	**1a**	3.0	Et_2O–MeOH	$(CH_3)_2NCON{=}NCON(CH_3)_2$,[a] >98% purity, ~20% yield
Piperidine	**1a**	2.0	Ligroin	$(CH_2)_5NCON{=}NCON(CH_2)_5$,[b] ~80% purity, 14% yield
Piperidine	**1a**	10.0	Et_2O (reflux)	$(CH_2)_5NCONHNHCON(CH_2)_5$, >10% yield[c]
Pyrrolidine	**1a**	2.0	Ligroin	$(CH_2)_4NCONHNHCON(CH_2)_4$, >8% yield[d]
$(C_4H_9)_2NH$	**1a**	2.0	Ligroin	EtOCONHNHCOOEt, 34% yield
$(C_4H_9)_2NH$	**1c**	2.0	Et_2O	i-$C_3H_7OCONHNHCOOC_3H_7$-i, 36% yield

[a] R. J. Crawford and R. Rapp, *J. Org. Chem.*, **28**, 2423 (1963). [b] O. Diels and R. Fritzche, *Ber.*, **44**, 3020 (1911). [c] After repeated crystallization from aqueous EtOH, mp 188–190°, lit.[7] mp 188°. [d] After chromatographic purification.

$$1 + RNH_2 \longrightarrow R'OCONHN(COOR')NHR \quad (8)$$

$$2 + RNH_2 \longrightarrow RNHCONHN(CONHR)NHR \quad (9)$$

Aniline and **1a** yield the Michael addition product, diethyl 1-phenyltriazan-2,3-dicarboxylate,[6] by reaction 8. Aniline also reduced 1,1′-azobis(N-methylformamide) to 1,6-dimethylbiurea after 3 hr at 115°.[6] Under our milder conditions (Table I), aniline did not react to any detectable extent with **2a** according to either 4 or 9.

Experimental Section

Microanalyses were performed on a Fisher micro combustion apparatus. Melting points were determined in capillaries and are uncorrected.

1,1′-Azobis(N-*n*-heptylformamide).—*n*-Heptylamine (9.0 g, 0.08 mole) was added to a stirred solution of **1c** (8.0 g, 0.04 mole) in 40 ml of ether over 1.5 hr at room temperature. Stirring was continued for 0.5 hr after which the slurry was filtered with suction and the solid product was washed with ether until the washings were nearly colorless. The yield was 7.9 g (64%), mp 153–156° dec.

Anal. Calcd for $C_{16}H_{32}N_4O_2$: C, 61.50; H, 10.33; N, 17.93; equiv wt, 156.2. Found: C, 61.53; H, 10.54; N, 17.72; equiv wt (iodine titration),[2] 159.0.

1,6-Di-*n*-heptylbiurea.—Mothers liquors from the preparation of 1,1′-azobis(N-*n*-heptylformamide) from **1c** and *n*-heptylamine were left at room temperature for 10 days, after which the white solid which precipitated was removed by filtration and washed with ethanol (1.5 g, 12%), 222–238° dec. Its ir spectrum was indistinguishable from that of other 1,6-dialkylbiureas[1] in the NH and C=O stretching regions; ir (Fluorolube fluorocarbon mull on Perkin-Elmer 521 instrument), 3290, 3205, 3090 (NH), 1665 (C=O), 1565 (CNH) cm^{-1}.

Anal. Calcd for $C_{16}H_{34}N_4O_2$: C, 61.08; H, 10.90; N, 17.84. Found: C, 60.84; H, 10.70; N, 17.53.

Attempted Reduction of 2a by Ethanol (Table I).—A slurry of 5.0 g of **2a** in 100 ml of ethanol in a stoppered flask was left in the dark (cupboard). After 192 hr at room temperature, the color of the slurry was unchanged. The solid collected (1.6 g) had an equivalent weight of 100.4 (theoretical for **2a** in 100.1). Evaporation of the mother liquors to dryness yielded 3.2 g of residue with an equivalent weight of 102.0.

Reduction of 2a by *n*-Butylamine (Table I).—A slurry of 5.0 g of **2a** in 4.0 g of *n*-butylamine and 100 ml of ethanol was left in the dark (cupboard) for 51 hr at room temperature. The slurry was washed repeatedly with ethanol until a white solid (1.0 g), 1,6-di-*n*-propylbiurea (**4b**, R = n-C_3H_7), remained; ir (in Fluorolube), 3300, 3200, 3090 (NH), 1660 (C=O), 1570 (CNH) cm^{-1}.

Anal. Calcd for $C_8H_{18}N_4O_2$: C, 47.49; H, 8.95; N, 27.73. Found: C, 47.21; H, 8.95; N, 27.65.

The ethanol-soluble material was unreduced **2a**, not **4b**.

Aminolysis of 3a. A. In Ethanol.—Diethyl bicarbamate (**3a**, 10 g, 0.085 mole), 20 ml (0.2 mole) of *n*-butylamine, and 100 ml of ethanol were stirred and heated under reflux for 64 hr. Volatile materials were evaporated from the clear solution and the residual material was crystallized from aqueous ethanol and identified as **3a**, mp 132–134° (58% recovery after crystallization). Its ir was identical with that of **3a**.[1]

B. In Water.—A mixture of *n*-butylamine, water, and **3a** (4:4:1 molar ratio) was heated under reflux for 1.3 hr, after which 80% of the **3a** was recovered unchanged. A similar mixture, after 18 hr under reflux, gave 8% of an insoluble material, **4a**: ir (in Fluorolube), 3300, 3200, 3090 (NH), 1665 (C=O), 1570 (CNH) cm^{-1}.

Anal. Calcd for $C_{10}H_{22}N_4O_2$: C, 52.18; H, 9.62; N, 24.32. Found: C, 51.94; H, 9.46; N, 24.27.

After 64 hr under reflux, the yield of **4a** was 18%.

Attempted Preparation of 1,1′-(Azodicarbonyl)dipyrrolidine. Isolation of 1,2-Bis(1-pyrrolidinylcarbonyl)hydrazine.—To a stirred solution of 26.7 g (0.15 mole) of **1a** in 50 ml of ligroin was added 21.3 g (0.3 mole) of pyrrolidine in 50 ml of ligroin. After an exothermic reaction, a pale orange solid was precipitated by adding ether. The soluble portion was not worked up. The solid did not liberate iodine from potassium iodide solution; 210–215° dec (chars).

The solid was chromatographed on acid-washed alumina; the major fraction (2.9 g, 8%), eluted with benzene, was a white solid: mp 235–237; lit.[7] mp 176°; nmr ($CDCl_3$), multiplets at τ ~6.7 and ~8.2 and a singlet at 2.77 with relative intensities of 4.0:4.0:1.0; ir (Fluorolube mull), 3230 (shoulder at 3300, NH), 1650 and 1630 (C=O), and 1545 and 1525 (broad doublet, CNH) cm^{-1}.

Anal. Calcd for $C_{10}H_{18}N_4O_2$ [1,2-bis(1-pyrrolidinylcarbonyl)-hydrazine]: C, 53.07; H, 8.02; N, 24.76. Found: C, 52.72; H, 7.81; N, 24.74.

1,1′-Azobis(N,N-dibutylformamide). Attempted Preparation.—Dibutylamine (25.8 g, 0.20 mole) was added dropwise to a stirred solution of 20.2 g (0.10 mole) of **1c** in 100 ml of ether. The resulting colorless mixture was evaporated to dryness and the semicrystalline mass was triturated with hexane to give a white solid melting at 105–110° (7.3 g, 36%). Its ir spectrum (in Fluorolube) was very similar in the NH and C=O regions to that of **3a**: 3250, 1755, 1690, 1525 cm^{-1}.

Anal. Calcd for $C_8H_{16}N_2O_4$ (diisopropyl bicarbamate): C, 47.00; H, 7.90; N, 13.72. Found: C, 46.73; H, 7.81; N, 14.06.

A similar reaction using **1a** in ligroin as solvent gave **3a** (34% isolated).

Registry No.—1,1-Azobis(*N*-*n*-heptylformamide), 19740-68-2; 1,6-di-*n*-heptylbiurea, 19740-69-3; **4a**, 16314-55-9; **4b** (R = n-C_3H_7), 17696-84-3; 1,2-bis(1-pyrrolidinylcarbonyl)hydrazine, 19740-71-7; diisopropyl bicarbamate, 19740-72-8.

(6) K. E. Cooper and E. H. Ingold, *J. Chem. Soc.*, 1894 (1926).

(7) W. Reid, H. Hillenbrand, and G. Oertel, *Ann.*, **690**, 126 (1954).

Acknowledgment.—We thank Mr. J. J. Kobliska and his staff for the analyses report herein.

Synthetic Approaches to Oxygen-Bridged Cyclooctyl Compounds[1]

A. C. COPE, M. A. MCKERVEY,[2a] AND N. M. WEINSHENKER[2b]

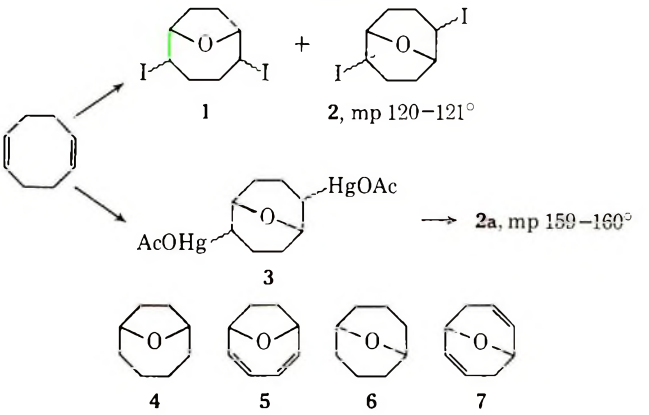
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received October 22, 1968

During our studies on transannular reactions in cyclooctyl compounds we observed that treatment of *cis,cis*-1,5-cyclooctadiene with mercuric oxide and iodine produced two new substituted 9-oxabicyclononanes. Since this structural feature is common to several products isolated from other transannular reactions,[3] we have investigated this reaction as a synthetic route to various substituted 9-oxabicyclononanes.

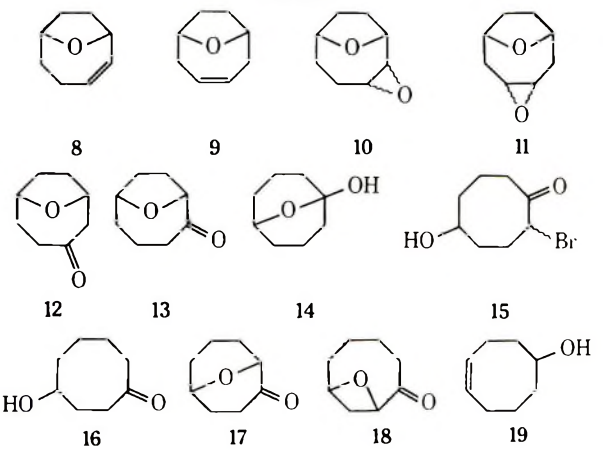
Addition of iodine to a mixture of the diene and mercuric oxide in chloroform at 35–45° led to the formation of mercuric iodide and a crystalline solid. Elemental and mass spectral analysis of the solid indicated the molecular formula $C_8H_{12}I_2O$. The molecular ion peak at *m/e* 378 in the mass spectrum was followed by intense peaks at *m/e* 251 and 124, indicating the successive loss of two iodine atoms. Glpc analysis showed the presence of two components in the ratio 2:3. Attempts to obtain pure samples of the individual components by preparative glpc were not successful although a pure sample of one was eventually obtained by selectively removing the other. Thus treatment of the mixture with potassium *t*-butoxide in ether gave a liquid and a crystalline solid. Support for structure **5** for the liquid product was obtained from spectroscopic measurements (see the Experimental Section) and from its transformation into 9-oxabicyclo[4.2.1]nonane (**4**)[4] on catalytic hydrogenation. The crystalline product, mp 120–121°, which had a glpc retention time identical with that of one of the components of the original mixture, gave (a) 9-oxabicyclo[3.3.1]nonane (**6**)[5] on exposure to tri-*n*-butyltin hydride and (b) 9-oxabicyclo[3.3.1]nona-2,6-diene (**7**)[6] on heating with potassium *t*-butoxide in tetrahydrofuran. From these experiments it was concluded that the products of the initial reaction were 2,5-diiodo-9-oxabicyclo[4.2.1]-nonane (**1**) and 2,6-diiodo-9-oxabicyclo[3.3.1]nonane (**2**) (Scheme I). Stetter and Meissner[6] have prepared an isomer of **2**, mp 159–160°, starting also with 1,5-cyclooctadiene. Treatment with aqueous mercuric acetate gave the bisacetoxymercuri compound **3** which yielded diiodide **2a** on exposure to iodine in chloroform.

SCHEME I



Diene **5** was a useful intermediate for the synthesis of other substituted 9-oxabicyclo[4.2.1]nonanes. Hydrogenation in aqueous potassium pentacyanocobaltate[7] gave a mixture of **8** and **9** in the ratio of 4:1 (Chart I).

CHART I



These olefins were separated by preparative glpc and their nmr spectra confirmed the assigned structures. Epoxidation of the olefin mixture with *m*-chloroperbenzoic acid in methylene chloride gave the isomeric epoxides **10** and **11** which on reduction with lithium aluminum hydride followed by chromic acid oxidation gave 9-oxabicyclo[4.2.1]nonan-3-one (**12**) and 9-oxabicyclo[4.2.1]nonan-2-one (**13**) in the ratio 1:3. Partial separation of these ketones was achieved by adsorption chromatography over alumina and subsequent preparative glpc gave the pure isomers.

In an attempt to find a more direct route to ketone **13** we investigated the bromination of 5-hydroxycyclooctanone.[8] This compound, which exists almost exclusively in the hemiketal form **14** (the infrared spectrum shows no carbonyl absorption), on treatment with pyridinium bromide perbromide in aqueous acetic acid at 60° gave a brominated product which showed a strong carbonyl absorption in the infrared spectrum and is therefore formulated as **15**. When this com-

(1) Supported in part by Research Grant GP-1587 of the National Science Foundation.

(2) (a) To whom correspondence should be addressed at the Department of Chemistry, Queen's University, Belfast, N. Ireland; (b) N.I.H. Predoctoral Fellow, 1965–1968.

(3) (a) A. C. Cope, M. Gordon, S. Moon, and C. H. Park, *J. Amer. Chem. Soc.*, **87**, 3119 (1965); (b) A. C. Cope, M. A. McKervey, and N. M. Weinshenker, *ibid.*, 2932 (1967); (c) A. C. Cope, B. S. Fisher, W. Funke, J. M. McIntosh, and M. A. McKervey, *J. Org. Chem.*, **34**, 2231 (1969); (d) A. C. Cope, R. B. Kinnel, M. A. McKervey, and N. M. Weinshenker, to be published.

(4) A. C. Cope and B. C. Anderson, *J. Amer. Chem. Soc.*, **79**, 3892 (1957).

(5) A. C. Cope and A. Fournier, *ibid.*, **79**, 3896 (1957).

(6) H. Stetter and H. J. Meissner, *Tetrahedron Lett.*, 4599 (1966).

(7) J. Kwiatek, I. L. Mador, and J. K. Seyler, Advances in Chemistry Series, No. 37, American Chemical Society, Washington, D. C., 1963, p 201.

(8) We thank Badische Anilin und Soda Fabrik, Ludwigshafen, Germany, for this material.

pound (without purification) was dissolved in methanol containing potassium hydroxide ketone **13** was obtained (47% yield from **14**). The structural assignment follows from the infrared spectrum of **13** and from its transformation by the Wolff–Kishner method into a mixture of 9-oxabicyclo[4.2.1]nonane (**4**) and 4-cycloocten-1-ol (**19**) in the ratio 4:1. The formation of the latter compound in this reaction confirms the position of the carbonyl group since it is an example of an eliminative reduction of an α-substituted ketone.[9] The above synthetic sequence was also applied successfully to two other oxygen-bridged cyclooctanones. Thus bromination of 4-hydroxycyclooctanone (**16**)[8] with pyridinium bromide perbromide followed by treatment of the mixture of crude bromo ketones with potassium hydroxide in methanol gave 9-oxabicyclo-[3.3.1]nonane-2-one (**17**) and 9-oxabicyclo[5.1.1]nonan-2-one (**18**) in the ratio 1:2.5 (30% yield from **16**). Wolff–Kishner reduction of **17** yielded 9-oxabicyclo-[3.3.1]nonane (**6**) and 4-cycloocten-1-ol (**19**) in the ratio 3:1. A similar reaction with **18** failed to give 9-oxabicyclo[5.1.1]nonane; attempts to reduce the carbonyl group of **18** with sodium borohydride gave a mixture containing at least seven components.

Experimental Section[10]

2,5-Diiodo-9-oxabicyclo[4.2.1]nonane (1) and 2,6-Diiodo-9-oxabicyclo[3.3.1]nonane (2).—A slurry of red mercuric oxide (108 g) in chloroform (500 ml) containing *cis,cis*-1,5-cyclooctadiene (54 g) was stirred in a 1-l. flask fitted with a condenser. Iodine (252 g) was added in small portions through the condenser during 2.5 hr and the addition rate was adjusted so that the internal temperature remained between 35 and 45°. The mixture was cooled and the solid (HgI_2, 230 g) was removed by filtration. The filtrate was washed with sodium thiosulfate solution and dried. Removal of the solvent gave an oil which deposited crystals on standing. Methanol (100 ml) was added and the crystals were isolated by filtration. There was obtained 119 g (63%) of a mixture of diiodides **1** and **2**, mp 62–70°. A sample recrystallized from methanol had mp 75–80°. Glpc analysis on 2-ft 20% SE-30 at 180° showed the presence of both isomers in the ratio 2:3.

Anal. Calcd for $C_8H_{12}I_2O$: C, 25.39; H, 3.20; I, 67.12. Found: C, 25.29; H, 3.26; I, 67.69.

Reaction of the Diiodides with Potassium *t*-Butoxide.—Potassium *t*-butoxide (30 g) was added to a solution of the diiodide mixture (50 g) in dry ether (500 ml). The mixture was stirred and cooled during the addition and then was heated under reflux for 1.5 hr. The mixture was cooled, filtered through Celite, and the filtrate was washed with two 300-ml portions of water and dried. Removal of the solvent gave a residue which deposited crystals on trituration with pentane. Filtration yielded **2** (15 g), mp 120–121°, after recrystallization from methanol. This material was identical in glpc retention time with the minor component of the diiodide mixture.

Anal. Calcd for $C_8H_{12}I_2O$: C, 25.39; H, 3.20; I, 67.12. Found: C, 25.55; H, 3.18.

Concentration of the pentane solution followed by distillation gave 7.6 g (79.3%) of 9-oxabicyclo[4.2.1]nona-2,4-diene (**5**), bp 50–60° (*ca.* 5 mm). A second distillation gave an analytical sample, bp 46–48° (4 mm); ir (neat) 3025 (m), 1075 (s), 1000 (s), 920 (s), 780 (s), and 700 cm^{-1} (s); uv max (EtOH) 257 mμ (ϵ 5650); nmr ($CDCl_3$) δ 5.6–6.35 (m, 4 H), 4.5–4.8 (m, 2 H), and 2.2 (m, 4 H).

Anal. Calcd for $C_8H_{10}O$: C, 78.57; H, 8.24. Found: C, 78.42; H, 8.16.

Catalytic Hydrogenation of 5.—A sample of **5** (100 mg) in methanol (5 ml) containing 5% palladium on carbon (15 mg) was hydrogenated at room temperature and atmospheric pressure until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate was diluted with pentane. The pentane solution was then washed with water and dried. Removal of the solvent gave an oil (*ca.* 100 mg) which was shown by glpc analysis (5 ft × 20% TCEP at 90°) to contain one component with a retention time identical with that of 9-oxabicyclo[4.2.1]nonane (**4**). The ir spectrum of a sample collected by preparative glpc was superimposable with that of an authentic sample of **4**.

Tri-*n*-butyltin Hydride Reduction of 2.—A sample of **2** (1.0 g), mp 121–121.5°, was added to tri-*n*-butyltin hydride (2.0 g) and the mixture was stirred. After gentle warming on a water bath the solid went into solution. The solution was stirred overnight and the product was then flash distilled at 25° (0.2 mm) into a receiver cooled at −78°. The yield of material, mp 48–51°, was 300 mg (83%). The ir spectrum was superimposable with that of an authentic sample of **6**.

9-Oxabicyclo[4.2.1]non-2-ene (8) and 9-Oxabicyclo[4.2.1]non-3-ene (9).—The catalyst used in the hydrogenation of **5** was prepared as follows: 50 ml of a 0.3 *M* cobalt chloride solution was placed in a 250-ml flask fitted with an efficient magnetic stirrer, a hydrogen inlet, a dropping funnel with an equilibrating side arm, and a syringe cap inlet. A solution of potassium cyanide (50 ml, 1.35 *M*) was placed in the dropping funnel and the flask was flushed three times with hydrogen. The cyanide solution was then allowed to flow rapidly into the flask with very rapid stirring. Hydrogen uptake was recorded and was complete (110–130 ml) in *ca.* 30 min.

The diene (5.78 g) was then added with a syringe and hydrogen uptake was recorded. The reaction stopped after 2 hr when 38.9 mmol of hydrogen had been absorbed. Glpc analysis indicated the absence of diene. The mixture was extracted with 50-ml portions of ether and the ether solution was washed with sodium chloride solution and dried. Removal of the solvent gave 5.84 g (98%) of a mixture of **8** and **9** in the ratio 4:1, bp 40–43° (4.5 mm). Pure samples of each isomer were obtained by preparative glpc on 8-ft 20% LAC-728. **8** showed the following characteristics: ir (film) 3010 (m), 1110 (m), 1060 (vs), 1015 (m), 885 (m), 820 (m), 715 (m), and 660 cm^{-1} (m); nmr (CCl_4) 1.2–1.9 (m, 6 H), 1.9–2.3 (m, 2 H), 4.15 (bs, 2 H), and 5.2 (m, 2 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.50; H, 9.78. **9** showed the following characteristics: ir (film) 2990 (m), 1200 (m), 1085 (m), 1055 (s), 1000 (m), 960 (m), 900 (m), 860 (m), and 660 cm^{-1} (s); nmr (CCl_4) 1.3–2.0 (m, 4 H), 2.0–2.7 (m, 4 H), 4.3 (bs, 2 H), and 5.5 (m, 2 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.36; H, 9.69.

9-Oxabicyclo[4.2.1]nonan-3-one (12) and 9-Oxabicyclo[4.2.1]-nonan-2-one.—A mixture of the epoxyolefins (79% **8** and 21% **9**) (6.0 g) was dissolved in methylene chloride (30 ml) at 5° and a solution of *m*-chloroperbenzoic acid (15.0 g) in methylene chloride (150 ml) was added dropwise with stirring during 1 hr. The mixture was then allowed to stand at room temperature for 2 hr. The precipitated solid was removed by filtration and the filtrate was washed twice with 10% aqueous potassium hydroxide and dried ($MgSO_4$). Removal of the solvent gave a semisolid which, on sublimation at 70° (0.5 mm), gave 5.0 g (72%) of a mixture of epoxides **10** and **11**. Glpc analysis on an 8-ft 20% LAC-728 at 180° indicated the presence of all four isomers. A sample of the epoxide mixture was collected by preparative glpc on 2-ft 20% SE-30 at 140° and analyzed.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.50; H, 8.76.

A solution of the epoxide mixture (4.55 g) in ether (20 ml) was added dropwise to a slurry of lithium aluminium hydride (1.5 g) in ether (75 ml). The mixture was stirred for 30 min and then treated successively with cold water and dilute hydrochloric acid. The precipitated solids were removed by filtration and the filtrate concentrated to afford 4.65 g (95%) of an oil. Glpc analysis on an 8-ft 20% LAC-728 at 120° showed the presence of three isomers. A sample of the alcohol mixture was purified by preparative glpc on a 2-ft 20% SE-30 at 140° and analyzed.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.58; H, 9.77.

The crude alcohol mixture (4.55 g) was dissolved in acetone (35 ml) at 0° and an excess of 8 *N* chromic acid was added drop-

(9) N. J. Leonard and S. Gelfand, *J. Amer. Chem. Soc.*, **77**, 3272 (1955); see also P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).

(10) Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected; boiling points are uncorrected. Glpc analyses were carried out using an F & M Model 720 instrument. Liquid phases are abbreviated in the following way: SE-30, silicone gum rubber; XF-1150, GE-fluorosilicone, TCEP, 1,2,3-tris(2-cyanoethoxy)propane; LAC-728, diethyleneglycol succinate. Nmr spectra were recorded on a Varian Associates A-60 spectrometer. Microanalyses were performed by Dr. S. M. Nagy and his associates.

wise. The mixture was allowed to stand overnight and then the solvent was removed at reduced pressure. The residue was dissolved in ether and washed with water. The aqueous layer was saturated with sodium chloride and extracted with ether. The combined ether extracts were dried and concentrated to give 3.98 g (88.5%) of an oil. Glpc analysis on 8-ft 20% LAC-728 at 190° indicated the presence of two components in the ratio 1:3. Analytical samples of the individual ketones were obtained by preparative glpc on the same column. The minor component **12** had mp 29.5–32°; ir (KBr) 1700 (vs), 1190 (m), 1140 (w), 1105 (m), 1090 (s), 1060 (m), 1035 (s), 1005 (w), 960 (w), 945 (m), 860 (w), and 760 cm^{-1} (w); nmr (CCl_4) 1.1–2.3 (m, 6 H), 2.4–3.0 (m, 4 H), 4.15–4.65 (bs, 2 H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.32; H, 8.61.

The major component **13** was identical in every respect with the material described below.

9-Oxabicyclo[4.2.1]nonan-2-one (13).—5-Hydroxycyclooctanone (**14**, 7.8 g) was dissolved in glacial acetic acid (75 ml) containing water (25 ml). The solution was heated to 60° and pyridinium bromide perbromide (19.5 g) was added slowly with stirring during 1 hr. When the addition was complete, the solution was left overnight at room temperature. It was then poured into cold water (700 ml) and extracted six times with methylene chloride. The combined extracts were washed twice with water and dried. Removal of the solvent left a viscous brown oil (12.8 g) which was dissolved in methanol and added to a solution of potassium hydroxide (3.0 g) in methanol (20 ml). After 5 min, the solution was poured into cold water (700 ml) and extracted with methylene chloride. The combined extracts were washed with water and dried. Removal of the solvent followed by fractional distillation gave **13**, 3.7 g (47%), bp 76–77.5° (3 mm). A sample of >99% purity was obtained by adsorption chromatography over alumina.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.57.

Wolff–Kishner Reduction of 9-Oxabicyclo[4.2.1]nonan-2-one (13).—The ketone (1.0 g), potassium hydroxide (1.5 g), hydrazine hydrate (1.0 ml), and diethylene glycol (10 ml) were placed in a flask fitted with a reflux condenser. The mixture was heated in an oil bath at 160° for 2 hr. After cooling, cold water was added and the solution was extracted with ether. The ether solution was washed with water and dried ($MgSO_4$). Cautious removal of the solvent left an oil which was shown by glpc on 2-ft 20% SE-30 to contain components in the ratio 4:1. The individual components were isolated by preparative glpc and identified as 9-oxabicyclo[4.2.1]nonane (**4**) and 4-cycloocten-1-ol (**19**) by comparison of their ir spectra and glpc retention times with those of authentic samples.

Wolff–Kishner Reduction of 9-Oxabicyclo[4.2.1]nonan-3-one (12).—A sample of **12** (24.5 mg) was dissolved in ethylene glycol (0.5 ml) containing 85% hydrazine hydrate (50 μl) and potassium hydroxide (10 mg). The mixture was heated under reflux for 1 hr and then cooled, diluted with water, and extracted with pentane. The pentane solution was dried ($MgSO_4$) and concentrated. The ir spectrum of the residue was identical with that of an authentic sample of 9-oxabicyclo[4.2.1]nonane (**4**). Glpc analysis on a 2-ft 20% SE-30 showed only one component. A sample obtained by preparative glpc had mp 28–30° (lit.[4] mp 31°).

9-Oxabicyclo[3.3.1]nonan-2-one (17) and 9-Oxabicyclo[5.1.1]-nonan-2-one (18).—4-Hydroxycyclooctanone (**16**, 5.0 g) was dissolved in glacial acetic acid (19 ml) containing water (6 ml). The solution was heated to 60° and pyridinium bromide perbromide (11.1 g) was added slowly with stirring during 15 min. When the addition was complete, the solution was left overnight at room temperature. It was then diluted with cold water (200 ml) and extracted with methylene chloride. The combined extracts were washed with saturated sodium bicarbonate solution and dried. Removal of the solvent left 7.2 g of a brown oil which was then dissolved in methanol (50 ml) and added to a solution of potassium hydroxide (5.0 g) in methanol (35 ml). After 10 min, the volume of the solution was reduced and the residue was dissolved in ether and poured into water (200 ml). The ether layer was separated and the aqueous layer was extracted with an additional 100 ml of ether. The combined extracts were washed with water and dried. Removal of the solvent followed by distillation gave 1.0 g (20%) of a mixture of **17** and **18**, bp 50° (0.3 mm). Glpc analysis on a 5-ft 5% XF-1150 at 148° indicated an isomer ratio of 1:2.5. Separation of the two isomers was achieved by adsorption chromatography on alumina. Elution with methylene chloride–pentane (1:4) gave pure **17** (200 mg) in the first three fractions. Fractions 4–8 (410 mg) contained equal amounts of the two ketones. Finally, elution with 300 ml of methylene chloride gave **18** (300 mg) of 90–95% purity. Further purification was achieved by preparative glpc on an 8-ft 20% LAC-728 at 180°. Ketone **18** had principle ir bands at 1700 (vs), 1050 (s), 1020 (s), 980 (s), 940 (m), and 865 cm^{-1}; mass spectrum major peaks (*m/e*, relative intensity) 140 (17, molecular ion), 84 (45), 83 (46), 68 (45), 55 (100), 41 (100), and 39 (99).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.59; H, 8.80.

Structure Proof of 9-Oxabicyclo[3.3.1]nonan-2-one (17).—A sample of **17** (17 mg) was dissolved in ethylene glycol (250 μl) containing 95% hydrazine (75 μl) and potassium hydroxide (10 mg). The mixture was heated under reflux for 1 hr and then cooled, diluted with water, and extracted with ether. The ether solution was dried ($MgSO_4$) and concentrated. Glpc analysis of the residue on a 2-ft 20% SE-30 showed the presence of 9-oxabicyclo[3.3.1]nonane (**6**) and 4-cycloocten-1-ol (**19**) in the ratio 3:1.

Registry No.—**1**, 19740-73-9; **2**, 10299-46-4; **5**, 19740-75-1; **8**, 19740-76-2; **9**, 19771-17-6; **12**, 19740-77-3; **13**, 19740-78-4; **17**, 19740-79-5; **18**, 19740-80-8.

---

cis,cis-1,5-Cyclooctadiene Diepoxide[1]

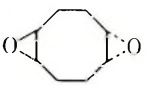
ARTHUR C. COPE, BRUCE S. FISHER, WOLFGANG FUNKE, JOHN M. MCINTOSH, AND MICHAEL A. MCKERVEY[2]

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

Received October 22, 1968

The epoxidation of *cis,cis*-1,5-cyclooctadiene with excess peracid can give *cis*- and/or *trans*-diepoxides **1a** and **b**. The use of perbenzoic acid in this reaction was studied by Criegee and Kerkow,[3] although no experiments concerning the configuration of the product were carried out. We have investigated the stereochemistry of this reaction and have observed some transannular reactions with the diepoxide. A study of the diepoxidation of 1,4-cyclohexadiene revealed that depending

1a



1b

on the peracid used, *trans*-1,4-cyclohexadiene diepoxide or mixtures of the *cis* and *trans* isomers were obtained.[4] It appeared possible that changing the peracid would lead to similar effects in the case of *cis,cis*-1,5-cyclooctadiene. However, we found that peracetic acid in acetic acid gave a diepoxide identical in glpc retention time, infrared spectrum, and refractive index with that obtained using perbenzoic acid in chloroform; according to the glpc analysis, performed on various liquid phases, only one isomer of the diepoxide was obtained from both reactions.

The well-established mode of reaction of lithium

(1) Supported in part by a research grant (GP-1587) from the National Science Foundation.

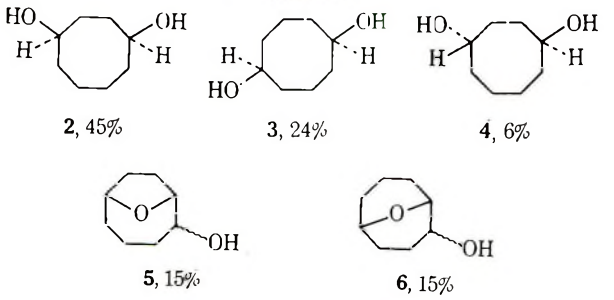
(2) To whom enquiries should be addressed at The Chemistry Department, Queen's University, Belfast, N. Ireland.

(3) Unpublished results of R. Criegee and A. Kerkow. We thank Professor Criegee for an account of this work.

(4) T. W. Craig, G. R. Harvey, and G. A. Berchtold, *J. Org. Chem.*, **32**, 3743 (1967); H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 221 (1959).

aluminum hydride with epoxides offered a method for determining the stereochemistry of the diepoxide. Normally, the epoxide ring is opened in an SN2-type process. On this basis, **1a** should give *cis*-1,4-and/or *cis*-1,5-cyclooctanediol whereas **1b** should give *trans*-1,4- and/or *trans*-1,5-cyclooctanediol. In this event, reduction of the diepoxide with lithium aluminum hydride in tetrahydrofuran gave a mixture of products (Chart I) from which a cyclooctanediol fraction could

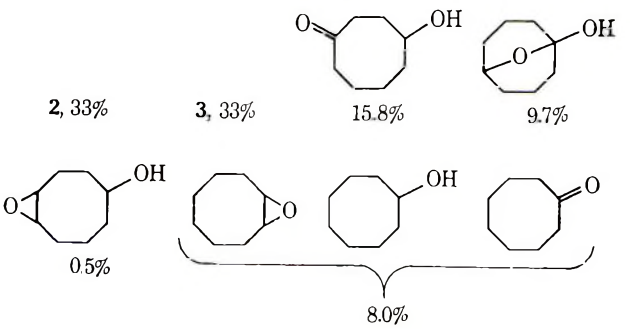
CHART I



be obtained by fractional distillation. The cyclooctanediols, which were inseparable on glpc analysis, were converted into the corresponding ditrifluoroacetates which were separated and identified as derivatives of *cis*-1,4-cyclooctanediol (**2**), *cis*-1,5-cyclooctanediol (**3**), and *trans*-1,4-cyclooctanediol (**4**) by comparison of their glpc retention times and infrared spectra with those of authentic samples.[5] A lower boiling fraction was also isolated from the product mixture and was shown to contain at least three of the four possible isomers of **5** and **6**. A mixture of *endo* **5** and *endo* **6** was synthesized by the method of Moon and Hayes[6] and *endo* **5** was isolated by preparative glpc. Its mass spectrum and glpc retention time were identical with those of the major component (70%) of the mixture of epoxy alcohols obtained from the diepoxide. The presence of *endo* **6** was not definitely established but two other isomers, assumed to be *exo* **5** and *exo* **6**, were isolated by preparative glpc. Their mass spectra ($M^+ = 142$) showed fragmentation patterns almost identical with those of *endo* **5** and *endo* **6**; only slight differences in peak intensities were observed. The results of the lithium aluminum hydride reduction are not completely understood. If the reaction proceeds in the anticipated stereospecific way, then the diepoxide must be a mixture of **1a** and **b**, **1a** being the dominant isomer since *cis* diols were the major products of the reduction. On the other hand, a nonstereospecific reaction involving a small amount of isomerization of one epoxide group to a carbonyl group prior to reduction could account for the small amount of *trans*-diol in the products. The epoxy alcohol *endo* **5** can arise *via* a transannular mechanism in which the oxygen anion resulting from the opening of the first epoxide group reacts with the second epoxide group in the *trans* isomer **1b**; no *exo* isomers can be formed by this mechanism.

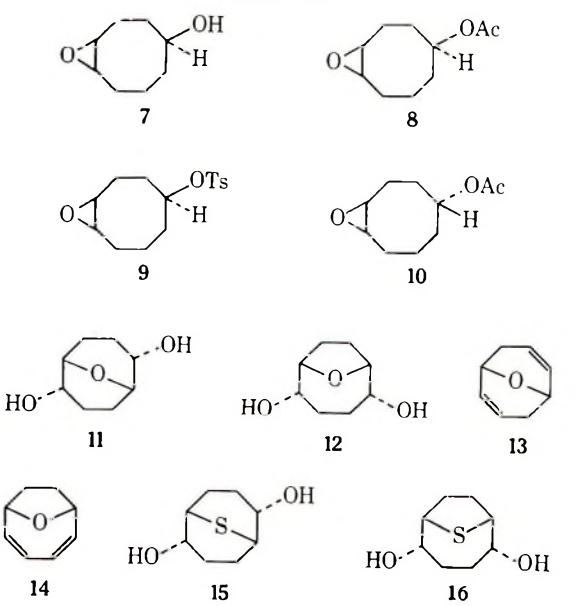
Catalytic hydrogenation of the diepoxide at room temperature using palladium on carbon as catalyst and a hydrogen pressure of 900 psi gave the products listed in Chart II. Comparisons, similar to those used in the

CHART II



lithium aluminum hydride reduction, revealed that the diol fraction contained *cis* isomers exclusively. The remaining products were identified by comparisons with authentic samples.[7] The isolation of considerable quantities of 4- and 5-hydroxycyclooctanone makes it difficult to assign an exact ratio to the diepoxide although the results confirm that **1a** is the major isomer. In another series of experiments it was established that reduction of the diepoxide with a deficiency of lithium aluminum hydride in ether gave a single epoxy alcohol, assigned *cis* configuration **7**. This alcohol was converted into (a) the crystalline epoxy acetate **8** and (b) the epoxy tosylate **9**. This latter compound on exposure to tetraethylammonium acetate gave the liquid epoxy acetate **10** (Chart III). Comparison of the two

CHART III



epoxy acetates **8** and **10** showed that no trace of one could be found in the crude reaction mixture containing the other under glpc conditions which cleanly separated the two.

Criegee and Kerkow[3] did not obtain the expected tetrols from hydrolysis of the diepoxide with dilute sulfuric acid. Instead, a product was isolated for

(5) A. C. Cope and B. C. Anderson, *J. Amer. Chem. Soc.*, **79**, 3892 (1957); A. C. Cope and A. Fournier, *ibid.*, **79**, 3896 (1957).

(6) S. Moon and L. Hayes, *J. Org. Chem.*, **31**, 3067 (1966); see also A. C. Cope, M. A. McKervey, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **89**, 2932 (1967).

(7) We thank Badische Anilin und Soda Fabrik, Ludwigshafen, Germany, for samples of 5-hydroxycyclooctanone (which exists in the hemiketal form) and 4-hydroxycyclooctanone.

which they suggested structure **11**. We repeated the hydrolysis under the same conditions and obtained a product (97.5%), the spectral characteristics of which were consistent with **11** and/or **12**. That the product was a mixture of the two isomers was established by conversion to the ditosylates followed by elimination with potassium hydroxide in triethylene glycol to give a mixture of the epoxy dienes **13** and **14**.[8] Subsequent hydrogenation gave 9-oxabicyclo[4.2.1]nonane (75%) and 9-oxabicyclo[3.3.1]nonane (25%). Hydrolysis of the diepoxide therefore gives **11** and **12**, **12** being the dominant product. The formation of these two products can be explained by a mechanism involving solvolytic opening of one of the epoxide groups in the first step followed by a transannular nucleophilic substitution by one of the hydroxyl groups on the second epoxide group, leading to di-*endo*-epoxydiols.

Transannular reaction also occurred when the diepoxide was treated with sodium sulfide in aqueous ethanol.[9] The product, obtained in 88% yield, analyzed correctly for **15** and/or **16**. That 9-thiabicyclo[4.2.1]nonane-2,5-diol (**16**) was the major component was established by desulfurization with Raney nickel. This reaction gave a complex mixture of products from which three components (representing 80% of the total) were isolated by preparative glpc and identified as 4-hydroxycyclooctanone, 5-hydroxycyclooctanone, and *cis*-1,4-cyclooctanediol (major product). 1,5-Cyclooctanediol was not detected; apparently, 5-hydroxycyclooctanone is the only product of desulfurization of **15**. Although the configurations of the hydroxyl groups in **15** and **16** were not established, they are represented as possessing the *endo* positions since nucleophilic attack by sulfide ion on *cis*-diepoxide **1a** should give this stereochemical result. Berchtold and coworkers[4] have established that the analogous reaction of sodium sulfide with *cis*-1,4-cyclohexadiene bisepoxide gives di-*endo*-7-thiabicyclo[2.2.1]heptane-2,7-diol.

Experimental Section[10]

Epoxidation of *cis*-1,5-Cyclooctadiene.—The diene (15.5 g) was added dropwise to a stirred solution of perbenzoic acid (41.6 g) in chloroform (1350 ml) at −5°. When the addition was completed the solution was allowed to stand at 0° for 5 days. The chloroform solution was then shaken twice with 10% aqueous sodium hydroxide, washed with water, and dried (Na_2SO_4). Removal of the solvent followed by fractional distillation gave 11.4 g (57%) of the diepoxide: bp 64° (0.3 mm); $n^{25}D$ 1.4952.

Repetition of the epoxidation using peracetic acid (1.4 equiv) in acetic acid containing sodium acetate gave a mixture of unreacted diene (16%), the monoepoxide (51%), and the diepoxide (14%). The monoepoxide had bp 64–66° (6 mm).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.62; H, 9.92.

The diepoxide had bp 65–72° (*ca.* 0.35 mm); mp 25–27°; ir (CCl_4) 915 cm^{-1}; nmr ($CDCl_3$) 2.95 (m, 4 H), 1.92 (m, 8 H); mass spectrum (80 eV) *m/e* no molecular ion species at 140 but peaks in order of decreasing intensity occurred at 41, 67, 68, 39, 55, and 79. Glpc analysis, performed on a variety of liquid phases, showed a single peak.

Reduction of the Diepoxide with Lithium Aluminum Hydride.—To a stirred suspension of lithium aluminum hydride (45 g) in tetrahydrofuran (650 ml) was added dropwise a solution of the diepoxide (45 g) in tetrahydrofuran (300 ml). The mixture was stirred at room temperature for 42 hr and at reflux temperature for 4 hr after which aqueous methanol was added. After the addition of chloroform, the mixture was filtered and the solid residue was washed with chloroform and acetone. The combined organic solutions were dried ($MgSO_4$) and concentrated at reduced pressure. Distillation of the residue gave 41 g of an oil (89% yield, calculated for cyclooctanediol), bp 100–113° (0.15–0.3 mm). Glpc analysis on an 8-ft 20% silicon rubber at 150° showed the presence of three components—A (9%), B (15%), and C (75%)—in order of increasing retention time. Samples of each were obtained by preparative glpc. Component A, which had a very short retention time compared with B and C, was not investigated further. Component B was further partially resolved into three compounds by glpc on an 8-ft 5% XF-1150 at 160°. The major compound of this mixture was found to be identical with a sample of *endo* **5**, prepared by the method of Moon and Hayes.[6]

A sample of component C (cyclooctanediols) was purified by preparative glpc and analyzed.

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.30; H, 11.02.

Ditrifluoroacetates of C.—To a solution of C (90 mg) in pyridine (2 ml) was added trifluoroacetic anhydride (2 ml) at 0°. The mixture was stirred at room temperature for 30 min, poured into cold dilute hydrochloric acid, and extracted with ether. The ether solution was washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Removal of the solvent gave an oil from which *trans*-1,4-cyclooctanediol ditrifluoroacetate, *cis*-1,5-cyclooctanediol ditrifluoroacetate, and *cis*-1,4-cyclooctanediol ditrifluoroacetate were isolated by preparative glpc on a 12-ft 5% XF-1150 at 120° and identified by comparison of their retention times and spectral properties with those of authentic samples.[5]

Catalytic Hydrogenation of the Diepoxide.—A solution of the diepoxide (3 g) in ethyl acetate (150 ml) was hydrogenated at room temperature with a hydrogen pressure of 900 psi and 10% palladium on charcoal (1.5 g) as catalyst. The solution was filtered, concentrated to a volume of 20 ml, and analyzed by glpc on an 8-ft 20% silicon rubber at 150°. The diol fraction was isolated by preparative glpc and shown to contain *cis*-1,4-cyclooctanediol and *cis*-1,5-cyclooctanediol by conversion to the ditrifluoroacetates as described above. The remaining products are listed in Chart II.

4,5-Epoxycyclooctanol (7).—Reduction of the diepoxide with lithium aluminum hydride in ether as previously described[11] gave a mixture containing unreacted diepoxide, epoxy alcohol **7**, and a trace of diol. The epoxy alcohol was purified by fractional distillation.

4,5-Epoxycyclooctyl Acetate (3).—To a solution of **7** (200 mg) in dry pyridine (2 ml) was added acetic anhydride (0.75 ml) at room temperature. After 46 hr, water was added and the mixture was extracted with three 20-ml portions of ether. The ether solution was washed with water and dried ($MgSO_4$). Removal of the solvent gave a solid which was homogeneous on glpc analysis on a 10-ft 20% LAC-728. Recrystallization from pentane gave 210 mg (80%) of the crystalline epoxy acetate **8**: mp 66.5–67°; ir (CCl_4) 1740, 1250, and 1025 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.04; H, 8.77.

4,5-Epoxycyclooctyl Tosylate (9).—To a solution of **7** (1.6 g) in dry pyridine (10 ml) was added *p*-toluenesulfonyl chloride (2.5 g). The solution was left at room temperature for 60 hr. Dilution with cold water followed by filtration gave a white solid which was recrystallized from pentane to give 1.53 g (46%) of epoxy tosylate **9**: mp 94.5–96°; nmr (CCl_4) 7.50 (q, 4 H), 4.41–4.82 (m, 1 H), 3.00–1.05 (m, 12 H), 2.44 (s, 3 H).

Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.80; H, 6.80; S, 10.80. Found: C, 60.65; H, 6.74; S, 10.66.

(8) A more convenient route to **13** and **14** is described in a forthcoming publication by A. C. Cope, M. A. McKervey, and N. M. Weinshenker.

(9) Other transannular routes to sulfur-bridged cyclooctyl compounds have been described by E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966), and E. D. Weil, K. J. Smith, and R. J. Gruber, *ibid.*, 1669 (1966).

(10) Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Boiling points are uncorrected. Glpc analyses were performed using an F & M Model 720 instrument. Liquid phases are abbreviated in the following way: SE-30, silane gum rubber; TCEP, 1,2,3-tris(2-cyanoethoxy)propane; XF-1150, GE-fluorisilicone, LAC-728, diethyleneglycol succinate. Nmr spectra were recorded on a Varian A-60 spectrometer and chemical shifts are expressed in δ values relative to tetramethylsilane. Microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(11) A. C. Cope, R. S. Bly, M. M. Martin, and R. C. Petterson, *J. Amer. Chem. Soc.*, **87**, 3111 (1965).

4,5-Epoxycyclooctyl Acetate (10).—Tetraethylammonium acetate (5.10 g) was added to a solution of **9** (1.15 g) in dry acetone (40 ml) and the mixture was heated under reflux for 46 hr. Removal of the solvent at reduced pressure gave a semisolid which was treated with water (80 ml) and extracted with ether. The ether extracts were washed with water, dried ($MgSO_4$), and concentrated to an oil (0.62 g). Glpc analysis showed the presence of three components, two of which had retention times similar to that of 4,5-epoxycyclooctene. The third component, which had a retention time close to that of epoxy acetate **8**, was obtained by preparative glpc: ir (CCl_4) 1740, 1250, 1035, and 1020 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.02; H, 8.68.

Glpc analysis of a mixture of **8** and **10** showed that these isomers were cleanly separated on a 10-ft 20% LAC-728.

Hydrolysis of the Diepoxide.—A mixture of the diepoxide (10 g) and 0.02 *N* sulfuric acid (100 ml) was heated on a steam bath for 20 hr. After cooling, solid sodium bicarbonate was added followed by sodium chloride. Continuous extraction with ethyl acetate for 12 hr then gave 11 g (97%) of a solid. A sample collected by preparative glpc had mp 60–85°, mol wt (mass spectrometry), 158.19.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.33; H, 8.90.

Ditosylates of 11 and 12.—To a cold solution of the crude diol mixture (3.1 g) in pyridine (30 ml) was added *p*-toluenesulfonyl chloride (8.2 g). The mixture was stirred at room temperature for 4 hr and was then poured into cold water. The precipitated solid was collected by filtration and dissolved in benzene. The benzene solution was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate, and water, and dried ($MgSO_4$). Removal of the solvent gave an oil 8.7 g (97%) which solidified on standing, mp 117–125°. Thin layer chromatography indicated the presence of two components. A sample had mp 153° after three recrystallizations from ethyl acetate–hexane.

Anal. Calcd for $C_{22}H_{26}O_7S_2$: C, 56.63; H, 5.62. Found: C, 56.62; H, 5.60.

9-Oxabicyclo[4.2.1]nonane and 9-Oxabicyclo[3.3.1]nonane.—To a solution of potassium hydroxide (1.4 g) in triethyleneglycol (6 ml) in a flask fitted with a condenser set for distillation was added the crude ditosylate mixture (2.0 g). The flask was heated for 30 min with a flame and a mixture of the epoxydienes **13** and **14** (0.6 g) was collected in a cold trap. The mixture was dissolved in ethyl acetate and hydrogenated during 12 hr at room temperature using Adams catalyst. The catalyst was removed by filtration and the filtrate was concentrated at reduced pressure. Preparative glpc of the residue gave 9-oxabicyclo[4.2.1]nonane (75%) and 9-oxabicyclo[3.3.1]nonane (25%), identified by spectral comparisons with authentic samples.

Reaction of the Diepoxide with Sodium Sulfide.—A solution of the diepoxide (2.8 g) in ethanol (20 ml) was mixed with a solution of sodium sulfide (4.8 g) in 50% aqueous ethanol (40 ml) and the mixture was heated under reflux for 14 hr. The mixture was cooled, diluted with water, and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to give a mixture of **15** and **16**, 3.1 g (88%), as a solid. Recrystallization from benzene–ethyl acetate gave colorless needles, mp 179°. A sample which was sublimed at 120° (0.5 mm) had mp 175–176°. Thin layer chromatography indicated the presence of both isomers. The major isomer **16**, mp 174°, could be obtained pure by adsorption chromatography of the mixture on alumina.

Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.10; S, 18.40. Found: C, 55.12; H, 8.05; S, 18.33.

Desulfurization of 15 and 16 with Raney Nickel.—A solution of of the above mixture of **15** and **16** (1.5 g) in 95% ethanol was stirred and heated under reflux with excess W_2 Raney nickel for 15 hr. The catalyst was removed by filtration and the filtrate analyzed by glpc on an 8-ft 20% silicon rubber column at 150°. The three major components (representing 80% of the total) were isolated and identified as 4-hydroxycyclooctanone, 5-hydroxycyclooctanone, and *cis*-1,4-cyclooctanediol.

Registry No.—**1a**, 19740-81-9; **8**, 19740-82-0; **9**, 19740-83-1; **10**, 19740-84-2; **11**, 19771-18-7; **11** (ditosylate), 19740-85-3; **12**, 19740-86-4; **12** (ditosylate), 19740-87-5; **15**, 19740-88-6; **16**, 19740-89-7; *cis,cis*-1,5-cyclooctadiene monoepoxide, 19740-90-0.

Purification of Hydrocarbon Solvents with a Silver Nitrate Column

E. C. MURRAY AND R. N. KELLER[1]

Department of Chemistry, University of Colorado, Boulder, Colorado

Received December 30, 1968

Hydrocarbon solvents of the utmost purity were required in a research program dealing with the properties of niobium and tantalum halides in nonaqueous systems. The usual procedures and combinations of procedures for purifying these liquids were tried with little success.

The predominant impurities in commercial and reagent grades of saturated hydrocarbon solvents are olefinic and aromatic compounds. One method[2a] for the removal of these impurities involves washing the hydrocarbon with a nitrating mixture of sulfuric and nitric acids followed by several washings with sulfuric acid, water, and finally with sodium bicarbonate solution. Alternatively, the hydrocarbon can be passed through silica gel columns.[2b,3,4] Maclean, Jencks, and Acree[4] demonstrated that several passes are necessary to obtain reasonably pure solvent by this latter method; their sample of purified cyclohexane had an absorbance of 0.4 in a 1.0-cm cell at 220 mμ. The data of Mair and Farziati[3b] indicate that the yield of pure solvent is equal approximately to the mass of silica gel used in their purification procedure. In our work distillation from solutions containing niobium pentachloride as outlined by Fairbrother, *et al.*,[5] was found to add an impurity which interfered with the measurements being made; a similar phenomenon was observed with the sulfuric acid treatment referred to above. Hydrocarbon solvents which were pure enough for our purposes were not obtained after repeated and frustrating attempts to apply the above methods.

Solid silver nitrate as an adsorbent for the hydrocarbon impurities was then investigated. Reports in the literature indicate that silver nitrate on alumina has been used in columns for the separation of olefinic mixtures in both liquid–solid[6–8] and gas–solid[9–11] partition chromatography; silver nitrate on alumina and on silica gel has been used in thin layer chromatography[12,13] for the separation of unsaturated compounds.

Columns filled with silver nitrate on alumina have been used in our study for the facile preparation of

(1) To whom correspondence should be directed.

(2) "Technique of Organic Chemistry," Arnold Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y.: (a) J. A. Riddick and E. E. Toops, Jr., Vol. VII, 2nd ed, 1955, Chapter 5; (b) H. G. Cassidy, Vol. V, 1951, p 110.

(3) (a) B. J. Mair and A. F. Farziati, *J. Res. Natl. Bur. Std.*, **32**, 151 (1944); (b) *ibid.*, **32**, 165 (1944).

(4) M. E. Maclean, P. J. Jencks, and S. F. Acree, Jr., *ibid.*, **34**, 271 (1945).

(5) F. Fairbrother, N. Scott, and H. Prophet, *J. Chem. Soc.*, 1164 (1956).

(6) R. V. Barbour, Doctoral Dissertation, University of Colorado, Boulder, Colo., 1966, p 48.

(7) L. R. Chapman and D. F. Kuemmel, *Anal. Chem.*, **37**, 1598 (1965).

(8) D. deVries, *Chem. Ind.* (London), 1049 (1962).

(9) J. Shabtai, J. Herling, and E. Gil-Av, *J. Chromatog.*, **11**, 32 (1963); **2**, 406 (1959).

(10) J. Herling, J. Shabtai, and E. Gil-Av, *ibid.*, **8**, 349 (1962).

(11) E. Gil-Av, J. Herling, and J. Shabtai, *ibid.*, **1**, 508 (1958).

(12) C. B. Barrett, M. S. J. Dallas, and F. B. Padley, *Chem. Ind.* (London), 1050 (1962).

(13) L. J. Morris, *ibid.*, 1238 (1962).

TABLE I

COMPARISON OF ABSORBANCES OF PURIFIED *vs.* UNPURIFIED HYDROCARBON SOLVENTS AT SPECIFIC WAVELENGTHS[a,b]

Hydrocarbon	Wavelength, mμ								
	210	220	230	240	250	260	270	280	300
Cyclohexane		2	0.55	0.24	0.31	0.32		0.13	0.02
		0.25	0.12	0.034	0.010	0.005		0.003	0.001
Hexane	>2		>2		>2		2	0.36	0.10
	0.18		0.032		0.008		0.003	0.003	0.001
Pentane	>2	>2	>2	0.55		0.10		0.05	0.033
	0.065	0.03	0.018	0.012		0.006		0.003	0.002
3-Methylpentane	1.15	1.25		0.32		0.25		0.17	0.07
	0.15	0.055		0.012		0.005		0.003	0.002
2,2,4-Trimethyl-pentane		0.40		0.10		0.05		0.03	0.02
		0.08		0.015		0.005		0.002	0.001
Methylcyclo-hexane		0.57	0.35	0.22		0.065		0.025	0.015
		0.2	0.010	0.035		0.007		0.003	0.001

[a] The upper number for a specific wavelength in the series of numbers following a given hydrocarbon is the absorbance of the unpurified hydrocarbon, and the lower number is the absorbance of the hydrocarbon after one pass through a silver nitrate on alumina column. [b] Absorbances were obtained on the unpurified hydrocarbons in a 1.0-cm cell while those for the purified liquids were obtained in a 10-cm cell; in order to make comparisons, the latter values were divided by 10 for inclusion in this table.

spectroscopically pure cyclohexane, hexane, pentane, 3-methylpentane, 2,2,4-trimethylpentane, and methylcyclohexane. The exceptional efficiency of this method is reflected in the specific data summarized for each hydrocarbon in Table I. A 90-cm length of the silver nitrate–alumina in a 16-mm (i.d.) column was found to remove effectively the impurities from as much as 6 l. of cyclohexane.

Experimental Section

The silver nitrate–alumina column material was prepared in the following way. A sample of alumina (360 g) was mixed thoroughly with 500 ml of 2 *M* nitric acid. This slurry was filtered through a coarse sintered-glass funnel and the solid was washed with water until the filtrate was neutral to Hydrion paper. Reagent grade silver nitrate (40 g) was dissolved in 20 ml of distilled water and the resulting solution was diluted with 350 ml of reagent grade methanol. This solution was used to wash the damp alumina from the filter into a 2-l. flash evaporator flask. After removal of the solvent by means of the flash evaporator, the solid was poured from the flask and air dried at 140° for 24 hr. The silver nitrate–alumina column material prepared by this procedure is white in contrast to the brown material obtained by Barbour.[6]

A 13-mm (i.d.) column was packed to a depth of 25 cm with the silver nitrate–alumina for the survey experiments reported here. The solvent to be purified was dried over phosphorus pentoxide and then decanted into a reservoir on the top of the column. The column was evacuated with an aspirator before the solvent was allowed to flow; the flow of liquid through the column was then adjusted to approximately 1 drop/sec. One hundred milliliters of solvent was collected and its spectrum was recorded in a 10-cm cell using a Cary Model 14 spectrophotometer.

Registry No.—Silver nitrate, 7761-88-8; cyclohexane, 110-82-7; hexane, 110-54-3; pentane, 109-66-0; 3-methylpentane, 96-14-0; 2,2,4-trimethylpentane, 540-84-1; methylcyclohexane, 108-87-2.

Synthesis of 1-Azatricyclo-[7.2.1.$0^{6,11}$]dodecan-12-one

ROBERT L. AUGUSTINE AND WILLIAM G. PIERSON[1]

Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079

January 13, 1969

In previous work[2] it was found that 7-carboxytetrahydrobenzazepine (**1**) underwent facile cyclization to tricyclic lactam **2** on hydrogenation over ruthenium at 160°. It was thought of interest to determine whether this reaction would be useful in producing other lactams as well.

Homodihydrocarbostyril[3] (**3**) was reduced with lithium aluminum hydride and converted to N-acyltetrahydrobenzazepine (**4**). In contrast to the ultraviolet spectrum of acetanilide [λ_{max} 238 mμ (ϵ 10,500)][4] the spectrum of **4** had λ_{max} at 226 and 265 mμ. The latter peak had an extinction coefficient of 450 and was in the form of a typical benzene fingerprint. The appearance of the benzenoid fine structure indicated a nearly complete lack of conjugation between the amide group and the aromatic ring caused, presumably, by an interaction between the *peri* hydrogen and the amide carbonyl.

Because of this lack of conjugation it was felt that electrophilic attack would most likely take place on C-8 of the benzazepine.[5] Friedel–Crafts acylation of **4** gave

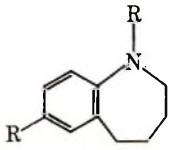
(1) Supported by Grant MH-10107 from the National Institutes of Health. This support is gratefully acknowledged.

(2) R. L. Augustine and W. G. Pierson, *J. Org. Chem.*, **34**, 1070.

(3) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Amer. Chem. Soc.*, **74**, 5153 (1952).

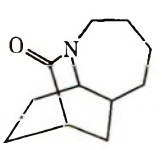
(4) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 18.

(5) N. P. Buu-Hoi, P. Jacquignon, and M. Marty, *Compt. Rend.*, **251**, 2978 (1960).

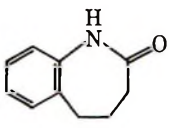


1, R = H; R′ = CO_2H

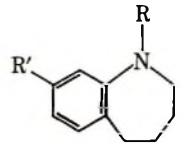
7, R = Ac; R′ = Et



2



3



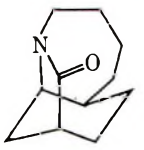
4, R = Ac; R′ = H

5, R = Ac; R′ = Ac

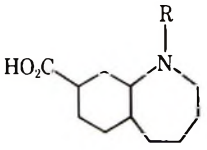
6, R = Ac; R′ = Et

8, R = Ac; R′ = CO_2H

9, R = H; R′ = CO_2H



10



11, R = Ac

12, R = H

a 50% yield of a ketone which had infrared and nmr spectral characteristics of a 1,2,4-trisubstituted benzene.[6] Further spectral characterization was, however, ambiguous. Catalytic hydrogenolysis of this ketone gave an ethyltetrahydrobenzazepine which was different from the 7-ethyl isomer **7** previously obtained.[2] Thus, the hydrogenolyzed material must be the 8-ethyl compound **6** and the ketone, 8-acylbenzazepine (**5**).

Sodium hypobromite oxidation of **5** gave the carbocyclic acid **8**, which on acid hydrolysis readily formed the amino acid **9** in good yield. Catalytic hydrogenation of **9** over ruthenium on carbon at 160° gave the tricyclic lactam **10** in 75% yield. The infrared spectrum of **10** showed a strong band at 1680 cm^{-1}, considerably higher than the lactam absorption reported for substituted isoquinuclidones such as **2**.[2,7]

In order to establish the ease with which this hydrogenative cyclization occurred **10** was prepared from **8** by an alternate route. Hydrogenation of **8** gave the saturated amido acid **11**, which was hydrolyzed to the amino acid **12**. Heating **12** at 260° for a short time[8] gave **10** in 9% over-all yield from **8**. It appears, therefore, that the direct hydrogenative cyclization of substituted aminobenzoic acids over ruthenium is a useful method for the preparation of lactams such as **2** and **10**.

Experimental Section[9]

1-Acetyl-2,3,4,5-tetrahydro-1H-1-benzazepine (4).—A solution of 20 g of **3**[3] in 300 ml of dry tetrahydrofuran was slowly added with stirring, over a 30-min period, to a refluxing mixture of 12 g of lithium aluminum hydride in 200 ml of tetrahydrofuran. The mixture was stirred and refluxed for 14 hr and, after slow addition of 100 ml of ethyl acetate, cooled and carefully hydrolyzed with 50 ml of water. The precipitated alumina was removed by filtration and washed thoroughly with ether and with methylene chloride. The combined filtrate was evaporated to a turbid yellow oil which was dissolved in methylene chloride, dried over potassium carbonate, filtered through a pad of Norit, and evaporated. The residual oil was dissolved in *n*-hexane and filtered through Norit and the solvent was removed by distillation to give 17.5 g of the crude amine as a light yellow oil.

The amine was dissolved in 150 ml of acetic anhydride and allowed to stand at room temperature for 2 days. After warming on a steam bath for 2 hr, the solvent was removed and the residual oil was dissolved in ether and washed with 5% hydrochloric acid, 5% sodium bicarbonate solution, water, and saturated brine. After drying over sodium sulfate, the solution was filtered through a pad of Norit and the ether was removed *in vacuo* to leave a yellow, crystalline mass which, after recrystallization from *n*-hexane, gave 19.67 g (84%) of white crystals, mp 79–81°. Further recrystallization from *n*-hexane followed by sublimation at 50° (0.5 mm) gave pure **4**: mp 80–81°; infrared spectrum (Nujol), C=O at 1634 cm^{-1}; ultraviolet spectrum, λ_{max} 226 mμ (ε 6900) and 265 (450). The 265-mμ peak had the form of a benzene fingerprint.[4] *Anal.* Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.18; H, 8.22; N, 7.65.

1,8-Diacetyl-2,3,4,5-tetrahydro-1H-1-benzazepine (5).—A mixture of 42.8 g of anhydrous aluminum chloride, 250 ml of carbon disulfide, and 10 g of **4** was stirred and refluxed while 13 ml of acetyl chloride was added over a 10-min period. After 20 hr of stirring and refluxing, 150 ml of the solvent was distilled from the reaction mixture. The residual, red oil was added to 550 g of ice and the resulting precipitate was extracted into methylene chloride. The extract was washed with water and saturated brine and dried over sodium sulfate. After filtration through a pad of Norit, the methylene chloride was removed and the residual, viscous, amber oil was dissolved in 75 ml of cyclohexane. Scratching induced the crystalline product to separate slowly. After standing at room temperature for 2 days, the reddish crystals were collected. The crude product was dissolved in methanol, boiled with Norit, and filtered and the solvent was removed. Recrystallization from cyclohexane gave 6.13 g (50.2%) of the tan, crystalline product, mp 105.5–108°. Further recrystallizations from cyclohexane gave pure, white **5**: mp 107–108.5°; infrared spectrum (Nujol), ketone at 1680, amide at 1650, and C–H bending at 874 and 828 cm^{-1}; ultraviolet spectrum, λ_{max} 234 mμ (ε 14,420), 248 (14,770) and 284 (1250, sh); nmr spectrum, CH_3 at δ 1.87 (singlet, 3) and at 2.59 (singlet, 3), aromatic CH at 7.39 (doublet, 1, J = 8 Hz), 7.78 (singlet, 1.5), and at 7.92 (doublet, 0.5, J = 2 Hz). *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.98; H, 7.31; N, 5.97.

1-Acetyl-8-ethyl-2,3,4,5-tetrahydro-1H-1-benzazepine (6).—A mixture of 465 mg of **5**, 100 mg of 10% palladium on carbon, and 25 ml of 95% ethanol was stirred under hydrogen at 1 atm for 6 hr. Removal of the catalyst followed by evaporation of the solvent gave 440 mg of colorless oil which crystallized on standing. Recrystallization from *n*-hexane gave 350 mg (80.5%) of white, crystalline **6**: mp 58–58.5°; infrared spectrum (Nujol), C=O at 1655 cm^{-1}; ultraviolet spectrum, λ_{max} 266 mμ (ε 460) and 208 (25,180, sh). *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.40; H, 8.71; N, 6.28.

1-Acetyl-2,3,4,5-tetrahydro-1H-1-benzazepine-8-carboxylic Acid (8).—A solution of 5 g of **5** in 25 ml of dioxane was slowly added to a cold (0–5°), stirred solution of sodium hypobromite (prepared from 7.20 g of sodium hydroxide, 75 ml of water, and 10.4 g of bromine). After stirring in an ice bath for 90 min, the mixture was acidified with concentrated hydrochloric acid and diluted with 100 ml of acetone. When the solution became colorless, evaporation *in vacuo* to a small volume caused white crystals to separate. Filtration and drying gave 4.77 g (94.5%) of the crude acid, mp 231–232°. Recrystallization from aqueous acetone gave pure **8**: mp 233.5–234°; infrared spectrum (Nujol), acid OH at 2580, acid C=O at 1712, and amide C=O at 1600 cm^{-1}; ultraviolet spectrum, λ_{max} 223 mμ (ε 18,610) and 276 (950). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.65; H, 6.37; N, 6.02.

2,3,4,5-Tetrahydro-1H-1-benzazepine-8-carboxylic Acid (9).—A solution of 2.0 g of **8** in 100 ml of 6 *N* hydrochloric acid was refluxed for 50 hr, cooled, and allowed to stand at room temperature for 2 days. Filtration and drying gave 2.06 g of the hydrochloride salt of **9** as white needles, mp 307–312° dec. The salt was dissolved in 75 ml of hot water and the acidity of the solution was adjusted to pH 3 by addition of ammonium hydroxide. The white precipitate which formed on cooling was filtered and dried. Recrystallization from acetonitrile, with hot filtration

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958, pp 78–79; ref 4, p 99.

(7) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Amer. Chem. Soc.*, **80**, 126 (1958); J. W. Huffman, C. B. S. Rao, and T. Kamiya, *J. Org. Chem.*, **32**, 697 (1967).

(8) L. H. Werner and S. Ricca, *J. Amer. Chem. Soc.*, **80**, 2733 (1958).

(9) Boiling points and melting points are uncorrected. Melting points were measured in open capillary tubes on a Mel-Temp apparatus. The infrared spectra were obtained on a Beckman IR 10 recording double-beam infrared spectrophotometer. Nuclear magnetic resonance spectra were obtained in deuteriochloroform using tetramethylsilane as the internal standard. Spectra were recorded on a Varian Associates Model A-60A spectrometer. The spectra data are reported in units of δ and the multiplicity of the resonance signal and the number of protons integrated for the peak are given in parentheses. Ultraviolet spectra were measured in methanol on a Beckman DB spectrophotometer.

through Norit, gave 1.11 g (68%) of crude **9**, mp 176.5–178°. Further recrystallizations from acetonitrile and from water gave pure **9**: mp 186–187°; infrared spectrum (Nujol), N–H at 3200 and C=O at 1680 cm^{-1}; ultraviolet spectrum, λ_{max} 218 mμ (ε 25,800) and 294 (2150). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.10; H, 6.85; N, 7.33. Found: C, 69.52; H, 6.88; N, 7.30.

1-Azatricyclo[7.2.1.0^{6,11}]dodecan-12-one (10). Method A. From 9.—A solution of 950 mg of **9** in 100 ml of 95% ethanol was stirred in the presence of 1.5 g of 5% ruthenium on carbon under 2000 psig of hydrogen at 160° for 43 hr in a stainless steel autoclave. The catalyst was removed by filtration. Evaporation of the solvent gave 800 mg of colorless oil. The oil was dissolved in 30–60° petroleum ether and filtered through a pad of Norit and the solvent was removed by evaporative distillation to give 760 mg (75.4%) of crude **10** as a coloress oil. Distillation *in vacuo* in a Hickman still gave pure **10**: bp 82° (0.05 mm); infrared spectrum (film), C=O at 1680 cm^{-1}. *Anal.* Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.40; H, 9.54; N, 7.97.

Method B. From 8.—A solution of 2.33 g of **8** in 200 ml of 95% ethanol containing 1 g of 5% rhodium on carbon was stirred under 1500 psig of hydrogen at 100° for 80 hr in a stainless steel reaction vessel. After cooling and filtering, the solvent was distilled *in vacuo* and the residual oil was dissolved in methylene chloride, washed with saturated brine, dried over sodium sulfate, filtered through a pad of Norit, and evaporated to 1.33 g of colorless gum. The gum was refluxed with 50 ml of concentrated hydrochloric acid for 42 hr, cooled, and filtered to remove 440 mg of **9** hydrochloride, mp 306–309°, which had separated as white needles on standing at room temperature overnight. The aqueous filtrate was evaporated *in vacuo* to a moist gum which was dissolved in 10 ml of water, neutralized to pH 4 with ammonium hydroxide, and evaporated to a white paste. The paste was boiled with methylene chloride and the solvent was separated by decantation; the product was dried and evaporated to give 460 mg of a white froth.

The crude amine was heated under nitrogen for 10 min at 250°, dissolved in methylene chloride, filtered through a pad of Norit, and washed with 5% sodium bicarbonate solution, water, and saturated brine. After drying with sodium sulfate, the solvent was evaporated and the residual yellow oil was dissolved in 30–60° petroleum ether, filtered through a pad of Norit, and evaporated to give 185 mg of colorless oil. Short-path distillation in a bulb-to-bulb distilling tube at 0.04 mm (bath temperature 120°) gave 166 mg (9.25%) of pure **10**, which was identical with the product obtained from **9** by method A.

Registry No.—**4**, 19886-89-6; **5**, 19886-87-4; **6**, 19886-90-9; **8**, 19886-88-5; **9**, 19886-91-0; **10**, 19922-51-1.

Effect of pH on ^{31}P–^{1}H Coupling Constants and ^{1}H Chemical Shifts in Methyl Phosphates[1]

ELLIOTT L. UHLENHOPP,[2] J. A. GLASEL, AND ALVIN I. KRASNA

Department of Biochemistry, College of Physicians and Surgeons, Columbia University, New York, New York 10032

Received January 6, 1969

The effect of pH on the chemical shift of methyl groups bonded to phosphorus has been reported[3] for substituted phosphine oxides, phosphinic acids, and phosphinate esters. The pK values for these compounds were determined by measuring the chemical shift (δ) as a function of sulfuric acid concentration. However, there are no data available on the change in the coupling constant (J_{P-H}) as a function of pH. This report describes the effect of pH on both δ and J_{P-H} for monomethyl and dimethyl phosphates. Both δ and J_{P-H} are pH dependent for monomethyl phosphate (I) and pH independent for dimethyl phosphate (II). The change in δ and J_{P-H} for I occurs between pH 4 and 8 and is due to the ionization of the second proton of the phosphate group.

The spectrum obtained from either I or II consists of two peaks which are due to the splitting of the proton peak of the methyl group by ^{31}P. Below pH 5, the spectra of the two compounds are similar, but, as the pH is raised, the spectrum of II remains unchanged while that of I shifts to higher field and shows a decreased J_{P-H}. Figure 1 shows the dependence of δ and J_{P-H} on pD[4] for both I and II. Tsubori, *et al.*,[5] reported a J_{P-H} of 10.3 Hz for the disodium salt of I and 10.5 Hz for the barium salt of II. They did not report the pH at which their measurements were made and did not investigate the effect of pH on J_{P-H}. Their reported values are somewhat at variance with the values reported here.

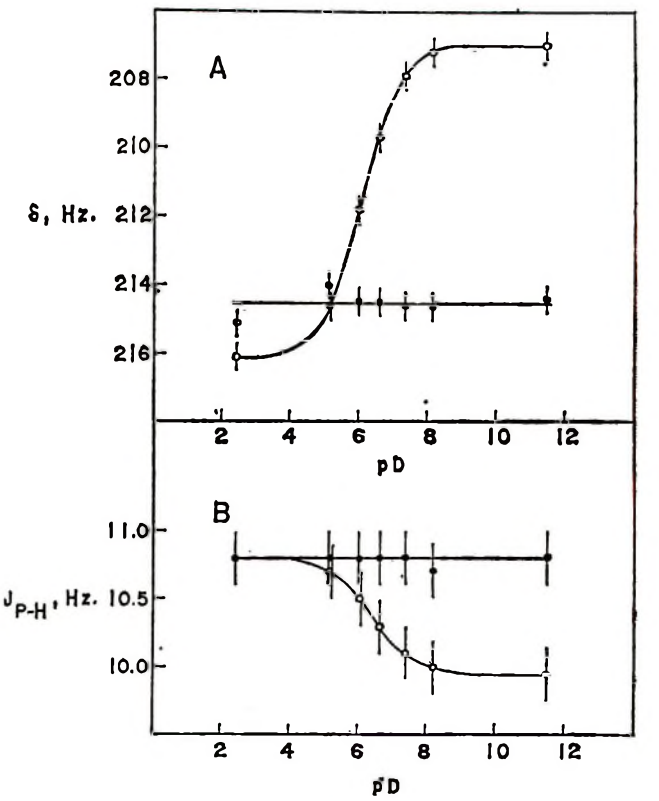


Figure 1.—Dependence of chemical shift and coupling constant on pD. Curve A gives chemical shifts and curve B gives coupling constants for monomethyl phosphate (—○—) and dimethyl phosphate (—●—). Each point represents an average of several determinations at each pH.

(1) This research was supported by the following research grants: NSF GB-8003 (to A. I. K.) and NSF GB-1788 (to J. A. G.) from the National Science Foundation and Contract No. AT (30-1) 3957 from the U. S. Atomic Energy Commission (to A. I. K.).

(2) Supported from NIH Training Grant No. GM-255, Sept 1965–Sept 1967. NASA Predoctoral Fellow, 1967–present. This report is from a dissertation to be submitted in partial fulfillment of the requirement for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(3) P. Haake, R. D. Cook, and G. H. Hurst, *J. Amer. Chem. Soc.*, **89**, 2650 (1967).

(4) pD was calculated from the equation pD = pH + 0.41. See A. K. Covington, M. Paabo, R. A. Robinson, and R. G. Bates, *Anal. Chem.*, **40**, 700 (1968).

(5) M. Tsubori, F. Kuriyagawa, K. Matsuo, and Y. Kyogoku, *Bull. Chem. Soc. Jap.*, **40**, 1813 (1967).

The pK of II is 1.29,[6] and at pH 2 and above it is present only as a monoanion. One would not expect any change in structure with pH, and indeed the nmr spectrum of II remains constant with changing pH. I, on the other hand, is a dibasic acid with a pK_1 of 1.54[6] and a pK_2 of 6.4.[7] From pH 2 to 4 it exists as a monoanion, and, as the pH is increased, the second proton is removed, giving rise to a phosphate group with two negative charges. The shift of δ to higher field owing to this increased negative charge is similar to that described by Haake, *et al.*,[3] and is in agreement with the relationship between δ and distribution of electron charge established by Mavel and Martin[8] for a series of compounds bearing the CH_3OP moiety but containing different substituent groups of different electronegativity, magnetic anisotropy, and δ. In the present case, I represents a single compound whose average electronic distribution can be altered in a continuous manner without greatly altering its molecular structure and introducing a multiplicity of complicating effects. As the pH of a solution of I is increased, the change in the value of δ or J_{P-H} is a direct measure of the proportion of total I converted into its dianionic form and can be used to estimate the pK value. Figures 1A and 1B can be considered as titration curves and the average of the inflection points is 6.35, the pK_2 value for I. This value agrees well with the reported pK_2 for I of 6.4.

The above results show that not only δ but also J_{P-H} of I is pH dependent. Electronegative substituents have a profound effect on the value of the coupling constant[9] and, in a series of substituted CH_3OP compounds,[8] J_{P-H} decreases as the average electron-donating character of the substituent group increases. In the present case, J_{P-H} decreases as the negative charge on the phosphate group increases. In addition, a plot of δ *vs.* J_{P-H} for I shows a linear relationship between these two parameters similar to that described by Mavel and Martin.[8] This linearity is interpreted as being due to the fact that δ and J_{P-H} in these compounds are both dominated by inductive effects.

Experimental Section

Practical grade dimethyl phosphate (II) and reagent grade monomethyl phosphate (I) were obtained from K and K Laboratories, Plainview, N. Y., and the practical grade II was purified as described by Harlay.[10] The samples were dissolved in D_2O to give 1 *M* solutions, and the pH was adjusted by the addition of 37% DCl in D_2O or 50% NaOD in D_2O. pH measurements were carried out on a Radiometer pH meter TTT1a with a scale expander, making possible pH measurements accurate to ±0.01 pH unit. Nmr spectra were obtained on a Varian DA-60-EI spectrometer using 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an internal standard.

Registry No.—I, 812-00-0; II, 813-78-5.

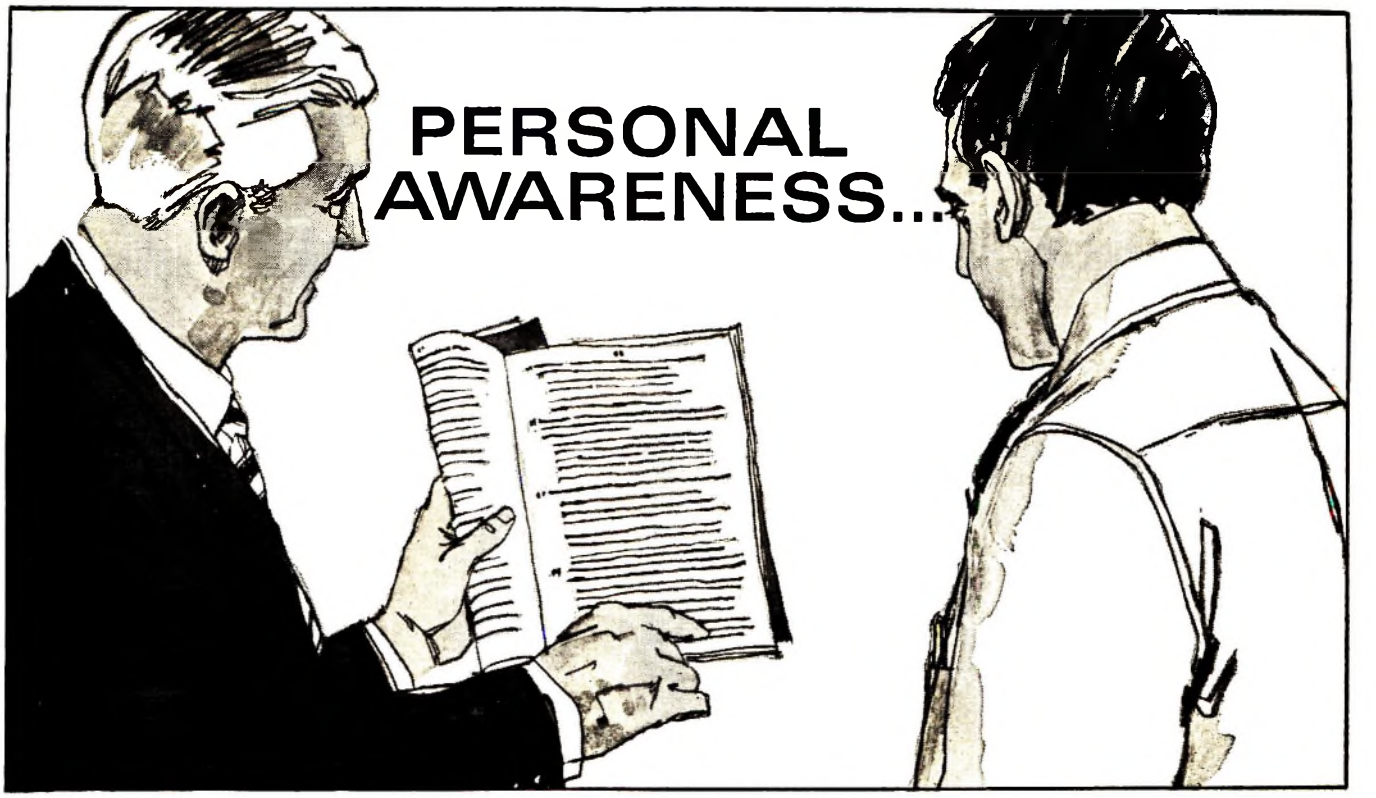
(6) W. D. Kumler and J. J. Eiler, *J. Amer. Chem. Soc.*, **65**, 2356 (1943).

(7) The value 6.4 is an average of 6.31 reported by Kumler and Eiler[6] and 6.58 reported by C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3575 (1958).

(8) G. Mavel and G. Martin, *J. Chim. Phys.*, **59**, 762 (1962).

(9) G. Mavel, *ibid.*, **59**, 683 (1962).

(10) M. V. Harlay, *J. Pharm. Chim.*, **20**, 161 (1934).



. . . . . of research and development activities currently taking place is an important contributor to the success of your own scientific efforts. This awareness is gained through personal contact and discussions with colleagues, attendance at meetings and symposia, and through the published literature.

To help you use the literature more effectively and quickly, you may obtain **personal copies** of CHEMICAL-BIOLOGICAL ACTIVITIES (CBAC)—an express digest service covering the literature published on the interface between organic compounds (drugs, pesticides, fertilizers, etc.) and biochemical systems (both plant and animal). Nearly 600 journals are regularly monitored for you to enable you to use CBAC with confidence as a consolidated source of up-to-date information. You are quickly guided to digests of interest through use of the several indexes in each of the issues of CBAC published during the year (an issue every two weeks).

To Become Aware . . .

. . . . check with your librarian or information group on whether your organization now subscribes to CBAC. If so, request that a supplementary subscription be ordered for you. If not, fill out and mail the coupon and you will receive complete information about the *new* **personal subscription** program.

CHEMICAL ABSTRACTS SERVICE
American Chemical Society
Columbus, Ohio 43216

Subscriber Information Department CBP
Chemical Abstracts Service
Columbus, Ohio 43216

Please send me full information on the personal subscription program for CHEMICAL-BIOLOGICAL ACTIVITIES.

Name_____

Title_____

Organization_____

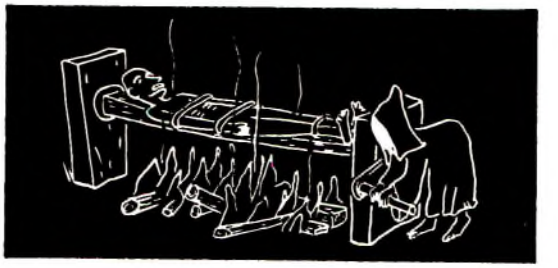
_____

Address_____

_____

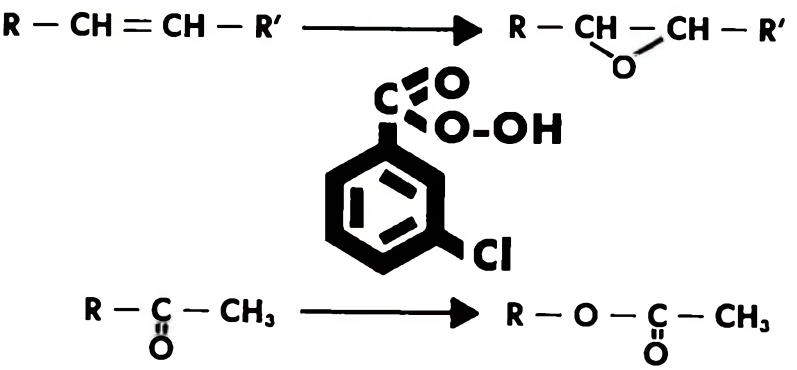
_____

There are Those who could use a better Oxidizing Agent –



m-CHLOROPEROXYBENZOIC ACID

The oxidizing agent of choice for epoxidations[1-3] and Baeyer-Villiger oxidations[1].



Also of great interest in the preparations of N-oxides[4] and nitrosteroids[5].

(1) L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, p. 135, Wiley, 1967

(2) J. Fried et al., Tetrahedron Letters, 849 (1965)

(3) D. J. Pasto et al., J. Org. Chem., 30, 1271 (1965)

(4) T. J. Delia et al., ibid, 30, 2766 (1965)

(5) C. H. Robinson et al., ibid, 31, 524 (1966)

Stable (less than 1% decomposition per year when stored at room temperature) m-CHLOROPEROXYBENZOIC ACID, tech., 85%, our C6270-0 is available from stock at 25g. – $8.00, 100g. – $23.50 and in kilo lots at $150.00. Write for descriptive literature.

For our latest Catalog, write to —

ALDRICH

Aldrich Chemical Company, Inc.

CRAFTSMEN IN CHEMISTRY

2371 NORTH 30TH STREET · MILWAUKEE, WISCONSIN 53210

– 2 C.A. 2512