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ANODIC OXIDATION

by SIDNEY D. ROSS, MANUEL FINKELSTEIN, and ERIC RUDD
A Volume in the ORGANIC CHEMISTRY Series

ANODIC OXIDATION not only presents the theory and practice of the anodic oxidation of organic substrates, but it also offers a detailed survey of the results obtained by the application of this technique. The author explains reaction mechanisms in a way designed to enable the reader to predict the course of these reactions.

The book is divided into two sections. The first section (Chapters 1-4) presents the underlying theory for the electrochemical oxidation of organic substrates and briefly discusses the experimental methods and required equipment. The second section (Chapter 5-12) assesses the available literature of the anodic oxidation of organic compounds, classifying the compounds according to the functional group being oxidized, e.g., there are chapters on the oxidation of hydrocarbons, acids, amines, alcohols, ethers, etc. Although the book does not include every example of anodic oxidation, it certainly provides enough of them to illustrate the fundamental concepts and permit a unifying treatment.

1975, 352 pp., $37.00/£17.75

Second Edition

INTRODUCTION TO INFRARED AND RAMAN SPECTROSCOPY

by NORMAN B. COLTHUP, LAWRENCE H. DALY, and STEPHEN E. WIBERLEY

This book covers in one volume most of those aspects of infrared and Raman spectroscopy which are generally important to the chemist doing structural or compositional analyses. This includes much material of both a practical and theoretical nature on the interpretation of the spectra, as well as some discussion of experimental techniques.

One of the most important topics presented is that on the group frequencies. This book features an unusual treatment of group frequencies in that it stresses their mechanical origin. Group frequencies are discussed in detail, summarized in extensive tables, and illustrated by means of over 600 carefully chosen spectral examples.

The book also: shows how to use Raman polarization data, infrared gas phase contours, infrared polarized spectra and isotopically substituted molecules; includes a brief introduction to quantum effects, a discussion of the use of symmetry and group theory in spectroscopic problems, and an introduction to vibrational theory and normal coordinate treatments for those unfamiliar with these disciplines (the vibrational-rotational spectra of diatomic molecules is discussed); and devotes a chapter to instrumentation and techniques which includes basic descriptions of instrumental components, various sample preparation techniques and quantitative analysis.

1975, 544 pp., $24.00/£11.50

ORGANOCHLORINE INSECTICIDES

Persistent Organic Pollutants

edited by F. MORIARTY

While the range of topics covered in this work is wide—from analytical chemistry to possible legal and economic restraints, with the major emphasis being placed on biological effects and responses—attention is restricted to persistent organic pollutants, and in particular to the organochlorine insecticides which are by far the most studied. The ideas that are proposed will however apply to a far wider range of pollution problems.

CONTENTS: *A. V. Holden,* Monitoring Persistent Organic Pollutants. *F. Moriarty,* Exposures and Residues. *C. H. Walker,* Variations in the Intake and Elimination of Pollutants. *D. J. Jefferies,* The Role of the Thyroid in the Production of Sublethal Effects by Organochlorine Insecticides and Polychlorinated Biphenyls. *J. P. Dempster,* Effects of Organochlorine Insecticides on Animal Populations. *P. A. Victor and W. M. Mansell,* Persistent Pesticides: An Economic and Legal Analysis.

1975, 314 pp., $21.00/£7.90

FUNCTIONAL GROUP DETERMINATION OF OLEFINIC AND ACETYLENIC UNSATURATION

by K. MULLER
translated from German by M. R. F. Ashworth
Number 6 in THE ANALYSIS OF ORGANIC MATERIALS/An International Series of Monographs

This book is based on the author's long experience in the analysis of saturated compounds (olefins and acetylenes) at the organo-analytical laboratory of a large industrial chemical concern. The emphasis throughout is on the numerous and versatile chemical techniques of analysis, which are directly applicable to wide areas of organic chemistry. These have been treated in a comprehensive and critical way, and are supplemented by polarographic methods of determination and also by paper and thin-layer chromatographic methods of detection. Full experimental details are given for the particular methods recommended by the author, obviating the need to consult original literature. *1975, 334 pp., $24.25/£9.20*

DETERMINATION OF ORGANIC COMPOUNDS WITH N-BROMO SUCCINIMIDE AND ALLIED REAGENTS

by N. K. MATHUR and C. K. NARANG
Number 8 in THE ANALYSIS OF ORGANIC MATERIALS/An International Series of Monographs

CONTENTS: Introduction and Historical Preparation and Properties of N-Haloamides and Imides. Types and Mechanisms of Reactions Undergone by N-Bromosuccinimide and Allied Reagents. Oxidation of Hydroxyl Compounds by N-Bromosuccinimide and Allied Reagents. Determination of Phenols, Aromatic Amines and Sulphonamides. Determination of Olefinic Unsaturation. Determination of Hydrazine and Derivatives. Determination of Certain Amino Acids and Their Sequence in Peptides and Proteins. Determination of Sulphur Compounds. Proof of Structure of Organic Molecules. Differentiation of Primary, Secondary and Tertiary Alcohols and Amines, and Certain Aromatic Positional Isomers. Determination of Miscellaneous Compounds.

1975, 176 pp., $13.75/£5.20

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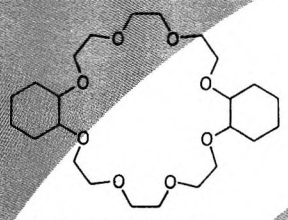
from Parish, the "Poly Ether People"

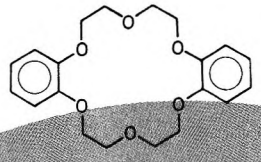
The crown ethers are probably some of the most fascinating compounds that have been investigated in recent years. Their remarkable ability to form stable complexes with the alkali and alkaline earth cations gives rise to highly reactive nuceoplulic anions. For example, potassium fluoride in acetonitrite with 18-crown-6 converts alkylbromides to the corresponding alkylfluorides in nearly quantitative yields. Elimination to give alkenes is negligable. Potassium acetate in the same system converts alkylbromides to the corresponding acetoxy compoungs. In the absence of crown ethers, these reactions proceed only under forcing conditions with greatly reduced yields.

X-ray crystallographic studies indicate that many of the crown complexes exist with the cation burled in the center of a hydrophilic cavity and the lipophilic hydrocarbon chain exposed to the solvent. Binding constants indicated a correlation between cation size and the ring size. For example, 18-crown-6, dicyclohexyl-18-crown-6 and dibenzo-18-crown-6 bind strongest to potassium cation although other ions are also bound to some extent. Smaller crowns such as 15-crown-5 and related compounds bind more strongly to the smaller sodium cation. 4, 7, 13, 16, 21, 24-Hexaoxy-1, 10-diazabicyclo [8.8.8] hexacosane gives extremely stable complexes with Na, K, Rb, Ca, Ba, and Sr with marked preference for Ba, Sr and K. Dibenzo-24-crown-8 binds strongly with both K and Cs with some preference for Cs. Although data are not available CTV and CTP might be expected to bind the larger solvated cations or guanidinium ions where the positive charge is delocalized over several atoms.

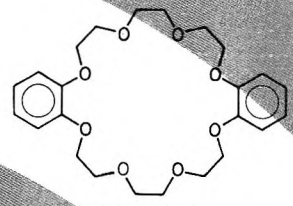
The potential fields of application are almost limitless. Indeed many areas have scarcely been touched. Consider these: starting materials for the preparation of novel types of pharmaceuticals; selective complexation and separation of alkali and alkline earth cations; solubilization of salts in non-polar solvents; selective removal of cations from solutions; activation of anions via the formation of ligand-separated ion-pairs and their subsequent application in various synthetic problems; formation of highly hindered Lewis acid complexes for use in homogeneous catalysis of polymerizations; oligimerizations, and hydrogenations; production of novel types of ion-selective membrane electrodes; models for studies of biological cation transport mechanisms; solubilization of alkoxides in non-polar solvents; alteration of the sterochemical course and rate of alkoxide produced carbanion reactions, selective decorporation of radioactive elements such as strontium, thallium, lead, etc. from living organisms; carriers of trace metals in nutritional experiments. Let one of our polyethers put you on target. With our selection, price and quality you can't miss.



Dicyclohexyl-24-crown-8
2262 1g/16.85 5g/59.95



Dibenzo-18-crown-6
1350 2.5g/8.25 10g/21.50



Dibenzo-24-crown-8
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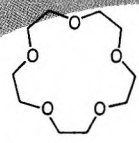
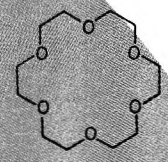


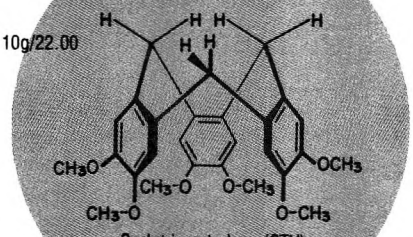
15-Crown-5
2259 5g/18.00 25g/69.30



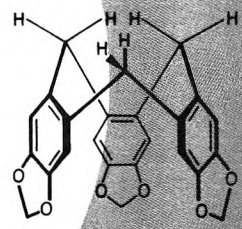
18-Crown-6
2260 5g/12.50 25g/49.10

18-Crown-6 • acetonitrile complex
2428 10g/15.00 50g/57.75

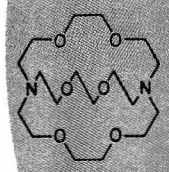
Dicyclohexyl-18-crown-6
2032 Pure (white solid) 25g/10.55 10g/27.85
1406 technical (orangish gum or oil) 2.5g/7.00 10g/22.00



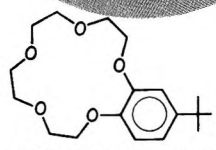
Cyclotriveratrylene (CTV)
1155 10g/12.50



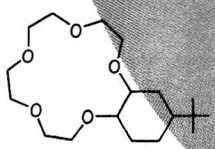
Cyclotripiperonylene (CTP)
1163 10g/15.00



4,7,13,16,21,24-Hexaoxy-1,10-diazabicyclo [8.8.8] hexacosane
1149 100mg/10.00



4-t-Butylbenzo-15-crown-5
1401 1g/29.95



4-t-Butylcyclohexyl-15-crown-5
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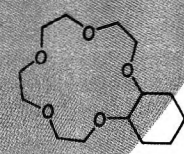
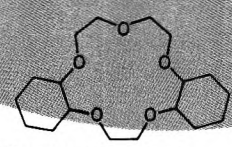
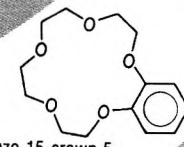


Cyclohexyl-15-crown-5
1404 5g/14.50 25g/51.48

Dibenzo-15-crown-5
2033 1g/18.95 5g/72.95



Dicyclohexyl-15-crown-5
2258 100mg/12.50 500mg/48.15



Benzo-15-crown-5
1405 5g/12.00 25g/42.60

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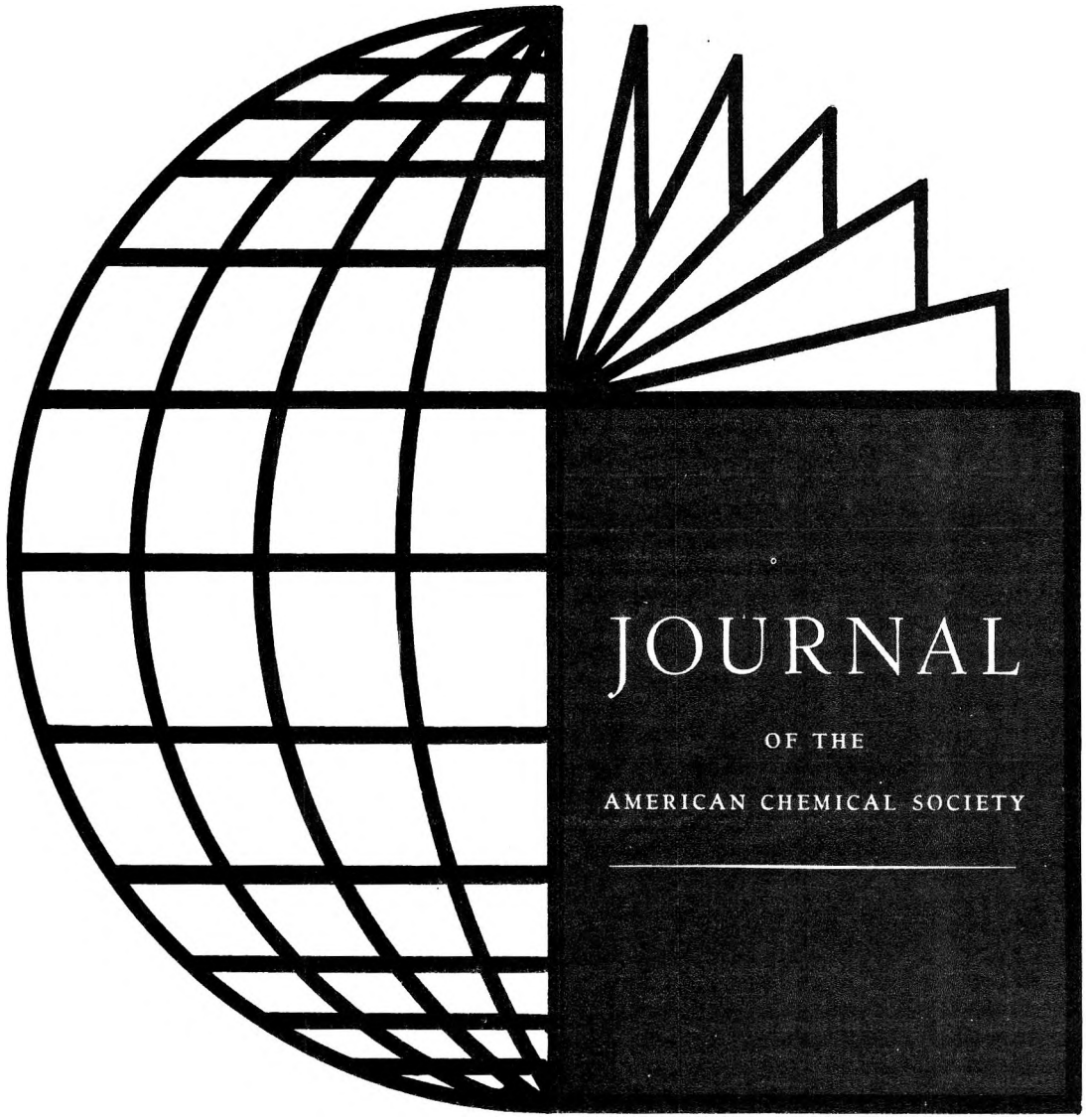

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SEPTEMBER 5, 1975

Reactions of 4,5-Dicyano-1,3-dithiole-2-thione and -1,3-dithiol-2-one with Tervalent Phosphorus Compounds

Malcolm G. Miles,* Janice S. Wager, and James D. Wilson

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

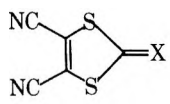
Allen R. Siedle*

Inorganic Chemistry Section, National Bureau of Standards, Washington, D.C. 20234

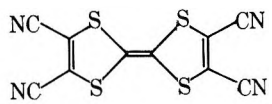
Received March 25, 1975

In contrast to other reported reactions of 1,3-dithiol-2-ones and 1,3-dithiole-2-thiones with tervalent phosphorus compounds, which yield only tetrathiafulvalenes, the reaction of 4,5-dicyano-1,3-dithiole-2-thione (**1**) and -1,3-dithiol-2-one (**2**) with phosphines and phosphites is complex. Either tetracyanotetrathiafulvalene [$\Delta^{2,2'}$-bi(4,5-dicyano-1,3-dithiolidene)] (**3**), a betaine {(4,5-dicyano-1,3-dithiol-2-ylidene)methylene [tri(substituents)phosphonio](-2-thio-1-mercaptomaleonitrilate)} (**4**), or a dialkyl (4,5-dicyano-1,3-dithiol-2-yl)phosphonate may be formed, depending on the choice of reactant and conditions. In addition, Wittig-type products are formed on addition of aryl aldehydes to the reaction mixture. All of these products can be rationalized by means of a reaction scheme which assumes the ylide 4,5-dicyano-1,3-dithiolidenetri(substituent)phosphorane to be the key intermediate. Only tetracyanotetrathiafulvalene was isolated from the reaction of trimethyl phosphite with either **1** or **2** and tris(*p*-chlorophenyl)phosphine with **1**, but reactions of other triarylphosphines and methyl diphenylphosphinite with **1** yielded varying amounts of fulvalene and betaine. Phosphorus trichloride, triphenyl phosphite, and triphenylarsine did not react with **1**. The stoichiometric reaction of triphenylphosphine, **1**, and terephthalaldehyde gave a near-quantitative yield of 2,2′-*p*-xylylidenebis(4,5-dicyano-1,3-dithiole) (**8**), which undergoes a reversible, electrochemical oxidation at E_p = 1.07 V (vs. SCE) and an irreversible oxidation at E_p = 1.39 V. With benzaldehyde under these conditions, however, both **4** and 2-benzylidene-4,5-dicyano-1,3-dithiole were isolated. The novel ester dimethyl (4,5-dicyano-1,3-dithiol-2-yl)phosphonate was isolated from a reaction of trimethyl phosphite plus **2** in the presence of benzoic acid.

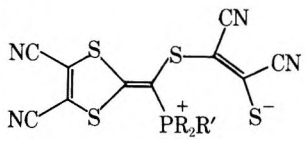
Interest in the salts and charge-transfer compounds of tetrathiafulvalenes[1] prompted us to investigate the possibility of preparing cyano-substituted derivatives by means of desulfurization of 4,5-dicyano-1,3-dithiole-2-thione (**1**)



1, X = S
2, X = O



3



4a, R = C_6H_5; R′ = CH_3
b, R = R′ = *p*-$CH_3OC_6H_4$
c, R = R′ = *m*-$CH_3C_6H_4$
d, R = R′ = C_6H_5
e, R = C_6H_5; R′ = CH_3O

with phosphorus(III) compounds. Several reports have appeared in which clean, high-yield conversions of various 1,3-dithiole-2-thiones to $\Delta^{2,2'}$-bi(1,3-dithiolidenes)[2] and 1,3-diselenole-2-thiones to $\Delta^{2,2'}$-bi(1,3-diselenolidenes)[3] by the action of phosphines and phosphites have been described, and Corey and Märkl[4] have reported a Wittig-type reaction between trithiocarbonates, aldehydes, and trialkyl phosphites. We have found that the reactions of **1** under these conditions are more complex than those of other trithiocarbonates, and report our results here.

Results

The thione **1** was allowed to react with 11 different phosphines and phosphites and triphenylarsine. The results appear in Table I. Three different products could be isolated from the reaction of triphenylphosphine with **1** at different temperatures: at 25°, an adduct of composition $C_6S_4(CN)_4(Ph_3P)_2S$, **5**, can be isolated in good yield; at 60–80°, a product identified as the betaine (4,5-dicyano-1,3-dithiol-2-ylidene)methylene (triphenylphosphonio)(2-thio-1-mercaptomaleonitrolate) (**4d**) is obtained (and, in fact, at that temperature **5** transforms quantitatively into **4**); at 125°, $\Delta^{2,2'}$-bi(4,5-dicyano-1,3-dithiolidene) (**3**) is slowly formed. Tri-*n*-butylphosphine reacts with **1** at 0° in toluene to give a mixture of products including tri-*n*-butyl phosphine sulfide, identified by its ^{31}P NMR and mass

Table I
Reaction Products of 4,5-Dicyano-1,3-dithiole-2-thione with Phosphines and Phosphites

Reactant, $R_2R'P$			% Products, isolated yield		
R	R′	Registry no.	3	4	Other
C_6H_5	CH_3	1486-28-8		20	
C_6H_5	$-CH_2-$	2071-20-7		49[a]	
p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	855-38-9		39	
m-$CH_3C_6H_4$	m-$CH_3C_6H_4$	6224-63-1		45	
C_6H_5	C_6H_5	603-35-0	25[b]	46–85[c]	5, 70%[d]
p-ClC_6H_4	p-ClC_6H_4	1159-54-2	25		
C_6H_5	CH_3O	4020-99-9		30	
CH_3O	CH_3O	121-45-9	25–30		
C_6H_5O	C_6H_5O	101-02-0			No reaction observed
Cl	Cl	7719-12-2			No reaction
C_6H_5	C_6H_5[e]	603-32-7			No reaction

[a] Product $Ph_2PSCH_2CH_2PPh_2S$-adduct. [b] Conditions: 2 hr at 125° in *o*-dichlorobenzene. [c] Higher yield, 2 hr at 60° in benzene; lower, 12 hr at 80° in cyclohexane (also 3% 3). [d] Conditions: 1 hr at 25° in benzene. [e] Triphenylarsine.

Table II
^{31}P Chemical Shifts of Compounds 4

$R_2R'PC_6S_4(CN)_4$	δ[a]	$\Delta\delta$[b]
4a, R = C_6H_5; R′ = CH_3	91.5[c]	−48.5
4b, R = R′ = p-$CH_3O_6H_4$	96.3	−20.3[d]
4c, R = R′ = m-$CH_3C_6H_4$	95.1	−22[e]
4d, R = R′ = C_6H_5	95.3	−23
4e, R = C_6H_5; R′ = CH_3O	82.2	+86
$Ph_2PSCH_2CH_2P(Ph)_2C_6S_4(CN)_4$	86.9, 67.4[f]	

[a] Relative to external P_4O_6; CH_2Cl_2 solvent except as otherwise indicated. [b] Change in chemical shift from free phosphine or phosphinite, parts per million. [c] Acetone solvent. [d] R. Pinnell, C. Megerle, S. L. Manatt, and P. A. Kroon, *J. Am. Chem. Soc.*, **95**, 977 (1973). [e] This work. [f] AB quartet, J_{AB} = 55 Hz.

spectra, and an unidentified phosphorus compound. The chemical shift of this latter species, +59 ppm from P_4O_6 (−54.2 ppm from H_3PO_4), is considerably downfield from those of **4a–e**; no structure can be assigned to this compound. With **1** and other phosphorus reactants either **3** or **4** was produced, or no reaction occurred. (However, it should be noted that in no cases other than the first two cited were the reactions carried out under conditions designed specifically to give products other than **3**. In particular, since the original objective of the work was the preparation of **3**, the reactions were generally carried out at higher temperatures and for longer times than would allow the isolation of analogs of **5**.)

Heating **2** with triphenyl- or tributylphosphine at reflux in benzene gave no evidence for reaction, even after several days.

The preparation of **3** in high yield from the reaction of trimethyl phosphite with **2** has been described;[5] a description of this procedure and the characterization of **3** are given in the Experimental Section.

The conversion of **1** into **3**, in 10% yield, can also be effected by triiron dodecacarbonyl.

The structure of **4** was assigned through the ^{31}P NMR chemical shifts of **4a–e**, the proton spectrum of **4a**, the ir spectrum of **4d**, and analogy with the product formed from the reaction of triphenylphosphine with 2-dicyanomethylene-1,3-dithietane.[6]

(a) The ^{31}P chemical shifts of **4a–e** and the reaction product of 1,2-bis(diphenylphosphino)ethane with **1** are compiled in Table II. The shifts of the phosphine adducts **4a–d** are remarkably constant at 90–95 ppm upfield of P_4O_6 (−17 to −22 from H_3PO_4) and that of the phosphinite adduct appears only slightly to lower field. This chemical shift is appropriate for arylphosphonium salts or ylides, and not appropriate for five-coordinate phosphorus.[7]

(b) In the proton NMR spectrum of **4a**, the methyl protons appear as a doublet at δ 3.05 ppm with J_{PCH} = 14 Hz. For comparison, the methyl resonances in Ph_2PMe and $Ph_3PMe^+Br^-$ appear at $\delta_{acetone}$ = 1.58 and 3.16 ppm, respectively, with J_{PCH} = 4 and 15 Hz. The close correspondence of δ and J_{PCH} between **4a** and Ph_3PMe^+ suggests very strongly that the phosphorus in **4** is present as a phosphonium ion.

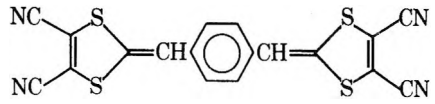
(c) The infrared spectrum of **4d** contains, in addition to the band at 1540 cm^{-1} assigned to the double bond conjugated to the cyano groups, a strong band at 1450 cm^{-1} attributable to an unsymmetrically substituted C–C double bond. No comparable band is present in the symmetrical **3**, but bands at similarly low frequencies have been reported by Blount et al.[8] for other multithiaethylenes.

(d) Finally, treatment of **4d** with HBF_4 in acetone–dichloromethane at room temperature afforded a yellow, crystalline salt, whose composition corresponded to **4d** + HBF_4. The infrared spectrum of the salt retained the bands at 1540 and 1450 cm^{-1}, and, in addition, exhibited bands at 3390 and 1060 cm^{-1}, attributable to S–H and B–F stretches, respectively, and resulting from the protonation of thiolate and consequent formation of a normal fluoroborate salt.

Taken together, these results are compatible only with an open, betaine structure for **4**.

Bromine was found to react with **4d**, giving a tetrabromide. The ir spectrum of this compound shows no band near 1540 cm^{-1}, suggesting that the dicyanoethylene groups have become saturated, and the ^{31}P chemical shift, +93.5 ppm from P_4O_6 in CH_2Cl_2 solution, suggests that the phosphorous is still present as a phosphonium ion. The data available do not allow us satisfactorily to assign a structure to this product; however, one plausible structure would be that formed by addition of bromine across both dicyanoethylene groups.

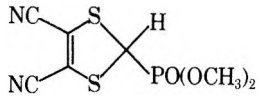
Reactions in the Presence of Aldehydes. Addition of terephthaldehyde to a solution of trimethyl phosphite and **2** in benzene inhibits the coupling reaction, reducing the yield of **3** to about 40% without yielding any other easily isolable products. However, addition of terephthaldehyde to a solution of triphenylphosphine and **1** in benzene results in a quantitative yield of dark red needles, identified



8

as 8 by elemental analysis and mass spectrometry. In contrast, reaction of benzaldehyde, triphenylphosphine, and 1 in benzene gave both **4d** and 2-benzylidene-4,5-dicyano-1,3-dithiole.

Addition of benzoic acid or an excess of impure benzaldehyde to a solution of 2 and trimethyl phosphite completely suppressed the coupling reaction, instead leading to a pale yellow compound, **9**. On the basis of its mass spec-

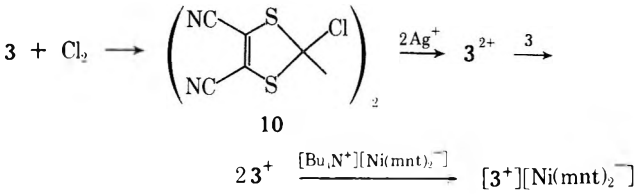


9

trum [parent ion, *m/e* 262; major fragments ions *m/e* 153 ($C_3HS_2(CN)_2$) and 109 ($C_2H_5PO_3$)] and ^1H NMR spectrum [doublets at δ 4.0 (J = 10.84 Hz) and 5.3 (J = 5.7 Hz), area ratio 6:1], **9** is identified as 4,5-dicyano-1,3-dithiol-2-ylphosphonic acid dimethyl ester.[9]

Redox Chemistry. The electrochemical behavior of **3** has been described.[4] In an attempt to isolate the oxidation products of **3**, a solution in dichloromethane was treated with chlorine. The deep wine color of **3** was slowly discharged and a new compound, **10**, was isolated as pale straw-colored, moisture-sensitive crystals. The mass spectrum of **10** exhibits no apparent molecular ion; however, $M^+ - Cl$ and other chlorine-containing fragments are observed, indicative of chlorine addition most probably across the central double bond. Thus the compound is assigned the structure 2,2′-bis(2-chloro-4,5-dicyano-1,3-dithiolyl). The chlorines can be removed quantitatively by reaction with 2 equiv of silver fluoroborate in acetonitrile. Addition of 1 equiv of **3** to a solution of **10** followed by reaction with silver ion gave a red solution of the monocation, which was isolated as its bis(maleonitriledithiolato)nickel, [Ni(mnt)$_2^-$], salt (Scheme I).

Scheme I



10

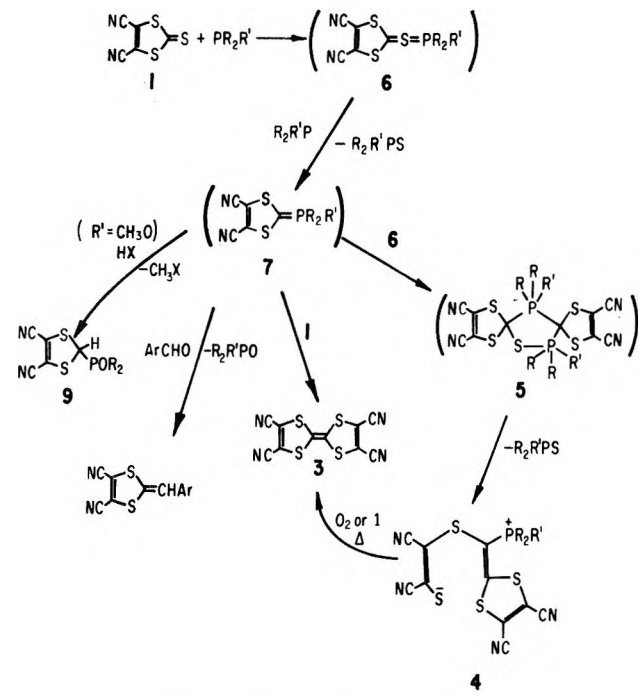
8 is reversibly oxidized in benzonitrile at E_p = 1.07 V. It also undergoes an irreversible oxidation at E_p = 1.39 V and an irreversible reduction at E_p = −1.18 V. Chemical oxidation was not studied.

Discussion

To allow the isolation of the spectrum of products found in this series of reactions there clearly must exist a much more delicate balance of electronic and other energetic effects than commonly obtains in other phosphine– or phosphite–thione reactions. We believe that the series of transformations outlined in Scheme II rationalizes the products observed; they also give us a basis for discussion of some of the factors involved.

Following Corey and Märkl,[3] we assert that the ylide **7** is a key intermediate in these reactions.[10] Whether it forms via displacement of $R_2R'PS$ by $R_2R'P$ from **6**, or by dissociation of **6** into carbene and phosphine sulfide followed by

Scheme II



junction of phosphine and carbene, cannot be answered by the available data.

Formation of **5** requires the conjoining of **6** with **7**. Both these species are strongly polarized, which suggests that they might react by a [3 + 2] dipolar addition. The initial product of such a reaction would have the structure given for **5** in Scheme II, but we have no evidence to support this structure assignment. A heterocycle of that structure could be expected readily to lose Ph_3PS,[12] the remainder collapsing to an epiphosphorane. This, in turn, could easily transform into the observed betaine.

In like manner, the Wittig reactions with terephthaldehyde and benzaldehyde presume the intermediacy of **7**. The isolation of both **4d** and the Wittig product in the benzaldehyde reaction, however, suggests that **6** competes strongly with aldehyde for the **7** available.

The formation of **9** presumably occurs via protonation of **7** at C-2, followed by displacement of a methyl group from methoxyl by the conjugate base (benzoate) of the protonating species, as in the Arbuzov reaction. One can invoke the existence of an adduct of benzaldehyde with **6**, which is decomposed on protonation, to rationalize the high yield of **9**, but its formation in the presence of benzoic acid, a very likely contaminant of the benzaldehyde used in that particular experiment, renders this unnecessary.

The bidithiolidene **3** can be formed either from the reaction of **1** plus **7** or from the dephosphinization of **4**. In the case of the phosphines investigated in this work, it seems likely that the route via **4** predominates. In the reaction of **1** and **2** with phosphites, however, either route (or both!) may be followed; our results do not bear on this question.

The remaining observations to be rationalized can be summed up in the question of why **5** and **4** are observed in the reactions described here but not when other 1,3-dithiole-2-thiones are allowed to react with phosphines. It seems likely that the conjugated cyano groups must strongly stabilize both **6** and **7**, compared to similar intermediates from other thiones, making their lifetimes in solution unusually long. Furthermore, **6** must be rather unreactive toward Brønsted acids, since no evidence was seen for products of the type reported very recently by Scherowsky and Weiland.[11]

Table III
Data for the Characterization of Compounds 4

Compd	Mp, °C[a]	Yield,[b] %	% C		% H		% S	
			Calcd	Found	Calcd	Found	Calcd	Found
4a	142	20	54.76	54.41	2.58	2.36	25.40	25.54
4b	179	39	56.70	56.41	3.20	3.22	19.51	19.81
4c[c]	193–195	45	61.18	60.95	3.45	3.60	21.05	20.87
4d[d]	169	46	59.36	59.62	2.65	2.93	22.61	22.64
4e	237	30	53.08	53.15	2.50	2.71	24 62	25.24
$(Ph_2PCH_2)_2$ adduct[e]	164–166	49	56.39	56.04	3.13	2.82	25.06	25.24

[a] Usually with decomposition. [b] Conditions as in method A for 4d. [c] Molecular weight: calcd, 608; found (osmometric in dimethylformamide), 589. [d] Analysis for nitrogen: calcd, 9.89; found, 9.27. [e] $(C_6H_5)_2P(S)CH_2CH_2P^+(C_6H_5)_2C[=C_3S_2(CN)_2]SC(CN)=C(CN)S^-$.

It seems likely, too, that the π-donor properties of the phosphine must be important in stabilizing **6**, particularly. This follows from the highest yields of **4** being observed from those reactions involving the better π-donor phosphines, near the top of Table I, although the reactions involving tri(*p*-chlorophenyl)phosphine and methyl diphenylphosphonite are apparently anomalous if this is correct.

Conversely, in the reactions of **2** with phosphites, the intermediate corresponding to **6** should not be long lived, and no products comparable to **4** should be expected. However, the ylide **7** should be stable, and we observe the formation of products derived from it.

The relative stability of these intermediates, and the ease with which small variations in the stability can be effected by suitable choice of phosphine reagents, suggest that this system ought to be an interesting subject for a kinetic study. In particular, it may well be possible to resolve the questions of the intermediacy of any two-coordinate carbon species in the conversion of **6** to **7** and of the route by which **3** is formed. Studies such as these are outside the scope of our investigations, and we welcome any interest others may have in this subject.

The deep red-purple color of **3** is interesting inasmuch as tetrathiafulvalenes [including the tetrakis(trifluoromethyl) derivative] are normally yellow-orange. The absorption band at 495 nm (CH_2Cl_2) in the spectrum of **3** is not far from the corresponding long-wavelength band in tetrathiafulvalene itself (450 nm).[13] Its extinction coefficient (ϵ_{495} 2000) is an order of magnitude larger (TTF, ϵ_{450} 270), however, which suggests that a transition other than the $b_{1u} \leftarrow a_g$ assigned to the long-wavelength band in TTF[13] is responsible for this band. The band exhibits a small solvent shift [λ_{max} (CH_2Cl_2) 495 nm, λ_{max} (CH_3CN) 501 nm] in the direction expected for an internal charge-transfer transition, and we suggest that in such a transition lies the origin of the band. Furthermore, the long-wavelength transition of tetrakis(trifluoromethyl)tetrathiafulvalene, which is unlikely to possess such a charge-transfer band, is shifted considerably to the blue from that of TTF (λ_{max} 412 nm).[14]

Experimental Section

Cyclic voltammetry was conducted in either dry acetonitrile or benzonitrile, containing 0.1 *N* tetraethylammonium perchlorate, at a platinum button electrode in the manner previously described.[15]

X-Ray studies were performed with a conventional Nonius precession. Photographs were recorded using Ni-filtered Cu Kα radiation. Infrared spectra were recorded using cesium iodide or potassium bromide disks. Proton NMR spectra were recorded at 60 MHz and are referenced to internal tetramethylsilane. Fourier transform ^{31}P spectra were recorded, with white noise ^1H decoupling, at 40.5 MHz and, except where otherwise noted, are referenced to external P_4O_6.[16] Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Galbraith Laboratories.

4,5-Dicyano-1,3-dithiole-2-thione (**1**) was prepared as described by Klingsberg[17] and 4,5-dicyano-1,3-dithiol-2-one (**2**) as reported by Ciganek and Krespan.[18] The phosphines were commercial materials and were used as received.

$\Delta^{2,2'}$-Bis(4,5-dicyano-1,3-dithiolidene) (3). A. Trimethyl phosphite (3.1 g, 0.025 mol) was added to a solution of **2** (4.2 g, 0.025 mol) in benzene (150 ml) and the resulting solution was heated under reflux in a nitrogen atmosphere for 3 hr. The solution slowly turned to a deep wine color and crystals started forming toward the end of the reaction. The reaction mixture was allowed to cool overnight. The product was collected and washed with benzene, yield 3.7 g (95%) of purple needles, mp 265–267°.

B. Trimethyl phosphite (0.27 g, 2.18 mmol), **1** (0.40 g, 2.18 mmol), and 25 ml of cyclohexane were refluxed and stirred for 15 min, then stirred overnight at room temperature. The cyclohexane phase was discarded and the residue was washed with 10 ml of cold benzene. The remaining solids were dissolved in a minimum amount of warm acetone. Benzene (5 ml) was added and the solution was concentrated on a hot plate until a solid phase appeared. On cooling, the product separated as purple needles. After an additional recrystallization, the yield was 0.1 g (30%), mp 263–265°. A thin layer chromatogram (silica, benzene) revealed only one component.

C. A suspension of **4d** (2 mmol) in *o*-dichlorobenzene (25 ml) containing **1** (3 mmol) was heated at 125°. After 1 hr the solid had dissolved and a deep red solution was obtained; heating was continued for 1 hr more. The solvent was removed under reduced pressure and the residue was recrystallized from dichloromethane–benzene, yield of 0.24 g (25%).

D. Triiron dodecacarbonyl (0.6 g, 1.43 mmol), **1** (0.65 g, 3.54 mmol), and 35 ml of dry, thiophene-free benzene were refluxed for 4 hr under nitrogen. The reaction mixture was filtered through Celite; slow evaporation of the filtrate with a nitrogen jet caused the separation of 0.055 g of **3** (10%), identified by its infrared spectrum and R_f.

Anal. Calcd for $C_{10}N_4S_4$: C, 39.47; N, 18.42; S, 42.11. Found: C, 39.31, 39.70; H, 0.02, 0.06; N, 18.20, 18.25; S, 41.88, 41.84. Spectral data: uv–visible λ_{max} (CH_2Cl_2) 262 nm (ϵ 2 × 10^4), 290 sh, 323 (1.4 × 10^4), 495 (2 × 10^3); λ_{max} (CH_3CN) 260 nm (ϵ 2.3 × 10^4), 325 (1.4 × 10^4), 501 (1.6 × 10^3); ir 2242 (m), 2218 (m), 2212 (m), 1530 (s), 1135 (s), 1064 (s), 877 cm^{-1} (w); mass spectrum (70 eV) *m/e* (rel intensity) 304 (100), 234 (48), 152 (64), 88 (0), 76 (57).

(4,5-Dicyano-1,3-dithiol-2-ylidene)methylene (Triphenylphosphonio)(2-thio-1-mercaptomaleonitrilate) (4d). A. A mixture of 0.34 g (2 mmol) of **1**, 0.52 g (2 mmol) of triphenyl phosphine, and 15 ml of cyclohexane was refluxed and stirred for 12 hr. Filtration of the reaction mixture gave an orange solid which was washed with benzene. The filtrate and washings were combined and evaporated to dryness. Crystallization from ethanol gave 0.01 g of **3** as the less soluble component and 0.32 g (54%) of triphenylphosphine sulfide, identified by its infrared spectrum. The orange solid was dissolved in 50 ml of warm dichloromethane and 10 ml of acetonitrile was added. Concentration of this solution on a rotary evaporator without heating gave 0.26 g (46%) of **4d** as small orange crystals, mp 169° dec.

B. A solution of **1** (0.184 g, 1 mmol) and triphenylphosphine (0.39 g, 1.5 mmol) in benzene (10 mol) was warmed at 60° for 1 hr. The reaction mixture was cooled and 0.24 g (85% yield) of orange crystals was collected.

Analytical data on this compound appear in Table III.

Spectral data: ir (KBr disk) 2200 (s), 2175 (s), 1585 (s), 1540 (s), 1480 (s), 1450 (sh), 1429 (s), 1183 (s), 1150 (s), 1105 (s), 995 (s), 844

(s), 743 (s), 719 (s), 683 cm^{-1} (s); uv λ_{max} ($CHCl_3$) 268 nm (ϵ 2.75 × 10^3), 362 (5.6 × 10^3).

The analogous compounds **4a–c** and **4e** were prepared by similar methods and purified by preparative thin layer chromatography or recrystallization. Their analytical data are collected in Table III.

The 1,2-bis(diphenylphosphino)ethane complex was purified by preparative scale thin layer chromatography (silica gel, dichloromethane) and recrystallized from acetone–2-propanol to give small orange needles of product. The ^{31}P NMR spectrum of the crude product disclosed an additional small peak at +68.4 ppm, but the product responsible for this signal could not be purified.

Dichloromethane Solvate of 4d. **5** (3 g, 3.3 mmol) was suspended in benzene (50 ml) and warmed at 60°. The crystals slowly dissolved, giving a purple-red solution with simultaneous formation of an orange, crystalline solid. The conversion was complete in 10 min. Recrystallization from dichloromethane gave 2 g (95%) of triclinic crystals, mp 187–189°.

Anal. Calcd for $C_{28}H_{15}N_4PS_4 \cdot 0.5CH_2Cl_2$: C, 56.20; H, 2.63; N, 9.20; P, 5.08; S, 21.05. Found: C, 56.73; H, 2.61; N, 9.26; P, 5.08; S, 21.20. Crystallographic data: reduced triclinic cell, a = 12.779, b = 12.951, c = 10.645 Å, α = 102.1, β = 111.4, γ = 110.0; space group $P1$ or $P\bar{1}$; for Z = 2 the calculated density for $C_{28}H_{15}N_4PS_4 \cdot 0.5CH_2Cl_2$ is 1.43 g cm^{-3}; density measured by flotation is 1.42 g cm^{-3}. Ir (CsI disk) 3060, 3025, 2210, 2175, 1586, 1540, 1483, 1440, 1150, 1105, 748, 720, 687, 528, 511, 500 cm^{-1}.

HBF_4 Adduct of 4d. To a solution of 0.3 g (0.53 mmol) of **4d** in 20 ml of 1:1 acetone–dichloromethane was added 1 ml of 48% aqueous fluoroboric acid. The mixture was stirred for 1.5 hr while the color changed from orange to yellow, then evaporated to ca. 5 ml under reduced pressure. The product was precipitated by addition of diethyl ether and recrystallized three times from acetone–ether to afford 0.3 g (88%) of **12** as yellow microcrystals. Anal. Calcd for $C_{28}H_{16}BF_4N_4PS_4$: C, 51.38; H, 2.45. Found: C, 51.35; H, 2.45. The infrared spectrum contained bands at 2.9 (SH) and 9.4 μm (BF_4^-).

Bromination of 4d. Compound **4d** (0.8 g, 1.4 mmol) and 40 ml of dichloromethane were cooled in an ice bath. A solution of bromine (0.49 g, 3 mmol) in 10 ml of dichloromethane was added dropwise with stirring. The color changed from orange to yellow-orange. The reaction mixture was stirred for 2 hr at 0° after the addition was complete, then filtered to give 0.85 g (69%) of golden yellow microcrystals. Anal. Calcd for $C_{28}H_{15}Br_4N_4PS_4$: C, 37.92; H, 1.69. Found: C, 37.85; H, 1.87. Ir (KBr) 3030 (w), 2220 (w), 1590 (w), 1470 (m), 1450 (m), 1390 (s), 1176 (m), 1156 (s), 1100 (s), 995 (m), 746 (s), 719 (s), 687 cm^{-1} (s).

Adduct 5. Triphenylphosphine (5.24 g, 0.02 mol) and **3** (3.68 g, 0.02 mol) were dissolved in benzene (100 ml) and stirred under nitrogen at room temperature. The solution turned deep red and after a period of 1 hr a red-brown solid slowly crystallized. This was collected (3 g, 70%), washed with benzene, and air dried, mp 94–95°. Anal. Calcd for $C_{46}H_{30}N_4S_5P_2$: C, 64.16; H, 3.51; N, 6.51; S, 18.62; P, 7.20. Found: C, 64.07; H, 3.47; N, 6.25; S, 18.49; P, 6.95.

Reaction of 1 with Tri-*n*-butylphosphine. A solution of 400 mg (2 × 10^{-3} mol) of **1** in 50 ml of toluene was cooled in an ice–water bath; tri-*n*-butylphosphine (0.5 ml, 2 × 10^{-3} mol) was added dropwise. The solution quickly became dark red in color. It was allowed to stir at 0° for 30 min, and then to warm to room temperature over 18 hr. Evaporation of the toluene under vacuum left a dark red oil, evidently a mixture of compounds, one of which was identified as tri-*n*-butylphosphine sulfide by its mass (parent ion, m/e 234) and ^{31}P NMR spectra (a sharp resonance, −46.7 ppm from H_3PO_4).[19] A second phosphorus-containing component, which exhibited a broad peak at −54.2 ppm, apparently was not volatile in the mass spectrometer. No further attempt was made to identify it.

2,2′-(*p*-Xylylene)bis(4,5-dicyano-1,3-dithiolidene) (8). Triphenylphosphine (4 mmol), terephthalaldehyde (0.5 mmol), and **1** (1 mmol) were dissolved in benzene (10 ml) and the solution was left standing at ambient temperature overnight. The solution slowly turned red and dark red crystals formed. The crystals were filtered off, washed with benzene, and air dried. Recrystallization from benzonitrile gave a 95% yield of purple needles, mp >300° dec.

Anal. Calcd for $C_{18}H_6N_4S_4$: C, 53.18; H, 1.49; N, 13.78; S, 31.55. Found: C, 53.40; H, 1.55; N, 13.68; S, 31.38. Mass spectrum (70 eV) m/e 406 (100), 298, 285, 266, 253, 221; ir (Nujol mull) 2210, 1690, 1575, 1550 (sh), 1410, 1280, 1180, 1070, 848, 785, 685 cm^{-1}.

2-Benzylidene-4,5-dicyano-1,3-dithiole. Triphenylphosphine (5.24 g, 0.02 mol), **1** (1.84 g, 0.01 mol), and benzaldehyde (from a freshly opened commercial supply, 1.06 g, 0.01 mol) were dissolved in benzene and allowed to stir under nitrogen for 24 hr at room temperature. At the end of this time the solution was dark red and an orange precipitate was present. The orange solid (0.55 g) was recovered by filtration and identified as **4d** by its melting point (169°); the yield of **4d** was 20%.

Evaporation of the filtrate left an oily, red residue which left an orange-brown solid upon treatment with 100 ml of absolute ethanol. Extraction of this solid with petroleum ether in a Soxhlet apparatus gave a mixture of red and colorless crystals, identified as 2-benzylidene-4,5-dicyano-1,3-dithiole (mp 142–145°) and triphenylphosphine sulfide, respectively, by their mass spectra. The mass spectrum of the former compound consists of a parent ion, m/e 242 (100%), and major fragments at m/e (rel intensity) 166 [27, M − C_6H_4 or M − $C_2(CN)_2$], 134 (37); 121 (27, C_6H_5CS), 102 (30, $C_8H_2N_2$), 90 (33), and 89 (43).

Dimethyl (4,5-Dicyano-1,3-dithiol-2-yl)phosphonate (9). A. Benzoic acid (0.59 g, 0.005 mol), **2** (0.84 g, 0.005 mol), and trimethyl phosphite (1.15 ml, 0.01 mol) were dissolved in 100 ml of methylcyclohexane. This solution was heated at reflux for 4 hr, during which time it became red. A brown solid separated on cooling; it was recovered by filtration. Recrystallization from benzene afforded 0.45 g (34%) of pale yellow plates, mp 142–143°.

B. Trimethyl phosphite (2 mmol), **2** (1 mmol), and aged benzaldehyde (4 mmol) were dissolved in hot methylcyclohexane (40 ml) and heated at 90° for 30 min. The solution slowly turned yellow. The reaction mixture was concentrated to 20 ml and set aside. The yellow crystals which slowly formed were collected, washed with methylcyclohexane, and air dried, yield 0.11 g (42%). Recrystallization from methylcyclohexane gave 90% recovery of pale yellow plates, mp 142–143°.

Anal. Calcd for $C_7H_7N_2S_2PO_3$: C, 32.06; H, 2.69; N, 10.68; S, 24.45; P, 11.81. Found: C, 32.26; H, 2.70; N, 10.63; S, 24.54; P, 11.64. Mass spectrum (70 eV) m/e 262, 153 (100), 109; NMR ($CDCl_3$) δ 4.00 (d, J = 10.84 Hz, 6 H), 5.28 (d, J = 5.7 Hz, 1 H); ^{31}P NMR ($CDCl_3$) −14.6 ppm (vs. H_3PO_4).

2,2′-Bis(2-chloro-4,5-dicyano-1,3-dithiolyl) (10). 3 (1 mmol) was dissolved in warm dichloromethane (50 ml) and chlorine gas was bubbled through the solution. The deep wine color was slowly discharged and a pale yellow solution was obtained. The solution was concentrated to 20 ml, methylcyclohexane (20 ml) was added, and the solution was further concentrated to 20 ml. On cooling, a 90% yield of pale straw-colored crystals formed. These were collected, dried under vacuum, and stored under nitrogen, mp 170–172° dec.

Anal. Calcd for $C_{10}N_4S_4Cl_2$: C, 32.00; N, 14.93; Cl, 18.93. Found: C, 32.02; H, 0.10; N, 14.69; Cl, 18.77. Mass spectrum (70 eV) m/e 339, 304 (100), 236, 234, 189, 187. Spectral data: uv λ_{max} (CH_2Cl_2) 349 nm (ϵ 8080), 300 sh (6100), 282 (5730), 248 (11,500); ir (CsI disk), 2242, 2225, 1548, 1525, 1181, 1160, 1060, 694, 515, 490, 480 cm^{-1}.

On treatment of a solution of **10** in acetonitrile with 2 equiv of silver hexafluoroantimonate a quantitative yield of silver chloride was obtained.

$\Delta^{2,2'}$-Bi(4,5-dicyano-1,3-dithiolidene)bis(maleonitriledithiolato)nickel. 3 (0.5 mmol) was dissolved in dichloromethane (50 ml) and chlorine gas was bubbled through the solution. The resulting yellow solution was degassed and treated with **3** (0.5 mmol) followed by a solution of silver hexafluoroantimonate (1.0 mmol) in acetonitrile (40 ml). The precipitated silver chloride was filtered off and the resulting red solution was treated with a solution of tetra-*n*-butylammonium bis(maleonitriledithiolato)nickel (1 mmol) in acetonitrile (20 ml). The resulting solution was evaporated to dryness, treated with hot dichloromethane (50 ml), and filtered. The violet-black solid was washed with hot dichloromethane and dried under nitrogen. Recrystallization from acetonitrile gave 0.44 g (68%) of black crystals, mp >360°.

Anal. Calcd for $C_{18}N_8S_8Ni$: C, 33.60; N, 17.62; S, 39.87. Found: C, 33.74; H, 0.22; N, 17.32; S, 39.81.

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Registry No.—**1**, 1005-10-3; **2**, 934-31-6; **3**, 55052-32-9; **4a**, 55758-94-6; **4b**, 55758-95-7; **4c**, 55758-96-8; **4d**, 55758-97-9; **4d** CH_2Cl_2, 55758-98-0; **4d** tetrabromide, 55758-99-1; **4e**, 55759-00-7; **5**, 55759-01-8; **8**, 55759-02-9; **9**, 55759-03-0; **10**, 55759-04-1; **12**, 55822-52-1; $Ph_2PSCH_2CH_2P(Ph)_2C_6S_4(CN)_4$, 55759-05-2; fluoroboric acid, 16872-11-0; tributylphosphine, 998-40-3; tributylphosphine sulfide, 3084-50-2; terephthaldehyde, 623-27-0; 2-benzylidene-4,5-dicyano-1,3-dithiole, 55759-06-3; $\Delta^{2,2'}$-bi(4,5-dicyano-1,3-dithiolidene)bis(maleonitriledithiolato)nickel, 55663-96-2.

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(10) Very recently Scherowsky and Weiland published[11] results which call into question the intermediacy of ylides such as **7** in reactions of this sort. Under their conditions, however (they studied the reactions of benzo[*d*]-1,3-dithiole-2-thione with triethyl phosphite, alone and in the presence of sundry reagents), their intermediate **14** (which corresponds to our **6**) would be expected to be more reactive than **6**, especially toward electrophilic reagents. Conversion to an ylide, in their case, is being forestalled by other reactions.

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Organophosphorus Compounds. XIII.[1a] Protonation, Cleavage, and Alkylation of Thiophosphates and Thiophosphites

George A. Olah* and Charles W. McFarland[1b,c]

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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Protonation, cleavage, and alkylation reactions of phosphorothioic acids, $H_3PS_nO_{4-n}$ (n = 0–3), alkyl mono- and dithiophosphates, and systematically substituted phosphorothioites $P(SC_2H_5)_n(OCH_3)_{3-n}$, phosphorothiolates, $OP(SC_2H_5)_n(OCH_3)_{3-n}$, and phosphorothionates, $SP(SC_2H_5)_n(OCH_3)_{3-n}$ (n = 0–3), were studied in fluorosulfuric acid solution by ^1H and ^{31}P NMR spectroscopy (primarily at −60 to −80°). Trivalent phosphorus compounds are protonated at phosphorus, phosphoryl compounds at the phosphoryl oxygen, and thiophosphoryl compounds at the thiono sulfur atom. In the last case, the two-bond coupling, $^2J_{PSH}$, is observed below −50°. In general, sulfur is less able than oxygen to donate nonbonded electron pairs to phosphorus in the stabilization of phosphonium ions. The change in the ^{31}P chemical shift of thiophosphates and thiophosphites upon protonation is a function of the site of protonation and the relative numbers of oxygen and sulfur atoms bonded to phosphorus. Isopropoxymercaptophosphonium ions undergo rearrangements by isopropyl group migration from oxygen to sulfur. All intermediates in these processes can be individually observed.

Since our report of nuclear magnetic resonance spectroscopic studies of protonated phosphates and phosphites (oxyphosphonium ions),[1a] we have extended our work to many thiophosphorus analogs. Considering that the most important influence on the structures of the oxyphosphonium ions, as particularly revealed by their ^{31}P chemical shifts, is electron donation by the oxygen atoms to phosphorus by means of $p\pi$–$d\pi$ bond formation,[1a] our interest was in determining the relative ability of sulfur atoms bonded to phosphorus to similarly stabilize phosphonium ions. In general, phosphorus–sulfur π-bond formation is less favored geometrically than is phosphorus–oxygen π-bond formation.[2] Our expectation was that NMR spectroscopy would be a sensitive tool for determining the effects of sulfur substitution for oxygen in positively charged phosphorus intermediates.

We were particularly interested in whether the phosphorus lone electron pair (in the phosphites) is the site of protonation in strong acid solution, and otherwise whether the phosphoryl sulfur or oxygen atoms are protonated. These expectations, which were based on our work with phosphates and phosphites,[1a] would not necessarily arise from other earlier chemical observations. Trialkyl phosphorotrithioites undergo neither the Michaelis–Arbuzov reaction with alkyl or acyl halides nor the anti-Arbuzov reaction with polyhalocyclopentadienes[28] (nucleophilic attack by phosphorus). Rather, the sulfur atoms are the reactive sites, yielding, for example, dialkyl phosphorodithious halides and dialkyl sulfides in the first case,[3] and halocyclopentadienyl alkyl sulfides and the phosphorodithious halides in the second case.[29] Mixed phosphorothioites of the types $(RO)_2PSR$ and $ROP(SR)_2$ react in mixed fashion, giving products arising from both phosphorus and sulfur atom alkylation.[4] The nucleophilic reactivity of thiophosphoryl sulfur atoms has been interpreted in terms of the "hard–soft" acid–base concept,[5] with the "soft" sulfur

Table I
^{31}P and ^{1}H NMR Parameters of Protonated Alkyl Mono- and Dithiophosphates (−60 to −80°)

Phosphonium ion[e]	$\delta\ ^{31}P$ (85% H_3PO_4 = 0)			$\delta\ ^{1}H$ (J, Hz)			
				Mercapto proton(s)		α-Alkyl proton(s) ($^{3}J_{PH}$)	
	Ion	Precursor[f]	$\Delta\delta_P$[a]	Ion ($^{2}J_{PSH}$)	Precursor	Ion	Precursor
$(HS)_2P(OCH_3)_2^+$	−94.2	−89.8	−4.4	*b*	*b*	4.37 (15.6)	4.33 (15.5)
$HS(H_3CS)P(OCH_3)_2^+$	−99.6	−99.0	−0.6	4.01 (13.3)		4.34 (15.0)[c]	4.28 (15.0)[c]
						2.79 (20.3)[d]	2.81 (15.8)[d]
$(HS)_2P(OC_2H_5)_2^+$	−87.0	−84.6	−2.4	4.33 (13.9)	4.18	4.77 (9.8)	4.66 (10.5)
$HS(HO)P(OC_2H_5)_2^+$	−43.8	−58.3	+14.5	3.84 (17.2)	8.48	4.74 (8.5)	4.59 (9.7)
$(HS)_2P(O\text{-}i\text{-}C_3H_7)_2^+$	−80.1	−81.1	+1.0	4.38 (13.7)	4.07	5.41 (7.7?)	5.26 (12.5)
$(HS)_2P(O\text{-}i\text{-}C_4H_9)_2^+$	−88.1	−85.0	−3.1	4.34 (14.0)	3.98	4.46 (7.4)	4.32 (8.8)

[a] Change in δ_P upon protonation. [b] Could not be determined. [c] Methoxy protons. [d] Thiomethyl protons. [e] Registry no. are, respectively, 55649-05-3, 55649-06-4, 55649-07-5, 55649-08-6, 55649-09-7, 55649-10-0. [f] Registry no. are, respectively, 756-80-9, 2953-29-9, 298-06-6, 2465-65-8, 107-56-2, 2253-52-3.

atom showing relative disinclination to react with a "hard" proton. Schmidpeter and Brecht utilized the susceptibility of thiophosphoryl sulfur toward alkylation to methylate a series of tetravalent thiophosphorus compounds $L_n(C_6H_5)_{3-n}$ PS (L = dimethylamino, methoxy; n = 0–3), obtaining the ions $L_n(C_6H_5)_{3-n}PSCH_3^+$.[6] In this case it was suggested that the L substituents do increase their shielding of the ^{31}P nucleus (through $p\pi$–$d\pi$ contributions) upon methylation, at the expense of decreased shielding by the sulfur atom. In this paper the effects of protonation of a variety of thiophosphates and thiophosphites are examined.

Results and Discussion

Protonated Alkyl Mono- and Dithiophosphates. A series of *O,O*-dialkyl hydrogen phosphorodithioates in which the alkyl substituents were varied, as well as a closely related trialkyl phosphorodithioate (with a mercapto group replaced by a thiomethyl) and an *O,O*-dialkyl hydrogen phosphorothioate (with a mercapto group replaced by a hydroxyl group), were studied. These starting compounds were examined by ^{1}H and ^{31}P NMR spectroscopy as neat liquids at room temperature; in all cases first-order spectra were observed. The NMR parameters are summarized in Table I. The only anomaly in these spectra was that the mercapto proton in *O,O*-dimethyl hydrogen phosphorodithioate (which contained an approximately equal amount of trimethyl phosphorothiolothionate as a side product; see Experimental Section) was very difficult to observe. Possibly the peak due to this proton was obscured by peaks due to methoxy protons; the chemical shifts of the methoxy protons are in the region (δ 4.3) of mercapto proton shifts observed in other *O,O*-dialkyl hydrogen phosphorodithioates (δ 4.0–4.2). However, the ^{31}P chemical shift had the expected value. The ^{31}P chemical shift of *O,O*-diethyl hydrogen phosphorothioate (−58.3 ppm relative to 85% H_3PO_4) lies in between that of *O,O*-diethyl-*S*-methyl phosphorothioate (−28.6 ppm[7]) and that of diethylmethyl phosphorothionate (−69.6 ppm[7]). This observation can be interpreted on the basis of the hydrogen phosphorothioate somewhat preferring the thiono form, $(C_2H_5O)_2P(S)OH$, rather than the thiolo form, $(C_2H_5O)_2P(O)SH$ (the acidic protons are, of course, rapidly exchanging).

When dissolved in excess fluorosulfuric acid at low temperature (below −60°), stable ions resulting from protonation of the preceding compounds are obtained. In the ^{1}H NMR spectra, in addition to the expected alkyl proton peaks and a low-field (δ 11–12) singlet due to excess acid solvent, a doublet absorption (coupling constant 13–17 Hz) is found at δ 3.8–4.4. This doublet is attributed to thiophosphoryl sulfur atom protonation. Proton–phosphorus spin–spin coupling through one intervening sulfur atom is not commonly observed, although it has been cited in support of the formulation of bis(trifluoromethyl)phosphinothious acid as a trivalent mercapto compound ($^{2}J_{PSH}$ = 22.6 Hz).[8] Either component of the doublet observed with the protonated thiophosphates is useful for obtaining the ^{31}P chemical shift by the INDOR technique. In those cases where sufficient resolution could be achieved, the ^{31}P INDOR spectra exhibited the multiplicities expected of the protonated ions. None of the hydrogen phosphorodithioate precursors exhibit P–S–H coupling down to their freezing points.

The doublet absorptions due to the sulfur-bound protons are affected by temperature changes. Not unexpectedly, intra- and intermolecular exchange processes become more rapid at higher temperature, and the doublets coalesce in the temperature range −10 to −50°. Exchange with excess fluorosulfuric acid causes the low-field acid peak to become significantly broadened at room temperature. The doublets become increasingly sharp as the temperature is lowered; the listed ^{31}P chemical shifts of the ions, obtained by the INDOR method from the mercapto protons, and the NMR parameters of the mercapto protons were obtained at −80°. NMR parameters of the alkyl protons of the ions were obtained at −60°, where better resolution of the multiplets was found. In general, the α-alkyl protons show the expected slight deshielding upon protonation. In many cases, the ^{31}P chemical shifts of the ions were confirmed by use of the INDOR method with the α-alkyl proton peaks. As a rule, the ^{31}P shifts move to higher field by several tenths of a part per million in going from −80 to −60°.

The phosphorus nuclei in these phosphorodithioates undergo only small shifts upon protonation. This finding is characteristic of the protonation of phosphorothiolothionates, as will be seen in a later section. As also will be seen, the upfield shift of 14.5 ppm upon protonation of *O,O*-diethyl hydrogen phosphorothioate is more like the change undergone by phosphorothionates as compared to phosphorothiolates. Protonated *O,O*-diisopropyl hydrogen phosphorodithioate (diisopropoxydimercaptophosphonium ion) is the first intermediate in a series of cleavage and alkylation reactions in fluorosulfuric acid solution. These are discussed in the next section.

Protolytic Cleavage of *O,O*-Diisopropyl Hydrogen Phosphorodithioate and Triisopropyl Phosphorothionate in Fluorosulfuric Acid. It was earlier observed by us[1a] that protonated isopropyl phosphates and phosphites are quite sensitive to dealkylation, even at low temperature. One would expect that *O*-isopropyl phosphorothioates

Table II
^{31}P and ^{1}H NMR Parameters of Protonated Isopropyl Phosphorothioates, $(HS)_w(i\text{-}C_3H_7S)_xP(OH)_y(O\text{-}i\text{-}C_3H_7)_z^+$

Registry no.	w	x	y	z	$\delta^{31}P$ (85% H_3PO_4 = 0)	Mercapto proton(s) δ^1H	Mercapto proton(s) $^2J_{PSH}$, Hz	Mercapto proton(s) Temp, °C
	2	0	0	2	−80.1	4.38	13.7	−80
55649-11-1	2	0	1	1	−82.4	4.46	14.3	−80
55649-12-2	2	0	2	0	−83.8	4.59	14.6	−80
55649-13-3	1	1	2	0	−86.1	4.32	13.9	−80
55649-14-4	0	2	2	0	−87.8			0
55649-15-5	1	0	0	3	−36.7	3.83	16.3	−60
55649-16-6	1	0	1	2	−39.2	3.87	16.7	−60
55649-17-7	1	0	2	1	−41.2	3.96	17.0	−60
55649-18-8	1	0	3	0	−43.0	4.05	17.2	−60
55649-19-9	0	1	3	0	−44.8			−20

would behave similarly. This is found to be the case with *O,O*-diisopropyl hydrogen phosphorodithioate. All intermediates resulting from sequential protolytic carbon–oxygen bond cleavage can be observed in the proton spectra, since the mercapto protons in each intermediate can be individually distinguished.

$$(HS)_2P(O\text{-}i\text{-}C_3H_7)_2^+ \rightarrow (HS)_2P(OH)O\text{-}i\text{-}C_3H_7^+ \rightarrow (HS)_2P(OH)_2^+$$

$$HSP(O\text{-}i\text{-}C_3H_7)_3^+ \rightarrow HS(HO)P(O\text{-}i\text{-}C_3H_7)_2^+ \rightarrow HS(HO)_2PO\text{-}i\text{-}C_3H_7^+ \rightarrow HSP(OH)_3^+$$

These processes take place fairly slowly at −60°, and ^{31}P chemical shifts of each ion were obtained by the INDOR technique utilizing the mercapto proton peaks. The cleaved isopropyl groups form isopropyl fluorosulfate and can be identified as such (in part, by ^{19}F NMR spectroscopy).

The protonated phosphorothioic acids which are formed, $(HS)_2P(OH)_2^+$ and $HSP(OH)_3^+$, take part in further reactions. Upon standing, the methine proton resonance of isopropyl fluorosulfate (δ 5.5–5.6) is seen to move substantially upfield (to δ 4.0–4.1). In keeping with Teichmann and Hilgetag's generalization of thiophosphoryl sulfur atoms showing greater nucleophilic reactivity toward carbon centers rather than protons,[5] isopropyl fluorosulfate alkylates the sulfur atoms of protonated phosphorothioic acids.

$$(HO)_2P(SH)_2^+ \rightarrow (HO)_2P(SH)S\text{-}i\text{-}C_3H_7^+ \rightarrow (HO)_2P(S\text{-}i\text{-}C_3H_7)_2^+$$

$$(HO)_3PSH^+ \rightarrow (HO)_3PS\text{-}i\text{-}C_3H_7^+$$

Under these reaction conditions the mercaptophosphonium ions are more nucleophilic toward the isopropyl group than are fluorosulfate ions. The methine protons exhibit three-bond coupling to phosphorus ($^3J_{PSCH}$), allowing ^{31}P INDOR observations to be made in those cases where no mercapto proton can be so utilized. The end result of the multistep reactions that the protonated *O*-isopropyl phosphorothioates undergo is rearrangement of the alkyl substituents from oxygen to sulfur. These reactions are closely related to the well-known thiono–thiolo rearrangement equilibria of neutral phosphorothionate esters,[9] and in mechanism are similar to the alkyl exchange reactions of phosphorothionates with alkyl halides.[10] The alkyl exchange reactions usually require vigorous conditions,[5] but in our work the strong acid facilitated rearrangements can be followed by NMR spectroscopy at 0°. The ease of rearrangement of the *O*-isopropyl phosphorothioates in fluorosulfuric acid solution arises from the facile carbon–oxygen bond cleavage at even lower temperature.[11]

The NMR parameters of all of the isopropyl phosphorothioate intermediates are summarized in Table II. In each protonated phosphorothioate the phosphorus nucleus becomes increasingly deshielded as each *O*-isopropyl group is cleaved off and (later) becomes attached to a sulfur atom. It is of interest to note that the phosphorus in triisopropyl phosphorothionate (δ_P −64.5) becomes substantially more shielded upon protonation ($\Delta\delta_P$ +27.8). This is characteristic of trialkyl phosphorothionates, as discussed subsequently.

Protonation of Systematically Substituted Phosphorothioites, Phosphorothiolates, and Phosphorothionates. A suitable way of determining the relative charge-delocalizing abilities of sulfur and oxygen in phosphonium ions is to study systematically substituted series of compounds. One can look for general trends in, for example, NMR parameters as oxygen substituents are successively replaced by sulfur substituents. Accordingly, a series of phosphorothioites, $(C_2H_5S)_nP(OCH_3)_{3-n}$, phosphorothiolates, $(C_2H_5S)_nP(O)(OCH_3)_{3-n}$, and phosphorothionates, $(C_2H_5S)_nP(S)(OCH_3)_{3-n}$, were prepared; NMR spectra of these compounds and of the phosphonium ions which result from protonation in fluorosulfuric acid solution have been obtained. The parameters involving phosphorus and the protons closest to it are summarized in Table III. The precursor compounds were all examined as neat liquids at room temperature. The NMR spectra were all interpreted on a first-order basis. The methoxy proton resonance signals, or (if no methoxy protons were present) the ethylthio methylene proton signals, were utilized to obtain ^{31}P chemical shifts by the INDOR technique.

We have so far been unable to prepare one desired precursor, *S*-ethyl-*O,O*-dimethyl phosphorothioite. Although the synthesis of the triethyl analog has been reported,[4] NMR spectroscopic data for trialkyl phosphorothioites are quite scanty.[13] Several attempts to prepare the ethyldimethyl phosphorothioite by usual methods were made, but only mixtures of products were obtained (see Experimental Section). In order to obtain a dialkoxythiophosphonium ion, diethyl phosphonothionate was prepared (^{31}P shift found to be −68.8 ppm) and protonated (δ_P −64.3).

In certain of the ethyl thiophosphates and thiophosphites, the methylene protons are magnetically nonequivalent owing to molecular asymmetry. This asymmetry is present in molecules of the type, among others, CH_3CH_2(O or S) PXYZ, where X, Y, and Z are different from each other.[14] X, Y, and Z can be, as in this work, oxygen, sulfur, alkoxy groups, alkylthio groups, or a lone electron pair. However, the nonequivalence of the methylene protons is not always observed. In this work, diethyl phosphonothionate and *S,S*-diethyl-*O*-methyl phosphorodithioite demonstrated magnetic nonequivalence by a slight irregular splitting of the methylene proton resonance peaks. Each com-

Table III
^{31}P and ^{1}H NMR Parameters of Protonated Phosphorothioites, $HP(SC_2H_5)_n(OCH_3)_{3-n}^+$, Phosphorothiolates, $HOP(SC_2H_5)_n(OCH_3)_{3-n}^+$, and Phosphorothionates, $HSP(SC_2H_5)_n(OCH_3)_{3-n}^+$ (−60 to −80°)

		$\delta_{^{31}P}$ (85% H_3PO_4 = 0)			$\delta_{^1H}$ (J, Hz)					
					PH proton	Mercapto	O-Methyl protons ($^3J_{POCH}$)		S-Methylene protons ($^3J_{PSCH}$)	
Precursor class	n	Ion[g]	Precursor[h]	$\Delta\delta_P$[a]	($^1J_{PH}$)	proton ($^2J_{PSH}$)	Ion	Precursor	Ion	Precursor
Phosphorothioites	0[b]	−24.7	−139.7	+115.0	7.47 (827)		4.34 (12.1)	3.66 (10.8)		
	1	(−75)[c]	(−152)[d]	(+77)	[8.36 (761)][e]		*f*	*f*	*f*	*f*
	2	−87.8	−160.8	+73.0	8.85 (678)		4.23 (16.3)	3.88 (8.8)	3.46 (17.8)	3.16 (10.5)
	3	−63.3	−114.7	+51.4	8.69 (594)				3.41 (19.5)	3.29 (9.3)
Phosphorothiolates	0[b]	−2.0	−2.3	+0.3			4.42 (11.5)	4.15 (11.2)		
	1	−51.2	−30.0	−21.2			4.32 (12–13)	4.18 (12.7)	~3.33 (*f*)	3.27 (15.2)
	2	−96.7	−58.7	−38.0			4.33 (14.7)	4.28 (14.0)	3.36 (19.2)	3.40 (16.4)
	3	−118.6	−59.9	−58.7					3.42 (18.7)	3.48 (15.9)
Phosphorothionates	0	−50.2	−72.8	+22.6		3.82 (17.0)	4.34 (13.4)	4.13 (13.7)		
	1	−97.7	−99.3	+1.6		4.08 (13.0)	4.33 (15.0)	4.18 (15.2)	3.41 (19.9)	3.30 (16.6)
	2	−121.3	−112.4	−8.9		4.44 (11–14)	4.29 (17.4)	4.27 (16.0)	3.46 (19.2)	3.48 (17.4)
	3	−107.9	−91.5	−16.4		4.28 (12.7)			3.41 (19.2)	3.49 (17.5)

[a] Change in δ_P upon protonation. [b] Data from ref 1a. [c] Estimated from $(C_2H_5O)_2PH(SH)^+$ (δ_P −64.3). See text. [d] Estimated by comparison with the corresponding phosphorothiolate and thiolothionate. [e] Data on $(C_2H_5O)_2PH(SH)^+$. [f] Not available or could not be determined. [g] Registry no. are, respectively, 24151-48-2, 55649-20-2, 55649-21-3, 55649-22-4, 28180-50-9, 55649-23-5, 55649-24-6, 55649-25-7, 55649-26-8, 55649-27-9, 55649-28-0, 55649-29-1. [h] Registry no. are, respectively, 121-45-9, 20472-57-5, 20472-56-4, 688-62-0, 512-56-1, 6389-81-7, 22082-34-4, 1486-39-1, 152-18-1, 3347-21-5, 22082-28-6, 1642-43-9.

ponent split in this way in actuality consists of the central doublet of an AB quartet (if the ethyl group is considered to be an ABX_3 system, with the phosphorus nucleus causing further first-order splitting).[15] From this point of view, assuming J_{AB} is 10 Hz (as is found in ethyl sulfoxy compounds possessing similar asymmetry),[14b,d] the chemical shift between the A and B protons is no more than 0.053 ppm, and the intensity of the unobserved outer lines of each AB quartet is no more than 6% of the corresponding observed central doublet.[16] The ^1H spectrum of the ethyl group is most accurately analyzed as an ABC_3 system[14b] but no significant error results in obtaining parameters by treating the methylene protons as equivalent.

Precursors were dissolved in excess fluorosulfuric acid to form a homogeneous solution. The ^1H spectra at low temperature (−60 to −80°) indicated, in addition to the presence of solvent fluorosulfuric acid, the stable ions resulting from protonation of the precursors. The tabulated parameters (Table III) of the ions were generally obtained at −60°; the methoxy proton (or, if necessary, the *S*-methylene proton) resonance peaks were used to obtain (by the INDOR method) ^{31}P chemical shifts. The ^{31}P shifts were checked by obtaining them also from INDOR experiments involving peaks due to phosphorus-bound protons or mercapto protons. Parameters involving the mercapto protons (in protonated phosphorothionates) were obtained at −80°, at which temperature splitting due to $^2J_{PSH}$ is better resolved.

All of the phosphorothioites are protonated at phosphorus. The proton bound to phosphorus produces a characteristic widely separated doublet in the ^1H spectrum due to the large one-bond coupling constant, $^1J_{PH}$. $^1J_{PH}$ decreases as ethylthio substituents replace methoxy substituents. Neither the ions nor the precursors show a regular trend in the ^{31}P chemical shifts, but the changes upon protonation are quite significant. The phosphorus nuclei become substantially shielded upon protonation, and such shielding increases with each additional methoxy substituent. The large shielding effect of protonation in trimethyl phosphite was attributed by us earlier[1a] to extensive electron donation by the oxygen atoms to phosphorus. It seems clear that sulfur is less able to effect this, so that the change in the ^{31}P shift upon protonation ($\Delta\delta_P$) is less positive as ethylthio substituents replace methoxy substituents. Nevertheless, even with triethyl phosphorotrithioite, $\Delta\delta_P$ remains large and positive.

Since *S*-ethyl-*O,O*-dimethyl phosphorothioite could not be prepared, an estimate of its ^{31}P shift was based on the known phosphorothiolate and thiolothionate. In order to estimate the ^{31}P shift of the protonated species, the closely related protonated diethyl phosphonothionate was prepared. Estimates of the effect on the ^{31}P shift of replacing the ethoxy groups by methoxy groups, and of replacing the mercapto group by a thioethyl group, were made from observations on $(CH_3O)_2P(SH)_2^+$, $(C_2H_5O)_2P(SH)_2^+$, and $(CH_3O)_2P(SH)SC_2H_5^+$. The magnetic nonequivalence of

the methylene protons observed in diethyl phosphonothionate and *S,S*-diethyl-*O*-methyl phosphorodithioite could not be seen in the corresponding protonated species. Nor was in protonated diethyl phosphonothionate the theoretically possible three-bond H–P–S–H coupling observed.

Protonation of the phosphorothiolates is not directly observable, as is usual with phosphoryl compounds.[1a] However, as arguments have been presented for the protonation of trimethyl phosphate in fluorosulfuric acid solution,[1a] it is expected that ethylthio phosphoryl compounds are also capable of being protonated. Except for trimethyl phosphate, which shows a small positive value, $\Delta\delta_P$ becomes increasingly negative as ethylthio groups replace methoxy groups. This trend indicates that the electron donation to phosphorus by the fully formed phosphoryl bond in the precursors cannot be maintained upon protonation. Again, sulfur is less capable than oxygen of providing such donation in the phosphonium ions.

Protonation of the phosphorothionates can be observed directly at low temperature. The thiophosphoryl sulfur atom is the site of protonation; the two-bond coupling of the donated proton, $^2J_{PSH}$, is distinct. The ^{31}P shifts of the ions compare well with known shifts of related ions: $(CH_3O)_3PSH^+$ (δ_P −50.2) is close to $(CH_3O)_3PSCH_3^+$ (−53.2), and $(C_2H_5S)_3PSH^+$ (−107.9) is in the same region as a value assigned to $P(SC_6H_5)_4^+$ (−121.8).[17] As before, $\Delta\delta_P$ is the quantity which exhibits a regular trend. $\Delta\delta_P$ is substantially positive in the case of trimethyl phosphorothionate, decreasing in value and becoming negative as ethylthio groups replace methoxy groups. With one or two sulfur atoms attached to phosphorus, protonation permits increased electron donation by the remaining oxygen atoms through $p\pi$–$d\pi$ bond formation. With three or four sulfur substituents, there are not enough oxygen substituents to counteract the loss of shielding by the thiophosphoryl sulfur atom (fairly weak compared to an oxygen atom) upon protonation.

An interesting correlation between the protonated phosphorothiolates and the protonated phosphorothionates is that, regardless of whether phosphoryl oxygen or thiophosphoryl sulfur atom protonation is involved, the ^{31}P shifts of the ions are determined largely (within 3 ppm) by the relative numbers of oxygen and sulfur atoms attached to phosphorus. Compare, for example, $(C_2H_5S)_2(CH_3O)POH^+$ (δ_P −96.7) and $(C_2H_5S)(CH_3O)_2PSH^+$ (−97.7). The shifts of the precursors are quite different, of course, since there is a considerable difference in the amount of π bonding in a phosphoryl group as contrasted with a thiophosphoryl group. Protonation of either decreases π bonding. Other phosphorus-bound oxygen and sulfur atoms increase this contribution. Changes in ^{31}P shifts appear to be strongly affected by oxygen's greater tendency toward back-bonding.

Protonated Phosphorothioic Acids. As was pointed out earlier, among the cleavage products observed in solutions of isopropyl phosphorothioates in fluorosulfuric acid are protonated phosphorothioic acid (trihydroxymercaptophosphonium ion) and protonated phosphorodithioic acid (dihydroxydimercaptophosphonium ion). Since data on protonated phosphoric acid were available from our earlier work,[1a] it was desirable to obtain protonated phosphorotrithioic acid and protonated phosphorotetrathioic acid to complete the series of protonated phosphorothioic acids (hydroxymercaptophosphonium ions). These ions are the parent acids of all of the protonated thiophosphates. It was expected that if these ions could be produced in acid solution, the two-bond P–S–H coupling could be utilized to obtain ^{31}P chemical shifts by the INDOR method.

Table IV
^{31}P and ^1H NMR Spectral Parameters of Protonated Phosphorothioic Acids, $(HS)_nP(OH)_{4-n}^+$ (−80°)

		$\delta_{^{31}P}$ (85% H_3PO_4 = 0)		$\delta_{^1H}$, mercapto proton(s) ($^2J_{PSH}$, Hz)
n	Ion	Precursor,[a] $(PS_nO_{4-n})^{3-}$	$\Delta\delta_P$[b]	
0	−2.3[c]	0	−2	
1	−43.0	−32	−11	4.05 (17.2)
2	−83.8	−61	−23	4.59 (14.6)
3	−118.2	−86	−32	4.25 (11.4)

[a] L. Maier and J. R. Van Wazer, *J. Am. Chem. Soc.*, 84, 3054 (1962). Registry no., 29602-99-8; 55660-12-3. [b] Change in δ_P upon protonation. [c] From ref 1a.

The sodium salts of phosphorotrithioic and phosphorotetrathioic acids contain too much water of crystallization ($Na_3POS_3 \cdot 11H_2O$ and $Na_3PS_4 \cdot 8H_2O$)[18] for substantial hydrolysis to be prevented in acid solution. Protonated phosphorotrithioic acid was obtained by preparing tri-*tert*-butyl phosphorotrithiolate and dissolving it in fluorosulfuric acid. Expectedly, considering the nucleophilicity of the sulfur atoms, the trithiolate demonstrated considerable resistance to carbon–sulfur bond cleavage in acid solution. However, allowing the acid solution to stand at room temperature for 20 min resulted in the *tert*-butyl substituents being cleaved to form *tert*-butyl cations (which tend to deprotonate and escape as methylpropene vapor), leaving the desired hydroxytrimercaptophosphonium ion. Its NMR spectral data are included in a summary of protonated phosphorothioic acids (Table IV). Again, the change in the ^{31}P chemical shift upon protonation correlates very well with the number of oxygen and sulfur atoms bonded to phosphorus.

We have so far been unable to prepare tri-*tert*-butyl phosphorotetrathioate[19] in sufficiently pure form so as to obtain the tetramercaptophosphonium ion by similar alkyl group cleavage.

For the protonated thiophosphates and thiophosphites in this paper, the size of the coupling constant $^2J_{PSH}$ (11–17 Hz) permits one to estimate that, below the coalescence temperatures (−10 to −50°), proton exchange in FSO_3H solution takes place less than 25–38 times per second.[20]

Experimental Section

NMR Spectra. ^1H and ^{31}P nuclear magnetic resonance spectroscopic techniques have been earlier described by us.[1a]

Preparation of the Ions. Phosphorus compounds were dissolved in a tenfold molar excess of fluorosulfuric acid whenever possible. Stirring and cooling with a Dry Ice–acetone bath was almost always used to prevent decomposition of the protonated species. The phosphonium ions were kept at low temperature (below −60°), since most of them were observed to react further at room temperature.

Materials. We thank Dr. Alexis A. Oswald (Exxon Research and Engineering Co., Linden, N.J.) for samples of *O,O*-dialkyl hydrogen phosphorodithioates and *O,O*-diethyl hydrogen phosphorothioate. They were vacuum distilled before use. It was found by ^1H and ^{31}P INDOR spectroscopy that the *O,O*-dimethyl hydrogen phosphorodithioate contained an approximately equal amount of trimethyl phosphorothiolothionate which could not be separated by distillation. Triisopropyl phosphorothionate, trimethyl phosphorothionate, and *S,S*-diethyl-*O*-methyl phosphorotrithioate were prepared by refluxing the corresponding phosphite with sulfur in carbon disulfide solution.[21] The preparation of the phosphorothioites was based on the preparation of tertiary phosphites from phosphorus trichloride and the appropriate alcohol in the presence of *N,N*-dimethylaniline.[22] To obtain *S,S*-diethyl-*O*-methyl phosphorodithioite, phosphorus trichloride was first com-

bined with 2 mol of ethanethiol, then with 1 mol of methanol. Similarly, 3 mol of ethanethiol was used to obtain triethyl phosphorotrithioite.[23] However, attempts to make *S*-ethyl-*O,O*-dimethyl phosphorothioite were unsuccessful. Combining phosphorus trichloride with first 2 mol of methanol, then 1 mol of ethanethiol, or in the reverse order, yielded fractions distilling over a wide temperature range (30–81°, 0.02–8.0 mm). The lower boiling fractions consisted primarily of dimethyl phosphonate; higher boiling fractions contained *S*-ethyl-*O,O*-dimethyl phosphorothioate and *S*-ethyl-*O,O*-dimethyl phosphorodithioate. Treating freshly prepared ethyl phosphorodichloridothioite[24] with methanol led to similar results. Diethyl phosphonothionate was prepared by the reaction of distilled commercial diethyl phosphorochloridite with hydrogen sulfide in the presence of pyridine.[25] *S,S*-Diethyl-*O*-methyl phosphorodithioate resulted from air oxidation of the corresponding phosphite. Triethyl phosphorotrithiolate occurred as a high-boiling fraction in the distillation of the corresponding phosphite. Since it was found that sulfur does not add to this phosphite, triethyl phosphorotetrathioate was prepared by reaction of the sodium salt of ethanethiol with thiophosphoryl chloride.[26] Contrary to a statement in the reference, vacuum distillation of the product did not degrade it to triethyl phosphorotrithioite. Preparations of sodium phosphorotrithioate, sodium phosphorotetrathioate, and tri-*tert*-butyl phosphorotetrathioate were referred to earlier.[18,19] Extended refluxing of 2-methyl-2-propanethiol with phosphorus trichloride produced, not tri-*tert*-butyl phosphorotrithioite as has been indicated,[27] but pure tri-*tert*-butyl phosphorotrithiolate (as indicated by its ^{31}P NMR spectrum, particularly the chemical shift). Commercially available fluorosulfuric acid was twice distilled before use in the preparation of solutions.

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Nucleophilic Displacements on Halogen Atoms. V. Reactions of α-Halo Sulfones with Sterically Hindered Nucleophiles

Bruce B. Jarvis* and Bruce A. Marien

Department of Chemistry, University of Maryland, College Park, Maryland 20742

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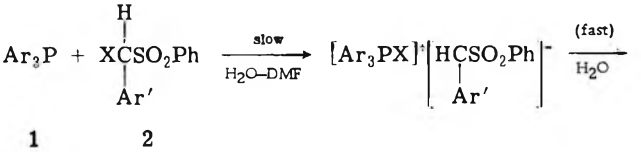
The rates of reaction of α-bromo- and α-iodo-*m*-cyanobenzyl phenyl sulfones (**3**) with a number of sterically hindered phosphines in aqueous DMF are reported. The variation in rates for tris(o-tolyl)phosphine (**4**) and tris(*o*-anisyl)phosphine (**5**) with **3a** is best explained in terms of a steric rather than special electronic effect. The reactions of **3** with *cis*-bis(diphenylphosphino)ethene (**8**) and bis(diphenylphosphino)ethane (**11**) exhibit no unusual characteristics.

The reductions of α-halobenzyl phenyl sulfones by triarylphosphines has been shown to involve nucleophilic attack on the halogen atom (eq 1).[1-3] Hydrolysis of the charged complex yields the phosphine oxide, the reduced sulfone, and a hydrohalic acid.

In these reports it was observed that, contrary to the normal SN2 reaction at carbon atoms, the reactivity decreased in the order α-Br > α-I ≫ α-Cl. The anomalous behavior of the α-iodobenzyl phenyl sulfones was rationalized in terms of the relative strengths of the bonds formed and broken upon entering the transition state.



1 **2**

HX + $Ar_3P{=}O$ $Ar'CH_2SO_2Ph$ (1)

It has been demonstrated that this reaction is strongly dependent upon the electron-withdrawing ability of the parent sulfone.[2] ρ values, determined from the variation of

Table I
Rate Constants for the Reactions of 3a and 3b with Phosphines 4-12 in 90% Aqueous DMF

Sulfone	Phosphine [a]	Temp, °C	$10^3 k_2$, M^{-1} sec^{-1}
3a	4	50.00	0.462 ± 0.018
		61.20	0.905 ± 0.012
		75.00	2.10 ± 0.06
		84.00	3.10 ± 0.08
3a	5	0.00	252 ± 7
		10.00	402 ± 5
		20.00	715 ± 9
		25.00	923 ± 2
3a	6	25.40	66.9 ± 0.4
		37.5	145 ± 5
		50.3	303 ± 8
		58.0	393 ± 6
3a	7	0.00	119 ± 10
		10.00	184 ± 7
		20.00	355 ± 6
		24.30	451 ± 5
3a	8	50.00	0.669 ± 0.004
		66.00	1.72 ± 0.09
		75.00	2.80 ± 0.20
3a	9	20.00	6.31 ± 0.07
		50.00	33.3 ± 0.7
		74.60	109 ± 10
		83.60	148 ± 12
3a	10	20.00	23.2 ± 0.5
		35.00	41.2 ± 0.5
		50.00	69.3 ± 0.9
		67.00	136 ± 8
3a	11	25.60	131 ± 2
		35.00	247 ± 3
		43.60	424 ± 10
		45.00	550 ± 10
3a	12	5.70	760 ± 30
		10.00	1040 ± 30
		14.80	1330 ± 10
		20.00	1820 ± 35
3b	5	10.00	32.8 ± 0.1
		20.00	64.1 ± 0.1
		35.00	219 ± 4
3b	6	43.30	11.2 ± 1.2
		50.00	17.8 ± 1.0
		58.50	30.8 ± 1.3
		60.50	36.0 ± 1.2
3b	7	0.00	6.66 ± 0.14
		20.00	29.1 ± 0.1
		35.00	94.3 ± 0.1
		52.50	318 ± 0.07
3b	8	20.00	0.0966 ± 0.005
		58.55	0.750 ± 0.022
		65.90	1.02 ± 0.20
		71.70	1.30 ± 0.02
3b	9	25.00	0.301 ± 0.01
		47.97	1.63 ± 0.05
		58.55	2.93 ± 0.18
		71.70	6.57 ± 0.26
3b	10	20.00	2.35 ± 0.18
		50.00	11.2 ± 1.0
		67.00	25.7 ± 1.8
3b	11	25.60	7.74 ± 0.20
		35.00	12.0 ± 0.1
		50.00	30.6 ± 0.4
		73.00	128 ± 10
3b	12	14.80	43.6 ± 0.7
		19.10	59.5 ± 1.2
		28.00	130 ± 1.5

[a] Rate of reaction of 3b with 4 was too slow to measure accurately owing to decomposition of 3b at high temperatures (>90°).

reaction rates with changes in the substituents on the benzyl group in the sulfones 2, are (Cl)ρ = +2.33, (Br)ρ = +5.97, and (I)ρ = +6.29. These data indicate a carbanionic transition state with respect to sulfone.

We have also shown,[3] by varying the substituents on the triarylphosphine, that the reaction is quite sensitive to changes in the nucleophile. These ρ values, determined from the changes in the phosphine, are (Cl)ρ = −1.84, (Br)ρ = −3.03, and (I)ρ = −3.30. These data indicate that a large degree of positive charge is present on the phosphorus atom during the transition state and that the phosphorus–halogen bond formation process is very near completion.

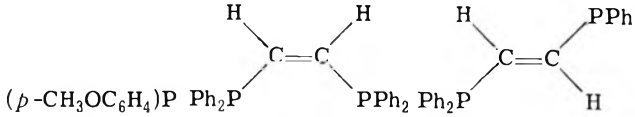
We have examined the rates of reaction of various hindered phosphine nucleophiles with α-halo-*m*-cyanobenzyl phenyl sulfone (3) in search of evidence for the steric requirement for the SN2 displacement by phosphines on halogen atoms. Two types of substituted tertiary phosphines were used in this study: ortho-substituted triarylphosphines (4 and 5) (rates for the para-substituted isomers 6 and 7 also are reported for comparison) and substituted vinyldiphenylphosphines (8–10) (rates for the ethyldiphenylphosphines 11 and 12 also are reported for comparison). The rate data for the reactions of 4–12 with 3a and 3b in 90% aqueous DMF (eq 2) are reported in Tables I and II.

$$m\text{-}CNC_6H_4CHXSO_2Ph + R_3P \xrightarrow{H_2O\text{-}DMF}$$

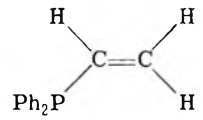
3a, X = Br; b, X = I; 4–12

$$m\text{-}CNC_6H_4CH_2SO_2Ph + R_3P{=}O + HX \quad (2)$$

$(o\text{-}CH_3C_6H_4)_3P$ (4); $(o\text{-}CH_3OC_6H_4)_3P$ (5); $(p\text{-}CH_3C_6H_4)_3P$ (6)



$(p\text{-}CH_3OC_6H_4)P$ (7); Ph_2P PPh_2 (8); Ph_2P PPh_2 (9)



Ph_2P (10); $Ph_2PCH_2CH_2PPH_2$ (11); $Ph_2PCH_2CH_3$ (12)

The most striking feature of Table II is the large difference in rates between 4 (ortho)/6 (para) when compared with the methoxy compounds 5 (ortho)/7 (para). An ortho methyl substituent greatly reduces the rate of reaction when compared to the *p*-methyl compound [$(k_p/k_o)_{CH_3}$ = 810 for the reactions of 6 and 4 with 3a], whereas for the reactions of the methoxyarylphosphines 5 and 7 the k_p/k_o ratio is reversed, i.e., $(k_p/k_o)_{OCH_3} = 0.5$. The ratio $k_{o\text{-}OCH_3}/k_{o\text{-}CH_3}$ for the reactions of 5 and 4 with the α-bromo sulfone 3a is greater than 10^4. These data may be compared with those rates measured for reactions 3–5.

$$XC_6H_4NH_2 + PhCOCl \longrightarrow XC_6H_4NHCOPh \quad \frac{k_{o\text{-}OCH_3}}{k_{o\text{-}CH_3}} = 3.2 \quad (3)^4$$

$$XC_6H_4N(CH_3)_2 + CH_3I \longrightarrow XC_6H_4\overset{+}{N}(CH_3)_3I^- \quad \frac{k_{o\text{-}OCH_3}}{k_{o\text{-}CH_3}} = 60 \quad (4)^5$$

$$(XC_6H_4)_3P + PhCH_2Cl \longrightarrow (XC_6H_4)_3\overset{+}{P}CH_2Ph\ Cl^- \quad \frac{k_{o\text{-}OCH_3}}{k_{o\text{-}CH_3}} = 610 \quad (5)$$

Table II
Rate Constants and Activation Parameters for the Reaction of α-Halo Sulfones 3 with Phosphines 4–12 in 90% Aqueous DMF at 25° [a]

Sulfone	Phosphine	k_2, M^{-1} sec^{-1}	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
3a	4	8.70×10^{-5}	12.2	−36
3a	5	9.06×10^{-1}	9.0	−33
3a	6	6.74×10^{-2}	11.7	-29_4
3a	7	4.53×10^{-1}	8.5	-32_5
3a	8	1.26×10^{-4}	12.2	−35
3a	9	8.55×10^{-3}	9.8	−35
3a	10	2.79×10^{-2}	6.8	−42
3a	11	1.23×10^{-1}	11.1	−25
3a	12	2.41	9.3	-26_6
3b	5	1.02×10^{-1}	12.6	−25
3b	6	2.82×10^{-3}	13.5	−25
3b	7	4.69×10^{-2}	12.4	−23
3b	8	9.59×10^{-5}	10.8	−39
3b	9	3.05×10^{-4}	12.8	-31_6
3b	10	3.11×10^{-3}	9.5	−38
3b	11	6.67×10^{-3}	11.7	-29_6
3b	12	1.01×10^{-1}	13.8	−27

[a] The k_2 at 25° for the reaction of 3a with triphenylphosphine is 2.07×10^{-3} M^{-1} sec^{-1}; the k_2 at 25° for the reaction of 3b with triphenylphosphine is 7.76×10^{-5} M^{-1} sec^{-1}.[2]

The data for eq 5 have been explained in terms of a through space $(2p–3d)_\pi$ overlap of the o-anisyl groups with the incipient phosphonium cation in the transition state.[6] Indeed, if $k_{o\text{-}OCH_3}/k_{o\text{-}CH_3}$ is a measure of such interaction, we are observing an even stronger interaction during the reaction of 5 with the bromo sulfone 3a.[7] However, this interpretation loses force when one compares the $(k_o/k_p)_{OCH_3}$ ratios for reactions 2–5; these ratios vary from 0.3 to 4.[11] The $(k_p/k_o)_{CH_3}$ ratios for reactions 3–5 are 11, 61, and 80, respectively. The small variation in $(k_o/k_p)_{OCH_3}$ for reactions 2–5 seems inconsistent with a special electronic effect on an o-methoxy group, i.e., if $(2p–3d)_\pi$ overlap is important,[10] then it seems most unlikely that this effect through bonds (viz., p-OCH_3) would parallel the effect through space (viz., o-OCH_3) for a series of such divergent reactions as 2–5.

Charton[12] maintains that the differences in the behavior of ortho substituents (other than H or very large groups such as *tert*-butyl) in the reactions of ortho-substituted arenes are due principally to electronic rather than steric factors, although some reactions do appear to be strongly influenced by the size of the ortho groups.[13] Steric influences likely may be involved for reactions 2 and 5. Certainly, in going from reaction 3 to reaction 5, the steric requirements are increasing in the transition states;[14] however, the steric requirements for a displacement reaction on a univalent bromine atom are not easy to assess relative to reactions at a tetrahedral carbon atom.[15] The transition state for reaction 2 lies very far toward bond making and bond breaking as shown by the large Hammett ρ values.[2,3] This means that the P–Br bond is nearly formed in the transition state, and the geometry of the activated complex is close to that of a halotriarylphosphonium cation in which the Ar–P–Ar bond angle is ca. 110°.[18] At first glance, this would seem to result in a reduction of back strain, since the Ar–P–Ar bond angle in tris(o-tolyl)phosphine is only 102.5°.[19] However, from crystal structure work and NMR studies in solution, there is known to be significantly more crowding in tris(o-tolyl)phosphine selenide (Ar–P–Ar bond angles of 107°) than in either the corresponding phosphine or phosphine oxide.[19] This crowding appears to be due to an unfavorable steric interaction between the o-methyl groups and the large selenium atom. Since bromine and selenium atoms are nearly the same size, one might expect a similar unfavorable effect in the transition state for reaction 2 in the case of tris(o-tolyl)phosphine. This effect would be greatly diminished for tris(o-anisyl)phosphine, since the methoxy group is effectively considerably smaller than a methyl group.[20]

The reactions of the vinyldiphenylphosphines with the α-bromo sulfone **3a** and the α-iodo sulfone **3b** show expected behavior with no special effect noted for those phosphines 8 and 11 in which a second phosphino group could have assisted in the transition state.[23] The difference in reactivity between *cis*-**8** and *trans*-**9** is probably steric in origin whereas the difference in reactivity of **9**, **10**, **11**, and **12** is electronic.

Experimental Section

Kinetic measurements were taken in 90% DMF–H_2O. Distilled deionized water was used. Reagent grade dimethylformamide was twice distilled from P_2O_5 and stored under nitrogen. Separate solutions of phosphine and sulfone were placed in a constant-temperature bath and allowed to equilibrate for 30 min. The solutions were mixed in a Freas conductivity cell which was thermostated in the same constant-temperature bath. Conductance readings were taken at various intervals with a Barnstead conductivity bridge, Model PM-70CB. The rate constants were obtained by plotting log $(C_\infty - C_t)$ vs. time, where C is the conductance reading in mhos. The second-order rate constants were obtained by dividing the pseudo-first-order rate constants by the concentrations of the phosphine. The phosphine concentrations were 0.10–0.20 M and the sulfone concentration was 0.0010 M.

All the phosphines used in this study have been prepared previously. The observed physical and spectral data agreed well with those reported in the literature. Triarylphosphines[25] were prepared from an excess of the appropriate aryl Grignard reagent with phosphorus trichloride and recrystallized from ethanol under nitrogen. *cis*- and *trans*-1,2-bis(diphenylphosphino)ethene and 1,2-bis(diphenylphosphino)ethane were prepared from the appropriate alkyl chloride and lithium diphenylphosphide according to the method of Aguiar.[26] The remaining alkyldiphenylphosphines were prepared via Grignard reaction with diphenylchlorophosphine.[27]

The preparation of the α-halobenzyl phenyl sulfones **3a** and **3b** have been described previously.[2] The reactions of **3a** and **3b** with phosphines 4–12 give the reduced sulfone, *m*-cyanobenzyl phenyl sulfone, in >90% yield.

Acknowledgment. Support from the University of Maryland Computer Science Center is gratefully acknowledged.

Registry No.—**3a**, 41037-82-5; **3b**, 41037-87-0; **4**, 6163-58-2; **5**, 4731-65-1; **6**, 1038-95-5; **7**, 855-38-9; **8**, 983-80-2; **9**, 983-81-3; **10**, 2155-96-6; **11**, 1663-45-2; **12**, 607-01-2.

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Ion Radicals. XXXIII. Reactions of 10-Methyl- and 10-Phenylphenothiazine Cation Radicals with Ammonia and Amines. Preparation and Reactions of 5-(*N*-Alkyl)sulfilimines and 5-(*N,N*-Dialkylamino)sulfonium Salts[1]

Baldev K. Bandlish,[2] A. Greg Padilla,[3] and Henry J. Shine*

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

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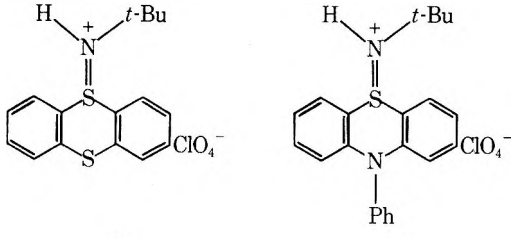
10-Phenyl- (**7**) and 10-methylphenothiazine cation radical perchlorate (**8**) reacted readily with primary alkyl amines in acetonitrile solution to form N-protonated *N*-alkylsulfilimine perchlorates, and the parent heterocycle was also formed. Reaction of **7** and **8** with dialkylamines gave *N,N*-dialkylsulfilimine perchlorates. Tertiary amines led to reduction of the cation radicals; with ammonia, dimeric products were formed. 5-(*tert*-Butylimino)-5,5-dihydro-10-methylphenothiazine perchlorate with perchloric acid gave 10-methylphenothiazine cation radical; with HCl, formation of the cation radical was followed by reduction and chlorination.

Although *N*-arylsulfilimines have been known since 1968,[4-10] *N*-alkylsulfilimines were unknown until very recently. Franz and Martin reported in 1973 that the reaction of diphenyl(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propoxy)sulfurane [**1**, $R_F = C(CF_3)_2Ph$] with primary amides gave *N*-aryl- and *N*-alkylidiphenylsulfilimines (**2**, eq 1).[8] Subsequently, Shine and Kim[11] reported that the cation radicals of thianthrene and 10-phenylphenothiazine reacted with *tert*-butylamine to give the perchlorates **3** and **4**, respectively, which were easily deprotonated to give the corresponding *N*-*tert*-butylsulfilimines. Also, dimethylamine reacted with thianthrene cation radical perchlorate to give **5**. At that time the curious reaction was also discovered in which not only ammonia but also methyl-, ethyl-, propyl-, and cyclohexylamine reacted with thianthrene cation radical perchlorate to give the dimeric product **6a**. It appeared at that time, therefore, that the preparation of *N*-alkylsulfilimines by reaction of organosulfur cation radicals with alkylamines would not be a viable reaction. We now show that this is not so. Most recently, Franz and Martin have reported that sulfuranes such as **1** react with primary aryl- and alkylamines to give *N*-aryl- and *N*-alkylsulfilimines (**2**).[12]

$$Ph_2S(OR_F)_2 + PhCONHR \longrightarrow \underset{1}{} \quad Ph_2S{=}NR + PhCO_2R_F + R_FOH \quad (1)$$
$$\underset{2}{}$$



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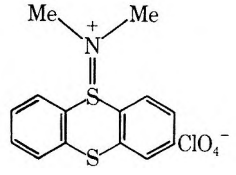

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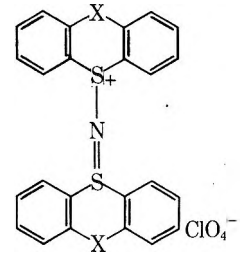


6a, X = S
b, X = *N*-Ph
c, X = *N*-Me

Results and Discussion

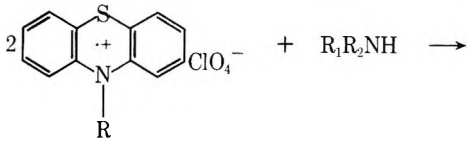
Preparation of Sulfilimines. We have found that, in contrast with thianthrene cation radical perchlorate, 10-phenyl- (**7**) and 10-methylphenothiazine cation radical perchlorate (**8**) react with a variety of simple primary alkylamines to give *N*-alkylsulfilimines. Reaction with dialkylamines gives products corresponding with **5**, i.e., *N,N*-dialkylaminosulfonium salts, while reaction with tertiary amines causes reduction to the parent compounds. Reaction with primary and secondary amines was carried out in acetonitrile solution and was rapid. Not only was the sulfilimine-

Table I
Yields[a] of Products of Reactions of 7 and 8 with Amines According to Equation 2

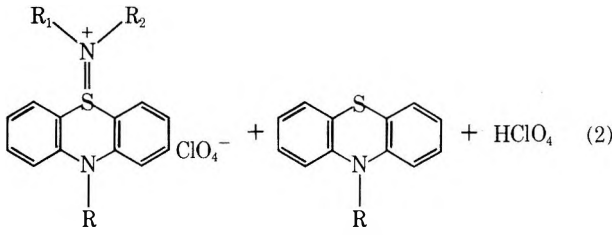
Code	R_1	R_2	% 9	% 11	Mp of 9, °C	% 10	% 12	Mp of 10, °C
a	H	Me	30[b]	52	148–150	29	58	134–136
b	H	Et	25[c]	53	140–141			
c	H	Pr	38[b]	60	153–154	22	65	143–145
d	H	*t*-Bu	*d*	*d*		11	80	163–165
e	H	C_6H_{11}	32[c]	55	167–169	*f*	62	*f*
f	H	$C_6H_5CH_2$	43[b]	52	148–149	25	60	127–129
g	Me	Me	36[b]	66	145–146	23	63	139–140
h	Et	Et	14[c]	78	150–151	0	89	
i	*i*-Pr	*i*-Pr	28[b,e]	65	*e*	18	72	150–151
j	$C_6H_5CH_2$	$C_6H_5CH_2$	27[b]	60	160	*g*		
k	$-(CH_2)_3-$		39[c]	57	155–160	39	61	136–137
l	$-(CH_2)_4-$		28[b]	67	139–140	24	77	139–140
m	$-(CH_2)_5-$		40[c]	50	157–158	28	65	146–147

[a] According to the stoichiometry of eq 2, quantitative conversion of 7 would give 50% of 9 and 50% of 11. A yield of 11 larger than 50% means that some reduction of 7 occurred. The same applies to the conversion of 8 into 10 and 12. [b] Work-up procedure A. [c] Work-up procedure B. [d] See ref 5. [e] Product could not be crystallized and was identified spectroscopically. [f] Product could not be crystallized. [g] Separation of products could not be achieved.

type product formed, but the parent heterocycle, too. The generalized stoichiometry is given in eq 2, although the



7, R = Ph
8, R = Me



9, R = Ph
10, R = Me

11, R = Ph
12, R = Me

(2)

yield of parent heterocycle (i.e., 11 or 12) obtained showed that in some cases reduction of the cation radical was a competing reaction. This is particularly noticeable in reactions with dialkylamines. For example, with diethylamine in the preparation of **9h** (see Table I), 78% of the cation radical 7 was converted into 10-phenylphenothiazine. Similarly, none of **10h** was obtained from reaction of 8 with diethylamine, the cation radical being reduced almost entirely (89%) to 10-methylphenothiazine.

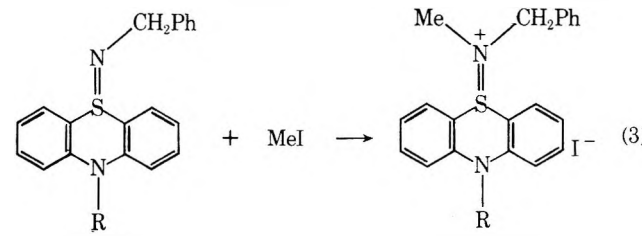
All of the sulfilimines listed in Table I were isolated as perchlorates. Properties of these products are given in Table II (supplementary material). Elemental analyses agreed with anticipated values and are given in Table III (supplementary material). Insofar as those compounds in which R_1 = H are concerned, their isolation indicates that the parent *N*-alkylsulfilimines are readily formed and are reasonably strong bases. All perchlorates were readily isolable and crystallizable except **9i** (from 7 and diisopropylamine), **10e** (from 8 and cyclohexylamine), and **10j** (from 8 and dibenzylamine). Reaction of 8 with ethylamine was not attempted. It should be noted that the maximum conversion of cation radicals into compounds **9** and **10**, according to eq 2, would be 50%, so that the data given in Table I show yields of 22–86% of theory. Yields of **9** were better than those of **10**.

Reaction of trimethylamine and triethylamine with **7** caused respectively 92 and 79% reduction to 10-phenylphenothiazine, while reaction of trimethylamine with **8** caused 85% to be reduced to 10-methylphenothiazine. Search for the products of oxidation of the amines was not made.

Reactions of 7 and 8 with ammonia were also carried out and gave **6b** (X = *N*-Ph, mp 192–193°, 76% yield) and **6c** (X = *N*-Me, mp 153–154°, 82% yield).

Reactions of Compounds 9 and 10 with Sodium Hydroxide. The protonated sulfilimines, i.e., **9a–f** and **10a–f**, were easily deprotonated by treatment with aqueous sodium hydroxide in methanol, giving parent *N*-alkylsulfilimines. Thus **9f** gave 88% of 5-(benzyliminio)-5,5-dihydro-10-phenylphenothiazine (**13**), mp 142–143°. The deprotonation of **9d** was reported earlier.[5] The 10-methyl analog (**14**) of **13** was prepared similarly (but not isolated) for methylation (see later). In contrast with deprotonation of *N*-alkylsulfilimine salts, *N,N*-dialkyl salts, i.e., **9g–m** and **10g–m**, were hydrolyzed by sodium hydroxide, giving respectively 10-phenyl- and 10-methylphenothiazine 5-oxide. Thus, **9m** gave 98% of the former, and **10m** gave 91% of the latter.

Methylation of *N*-Alkylsulfilimines. Addition of methyl iodide to a solution of **13** in ether gave immediately a precipitate of 5-(benzylmethyliminio)-5,5-dihydro-10-phenylphenothiazine iodide (**15**) in 96% yield (eq 3). Methylation of **14** in methylene chloride gave 77% of the 10-methyl analog (**16**). Thus, this type of reaction allows the conversion of *N*-alkylsulfilimines into unsymmetrical *N,N*-dialkylaminosulfonium salts. Similar reactions were reported by Franz and Martin with *N*-alkyldiphenyl sulfilimines.[12] By exchange of anions a large variety of both symmetrical and unsymmetrical salts can be made, as illustrated below.



13, R = Ph
14, R = Me

15, R = Ph
16, R = Me

(3)

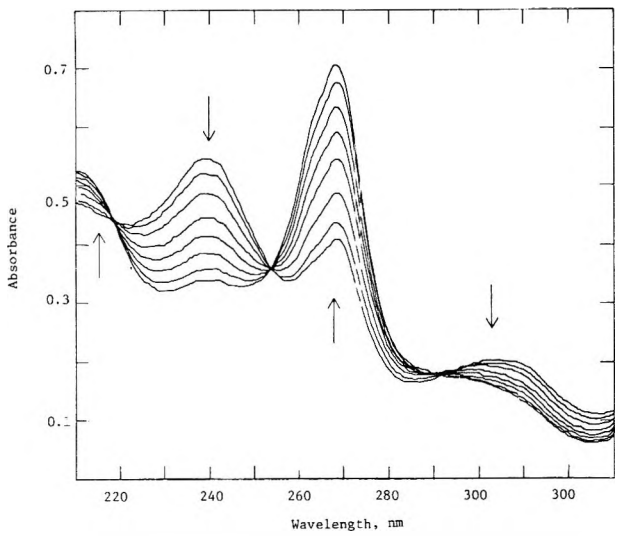
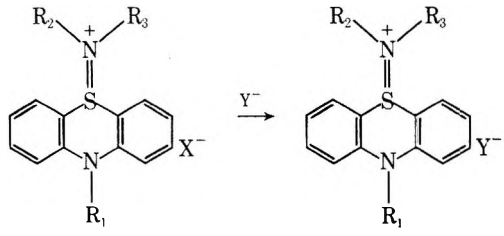


Figure 1. Changes in the spectrum of a 1.58×10^{-5} *M* solution of 5-(diisopropyliminio)-5,5-dihydro-10-methylphenothiazine perchlorate (**10i**) in acetonitrile which was 4.9×10^{-2} *M* in perchloric acid. The eight tracings were recorded at 1, 3, 10, 17, 25, 30, 37, and 44 min after adding the acid, and show the disappearance of protonated **10i** at 240 nm and the appearance of the 10-methylphenothiazine cation radical at 269 nm. Isosbestic points occur at 219, 254, and 292 nm.

Table IV
Exchange of Anions According to Equation 4

Compd	X	R_1	R_2	R_3	Y	Compd
9f	ClO_4	Ph	H	$C_6H_5CH_2$	I	17
10m	ClO_4	Me		$-(CH_2)_5-$	I	18
16	I	Me	Me	$C_6H_5CH_2$	ClO_4	10n
16	I	Me	Me	$C_6H_5CH_2$	NO_3	20

Exchange of Anions in Sulfilimine Salts. Reaction of **9m** and **10m** with excess of potassium iodide in methanol solution gave the corresponding iodides **17** (94%) and **18** (86%). Conversion of an iodide into a perchlorate (**16** into **10n**) was carried out with silver perchlorate, while treatment of **16** with silver nitrate gave the corresponding nitrate (**20**) (eq 4 and Table IV).



(4)

Reactions of Compounds 9 and 10 with Acids. Kim and Shine found that addition of a small amount of concentrated hydrochloric acid to a solution of **3** in acetonitrile led to the quantitative formation of thianthrene.[11] Recently, Franz and Martin applied this reaction to *N*-alkyldiphenyl sulfilimines and observed the formation of diphenyl sulfide and chlorodiphenyl sulfides.[12] Reactions of acids with *N*-alkyl- and *N,N*-dialkylsulfilimines in the phenothiazine series is not as straightforward as the previous findings might lead us to believe, however. We have isolated the products of reaction of **9f** and **10d** with hydrochloric acid, and of **9f** and **10m** with hydriodic acid, and we have followed spectroscopically the reactions of some of these compounds with hydrochloric acid (**9c, 10d, 10i,** and **10m**) and perchloric acid (**10i**). Illustrations of spectroscopic changes which occur are given for **10i** with perchloric acid (Figure 1) and for **10d** with hydrochloric acid (Figure 2).

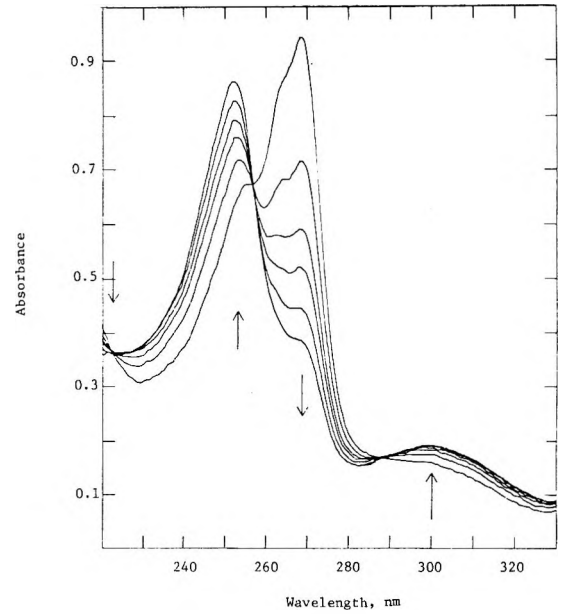
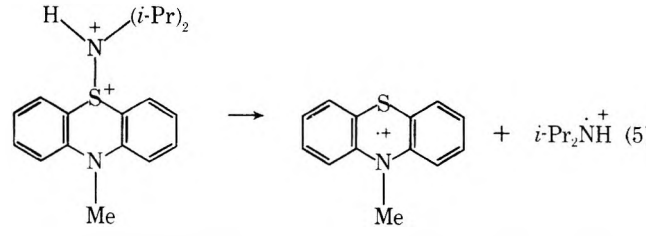


Figure 2. Changes in the spectrum of a 2.5×10^{-5} *M* solution of 5-(*tert*-butyliminio)-5,5-dihydro-10-methylphenothiazine perchlorate in acetonitrile which was 2.8×10^{-2} *M* in hydrochloric acid. The six tracings were recorded at 1, 3.5, 6.5, 10, 15, and 28 min after adding the acid, and show the disappearance of the 10-methylphenothiazine cation radical (formed immediately on adding the acid) at 269 nm and the appearance of a product peak at 252 nm. Isosbestic points occur at 223, 257, and 287 nm.

All reactions with acids were carried out in acetonitrile solution.

Reaction of **9f** with hydrochloric acid gave 19% of 10-phenylphenothiazine, 55% of 3-chloro-10-phenylphenothiazine, and a small amount (11%) of 3,7-dichloro-10-phenylphenothiazine. Reaction of **10d** with hydrochloric acid gave 23% of 10-methylphenothiazine, 65% of 3-chloro-10-methylphenothiazine, and also a small amount (not determined) of the 3,7-dichloro compound. Separation of the products was troublesome and was achieved only with TLC, for which purpose a large number of plates, each streaked with about 4 mg of product mixture, was used.

The complexity of the reactions with acids was revealed when they were followed spectroscopically. Reaction with perchloric acid is illustrated with **10i** in acetonitrile which was 4.9×10^{-2} *M* in acid (Figure 1). Here one sees the disappearance of protonated **10i** at 240 nm and the appearance of the 10-methylphenothiazine cation radical at 269 nm. Three isosbestic points are to be seen, indicating that a simple transformation is occurring. The behavior of **10i** is very much like the behavior of 10-methylphenothiazine 5-oxide and analogous 5-oxides in acid solutions,[13,14] and suggests that protonated **10i** is undergoing homolytic cleavage (eq 5). We do not have, as yet, confirming evidence for

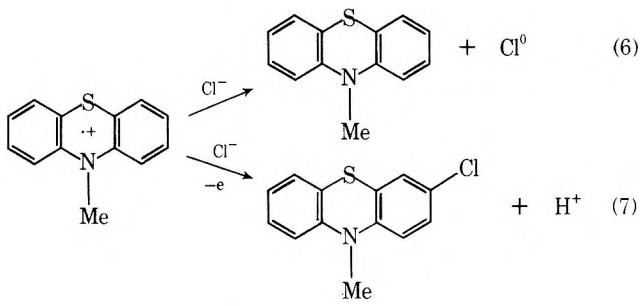


(5)

the formation of the second cation radical, that of diisopropylamine.

Reaction with hydrochloric acid in concentrations near 10^{-2} *M*, in each of the four cases investigated so far (**9c, 10d, 10i, 10m**), led first, rapidly, to the appearance of the parent cation radical. This was followed by the slower dis-

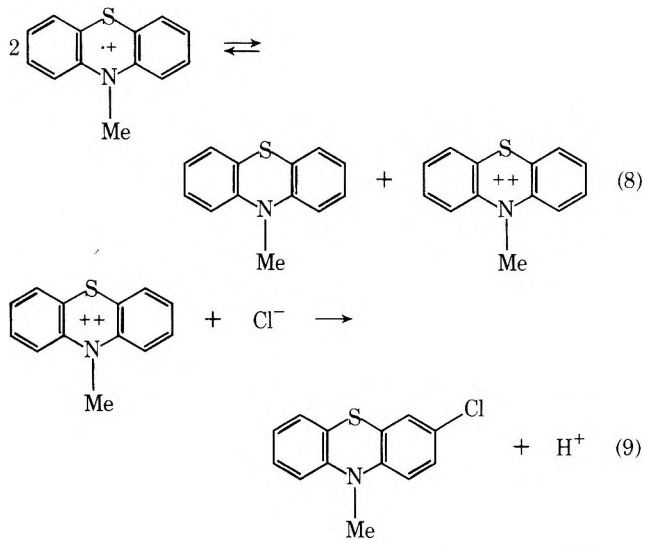
appearance of the cation radical. By adjustment of acid concentration it was possible in some instances to record the rapid rise in concentration of the cation radical before its slower fall. An example of the disappearance of the cation radical, once it had been formed, is given in Figure 2 for the reaction of **10d** in acetonitrile which was 2.8×10^{-2} *M* in acid. Here one sees the disappearance of the 10-methylphenothiazine cation radical at 269 nm and the appearance of a peak at a wavelength approaching 252 nm. (The maximum moves from 254 nm to 252 nm over the run, reflecting the influence of the cation radical's absorbance at 256 nm.) Again, isosbestic points are observed (at 223, 257, and 287 nm), indicating that the transformation of the cation radical into product(s) is direct. This presents a problem at the present time which will require further experimental analysis. That is, the two major products of reaction of **10d** with hydrochloric acid were 10-methyl- and 3-chloro-10-methylphenothiazine. These have very similar absorption spectra, i.e., respectively λ_{max} ($10^{-4}\epsilon$) 250 (3.83), 302 (0.533) and 253 (3.92), 306 (0.529). These data and the changes in Figure 2 suggest that both 10-methyl- and 3-chloro-10-methylphenothiazine are being formed directly from the cation radical, as illustrated in eq 6 and 7. A problem with this interpretation is that some 3,7-dichloro-10-methylphenothiazine was also obtained from **10d**, and some 3,7-dichloro-10-phenylphenothiazine was obtained from **9f**. In contrast, reaction of 10-methylphenothiazine cation radical directly with hydrochloric acid in acetonitrile gave only 10-methyl- and 3-chloro-10-methylphenothiazine. None of the 3,7-dichloro compound was detectable by TLC. Similar results were obtained with 10-phenylphenothiazine cation radical.



+ Cl^0 (6)

+ H^+ (7)

It is possible, therefore, that eq 6 and 7 do not represent correctly the reaction of the cation radicals with chloride ion, but that this involves disproportionation (eq 8 and 9).



(8)

+ H^+ (9)

To satisfy Figure 2, the disproportionation equilibrium would have to be very small and rapidly reached. The difference in reactions of, say, **10d** and 10-methylphenothiazine cation radical with hydrochloric acid (that is, formation of 3,7-dichloro-10-methylphenothiazine from **10d**) might then lie in the involvement of the alkylamine cation radical (t-$BuNH_2{\cdot}^+$, which may be formed from **10d**) with chloride ion (eq 10).

$$RNH_2{\cdot}^+ + Cl^- \rightarrow RNH_2 + Cl^0 \quad (10)$$

Chlorine so formed would be available to chlorinate 10-methyl- and 3-chloro-10-methylphenothiazine.

The reaction of hydrochloric acid with *N*-alkyldiphenyl sulfilimines is represented by Franz and Martin[12] as involving the stepwise formation of diphenyl sulfide dichloride, which dissociates into diphenyl sulfide and chlorine. The chlorine then is available to cause nuclear chlorinations of the diphenyl sulfide (eq 11–13). Analogous proposals are to be found in the literature for the reactions of sulfoxides with hydrogen chloride (e.g., in the racemization of optically active sulfoxides[15]). Our present results show that the reactions of sulfilimines with HCl must follow other paths besides this, and that common features are to be seen[13,14] in the reactions of sulfilimines and sulfoxides with acids.

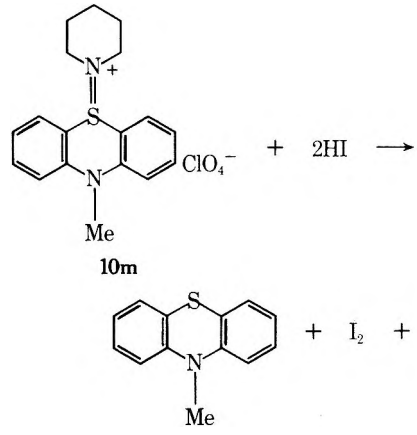
$$Ph_2S{=}NR + HCl \rightarrow \rightarrow Ph_2SCl_2 + RN^+H_3Cl \quad (11)$$

$$Ph_2SCl_2 \rightleftarrows Ph_2S + Cl_2 \quad (12)$$

$$Ph_2S + Cl_2 \rightarrow ClC_6H_4SPh + HCl \quad (13)$$

Certainly, the reactions of sulfilimines in the phenothiazine and related series with acids have unanticipated complexities and merit further study. Our results are reported here in a preliminary way to give some measure of the scope of these reactions which is not apparent from the earlier reports.[11,12]

It is not surprising that hydriodic acid reduces the sulfilimines. Reaction with **10m** gave 93% of 10-methylphenothiazine and 95% of iodine based on the stoichiometry of eq 14. The fate of the piperidine group was not pursued. Reaction of iodide ion alone (as potassium iodide) with **10m** did not cause reduction, but gave 88% of **18**. Similarly, **9f** with hydriodic acid gave 99% of 10-phenylphenothiazine, and **9m** with potassium iodide gave only the iodide salt of **17** in 94% yield. The data can be accommodated with homolytic cleavage of protonated salt (e.g., protonated **10m**) followed by reduction of the two cation radicals (e.g., of 10-methylphenothiazine and piperidine) by iodide ion.



+ 2HI ⟶

+ I_2 + $HClO_4$ + ? (14)

We recognize also, though, that reduction by hydrogen iodide could take place as in eq 11–13. Dimethyl sulfilimine,[16] its *N*-arylsulfonyl derivatives, and the *N*-arylsulfonyl derivatives of diethyl sulfilimine[17] have been reduced with sodium iodide in aqueous perchloric acid, and the kinetics of reduction have been explained[17] by steps analogous to those in these equations. At the same time, these

dialkyl sulfilimines were stable toward perchloric acid alone and were not reduced by sodium chloride and bromide in perchloric acid.[17] Thus, the behavior of our sulfilimines is different from that of the dialkyl ones in these respects, so that reduction of ours by hydrogen iodide may indeed follow the unusual, cation radical pathway.

Analogously, reaction of some of our sulfilimine perchlorate salts with hydrobromic acid led immediately to the formation of bromine, but we have not given further attention to these reactions yet. We hope to do so, and to report on these hydrogen halide reactions in more detail later.

Experimental Section

10-Phenyl- and 10-methylphenothiazine were commercial samples and were recrystallized before use. 10-Phenylphenothiazine cation radical perchlorate (7) was prepared as follows. To a stirred solution of 1.65 g (6 mmol) of *N*-phenylphenothiazine and 1.26 g (5.8 mmol) of $AgClO_4$ in 8 ml of dry MeCN and 25 ml of dry CH_2Cl_2 was added 1.02 g (8 mmol) of solid I_2. The mixture was filtered after being stirred for 1 hr, and 7 was obtained by adding dry ether to the filtrate. The precipitate of 7 (2.1 g, 5.6 mmol, 93%) was filtered on glass-fiber paper and washed with ether. Its purity was determined by reaction with KI and potentiometric titration of the liberated I_2. Routinely, assays of 96–98% cation radical were obtained. 10-Methylphenothiazine cation radical perchlorate (8) was prepared by reaction of 3.45 g (15 mmol) of 10-methylphenothiazine 5-oxide and 3.21 g (15 mmol) of 10-methylphenothiazine in 35 ml of 70% $HClO_4$. After 5 min 150 ml of dry acetone and 500 ml of dry ether were added in sequence. The precipitate of 8.27 g (26.4 mmol, 88%) of 8 was filtered on glass-fiber paper and washed with dry ethyl acetate. Iodimetric analysis gave an assay of 92% cation radical. The preparation of 8 by oxidizing 10-methylphenothiazine with I_2–$AgClO_4$ in ethanol has been reported recently,[18] and analysis of the product indicated that it was a monohydrate. If the 8 isolated by us is the hydrate, its cation radical content would be 97%. All yields of products of reactions of 8, however, were calculated on the basis of 92% cation radical content.

Acetonitrile was Eastman anhydrous grade (0.01% water) and was stored over molecular sieve in a septum-capped bottle. Thick layer chromatography was performed with Merck silica gel GF254. Commercial amines and ammonia gas were used without further purification.

Reactions of 7 and 8 with Amines and Ammonia. To a solution of 7 or 8 in 5 ml of acetonitrile was added an excess of the reactant. In the case of gaseous amines and ammonia, the gas was bubbled into the acetonitrile solution. Reactions appeared to be over within 1 min, but the reaction mixture was stirred for about 30 min before being worked up.

Work-Up Procedure A. The reaction mixture was extracted with 5 × 50 ml of petroleum ether (bp 30–60°) to remove the 10-substituted phenothiazine and its 5-oxide. The petroleum ether solution was concentrated and chromatographed on silica gel plates with ether as the developer. The acetonitrile solution was diluted with methylene chloride, and this solution was washed with 3 × 100 ml of water, dried, and concentrated to give the crude sulfilimine perchlorate (9 or 10) which was crystallized from methylene chloride–pentane.

Work-Up Procedure B. The reaction mixture was streaked on TLC plates and chromatographed using as developer ether for reactions of 7 and carbon tetrachloride for reactions of 8. The sulfilimine and ammonium perchlorates remained as one band at the origin from which they were removed with methylene chloride and washed with water. The crude sulfilimine perchlorate was crystallized as above.

Reactions of Sulfilimines 9 and 10 with Acids. A. Spectroscopic Changes. Three milliliters of a solution of the sulfilimine (**9c, 10d, 10i, 10m**) of known concentration was placed in a cuvette and to this was added a small amount of acid. A measured volume (0.02–0.05 ml) of standardized aqueous acid was added from a microburet and the final concentration of acid in the acetonitrile solution was calculated. Recording of spectra was begun immediately after the glass-stoppered cuvette was shaken for mixing, and was continued at timed intervals. A Beckman DK-2A spectrophotometer was used.

B. Reaction of 9f with HCl. Products. To a solution of 217 mg (0.519 mmol) of **9f** in 10 ml of acetonitrile was added 1 ml of concentrated HCl. An immediate development of purple-brown color occurred. The mixture was stirred for 4 days, quenched with aqueous Na_2CO_3 solution, dried over K_2CO_3, and evaporated to give 205 mg of solid residue. The residue was separated by TLC, for which purpose about 4 mg at a time was streaked on a plate and developed with CCl_4. Three bands were obtained on each plate, and these were removed and extracted with acetone. The lowest band consisted of 10-phenylphenothiazine (35 mg, 0.127 mmol, 19% of the **9f** used), mp 92° after crystallization from aqueous ethanol. The second band consisted of 3-chloro-10-phenylphenothiazine (89 mg, 0.29 mmol, 55%), mp 82–83° (aqueous ethanol) (lit. mp 76–77°),[19] λ_{max} (MeCN) 255 nm (ϵ 5.04 × 10^4) and 320 (4.30 × 10^3). The uppermost band which overlapped the top of the second band gave 20 mg of a semisolid product which we believe to be 3,7-dichloro-10-phenylphenothiazine, mp 110–112.5° (from ethanol–water), with satisfactory mass spectrum. Yield of crude product was 11%.

C. Reaction of 10d with HCl. Products. A similar procedure was used with 103 mg (0.269 mmol) of **10d.** TLC of the residue (total 70 mg) gave again three bands, the lowest of which gave 13 mg (0.061 mmol, 23% of the **10d** used) of 10-methylphenothiazine, mp 97–99° (from ethanol–water). The second band gave 43.5 mg (0.176 mmol, 65%) of 3-chloro-10-methylphenothiazine, mp 112–113° (from ethanol) (lit. mp 110–112°),[20] λ_{max} (MeCN) 253 nm (ϵ 3.92 × 10^4), 306 (5.29 × 10^3). The uppermost band, which overlapped the top of the second, gave 6 mg of an unidentified product, believed from mass spectrum to be 3,7-dichloro-10-methylphenothiazine.

D. Reaction of 10m with HI. Products. To a solution of 14.2 mg (0.0355 mmol) of **10m** in 15 ml of MeCN was added 4 drops of concentrated HI. The solution immediately turned yellow. Twenty milliliters of water was added, and the iodine in the aqueous solution was titrated potentiometrically with $Na_2S_2O_3$ solution, giving 0.0338 mmol (95%) of I_2.

A second reaction was carried out using 52.9 mg (0.131 mmol) of **10m** in 20 ml of MeCN and 0.5 ml of concentrated HI in 0.2 ml of water. The iodine was reduced with aqueous $Na_2S_2O_3$ and the solution was extracted with petroleum ether, giving, after drying over $MgSO_4$, 26 mg (0.122 mmol, 93%) of 10-methylphenothiazine, mp 98–100°.

E. Reaction of 9f with HI. Product. To a solution of 102 mg 0.212 mmol) of **9f** in 5 ml of MeCN was added 1 ml of concentrated HI. Iodine was formed but not assayed. Work-up (extraction with ether) gave 59 mg (0.212 mmol, 100%) of 10-phenylphenothiazine, mp 93–94°.

Reactions of Sulfilimine Salts with NaOH. A. Formation of 5-(Benzyliminio)-5,5-dihydro-10-phenylphenothiazine (13) from 9f. A solution of 276 mg (0.56 mmol) of **9f** in 20 ml of MeOH was stirred for 2 hr with a few drops of 50% aqueous NaOH. After concentration at room temperature water was added and the precipitated solid was taken up in ether to give 188 mg (0.495 mmol, 88%) of **13**: mp 146–147° (from ether); λ_{max} (MeCN) 207 nm (10^{-4} ϵ 5.19), 254 (1.71), 275 (1.58), 304 (0.86), and 335 (0.77); ^{1}H NMR ($CDCl_3$) δ 8.5–6.3 (m, 18 H, aromatic) and 3.45 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_{25}H_{20}N_2S$: C, 78.9; H, 5.29; N, 7.36. Found: C, 79.0; H, 5.41; N, 7.36.

B. Hydrolysis of 9m to 10-Phenylphenothiazine 5-Oxide. Treatment of 85 mg (0.183 mmol) of **9m** as above gave 52 mg (0.179 mmol, 98%) of 10-phenylphenothiazine 5-oxide, mp 171–172° (lit. mp 172–173°).[21]

C. Hydrolysis of 10m. Formation of 10-Methylphenothiazine 5-Oxide. A solution of 103 mg (0.260 mmol) of **10m** in 25 ml of EtOH and 1 ml of 50% NaOH was boiled for 24 hr. Dilution with water and extraction with CH_2Cl_2 gave 54.2 mg (0.236 mmol, 91%) of 10-methylphenothiazine 5-oxide, mp 192–194° (lit. mp 194–196°).[13]

Methylation of *N*-Benzylsulfilimines. A. Formation of 5-(Benzylmethyliminio)-5,5-dihydro-10-phenylphenothiazine Iodide (15) from 13. To a solution of 300 mg (0.79 mmol) of **13** in 25 ml of dry ether was added several milliliters of MeI. The immediately formed white precipitate was removed and washed with ether, giving 401 mg (0.77 mmol, 96%) of **15**: mp 149–150° (from CH_2Cl_2–ether); λ_{max} (MeCN) 347 nm (10^{-3} ϵ 9.3), 308 (9.7), and 243 (42.7); ^{1}H NMR ($CDCl_3$) δ 8.4–8.16 (m, 2 H, aromatic), 7.9–7.0 (m, 14 H, aromatic), 6.83–6.6 (m, 2 H, aromatic), 4.4 (s, 2 H, NCH_2-), 2.45 (s, 3 H, *N*-Me).

Anal. Calcd for $C_{26}H_{23}N_2SI$: C, 59.8; H, 4.43; I, 24.3. Found: C, 59.6; H, 4.52; I, 24.1.

B. Formation of 5-(Benzylmethyliminio)-5,5-dihydro-10-methylphenothiazine Iodide (16) from 10f. To a solution of 563 mg (1.34 mmol) of **10f** in 30 ml of MeOH was added 1 ml of 50% NaOH. After adding 30 ml of water the solution was extracted with

CCl_4, and to the dried ($MgSO_4$) CCl_4 solution was added 3 ml of MeI. The solution was evaporated, the residue was taken up in CH_2Cl_2, and ethyl acetate was added to induce crystallization, giving 476 mg (1.03 mmol, 77%) of **16**: mp 128–129°; λ_{max} (MeCN) 355 nm (10^{-3} ϵ 6.7), 302 (7.1), 241 (30.0); ^{1}H NMR ($CDCl_3$) δ 8.32–7.16 (m, 13 H, aromatic), 4.27 (s, 2 H, NCH_2–), 3.94 (s, 3 H, 10-Me), 2.31 (s, 3 H, *N*-Me).

Anal. Calcd for $C_{21}H_{21}N_2SI$: C, 54.8; H, 4.60; N, 6.08; S, 6.96; I, 27.6. Found: C, 55.0; H, 4.54; N, 5.98; S, 6.75; I, 27.4

Exchange of Anions in Sulfilimine Salts. A. Formation of 5-(Benzyliminio)-5,5-dihydro-10-phenylphenothiazine Iodide (17) from 9. To a solution of 125 mg (0.26 mmol) of **9** in 20 ml of MeOH was added several grams of KI. The mixture was stirred for 2 hr, diluted with 200 ml of water, and extracted with CH_2Cl_2. The dried CH_2Cl_2 solution was evaporated, and the residue was crystallized from CH_2Cl_2–ether, giving 125 mg (0.246 mmol, 94%) of **17**: mp 147–148.5°; λ_{max} (MeCN) 346 nm (10^{-3} ϵ 7.78), 311 (8.35), 271 (13.7), and 243 (38.2).

Anal. Calcd for $C_{25}H_{21}N_2SI$: C, 59.1; H, 4.16; I, 24.9. Found: C, 59.5; H, 4.07; I, 24.7.

B. Formation of 5,5-Dihydro-10-methyl-5-piperidinium-1-ylidenephenothiazine Iodide (18) from 10m. To a solution of 497 mg (1.25 mmol) of **10m** in 75 ml of MeOH was added 5 g of KI in 15 ml of water. After 20 min the solution was extracted with CH_2Cl_2. Drying and evaporation of the CH_2Cl_2 gave 457 mg (1.08 mmol, 86%) of **18**: mp 137–138° (from CH_2Cl_2–ether); λ_{max} (MeCN) 350 nm (10^{-3} ϵ 6.1), 307 (7.0), 267 (14.0), and 242 (29.0); ^{1}H NMR ($CDCl_3$) δ 8.4–7 (m, 8 H, aromatic), 3.95 (s, 3 H, 10-Me), 2.8 (s, 4 H, 2 $-CH_2-$), and 1.43 (s, 6 H, 3 $-CH_2-$).

Anal. Calcd for $C_{18}H_{21}N_2SI$: C, 50.9; H, 4.99; I, 29.9. Found: C, 50.6; H, 4.95; I, 29.6.

C. Formation of 5-(Dibenzyliminio)-5,5-dihydro-10-phenylphenothiazine Iodide (19) from 9j. The procedure for making **17** was followed, using 106 mg (0.185 mmol) of **9j**, and giving 102 mg (0.171 mmol) of **19**, mp 138.5–140°.

Anal. Calcd for $C_{32}H_{27}N_2SI$: C, 64.2; H, 4.54; I, 21.2. Found: C, 64.2; H, 4.51; I, 20.9.

D. Formation of 5-(Benzylmethyliminio)-5,5-dihydro-10-methylphenothiazine Perchlorate (10n) from 16. To a solution of 90.3 mg (0.196 mmol) of **16** in 10 ml of MeOH was added 500 mg of $AgClO_4$ in 5 ml of water. AgI precipitated and was filtered. Extraction of the filtrate with CH_2Cl_2 and drying ($MgSO_4$) gave 73 mg (0.168 mmol, 86%) of **10n**: mp 137–138° (from CH_2Cl_2–ether); λ_{max} (MeCN) 355 nm (10^{-3} ϵ 6.9), 308 (7.5), 266 (14.0), and 220 (34.0); ^{1}H NMR (CD_3CN) δ 8.12–7.12 (m, 13 H, aromatic), 4.08 (s, 2 H, $-CH_2-$), 3.78 (s, 3 H, 10-Me), 2.22 (s, 3 H, *N*-Me).

Anal. Calcd for $C_{21}H_{21}N_2O_4SCl$: C, 58.3; H, 4.89; Cl, 8.19. Found: C, 57.95; H, 5.07; Cl, 7.98.

E. Formation of 5-(Benzylmethyliminio)-5,5-dihydro-10-methylphenothiazine Nitrate (20) from 16. A similar procedure using $AgNO_3$ gave 96% of **20**: mp 129–130° (from CH_2Cl_2–ether); λ_{max} (MeCN) 354 nm (10^{-3} λ 7.0), 308 (7.7), and 266 (15.0); ^{1}H NMR ($CDCl_3$) δ 8.18–6.91 (m, 13 H, aromatic), 4.15 (s, 2 H, NCH_2–), 3.85 (s, 3 H, 10-Me), and 2.25 (s, 3H, *N*-Me).

Anal. Calcd for $C_{21}H_{21}N_3O_3S$: C, 63.8; H, 5.35; N, 10.6. Found: C, 63.9; H, 5.38; N, 10.5.

Reaction of 8 with HCl. Products. To a solution of 100 mg (0.321 mmol) of **8** in 10 ml of MeCN was added 1 ml of concentrated HCl. The solution was stirred for 4 days, quenched with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. Work-up by TLC (see earlier) gave 34.8 mg (0.163 mmol, 55%) of 10-methylphenothiazine and 25 mg (0.101 mmol, 34%) of 3-chloro-10-methylphenothiazine, mp 112–113° (from ethanol). No 3,7-dichloro-10-methylphenothiazine appeared to have been formed.

Registry No.—**7**, 52156-15-7; **8**, 54014-67-4; **9a**, 55222-71-4; **9b**, 55222-73-6; **9c**, 55267-56-6; **9e**, 55222-75-8; **9f**, 55222-77-0; **9g**, 55222-79-2; **9h**, 55222-81-6; **9i**, 55222-83-8; **9j**, 55222-85-0; **9k**, 55222-87-2; **9l**, 55222-89-4; **9m**, 55222-91-8; **10a**, 55222-93-0; **10c**, 55222-95-2; **10d**, 55222-97-4; **10e**, 55222-99-6; **10f**, 55223-01-3; **10g**, 55223-03-5; **10i**, 55223-05-7; **10k**, 55223-07-9; **10l**, 55223-09-1; **10m**, 55223-11-5; **10n**, 55223-13-7; **11**, 7152-42-3; **12**, 1207-72-3; **13**, 55223-14-8; **15**, 55223-15-9; **16**, 55223-16-0; **17**, 55223-17-1; **18**, 55223-18-2; **19**, 55223-19-3; **20**, 55223-20-6; propylamine, 107-10-8; *tert*-butylamine, 75-64-9; cyclohexylamine, 108-91-8; benzylamine, 100-46-9; dimethylamine, 124-40-3; diethylamine, 109-89-7; diisopropylamine, 108-18-9; dibenzylamine, 103-49-1; azetidine, 503-29-7; pyrrolidine, 123-75-1; piperidine, 110-89-4; methylamine, 74-89-5; ethylamine, 75-04-7; ammonia, 7664-41-7; 10-methylphenothiazine 5-oxide, 2234-09-5; 3-chloro-10-phenylphenothiazine, 16684-59-6; 3,7-dichloro-10-phenylphenothiazine, 16717-05-8; 3-chloro-10-methylphenothiazine, 4048-46-8; 3,7-dichloro-10-methylphenothiazine, 55223-21-7; 10-phenylphenothiazine 5-oxide, 23099-78-7.

Supplementary Material Available.—Tables II and III will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2590.

References and Notes

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(2) Postdoctoral Fellow. We thank Texas Tech University for support under Grant 191-4731.
(3) The work on *N*-methylphenothiazine cation radical reactions is taken in part from the M.S. Thesis of A.G.P.
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Mesoionic Compounds. XXXIII. Thermal Rearrangement of 4*H*-1,3-Thiazinium Betaines to 4-Quinolones[1]

K. T. Potts*, R. Ehlinger, and W. M. Nichols

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

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Condensation of monosubstituted arylthioamides and trisubstituted thioureas with chlorocarbonylphenylketene in anhydrous nonprotic solvents readily gave a variety of *anhydro*-6-hydroxy-4-oxo-2,3,5-trisubstituted 4*H*-1,3-thiazinium hydroxides in excellent yields. At 80° in benzene these underwent ready elimination of carbonyl sulfide to give 4-quinolones, an azetinone and its open-chain iminoketene valence tautomer being implicated as intermediates in the rearrangement. In addition to spectral data, the structures of the quinolones were established by alternative syntheses. These betaines, containing "masked" 1,4 dipoles, did not undergo cycloaddition reactions with a variety of acetylenic and olefinic dipolarophiles, conversion into the 4-quinolones being the preferred reaction pathway.

In the general class of five-membered mesoionic ring systems one of their most interesting, and synthetically useful, properties is their ability to undergo 1,3-dipolar cycloaddition reactions.[2] In six-membered ring systems of this general type both 1,3-dipolar[3] and 1,4-dipolar[4] cycloadditions have been observed, the latter in ring systems in which the "masked" 1,4 dipole results from a suitable arrangement of peripheral heteroatoms and substituent groups. In our previous communications[4] we showed that several pyrimidinium betaines were reactive substrates for 1,4-dipolar cycloadditions. This present communication describes the extension of these concepts to a series of 4*H*-1,3-thiazinium betaines that have an added interest in that they underwent ready thermal elimination of carbonyl sulfide to form 4-quinolones rather than undergo 1,4-dipolar cycloaddition reactions.

The 1,3-thiazine system has been known for several years[5] and recently, independent of our study, a brief report describing the synthesis of several 1,3-thiazinium betaines from thioamides and malonic acid derivatives has appeared.[6] In our study we utilize for the first time in heterocyclic synthesis chlorocarbonylphenylketene (**2**), a versatile 1,3-bielectrophilic species that is prepared from phenylmalonic acid and PCl_5 or $SOCl_2$, followed by distillation under vacuum.[7] Obtained as a crystalline product that can be stored for considerable time, there is no doubt that this is the reactive species in the reactions utilizing phenylmalonyl chloride in the above synthesis of this ring system.[6]

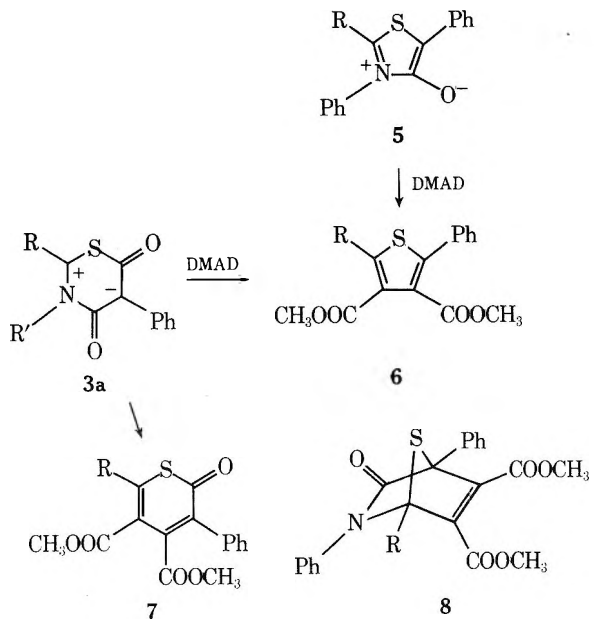
Thiobenzanilide (**1**, R = R′ = Ph) and chlorocarbonylphenylketene (**2**) underwent ready reaction to give *anhydro*-6-hydroxy-4-oxo-2,3,5-triphenyl-4*H*-1,3-thiazinium hydroxide (**3**, R = R′ = Ph), a product that decomposed readily on exposure to moisture. Incorporation of an electron-releasing group in the 2 substituent imparted greater stability to the thiazinium system **3**. Thus, the 2-*p*-chlorophenyl and 2-*p*-methoxyphenyl derivatives of **3** were obtained as high-melting, relatively stable products, and the variety of derivatives of this ring system prepared in this way are described in Table I. In no instance was the molecular ion detected in the mass spectra of these derivatives, whose physical constants, described in Table I, are consistent with the assigned structures. Assuming that the resultant stability of the system is due to some extent to delocalization of the positive charge associated with positions 1–3 of the nucleus, a logical extension would be to incorporate substituents into the 2 position that have appreciable electron-releasing ability. This objective was achieved utilizing disubstituted amino groups, the requisite starting material being the readily available trisubstituted thioureas formed by condensation of an appropriate amine and an isothiocyanate.

N-Methyl-*N*,*N*′-diphenylthiourea (**4**, R = R′ = Ph; R^2 = CH_3), from *N*-methylaniline and phenyl isothiocyanate, and **2** yielded the betaine **3** [R = CH_3(Ph)N; R′ = Ph] as yellow prisms, mp 157° dec, in 88% yield. A single carbonyl absorption was observed in the infrared spectrum of this product at 1600 cm^{-1} and the NMR spectrum indicated an aromatic multiplet at δ 6.8–7.5 in addition to the NCH_3 singlet at δ 3.67. The variety of derivatives of **3** prepared by this route is shown in Table I.

The nature of the substituents in **4** had considerable influence on the basicity of the betaine **3**. Thus, *N*,*N*′-dimethyl-*N*′-phenylthiourea (**4**, R = R′ = CH_3; R^2 = Ph), from dimethylamine and phenyl isothiocyanate, and the ketene **2** gave 6-hydroxy-3-methyl-2-(*N*-methylphenylamino)-4-oxo-5-phenyl-4*H*-1,3-thiazinium chloride as pale yellow prisms (89%), mp 134° dec, which was readily converted into the corresponding betaine **3** [R = CH_3(Ph)N; R′ = CH_3] on treatment with an organic base or on gentle heating under vacuum. Similarly, reaction of *N*,*N*′,*N*′-trimethylthiourea (**4**, R = R′ = R^2 = CH_3) and **2** also resulted in the initial formation of the salt, readily converted into the betaine **3** [R = $(CH_3)_2$N; R′ = CH_3] with triethylamine. As salt formation also was observed with *N*,*N*-dimethyl-*N*′-phenylthiourea (**4**, R = R^2 = CH_3; R′ = Ph), it is clear that the 2 substituent plays an important role both in stabilizing the nucleus and in increasing its basicity.

The betaine **3** may be considered to contain a "masked" 1,4-dipolar system **3a** and, as such, would be anticipated to undergo 1,4-dipolar cycloadditions with acetylenic and olefinic dipolarophiles in analogy to the corresponding pyrimidinium system.[4] With acetylenic dipolarophiles, depending on the fragment extruded from the initial cycloadduct, 2-pyridones or 2-thiapyrones would be formed. The reaction of *anhydro*-3,5-diphenyl-6-hydroxy-2-*p*-methoxyphenyl-4-oxo-4*H*-1,3-thiazinium hydroxide (**3**, R = *p*-$CH_3OC_6H_4$;

R′ = Ph) and dimethyl acetylenedicarboxylate (DMAD) in refluxing xylene resulted in the formation of two major products. The predominant product was ultimately characterized as the quinolone **9** due to thermal rearrangement of the betaine; the minor product (28%) was identified as ethyl 2-*p*-methoxyphenyl-5-phenylthiophene-3,4-dicarboxylate (**6**), synthesized in an alternative way[2b] from DMAD and *anhydro*-3,5-diphenyl-4-hydroxy-2-*p*-methoxyphenylthiazolium hydroxide (**5**). An anticipated product from the



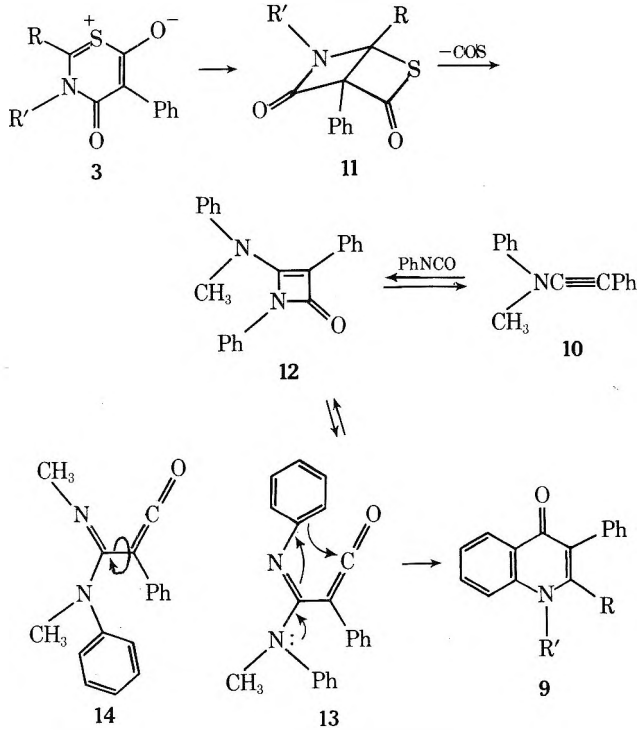
R = *p*-$CH_3OC_6H_4$

reaction of **3** and DMAD was the thiapyrone **7** but the formation of the thiophene may be readily rationalized. Thermal elimination of CO from **7** would afford **6** or, alternatively, elimination of CO from **3** would result in **5**, known to be converted into 8 with DMAD and which, in turn, forms **6**.

The quinolone **9** was also obtained when **3** was heated in xylene or acetonitrile in the absence of DMAD. In the latter solvent a considerably reduced reaction time was required. A gas evolved in the reaction was identified as carbonyl sulfide by reaction with piperidine to give *N,N*-pentamethylenethiocarbamic acid.[8] On the basis of analytical and spectral data (Table II) it was clear that the thermolysis product did not incorporate a molecule of DMAD and its molecular formula indicated that it was derived from the initial betaine by loss of carbonyl sulfide. This product was identified as 2-*p*-methoxyphenyl-3-phenyl-4-quinolone (**9**, R = *p*-$CH_3OC_6H_4$; R′ = H). When the reaction was repeated using variously substituted betaines, it became clear that only those betaines substituted with an aromatic group at N-3 gave the thermolysis product.

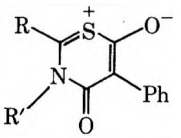
Thermolysis of *anhydro*-2-*p*-chlorophenyl-3,5-diphenyl-6-hydroxy-4-oxo-4*H*-1,3-thiazinium hydroxide (**3**, R = *p*-ClC_6H_4; R′ = Ph) in xylene or in the solid state afforded 2-*p*-chlorophenyl-3-phenyl-4-quinolone (**9**, R = *p*-ClC_6H_4; R′ = H). An unambiguous synthesis of this product was obtained from the fusion of anthranilic acid and benzyl *p*-chlorophenyl ketone.[9] The quinolones obtained by this thermolysis procedure from the thiazinium betaines **3** (R = aryl) had spectral data consistent with the assigned structures and are shown in Table II. That elimination of COS was the preferred reaction, especially in boiling xylene (bp 142°), was shown on attempted reaction of **3** with a variety of dipolarophiles such as fumaronitrile, tetracyanoethylene, *N*-phenylmaleimide, DMAD, diphenylacetylene, ethoxyacetylene, and *n*-butyl vinyl ether; in the majority of cases the thermolysis product was obtained, other products being those derived from hydrolysis of **3**.

Introduction of a more effective electron-releasing group such as a substituted amino group into the 2 position of **3** resulted in a more facile rearrangement to the quinolone and suppression of any 1,4-dipolar cycloaddition characteristics in **3**. *anhydro*-3,5-Diphenyl-6-hydroxy-2-(*N*-methylphenylamino)-4-oxo-4*H*-1,3-thiazinium hydroxide [**3**, R = N(Ph)CH_3; R′ = Ph], on reflux in anhydrous benzene, gave 2-(*N*-methylphenylamino)-3-phenyl-4-quinolone [**9**, R = N(Ph)CH_3; R′ = H] whose physical characteristics, described in Table II, are in agreement with the assigned structure. The proton at δ 8.9, due to an NH (or OH) proton, was rapidly exchanged with D_2O and the multiplet at δ 8.2 was assigned to the C_5 proton shifted downfield by the 4-oxo group. The ultraviolet data are in accord with data reported[10] in the literature for 4-quinolones of this type, which have also been synthesized from ethyl anthranilate and ynamines.[11] The quinolone **9** [R = N(Ph)CH_3; R′ = H] was also prepared by us by condensation of *N*-methyl-*N*,2-diphenylethynylamine[12] (**10**) and phenyl isocyanate, an azetinone intermediate being postulated in the latter reaction.[13] After removal of the solvent and the quinolone from the thermolysis mixture, the infrared spectrum of the residual oil showed strong absorptions at 2000–2200, 1595, and 1640 cm^{-1} and the NMR spectrum aromatic protons at δ 6.6–7.6 and several singlets between δ 3.1 and 3.7. These data were consistent with the presence of the ynamine and phenyl isocyanate in the reaction residue and indicated the likelihood of an azetinone intermediate. The rearrangement may be rationalized in terms of initial loss of COS from a possible valence tautomer **11** with formation of the azetinone **12**. Electrocyclic ring opening of **12**, followed by intramolecular recyclization of the intermediate iminoketone **13** leads readily to the quinolone **9**.



This reaction is analogous to the electrocyclic ring opening of 2,3,4,4-tetraphenyl-2-cyclobuten-1-one to 2,3,4-triphenylnaphthol[14] and 3-ethoxy-2-methyl-4,4-diphenyl-2-cyclobuten-1-one to 3-ethoxy-2-methyl-4-phenyl-1-naphthol,[15] and related ring closures have been observed with arylimidoyl isothiocyanates to quinazolinethiols[16] and the

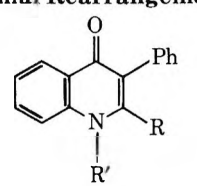
Table I
Some 4*H*-1,3-Thiazinium Betaines Derived from Substituted Thioamides and Thioureas and Chlorocarbonylphenylketene[a]



R	R′	Mp, °C	% yield	Formula	λ_{max} ($CHCl_3$), nm (log ε)	ν_{CO}, cm^{-1}	NMR data, δ ($CDCl_3$)	Registry no.
p-ClC_6H_4	Ph	166–168	94	$C_{22}H_{14}ClNO_2S$	240 (4.27), 315 (3.64)	1680, 1605, 1600	7.25 (m, aromatic)	55712-14-6
p-ClC_6H_4	*p*-$CH_3C_6H_4$	188–189	96	$C_{23}H_{16}ClNO_2S$	270 (3.78), 320 (3.43), 480 (2.55)	1680, 1610	2.25 (s, 3, $ArCH_3$), 6.8–7.8 (m, 13, aromatic)	55712-15-7
p-ClC_6H_4	CH_3	183–185	75	$C_{17}H_{12}ClNO_2S$	252 (4.32), 460 (3.32)	1660, 1610	3.64 (s, 3, NCH_3), 7.20–7.73 (m, 9, aromatic)	55712-16-8
p-$CH_3OC_6H_4$	Ph	172–174	86	$C_{23}H_{17}NO_3S$		1680, 1605	4.05 (s, 3, OCH_3), 7.65 (m, 14, aromatic)	55712-17-9
$CH_3(Ph)N$	Ph	157	88	$C_{23}H_{18}N_2O_2S$	251 (4.24), 285[b] (3.77)	1600	3.67 (s, 3, NCH_3), 6.8–7.5 (m, 15, aromatic)	55712-18-0
$CH_3(Ph)N$	CH_3	154	67	$C_{18}H_{16}N_2O_2S$	252 (4.23)	1595	3.02 (s, 3, 2-NCH_3), 3.48 (s, 3, 3-CH_3), 7.0–7.7 (m, 10, aromatic)	55712-19-1
$CH_3(Ph)N$	CH_3	134[c]	89	$C_{18}H_{17}ClN_2O_2S$[d]	245 (3.83), 283 (4.01)	1665, 1575	3.06 (s, 3, 2-NCH_3), 3.62 (s, 3, 3-CH_3), 7.0–7.6 (m, 10, aromatic)	55712-20-4
$(CH_3)_2N$	CH_3	144	78	$C_{13}H_{14}N_2O_2S$	243 (3.78), 281 (3.96)	1590	3.06, 3.14, 3.46 (s, 9, CH_3), 7.0–7.5 (m, 5, aromatic)	55712-21-5
$(CH_3)_2N$	CH_3	120[c]	83	$C_{13}H_{15}ClN_2O_2S$[d]	240 (3.62), 292 (4.07)	1600	3.12 (br s, CH_3)	55712-22-6
$(CH_3)_2N$	Ph	127[c]	81	$C_{18}H_{17}ClN_2O_2S$	241 (3.91), 287 (4.02)	1675, 1580	3.37 (br s, 6, CH_3), 7.1–7.5 (m, 10, aromatic)	55712-23-7

[a] All obtained as yellow prisms, decomposing at melting point; satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table. Ed. [b] Shoulder. [c] HCl. [d] Readily lost HCl during purification.

Table II
Some 4-Quinolones Formed by Thermal Rearrangement of 4*H*-1,3-Thiazinium Betaines[a]



R	R′	Mp, °C	% yield	Formula	$M^{\cdot+}$	λ_{max} (CH_3OH), nm (log ε)	ν_{CO}, cm^{-1}	NMR data, δ	Registry no.
p-ClC_6H_4	H	380–381	47	$C_{21}H_{14}ClNO$	331 (50)	213 (3.72), 260 (3.68), 335 (3.27)	1610, 1605	7.45–8.13 (m, aromatic)[b]	55712-24-8
p-ClC_6H_4	H	384–385[c]	56	$C_{22}H_{16}ClNO$	345 (53)	215 (4.06), 264 (4.01), 340 (3.56)	1615, 1610	2.13 (s, 3, 6-CH_3), 6.8–8.0 (m, 13, aromatic)[b]	55712-25-9

p-$CH_3OC_6H_4$	H	367	40	$C_{22}H_{17}NO_2$	325 (55)	208 (3.54), 273 (3.45), 345 (2.98)	1630, 1610	3.37 (s, 3, OCH_3), 6.7–8.3 (m, 14, aromatic)[b]	55712-26-0
$CH_3(Ph)N$	H	284	34	$C_{22}H_{18}N_2O$	326 (60)	220 (4.47), 244 (4.34), 285 (4.09), 332 (4.06)	1600, 1550	2.80 (s, 3, CH_3), 6.7–7.4 (m, 13, aromatic), 8.20 (m, 1, C_5 H), 8.9 (br s, 1, OH or NH)[d]	55712-27-1
CH_3NH	CH_3	274	16	$C_{17}H_{16}N_2O$	264 (77)	206 (4.34), 228 (4.44), 242 (4.43), 259 (4.33), 321 (4.18)	1600, 1550	2.75 (d, 3, $NHCH_3$, J = 6.0 Hz), 3.78 (s, 3, 1-CH_3), 7.3 (s, 8, aromatic), 8.34 (d, 1, C_5 H, $J_{5,6}$ = 6.0 Hz)[d]	55712-28-2
CH_3NH	CH_3	264[e]	36	$C_{17}H_{17}ClN_2O$	264 (18) (M − HCl)	222 (4.63), 249 (4.59), 300 (4.09), 324 (4.14)	1600, 1570	2.60 (s, 3, $^+NH_2CH_3$), 3.98 (s, 3, 1-CH_3), 7.5 (s, 6, aromatic and NH), 7.94 (d, 2, aromatic, J = 4 Hz), 8.44 (d, 1, C_5 H, $J_{5,6}$ = 6 Hz)[f]	55712-29-3
$(CH_3)_2N$	H	255–256[g]	92	$C_{17}H_{16}N_2O$	264 (65)	206 (4.40), 229 (4.44), 257 (4.43), 275 (4.29),[h] 321 (4.22)	1630, 1587	2.60 (s, 6, NH_3), 7.23 (br s, 9, aromatic and NH), 8.2 (d, 1, C_5 H, $J_{5,6}$ = 6 Hz)[d]	25083-38-9
$(CH_3)_2N$	H	252–253[g,i]	43	$C_{17}H_{17}ClN_2O$	264 (14) (M − HCl)	224 (4.63), 257 (4.60), 297 (3.98), 334 (4.18)	1640, 1600	2.80 (s, 6, NCH_3), 7.35 (s, 9, aromatic and NH), 8.2 (d, 1, C_5 H, $J_{5,6}$ = 6 Hz)[f]	25083-39-0

[a] All colorless prisms; those with 2-aryl substituents crystallized from acetic acid, others from ethanol; satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table. Ed. [b] CF_3COOH. [c] 6-Methyl product, from the betaine derived from 4-chloro-4′-methylthiobenzanilide. [d] $CDCl_3$. [e] HCl. [f] DMSO-d_6. [g] Lit.[11] mp 256°. [h] Shoulder. [i] Lit.[11] mp 244–248°.

photodesulfurization of dibenzoylstilbene episulfide to 2,3-diphenyl-4-phenoxy-1-naphthol.[17]

The presence of one aromatic nucleus in the initial thiourea is essential for the rearrangement of the thiazinium betaine to the quinolone. Thus, thermolysis of *anhydro*-6-hydroxy-3-methyl-2-(*N*-methylphenylamino)-4-oxo-5-phenyl-4*H*-1,3-thiazinium hydroxide [**3**, R = $CH_3(Ph)N$; R′ = CH_3] readily gave 1,4-dihydro-1-methyl-2-methylamino-3-phenyl-4-quinolone (**9**, R = CH_3NH; R′ = CH_3). In this case the iminoketene intermediate **13** must undergo a 180° rotation about the C_2–C_3 bond as in **14** since there is no 3-phenyl substituent. The corresponding thiazinium chloride also underwent this rearrangement, in this case the quinolinium chloride being isolated. As anticipated, *anhydro*-2-dimethylamino-6-hydroxy-3-methyl-4-oxo-5-phenyl-4*H*-1,3-thiazinium hydroxide [**3**, R = $(CH_3)_2N$; R′ = CH_3] did not undergo rearrangement under the above conditions. An interesting feature of the NMR spectrum of this betaine was the nonequivalency of the *N*-methyl groups at the 2 position (δ 3.14, 3.06), indicating some double bond character in the C_2–N bond owing to delocalization of the positive charge over the thiourea partial structure.

Experimental Section[18]

General Procedure for the Synthesis of the 1,3-Thiazinium Betaines. Preparation of *anhydro*-3,5-Diphenyl-6-hydroxy-2-(*N*-methylphenylamino)-4-oxo-4*H*-1,3-thiazinium Hydroxide [3, R = $CH_3(Ph)N$; R′ = Ph]. *N*-Methyl-*N*,*N*′-diphenylthiourea (2.4 g, 10 mmol) was added with stirring to chlorocarbonylphenylketene (2.0 g, 11 mmol) in dry benzene (50 ml). After stirring at room temperature for 1 hr, the solid product was collected and washed well with dry benzene (50 ml), yielding yellow prisms, 3.4 g (88%), mp 157° dec (Table I). When the product separated as the thiazinium chloride it was converted into the betaine by treatment with Et_3N in THF followed by pouring the reaction mixture into water. Alternatively, the chloride was heated to ca. 40° (0.1 mm) for approximately 48 hr.

General Procedure for the Thermolysis of the 1,3-Thiazinium Betaines. Formation of 2-(*N*-Methylphenylamino)-3-phenyl-4-quinolone [9, R = $CH_3(Ph)N$; R′ = H]. The betaine **3** [R = $CH_3(Ph)N$; R′ = Ph] (2.2 g, 5.7 mmol) was refluxed for 12 hr in dry benzene (50 ml). Upon cooling, the separated solid was collected and recrystallized from ethanol, forming colorless needles, 0.63 g (34%), mp 284° (Table II).

Alternative Synthesis of 2-(*N*-Methylphenylamino)-3-phenyl-4-quinolone [9, R = $CH_3(Ph)N$; R′ = H]. *N*-Methyl-*N*,2-diphenylethynylamine (0.5 g, 2.5 mmol) and phenyl isocyanate (0.29 g, 2.5 mmol) in dry benzene (50 ml) were refluxed for 12 hr. Upon cooling, the separated solid was collected and recrystallized from benzene, forming colorless needles, 0.15 g (18%), mp 284°.

Reaction of *anhydro*-2,3-Diphenyl-6-hydroxy-2-(*p*-methoxyphenyl)-4-oxo-4*H*-1,3-thiazinium Hydroxide (3, R = *p*-$CH_3OC_6H_4$; R′ = Ph) and Dimethyl Acetylenedicarboxylate. The thiazinium betaine (0.3 g, 10 mmol) and DMAD (1.0 g, 5 mmol) were refluxed in dry xylene (50 ml) for 3 hr. After removal of the solid that separated on cooling, the mother liquor was evaporated and the crude residue was chromatographed on silica gel using $CHCl_3$ as eluent. The first fraction eluted from the column crystallized from $CHCl_3$–hexane as colorless prisms and was identified as methyl 2-*p*-methoxyphenyl-5-phenylthiophene-3,4-dicarboxylate (**6**): 0.07 g (28%), mp 107–109° dec; ir (KBr) ν_{CO} 1730 cm^{-1}; λ_{max} (CH_3OH) 300 nm (log ε 3.95), 240 (4.10), 255 (4.17); NMR ($CDCl_3$) δ 3.72 (s, 3, OCH_3), 3.75 (s, 3, $COOCH_3$), 3.76 (s, 3, $COOCH_3$), 7.0–7.5 (m, 9, aromatic); $M^{\cdot+}$ 382 (100).

Anal. Calcd for $C_{21}H_{18}O_5S$: C, 65.95; H, 4.75. Found: C, 66.22; H, 4.85.

The solid separated from the initial reaction mixture crystallized from acetic acid as colorless prisms and was identified as 2-(*p*-methoxyphenyl)-3-phenyl-4-quinolone, 0.1 g (40%), mp 367° (Table II).

Alternative Synthesis of Methyl 2-(*p*-Methoxyphenyl)-5-phenylthiophene-3,4,-dicarboxylate. *p*-Methoxythiobenzanilide (10.0 g, 0.041 mol), α-bromophenylacetic acid (5.0 g, 0.023 mol), and NEt_3 (6.0 g, 0.085 mol) in benzene were refluxed for 2 hr. After

cooling, Et_3NHBr was filtered off and the benzene was removed in vacuo. Ac_2O (6.0 g, 0.059 mol) was added to the resulting red oil and the solution was shaken. Ether was added after crystallization started; the product was collected, washed with ether, and dissolved in dry benzene (100 ml). DMAD (3.0 g, 0.013 mol) was added and, after 24-hr reflux, removal of solvent, and chromatography on silica gel with $CHCl_3$ as eluent, methyl 2-(*p*-methoxyphenyl)-5-phenylthiophene-3,4-dicarboxylate, mp 107–109° (80%), was obtained identical with that isolated above.[19]

Registry No.—**2**, 17118-70-6; **6**, 20851-14-3; **10**, 32907-84-9; *N*-methyl-*N*,*N*′-diphenylthiourea, 4949-93-3; phenyl isocyanate, 103-71-9; dimethyl acetylenedicarboxylate, 762-42-5; *p*-methoxythiobenzanilide, 26060-23-1; α-bromophenylacetic acid, 4870-65-9.

References and Notes

(1) (a) Support of this work by U.S. Public Health Service Research Grant HL 15021, National Heart and Lung Institute, is gratefully acknowledged. (b) Abstracted from the Ph.D. Thesis of R.E., 1975, and M.S. Thesis of M.N., 1973, Rensselaer Polytechnic Institute. (c) Part XXXII: K. T. Potts, J. Baum, and E. Houghton, *J. Org. Chem.*, **39**, 3631 (1974).

(2) Numerous references relating to earlier work may be found in (a) K. T. Potts, J. Baum, E. Houghton, D. N. Roy, and U. P. Singh, *J. Org. Chem.*, **39**, 3619 (1974); (b) K. T. Potts, E. Houghton, and U. P. Singh, *ibid.*, **39**, 3627 (1974); ref 1c.

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(18) Spectral characterizations were carried out on the following instrumentation: infrared spectra, Perkin-Elmer Model 337 spectrophotometer; ultraviolet spectra, Cary 14 spectrophotometer; NMR spectra, Varian T-60 spectrometer, using Me_4Si as internal standard; mass spectrometer, Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV, with a source temperature of ca. 150°. Melting points were determined in capillaries and all evaporations were carried out using a Rotovap apparatus. Microanalyses were performed by Instranal Laboratories, Inc., Rensselaer, N.Y.

(19) Criteria used to establish identity were superimposable ir spectra, no depression in mixture melting point, and identical R_f values.

Bridgehead Nitrogen Heterocycles. IX. Fused-Ring Systems Derived from Fusion of the 1,2,4-Thiadiazole System with the Isoxazole, 1,3,4-Oxadiazole, Thiazole, 1,2,4-Thiadiazole, and 1,3,4-Thiadiazole Systems[1]

K. T. Potts* and J. Kane[1b]

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

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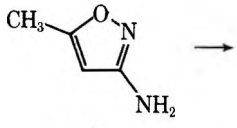
Amino derivatives of the title heterocycles containing the amino group as part of a partial amidine structure reacted with trichloromethanesulfenyl chloride via an isolable trichloromethanesulfenamide intermediate to yield the 3*H*-isoxazolo[3,2-*c*]-, 3*H*-thiazolo[2,3-*c*]-, 3*H*-1,3,4-thiadiazolo[2,3-*c*]-, and the 3*H*-1,2,4-thiadiazolo[4,3-*d*][1,2,4]thiadiazole as well as the 3*H*-1,2,4-thiadiazolo[3,4-*b*][1,3,4]oxadiazole systems. These were characterized by spectral and chemical properties.

In contrast to the large number of substituted, monocyclic 1,2,4-thiadiazoles described in the literature,[2] examples of ring-fused 1,2,4-thiadiazole derivatives remain relatively few. Conceptually there are two general methods for the synthesis of systems containing the ring-fused 1,2,4-thiadiazole moiety. The most direct method involving fusion of an appropriately substituted 1,2,4-thiadiazole has attained only limited usage.[3] The second method, involving ring closure of a 2-amino heterocycle containing a partial amidine structure with a sulfur-containing cyclization agent[4] or by oxidation of an appropriately substituted thiourea,[5] constitutes the most commonly encountered route to these fused ring systems. In earlier publications[6] we have shown that trichloromethanesulfenyl chloride is a particularly efficacious cyclization agent for the synthesis of a variety of six-membered ring systems fused to the 1,2,4-thiadiazole nucleus. This present communication describes the extension of this synthetic route to the preparation of a variety of 5,5-fused ring systems, to a large part unavailable by earlier procedures.

3*H*-Isoxazolo[3,2-*c*][1,2,4]thiadiazole System (4). Reaction of trichloromethanesulfenyl chloride with 2 equiv of 3-amino-5-methylisoxazole (1) and 4 equiv of Et_3N proved to be extremely exothermic and resulted in an intractable complex mixture of at least seven components over a range of reaction temperatures (0–20°). However, addition of an aqueous solution of 1 to a stirred, aqueous suspension of trichloromethanesulfenyl chloride, potassium carbonate, Alconox, and crushed ice afforded a cream-colored solid which crystallized from ethanol as colorless needles. Analytical and spectral data (ν_{NH} 3180, $\nu_{C=N}$ 1620 cm^{-1}) supported the product's formulation as the sulfenamide **2**, which was confirmed by the following transformations. Reaction with 2-amino-5-methylpyridine in the presence of Et_3N produced a complex reaction mixture which could be partially resolved using preparative layer chromatography. The major component isolated from this mixture was identified[6] as 6-methyl-3-(5-methyl-2-pyridylimino)-3*H*-1,2,4-thiadiazolo[4,3-*a*]pyridine (**3**, R = 5-CH_3-2-C_5H_3N; R_1 = 6-CH_3) and presumably occurs via a transamination reaction such as was observed in the reactions of 1,1,1-trichloro-*N*-(2-pyrimidyl)methanesulfenamide and 2-aminopyridines.[6] The second component isolated from the mixture crystallized from acetone as cream needles and was

identified as S_8. In contrast to this reaction, condensation of **2** and 3-nitroaniline in the presence of Et_3N proceeded quite cleanly and ultimately afforded a greenish-gold product in 62% yield. This was assigned the structure of 6-methyl-3-(3-nitrophenylimino)-3*H*-isoxazolo[3,2-*c*][1,2,4]thiadiazole (**4**, R = 3-$NO_2C_6H_4$) upon consideration of the analytical and spectral data (Table I).



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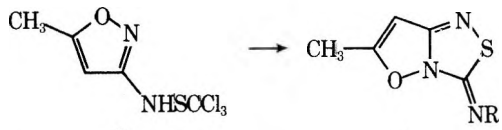
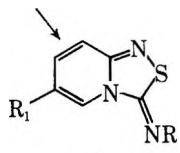


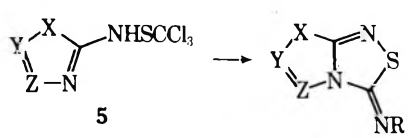
2 **4**



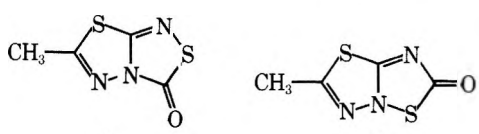
3

In a similar fashion, several additional examples of the 3*H*-isoxazolo[3,2-*c*][1,2,4]thiadiazole system have been prepared and the characteristics of these derivatives are described in Table I. It should be noted that examples of this system do not appear to be photostable. This is especially true of **4** (R = 3-$NO_2C_6H_4$), which, if not shielded from light, turns from greenish-gold to orange in less than 1 hr; although isoxazoles are known to be photoreactive,[7] the exact nature of this present decomposition is as yet unknown. Hydrolysis of **4** (R = 3-$NO_2C_6H_4$) in a hot solution of 10% HCl and ethanol resulted in complete disruption of the nucleus to 3-nitroaniline, 3-amino-5-methylisoxazole, and sulfur. Similarly, attempted exchange of the nuclear oxygen atom for sulfur by heating with P_4S_{10} in pyridine was unsuccessful, deep-seated decomposition being observed.

3*H*-1,2,4-Thiadiazolo[3,4-*b*][1,3,4]oxadiazole System (6, X = O; Y = CPh; Z = N). 1,1,1-Trichloro-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)methanesulfenamide (**5**, X = O; Y = CPh; Z = N) reacted with 4-nitroaniline to yield an insoluble, yellow product which required purification by preparative layer chromatography. Analytical and spectral data were consistent with the product's formulation as 6-phenyl-3-(4-nitrophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*][1,3,4]oxadiazole (**6**, X = O; Y = CPh; Z = N; R = 4-$NO_2C_6H_4$). Owing to difficulties experienced in its purification further studies on this ring system were abandoned.



5 **6**



7 **8**

X = O, S
Y = CR, N
Z = CR, N

3*H*-Thiazolo[2,3-*c*][1,2,4]thiadiazole System (6, X = S; Y = Z = CH). The reaction of 1,1,1-trichloro-*N*-(2-thiazolyl)methanesulfenamide (**5**, X = S; Y = Z = CH) and 3-nitroaniline produced a complex reaction mixture. Partial resolution of this mixture using preparative layer chromatography afforded a yellow product crystallizing from 1,2-dichloroethane as yellow needles. The structure of this material was assigned that of 3-(3-nitrophenylimino)-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazole (**6**, X = S; Y = Z = CH; R = 3-$NO_2C_6H_4$) upon consideration of the analytical and spectral data. Its ultraviolet spectrum was quite similar to that of 3-(3-nitrophenylimino)-3*H*-thiadiazolo[3,4-*b*]benzothiazole[8] and the NMR spectrum consisted of three sets of absorptions, the first occurring as a doublet at δ 6.68 assigned to H_6 by analogy to derivatives of the pyrrolo[2,1-*b*]thiazole system,[9] the second occurring as a three-proton multiplet in the region of δ 7.35. Within this multiplet a doublet attributable to H-5 could be distinguished at δ 7.38, and the last set occurred as a two-proton multiplet centered at δ 7.88. The mass spectral fragmentation pattern of **6** (X = S; Y = Z = CH; R = 3-$NO_2C_6H_4$) was also in close agreement with the assigned structure. Cleavage of the 2,3 and 3,4 bonds of the fused nucleus gave the 2-thiazolylthionitroso ion as the most intense ion in the spectrum, while cleavage of the 1,2 and 3,4 bonds resulted in the 3-nitrophenylisothiocyanate ion. Similar fragmentations have been observed[6,8] in the 3*H*-1,2,4-thiadiazolo[4,3-*a*]pyridine, -[4,3-*a*]pyrimidine, -[4,3-*a*]pyrazine, and -[3,4-*b*]benzothiazole systems. Additional derivatives of this system are described in Table I.

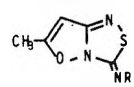
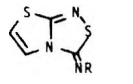
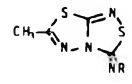
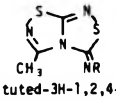
The 3*H*-1,3,4-Thiadiazolo[2,3-*c*][1,2,4]thiadiazole System (6, X = S; Y = CCH_3; Z = N). 1,1,1-Trichloro-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)methanesulfenamide (**5**, X = S; Y = CCH_3; Z = N) reacted with 3-nitroaniline giving 6-methyl-3-(3-nitrophenylimino)-3*H*-1,3,4-thiadiazolo[2,3-*c*][1,2,4]thiadiazole (**6**, X = S; Y = CCH_3; Z = N; R = 3-$NO_2C_6H_4$) in 96% yield. While all available data (Table I) were in agreement with the assigned structure, the ultraviolet and mass spectra are particularly definitive. The ultraviolet spectrum of **6** (X = S; Y = CCH_3; Z = N; R = 3-$NO_2C_6H_4$) (λ_{max} 322, 267, and 245 nm) was almost superimposable with that of the corresponding thiazole derivative (**6**, X = S; Y = Z = CH; R = 3-$NO_2C_6H_4$). The mass spectrum also displayed the characteristic thionitroso and isothiocyanate ions. Rupture of the 1,3,4-thiadiazole moiety could be seen in the thioacylium ion *m/e* 59 (80).

In a similar fashion, two additional examples of the title system were prepared by the reactions of **5** (X = S; Y = CCH_3; Z = N) and primary, aromatic amines. These derivatives are described in Table I.

In an attempt to prepare 6-methyl-3*H*-1,3,4-thiadiazolo[2,3-*c*][1,2,4]thiadiazol-3-one (**7**), whose properties were to be contrasted with those of the isomeric 6-methyl-2*H*-1,3,4-thiadiazolo[3,2-*b*][1,2,4]thiadiazol-2-one[4b] (**8**), **6** (X = S; Y = CCH_3; Z = N; R = 3-$NO_2C_6H_4$) was hydrolyzed in a mixture of 10% HCl in ethanol. Partial resolution of the resulting mixture using preparative layer chromatography afforded three isolatable products, identified as 3-nitroaniline, 2-amino-5-methyl-1,3,4-thiadiazole, and sulfur.

The 3*H*-1,2,4-Thiadiazolo[4,3-*d*][1,2,4]thiadiazole System (6, X = S; Y = N; Z = CCH_3). 1,1,1-Trichloro-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)methanesulfenamide (**5**, X = S; Y = N; Z = CCH_3) reacted with 3-nitroaniline, giving 5-methyl-3-(3-nitrophenylimino)-3*H*-1,2,4-thiadiazolo[4,3-*d*][1,2,4]thiadiazole (**6**, X = S; Y = N; Z = CCH_3; R = 3-$NO_2C_6H_4$) in 72% yield. This structural assignment was based on consideration of the analytical and spectral data. The ultraviolet spectrum of **6** (X = S; Y = N; Z = CCH_3; R

Table I
Some Ring-Fused 1,2,4-Thiadiazoles

R	mp °C	Yield %	Crystal Habit	Formula[a]	M+ (rel int)	Ir, cm⁻¹ C=N-	Ir, cm⁻¹ Thiadiazole ring deformation[b]	uv λmax nm	uv log ε[c]	Nmr Chemical Shift, δ[d]
										
Some 6-Methyl-3-substituted-3H-isoxazolo[3,2-c][1,2,4]thiadiazoles										
2,5-$Cl_2C_6H_3$	117-118[e]	22	Cream needles[f]	$C_{11}H_7Cl_2N_3OS$	299 (17)	1630	1470	312	3.84	2.43 (d, 3, 6-CH_3, $J_{6,7}$ = 1.2 Hz)
								268	3.87	5.90 (d, 1, H_7)
								238	4.08	6.97 (dd, 1, H_4', $J_{3',4'}$ = 7.6 Hz)
										7.08 (dd, 1, H_6', $J_{4',6'}$ = 2.3 Hz)
										7.36 (dd, 1, H_3', $J_{3',6'}$ = 1.0 Hz)
2-$NO_2C_6H_4$	142-143[e]	12	Gold plates[f]	$C_{11}H_8N_4O_3S$	276 (19)	1650	1440	305	3.89	2.47 (d, 3, 6-CH_3, $J_{6,7}$ = 1.2 Hz)
								260	4.09	5.93 (d, 1, H_7)
								238	4.18	7.53 (m, 4, aromatic)
3-$NO_2C_6H_4$	139-141[e]	62	Greenish-gold needles[g]	$C_{11}H_8N_4O_3S$	276 (20)	1640	1410	318	3.98	2.48 (d, 3, 6-CH_3, $J_{6,7}$ = 1.2 Hz)
								272	4.20	5.96 (d, 1, H_7)
								241	4.14	7.72 (m, 4, aromatic)
4-$NO_2C_6H_4$	167[h]	43	yellow, irreg. prisms[i]	$C_{11}H_8N_4O_3S$	276 (46)	1630	1410	372	4.17	2.48 (d, 3, 6-CH_3, $J_{6,7}$ = 1.2 Hz)
								290	3.92	5.97 (d, 1, H_7)
								238	4.03	7.18 (d, 2, H_2' and H_6', $J_{2',3'} = J_{5',6'}$ = 9.2 Hz)
										8.22 (d, 2, H_3' and H_5')
										
Some 3-Substituted-3H-thiazolo[2,3-c][1,2,4]thiadiazoles										
3-$NO_2C_6H_4$	140-142[e]	18	yellow needles[j]	$C_{10}H_6N_4O_2S_2$	278 (63)	1610	-	331	4.18	6.68 (d, 1, H_6, $J_{5,6}$ = 5.0 Hz)
								270[k]	4.04	7.35 (m, 2, aromatic)
								248	4.13	7.38 (d, 1, H_5), 7.88 (m, 2, aromatic)
4-$NO_2C_6H_4$	240-242[e]	11	orange needles[l]	$C_{10}H_6N_4O_2S_2$	278 (72)	1640	-	390	4.26	-
								283	4.05	-
										
Some 6-Methyl-3-substituted-3H-1,3,4-thiadiazolo[2,3-c][1,2,4]thiadiazoles										
2,5-$Cl_2C_6H_3$	146-147	54	cream prisms[m]	$C_{10}H_6Cl_2N_4S_2$	316 (90)	1620	1470	310	3.92	2.64 (s, 3, 6-CH_3)
								238	4.06	6.99 (dd, 1, H_4', $J_{3',4'}$ = 8.0 Hz)
										7.07 (dd, 1, H_6', $J_{4',6'}$ = 2.5 Hz)
										7.34 (dd, 1, H_3', $J_{3',6'}$ = 0.8 Hz)
3-$NO_2C_6H_4$	178-179	96	yellow, matted needles[n]	$C_{10}H_7N_5O_2S_2$	293 (100)	1630	1430	322	4.11	2.70 (s, 3, 6-CH_3)
								267	4.05	7.53 (m, 2, aromatic)
								245	4.13	8.04 (m, 2, aromatic)
4-$NO_2C_6H_4$	240-242	38	yellow, irreg. prisms[o]	$C_{10}H_7N_5O_2S_2$	293 (96)	1620	1450	370	4.23	2.71 (s, 3, 6-CH_3)
								275	3.91	7.24 (d, 2, H_2' and H_6', $J_{2',3'} = J_{5',6'}$ = 9.2 Hz)
								237	3.93	8.27 (d, 2, H_3' and H_5')
										
Some 5-Methyl-3-substituted-3H-1,2,4-thiadiazolo[4,3-d][1,2,4]thiadiazoles										
2,5-$Cl_2C_6H_3$	185-187	36	cream needles[p]	$C_{10}H_6Cl_2N_4S_2$	316 (81)	1630	1470	335[k]	3.82	2.87 (s, 3, 5-CH_3)
								319	3.87	7.22 (m, 4, aromatic)
								270	3.67	
								239	3.98	
3-$NO_2C_6H_4$	181-183	72	yellow, matted needles[q]	$C_{10}H_7N_5O_2S_2$	293 (100)	1630	1470	330	4.04	2.85 (s, 3, 5-CH_3)
								260[k]	4.03	7.56 (m, 4, aromatic)
								245	4.10	

[a] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table: Ed.; [b] KBr; [c] $CHCl_3$; [d] $CDCl_3$; [e] Decomposition; [f] Method B, prep. layer chromatography, $CHCl_3$: EtOAc:: 80:20, recrystallized from EtOH; [g] Method A, recrystallized from EtOH; [h] Violent decomposition; [i] Method A, recrystallized from EtOAc; [j] Purified by prep. layer chromatography, $CHCl_3$: EtOAc:: 70:30, recrystallized from 1,2-dichloroethane; [k] Shoulder; [l] Purified by prep. layer chromatography, $CHCl_3$: EtOAc:: 80:20, recrystallized from 1,2-dichloroethane; [m] Method B, recrystallized from EtOH; [n] Method A, recrystallized from EtOH; [o] Method A, recrystallized from 1,2-dichloroethane; [p] Recrystallized from EtOAc; [q] Recrystallized from 1,2-dichloroethane.

= 3-$NO_2C_6H_4$) (λ_{max} 330, 260, and 245 nm) compared very favorably with that of its 1,3,4 isomer. In addition, the infrared spectrum displayed a C=N absorption at 1630 cm^{-1} and a thiadiazole ring deformation at 1470 cm^{-1}. The NMR spectrum, in addition to a complex aromatic multiplet centered at δ 7.56, exhibited a methyl absorption at δ 2.85 which was shifted downfield relative to that observed for the methyl group of 5-amino-3-methyl-1,2,4-thiadiazole at δ 2.54. This downfield shift presumably reflects the 1,3 relationship between the methyl group and the exocyclic imine function.

In a similar fashion, the 2,5-dichloro analog **6** (X = S; Y = N; Z = CCH_3; R = 2,5-$Cl_2C_6H_3$) was prepared from **5** (X = S; Y = N; Z = CCH_3) and 2,5-dichloroaniline. The analytical and spectral data were entirely consistent with those of its predecessor (Table I).

Experimental Section[10]

Preparation of the Intermediate Sulfenamides.[11] A. 1,1,1-Trichloro-*N*-(5-methyl-3-isoxazolyl)methanesulfenamide (2). $ClSCCl_3$ (18.6 g) was suspended in a stirred solution of K_2CO_3 (13.8 g), Alconox[12] (1 g), H_2O (300 ml), and crushed ice. A solution of 3-amino-5-methylisoxazole (9.80 g) and H_2O (100 ml) was then added over 15 min. The precipitated product was collected, washed with H_2O, and dried by suction. This was sufficiently pure for further use. Additional purification by crystallization from EtOH gave colorless needles: 14.8 g (60%); mp 140–142° dec; ir (KBr) 3180 (NH), 1620 cm^{-1} (C=N); λ_{max} (CH_3OH) 223 nm (log ϵ 3.86); NMR ($CDCl_3$) δ 2.38 (s, 3, CH_3), 6.09 (s, 1, H_4), 7.99 (broad s, 1, NH); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 246 (35).

Anal. Calcd for $C_5H_5Cl_3N_2OS$: C, 24.26; H, 2.04; N, 11.32. Found: C, 24.24; H, 2.01; N, 11.36.

B. 1,1,1-Trichloro-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)methanesulfenamide (5, X = O; Y = CPh; Z = N). A solution of $ClSCCl_3$ (4.65 g) in $CHCl_3$ (50 ml) was added over 30 min to a stirred suspension of 2-amino-5-phenyl-1,3,4-oxadiazole (8.05 g) and $CHCl_3$ (500 ml). After stirring for 4 hr, the precipitate was collected, washed with H_2O, and dried by suction, 5.9 g (76%), mp 147–150° dec. This was sufficiently pure for further use.

C. 1,1,1-Trichloro-*N*-(2-thiazolyl)methanesulfenamide (5, X = S; Y = Z = CH). A solution of $ClSCCl_3$ (5.58 g) in Et_2O (25 ml) was added over 15 min to a stirred solution of 2-aminothiazole (6.0 g) and Et_2O (400 ml). After stirring for 10 min the solvent was removed from the reaction mixture and the residue was washed with aqueous EtOH. Filtration gave an orange solid which was dried by suction, 3.3 g (44%), mp 53–59° dec. Although attempts to purify the material further resulted in complete decomposition, it was sufficiently pure for further use.

D. 1,1,1-Trichloro-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)methanesulfenamide (5, X = S; Y = CCH_3; Z = N). A solution of $ClSCCl_3$ (7.44 g) and $CHCl_3$ (50 ml) was added over 15 min to a stirred solution of 2-amino-5-methyl-1,3,4-thiadiazole (9.2 g) and $CHCl_3$ (450 ml). After stirring for 1 hr the reaction mixture was evaporated to dryness, yielding a cream product which was washed with EtOH and dried by suction: 6.5 g (61%); mp 126–129° dec; mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 263 (18). Although this material could be partially purified by crystallization from benzene, it was sufficiently pure for further use.

E. 1,1,1-Trichloro-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)methanesulfenamide (5, X = S; Y = N; Z = CCH_3). A solution of $ClSCCl_3$ (0.93 g) and CH_3OH (15 ml) was added over 10 min to a stirred solution of 5-amino-3-methyl-1,2,4-thiadiazole (1.15 g) and CH_3OH (50 ml). After stirring for 3 hr the solvent was removed from the reaction mixture and the residue was washed with H_2O. Filtration gave a cream product which was dried by suction, 0.38 g (29%), mp 128–130° dec. This was sufficiently pure for further use.

General Procedure for the Preparation of Some 3-Substituted 3*H*-Isoxazolo[3,2-*c*][1,2,4]thiadiazoles (4). 1,1,1-Trichloro-*N*-(5-methyl-3-isoxazolyl)methanesulfenamide (0.01 mol) was added portionwise to a stirred solution of an aromatic amine (0.01 mol), Et_3N (0.03 mol), and $CHCl_3$ (150 ml). After stirring for 14 hr the reaction mixture was evaporated to dryness. Reaction work-up was by either of two procedures. **A.** The residue, after washing with CH_3OH, was purified as indicated. **B.** The residue was washed with H_2O, yielding an oil which was extracted with $CHCl_3$. Drying over $MgSO_4$ and removal of the $CHCl_3$ gave a solid which was purified as indicated (Table I).

Reaction of 2 with 2-Amino-5-methylpyridine. 1,1,1-Trichloro-*N*-(5-methyl-3-isoxazolyl)methanesulfenamide (**2**, 2.48 g) was added portionwise to a stirred solution of 2-amino-5-methylpyridine (1.08 g), Et_3N (3.04 g), and $CHCl_3$ (150 ml). After stirring for 24 hr the reaction mixture was evaporated to dryness and the residue was resolved by preparative layer chromatography [1.00 mm, $CHCl_3$–EtOAc (90:10)]. One component crystallized from $(CH_3)_2CO$ as orange prisms and was identified as **3** (R = 5-CH_3-2-C_5H_3N; R_1 = 6-CH_3) being identical in all respects with an authentic sample, mp 194–196°, mmp 194–196°. A second component crystallized from $(CH_3)_2CO$ as cream needles and was identified as S_8 from its mass spectrum: *m/e* (rel intensity) $M^{\cdot+}$ 256 (100).

Acid Hydrolysis of 4 (R = 3-$NO_2C_6H_4$). 6-Methyl-3-(3-nitrophenylimino)-3*H*-isoxazolo[3,2-*c*][1,2,4]thiadiazole (0.25 g) was refluxed 2 hr in a solution of HCl (10%, 10 ml) and EtOH (15 ml). Neutralization with $NaHCO_3$ and evaporation to dryness gave a solid which was extracted with a $CHCl_3$–H_2O mixture. The $CHCl_3$ layer was separated and dried over Na_2SO_4 before being evaporated to dryness. TLC [$CHCl_3$–CH_3OH (80:20)] of the residue indicated a complex mixture, with unreacted starting material, 3-nitroaniline, 3-amino-5-methylisoxazole, and S_8 shown by comparison of R_f values with those of authentic samples. Trituration of the residue with $(CH_3)_2CO$ gave a cream solid which was identified as S_8 from its mass spectrum: *m/e* (rel intensity) $M^{\cdot+}$ 256 (100).

6-Phenyl-3-(4-nitrophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*][1,3,4]oxadiazole (6, X = O; Y = CPh; Z = N; R = 4-$NO_2C_6H_4$). Sulfenamide **5** (X = O; Y = CPh; Z = N) (3.10 g) was added portionwise to a stirred solution of 4-nitroaniline (1.38 g), Et_3N (3.04 g), and $CHCl_3$ (150 ml). After stirring for 14 hr, the solvent was removed from the reaction mixture, yielding an orange product which, after washing with CH_3OH, was purified by preparative layer chromatography (1.00 mm, $CHCl_3$). Subsequent crystallization from $CHCl_3$ gave yellow prisms: 0.48 g (14%); mp 238–240°; ir (KBr) 1660, 1630 (C=N), 1560, 1340 (NO_2), 1460 cm^{-1} (thiadiazole ring deformation); λ_{max} ($CHCl_3$) 373 nm (log ϵ 4.34), 258 (4.43); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 339 (100).

Anal. Calcd for $C_{15}H_9N_5O_3S$: C, 53.09; H, 2.67; N, 20.64. Found: C, 52.93; H, 2.56; N, 20.48.

Representative Procedure for the Preparation of Some 3-Substituted 3*H*-Thiazolo[2,3-c][1,2,4]thiadiazoles. 3-(3-Nitrophenylimino)-3*H*-thiazolo[2,3-c][1,2,4]thiadiazole (6, X = S; Y = Z = CH; R = 3-$NO_2C_6H_4$). Sulfenamide **5** (X = S; Y = Z = CH) (2.5 g) was added portionwise to a stirred solution of 3-nitroaniline (1.38 g), Et_3N (3.04 g), and $CHCl_3$ (150 ml). After stirring for 14 hr, the solvent was removed from the reaction mixture, giving a brown product which, after washing with CH_3OH, was purified by preparative layer chromatography [1.00 mm, $CHCl_3$–EtOAc (70:30)]. Subsequent crystallization from 1,2-dichloroethane gave yellow needles, 0.50 g (18%), mp 140–142° dec (Table I).

General Procedure for the Preparation of Some 3-Substituted 3*H*-1,3,4-Thiadiazolo[2,3-*c*][1,2,4]thiadiazoles (6, X = S; Y = CCH_3; Z = N). Sulfenamide **5** (X = S; Y = CCH_3; Z = N) (0.01 mol) was added portionwise to a stirred solution of a primary, aromatic amine (0.01 mol), Et_3N (0.03 mol), and $CHCl_3$ (150 ml). After stirring for 14 hr the reaction mixture was evaporated to dryness. **A.** The residue was washed with CH_3OH and purified by crystallization from a suitable solvent. **B.** The residue was washed with H_2O yielding a semisolid which was extracted with $CHCl_3$. Separation and drying of the $CHCl_3$ over $MgSO_4$ and evaporation to dryness afforded a solid which was purified by crystallization from a suitable solvent (Table I).

Acid Hydrolysis of 6 (X = S; Y = CCH_3; Z = N; R = 3-$NO_2C_6H_4$). 6-Methyl-3-(3-nitrophenylimino)-3*H*-1,3,4-thiadiazolo[2,3-c][1,2,4]thiadiazole (0.50 g) was refluxed in HCl (10%, 20 ml) and EtOH (40 ml). After 24 hr the solvent was removed from the reaction mixture and the residue was neutralized with aqueous $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$ which was subsequently separated and dried over Na_2SO_4. The $CHCl_3$ was then removed and the residue, after preparative layer chromatography [1.00 mm, $CHCl_3$–EtOAc (80:20)], afforded three components which were identified as 3-nitroaniline, 2-amino-5-methyl-1,3,4-thiadiazole, and S_8. All three were identical in all respects with authentic samples.

Representative Procedure for the Preparation of Some 3-Substituted 3*H*-1,2,4-Thiadiazolo[4,3-*d*][1,2,4]thiadiazoles (6, X = S; Y = N; Z = CCH_3). 5-Methyl-3-(2,5-dichlorophenylimino)-3*H*-1,2,4-thiadiazolo[4,3-*d*][1,2,4]thiadiazole (6, X = S; Y = N; Z = CCH_3; R = 2,5-$Cl_2C_6H_3$). Sulfenamide **5** (X = S; Y = N; Z = CCH_3) (0.53 g) was added portionwise to a stirred solution of 2,5-dichloroaniline (0.32 g), Et_3N (0.61 g), and $CHCl_3$ (50 ml).

After stirring for 14 hr, the solvent was removed from the reaction mixture, yielding a cream product which, after washing with CH_3OH, crystallized from EtOAc as cream needles, 0.23 g (36%), mp 185–187° (Table I).

Registry No.—6-Methyl-3-substituted 3*H*-isoxazolo[3,2-*c*]-[1,2,4]thiadiazoles, 55723-65-4 (R = 2,5-$Cl_2C_6H_3$), 55723-66-5 (R = 2-$NO_2C_6H_4$), 55723-67-6 (R = 3-$NO_2C_6H_4$), 55723-68-7 (R = 4-$NO_2C_6H_4$; 3-substituted 3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazoles, 55723-69-8 (R = 3-$NO_2C_6H_4$), 55723-70-1 (R = 4-$NO_2C_6H_4$); 6-methyl-3-substituted 3*H*-1,3,4-thiadiazolo[2,3-c][1,2,4]thiadiazoles, 55723-71-2 (R = 2,5-$Cl_2C_6H_3$), 55723-72-3 (R = 3-$NO_2C_6H_4$), 55723-73-4 (R = 4-$NO_2C_6H_4$); 5-methyl-3-substituted 3*H*-thiadiazolo[4,3-*d*][1,2,4]thiadiazoles, 55723-74-5 (R = 2,5-$Cl_2C_6H_3$), 55723-75-6 (R = 3-$NO_2C_6H_4$); **1**, 1072-67-9; **2**, 55723-76-7; **3** (R = 5-CH_3-2-C_5H_3N; R_1 = 6-CH_3), 24097-95-8; **5** (X = O; Y = CPh; Z = N), 55723-77-8; **5** (X = S; Y = Z = CH), 55723-78-9; **5** (X = S; Y = CCH_3; Z = N), 55723-79-0; **5** (X = S; Y = N; Z = CCH_3), 55723-80-3; 2-amino-5-phenyl-1,3,4-oxadiazole, 1612-76-6; 2-aminothiazole, 96-50-4; 2-amino-5-methyl-1,3,4-thiadiazole, 108-33-8; 5-amino-3-methyl-1,2,4-thiadiazole, 17467-35-5; 2-amino-5-methylpyridine, 1603-41-4; trichloromethanesulfenyl chloride, 594-42-3.

References and Notes

(1) (a) Support of this work by U.S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged; (b) Eastman Kodak Fellow, 1974.

(2) For reviews on this topic see L. L. Bambas in "Five Membered Heterocyclic Compounds", Interscience, New York, N.Y., 1952, p 35; W. A. Shermann in "Heterocyclic Compounds", Vol. 7, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1961, p 558; F. Kurzer, *Adv. Heterocycl. Chem.*, **5**, 119 (1965); F. Kurzer in "Organic Compounds of Sulfur, Selenium, and Tellurium", Vol. 1, D. H. Reid, Ed., The Chemical Society, London, 1970, p 446; F. Kurzer, *ibid.*, Vol. 2, 1973, p 721.

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(10) Spectral characterizations were carried out on the following instrumentation: infrared spectra, Perkin-Elmer Model 337 spectrophotometer; ultraviolet spectra, Cary 14 spectrophotometer; NMR spectra, Varian T-60 and HA-100 spectrometers, using Me_4Si as an internal standard; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV, utilizing the direct insertion probe technique with a source temperature of ca. 150°. All melting points were determined in capillaries using a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus. Evaporations were carried out under reduced pressure using a Buchi Rotovap apparatus. PLC was carried out on 20 × 20 mm plates using silica gel PF 254 with $CaSO_4$ (thickness and solvent as indicated). Microanalyses were by Galbraith Laboratories, Knoxville, Tenn., and Instranal Laboratory, Inc., Rensselaer, N.Y.

(11) Generally, partial decomposition of these sulfenamides during purification resulted in unsatisfactory analytical data.

(12) Alconox is the registered trade name of a phosphorus base wetting agent and detergent manufactured by Alconox Inc., New York, N.Y.

Reaction of 2-Arylhydrazono-3-oxonitriles with Hydroxylamine. Synthesis of 3-Amino-4-arylazoisoxazoles

Mohamed Hilmy Elnagdi,* Mohamed Rifaat Hamza Elmoghayar, Ebtisam Abdel Aziz Hafez, and Hikmat Hussein Alnima

Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R., Egypt

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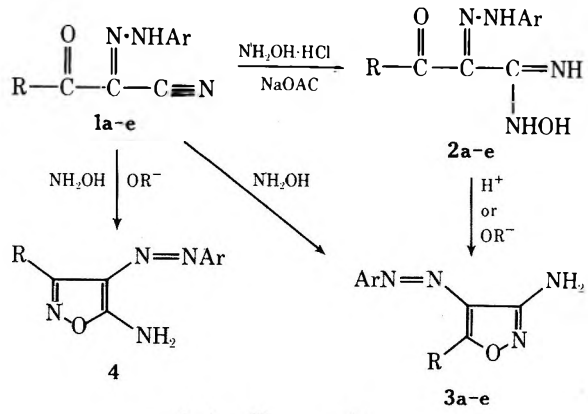
Whereas the 2-arylhydrazono-3-oxonitriles **1a–e** react with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol to yield the amidoximes **2a–e**, 3-amino-4-arylazo 5-substituted isoxazoles (**3a–e**) are formed when **1a–e** are treated with hydroxylamine in aqueous ethanol. On the other hand, treatment of **1a–e** with hydroxylamine in the presence of excess methanolic sodium methoxide has resulted in the formation of the 5-amino-4-arylazo 3-substituted isoxazoles **4a–e**. Ethyl arylazocyanoacetate (**11a–e**) reacts with hydroxylamine hydrochloride and sodium acetate to yield the amidoximes **12a–e**, which could be readily cyclized into the 3-aminoisoxazoles **13a–e** by the action of methanolic sodium methoxide. The behavior of **2** toward the action of thionyl chloride, benzaldehyde, and hydrazines is reported.

Although several recent papers have dealt with the synthesis and biological evaluation of 4-arylazo-5-isoxazolones,[1-3] 4-arylazo-5-aminoisoxazoles have been neglected. We have now studied the reaction of some 2-arylhydrazono-3-oxonitriles with hydroxylamine as a source of aminoarylazoisoxazoles.

Treatment of the β-ketonitriles **1a–e** with NH_2OH·HCl and sodium acetate in refluxing ethanol led to amidoximes **2a–e**. Cyclization of these products with H_2SO_4 or sodium ethoxide gave the 3-aminoisoxazoles **3a–e**; these compounds were also obtained directly from the reaction of **1a–e** with NH_2OH in aqueous ethanol. The preferential attack of NH_2OH at the C≡N group in these reactions is in contrast to other findings,[4,5] which indicate that the CO group in **1a–e** is the more reactive electrophilic center in nonprotic media. The enhanced reactivity of the C≡N group in the hydroxylamine reactions is attributed to protonation. Consistent with this view are the findings that at pH 11, no reaction with NH_2OH occurred, and that in the presence of alkoxides, the 5-amino compounds **4a–e** were formed in good yield. Compounds **4a–d** were also obtained via action of aryldiazonium salts on 5-amino-3-phenylisoxazole (**5**). Although ethyl cyanoacetate derivatives have been shown to react with NH_2OH to yield either 3- or 5-aminoisoxazoles depending on reaction conditions,[6] 5-aminoisoxazoles or 5-isoxazolones are the only reported products from reaction of 3-oxonitriles with NH_2OH under a variety of acidic and basic conditions.[7-11]

In contrast to the behavior of **1a–e**, the methylarylhydrazones **6a–d** reacted with NH_2OH·HCl and sodium acetate in refluxing ethanol to yield the 5-imino-2-isoxazolines **7a–d.** Compound **7a** was converted into 4-methylphenylhydrazono-3-phenyl-2-isoxazolin-5-one (**8**) by the action of ACOH–HCl mixture.

Similar to the behavior of **1a–e** toward the action of NH_2OH, the 2-phenylhydrazono-3-iminonitriles **9a,b**



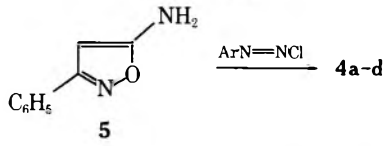
1a-e

2a-e

4

3a-e

1-4	R	Ar
a	C_6H_5	C_6H_5
b	C_6H_5	3-$CH_3C_6H_4$
c	C_6H_5	4-$CH_3C_6H_4$
d	C_6H_5	4-ClC_6H_4
e	CH_3	C_6H_5



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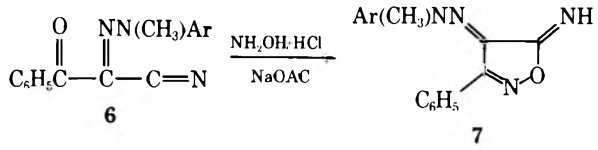
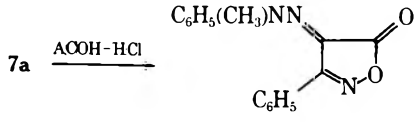


6

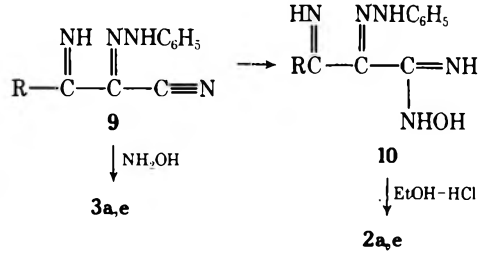
7

6, 7	Ar
a	C_6H_5
b	3-$CH_3C_6H_4$
c	4-$CH_3C_6H_4$
d	4-ClC_6H_4



8

reacted with NH_2OH·HCl and sodium acetate to yield the amidoximes **10a,b.** The latter derivatives could be converted into **2a,e** by the action of ethanolic hydrochloric acid. On the other hand, **9a,b** reacted with NH_2OH in aqueous ethanol to yield compounds **3a,e.**



9

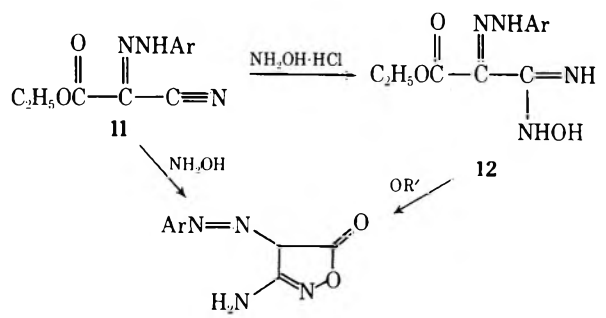
10

3a,e

2a,e

9, 10a, R = CH_3
b, R = C_6H_5

Conflicting results have been reported[12-14] for the reaction of ethyl arylazocyanoacetate (11) with hydroxylamine. As a part of the present investigation it was thought worthwhile to establish the behavior of **11a-e** toward NH_2OH. Thus, treatment of **11a-e** with NH_2OH·HCl and sodium acetates using the experimental procedure described by Bianchi[14] led to the formation of the amidoximes **12a-e** in good yields. Cyclization of **12a-e** by alkoxides afforded



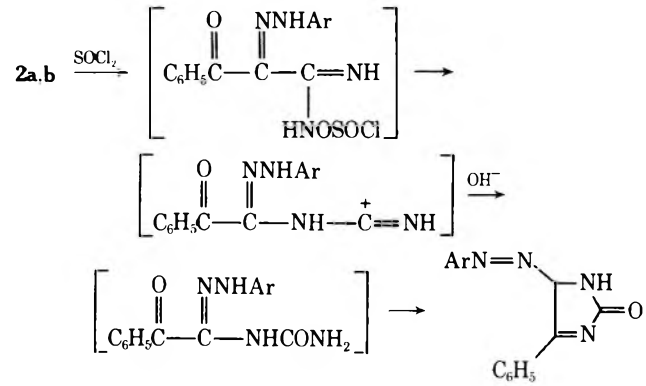
11

12

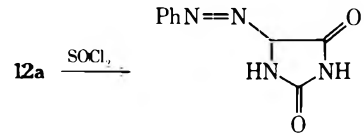
13

11-13	Ar
a	C_6H_5
b	3-$CH_3C_6H_4$
c	4-$CH_3OC_6H_4$
d	4-ClC_6H_4
e	4-BrC_6H_4

13a-d. The latter compounds were obtained directly from reaction of **11a-e** with NH_2OH in aqueous ethanol. Treatment of **2a,b** with thionyl chloride, in benzene solution, resulted in their rearrangement into the 2-imidazolin-2-one derivatives **14a,b.** Similarly, the amidoxime **12a** rearranged into 4-phenylazohydantoin (**15**) by the action of the reagent.



14a, Ar = C_6H_5
b, Ar = 3-$CH_3C_6H_4$



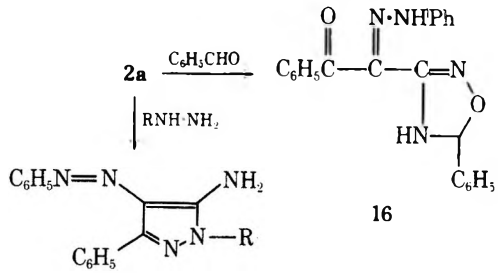
15

The formation of **14a,b** and **15** via rearrangement of **2a,b** and **12a** with thionyl chloride may be assumed to proceed by the rearrangement of the latter compounds into a urea derivative which then cyclizes into the corresponding imidazoline derivatives **14a,b** and **15.** This is similar to the reported Tiemann rearrangement of amidoximes with sulfonyl halides to give ureas.[15] An alternative to this mechanism may be the cyclization of the amidoximes **2a,b** and **12a** into the corresponding 2-aminoisoxazole derivative, which then rearranges into the final product via a mechanism similar to that considered recently by Nishiwaki et al.[16] for the rearrangement of 5-aminoisoxazoles into 3-imidazolin-2-ones. The latter possibility was however readily ruled out, since **3a,b** and **12a** were recovered almost unreacted when treated with thionyl chloride in benzene solution under the experimental conditions used to affect rearrangement of **2a,b** and **12a.**

When amidoximes are treated with aromatic aldehydes they are converted into 4,5-dihydro-1,2,4-oxadiazole deriv-

atives.[17] Thus, when **2a** was treated with benzaldehyde in the presence of piperidine, the 1,2,4-oxadizole derivative **16** was formed.

Compound **2a** reacted with hydrazine hydrate and with phenylhydrazine to yield the aminopyrazole derivatives **17a,b.**



17a, R = H
b, R = C_6H_5

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded (KBr) on a Perkin-Elmer Model 337 spectrophotometer. Satisfactory analytical data (±0.3% for C, H, N) were presented for all compounds in Tables I–IV.

Reaction of 1a–e, 9a,b, and 11a–e with Hydroxylamine Hydrochloride and Sodium Acetate. General Procedure. To a suspension of the compound (0.1 mol) in ethanol (100 ml) a solution of NH_2OH·HCl (0.1 mol) in 30 ml of water and 10 g of anhydrous sodium acetate were added. The reaction mixture was refluxed for 3 hr and then poured onto water. The solid product, so formed, was collected by filtration and crystallized from the proper solvent. The amidoxime derivatives **2a–e, 10a,b** and **12a–e** are listed in Table I.

Compounds **2a–e** showed ir bands at 1600–1610 (ν C=N), 1620–1625 (δ NH_2), 1630–1640 cm^{-1} (ν CO), 3265–3280 and 3340–3350 (ν NH_2), and 3470–3475 cm^{-1} (ν OH).

Compounds **10a,b** showed ir bands at 1625–1630 (ν C=N), 1640–1645 (δ NH_2), 3300 and 3400–3410 (ν NH_2), and 3450 cm^{-1} (ν OH).

Compounds **12a–e** showed ir bands at 1605–1610 (ν C=N), 1625–1640 (δ NH_2), 1690–1695 (ester CO), 3270–3275 and 3350–3355 (ν NH_2), and 3475–3480 cm^{-1} (ν OH).

3-Amino-4-arylazo 5-Substituted Isoxazoles (3a–e). A. From 1a–e or 9a,b and hydroxylamine. To a solution of the appropriate compound (0.1 mol) in ethanol (100 ml) was added an aqueous solution of NH_2OH (prepared by dissolving 0.1 mol of NH_2OH·HCl in 20 ml of water and neutralizing the resulting solution by addition of 0.1 equiv of Na_2CO_3). The reaction mixture was then refluxed for 4 hr, cooled, poured onto water, acidified with acetic acid, and left to stand. The solid product, so formed, was collected by filtration and crystallized from ethanol. The isoxazole derivatives **3a–e** are listed in Table II.

Compounds **3a–e** showed ir bands at 1616–1630 (δ NH_2), 3350–3365, and 3420–3450 cm^{-1} (ν NH_2).

B. From 2a–e and Concentrated Sulfuric Acid. Concentrated sulfuric acid (2 ml, 98%) was added to each of **2a–e** (3 g). The reaction mixture was kept at room temperature for 2 hr and then poured onto ice-cold water. The solid product, so formed, was collected by filtration, crystallized from ethanol, and identified (melting point, mixture melting point, and ir) as **3a–e.**

C. From 2a–e and Methanolic Sodium Methoxide. To a sodium methoxide solution (prepared from 1.0 g of sodium metal and 80 ml of methanol), 5 g of each of **12a–e** was added. The reaction mixture was then refluxed for 1 hr, left to cool, poured over water, and acidified with concentrated hydrochloric acid. The solid product, so formed, was collected by filtration and identified (melting point and mixture melting point) as **3a–e.**

Reaction of 1a–e with Hydroxylamine at pH 11. Compounds **1a–e** were recovered almost unaffected after being refluxed with an equivalent amount of NH_2OH in ethanolic solution the pH of which was adjusted to 11.

5-Amino 3-Substituted 4-Arylazoisoxazoles (4a–e). A. From 1a–e and Hydroxylamine. To a suspension of each of **1a–e** (0.1 mol) in ethanol (50 ml), hydroxylamine hydrochloride (0.1 mol) and methanolic sodium methoxide (prepared from 5 g of sodium metal and 100 ml of ethanol) were added. The reaction mixture was refluxed for 12 hr and then evaporated in vacuo. The remaining solid product was dissolved in water and neutralized by addition of acetic acid. The resulting solid product was collected by filtration and crystallized from ethanol. The isoxazole derivatives **4a–e,** listed in Table III, were further purified by crystallization from ethanol.

Compounds **4a–e** showed ir bands at 1615–1620 (δ NH_2) and 3330–3340 and 3420–3430 cm^{-1} (ν NH_2).

B. From 5-Amino-3-phenylisoxazole and Aryldiazonium Salts. A solution of **5** (14.6 g) in acetic acid (100 ml) was treated with a solution of 5 g of anhydrous sodium acetate in 35 ml of water and then with the appropriate aryldiazonium salt (prepared from 0.1 mol of the amine and the corresponding quantity of sodium nitrite). The reaction mixture was left at room temperature for 1 hr and the solid product, so formed, was collected by filtration, crystallized, and identified (melting point and mixture melting point) as **4a–e.**

5-Ketimino-4-methylarylhydrazono-3-phenyl-2-isoxazolines (7a–d). Each of **6a–d** was treated with NH_2OH·HCl and anhydrous sodium acetate using the same experimental procedure previously described for the reaction of **1a–e** with the same reagents. The resulting reaction solution was poured onto water and the resulting solid products were collected by filtration and crystallized from ethanol. The 5-imino-2-isoxazoline derivatives **7a–d** are listed in Table IV.

Compounds **7a–d** showed ir bands at 1610–1620 (ν C=N) and 3400–3410 cm^{-1} (ν NH).

4-Methylphenylhydrazono-3-phenyl-2-isoxazolin-5-one (8). A suspension of **7a** (5 g) in acetic acid (90 ml) and hydrochloric acid (10 ml, 30%) was refluxed for 1 hr and then evaporated in vacuo. The remaining solid product was identified (melting point and mixture melting point) as the known 8.[18]

Hydrolysis of 10a,b with Ethanolic Hydrochloric Acid. To a suspension of each of **10a,b** (5 g) in ethanol (80 ml) was added 20 ml of hydrochloric acid (30%). The reaction mixture was refluxed for 10 min and then left to cool. The solid product, so formed, was

Table I
List of the Amidoxime Derivatives 2a–e, 10a, b, and 12a–e

Compd	Yield, %	Crystn solvent[a]	Mp, °C	Formula
2a	90	a	156	$C_{15}H_{14}O_2N_4$
2b	95	a	165	$C_{16}H_{16}O_2N_4$
2c	85	a	169	$C_{16}H_{16}O_2N_4$
2d	80	a	166	$C_{15}H_{13}O_2N_4Cl$
2e	85	b	180	$C_{10}H_{12}O_2N_4$
10a	78	c	191	$C_{10}H_{13}ON_5$
10b	75	c	126	$C_{15}H_{15}ON_5$
12a	70	d	198	$C_{11}H_{14}O_3N_4$
12b	82	d	200	$C_{12}H_{16}O_3N_4$
12c	85	d	222	$C_{12}H_{16}O_4N_4$
12d	80	c	192	$C_{11}H_{13}O_3N_4Cl$
12e	80	c	200	$C_{11}H_{13}O_3N_4Br$

[a] a, ethanol; b, dioxane; c, 2-propanol; d, dioxane–2-propanol (1:1).

Table II
List of 4-Arylazo-3-amino 5-Substituted Isoxazoles 3a–e and 13a–e

Compd	Yield, %	Mp, °C	Formula
3a	90	186	$C_{15}H_{12}ON_4$
3b	92	150	$C_{16}H_{14}ON_4$
3c	95	194	$C_{16}H_{14}ON_4$
3d	89	225	$C_{15}H_{11}ON_4Cl$
3e	89	171	$C_{10}H_{10}ON_4$
13a	80	208	$C_9H_8O_2N_4$
13b	85	245	$C_{10}H_{10}O_2N_4$
13c	85	228	$C_{10}H_{10}O_3N_4$
13d	80	210	$C_9H_7O_2N_4Cl$
13e	90	260	$C_9H_7O_2N_4Br$

Table III
List of 5-Amino-4-arylazo 3-Substituted Isoxazole Derivatives (4a–e)

Compd	Yield, %	Mp, °C	Formula
4a	60	141	$C_{15}H_{12}ON_4$
4b	65	151	$C_{16}H_{14}ON_4$
4c	58	144	$C_{16}H_{14}ON_4$
4d	57	172	$C_{15}H_{11}ON_4Cl$
4e	50	166	$C_{10}H_{10}ON_4$

Table IV
List of 5-Ketimino-4-methylarylhydrazono-3-phenyl-2-isoxazolines (7a–d)

Compd	Yield, %	Mp, °C	Formula
7a	68	136	$C_{16}H_{14}ON_4$
7b	70	164	$C_{17}H_{16}ON_4$
7c	70	198	$C_{17}H_{16}ON_4$
7d	67	154	$C_{16}H_{13}ON_4Cl$

collected by filtration and identified (melting point and mixture melting point) as **2a** and **2e**, respectively.

3-Amino-4-arylazo-2-isoxazolin-5-ones (13a–e). A. From 11a–e and Hydroxylamine. The experimental conditions described previously for the synthesis of **3a–e** from **1a–e** and hydroxylamine were adopted. The reaction products **13a–e** are listed in Table II.

Compounds **13a–e** showed ir bands at 1625–1635 (δ NH_2), 1690–1695 (CO), and 3350–3360 and 3415–3420 cm^{-1} (ν NH_2).

B. From 12a–e and Methanolic Sodium Methoxide. The experimental conditions previously used to effect cyclization of **2a–e** into **3a–e** by the action of sodium methoxide were adopted and the reaction products were identified (melting point and mixture melting point) as **13a–e**.

4-Arylazo-3-imidazolin-2-one (14a,b). To a solution of each of **2a,b** (5 g) in dry benzene (100 ml), thionyl chloride (10 ml) was added. The reaction mixture was kept for 2 hr at room temperature and then poured onto ice-cooled water. The benzene layer was then separated, dried, and evaporated. The resulting solid products, **14a,b**, were crystallized from ethanol.

14a: red crystals, mp 200°, ir 1615 (C=N), 1680 (C=O), and 3430 cm^{-1} (NH).

Anal. Calcd for $C_{16}H_{14}ON_4$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.97; H, 5.00; N, 20.20.

4-Phenylazohydantoin (15). Compound **12a** was treated with benzene and thionyl chloride using the same experimental procedure previously adopted for synthesis of **14a,b** from **2a,b**. The reaction product was purified by crystallization from acetic acid and identified (melting point, mixture melting point, and ir) as the known **15**.[19]

Reactions of 2a. A. With Benzaldehyde. To a mixture of **2a** (2 g) and benzaldehyde (1 ml) 1 drop of piperidine was added. The reaction mixture was heated at 100° (bath temperature) for 4 hr, then triturated with ethanol and left to stand. The crystals that separated were collected by filtration and recrystallized from ethanol to yield 1.5 g of **16**: mp 100°; ir 1660 (CO) and 3340 and 3420 cm^{-1} (ν NH groups).

Anal. Calcd for $C_{22}H_{18}O_2N_4$: C, 71.33; H, 4.90; N, 15.13. Found: C, 71.50; H, 4.61; N, 15.00.

B. With Hydrazines. A mixture of **2a** (2 g) and hydrazine hydrate (1 ml, 98%) or phenylhydrazine (1.5 ml) was heated at 100° (bath temperature) for 3 hr. The reaction mixture was then treated with dilute hydrochloric acid to remove the excess hydrazine and the resulting solid product was collected by filtration, crystallized, and identified (melting point and mixture melting point) as **16a** in case of **2a** and hydrazine hydrate and **16b** in case of **2a** and phenylhydrazine.

Registry No.—**1a**, 13491-70-8; **1b**, 40257-77-0; **1c**, 22744-14-5; **1d**, 22744-17-8; **1e**, 28317-57-9; **2a**, 55621-95-9; **2b**, 55621-96-0; **2c**, 55621-97-1; **2d**, 55621-98-2; **2e**, 55621-99-3; **3a**, 55622-00-9; **3b**, 55622-01-0; **3c**, 55622-02-1; **3d**, 55622-03-2; **3e**, 55622-04-3; **4a**, 55622-05-4; **4b**, 55622-06-5; **4c**, 55622-07-6; **4d**, 55622-08-7; **4e**, 55622-09-8; **5**, 4369-55-5; **6a**, 54670-89-2; **6b**, 54670-91-6; **6c**, 54670-92-7; **6d**, 54670-93-8; **7a**, 55622-12-1; **7b**, 55622-11-2; **7c**, 55622-12-3; **7d**, 55622-13-4; **9a**, 5110-91-8; **9b**, 15590-17-7; **10a**, 55622-14-5; **10b**, 55622-15-6; **11a**, 5335-36-4; **11b**, 3994-20-5; **11c**, 51337-35-0; **11d**, 3994-24-9; **11e**, 3994-25-0; **12a**, 55622-16-7; **12b**, 55622-17-8; **12c**, 24793-33-7; **12d**, 55622-18-9; **12e**, 55622-19-0; **13a**, 55622-20-3; **13b**, 55622-21-4; **13c**, 55622-22-5; **13d**, 55622-23-6; **13e**, 55622-24-7; **14a**, 55622-25-8; **14b**, 55622-26-9; **16**, 55622-27-0; hydroxylamine hydrochloride, 5470-11-1; benzaldehyde, 100-52-7; benzenediazonium chloride, 100-34-5; 3-methylbenzenediazonium chloride, 2028-72-0; 4-methylbenzenediazonium chloride, 2028-84-4; 4-chlorobenzenediazonium chloride, 2028-74-2.

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Curtius and Lossen Rearrangements. III. Photolysis of Certain Carbamoyl Azides

Walter Lwowski,* Richard A. de Mauriac,[1] and Margaret Thompson

Department of Chemistry, New Mexico State University, Las Cruces, New Mexico 88003

Richard E. Wilde* and Sis-Yu Chen

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

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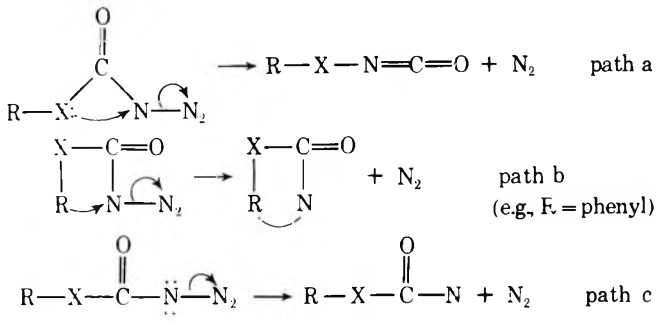
The photo-Curtius rearrangement of several substituted carbamoyl azides gives aminoisocyanates, PhHN–NCO, EtHN–NCO, Me_2N–NCO, and Et_2N–NCO. These can be trapped by nucleophiles. Neon-matrix isolated photolysis of dimethylcarbamoyl azide gave *N,N*-dimethylaminoisocyanate, whose ir spectrum was recorded and whose photodecomposition was observed. Products attributable to the carbamoylnitrenes, RR'NCON, isomers of the aminoisocyanates mentioned, were not found.

The familiar 1,2 migrations of carbon moieties from a carbon to a heteroatom often have counterparts in which a heteroatom migrates: RX–C–Y → RX–Y–C. The thermal Curtius rearrangement (migration of a carbon moiety from C to N) is concerted,[2-7] migration of the carbon moiety and loss of nitrogen occurring simultaneously. This is also true for the photoinduced Curtius rearrangement.[5-7]

Heteroatom migrations analogous to the Curtius rearrangement compete with alternate reactions such as the concerted displacement of nitrogen not by the heteroatom X (path a, Curtius rearrangement), but by another part of the group attached to the carbonyl (path b). Another competing reaction is the breaking of the N_α–N_β bond without assistance, resulting in a nitrene (path c).



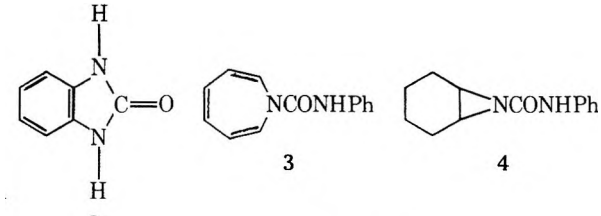
(charges and valence-balancing reactions omitted)

Examples for all three paths are provided by decompositions of diaryl- and arylalkylcarbamoyl azides.[8,9] For example, the thermolysis of diphenylcarbamoyl azide gives *N,N*-diphenylaminoisocyanate and 1-phenylbenzimidazole by concerted paths a and b, while photolysis leads to the nitrene Ph_2NCON, which then cyclizes.[8,9]

We have communicated earlier[10] the Curtius rearrangement in the photolyses of $PhNHCON_3$, $EtNHCON_3$, and Et_2NCON_3, both in protic[10] and in aprotic media.[11] The intermediacy of aminoisocyanates RR'N–N=C=O was inferred from the isolated end products, which are also formed when *N,N*-dialkylaminoisocyanates are generated thermally in the presence of the appropriate reactants.[12] Some questions remain. Are carbamoylnitrenes formed together with the aminoisocyanates, as one might expect in view of the nitrene formation from diarylcarbamoyl azides?[8,9] Can the assumption of intermediate aminoisocyanates be supported spectroscopically? The present paper addresses itself to these questions.

Results

Phenylcarbamoyl azide (1) was photolyzed with 254-nm light in benzene, cyclohexene, and cyclohexane solutions



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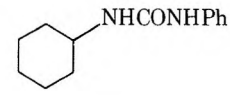

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and a search for the expected nitrene products 2–5 was made. Although the compounds 3 and 4 were prepared independently and could have been easily detected, none of the compounds 2–5 was found in the photolysis reaction mixture. What we did obtain was a complex mixture which seems to arise from dimerization of PhNHNCO, followed by tautomerizations and perhaps subsequent photoreactions. We have not studied these products further. The infrared spectra of the total reaction mixtures from the photolyses in benzene, cyclohexene, and cyclohexane were practically identical, indicating that solvent had not been incorporated in the products. In contrast to these photolyses, clean reactions were observed in methanol solution, where a 65% yield of methyl 2-phenylhydrazinecarboxylate (6) was obtained. This indicates the formation of PhNHNCO, followed by addition of methanol to give $PhNHNHCOOCH_3$ (6).

Photolysis of *N*-ethylcarbamoyl azide (7) in cyclohexene did not give any apparent nitrene products. Addition of EtNHCON to the double bond would give 7-(*N*-ethylcarbamoyl)-7-azabicyclo[4.1.0]heptane (8), which was prepared independently. It could have been detected easily in the photolysis reaction mixture. The amorphous product actually obtained from the photolysis in cyclohexene was very similar to that obtained by photolyzing 7 in benzene—both photolyses did not lead to incorporation of solvent into the product mixtures, which were not studied further. Photolysis in methanol gave a 50% (not maximized) yield of methyl 2-ethylhydrazinecarboxylate (9), the apparent product of methanol addition to EtNHNCO.

Photolysis of diethylcarbamoyl azide (10) did not give *N*-cyclohexyl-*N'N'*-diethylurea (11), the product expected from C–H insertion of Et_2NCON. Instead, a 18% yield of a dimer 12 of Et_2N–NCO was isolated. Thermally generated Et_2N–NCO gives the same dimer.[12] Its structure, 1,1-diethyl-4-diethylamino-1,2,4-triazolidin-3,5-dion-1,2-aminimide, has been discussed elsewhere.[11] Photolysis of 10 in

Table I
Wave Numbers and Assignments of New Bands Observed after Photolysis of $(CH_3)_2NCON_3$ in a Neon Matrix

Cm^{-1}	Assignment	Species
455 ± 5 w		
555 ± w		
760 ± 5 w		
957 ± 2 w[b]		$(CH_3)_2NNCO$
1025 ± 5 w[b]		$(CH_3)_2NNCO$
1445 ± 2 m[a]	ν_3 CH_3 def	CH_3NC
1456 ± 2 m[a]		CH_3NC
1472 ± 2 m[a]	ν_{6b} CH_3 def	CH_3NC
1479 ± 2 m[a]	ν_{6a} CH_3 def	CH_3NC
1599 ± 2 vw		
1608 ± 2 vw		
2141 ± 2 s[a]	ν_2–N≡C str	CH_3NC
2230 ± 2 s[b]	–N=C=O str	$(CH_3)_2NNCO$
2269 ± 2 m–s[a]	ν_2 –N=C=O str	HNCO
2899 ± 3 m[a]	$2\nu_6$	CH_3NC
2957 ± 5 m[a]	ν_1 C–H str	CH_3NC
2993 ± 3 m[a]	ν_5 C–H str	CH_3NC

[a] Increases in intensity upon prolonged photolysis. [b] Decreases in intensity upon prolonged photolysis.

Table II
Wave Numbers and Assignments of New Bands Observed after Photolysis of $(CD_3)_2NCON_3$ in a Neon Matrix

Cm^{-1}	Assignment	Species
600 ± 5 w		
1080 ± 5 w–m		
1115 ± 5 vw[b]		$(CD_3)_2NNCO$
1612 ± 5 w[b]		$(CD_3)_2NNCO$
1640 ± 5 w[a]	ν_{3+8}	CD_3NC
1680 ± 5 w[a]	ν_{6+8}	CD_3NC
1830 ± 5 w[a]	$2\nu_4$	CD_3NC
2091 ± 2 w–m		
2141 ± 2 s[a]	ν_2 –N≡C str	CD_3NC
2226 ± 2 m–s[a]	ν_2 –N=C=O str	DNCO
2241 ± 2 s[b]	–N=C=O str	$(CD_3)_2NNCO$
2255 ± 2 m[a]	ν_1 C–D str	CD_3NC
2268 ± 2 m[a]	ν_5 C–D str	CD_3NC
2350 ± 2 m–s[a]	ν_1 N–D str	DNCO

[a] Increases in intensity upon prolonged photolysis. [b] Decreases in intensity upon prolonged photolysis.

cyclohexene did not give the aziridine expected from the addition of Et_2NCON to the double bond. The product mixture obtained was remarkably similar to that produced by the photolysis in cyclohexane, but a 15% yield of 3,3′-biscyclohexenyl and some diethylurea (**13**) were also found. The last two products might well have been formed by mechanisms analogous to those found with triplet excited ethyl azidoformate;[13] thus they furnish no proof for the intervention of a nitrene. Photolyses of **10** in solvents of different polarity, ether and acetonitrile, again gave no nitrene addition or insertion products, nor did we find the known 1-ethylimidazolidin-2-one,[14] expected from intramolecular C–H insertion of the nitrene $(H_3C–CH_2)_2NCON$. The dimer **12** was obtained in 22% yield in ether solution and in 14% yield in acetonitrile. Photolysis of **10** in methanol, however, gave methyl 2,2-diethylhydrazinecarboxylate (**14**) in 78% crude yield (57% after purification to an undepressed mixture melting point). Low concentrations of methanol (or of diethylamine, see below) are sufficient to intercept the $Et_2N–NCO$. Photolysis of a cyclohexane solution 0.05 *M* in the azide **10** and 0.05 *M* in methanol gave a 41% yield of **14** (by weight after sublimation). In another experiment, 9.73 mmol of **10** in 200 ml of cyclohexane (a 0.05 *M* solution) was irradiated until ca. 69% of the theoretical yield of nitrogen had been evolved. The lamps were turned off, and 5.12 mmol of methanol was then injected into the stirred solution. By VPC, the yield of **14** was found to be 0.8%. Apparently, the photolysis produces an intermediate that reacts readily even with low concentrations of methanol to give **14**, but which reacts via a slower path in the absence of methanol. The contention that this intermediate is $Et_2N–NCO$ is strengthened by the irradiation of cyclohexane solution, 0.25 *M* both in diethylamine and **10**. The adduct of diethylamine to the presumed *N,N*-diethylaminoisocyanate, *N,N*,2,2-tetraethylhydrazinecarboxamide, $Et_2N–NHCONEt_2$ (**15**), was isolated in 53% yield and identified by comparison with an authentic sample. Irradiation of **10** in pure *tert*-butyl alcohol gave a 20–40% yield of *tert*-butyl 2,2-diethylhydrazinecarboxylate (**16**). Irradiation of 25.5 mmol of **10** in 500 ml of water and isolation of the oxalic acid salts gave that of diethylamine (by hydrolysis and decarboxylation from **10**) in 35% yield, and the oxalate of 1,1-diethylhydrazine (by hydrolysis and decarboxylation of $Et_2N–NCO$) in 19% yield.

The photolysis of *N,N*-dimethylcarbamoyl azide (**17**) in methanol solution gave a 32% yield of methyl 2,2-dimethylhydrazinecarboxylate (**18**) when light of 254-nm wavelength was used. A 46% yield of **18** was obtained when we used fluorescent uv lamps which emit most of their light around 300 nm (RPR 3000 lamps of The Southern New England Ultraviolet Co.).

Matrix Isolation Studies. Physical evidence for the nature of the primary photolysis product of *N,N*-dimethylcarbamoyl azide was obtained by matrix-isolation photolysis and infrared spectroscopy. Both $(CH_3)_2NCON_3$ and $(CD_3)_2NCON_3$ were photolyzed in neon matrices at 6 K and the reactions monitored by ir spectroscopy. The wave numbers of the bands which appear and disappear during times up to 390 min are listed in Tables I and II. After 15 min of photolysis, all the bands in the matrix-isolated spectrum of $(CH_3)_2NCON_3$ showed a marked decrease in intensity. However, in the 2230-cm^{-1} region there appeared a very intense new band, as seen in Figure 1, trace b. Upon continued photolysis, this band decreased in intensity. Based on the chemical studies discussed above, and the results of photolysis of methyl azidoformate in a neon matrix,[15] it is reasonable to assign the 2230-cm^{-1} band to $(CH_3)_2N–NCO$. Two weak bands at 957 and 1025 cm^{-1} also decreased in intensity upon prolonged photolysis and therefore have been assigned to the $(CH_3)_2N–NCO$ molecule.

As shown in Figure 1, upon photolysis a new band appeared at 2141 cm^{-1} and continued to increase in intensity upon prolonged photolysis, as did the band at 2269 cm^{-1}. It is well known[15] that the isocyanate asymmetric stretching vibration of isocyanic acid occurs near 2270 cm^{-1}. The band at 2141 cm^{-1} is in the region of the –N≡C stretching vibration. In view of the data in Table I and the known[16] ir spectrum of H_3CNC [1410 (m), 1459 (m), 2166 (vs), 2966 (vs), and 3014cm^{-1} (vs)], we assign the 2141-cm^{-1} band to H_3CNC. The interaction between HNCO and $H_3C–CN$ trapped in the matrix is responsible for the 25-cm^{-1} lowering of the isocyanide stretching frequency. The C–H stretching frequencies are also lowered somewhat by the matrix environment. The CH_3 deformation modes listed in Table I appear in the 1400–1500-cm^{-1} region. These bands increase in intensity upon prolonged photolysis, and can be assigned to the H_3CNC molecule. The bands are surpris-

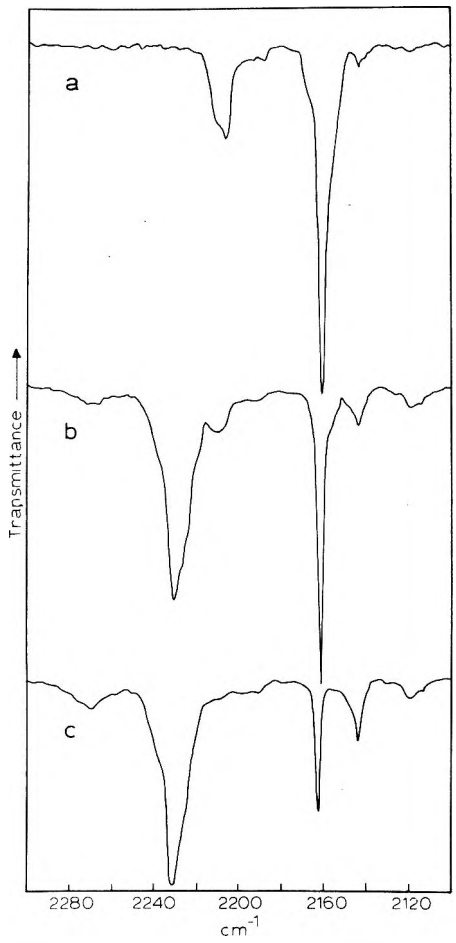

Figure 1. Infrared spectra of $(CH_3)_2NCON_3$ in Ne at 6 K (a) before photolysis, (b) after 15 min photolysis, and (c) after 45 min photolysis.

ingly blue shifted with respect to the gas-phase values. However, no matrix-isolation work has been done on methyl isocyanide, and earlier gas-phase work[17] reported these frequencies at 1429 and 1467 cm^{-1}. We believe that these assignments are reasonable. Some very weak bands have not been assigned. They may arise from the isocyanic acid–methyl isocyanide molecule pair, from dimethylaminoisocyanate, or from the products of some other decomposition occuring to a small extent.

In the region below 2000 cm^{-1} the absorption bands of the deuterio species are considerably weaker than those of their protic counterparts. Above 2000 cm^{-1} the isocyanate asymmetric stretching vibration of DNCO is observed at 2226 cm^{-1} in agreement with our previous study.[15] The hydrogen-bonded N–D stretching vibration appears as a broad band at 2350 cm^{-1}, and the C–D stretching frequencies of D_3CNC are clearly observed at 2255 and 2268 cm^{-1}. The $-N{\equiv}C$ stretching frequency remains practically unchanged in the deuteriomethyl isocyanide. The only anomaly seems to be the $(D_3C)_2N$–NCO isocyanate stretching frequency, which is 11 cm^{-1} higher than that of $(H_3C)_2N$–NCO. However, the azide stretching frequencies of the parent dimethylcarbamoyl azides are themselves somewhat anomalous, the matrix isolation spectrum of $(H_3C)_2NCON_3$ exhibiting a single band at 2162 cm^{-1}, while the spectrum of $(D_3C)_2NCON_3$ shows a doublet at 2167 and 2161 cm^{-1}. We have no explanation for the higher frequencies of the deuterated species.

In conclusion, the ir matrix-isolation studies argue strongly for an intermediate dimethylaminoisocyanate which decomposes upon prolonged photolysis to an isocyanic acid–methyl isocyanide molecule pair. The methyl isocyanide might arise from *N*-methylenemethanamine, which could be formed as an intermediate by β-elimination from the aminoisocyanate: $HCH_2NMeNCO \rightarrow H_2C{=}NMe + HNCO$. However, no data on the photochemistry of $H_2C{=}NMe$ seem to be available, neither for fluid solutions nor for isolated molecules (in the gas phase or in a matrix).

Discussion

The results presented show that photolysis of alkylcarbamoyl azides (and of monophenylcarbamoyl azide) leads to intermediates identified by their chemistry and by a matrix-isolated ir spectrum as substituted aminoisocyanates RR'N–NCO. If the corresponding nitrenes RR'NCON are formed at all, they must be unreactive toward C=C double bonds, C–H bonds, and benzene rings—a behavior not in accord with the properties of diaryl- and arylalkylcarbamoylnitrenes studies by Kametani[8] and Anselme.[9] An earlier suggestion[10] that hydrogen bonding favors the photo-Curtius rearrangement of carbamoyl azides has been elegantly substantiated by Anselme.[9] Photolysis of diphenylcarbamoyl azide in tetrahydrofuran solution gave a 84% yield of nitrene products, while in protic solvents both nitrene and rearrangement products were formed (e.g., in ethanol 54% nitrene and 22% rearrangement products). Kametani[8] photolyzed arylalkylcarbamoyl azides in tetrahydrofuran and obtained only nitrene products (e.g., in 44% yield from anisylbenzylcarbamoyl azide). Our chances for finding nitrene formation should therefore be best in aprotic media. Using a variety of these, we were still unable to detect any nitrene products. Thus arylalkylcarbamoyl azides seem to form the borderline between nitrene-forming, "rigid", and rearranging carbamoyl azides, as far as the photolytic decomposition is concerned. The reasons for the change of reaction course with structure are not clear. Diarylcarbamoyl azides give nitrenes and do not rearrange in aprotic solvents, and give mixed reaction paths in protic solvents. Arylalkylcarbamoyl azides still give nitrenes in aprotic solvents, and it might well be that at least some of them will rearrange when photolyzed in protic media. The azides studied here did not give detectable amounts of nitrenes, not even in various aprotic solvents. Given the detectability of 1% yields of nitrene products, a difference of 2 kcal/mol in free energy of activation is all that is needed for an apparent change of reaction course. Nitrene stability and migratory aptitudes might be reflected in the respective transition states, but many other factors could be responsible as well. Unsubstituted carbamoyl azide, H_2HCON_3, seems to give H—O insertion products of H_2NCON upon photolysis in alcohols.[18]

Photolysis of the aminoisocyanates once formed from the azides occurs in the neon matrix, and most likely in fluid solutions as well. This should be less important in nucleophilic solvents, in which the aminoisocyanates are quickly intercepted. Nevertheless, it might contribute to the lesser yield of 17 obtained when 254-nm rather than 300-nm light was used. In hydrocarbon solutions, considerable photolysis of the aminoisocyanates seems likely. This might cause the formation of the intractable viscous materials formed. Photodecomposition products could react with carbamoyl azides, giving rise to their radical-chain decomposition, or do other chemical mischief.

The photolysis of substituted carbamoyl azides is a good route to 2-substituted hydrazinecarboxylic esters, which are sometimes difficult to obtain, free of isomers, by acylating alkylhydrazines.[19] The thermolysis of carbamoyl azides in alcohols and amines is synthetically valuable,[20,21] but the temperatures required sometimes results in nucleophil-

ic displacement of azide ion, or in the decomposition of the desired product.

Experimental Section

Photolyses. For the matrix-isolation studies, dimethylcarbamoyl azide[22] was kept below 0° and protected from light until used. It was then introduced into a high-vacuum system and mixed with neon at a concentration of 0.2 mol % at least 24 hr before deposition. The experimental procedure has been described previously.[15] Photolyses in fluid solution were carried out in fused silica vessels in a Rayonet[23] photochemical reactor, using low-pressure mercury lamps (emitting most of their light at 254 nm) unless otherwise specified.

Phenylcarbamoyl azide[24] **(1)** was purified by sublimation at 80–90° (760 mmHg), mp 107–108° (lit.[20] mp 103–104°).

Ethylcarbamoyl azide[25] **(7)** was distilled, bp 90° (17 mmHg), ir (CCl_4) N_3 at 2150, C=O at 1700 cm^{-1}.

Diethylcarbamoyl Azide (10). Freshly distilled diethylcarbamoyl chloride (14.2 g, 117 mmol) in 150 ml of acetone and sodium azide (20 g, 300 mmol) were stirred and heated to reflux for 18.5 hr. The solution was cooled, filtered, and concentrated in vacuo. Distillation over a Vigreux column (5 in.) gave 12.3 g (74% yield) of **10**, bp 47–49° (2 mm). Redistillation gave pure **10**: $n^{22.5}$D 1.4625; bp 53–53.5° (3 mm);[26] ir spectrum (CCl_4) 2980 (s), 2840 (s), 2778 cm^{-1} (w). The azide and carbonyl bands were solvent dependent: in CCl_4 2155 (s), 2140 (sh), and 1690 cm^{-1}; in cyclohexane 2156 (s), 2146 (sh), and 1693 cm^{-1}; in methanol 2155 (s), 2145 (sh), and 1665 cm^{-1}. The uv absorption lacked maxima between 230 (cyclohexane, log ϵ 3.63) and 260 nm (cyclohexane, log ϵ 2.82). At 255 nm, log ϵ in MeOH was 2.74, in cyclohexane 2.80. The NMR spectrum showed NCH_2 as a multiplet at δ 2.3 (hindered N–CO rotation) and CH_3 at δ 1.12 (t). Heating the azide to 40° in the NMR probe led to coalescence of the NCH_2 multiplet to a quartet, J = 7Hz, unchanged to 120°. The azide seems indefinitely stable when stored in a brown bottle at room temperature.

Dimethylcarbamoyl azide (17),[22] bp 53–55° (5 mm), showed two methyl signals of equal area in its NMR spectrum (22°, $CDCl_3$), at δ 2.920 and 2.967, indicating a barrier to free rotation around the N–CO bond.

Dimethylcarbamoyl azide-d_6[27] was prepared from hexadeuteriodimethylammonium chloride, $(D_3C)_2NH_2^+$ $^-$Cl (EM Laboratories, 99+% deuterated), 3.9 g (45 mmol) of which was converted to the free amine with 4 g of NaOH in 8.5 ml of water and 50 ml of dichloromethane. After 15 min of stirring, the dichloromethane phase was separated, dried over KOH, and added over 45 min at −15° to 12 g of phosgene in 30 ml of dichloromethane. After removal of the excess of $COCl_2$ and concentrating in vacuo the dichloromethane solution to one-fourth of its original volume, ether was added to precipitate 1.5 g of $(D_3C)_2NH_2^+$ $^-$Cl. Evaporating the filtrate left 2.32 g of $(D_3C)_2NCOCl$. This was dissolved in 3 ml of acetonitrile and added to 1.4 g of NaN_3 suspended in 4 ml of acetonitrile. After 2 hr of stirring, filtration, and distillation, the hexadeuterated azide was obtained in an average yield of 65%. The ir spectrum (neat) shows the N_3 band at 2155 cm^{-1}, C–D stretching vibrations at 2240 and 2215 cm^{-1}, C=O at 1685 cm^{-1}, and other strong bands at 1395, 1256, 1229, 1016, and 712 cm^{-1}.

Photolysis of 2 g of dimethylcarbamoyl azide (17) in 30 ml of methanol was done in a Rayonet reactor at 0° until about 80% of the calculated volume of nitrogen had been evolved. Gas chromatography on a 20-ft UCON Polar column at 140° gave **methyl 2,2-dimethylhydrazinecarboxylate (18).** The yield was 32% when 254-nm light was used, but 46% when fluorescent uv lamps with a peak output at 300 nm (Rayonet RPR 3000 lamps) were employed. The compound[26] of mp 43° had NMR signals ($CDCl_3$) at δ 3.70 (s, 3 H) and 2.57 (s, 6 H) and ir bands at 3270 and 1710 cm^{-1} (in CCl_4). The mass spectrum showed P 118 (28%) and a base peak at 58 (100%, Me_2N_2) as well as the expected other fragmentations.

Methyl 2,2-diethylhydrazinecarboxylate (14)[26] was obtained by photolyzing (254 nm) 3.47 g (24.4 mmol) of diethylcarbamoyl azide (**10**) in 500 ml of degassed spectrograde methanol until 80% of the calculated volume of N_2 had been evolved. The residue left after evaporating the solvent was a off-white solid, mp 85–95° (2.23 g). Sublimation at 80–90° (760 mm) gave white crystals, mp 108–109°, identical in all respects with the authentic material (see below), in a 57% yield based on azide decomposed. The ir spectrum in KBr 3190 (s, sharp), C=O at 1715 cm^{-1}; NMR spectrum OCH_3 at δ 3.75 (s, 3 H), NCH_2 at 2.75 (q, 3.8 H), CH_3 at 1.12 (t, 6 H).

Refluxing 1.05 g of the azide **10** in 150 ml of methanol for 22 hr gave only unchanged starting material.

Authentic **14** was prepared from *N,N*-diethylhydrazine and methyl chloroformate. Sublimation gave white needles, mp 107–108°, mixture melting point undepressed, with spectra identical with those of the material obtained from the photolyses of **10** in methanol.

***tert*-Butyl 2,2-Diethylhydrazinecarboxylate (16).**[26] **10** (1.38 g, 9.73 mmol) was photolyzed in 200 ml of *tert*-butyl alcohol (mp 24.5–25.5) until the calculated volume of nitrogen had been evolved. Removal of the solvent and distillation of the residue at 43–68° (5.5 mm) gave a clear liquid. Its analysis on a 5 ft × 0.25 in. UCON Polar 50 HB 2000 VPC column at 130° gave as a major component **16:** mp 57–58°; ir ($CHCl_3$) 3450 (s), 3345 (s), 1700 cm^{-1} (vs); NMR (CCl_4) CH_3 at δ 1.05 (t, 6 H), *t*-Bu at 1.42 (s, 9 H), CH_2 at 2.76 (q, 4 H).

***N,N*,2,2-Tetraethylhydrazinecarboxamide (15).**[26] A solution containing 1.97 g (27 mmol) of diethylamine and 3.07 g (26 mmol) of diethylcarbamoyl azide (**10**) in 200 ml of cyclohexane was irradiated until 85% of the calculated volume of nitrogen had been evolved. Removal of solvent and distillation through a 5 in. Vigreux column at 105–110° (1.5 mm) gave a 2.2 g (53%) of colorless **15,** identical in all respects with the sample prepared from *N,N*-diethylhydrazine and methyl chloroformate (see below).

To a solution of 22 mmol of diethylcarbamoyl chloride in 15 ml of ether was added a solution of 22 mmol of triethylamine and 22 mmol of *N,N*-diethylhydrazine in 15 ml of ether. After boiling for 2 days, 2.11 g of triethylammonium chloride had precipitated. Removal of the ether left 3.36 g (81% crude yield) of a yellow syrup, distillation of which at 70–74° (0.5 mm) gave pure[26] **15:** ir spectrum (CCl_4) 3295, 1647 cm^{-1}; NMR spectrum (CCl_4) CH_3 overlapping triplets around δ 1.07 (12 H), NCH_2 overlapping quartets at 2.85 and 3.19 (combined area 8 H), NH at 2.44.

Photolysis of 10 (25.5 mmol) in 500 ml of water gave a basic reaction mixture. After acidification with 2.2 g of oxalic acid, the solution was gradually concentrated under nitrogen. First precipitated 0.81 g (18.7% yield) of diethylhydrazinium oxalate, and later 1.0 g of diethylammonium oxalate, recrystallized from water–acetone, mp 209–210°, 33.6% yield based on 24.4 mmol of **10** decomposed.

Photolysis of 39.2 mmol of 10 in 500 ml of cyclohexane until 80% of the calculated volume of nitrogen had been evolved gave 6.42 g of a viscous liquid. Its ir spectrum exhibited NH, N_3, and C=O absorptions, the latter at 1815, 1770, and 1685 cm^{-1}. Essentially the same ir spectra were obtained by substituting cyclohexene, acetonitrile, or ether for the cyclohexane solvent. Thin layer chromatography (silica, 1:1:2 heptane–chloroform–acetone eluent) revealed small quantities of four components in addition to material remaining at the origin and of residual **10.** Essentially the same TLC was obtained from the photolyses of **10** in the other nonprotic solvents. The TLC did not show any *N,N*-diethyl-*N'*-cyclohexylurea (**11**). Crystallization of the viscous liquid, using ether, gave a 17.5% yield of the dimer **12,** mp 112–115° dec.[11]

Photolyses of 10 in cyclohexene, ether, acetonitrile, or neat gave viscous materials very similar to that obtained in cyclohexane solution. The reaction mixture from cyclohexene gave, in addition, 3,3'-biscyclohexeneyl, separated by VPC (20% XF-1150 cyanosilicon column of 4 ft × 0.25 in. at 105°). Recrystallization from ether gave **12** from all reaction mixtures.

Methyl 2-Ethylhydrazinecarboxylate (9).[26] Monoethylcarbamoyl azide (**7,** 27 mmol) in 500 ml of spectrograde methanol, purged with nitrogen, was photolyzed, the solvent was removed, and the remaining yellow oil was distilled, bp 44–46° (0.13 mm), n^{22}D 1.4600, to give 1.6 g (50% yield) of **9:** ir spectrum ($CHCl_3$) 3445 (sharp), 3350 (broad), 1685 cm^{-1}; NMR spectrum ($CDCl_3$) CH_3 at δ 1.11 (3.1 H), NCH_2 2.96 (m, 2.0 H), OCH_3 3.80 (s, 3 H).

Photolysis of 7 (32.3 mmol) in 200 ml of carefully purified cyclohexene, until 86% of the calculated volume of nitrogen had been evolved, gave a brown deposit on the photolysis tube. More of the material was obtained by evaporating the cyclohexene. The melting point was very broad, around 200°. The ir spectrum showed NH and a broad C=O absorption around 1665 cm^{-1}. The material was rather insoluble in organic solvents and was not characterized further. The spectra gave no indication of the presence of **8.**

7-(*N*-Ethylcarbamoyl)-7-azabicyclo[4.1.0]heptane (8)[26] was prepared independently by adding to 14 mmol of 7-azabicyclo[4.1.0]heptane[28] in 10 ml of ether a solution of 21 mmol of ethyl isocyanate in 10 ml of ether. After a few minutes the mixture was cooled to −78° and deposited 1.8 g (77% yield) of crystals, mp 66–67.5°. Recrystallization from low-boiling petroleum ether gave white needles, ir (KBr) 3275, 1635 cm^{-1}. The NMR spectrum showed overlapping signals: ethyl CH_3 (t) and C^3 H and C^4 H

around δ 1.19, C^2 H and C^5 H at 1.83 (m) (area of all these 11.1 H), C^1 H and C^6 H at 2.53 (m, 2.0 H), ethyl CH_2 at 3.17 (m, 2.0 H), NH at 7.0 (broad).

Photolysis of 7 (17 mmol) in 400 ml of benzene until 82% of the calculated volume of nitrogen had been evolved gave a product mixture very similar to that obtained in the photolysis of 7 in cyclohexene. No indication of incorporation of benzene in this material could be found.

Methyl 2-Phenylhydrazinecarboxylate (6).[26] A solution of 6.17 mmol of monophenylcarbamoyl azide (1) in 200 ml of spectrograde methanol, purged with nitrogen, was photolyzed until a nearly quantitative yield of nitrogen had been evolved. Removal of the solvent left 1.06 g of a dark orange solid. Recrystallization from ether–hexane, then from water, gave 0.66 g (65% yield) of **6**, mp 113°, identical by spectra and mixture melting point with the authentic material, prepared by Heller's method[29] from methyl chloroformate and phenylhydrazine. The compound, mp 115–117°, had an ir spectrum with NH at 3385 and 3230 cm^{-1}, C=O at 1724 cm^{-1} (KBr).

Photolysis of 1 in Cyclohexene. The heterogeneous mixture of 12 mmol of 1 and 310 ml of purified cyclohexene (the azide is sparingly soluble in hydrocarbons) was irradiated with a low-pressure mercury lamp. During the irradiation a brown deposit built up on the wall of the quartz vessel. Filtration gave a pink solid (0.5 g), compound A, which darkened at 138° and melted between 238 and 250°. Its ir spectrum showed NH and C=O around 1700 cm^{-1}; the spectrum seemed identical with that of the insoluble material obtained by photolyzing 1 in cyclohexane or benzene. From the solution we obtained 0.77 g (38%) of crude, unchanged 1. A little *N,N'*-diphenylurea was also detected. No nitrene addition product 4 was present.

Authentic 4 was prepared by the method of Hassner[30] from 7-azabicyclo[4.1.0]heptane and phenyl isocyanate: mp 156.4–157.8°; ir (KBr) 3320, 3005, 1650, 1590 cm^{-1}; NMR spectrum ($DCCl_3$) C^3 H and C^4 H at δ 1.35 (m, 4.0 H), C^2 H and C^5 H at 1.83 (m, 4.0 H), C^1 H and C^6 H at 2.75 (m, 2.0 H), aromatic and NH at 7.37 (m, 6.0 H).

Photolyses in cyclohexane and in benzene gave compound A together with unchanged azide 1. Compound A was soluble in chloroform and acetone, but not in the other organic solvents we tried. It could be dissolved in 0.08 *N* aqueous NaOH and precipitated with dilute hydrochloric acid. The elemental analysis (C, 63.99; H, 4.96; N, 18.97) suggests that A might be an impure oligomer of $C_7H_6N_2O$. Among other data, the solubilities rule out that any substantial portion of A is benzimidazol-2-one (2).

***N*-Phenyl-*N'*-cyclohexylurea** (5) was prepared after Skita[31] from cyclohexaneamine and phenyl isocyanate: mp 187°; ir spectrum (KBr) 3325, 1630 cm^{-1}.

Benzimidazol-2-one (2) was prepared by the method of Mistry:[32] ir spectrum (KBr) 3120, 1740 cm^{-1}; mp 300°.

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Registry No.—**1**, 940-38-5; **2**, 615-16-7; **4**, 4714-51-6; **5**, 886-59-9; **6**, 2290-03-1; **7**, 18457-92-6; **8**, 55741-05-4; **9**, 31457-73-5; **10**, 922-12-3; **12**, 32515-28-9; **14**, 55131-08-3; **15**, 27827-93-6; **16**, 55741-06-5; **17**, 13750-17-9; **18**, 55741-07-6; diethylcarbamoyl chloride, 88-11-9; sodium azide, 26628-22-8; dimethylcarbamoyl azide-d_6, 55741-08-7; hexadeuteriodimethylammonium chloride, 53170-19-7; *N,N*-diethylhydrazine, 616-40-0; methyl chloroformate, 79-22-1; *tert*-butyl alcohol, 75-65-0; diethylamine, 109-89-7.

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Photocyclization of 2-(*N*-Chloroacetylpiperidylalkyl)indoles. A Novel Case of Stereoisomerism Dependent on Sterically Restrained Conformations

Richard J. Sundberg* and Francis X. Smith

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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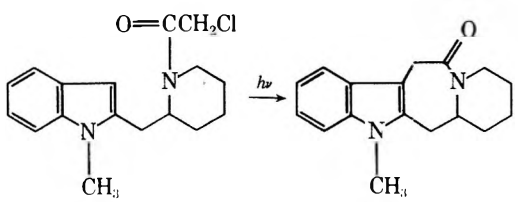
A series of 2-(*N*-chloroacetylpiperidylalkyl)indoles has been prepared. The photolysis of these compounds, in general, leads to cyclization resulting from alkylation of the indole 3 position by the chloroacetyl group when the indolylalkyl group is attached to the 2 or 3 position of the piperidine ring. A competing process observed in some reactions involves cyclization at a substituent group. This photocyclization permits fusion of seven- and eight-membered rings to the b side of the indole ring with moderate efficiency. A novel case of stereoisomerism was observed in certain of the resulting bicyclic amides.

Several years ago Yonemitsu, Cerutti, and Witkop reported a novel photocyclization of the chloroacetamide of tryptophan in which the chloroacetyl group alkylated C-4 of the indole ring.[2] Since that time photocyclization of aromatic chloroacetamides has been studied from a mechanistic point of view[3] and applied synthetically,[4] but with few exceptions[5] the subsequent studies have been focused on phenols and methoxy aromatics. We wished to develop a procedure of reasonable generality for the annelation of the b side of the indole ring with medium-sized nitrogen-containing rings. The recent demonstration that 2-lithioindoles[6] can serve as versatile precursors of pyridylalkylindoles led us to investigate the preparation and photocyclization of the *N*-chloroacetyl derivatives of the corresponding piperidines.

Scheme I shows the routes of synthesis of the amides studied in this work. In general, these reactions require no specific comment other than that they further document the synthetic utility of the 2-lithioindole intermediates. The catalytic reductions and acylations with chloroacetyl chloride or chloroacetic anhydride were straightforward in most cases. Table I gives the melting points and recrystallization solvents for new compounds prepared in the course of this work. The source of other intermediates are also indicated in footnote *a* of Table I.

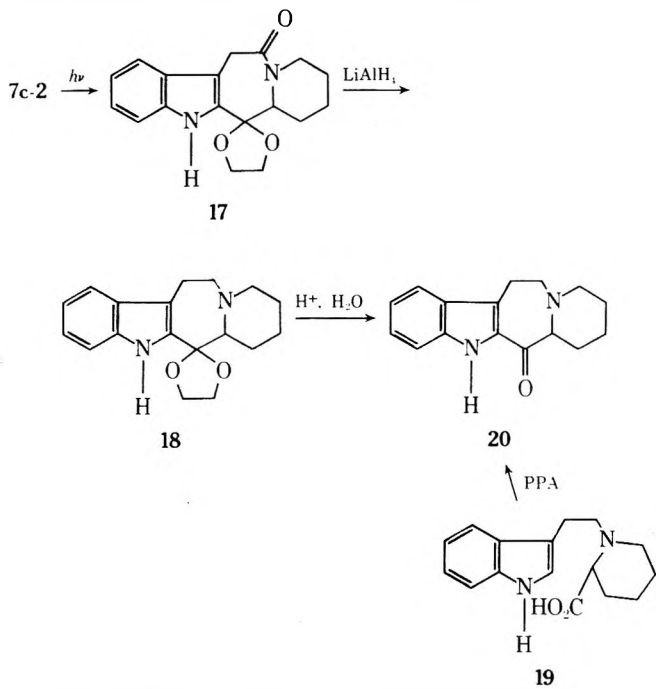
The photocyclization reactions were usually carried out in methanol. Benzene and 1-propanol were used for comparison in some cases. Benzene was not as satisfactory as methanol. Solid sodium carbonate was added in the case of the ketals, to eliminate hydrolysis. The reaction times varied markedly from compound to compound and were quite short in some cases. The identification of the individual photoproducts is discussed in the paragraphs which follow. The structures, yields, and certain physical properties of the photoproducts are given in Table II for those systems where cyclization was observed.

Photolysis of **10b-2** gave a single isolable photoproduct in 36% yield. The product was expected to be **15** and all

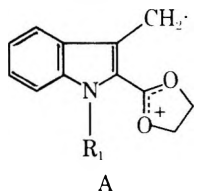


10b-2 **15**

available spectral data are in accord with this structure. The NMR spectrum shows no indole 3-H indicating the point of cyclization. The base peak in the mass spectrum is at *m/e* 157 consistent with a 2,3-disubstituted 1-methylindole. The ultraviolet spectrum is typical of an indole chromophore. Cyclization took a similar course when the ketals **7b-2** and **7c-2** were photolyzed. The structure of **17** the photoproduct from **7c-2** was proven by interrelating it with **20,** which was prepared by an alternative route involving polyphosphoric acid cyclization of **19,** which was prepared



from tryptophyl bromide and methyl piperidine-2-carboxylate.[7] The spectroscopic properties of **16** and **17** were also in accord with the assigned structures. In both cases the base peak in the mass spectrum appeared at the mass corresponding to ion A. The NMR spectra indicated that cy-

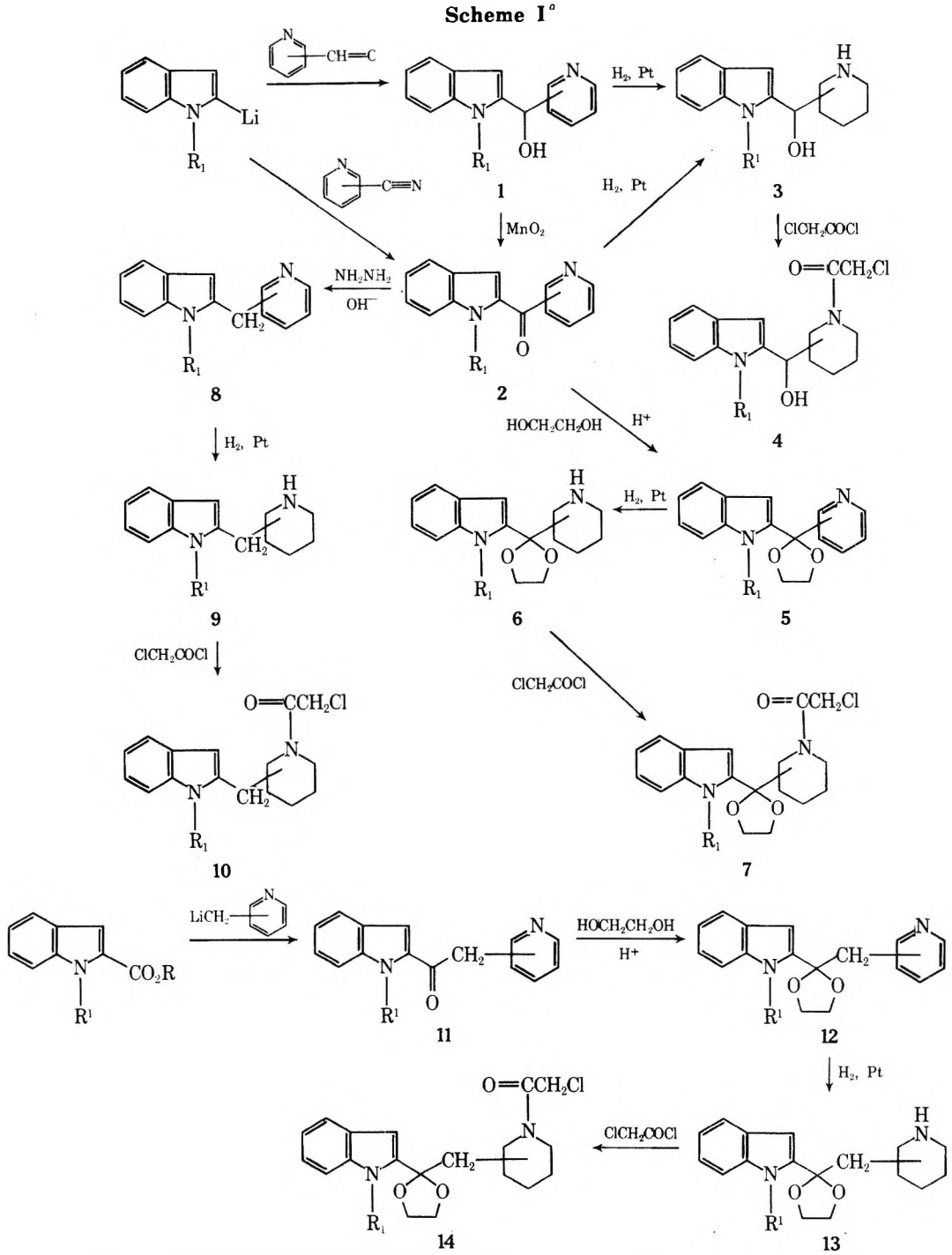


A

clization had occurred at the 3 position because of the absence of the characteristic 3-H signal. The ketones **21** and **22,** respectively, obtained by hydrolysis of **16** and **17,** were also characterized by spectral data and elemental analysis.

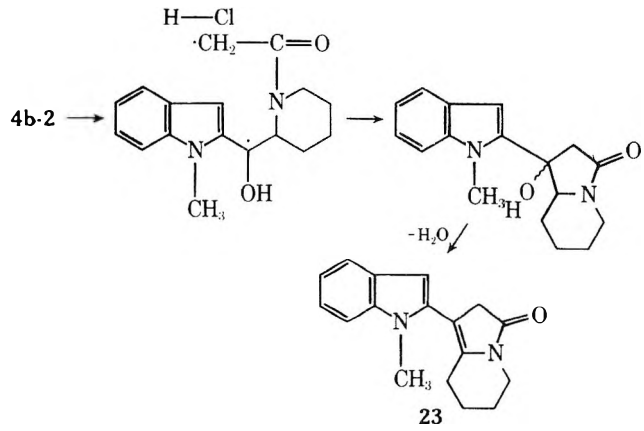
Two other compounds having the same 2-indolyl-2-piperidylmethane structural framework did not cyclize to C-3 on photolysis. Both diastereomers of the alcohol **4b-2**

Scheme I[a]



[a] Not all of the possible permutations were investigated. The compound numbers in Table I indicate which compounds have been synthesized. The designations a, b, or c specify the indole 1 substituent and -2, -3, or -4 the point of attachment to the piperidine ring: a, $R_1 = PhSO_2$; b, $R_1 = CH_3$; c, $R_1 = H$.

formed a mixture of two unstable photoproducts presumed to be diastereomeric hydroxypyrrolidones. Both unstable photoproducts dehydrated to give **23**. The NMR spectrum indicates that a 3-H proton remains on the indole ring and also reveals a two-proton singlet at δ 3.40 which can be assigned to the methylene group of the dihydropyrrolone ring. The ultraviolet spectrum also shows that the chromophore is more extended than that of a simple indole ring. An alternative structure which was considered would be the dehydration product of the alcohol formed by cyclization at C-3 of the indole ring. To rule out this structure compound **21** was reduced with $NaBH_4$. The reduction product was stable in refluxing methanol in contrast to the facile dehydration of the precursors of **23**. Also in agreement with the assignment of structure **23** is the fact that

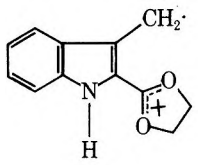


the methylene group was readily exchanged in aqueous sodium bicarbonate, as would be expected for a dihydropyrrolone. This type of cyclization, involving a substituent group in preference to the aromatic ring, has been formulated in terms of an intramolecular abstraction recombination mechanism.[3a,c,4i] The carbinyl hydrogen in **4b-2** may be particularly prone to abstraction, since the resulting radical is stabilized both by the indole ring and the hydroxyl group.

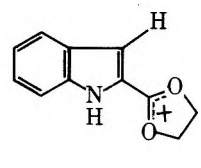
The *N*-benzenesulfonyl compound **7a-2** was apparently converted to the 3-benzenesulfonyl derivative **24** on photolysis with no involvement of the chloroacetyl group. The product is isomeric with starting material but lacks an indole 3-H in the NMR spectrum. Photoisomerization of 1-tosylindoles to 3-tosylindoles has been recorded.[8]

When the connecting chain between the piperidine and indole ring was lengthened to two atoms, the cyclization still proceeded but in somewhat decreased yield. Photolysis of **14b-2** gave a ~20% yield of **25**. The structure of this compound is assigned on the basis of analogy with the preceding compounds and consistent spectral properties including the absence of an indole 3-H signal. The corresponding ketone was also obtained by hydrolysis. Its NMR spectrum is also consistent with the assigned structure.

The compounds which were investigated in the 3-piperidyl series were **7b-3, 7c-3, 10b-3,** and **10c-3.** Structural investigation of the photoproducts from **7c-3** set the pattern for the other systems and will be discussed first. Two isomeric ketals were obtained on photolysis of **7c-3** and were separated by chromatography. The major product **33** (35%, mp 188–189°) was less polar than the minor product **34** (9%, mp 194–196°) on silica gel. Both appeared to be cyclized products since neither shows an indole 3-H signal, both have normal indole ultraviolet absorbance spectra, and both show peaks corresponding in mass to ions B and C as major peaks in their mass spectra. Indeed, the mass



B



C

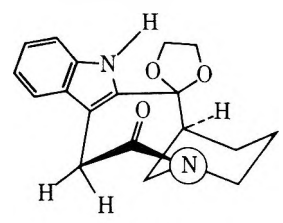
spectra of the two compounds are virtually identical. Acidic hydrolysis gave two ketones, **35** from **33** and **36** from **34**. Ketone **35** was converted to **36** by treatment with sodium ethoxide in ethanol.

The 300-MHz ^{1}H NMR spectrum of the stable isomer **36** is completely interpretable in terms of the assigned structure. The nonaromatic portion of the spectrum is shown in Figure 1. There are sufficient overlaps even in the 300-MHz spectrum of the unstable isomer **35** that it cannot be completely analyzed. However the fact that **35** is converted to **36** by mildly alkaline conditions and the near identity of the mass spectra of the two compounds argue against the possibility that the aliphatic portions of the structures of **35** and **36** might be different. The NMR and ultraviolet spectra leave no doubt that both compounds are 2,3-disubstituted indoles. These facts suggest that **33** and **34** (as well as **35** and **36**) are stereoisomers. The only stereoisomerism possible is in the formation of the bicyclic ring system. There are two ways in which the five-membered bridge of the bicyclic ring can be closed. If the ring closure is made with the side chain at C-3 of the piperidine ring in an axial position, the relatively unstrained ring system **34** results. Minor strain in this system results from partial double bond character in the amide at the bridgehead position. If, on the other hand, the ring is closed with the C-3 side chain in an equatorial position, a highly strained bicyclic system (**33**) results. The two rings can be interconverted by single bond rotations which pass the C-2 methylene of the piperidine ring through the bicyclic ring but this appears from models to be strongly prohibited by nonbonding interactions between the methylene hydrogens and the C-2–C-3 carbons of the indole ring.

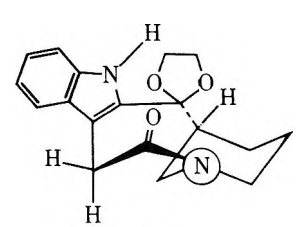
Table I
Synthetic Intermediates[a]

Compd	Mp, °C	Recrystn solvent
1b-4	167–168	Acetone–ether
2b-2	78–79	Ether–heptane
2b-3	87–88	Acetone–ether
4a-4	178–179	Acetone
4b-2[b]	142–143,	Ether
	156–157	Ether
5b-2	113–114	Ether
5b-3	105–106	Ether
5c-2	180–181	Dichloromethane–hexane
5c-3	127–129	Dichloromethane–hexane
7a-2	197–198	Acetone–ether
7b-2	148–150	Acetone–ether
7b-3	142–143	Acetone–ether
7b-4	106–108	Ether
7c-2	162–163	Acetone–ether
7c-3[c]		
8b-2	68–69	Heptane
8b-3	58–59	Heptane–ether
8b-4	64–65	Hexane
9c-3	172–173	Methanol–benzene
10b-2	76–78	Ether
10b-3[c]		
10b-4[c]		
10c-3	138–140	Ethyl acetate–ether
11b-2	68–70	Hexane–ether
11c-4	168–169	Acetone–ether
12c-4	208–207	Acetone–ether
14b-2	143–144	Chloroform–ether
14c-4	139–141	Chloroform–ether

[a] The following intermediates have been previously described in ref 6: **1a-2, 2a-2, 2a-3, 2a-4, 2c-2, 2c-3.** Alternative syntheses for some of the intermediates have been reported: **2c-2,** R. J. Sundberg, H. F. Russell, W. V. Ligon, Jr., and L.-S. Lin, *J. Org. Chem.*, **37,** 719 (1972); **2b-4, 2c-4,** A. Jackson, N. D. V. Wilson, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc. C,* 2738 (1969); **8c-2, 8c-3, 8c-4,** M. Hooper and W. N. Pitkethly, *J. Chem. Soc., Perkin Trans. 1,* 1607 (1972); **9c-4,** J. Eenkhoorn, S. O. de Silva, and V. Snieckus, *Can. J. Chem.*, **51,** 792 (1973). [b] Two diastereomers were separated. [c] Not obtained in crystalline form.



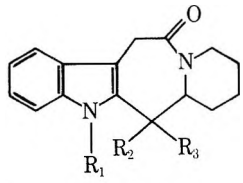
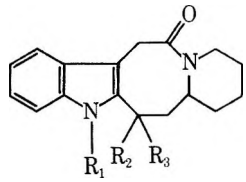
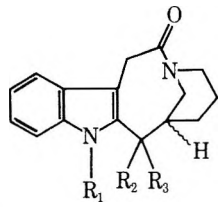
34



33

The nature of the stereoisomerism is related to that which is possible in bicyclic ring systems in which one of the bridges is sufficiently large to permit ring closure involving branches having a trans relationship relative to the

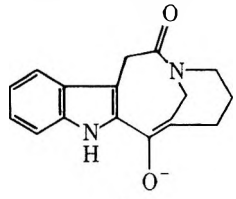
Table II
Cyclic Photoproducts and Derivatives

Compd	R_1	R_2	R_3	% yield[a]	Mp, °C	Recrystn solvent
						
15	CH_3	H	H	36	253–254	Acetone–ether
16	CH_3	$-OCH_2CH_2O-$		41	259–260	Chloroform–ether
17	H	$-OCH_2CH_2O-$		58	248–249	Ethyl acetate–ether
21	CH_3	=O			225–226	Ethanol–ether
22	H	=O			267–269	Chloroform–ether
						
25	CH_3	$-OCH_2CH_2O-$		20	178–179	Chloroform–ether
26	CH_3	=O			146–147	Ether
						
27[b]	CH_3	$-OCH_2CH_2O-$		5	226–227	Ether
28[b]	CH_3	$-OCH_2CH_2O-$		23	162–164	Ether
29[c]				5	185–186	Chloroform–ether
30	CH_3	=O			220–221	Chloroform–ether
31[c]					205–207	Methanol–water
32[c]					200–202	Ether
33[b]	H	$-OCH_2CH_2O-$		35	188–189[d]	Acetone–ether
34[b]	H	$-OCH_2CH_2O-$		9	194–196	Acetone–ether
35[b]	H	=O			286–287	Methanol–water
36[b]	H	=O			291–292	Ethanol–ether
37[b]	CH_3	H	H	15	227–228	Acetone–ether
38[b]	CH_3	H	H	7	192–193	Ether
39[b]	H	H	H	21	268–270	Chloroform–ether
40[b]	H	H	H	9	303	Chloroform–ether

[a] Yields are recorded only for photocyclization reactions. [b] See text for stereochemical assignment. [c] See text for structure. [d] Melts with desolvation; with very slow heating there is some resolidification followed by remelting at 240°.

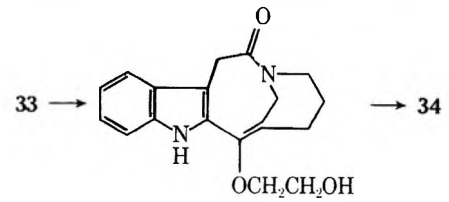
other component ring.[9] However, because of the planar character of the amide nitrogen the existence of stereoisomers also depends upon the conformational locking achieved by steric prohibition of chair–chair interconversion in the piperidine ring.

The conversion of **35** to **36** in basic solution can occur through the common enolate D. When this equilibration was carried out in the presence of D_2O in DMSO-d_6, the product was **36** consisting of a mixture of the d_3 and d_2 isotopic species. The location of the additional deuterium is in the methylene group adjacent to the amide carbonyl, so enolization of the amide group is apparently competitive with enolization at the bridgehead position adjacent to the ketone carbonyl. This probably reflects decreased amide character as a result of the ring strain. The carbonyl peak in **33** is at 1645 cm^{-1} as compared to 1635 cm^{-1} for **34**.



D

Thermal conversion of the ketal **33** to **34** occurs slowly at 170°. A series of experiments in which solutions of **33** in bis(2-ethoxyethyl) ether were sealed under nitrogen and



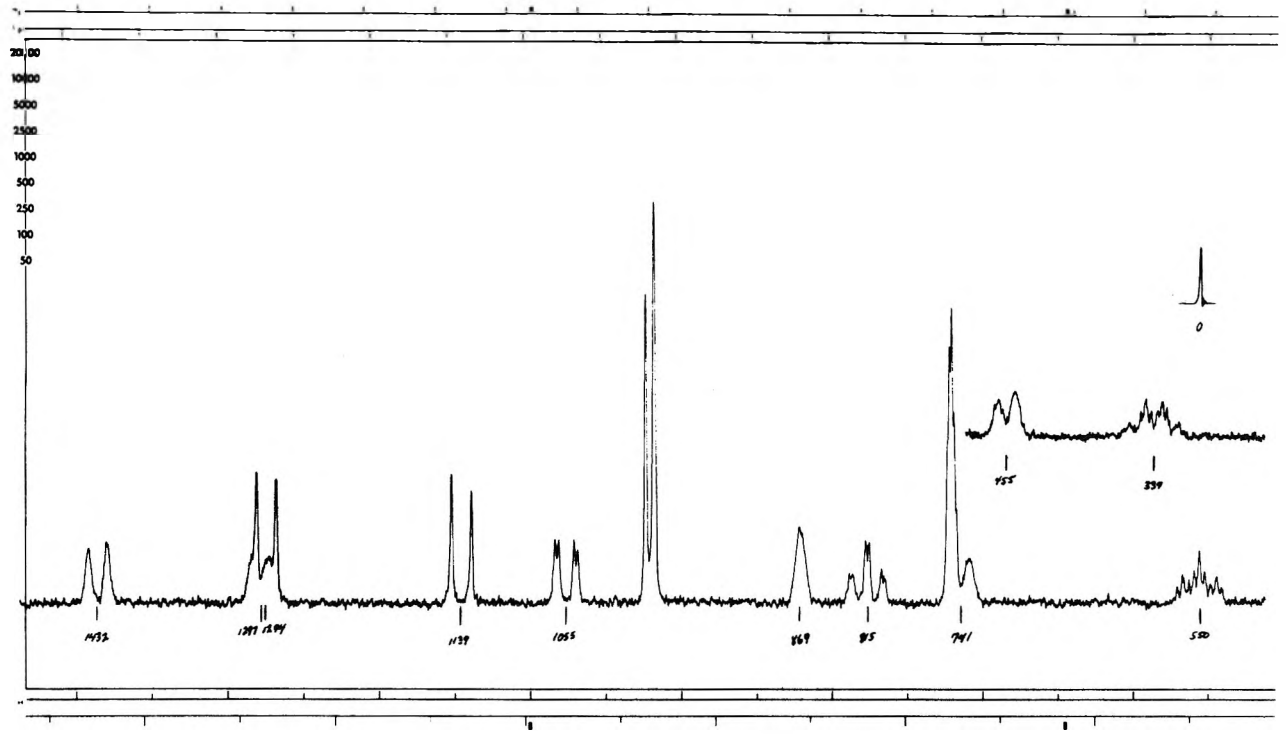


Figure 1. Proton NMR (in DMSO-d_6) of compound **36**. Chemical shifts are given in hertz from Me_4Si. Assignments are given with reference to the numbering given in Table III. 337, q of t, J = 12, 3 Hz (C-5 ax); 455, broad d, J = 12 Hz (C-5 eq); 550, t of t, J = 13, 4 Hz (C-4 ax); 741, broad d partially obscured by DMSO-d_5 (C-4 eq); 815, t of d, J = 13, 3 Hz (C-6 ax); 869, broad s (C-3); 1055, J = 15, 3 Hz (C-2 ax); 1139, 1294, AB doublets, J = 16 Hz (C-8 methylene); 1297, broad d partially obscured by AB doublet (C-6 eq); 1432, broad d, J = 13 Hz (C-2 eq).

maintained at 170° gave variable half-lives for the conversion, ranging from ~2.5 to ~8 hr. The reaction is apparently quite sensitive to adventitious catalysts. It is not clear that the thermal process which accomplishes the isomerization is purely conformational. It is quite possible that a reversible elimination might be involved.

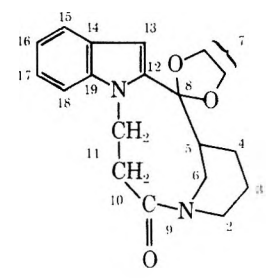
The ^{13}C chemical shifts of compounds **35** and **36** are given in Table III. The multiplicities in off-resonance decoupled spectra are given in parentheses. The number of peaks of each multiplicity and the general chemical shifts are in accord with the assigned structures. The most notable shifts in the spectra between the two isomers are at the two carbonyl carbons (C-7 and C-9) at C-2, C-3, and C-8. The shifts are downfield in the strained isomer **35** at the aliphatic carbons. Since steric compression normally results in an upfield shift, it seems unlikely that the observed shifts are due to this cause, although models indicate that the C-8 methylene group can interact with the hydrogens on both C-2 and C-3. The downfield shift is perhaps related to the ring strain. The relative chemical shifts of the bridgehead carbons of bicyclo[2.2.2]octane 23.9 ppm,[10a] and bicyclo[2.2.1]heptane, 36.8 ppm,[10b] suggest that ring strain may cause a downfield shift at sp^3 carbon atoms. The large shifts in the carbonyl groups may reflect differing degrees of conjugation or coplanarity with nitrogen and the indole ring as the result of the ring strain. The assignment of C-8 was made on the basis of gated decoupling[11] spectra of **35** and **36** which showed one of the upfield triplets (C-8) to have much less long-range coupling than the others.

At least one of the indole ring carbons shows a substantial downfield shift in **35** and **36** relative to **33** and other indoles[12] lacking 2-carbonyl groups. Resonance considerations suggest that C-15 and C-13 would be most strongly affected. In the absence of model compounds we have not made assignments to the three closely spaced aromatic carbons.

The ^{13}C NMR spectrum of the strained ketal **33** was recorded. The data are given in Table III. This spectrum exhibits no chemical shifts which are grossly discordant with previously reported spectra of indole derivatives,[12] although, of course, no close model for the strained ring system in **33** exists. The multiplicity of the peaks in the off-resonance decoupled spectrum is compatible with the assigned structure.

Three products, **27** (5%), **28** (23%), and **29** (5%), were obtained from the *N*-methyl compound **7b-3** when photolyzed in methanol. Two of these, **27** and **28**, appeared to be the stereoisomeric *N*-methyl analogs of **33** and **34** on the basis of the characteristic disappearance of the indole 3-H proton from the NMR spectra of these cyclization products. Methylation of the anion of **34** in dimethyl sulfoxide with methyl iodide led to **28**, confirming the structural relationship. The ketone, **30**, corresponding to **28** was obtained by acidic hydrolysis and characterized by elemental analysis and spectral data.

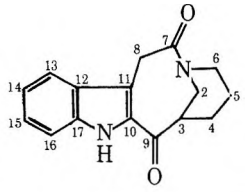
The third photoproduct, **29**, was formed in only 5% yield



29

in methanol, but the yield was around 20% when the photolysis was carried out in benzene or 1-propanol. It retained an indole 3-H proton as was evident from the ^1H NMR spectrum but the *N*-methyl signal was missing. This provided the initial basis for assigning structure **29**. The ^{13}C NMR spectrum, which is given in Table IV, is consistent

Table III
^{13}C NMR Spectra of Compounds 33, 35, and 36[a]

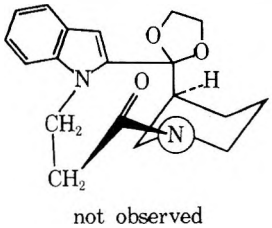


Carbon	33	35	36
2	52.8[b] (t)	54.5[b] (t)	46.3[b] (t)
3	56.0 (d)	58.6 (d)	48.0 (d)
4, 5	24.6, 26.6 (t)	23.6, 25.0 (t)	22.7, 26.7 (t)
6	45.1[b] (t)	45.3[b] (t)	42.0[b] (t)
7	177.0 (s)	177.2 (s)	169.5 (s)
8	~39.5[c]	39.0 (t)	33.1 (t)
9	107.7[d] (s)	189.8 (s)	196.3 (s)
10	134.3 (s)	132.7[g] (s)	132.5[g] (s)
11	106.2[d] (s)	116.1 (s)	114.7 (s)
12	128.3 (s)	128.2 (s)	127.7 (s)
13	118.8 (d)[e]	125.1 (d)	125.6 (d)
14	122.2 (d)[e]	120.1 (d)	120.8 (d)
15	118.4 (d)[e]	119.9 (d)	119.8 (d)
16	111.3 (d)[e]	112.5 (d)	112.2 (d)
17	137.3 (s)	135.0[g] (s)	135.5[g] (s)
	65.9, 65.3[f] (t)		

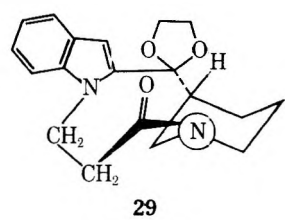
[a] Spectra were recorded in DMSO-d_6 with internal Me_4Si reference. Multiplicities were determined by off-resonance decoupling or gated decoupling.[11] [b] C-2 and C-6 assignments could possibly be interchanged. [c] Buried in DMSO-d_6. [d] C-9 and C-11 might be interchanged. [e] Assignments made in analogy with chemical shift relationships reported in ref 12. [f] Carbons of dioxolane ring. [g] Assignments of C-10 and C-17 might be reversed.

with the assigned structure. The peak at 103.3 is a doublet in the off-resonance decoupled spectrum, in agreement with the conclusion that the 3 position of the indole ring is unsubstituted. There are no quartets in the off-resonance decoupled spectrum, in agreement with the conversion of the *N*-methyl to a methylene group. Formation of **29** presumably involves a hydrogen abstraction–recombination mechanism. The reaction is similar to cyclizations involving methoxy substituents in some of the earlier studies.[3c,4i,k]

The ring system present in **29** should be capable of the same type of conformational isomerism detected in **33–34** and analogous pairs. For this reason, the stability of **31**, the ketone derived from **29**, in basic solution was examined. It was found to give an isomeric ketone **32**. The ketal evidently must have the more strained structure shown below. We



not observed



29

did not detect the less strained isomer as a photolysis product.

Both **10b-3** and **10-3** also gave two isomeric photocyclization products. For the *N*-methyl series a major product, **37** (15% yield, mp 227–228°), and minor product, **38** (7% yield, mp 192–193°), were obtained. From the unmethylated starting material **39** (21% yield, mp 268–270°) and **40** (9% yield, mp 303°) were obtained. The two major products

Table IV
Partial Assignment of ^{13}C NMR Spectrum of 29[a]

Carbon	Signal	Multiplicity
5	51.5	d
8	107.0	s
9	173.9	s
12	138.1	s
13	103.3	d
14	126.6	s
15	120.3	d
16	122.9	d
17	121.3	d
18	109.5	d
19	140.2	s

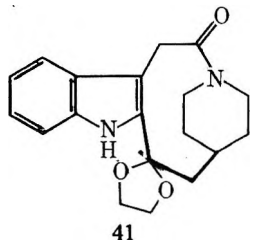
[a] Other signals, all of which are triplets in the off-resonance decoupled spectrum, are at 67.5, 63.3, 51.0, 45.7, 41.6, 40.3, and 25.2 ppm. One set of superimposed signals is required by the number of observed peaks and this is probably the two methylene groups of the dioxolane ring. Definitive assignments of these peaks is not possible. The following seem most likely: C-7, 67.5; C-2, C-6, 63.3, 51.0; C-11, 45.7; C-3, C-10, 41.6, 40.3; C-4, 25.2.

were interrelated by methylating **39** to give **37**. Compound **39** was also obtained by reducing the ketone **36** with triethylsilane in the presence of trifluoroacetic acid.[13] This not only relates the products from the **7-3** and **10-3** series of starting materials but also permits the conclusion that the major products **37** and **39** have the less strained stereochemistry of ketal **34**. It is assumed that the minor photoproducts **38** and **40** are the strained stereoisomers corresponding to ketal **33**, since all the spectroscopic data indicate that the gross structure of the minor isomer is identical with that of the major product in both cases.

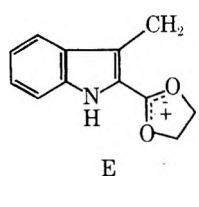
Thermal conversion of **40** to **39** was observed at 170° in bis(ethoxyethyl) ether but was exceedingly slow, being less than half complete after 60 hr.

No photocyclication products were observed in the 4-piperidylmethyl series. Attempts were made with the ketal **7b-4** and with **10b-4**. This may reflect a strong preference for an equatorial conformation for the indolyl substituent. In this conformation the indole ring and chloroacetyl substituent may be too remote for the electron transfer which is required for photocyclization.[3] It should be noted, however, that Snieckus and coworkers[5b] have achieved successful cyclization in this structural series using compound **10c-4**.

In the case of compound **14c-4**, in which an additional methylene group is interposed, some photocyclization apparently occurs. Composed **41**, in which the new ring formed is ten-membered, was isolated in trace yield. The



41



E

evidence for the assigned structure is the presence of a peak of the expected mass for the parent ion and for ion E in the mass spectrum. The amount of material was too small for complete characterization, however.

In several of the photocyclizations some formation of the acetyl derivative by dechlorination of the chloroacetyl group was observed. This has been observed before[3,4] and presumably involves a hydrogen abstraction from solvent.

The identity of these products was generally evident from the NMR spectrum. No effort was made to fully characterize this group of photoproducts.

The pattern which seems to emerge from these results is that the photocyclization is capable of forming medium-sized rings, even highly strained ones, if the indole ring and chloroacetyl substituent can achieve reasonable proximity to one another. It is interesting to note that in the case of photolysis of **7c-3** the more highly strained product which predominates is related to the more stable conformation of the starting material. No general argument for control of the product stereochemistry by reactant conformation can be developed, however, because in each of the other three 2-indolyl-3-piperidylmethane derivatives which were studied (**7b-3, 10b-3, 10c-3**), the less strained bicyclic ring system was the predominant product.

Experimental Section

2-Indolyl Pyridyl Ketones (2). The ketones were prepared from 1-methyl-2-lithioindole or 1-benzenesulfonyl-2-lithioindole by reaction with the appropriate cyanopyridine as described by Sundberg and Russell[6] or by a two-step procedure from the lithioindole and pyridinecarboxaldehyde followed by manganese dioxide oxidation. The preparations of **2a-3** and **2c-3** are illustrative of the latter procedure. A solution of 0.1 mol of 1-benzenesulfonyl-2-lithioindole in tetrahydrofuran was prepared following the procedure of Sundberg and Russell[6] and allowed to warm to room temperature. To this solution there was added slowly by syringe 10.0 ml of 3-pyridinecarboxaldehyde. The reaction mixture was stirred for 1 hr and then hydrolyzed with water. The product was obtained by extraction with methylene chloride. The residue crystallized when dissolved in a small amount of benzene, giving **1a-3** in 60% yield. This was not purified further but was dissolved in chloroform and stirred overnight with 50 g of activated manganese dioxide.[14] Clean conversion to **2a-3** occurred and the product was isolated in 94% yield. The infrared spectrum was identical with that of a previously prepared sample.[6] The hydrolytic removal of the *N*-benzenesulfonyl group to give **2c-3** has been previously described.[6]

Dioxolane Derivatives of 2-Indolyl Pyridyl Ketones (5). The ketones were dissolved in benzene (200 ml/g) and treated with excess ethylene glycol and 1.2 equiv of *p*-toluenesulfonic acid. The solution was refluxed using a Dean-Stark trap to collect azeotroped water. The progress of the reaction was monitored by TLC and was complete in 12–48 hr. When the ketone was nearly completely consumed, the solution was cooled and neutralized by addition of sodium bicarbonate and water. When evolution of CO_2 was complete, the mixture was transferred to a separatory funnel. The benzene layer was separated and the aqueous layer was extracted with ether. The combined organic solutions were dried and evaporated. Yields for the individual compounds follow: **5b-2**, 58%; **5b-3**, 51%; **5b-4**, 55%; **5c-2**, 68%; **5c-3**, 70%.

Wolff–Kishner Reduction of 2-Indolyl Pyridyl Ketones to 2-(Pyridylmethyl)indoles (8). The ketone (0.03 mol) was dissolved in a solution containing 10 ml of hydrazine hydrate and 10 g of potassium hydroxide in diethylene glycol. The resulting solution was stirred under a nitrogen atmosphere in an oil bath at 120–140° for 6 hr. The reaction mixture was then diluted with water (~300 ml) and extracted with ether. The ether extracts were dried over potassium carbonate and then evaporated to dryness. Pure products were obtained by crystallization of the residual oils. Yields follow: **8b-2**, 88%; **8b-3**, 92%; **8b-4**, 100%; **8c-3**, 85%.

Chloroacetylpiperidines 7 and 10. In most cases the pyridines were reduced to the corresponding piperidines and then chloroacetylated without full characterization of the intermediate piperidine. To a solution of the pyridine in glacial acetic acid (10 ml/g of reactant) there was added platinum oxide (50–100 mg/g of reactant) and the suspension was shaken under 50 psi hydrogen in a Parr apparatus. The speed of reduction was somewhat variable but was usually complete in 24–48 hr. Periodic monitoring by TLC was done to confirm completeness of reduction. The reaction mixture was then filtered through Celite[15] filter aid. The filtered catalyst was washed with methanol and the filtrate was evaporated to dryness using a rotary evaporator. The residual oil was dissolved in water, neutralized by addition of solid sodium bicarbonate, and extracted with chloroform when evolution of CO_2 was complete. To the chloroform solution there was added solid potassium carbonate and the mixture was stirred vigorously during addition of 1.5 molar equiv of chloroacetyl chloride or chloroacetic anhydride. Reaction was rapid and exothermic with the acid chloride and in a few instances there was an indication of some Friedel–Crafts acylation of the indole ring. Reaction using the anhydride required about 1 hr of stirring at room temperature. When reaction was complete, as judged by TLC, water was added and stirring was continued for 5–15 min to hydrolyze remaining anhydride or acid chloride. The chloroform layer was then separated and dried over potassium carbonate. Evaporation of the solution left the crude product, which was purified by crystallization or chromatography on silica gel. Yields follow: **7a-2**, 89%; **7b-2**, 81%; **7b-3**, 56%; **7b-4**, 72%; **7c-2**, 82%; **7c-3**, 85%; **10b-2**, 31%; **10b-3**, 56%; **10b-4**, 46%; **10c-3**, 33%.

1-Chloroacetylpiperidyl Indolyl Carbinols (4). Two diastereomers of **4b-2** were isolated after a sequence commencing with the ketone **2b-2**. To a solution of **2b-2** (2.36 g, 10 mmol) in methanol (50 ml) containing 1 ml of concentrated hydrochloric acid there was added platinum oxide catalyst (100 mg) and the solution was shaken under 50 psi hydrogen for 4 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residual oil was dissolved in water, neutralized by the addition of excess sodium bicarbonate, and extracted with ether. Chloroacetylation was carried out in the presence of excess solid potassium carbonate using 2 equiv of chloroacetyl chloride. The reaction was complete in 5 min. Water (100 ml) was added and the ether layer was separated, dried, and evaporated. The residue was chromatographed on silica gel (30 g) using toluene–ether for elution. The less polar diastereomer was obtained in 55% yield, mp 142–143°, after recrystallization from ether. The more polar diastereomer was obtained in 18% yield, mp 150–152°, after recrystallization from ether. Compound **4a-4** was obtained via **1a-4**. 1-Benzenesulfonyl-2-lithioindole and 4-pyridinecarboxyaldehyde reacted to give **1a-4** in 36% yield. It was not further purified. To a solution of 5.0 g of **1a-4** in glacial acetic acid (25 ml) there was added 20 mg of platinum oxide. The solution was shaken under 55 psi hydrogen for 72 hr, at which point TLC indicated complete reaction. The solution was filtered and evaporated to leave a glassy residue which was dissolved in water and neutralized with sodium bicarbonate. The alkaline solution was extracted with chloroform and the chloroform was evaporated, leaving 2.77 g of residual **3a-4**. This was acylated in chloroform over solid potassium carbonate to give 1.4 g (overall 24%) of **4a-4**, mp 178–179° after recrystallization from acetone.

2-(1-Methylindolyl) 2-Pyridylmethyl Ketone (11b-2). A solution of 2-methylpyridine (5 ml, ~50 mmol) in ether (20 ml) was treated with 10 ml of 2.2 *N* phenyllithium and the resulting amber suspension was stirred at room temperature for 2.5 hr. A solution of methyl 1-methylindole-2-carboxylate (4.2 g, 22 mmol) in ether (20 ml) was prepared and the suspension of 2-pyridylmethyllithium was then added to it. The resulting mixture was stirred overnight. It was then hydrolyzed with aqueous ammonium chloride and extracted thoroughly with ether. The ether solution was extracted with dilute hydrochloric acid. The acidic solution was made alkaline and extracted with ether. The ether was evaporated and the residue was purified by chromatography on silica gel using 1:1 ether–chloroform for elution. The major product, **11b-2**, was crystallized by trituration with hexane and obtained in 29% yield. A slightly more polar fraction contained the carbinol resulting from addition of two molecules of 2-pyridylmethyllithium to the ester, mp 166–167° after recrystallization from acetone–ether.

Conversion of 11b-2 to 14b-2. The conversion of **11b-2** to **14b-2** by ketalization, reduction, and chloroacetylation was carried out by the same procedures described for the 2 → 5 → 6 → 7 sequence. The overall yield from **11b-2** was 67%.

2-Indolyl 4-Pyridylmethyl Ketone (11c-4). A solution of 10 ml of 4-methylpyridine in ether (40 ml) was treated with 15.0 ml of 2.2 *N* phenyllithium. The solution was stirred at room temperature for 45 min and then added dropwise to ethyl indole-2-carboxylate (2.8 g, 15 mmol) in ether (100 ml). The mixture was stirred overnight and then hydrolyzed with aqueous ammonium chloride and extracted with ether. The extract was dried and concentrated. The residue was chromatographed on silica gel using ether for elution. The fraction containing **11c-4** crystallized from ether–hexane, giving pure ketone, mp 168–169° (31%).

Conversion of 11c-4 to 14c-4. The standard ketalization–reduction–chloroacetylation sequence gave **14c-4** in 17% yield, mp 139–141°.

General Photolysis Conditions. Most of the photolyses were run in dilute solution in methanol. The solutions were purged by a nitrogen stream before (0.5 hr) and during photolysis. In runs in-

volving ketals sodium carbonate was included to neutralize evolved hydrogen chloride and prevent hydrolysis or methanolysis. The photolysis apparatus consisted of a water-cooled quartz immersion well containing a Vycor filter sleeve and a 450-W Hanovia mercury lamp. Times required for photolysis were determined by monitoring the progress of the reaction by TLC. At the completion of the photolysis the solvent was evaporated and the residue was chromatographed on silica gel. Ether or ether–chloroform mixtures were used for elution. Product yields, melting points, and recrystallization solvents are given in Table II. A more detailed description of some of the photolyses follows.

Photolysis of 7c-3. A solution of **7c-3** (1.0 g) in methanol (750 ml) containing sodium carbonate (2.0 g) was irradiated for 20 min. At this point TLC indicated nearly complete disappearance of starting material and the formation of two photoproducts. The methanol was evaporated and the residue was stirred with 1:1 chloroform–ether and applied to a column of silica gel (30 g). The column was eluted with ether. The first component eluted was recovered **7c-3** (73 mg). This was followed by **33** (312 mg, 35%), which crystallized from ether. The third fraction was **34** (83 mg, 9%), obtained as crystals from ether. The final fraction gave 112 mg of the *N*-acetyl analog of starting material.

Photolysis of 4b-2. Both stereoisomers of the carbinol **4b-2** were photolyzed separately and showed identical behavior. A solution of the less polar stereoisomer (922 mg) in methanol (525 ml) was irradiated for 6.7 hr using a 200-W Hanovia lamp as the source. At the completion of the photolysis two products were evident by TLC. The solvent was evaporated and the residue was chromatographed on silica gel using 1:1 toluene–chloroform with gradual addition of ether for elution. The only product which was eluted was **23** (23% yield) obtained as colorless crystals, mp 205–206°, after recrystallization from acetone–ether. Subsequent TLC investigation revealed that **23** had been formed from the initial photoproducts during the evaporation of methanol prior to chromatography. Attempts to isolate the intermediate photoproducts were unsuccessful but it was possible to demonstrate by TLC that each stereoisomer of **4b-2** formed the two photoproducts in approximately the same ratio and that both products were converted to **23** on warming in methanol.

When **23** (16 mg) was refluxed with a solution of potassium carbonate (100 mg) in methanol-*O*-*d* (6 ml) and D_2O (2 ml) for 4 hr the peak due to the CH_2 group disappeared from the NMR spectrum.

Photolysis of 7b-3. A solution of **7b-3** (500 mg) in methanol (750 ml) containing sodium carbonate (250 mg) was photolyzed for 11 min in the standard apparatus, after which time disappearance of starting material was complete. The solvent was evaporated and the residue was chromatographed on silica gel using 1:1 ether–chloroform for elution. Eluted first was **29** (28 mg, 6%). The second fraction contained **28** (97 mg, 23%). The third fraction was **27** (23 mg, 5%) and finally the *N*-acetyl compound (67 mg, 15%) was eluted. When the photolysis was carried out in 1-propanol, little **27** or **28** was formed. The yield of **29** increased to 23% and the *N*-acetyl by-product was formed in 28% yield.

Photolysis of 7a-2. A solution of **7a-2** (700 mg) in benzene (700 ml) was photolyzed for 1.5 hr using the standard apparatus. The reaction solution was washed with aqueous sodium carbonate, dried, and then chromatographed on silica gel. The column was eluted with ether and 1:1 ether–ethyl acetate. The first material eluted was compound **7c-2** resulting from cleavage of the benzenesulfonyl group (147 mg, 29%). There was then obtained 142 mg of recovered starting material. This was followed by a third fraction (130 mg, 19%) which crystallized from ethyl acetate to give **24**, an isomer of the starting material.

Synthesis of Ketone 20 by Polyphosphoric Acid Cyclization. (This synthesis was carried out by D. E. Rearick.) Tryptophyl bromide (334 mg) and ethyl piperidine-2-carboxylate (491 mg) were refluxed in acetonitrile (10 ml) for 22 hr and the solvent was then evaporated. The residue was dissolved in 10% aqueous acetic acid. The solution was filtered and the filtrate was made basic with ammonium hydroxide. The product was extracted with chloroform and obtained as an oil. The oil was dissolved in ethanol (2 ml) and added to 12 ml of barium hydroxide solution. The mixture was refluxed for 7 hr, cooled, and neutralized with 20% sulfuric acid. The precipitated barium sulfate was washed several times with hot water. The combined aqueous solution was evaporated to dryness and further dried by azeotroping with benzene. A final evaporation of the residue from methanol left **19** as a foam (350 mg).

The noncrystalline acid **19** (3.90 g) was ground to a powder and heated with 400 g of polyphosphoric acid at 80–85° for 0.5 hr with frequent stirring. The reaction mixture was then stirred into 1200 ml of ice water and the resulting solution was made slightly basic (pH 9) with concentrated ammonium hydroxide. The resulting precipitate was extracted into chloroform and the combined extracts were dried. The crude product was chromatographed on Florisil (120 g). A fraction containing **20** (1.37 g, 38%) was eluted with chloroform. It was recrystallized from chloroform–hexane to give yellow prisms, mp 172–180° dec.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.64; H, 7.15; N, 11.06.

Conversion of 17 to Ketone 20. The ketal **17** (20 mg) was dissolved in tetrahydrofuran (10 ml) and lithium aluminum hydride (82 mg) was added. The solution was refluxed under nitrogen for 24 hr. The reaction mixture was then diluted with water and extracted thoroughly with chloroform. The total residue (18 mg) was heated with 5 ml of water containing 0.5 ml of concentrated hydrochloric acid for 10 min. The solution was extracted with chloroform and then made alkaline with excess potassium carbonate and extracted with chloroform. The extract contained **20** as indicated by TLC. It was filtered and evaporated, leaving a yellow gum (10 mg), which was dissolved in ether (1 ml). Crystallization gave compound **20** (3.9 mg, 24%) having an infrared spectrum identical with that of **20** prepared by the alternative synthesis.

Ketone 26 by Hydrolysis of 25. A solution of **25** (40 mg) in methanol (2 ml) and water (1 ml) was treated with 1 drop of concentrated hydrochloric acid. The solution was heated on a steam bath for 10 min, diluted with more water, and extracted with chloroform. The residue from evaporation of the chloroform gave **26** (14.6 mg, 40%), mp 146–147°, on crystallization from ether.

Similar procedures were used to convert **16** to **21** (68%), **28** to **30** (100%), **33** to **35** (47%), **34** to **36** (34%), and **29** to **31** (75%). Ketone **22** was isolated directly from a photolysis, probably by inadvertent hydrolysis catalyzed by HCl generated in the photolysis.

Conversion of 35 to 36. A solution of **35** (50 mg) in ethanol (30 ml) was treated with 1 ml of 0.4 *N* sodium ethoxide solution. The solution was stirred for 8 hr at room temperature, at which time TLC indicated that complete conversion to **36** had occurred. The solution was diluted with water and extracted with chloroform. Evaporation of the chloroform left crystalline **36** (40 mg, 80%) having an infrared spectrum identical with that of **36** prepared by hydrolysis of **34**.

The transformation was also monitored by NMR experiments. Addition of 1 drop of 2 *N* NaOD in D_2O to a DMSO-d_6 solution of **35** resulted in the appearance of a spectrum recognized as that of **36** but lacking the doublets at 3.80 and 4.32 ppm which are due to the CH_2 unit between the indole ring and amide carbonyl. Also missing from this final spectrum was the broad signal at 2.88 ppm assigned to the bridgehead proton. A similar experiment but with a eight-fold decrease in NaOD concentration revealed that considerable exchange at the CH_2 group took place prior to any isomerization to **36**.

Methylation of 34 to 28. Sodium hydride (30 mg of 57% mineral oil dispersion) was washed with hexane and then warmed for 0.5 hr with dimethyl sulfoxide (1 ml). To this solution **34** (10 mg) was added and stirred at room temperature for 15 min. Excess (0.5 ml) methyl iodide was then added and the solution was stirred for an additional 15 min. The reaction mixture was diluted with water and extracted with ether. TLC indicated complete conversion to **28**. The ether was evaporated and the residue was redissolved in a small amount of ether. Compound **28** (7.0 mg, 70%), having an infrared spectrum identical with that of **28** prepared by photocyclization of **7b-3**, crystallized.

Isomerization of Ketone 31 to 32. A solution of **31** (12 mg) in ethanol (3 ml) was treated with 1 drop of 2 *N* NaOH. Although TLC with ether on silica gel indicated no change, a plate developed in 3:1 chloroform–acetone showed complete conversion to a second substance in less than 30 min. The solution was diluted with water (2 ml) and concentrated. On standing, **32**, mp 204–205° (7.1 mg, 59%), crystallized.

Methylation of 39 to 37. Sodium hydride (30 mg of 57% mineral oil dispersion) was washed with hexane and then dimethyl sulfoxide was added. The mixture was warmed for 30 min. Compound **39** (5 mg) was added and the solution was stirred for 10 min. There was then added excess (0.5 ml) methyl iodide and the solution was stirred at room temperature for 20 min. The reaction mixture was diluted with water and extracted with ether. Evaporation of the ether left crystalline **37** (4 mg, 80%) having an infrared spectrum and TLC behavior identical with those of **37** prepared by photolysis of **10b-3**.

Reduction of 36 to 39. A solution of **36** (14.6 mg), triethylsilane

(1 ml), trifluoroacetic acid (1 ml), and carbon tetrachloride (1 ml) was refluxed under nitrogen for 3 days. Water was added and then excess sodium carbonate was added to the mixture. The solution was extracted with chloroform and the extract was evaporated to dryness. The residual oil was placed on a column of silica gel and eluted with 1:1 chloroform–ether. Two principal fractions were detected by TLC. The first was evaporated and the residue was crystallized by trituration to give **39** (3.2 mg, 24% yield) having an infrared spectrum identical with that of **39** prepared by photolysis of **10c-3**. The second fraction was 3.1 mg of recovered **36**. There was no indication of the formation of any **40**.

Thermal Stability of 33 and 40. Bis(ethoxyethyl) ether was distilled from sodium metal under nitrogen. Solutions of **33** and **40** (2.0 mg/2 ml) were prepared and portions of the solutions were sealed in Pyrex ampoules. The ampoules were maintained in oil baths at 170° and analyzed by HPLC.

Acknowledgment. The ^{13}C NMR spectrum and some of the 100-MHz spectra were recorded on a Jeol PS-100-P pulse Fourier transform NMR instrument purchased with the aid of National Science Foundation Grant MPS73-08469. The 300-MHz spectra were recorded at the NMR Center, Institute of Polymer Science, The University of Akron, Akron, Ohio.

Registry No.—**1a-4,** 54851-93-3; **1b-4,** 54851-94-4; **2b-2,** 54841-95-5; **2b-3,** 54851-96-6; **4a-4,** 54851-97-7; **4b-2** isomer 1, 54852-27-6; **4b-2** isomer 2, 54852-28-7; **5b-2,** 54851-98-8; **5b-3,** 54851-99-9; **5c-2,** 54852-00-5; **5c-3,** 54852-01-6; **7a-2,** 54852-02-7; **7b-2,** 54852-03-8; **7b-3,** 54852-04-9; **7b-4,** 54852-05-0; **7c-2,** 54852-06-1; **7c-3,** 54852-07-2; **8b-2,** 54852-08-3; **8b-3,** 54852-09-4; **8b-4,** 54852-10-7; **9c-3,** 54852-11-8; **10b-2,** 54852-12-9; **10c-3,** 54852-29-8; **11b-2,** 54852-13-0; **11c-4,** 54852-14-1; **12c-4,** 54852-15-2; **14b-2,** 54852-16-3; **14c-4,** 54852-17-4; **15,** 54852-18-5; **16,** 54852-19-6; **17,** 54852-20-9; **21,** 54852-21-0; **22,** 54852-22-1; **23,** 54852-23-2; **25,** 54852-24-3; **26,** 54852-25-4; **27,** 54852-30-1; **28,** 54910-63-3; **29,** 54852-31-2; **30,** 54852-32-3; **31,** 54852-33-4; **32,** 54910-64-4; **33,** 54852-34-5; **34,** 54910-65-5; **35,** 54852-35-6; **36,** 54910-66-6; **37,** 54852-36-7; **38,** 54910-67-7; **39,** 54852-37-8; **40,** 54852-38-9; 1-methyl-2-lithioindole, 54852-26-5; 1-benzenesulfonyl-2-lithioindole, 40900-03-6; 2-pyridinecarboxaldehyde, 1121-60-4; 3-pyridinecarboxaldehyde, 500-22-1; ethylene glycol, 107-21-1; chloroacetyl chloride, 79-04-9; 2-methylpyridine, 109-06-8; methyl 1-methylindole-2-carboxylate, 37493-34-8; 4-methylpyridine, 108-89-4; ethyl indole-2-carboxylate, 3770-50-1.

Supplementary Material Available. Spectral and analytical data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2613.

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Internal Catalysis in Imine Formation from Acetone and Acetone-d_6 and Conformationally Constrained Derivatives of *N,N*-Dimethyl-1,3-propanediamine

Jack Hine* and Wu-Shyong Li

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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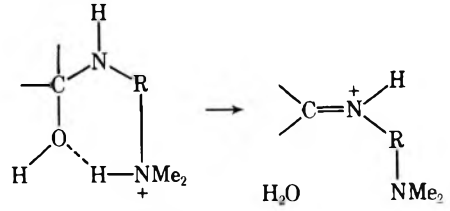
The kinetics of the reactions of 3-*exo*-dimethylaminomethyl-2-*endo*-norbornanamine (1), *cis*-2-(dimethylaminomethyl)cyclohexylamine (2), and 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine with acetone, and of these three diamines, neopentylamine, and 2-*endo*-norbornanamine with acetone-d_6 to give imines have been studied at 35° and various pH's by use of hydroxylamine to capture the imines as they are formed. Acetone-d_6 was more reactive than acetone in the reactions with hydroxylamine alone as well as in the reactions with each of the diamines; the average k^D/k^H was 1.2. The rate constants for the monoprotonated diamines were so large relative to those for the unprotonated diamines that reliable values for the latter could not be obtained. The dominant reaction mechanism appears to be a reversible formation of the carbinolamine derived from the tertiary-protonated form of the monoprotonated diamine followed by rate-controlling internal acid-catalyzed formation of the iminium ion. The rate constants are compared with those obtained as a by-product of deuterium exchange studies of reactions of **1**, **2**, **3**, and five other monoprotonated diamines by the same mechanism. The comparisons show that structural features that destabilize conformations in which the two amino groups are far apart may decrease the reactivity by relative stabilization of a cyclic hydrogen-bonded form of the monoprotonated diamine as well as increasing the reactivity by relative stabilization of the transition state. Freezing the H_2N–C–C–CH_2NMe_2 dihedral angle of 1,3-diamines at values near 0, 60, and 120° does not give large differences in reactivity. Comparison of the rate constants for reactions of unprotonated neopentylamine and 2-*endo*-norbornanamine with those obtained previously for amines of the type $XCH_2CH_2NH_2$ gives no evidence for steric hindrance.

Imine formation in the reactions of isobutyraldehyde[2] and acetone[3] with the monoprotonated forms of certain diamines is much faster than would be expected from data on primary amines with similar basicities and steric properties but without acidic substituents. This has been explained in terms of internal acid catalysis of the dehydration of the intermediate carbinolamine. Monoprotonated *trans*-2-



(dimethylaminomethyl)cyclopentylamine, which may be considered a derivative of monoprotonated 3-dimethylaminopropylamine in which rotation around the C-1–C-2 bond has been constrained, reacts with acetone to give imine more than four times as rapidly as monoprotonated 3-dimethylaminopropylamine does. To learn more about how such conformational constraints influence internal acid catalysis in imine formation we have studied additional derivatives of 3-dimethylaminopropylamine using more rigid compounds than used previously and constraining the dihedral angle between the C-1–N and C-2–C-3 bonds to values of about 0, 60, and 120°.

Rates of imine formation are useful in interpreting data on bifunctional catalysis of the dedeuteration of acetone-d_6 by derivatives of 3-dimethylaminopropylamine.[4] For this reason we have studied the kinetics of formation of imines from acetone-d_6 as well as ordinary acetone.

Results

The equilibrium constants for imine formation from acetone and most primary amines in aqueous solution are too small for reliable rate constants to be obtained by direct measurements on the reaction. Hence we used the method described previously, in which the imine is captured as rapidly as it is formed by hydroxylamine, which transforms it to the oxime almost irreversibly.[3] That is, the kinetics of oxime formation are studied in the presence of the primary amines as catalysts. In order to determine the extent of such catalysis we must know how fast the oximation is in the absence of the catalyst. The oximation of acetone-d_6 in the absence of primary amines was carried out under conditions similar to those used for acetone of normal isotopic composition.[3] The reaction was studied in water at 35° using 0.010 *M* acetone d_6, 0.097 *M* hydroxylamine, and an ionic strength of 0.297. Trimethylamine buffers were used between pH 7.24 and 10.51 and *N*-methylmorpholine buffers in the overlapping pH range 6.68–7.87. Since no general acid or base catalysis had been found with acetone, there was assumed to be none for acetone-d_6. The first-order rate constant obtained in a given run was divided by the initial concentration of unprotonated hydroxylamine to obtain a second-order rate constant. These second-order rate constants are probably made about 4% too small by neglect of the decrease in hydroxylamine concentration during the reaction and perhaps as much as another 9% too small by neglect of the small amount of hydroxylamine that was tied up as $Me_2C(OH)NHOH$. However, these uncertainties will have little effect on comparisons of the resulting rate constants with those obtained for ordinary acetone, which were calculated in the same way, or in using the rate constants to correct data obtained using primary amine catalysts for the "background" reaction rate, which is subject to essentially the same uncertainties. The second-order rate constants (k_{ox}) obtained are listed in Table III[5] and plotted logarithmically against the pH in Figure 1. They are fit by eq 1 with a standard deviation of 3.7%.[6] However, the reli-

$$k_{ox} = (2.71 \times 10^6 a_{H^+} + 2.20 \times 10^{-12}/a_{H^+} + 6.83 \times 10^{-3})\ M^{-1}\ \text{sec}^{-1} \quad (1)$$

ability of this division of the total reaction rate into three terms is reduced by the fact that the third term never contributed more than about 50% to the overall reaction rate, and in the low pH region where the first term dominates the reaction rate and the high pH region where the second term does, the reaction is so fast that the observed values of k_{ox} are of reduced reliability. Comparison of eq 1 with the

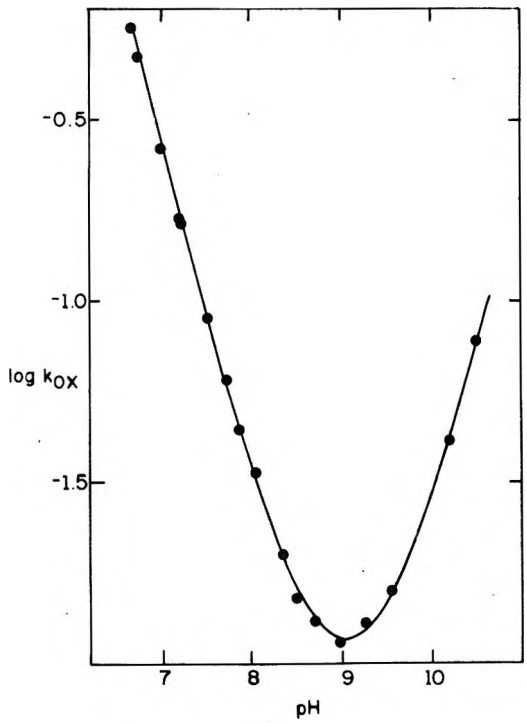


Figure 1. Plot of rate constants for oxime formation by acetone-d_6 vs. pH. Curve calculated from eq 1.

analogous equation obtained previously for ordinary acetone gives k^D/k^H values of 1.16, 1.47, and 1.31 for the first, second, and third terms, respectively.

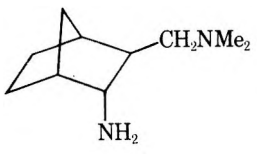
In the presence of a primary amine the reaction may be represented as shown in eq 2–4.

$$Me_2CO + H_2NOH \xrightarrow{k_{ox}} Me_2C{=}NOH \quad (2)$$

$$Me_2CO + H_2NR \underset{k_{-im}}{\overset{k_{im}}{\rightleftharpoons}} Me_2C{=}NR \quad (3)$$

$$Me_2C{=}NR + H_2NOH \xrightarrow{k_{hx}} Me_2C{=}NOH + RNH_2 \quad (4)$$

If $k_{hx}[H_2NOH]$ is much larger than k_{-im} capture of the imine will be essentially quantitative and the only effect of increases in the hydroxylamine concentration on the reaction rate will arise from the k_{ox} term. If $k_{hx}[H_2NOH]$ is comparable to or smaller than k_{-im} increases in hydroxylamine concentration will increase the rate both because of the direct reaction (the k_{ox} term) and because of increased efficiency of capturing the imine. Evidence was described that 0.08 *M* hydroxylamine was enough to capture essentially all the intermediate imine in the case of all the diamines studied previously, and 0.03 *M* was enough for the monoamines.[3] Hence these concentrations were used in the present study. In addition, runs were made in the presence of 3-*exo*-dimethylaminomethyl-2-*endo*-norbornanamine (**1**) at pH 9.1 using 0.04 and 0.15 *M* hydroxylamine and in the presence of *cis*-2-(dimethylaminomethyl)cyclohexylamine (**2**) using 0.15 *M* hydroxylamine at pH 8.7 and 10.1



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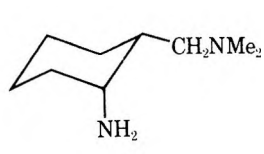

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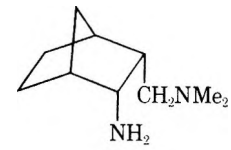
and the dependence of the observed reaction rate on the concentration of hydroxylamine found to be within the experimental uncertainty of that expected from the k_{ox} term alone.

First-order rate constants for the formation of oxime from acetone or acetone-d_6 in the presence of **1**, **2**, or 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine (**3**)



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are listed in Tables IV–VIII.[5] The observed first-order rate constants may be expressed as shown in eq 5

$$k_{obsd} = k_{ox}[H_2NOH] + k_a[Am] + k_{ah}[AmH^+] \quad (5)$$

in which k_{ox} is given by eq 1 for acetone-d_6 or an analogous equation[3] for acetone, k_a is the second-order rate constant for imine formation from the unprotonated diamine, and k_{ah} is the corresponding rate constant for monoprotonated diamine. Values of k_a and k_{ah} obtained from the data in Tables IV–VIII by least-squares fits[6] to eq 5 gave k_{calcd} values that differed from the k_{obsd} values by standard deviations of 5.1–10.7%. However, some of the values of k_a obtained were implausible. One value was zero and would have been negative if the method of treating the data had permitted it. In no run was the calculated value of $k_a[Am]$ as much as 21% as large as k_{obsd}. Hence it was decided that the k_a values could be estimated more reliably than they could be determined. A plot of the values of log k_a for six electrically neutral amines of the type $XCH_2CH_2NH_2$ vs. the pK_a values of the corresponding $XCH_2CH_2NH_3^+$ was earlier found[3] to closely approach a straight line of slope 0.59. In view of the possibility that the primary amino groups presently being studied are too hindered to be expected to give k_a values that would fall near this line, we studied the kinetics of imine formation of neopentylamine and 2-*endo*-norbornanamine using acetone-d_6. From the rate constants obtained in the individual runs, which are listed in Tables IX and X,[5] and the values of pK_a at 35° for the conjugate acids of these amines, which are 9.83 (calculated from data at 16–25°) and 10.03 for the neopentyl and norbornyl compounds, respectively,[7] second-order rate constants of 0.085 and 0.080 M^{-1} sec^{-1} were obtained. The latter value, referring to the norbornanamine, is essentially that required to fit on the plot of log k_a values for $XCH_2CH_2NH_2$ compounds vs. the corresponding pK_a values, when allowance is made for the ~20% greater reactivity of acetone-d_6 than ordinary acetone that may be seen in our other results. Even when allowance is made for this secondary deuterium kinetic isotope effect the value 0.085 M^{-1} sec^{-1} for the reaction of neopentylamine with acetone-d_6 is about 50% too large to fit the plot of log k_a values for $XCH_2CH_2NH_2$ compounds.

Having found no evidence for steric hindrance in the rate constants for imine formation we assumed that the values of log k_a for **1**, **2**, and **3** would fall on the plot for $XCH_2CH_2NH_2$ that we have referred to. This assumption and the pK_a values that have been estimated for the forms of the monoprotonated diamines that are protonated at the primary amino groups (that is, the pK_{TPH} values, which are 9.70, 9.55, and 9.24, respectively[7]) gave k_a values of 0.040, 0.032, and 0.021 M^{-1} sec^{-1}, respectively. The k_a values for reaction with acetone-d_6 were then obtained by multiplying these rate constants by a k^D/k^H value of 1.2 (the average of the values for k_{ah}). These estimated k_a values were used to calculate the corresponding k_{ah} values by the method of least squares.[6] The resulting k_{ah} values, which are listed in Table I, give the k_{calcd} values listed in Tables IV–VIII, whose standard deviations from the k_{obsd}

Table I
Kinetics of Imine Formation from Acetone or Acetone-d_6 and 2-Dimethylaminomethyl Cyclic Amines[a]

	CH_3COCH_3		CD_3COCD_3		
Amine	$10^3 k_a$[b]	$10^3 k_{ah}$	$10^3 k_a$[b]	$10^3 k_{ah}$	k^D_{ah}/k^H_{ah}
1	40	147	48	151	1.03
2	32	172	39	206	1.20
3	21	307	25	394	1.28

[a] In water at 35°. All rate constants in M^{-1} sec^{-1}. [b] Estimated as described in the text.

values ranged from 7.2 to 10.7% for the six sets of values. These standard deviations are very little larger than those obtained using k_a values obtained from the regression analysis. In fact, the k_a term in eq 5 may be completely neglected without changing the resultant k_{ah} values by more than 10% from those listed in Table I and without raising any standard deviation of the k_{calcd} values from a set of k_{obsd} values above 13.5%. Hence the values obtained for k_{ah} are relatively independent of the uncertainties in the k_a values.

Discussion

The values of k^D/k^H show that acetone-d_6 is more reactive than acetone in each of the three pathways for oxime formation covered by eq 1 and in imine formation by each of the three monoprotonated diamines studied. All these reactions are believed to involve relatively rapid reversible addition to the carbonyl group to give a carbinolamine whose dehydration is rate controlling.[8] The oximation of acetone-d_6 has also been found to be faster than that of acetone in acidic solution where attack of hydroxylamine on the carbonyl group is the rate-controlling step.[9] Our results are consistent with a steric explanation based on the smaller effective van der Waals radius of covalently bonded deuterium relative to protium.[9-12] A probable uncertainty of about 10% in our k^D/k^H values makes it unclear which of the differences among our k^D/k^H values are experimentally significant. Therefore discussion of whether any of the additional factors suggested to account for secondary deuterium kinetic isotope effects are important in our reactions is not warranted.

Values of k_{ah} for reactions of acetone-d_6 with a number of dimethylamino-substituted primary amines are listed in Table II. These include the three values obtained in the present work and values obtained less directly for some other 1,3-diamines and a 1,4-diamine as a by-product of studies of diamine catalysis of the deuterium exchange of acetone-d_6.[4,13] Also listed are values for compounds of the type $Me_2N(CH_2)_nNH_2$, where n is 2, 3, and 4, obtained from data on the reaction with acetone[3] and the assumption that the ratio k_{ah}^D/k_{ah}^H equals 1.2. The values of k_{ah} obtained from dedeuteration studies, which are parenthesized, deviate from those obtained (under slightly different conditions) from oximation rate measurements by an average of 22%. We do not believe that these deviations are large enough to mask any significant trends in the k_{ah} values listed.

According to the plot of log k vs. pK values referred to earlier, even the most basic of the monoprotonated diamines having three carbon atoms between the two amino groups should not have a k value larger than about 0.003 M^{-1} sec^{-1} if there were no internal acid catalysis of dehydration of the intermediate carbinolamine. Hence the k_{ah} values for all these amines probably arise largely from such catalysis.

The values of k_{ah} listed are second-order rate constants for reaction of acetone-d_6 with the *average* monoprotonated diamine. However, since the rate-controlling step is believed to be a first-order reaction of the carbinolamine arising from addition of the tertiary-protonated diamine to the acetone, we believe that it is more meaningful to compare second-order rate constants based on tertiary-protonated diamines. These, which are denoted k'_{ah}, are obtained by dividing k_{ah} by f_t, the fraction of the monoprotonated diamine that is protonated at the tertiary amino group. The values of f_t estimated previously[7,14] are listed in Table II. The largest variation in f_t values does not arise from variations in the ratio of f_t to f_p (the fraction of primary-protonated diamine); instead it arises from variations in f_c, the fraction of the monoprotonated diamine that exists as a cyclic hydrogen-bonded species in which the proton is attached to both amino groups at the same time.

The transition state for the internally acid-catalyzed transformation of the carbinolamine to an iminium ion and a molecule of water is presumed to be subject to the con-

Table II
Rate Constants for Imine Formation from Acetone-d_6 and Some Monoprotonated Diamines[a]

Diamine	$10^3 k_{ah}$[b] M^{-1} sec^{-1}	$100 k'_{ah}$ M^{-1} sec^{-1}	pK_1[c]	f_t[c]	f_c[c]
3	394 (406)	113	9.78	~0.35	~0.36
$Me_2NCH_2CH_2NH_2$	364[d]	96	9.30[e]	0.38[e]	0.0[e]
2	206 (176)	103	10.02	0.20	0.46
trans-(2-Dimethylaminomethyl)cyclopentylamine	168[d] (219)	51	9.80	0.33	~0.11
1	151 (214)	61	9.92	~0.25	~0.15
$Me_2NCH_2CHMeCH_2NH_2$	(63)	23	9.87	0.28	0.24
trans-(2-Dimethylaminomethyl)cyclohexylamine	(51)	46	10.29	0.11	0.71
$Me_2N(CH_2)_3NH_2$	39[d] (32)	13	9.91	0.30	0.0
$Me_2N(CH_2)_4NH_2$	27[d]	8	10.17[e]	0.33[e]	0.0[e]
$Me_2NCH_2CMe_2CH_2NH_2$	(~13)	~12	10.03	0.11	0.71
o-(Dimethylaminomethyl)benzylamine	(8)	37	10.07	0.022	0.934

[a] In water at 35°. [b] Parenthesized values were obtained from studies[4,13] of diamine catalysis of the dedeuteration of acetone-d_6. The other values were obtained from studies of diamine catalysis of oximation. [c] K_1 is the acidity constant of the monoprotonated diamine, which exists as a cyclic internally hydrogen-bonded species to the extent f_c and as a tertiary protonated species to the extent f_t. These data are from ref 7 unless otherwise noted. [d] From data on acetone of normal isotopic composition and the assumption that k^D_{ah}/k^H_{ah} equals 1.2. [e] From ref 14.

Table III

Kinetics of the Reaction of Acetone-d_6 with Hydroxylamine in Water at 35°[a]

pH	$10^3 k_1$ (sec^{-1})	$10^3 k_{ox}$ (M^{-1} sec^{-1}) obsd	calcd
6.679	49.7	564	574
6.747	42.3	475	492
7.006	24.2	263	274
7.211	16.2	170	174
7.242[b]	15.6	164	162
7.521	8.78	90.5	88.6
7.735[b]	5.92	60.6	56.8
7.872	4.33	44.2	43.4
8.049	3.29	33.6	31.3
8.351	1.96	19.9	19.4
8.500	1.48	15.1	16.1
8.697	1.29	13.0	13.4
8.980	1.12	11.4	11.8
9.266	1.27	12.9	12.4
9.561	1.53	15.8	15.6
10.201	3.93	41.2	41.9
10.507	7.48	78.0	77.6

[a] Initial concentrations of hydroxylamine and acetone, 0.0971 ± 0.0014 and 0.0100 M, respectively. Sodium chloride added to bring the ionic strength to 0.297 ± 0.003. Trimethylamine buffers were used in all runs above pH 8 and N-methylmorpholine buffers in all runs below pH 8 unless otherwise noted. Total buffer concentrations were 0.10 M. [b] Trimethylamine buffer used.

Table IV

Oximation of Acetone in the Presence of 3-exo-(Dimethylaminomethyl)-2-endo-norbornanamine (1)[a]

[Diamine]$_t$ M	[H_2NOH]$_t$ M	pH	$10^3 k_{obsd}$ sec^{-1}	$10^3 k_{ox}$[H_2NOH] sec^{-1}	$10^3 k_{calcd}$ sec^{-1}
0.0196	0.0806	7.601	5.32	5.08	5.80
0.0197	0.0808	7.652	5.40	4.58	5.37
0.0212	0.0815	7.681	4.37	4.35	5.25
0.0212	0.0815	8.042	4.04	2.16	3.65
0.0212	0.0815	8.245	2.78	1.52	3.36
0.0212	0.0815	8.697	2.77	0.87	3.30
0.0212	0.0875	8.882	3.39	0.82	3.39
0.0386	0.1543	9.080	6.70	1.38	6.19
0.0199	0.0375	9.082	3.38	0.34	2.82
0.0399	0.0375	9.090	6.26	0.34	5.32
0.0196	0.1562	9.102	4.21	1.40	3.84
0.0212	0.0815	9.266	3.49	0.75	3.40
0.0212	0.0814	9.395	3.28	0.80	3.42
0.0212	0.0815	9.575	3.48	0.93	3.46
0.0212	0.0815	9.772	3.46	1.18	3.55
0.0212	0.0815	9.970	4.02	1.58	3.76
0.0212	0.0815	10.142	4.04	2.13	4.12
0.0192	0.0805	10.258	5.95	2.67	6.07
0.0394	0.0808	10.458	7.07	3.91	7.00
0.0394	0.0808	10.695	9.21	6.43	9.17
0.0394	0.0808	11.075	16.0	14.8	17.2

[a] In water at 35° with an initial acetone concentration of 0.0100 M. Sodium chloride present to bring the ionic strength to 0.286 ± 0.006 unless otherwise noted.

Table V

Oximation of Acetone-d_6 in the Presence of 3-exo-(Dimethylaminomethyl)-2-endo-norbornanamine (1)[a]

pH	$10^3 k_{obsd}$ sec^{-1}	$10^3 k_{ox}$[H_2NOH] sec^{-1}	$10^3 k_{calcd}$ sec^{-1}
7.601	6.89	5.94	6.71
7.681	5.50	5.10	6.06
8.042	4.92	2.57	4.15
8.245	4.04	1.84	3.78
8.697	3.44	1.09	3.66
9.266	3.80	1.01	3.78
9.395	3.41	1.09	3.82
9.575	3.87	1.29	3.91
9.772	4.50	1.65	4.09
9.970	4.60	2.25	4.45
10.142	5.40	3.06	5.04
10.258	7.51	3.77	7.16
10.458	8.35	5.66	8.62
10.695	11.6	9.36	11.9
11.075	21.5	21.7	21.8

[a] In water at 35° with an initial acetone-d_6 concentration of 0.0100 M. The concentrations of diamine and hydroxylamine are the same as in the runs at the same pH listed in Table IV. Ionic strengths are 0.283 ± 0.006.

Table VI

Oximation of Acetone in the Presence of cis-2-(Dimethylaminomethyl)cyclohexylamine (2)[a]

[Diamine]$_t$ M	[H_2NOH]$_t$ M	pH	$10^3 k_{obsd}$ sec^{-1}	$10^3 k_{ox}$[H_2NOH] sec^{-1}	$10^3 k_{calcd}$ sec^{-1}
0.0207	0.0815	7.462	7.49	6.87	8.48
0.0206	0.0813	7.752	5.33	3.76	5.94
0.0205	0.0808	8.143	4.55	1.79	4.59
0.0207	0.0812	8.383	4.45	1.24	4.30
0.0206	0.0811	8.437	4.49	1.15	4.24
0.0207	0.0815	8.636	4.12	0.92	4.13
0.0203	0.1481	8.702	4.72	1.57	4.74
0.0206	0.0813	8.833	4.01	0.78	4.03
0.0206	0.0810	9.067	4.52	0.72	3.96
0.0207	0.0815	9.172	4.17	0.73	3.95
0.0206	0.0813	9.393	3.93	0.80	3.89
0.0206	0.0812	9.751	3.64	1.14	3.89
0.0206	0.0814	9.830	3.51	1.28	3.92
0.0201	0.1583	10.145[b]	6.30	4.20	6.28
0.0206	0.0810	10.197	4.30	2.35	4.43
0.0207	0.0815	10.335	5.40	3.08	4.95
0.0206	0.0813	10.512	6.36	4.46	6.00

[a] In water at 35° with an initial acetone concentration of 0.0100 M. Ionic strength 0.297 ± 0.017 unless otherwise noted. [b] Ionic strength 0.353.

Table VII

Oximation of Acetone-d_6 in the Presence of cis-2-(Dimethylaminomethyl)cyclohexylamine (2)[a]

pH	$10^3 k_{obsd}$ sec^{-1}	$10^3 k_{ox}$[H_2NOH] sec^{-1}	$10^3 k_{calcd}$ sec^{-1}
7.462	9.89	8.02	10.09
7.752	7.06	4.42	7.21
8.143	5.71	2.14	5.71
8.437	5.25	1.40	5.33
8.702	5.74	1.97	5.98
8.833	4.98	1.00	5.08
9.172	4.98	0.97	4.93
9.393	5.38	1.09	4.79
9.751	4.58	1.60	4.63
10.145	7.55	5.98	7.85
10.197	5.17	3.37	5.14

[a] In water at 35° with an initial acetone concentration of 0.0100 M. The concentrations of diamine and hydroxylamine and the ionic strengths are the same as in the runs at the same pH listed in Table VI.

Table VIII

Oximation of Acetone and Acetone-d_6 in the Presence of 1-endo-Dimethylaminomethyl-2-endo-norbornanamine (1)[a]

	CH_3-CO-CH_3			CD_3-CO-CD_3		
pH	$10^3 k_{obsd}$ sec^{-1}	$10^3 k_{ox}$[H_2NOH] sec^{-1}	$10^3 k_{calcd}$ sec^{-1}	$10^3 k_{obsd}$ sec^{-1}	$10^3 k_{ox}$[H_2NOH] sec^{-1}	$10^3 k_{calcd}$ sec^{-1}
7.292	13.4	9.42	12.4	13.7	11.0	14.9
7.817	7.88	3.16	7.66	10.2	3.72	9.64
8.013	6.70	2.17	7.05	9.14	2.58	9.00
8.302	6.88	1.33	6.57	8.63	1.61	8.49
8.608	6.70	0.90	6.28	8.88	1.12	8.18
9.046	5.95	0.70	5.96	7.62	0.91	7.76
9.177	5.93	0.70	5.85	7.63	0.93	7.61
9.489	5.84	0.82	5.54	6.68	1.13	7.16
9.631	4.82	0.95	5.40			
9.678	5.11	1.00	5.35	7.12	1.39	6.89
9.815[b]	9.01	1.20	9.29	10.8	1.68	11.8
10.318	6.47	2.84	5.80	8.28	4.10	7.53

[a] In water at 35°, with total hydroxylamine and diamine concentrations of 0.0778 and 0.0202 M, respectively, unless otherwise noted. Sodium chloride was present as needed to give an ionic strength of 0.028 ± 0.005. Initial concentration of acetone or acetone-d_6 0.0100 M. [b] Total diamine concentration 0.0403 M.

Table IX

Oximation of Acetone-d_6 in the Presence of Neopentylamine[a]

pH	$10^3 k_{obsd}$ sec^{-1}	$10^3 k_{ox}$[H_2NOH] sec^{-1}	$10^3 k_{calcd}$ sec^{-1}
8.606	0.986	0.432	0.775
8.798	1.04	0.375	0.898
9.250	1.68	0.368	1.70
9.612	3.25	0.495	3.04
9.820	4.16	0.653	4.12
9.930	5.33	0.776	4.78
10.260	5.50	1.410	6.99

[a] In water at 35°, with total initial concentrations of acetone-d_6, hydroxylamine, and neopentylamine of 0.0100, 0.0300, and 0.100 M, respectively. Sodium chloride was present as needed to give an ionic strength of 0.31.

Table X

Oximation of Acetone-d_6 in the Presence of 2-endo-Norbornanamine[a]

pH	$10^3 k_{obsd}$ sec^{-1}	$10^3 k_{ox}$[H_2NOH] sec^{-1}	$10^3 k_{calcd}$ sec^{-1}
8.618	0.513	0.430	0.642
9.252	1.14	0.358	1.04
9.568	2.14	0.473	2.05
9.718	2.78	0.553	2.62
9.912	3.93	0.756	3.57
10.110	4.30	1.06	4.75

[a] In water at 35°, with total initial concentrations of acetone-d_6, hydroxylamine, and norbornanamine of 0.0100, 0.0300, and 0.100 M, respectively. Sodium chloride was present as needed to give an ionic strength of 0.275 ± 0.015.

straints described previously, that the N–H–O angle be fairly near 180°, the C–N–H and C–O–H angles be fairly near 109°, and the four atoms attached to the C–N double bond that is being formed be fairly nearly coplanar.[3] Molecular models meeting these requirements for the carbinolamine derived from $H_2NCH_2CH_2CH_2NHMe_2^+$ can be constructed with H_2N–C–C–CH_2 dihedral angles ranging from about 0° to about 120° without obviously large differences in strain. Of the eight diamines listed that have three carbon atoms between their two amino groups, all five in which this dihedral angle is held between 0° and about 120° have k'_{ah} values of 0.79 ± 0.34 M^{-1} sec^{-1}. The parent compound *N,N*-dimethyl-1,3-propanediamine, which probably exists largely as a trans conformer with a H_2N–C–C–CH_2 dihedral angle of 180°, has a considerably smaller k'_{ah} value. Introduction of a 2-methyl substituent to give *N,N*,2-trimethyl-1,3-propanediamine, for which there is now no conformer that has the advantage of being free from any gauche interaction of the primary amino group with a methylene group, increases k'_{ah} by 70%. A second methyl substituent, which gives *N,N*,2,2-tetramethyl-1,3-propanediamine, causes a decrease in reactivity, however, presumably because of crowding in the transition state. This decrease in reactivity is seen to be merely to the level of reactivity of the parent compound, not to a lower level, as would be implied by the k_{ah} values. The smaller value of k_{ah} for *N,N*,2,2-tetramethyl-1,3-propanediamine arises from the relatively great stability of the cyclic hydrogen-bonded form of the monoprotonated amine.

The values of k_{ah} for the two compounds having four carbon atoms between the two amino groups show that freezing the H_2NC–C–C–$CNMe_2$ dihedral angle near 0°, as has been done in *o*-(dimethylaminomethyl)benzylamine, gives an almost threefold *decrease* in reactivity relative to *N,N*-dimethyl-1,4-butanediamine, in which this angle is free to change but is presumably 180° in the most highly populated conformer. The values of k'_{ah}, however, show that the 0° dihedral angle *increases* the reactivity almost sixfold when correction is made for the large fraction of monoprotonated diamine tied up in the cyclic hydrogen-bonded form.

The marked catalytic activity of the monoprotonated form of the highly flexible *N,N*-dimethylethylenediamine suggests that monoprotonated forms of appropriately conformationally constrained 1,2-diamines would be better catalysts for the oximation of acetone than any of the species studied in the present investigation. The differences in relative reactivities as measured by k_{ah} values and those as measured by k'_{ah} values warn us that structural features that disfavor conformers in which the two amino

groups are far apart may have the counterproductive result of relatively stabilizing the cyclic hydrogen-bonded form of the monoprotonated diamine as well as the desired result of relatively stabilizing the transition state for iminium ion formation. However, studies with molecular models indicate that when the two amino groups have rigidly been given the optimum relative geometry for internally acid-catalyzed iminium ion formation, their relative geometry is unfavorable for internal hydrogen bonding.

The reactions were not thoroughly tested for general acid and base catalysis. However, several tests, such as the four runs on 1 near pH 9.09, give no indication of general catalysis. Furthermore, none was found previously in similar reactions, where the case of 2-dimethylaminoethylamine was tested several times. Hence, general catalysis is not likely to be very important.

Experimental Section

The synthesis and properties of **1**, **2**, and **3** have been described previously,[15] as have the methods used in following the kinetics of oximation[3] and the pK values used for the amines.

Registry No.—**1**, 53369-68-9; **2**, 53369-73-6; **3**, 53403-34-2; acetone, 67-64-1; acetone-d_6, 666-52-4; hydroxylamine, 7803-49-8; neopentylamine, 5813-64-9; 2-*endo*-norbornanamine, 31002-73-0.

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Oxidation Reactions of 2,2,2-Fluorodinitroethylamine and Some *N*-Alkyl-2,2,2-fluorodinitroethylamines

Horst G. Adolph

Advanced Chemistry Division, U.S. Naval Surface Weapons Center, White Oak, Silver Spring, Maryland 20910

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2,2,2-Fluorodinitroethylamine is readily oxidized to the hydroxylamine, oxime, and nitrile oxide; further oxidation under forcing conditions leads to cleavage of the carbon-carbon bond. *N-tert*-Butyl-2,2,2-fluorodinitroethylamine behaves similarly, but *N*-alkyl derivatives possessing an α-methylene group are converted to *N*-fluorodinitroethylamides.

Oxidation reactions of β-polynitroalkylamines have apparently not been studied, although many such amines have been prepared by the Mannich reaction of β-polynitroalkanols and aliphatic amines (eq 1).[1,2]

$$XC(NO_2)_2CH_2OH + HNRR' \longrightarrow XC(NO_2)_2CH_2NRR' \quad (1)$$

X = halogen, alkyl, NO_2

R, R' = alkyl, H

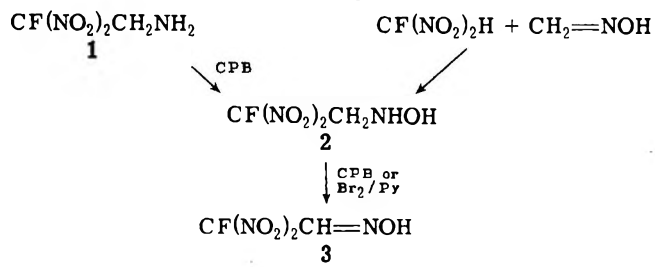
Most of the known β-polynitroalkylamines are secondary and tertiary; primary ones have limited stability and only one has been described.[3]

We report here on a number of oxidation reactions of 2,2,2-fluorodinitroethylamine and some of its derivatives. Since the electronic effects of the dinitroalkyl group appear to determine the reactivity behavior of these materials, many of our observations are probably applicable to oxidations of other β-polynitroalkylamines such as 2,2-dinitropropyl- and 2,2,2-trinitroethylamines as well.

Peracid Oxidations of 2,2,2-Fluorodinitroethylamine (1). The presence of strongly electron-withdrawing substituents in 1 (the fluorodinitromethyl group is reported to have a σ^* of 4.4)[4] decreases its basicity and has a general deactivating effect on its reactivity toward oxidizing agents. Thus, 1 is not affected by hydrogen peroxide in aqueous or methanolic solution, even in the presence of catalysts such as sodium tungstate and molybdate which bring about the rapid oxidation of primary alkyl- and aralkylamines.[5]

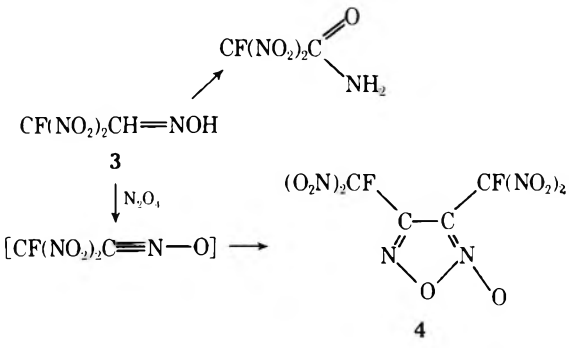
Oxidation occurred readily with various peracids, however. One equivalent of *m*-chloroperbenzoic acid (CPB) converted 1 to fluorodinitroethylhydroxylamine (2), which was isolated in 69% yield. It is noteworthy that here the oxidation can be halted at the hydroxylamine stage while simple alkylhydroxylamines can usually not be made in good yield by partial oxidation of primary amines.[6] The structure of 2 is supported by its independant preparation by the addition of fluorodinitromethane to formaldoxime (Scheme I).

Scheme I



Oxidation of **2** with a second equivalent of CPB or with bromine in the presence of pyridine gave fluorodinitroacetaldoxime (**3**), in moderate yield. **3** is not stable to extended storage and in the course of several weeks at ambient temperature was observed to rearrange quantitatively to fluorodinitroacetamide (Scheme II).

Scheme II



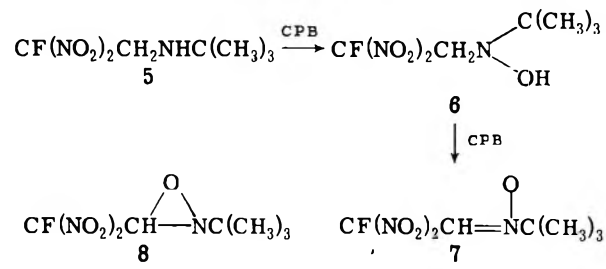
Further oxidation of the oxime **3** or of the hydroxylamine **2** beyond the oxime stage, with nitric acid or aqueous chromic acid, did not yield any useful products; a low yield of fluorodinitromethane was obtained in some cases, indicating C–C bond breaking during the oxidation process. **3** was also oxidized slowly by trifluoroperacetic acid, giving a product mixture which contained bis(fluorodinitromethyl)furoxane (**4**, isolated in ca. 10% yield), *N*-(2,2,2-fluorodinitroethyl)formamide (2–3% yield), and, as main component, an unidentified carbonyl compound which decomposed on standing.

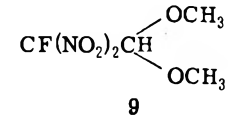
Formal further oxidation of **3** also occurs with N_2O_4, which converted the oxime to bis(fluorodinitromethyl)furoxane (**4**) in moderate yield (Scheme II). Fluorodinitroacetonitrile oxide appears to be an intermediate, since strong ir absorption at ca. 2300 cm^{-1} is exhibited during the reaction by the methylene chloride solution of the reactants. The reaction thus probably follows the established addition–elimination–dimerization path of other oxime–N_2O_4 reactions.[7]

The structure assignment of **4** is based on analytical data including molecular weight determinations, the absence of proton signals in the NMR spectrum, and the similarity of its uv spectrum to those of other furoxans, particularly bis(1,1-dinitroethyl)furoxane.[8] The latter had λ_{max} (EtOH) 264 nm (ϵ 4400). **4** was unstable in ethanol. Therefore its uv spectrum was obtained in 1,2-dichloroethane: λ_{max} 268 nm (ϵ 3,700). The possibility of **4** having the isomeric 1,2,4-oxadiazole 4-oxide structure is not completely ruled out, however.

Peracid Oxidations of *N*-*tert*-Butyl-2,2,2-fluorodinitroethylamine (5). The oxidation of **5** with peracids parallels to some extent that of **1**; however, the hydroxylamine **6** (a surprisingly unstable material, see Experimental Section) is readily oxidized further and could only be isolated in low yield. Oxidation of **5** with 2 equiv of CPB gave a substance whose ir and NMR spectra were in agreement with the nitrone structure **7** (Scheme III). The structure of **7** is also supported by analytical results (see Experimental Section). Further corroboration was sought by attempting 1,3-dipolar additions of **7** to phenyl isocyanate, propiolic acid, and methyl acrylate, but only intractable tars were obtained in all of these reactions. The alternate oxirane structure **8** can be ruled out with good certainty on the basis of the NMR data as follows: the methine proton signal is shifted only slightly from that of –CH= in the oxime **3** (δ 7.66 in **7** vs. 7.98 in **3**); the methine proton of **9**, on the other hand, is observed at δ 5.65. Additionally, the F–H coupling constants in such compounds are typically 15 ± 3 Hz when H is attached to sp^3 carbon, but are much lower (7 ± 2 Hz) when H is attached to sp^2 carbon.[9] Compound **7** has a H–F coupling constant of 6 Hz.

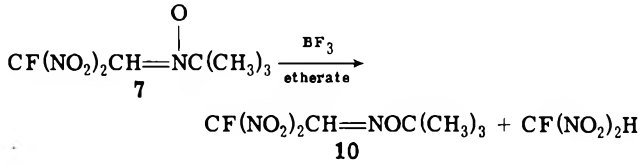
Scheme III





9

The nitrone **7** is somewhat more stable than the hydroxylamine **6**, but also decomposes slowly on storage. Reaction with trifluoroacetic anhydride gave a complex mixture of products. Treatment with boron trifluoride etherate effected partial transformation to the oxime ether **10**. The



structure assignment of **10** was again based on the characteristic shift and coupling constant to F of the methine proton which indicated the presence of the –CH= moiety; further, the migration of the *tert*-butyl group from positive nitrogen to neutral oxygen is indicated by the methyl signal shift from δ 1.57 to 1.30. A second, minor product of the reaction of **9** with boron trifluoride etherate was fluorodinitromethane.

Further oxidation of **7** with trifluoroperacetic acid in refluxing chloroform gave fluorodinitromethane as essentially the only fluoronitro species. The same product was formed in better yield by oxidation with 40–50% nitric acid.

Exploratory attempts were made to replace CPB in the oxidations of **1** and **5** by the more readily available commercial 40% peracetic acid. Somewhat less pure products were obtained than with CPB, but with proper attention to reaction conditions 40% peracetic acid should be suitable for these oxidations.

Reaction of *N*-*tert*-Butyl-2,2,2-fluorodinitroethylamine with Other Oxidizing Agents. The action of a number of other oxidizing agents on **5** was investigated briefly. No reaction was observed at ambient temperature with sodium dichromate and with the $K_2S_2O_8$–Ag^+ system in aqueous sulfuric acid. Manganese (IV) oxide in methylene chloride suspension was similarly without effect. Alkaline sodium hypochlorite also reacted very sluggishly; to the extent that reaction occurred, fluorochlorodinitromethane was formed.

Chromic Acid Oxidation of *N*-Alkylfluorodinitroethylamines. The course these oxidations take depends strongly on reaction conditions as well as on the structure of the substrate. The few examples studied indicate a considerable variation of behavior of *N*-alkylfluorodinitroethylamines toward chromic acid.

As has been mentioned above, *N*-*tert*-butylfluorodini-

troethylamine is fairly resistant to chromic acid oxidation. If an α proton is present in the alkyl group, oxidation occurs more readily but may be accompanied by extensive degradation. For example, the dichromate oxidation of *N,N'*-bis(fluorodinitroethyl)ethylenediamine (**11**) was studied in some detail as a potential method for the preparation of *N,N'*-bis(dinitroalkyl)oxamides. In dilute sulfuric acid oxidative degradation of **11** predominated; nitrous acid, apparently generated in the process, nitrosated part of the diamine to **13** which was stable under the reaction

$CF(NO_2)_2CH_2NHCH_2CH_2NHCH_2CF(NO_2)_2$

11

$CF(NO_2)_2CH_2NH—\overset{O}{\overset{\|}{C}}—\overset{O}{\overset{\|}{C}}—NHCH_2CF(NO_2)_2$

12

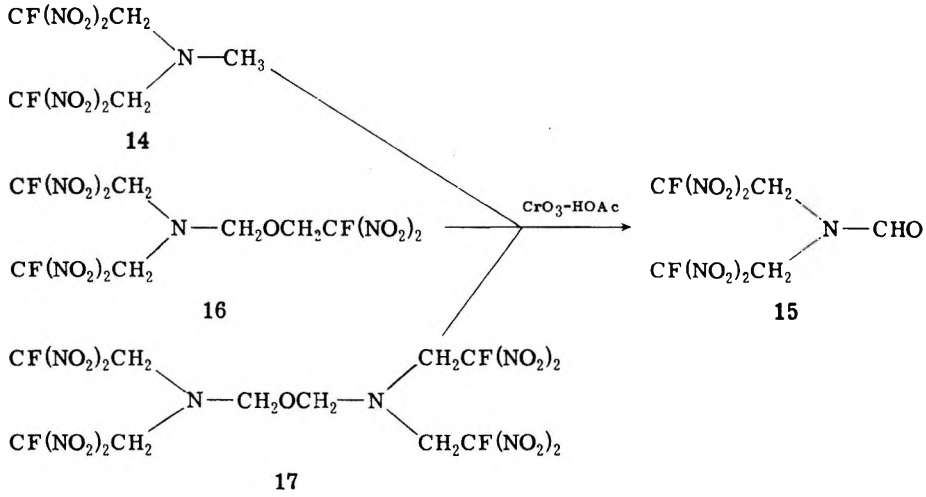
$CF(NO_2)_2CH_2\underset{NO}{\underset{|}{N}}—CH_2CH_2—\underset{NO}{\underset{|}{N}}CH_2CF(NO_2)_2$

13

conditions and could be isolated in low yield. At acid concentrations near 50% the desired oxidation occurred to some extent and the oxamide **12** was formed in ca. 20% yield. With further increasing acid concentrations the yield of **12** decreased and only degradation was again observed at acid strengths of 70–80%.

The oxidation of some *N*-alkylbis(2,2,2-fluorodinitroethyl)amines with chromium trioxide in acetic acid proceeded much smoother. The methyl group in **14** was oxidized to the formyl function in near quantitative yield. This reaction may be useful for the preparation of other bis(fluorodinitroethyl)amides, but its scope has not been explored. Further oxidation of **15** with potassium permanganate in acetone gave only degradation products. Oxidation of the amino ethers **16** and **17** with chromium trioxide–acetic acid also gave **15** in excellent yields (Scheme IV); the expected urethanes could not be found in either case. It may be assumed that intermediate chromic esters are formed in these oxidations which are readily fragmented or solvolyzed to **15**.

Scheme IV



Experimental Section

Caution. Most materials described here are explosives and appropriate care should be taken in their handling. Precautions recommended in working with fluorodinitromethyl compounds, especially 2,2,2-fluorodinitroethanol, have been described elsewhere.[10] Neat 2,2,2-fluorodinitroethylamine (**1**) must be handled with extreme care.[3]

Melting and boiling points are uncorrected; elemental analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. NMR spectra were obtained on a Varian HA-100 spectrometer; chemical shifts are relative to Me_4Si as internal standards.

***N*-(2,2,2-Fluorodinitroethyl)hydroxylamine (2). A. By Oxidation of 1.** To a stirred solution of 4.45 g of crude **1**[3] in 30 ml of methylene chloride was added at 0° 5.85 g of 86% *m*-chloroperbenzoic acid and the mixture was stirred for 2 hr with continued cooling. After washing with a solution of 6 g of sodium bicarbonate in 50 ml of water in several portions, the methylene chloride solution was dried ($MgSO_4$), concentrated, and chilled to give 3.4 g (68.6%) of **2**, mp 87.5–88.5° (from methylene chloride).

B. From Fluorodinitromethane and Formaldoxime. A mixture of 15 g of a 15% solution of formaldoxime in ether, 6.25 g of fluorodinitromethane, and 40 ml of water was cooled to 0°, 0.15 g of sodium bicarbonate was added, and the mixture was stirred for 20 hr at 0°. The phases were separated, the aqueous phase was extracted with ether, and the combined ethereal solutions were dried and freed from solvent in vacuo. The remaining oil was taken up in methylene chloride and the solution was chilled to give 1.95 g of **2** in two crops: NMR (CD_3CN) δ 6.20 s (NHOH), 5.88 broad s (NHOH), 4.19 d ($CFCH_2$, J_{HF} = 16.5 Hz).

Anal. Calcd for $C_2H_4N_3O_5F$ (169.07): C, 14.21; H, 2.38; N, 24.85; F, 11.24. Found: C, 14.3; H, 2.3; N, 24.4; F, 11.2.

Fluorodinitroacetaldoxime (3). A. By Oxidation of 1 with Peracid. To an ice-cooled and stirred solution of 7.65 g of crude **1** in 70 ml of methylene chloride was added 20 g of 86% *m*-chloroperbenzoic acid in small portions; the mixture was stirred for 3 hr with continued cooling and chilled in a Dry Ice–acetone bath, and the solids were filtered off. The filter cake was washed with precooled methylene chloride, and the filtrate was concentrated and again chilled with Dry Ice–acetone. In this manner 15 g of *m*-chlorobenzoic acid was obtained in three crops. When the methylene chloride solution was freed from solvent an oil admixed with some solid material remained. An ir spectrum of the oil showed all the bands present in the spectrum of **3** prepared from **2** and Br_2–pyridine as described below. No attempts at further purification were made.

B. From 2 with Br_2–Pyridine. To a solution of 1.7 g of **2** in 40 ml of methylene chloride was added 1.6 g of bromine in 10 ml of methylene chloride. Then 1.6 g of pyridine was added dropwise with stirring. After stirring for 1 hr the yellow solution was washed with dilute sulfuric acid and dried ($MgSO_4$), and the solvent was removed in vacuo. Infrared, NMR, and GLC analysis of the remaining oil indicated that it was essentially pure **3**. The compound could not be distilled or induced to crystallize and was not purified further: ir (film) 3560 (OH), 1605 (asymmetrical NO_2), 1415, 1310 (symmetrical NO_2), 995, 950, 815, 790 cm^{-1}; NMR ($CDCl_3$) δ 9.47 s (C=NOH), 7.98 d ($CFCH$=N, J_{HF} = 8 Hz).

After several weeks of storage at ambient temperature the ir spectrum of this material had changed drastically; it was now essentially superimposable on a spectrum of an authentical sample

of fluorodinitroacetamide, prepared by the procedure of Wiesboeck and Ruff.[11]

Bis(fluorodinitromethyl)furoxane (4). 3 was prepared from 7.65 g of 1 as described above, and after separation of the bulk of the *m*-chlorobenzoic acid the methylene chloride solution of 3 was diluted to ca. 75 ml and cooled in an ice bath. Dry N_2O_4 (7.5 g) was bubbled in and the solution was stored at ca. 0° overnight. The mixture was then heated to reflux for 24 hr until the evolution of nitric oxides had ceased, allowed to cool, washed twice with a dilute solution of sodium bicarbonate, dried, and freed from solvent in vacuo. The residual semisolid material was triturated with 50 ml and then with 30 ml of pentane–methylene chloride (9:1), the combined filtrates were freed from solvents in vacuo, and the remaining oil was taken up in a small amount of the same solvent mixture and chromatographed on silica (G. F. Smith, Columbus, Ohio) with 9:1 pentane–methylene chloride as eluent. All fractions collected had superimposable ir spectra and were devoid of proton signals in the NMR; only one product peak was found when dilute methylene chloride solutions were analyzed by GLC (flame ionization detector). Obtained was a total of 4 g of essentially pure **4**. The material was rechromatographed as described above and a center fraction was used for analytical purposes: ir (film) 1660 (furoxane ring), 1615 (asymmetrical NO_2), 1300 (symmetrical NO_2), 1260 (C–F stretch), 990, 840, 800 cm^{-1}.

Anal. Calcd for $C_4F_2N_6O_{10}$ (330.08): C, 14.55; F, 11.51; N, 25.46. Found: C, 14.5; F, 11.2; N, 25.2; mol wt (MEK), 325, 330.

***N*-*tert*-Butyl-2,2,2-fluorodinitroethylhydroxylamine (6).** A solution of 5 g of 86% *m*-chloroperbenzoic acid in 50 ml of methylene chloride was added with cooling to 5 g of **5**[12] in 50 ml of methylene chloride, the mixture was stirred for 2 hr at 0–5° and filtered, and the filtrate was washed twice with dilute sodium hydrogen sulfite solution, twice with dilute sodium bicarbonate solution, and twice with dilute sulfuric acid, dried ($MgSO_4$), and freed from solvent in vacuo at a temperature not exceeding 30–35°. The resulting mixture of **6** and **7** can be separated into its components by fractional crystallization from 2:1 hexane–methylene chloride, in which **7** is less soluble. Fairly pure **6** was obtained in this manner as an unstable oil which decomposed on standing (*Caution:* some samples fumed off after a few hours at room temperature): ir (film) 3650, 3500 (OH, broad), 1605, 1310 (NO_2 stretch), 1370, 1080, 850, 808 cm^{-1}; NMR ($CDCl_3$) δ 5.14 s (OH), 3.935 d (J_{HF} = 17 Hz), 1.09 s (CH_3).

***N*-*tert*-Butyl-α-fluorodinitromethylnitrone (7).** To a solution of 10 g of **5**[12] in 100 ml of methylene chloride was added at 0–5° and with efficient stirring 19.4 g of 86% *m*-chloroperbenzoic acid portionwise over a 0.5-hr period. After stirring for 2 hr at ice-bath and 1 hr at room temperature, the mixture was poured into a solution of 10 g of sodium bicarbonate and 0.5 g of sodium sulfite in 200 ml of water and triturated until the gas evolution ceased. The organic phase was dried ($MgSO_4$) and freed from solvent to give 10.4 g of crude **7**, mp 65–67° dec (from methylene chloride–hexane). The material decomposed slowly when stored at room temperature: ir (ATR spectrum) 1625 (asymmetrical NO_2), 1560 (C=N?), unidentified bands at 1370, 1305, 1275, 1165, 1085, 855, 785, 760 cm^{-1}; NMR ($CDCl_3$) δ 7.66 d (CFCH=N, J_{HF} = 6 Hz), 1.58 s [$NC(CH_3)_3$].

Anal. Calcd for $C_6H_{10}FN_3O_5$ (223.16): C, 32.29; H, 4.52; F, 8.51; N, 18.83. Found: C, 32.0; H, 4.4; F, 8.8; N, 18.7.

Fluorodinitroacetaldoxime *tert*-Butyl Ether (10). Boron trifluoride etherate (3 ml) was added to an ice-cold solution of 5 g of **7** in 15 ml of methylene chloride and the mixture was stirred for 24 hr at room temperature. The product was washed thoroughly with water and dried ($MgSO_4$) and the solvent was distilled off. The remaining oil was vacuum transferred at 0.1 mm into a Dry Ice cooled trap and then fractionated. At 15 mm there was obtained ca. 0.8 g of fluorodinitromethane; **10**, 2.3 g, boiled at 42–43° (0.5 mm). Refractionation gave the analytical sample: NMR ($CDCl_3$) δ 7.78 d (J_{HF} = 7 Hz), 1.30 s; area ratio, 1:9.

Anal. Calcd for $C_6H_{10}FN_3O_5$: C, 32.29; H, 4.52; F, 8.51; N, 18.83. Found: C, 32.1; H, 4.4; F, 8.6; N, 18.9.

Oxidation of 7 with Nitric Acid. To 40 ml of ice-cold 40% nitric acid was added in small portions 4.5 g of **7** and the mixture was stirred for 1 hr with continued cooling. The reaction mixture was diluted with an equal volume of water and extracted with methylene chloride. After drying ($MgSO_4$) and distilling off the solvent there remained 2.25 g of an oil whose main component was identified by GLC retention time and NMR and ir spectra as fluorodinitromethane.

***N,N'*-Bis(2,2,2-fluorodinitroethyl)oxamide (12) from 11.** A sample of **11** was prepared in situ by stirring a mixture of 25 ml of water, 5.4 g of 2,2,2-fluorodinitroethanol, and 1.05 g of ethylenediamine for 2 hr at room temperature.[13] The mixture was then cooled and 35 ml of concentrated sulfuric acid was added slowly, followed by 15 g of sodium dichromate dihydrate. After stirring overnight the mixture was poured on crushed ice and 1.3 g of crude **12** was isolated by filtration. The product was identified by comparison with an authentic sample.[12]

Preparation of *N,N*-Bis(2,2,2-fluorodinitroethyl)methylamine (14) and Oxidation to *N,N*-Bis(2,2,2-fluorodinitroethyl)formamide (15). A mixture of 13.75 g of crude *N*-(2,2,2-fluorodinitroethyl)methylamine,[14] 12.9 g of 2,2,2-fluorodinitroethanol, and 40 ml of methanol was heated to 65–70° for 72 hr, the mixture was poured into cold dilute sulfuric acid, and the product was taken up with methylene chloride. After filtration through a short column of silica (G. F. Smith, Columbus, Ohio) to remove unreacted fluorodinitroethanol, the solvent was removed in vacuo to give 16.1 g (64.5%) of crude **14**: mp 43–43.5° (from methylene chloride–pentane); NMR ($CDCl_3$) δ 4.04 d (J_{HF} = 18 Hz), 2.63 s; areas, 4:3.

Anal. Calcd for $C_5H_7F_2N_5O_8$ (303.14): C, 19.81; H, 2.33; F, 12.54; N, 23.10; O, 42.22. Found: C, 19.8; H, 2.4; F, 12.1; N, 23.0.

To a mixture of 2 g of chromium trioxide and 15 ml of glacial acetic acid was added a solution of 3 g of **14** in 10 ml of glacial acetic acid. The mixture was stirred for 3 days at room temperature and poured into water to give 3.05 g (97%) of **15**: mp 123.5–124.5° (from chloroform); NMR (CD_3CN) δ 8.18 s (CHO), 4.85, unsymmetrical multiplet ($CFCH_2$); area ratio, 1:4.

Anal. Calcd for $C_5H_5F_2N_5O_9$ (317.14): C, 18.92; H, 1.59; F, 11.98; N, 22.09. Found: C, 18.9; H, 1.8; F, 11.7; N, 21.4.

Preparation of *N,N*-Bis(2,2,2-fluorodinitroethyl)-*N*-2,2,2-fluorodinitroethoxymethylamine (16) and Oxidation to 15. A solution was made of 5.8 g of bis(2,2,2-fluorodinitroethyl)amine[3] and 0.6 g of paraformaldehyde in 25 ml of 90% sulfuric acid. After the solution was stirred at room temperature for 15 min, 4 g of sodium bromide was added. Stirring was continued for an additional 15 min, during which time some methylene chloride was added to prevent the mixture from becoming too thick. The phases were separated and the acid phase was extracted once with methylene chloride. The combined methylene chloride solutions were dried ($MgSO_4$) and freed from solvent in vacuo. The remaining oil crystallized on standing. It was assumed to be *N*-bromomethyl-*N,N*-bis(2,2,2-fluorodinitroethyl)amine, but was not characterized further.

The crude bromomethylamine (1.9 g) was added to a solution of 0.8 g of 2,2,2-fluorodinitroethanol and 0.5 g of triethylamine in 10 ml of acetonitrile, the mixture was stirred at room temperature for 2 hr and drowned, and the product was extracted into methylene chloride. After the solution was washed thoroughly with 0.01 *N* sodium hydroxide it was dried ($MgSO_4$) and freed from solvent. The remaining oil was taken up in 1:1 methylene chloride–hexane, and the solution was filtered to remove some insoluble solid and chromatographed on silica (G. F. Smith, Columbus, Ohio). The fractions containing pure **16** were combined and recrystallized from methylene chloride–hexane: mp 56–57.5°; yield ca. 0.7 g; NMR ($CDCl_3$) δ 4.48 d (J_{HF} = 17 Hz, $CFCH_2O$), 4.42 s (OCH_2N), 4.255 d (J_{HF} = 17 Hz, $CFCH_2N$).

Anal. Calcd for $C_7H_8F_3N_7O_{13}$ (455.18): C, 18.47; H, 1.77; F, 12.52; N, 21.54. Found: C, 18.4; H, 1.8; F, 12.3; N, 21.1.

A mixture of 0.9 g of **16**, 0.35 g of chromium trioxide, and 10 ml of glacial acetic acid was stirred for 20 hr at ambient temperature and drowned, and the solid material was filtered off to give 0.6 g (95%) of **15**.

Preparation of Bis(2,2,2-fluorodinitroethyl)aminomethyl Ether (17) and Oxidation to 15. A mixture of 9.6 g of bis(2,2,2-fluorodinitroethyl)amine,[3] 1 g of trioxane, and 50 ml of concentrated sulfuric acid was stirred at ambient temperature for 48 hr and poured over crushed ice and the semisolid product was taken up with methylene chloride. The solution was dried ($MgSO_4$), hexane was added to the cloud point, and the solution was chilled to give 5.4 g of **17**, which upon recrystallization from methylene chloride–hexane had mp 116.5–117.5°: NMR (CD_3CN) δ 4.34 d (J_{HF} = 17 Hz, $CFCH_2$), 4.07 s (NCH_2O).

Anal. Calcd for $C_{10}H_{12}F_4N_{10}O_{17}$ (620.28): C, 19.38; H, 1.95; F, 12.26; N, 22.59. Found: C, 19.5; H, 2.0; F, 11.8; N, 22.2.

To a solution of 2.45 g of **17** in 20 ml of acetic acid was added 1.2 g of chromium trioxide, the mixture was stirred at ambient temperature for 3 days and poured into water, and the product was isolated by filtration. Obtained was 2 g of crude **15**.

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Registry No.—**1**, 18139-02-1; **2**, 55702-16-4; **3**, 55702-17-5; **4**, 55702-18-6; **5**, 33046-34-3; **6**, 55702-19-7; **7**, 55702-20-0; **10**, 55702-21-1; **11**, 32765-49-4; **12**, 33191-90-1; **14**, 55702-22-2; **15**, 55702-23-3; **16**, 55702-24-4; **17**, 55702-25-5; fluorodinitromethane, 7182-87-8; formaldoxime, 75-17-2; 2,2,2-fluorodinitroethanol, 17003-75-7; ethylenediamine, 107-15-3; *N*-(2,2,2-fluorodinitroethyl)methylamine, 30409-33-7; *N*-bromomethyl-*N*,*N*-bis(2,2,2-fluorodinitroethyl)amine, 55702-26-6.

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Oxidation of Carbohydrates with Chromic Acid. Synthesis of 6-Acetamido-6-deoxy-D-*xylo*-hexos-5-ulose[1]

Donald E. Kiely*[2] and Laure Benzing-Nguyen

Department of Chemistry, University College, University of Alabama in Birmingham, University Station, Birmingham, Alabama 35294

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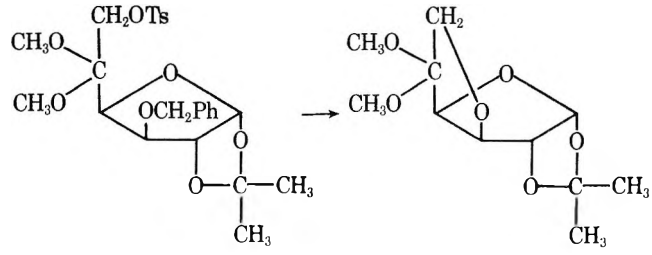
Preparation of the title compound (**8**) was routed through 6-azido-6-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**4**). Oxidation of **4** with the Jones reagent[3] gave the ketone **6**, which yielded crystalline 6-acetamido-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**7**) upon catalytic hydrogenolysis of the azido and benzyl groups, followed by N-acetylation of the intermediate amine. Alternatively, the hydrogenolyzable groups of **4** were first cleaved to give 6-acetamido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**), which, in turn, was selectively oxidized at the C-5 hydroxyl group with the chromic acid reagent to give **7**. Hydrolysis of the isopropylidene group of **7** afforded the δ-dicarbonyl amino sugar **8** as a mixture of pyranose and furanose ring forms.

Chromic acid in acetone (the Jones reagent[3,4]) is a very convenient and well-known reagent for the oxidation of secondary alcohols to ketones. As far as we are aware, recently published results from this laboratory described the first application of this oxidizing agent in the synthesis of dicarbonyl monosaccharide derivatives.[5] In this paper we describe the synthesis of a new δ-dicarbonyl amino sugar derivative, 6-acetamido-6-deoxy-D-*xylo*-hexos-5-ulose (**8**). As yet, no biological role for **8** or its parent amino sugar has been described, nor have these compounds been isolated from a natural source. However, they are structurally related to the unknown δ-dicarbonyl diamino sugar, 2,6-diamino-2,6-dideoxy-D-*xylo*-hexos-5-ulose, a predicated biogenetic precursor for neosamines B and C.[6] These amino sugars are components of the neomycins and a number of related aminoglycoside antibiotics. In the described synthesis of **8** the key oxidation of a secondary alcohol function was efficiently achieved with chromic acid reagent.

Results and Discussion

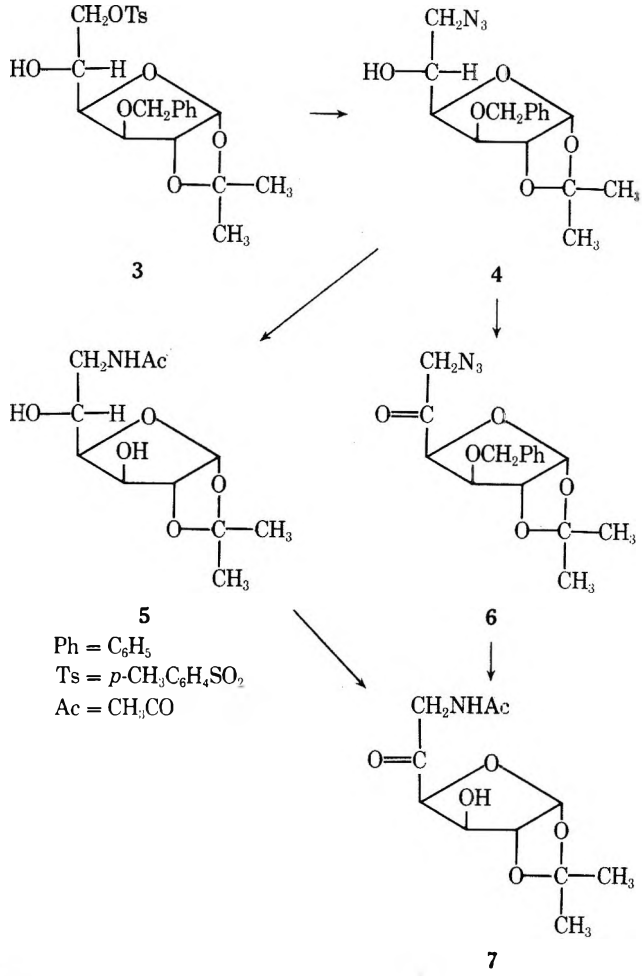
The first approach to the synthesis of the title compound began with the conversion of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal[7] to the corresponding 6-*O*-tosyl derivative **1**. However, compound **1** remained completely unchanged when treated with sodium azide in refluxing aqueous acetone. When **1** was treated with sodium azide under more vigorous conditions (in refluxing dimethylformamide) a single syrupy product, identified as the 3,6-anhydro derivative **2**, was isolated. Formation of **2** from **1** can be accounted for on the basis of a simple, direct nucleophilic displacement of the C-6 tosyloxy group by the oxygen of the C-3 benzyloxy group. Alternatively, it may be that a methoxy oxygen provides anchimeric assistance for removal of the proximate tosyloxy group, a step which is then followed by formation of the five-membered ether ring through the C-3 oxygen. Winstein and coworkers[8] concluded from a solvolysis study of 2-methyl-2-methoxy-1-propyl *p*-bromobenzenesulfonate that methoxyl group participation in the rate-determining ionization step is significant and takes place via a three-membered cyclic methyloxonium ion. The same mode of methoxy anchimeric assistance may be operative in the transformation of **1** to **2**.



1 **2**

Ph = C_6H_5
Ts = p-$CH_3C_6H_4SO_2$

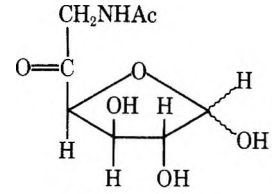
Alternate routes to **8** were then initiated originating from the azide **4**, a compound previously prepared by Saeki and Ohki.[9] Catalytic hydrogenolysis of the azido and benzyl groups of **4**, in acetic acid solution, was then followed by N-acetylation of the resulting amino sugar to give 6-acetamido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[10] (**5**). The C-5 hydroxyl group of **5** was then selectively oxidized with the chromic acid reagent, affording **7** in 38%



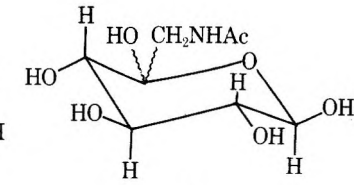
yield. This preference for oxidation at the C-5 hydroxyl has also been observed with other 6-deoxy furanose derivatives.[5,11] In the NMR spectrum of the oxidation product (**7**), the acetamido NH proton, coupled to the two C-6 protons, appeared as a broad triplet at δ 6.72 with a J value of 5.0 Hz. When this exchangeable proton was replaced with deuterium, the signal at δ 6.72 disappeared and the two-proton doublet at δ 4.28 (C-6 protons) collapsed to a broad singlet. The rest of the spectrum was also in agreement with the structure given for **7**.

A more efficient conversion of **4** to **7** was effected by reversing the order of the hydrogenolysis and oxidation steps. Oxidation of **4** with chromic acid in acetone at 0–5° for 6 hr gave, after purification of the reaction mixture by column chromatography, syrupy 6-azido-6-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**6**) in 67% yield. Subsequent hydrogenolysis of the azido and the benzyl groups of **6**, in acetic acid solution, followed by N-acetylation of the product, gave the crystalline acetamido derivative **7**. The yield from the conversion of **4** to **7** by this route was 33%, whereas when the hydrogenolysis was the first step in the sequence, the overall yield was only 15%. This difference is partly attributed to the efficient recovery of the water-insoluble ketone **6** during the oxidation work-up procedure. In contrast, the somewhat water-soluble crude acetamido derivative **7** was obtained in lower yields when isolated as the direct oxidation product of **5**.

In order to obtain the final desired product, 6-acetamido-6-deoxy-D-*xylo*-hexos-5-ulose (**8**), the isopropylidene group of **7** was removed by acid-catalyzed hydrolysis. The hydrolysate was concentrated by freeze drying and the residual gum was found to be chromatographically homogeneous by microcrystalline cellulose TLC. The ir spectrum of this material included a medium strength ketone carbonyl (5.75 μ) as well as a strong amide carbonyl absorption (6.05 μ), suggesting that **8**, as a mixture of ring isomers, contained a significant amount of the furanose forms **8a** and **8b**. A first-order analysis of the anomeric proton region (δ 4.7–5.7) of the NMR spectrum of **8** (Figure 1) provided further evidence that this was the case. However, after carrying out some proton decoupling experiments and measuring the coupling constants for coupled ring protons, we concluded that the pyranose anomer **8c** with H-1 and H-2 anti-diaxial is the major component in the tautomeric equilibrium mixture of **8**.



8a, α-furanose
8b, β-furanose



8c

The equilibrium between the pyranose and furanose forms of aldoses in deuterium oxide has been thoroughly investigated through the use of ^{1}H NMR spectroscopy.[12–15] The furanose anomeric protons have been generally observed at lower field strength than those of the corresponding pyranoses. Furthermore, the signal from the C-1 proton of the furanose 1,2-cis anomer ($J_{1,2} \simeq$ 3–5 Hz) is usually downfield to that of the furanose 1,2-trans anomer ($J_{1,2} \simeq$ 0–2 Hz). As regards the pyranose forms of the aldoses, a coupling constant of 7 Hz or more for the C-1 proton doublet indicates a 1,2-diaxial relationship between H-1 and H-2, whereas a smaller coupling constant signifies a gauche relationship between the two protons.

Three signals attributed to the anomeric protons of **8** were clearly observed in its spectrum, δ 5.60 (d, J = 4.0 Hz), 5.36 (s), and 4.93 (d, J = 8.0 Hz). The δ 5.60 and 5.36 signals have been assigned to the furanose 1,2-cis and 1,2-trans anomers (**8a** and **8b**) on the basis of the generalizations observed for the field positions and coupling constants of aldose anomeric protons.

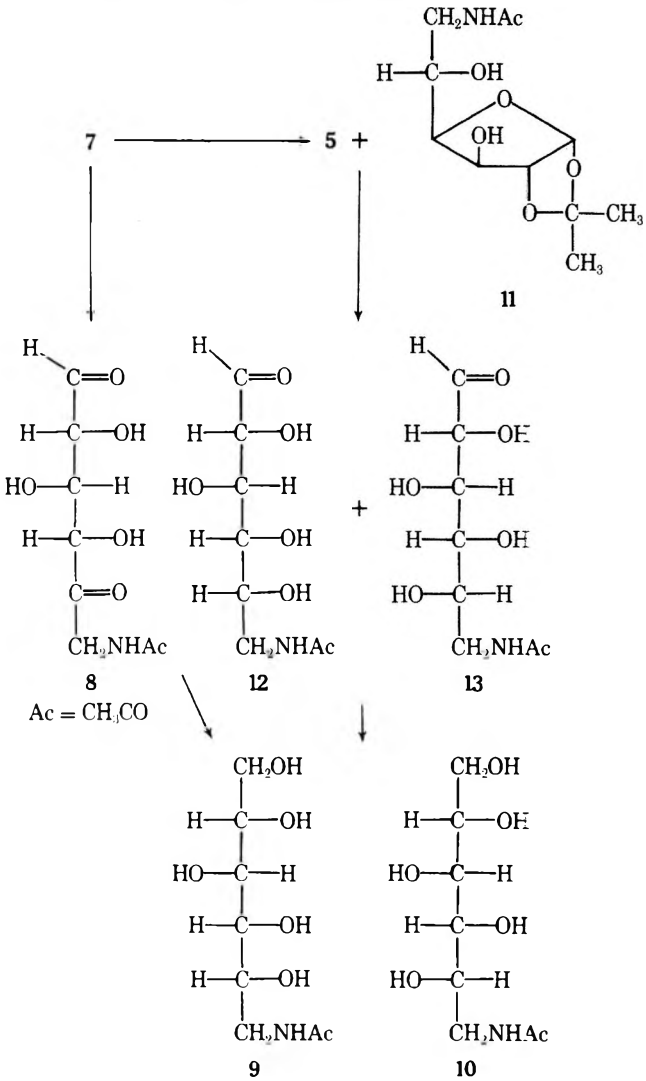
In the first decoupling experiment irradiation of the large δ 4.93 signal converted the δ 3.27 multiplet to a doublet with J = 9.2 Hz. Irradiation at the δ 3.27 signal simplified the quartet centered at δ 4.28, although the change was somewhat masked owing to overlapping signals from, in part, the methylene protons of the furanose rings **8a** and **8b**. These experiments established the anti-diaxial relationship for the H-1 (δ 4.93, $J_{1,2}$ = 8.0 Hz) and H-2 (δ 3.27) as well as the H-2 and H-3 (δ 4.28, $J_{2,3}$ = 9.2 Hz) protons of the pyranose ring **8c**. The large doublet at δ 3.65 (J = 9.2 Hz) is assigned to the H-4 proton of **8c**, it also being in a trans-diaxial relationship to the vicinal proton at C-3. An attempt to decouple H-3 from H-4 was unsuccessful because spectrometer beats obscured the resulting transitions at δ 3.68 when the signal at δ 4.28 was irradiated. The spectrum for the ring protons of **8c** was consistent with a theoretical spectrum generated by a full matrix computer program[16] for the spin system ABCD.

The singlet at δ 3.40 is attributed to the methylene protons of the predominant C-5 epimer of **8c**. Although we favor the predicted more stable epimer, i.e., with a C-5 equatorial acetamidomethyl substituent, direct evidence to support this particular stereochemical assignment is still lacking.

The mixture obtained from the acid hydrolysis of **7** is clearly a complex one. That it contains components in equilibrium with others than those already described is

borne out by the presence of additional overlapping, but yet unassigned, signals in the anomeric region of the spectrum.

Indirect evidence also helped to establish that the hydrolysis product of **7** was 6-acetamido-6-deoxy-D-*xylo*-hexos-5-ulose. When the hydrolysate was reduced with sodium borohydride, and the reduction products analyzed by GLC as their trimethylsilyl derivatives, a chromatogram with two predominant peaks (ratio of their areas 9:1) was obtained. The larger of the two peaks was unsymmetrical, suggesting that it resulted from two structurally related components in the reduction mixture. When an authentic sample of 6-acetamido-6-deoxy-D-glucitol (**9**), one of the two predicted reduction products from **8**, was cochromatographed with the mixture, the larger peak was enhanced. It is quite reasonable that the other predicted reduction product, 6-acetamido-6-deoxy-L-iditol (**10**), is also responsible in part for the principal peak in the gas chromatogram of the mixture. However, an authentic sample of **10** was not available for direct chromatographic comparison. The compound that gave rise to the very early smaller peak in the chromatogram has not been identified.



The ketone **7** was also converted to a mixture of **9** and **10** by an alternative route. Sodium borohydride reduction of the carbonyl group of **7** gave a two-component mixture composed of the diastereoisomeric alcohols **5** and **11**. Identification of **5** in the mixture was ascertained by TLC comparison with a sample of authentic material derived from **4**. Clearly then, the other component of the mixture must be the L-idose derivative **11**. The isopropylidene groups of **5** and **11** were then removed by acid-catalyzed hydrolysis to give a mixture readily resolved by microcrystalline cellulose TLC into two compounds. The D-glucose derivative, 6-acetamido-6-deoxy-D-glucose (**12**), was identified as one of the compounds in the mixture by comparison with authentic material obtained from pure **5**. The other spot on the chromatogram must then correspond to 6-acetamido-6-deoxy-L-idose (**13**). Reduction of the aldehydo carbonyl of these two isomers with sodium borohydride gave, as determined by GLC, the same mixture that resulted from **7** by way of compound **8**. The conversion of **7** to the final acetamidodeoxyalditols **9** and **10** by this route was straightforward and without complication. The fact that the same products resulted from **7** by the first sequence, hydrolysis then reduction, supports the premise that the conversion of **7** to **8** proceeded as depicted.

Experimental Section

General Methods. Proton magnetic resonance spectra were recorded using a Varian Model HA-60-IL or HA-100 spectrometer, in deuteriochloroform solution with tetramethylsilane serving as the internal standard, or in deuterium oxide, with chemical shifts measured from the δ 1.23 signal of *tert*-butyl alcohol as an internal standard. The ir spectra were obtained on a Perkin-Elmer Model 337 grating infrared spectrometer and optical rotations were measured with a Perkin-Elmer Model 141 polarimeter at 20°. GLC was carried out on a Beckman GC-5 gas chromatograph fitted with a flame ionization detector, using 0.25 in. o.d. × 6 ft stainless steel columns containing 3% SE-30 on Gas-Chrom Q, 80–100 mesh (Applied Science Laboratories, State College, Pa.). The oven temperature was maintained at 160° and the helium flow rate at 37 ml/min. Silica gel (0.06–0.20 mm, 70–230 mesh, E. Merck, Darmstadt) was used for column chromatographic separations. Precoated silica gel GF and Avicel plates (250 μ, Analtech Inc., Newark, Del.) were used for thin layer chromatography. All melting points were obtained on a Fisher-Johns melting-point apparatus and are uncorrected. Galbraith Laboratories, Inc., Knoxville, Tenn., performed the elemental analyses.

3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexofuranos-5-ulose Dimethyl Acetal (1). Crude 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal (2.5 g), prepared by the method of Kiely and Fletcher,[7] was purified on a column of silica gel (ca. 150 g) by eluting with benzene–ether (1:10) and collecting 10-ml fractions. Fractions 65–100 contained the chromatographically pure material and were pooled and concentrated in vacuo, yield 1.2 g. To a solution of the syrupy dimethyl acetal (0.55 g) in 5 ml of anhydrous pyridine was added *p*-toluenesulfonyl chloride (0.93 g). The reaction mixture was briefly agitated and after remaining for 5 hr at room temperature, was shown, by TLC to contain no starting material. Enough water was added to dissolve the pyridine hydrochloride and the reaction mixture was left undisturbed for 1 hr. The solution was then poured into 50 ml of ice water, which in turn was extracted with two 30-ml portions of chloroform. The combined chloroform extracts, washed successively with water, aqueous sodium hydrogen carbonate, and water, were then dried (Na_2SO_4). After the solvent was removed in vacuo, a methanol solution of the residue was decolorized (Norit) and concentrated in vacuo at 38° to give an almost colorless, syrupy product (**1**), 0.72 g, 92%: ir (neat) no OH stretch; NMR δ 7.68 and 7.22 (each d, J = 8.0 Hz, $SO_2C_6H_4CH_3$), 7.34 (s, $CH_2C_6H_5$), 5.84 (d, $J_{1,2}$ = 3.5 Hz, H-1), 4.63–4.16 (overlapping signals from ring protons, $CH_2C_6H_5$, and CH_2OTs), 3.96 (d, J_{4-3} = 3.3 Hz, H-3 or H-4), 3.32 and 3.29 [each s, $C(OCH_3)_2$], 2.42 (s, $SO_2C_6H_4CH_3$), 1.44 and 1.30 [each s, $C(CH_3)_2$]. The tosylate **1** slowly decomposed at room temperature and was used in the next step without further purification.

Treatment of 1 with Sodium Azide in *N,N*-Dimethylformamide. To a solution of crude **1** (0.723 g) in *N,N*-dimethylformamide (30 ml) was added 1.6 g of sodium azide. The reaction mixture was refluxed for 4 hr, at the end of which time TLC [benzene–ether (1:1)] showed that no starting material was left. The solvent was removed in vacuo (*ca.* 1 mmHg) at 27° and the residue was extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4) and concentrated in vacuo to give a syrupy residue, which was chromatographed on a column of silica gel (ca. 25 g) by eluting with benzene–ether (9:2) and collecting 6-ml fractions. The pure fractions were pooled and concentrated in vacuo to a yellow

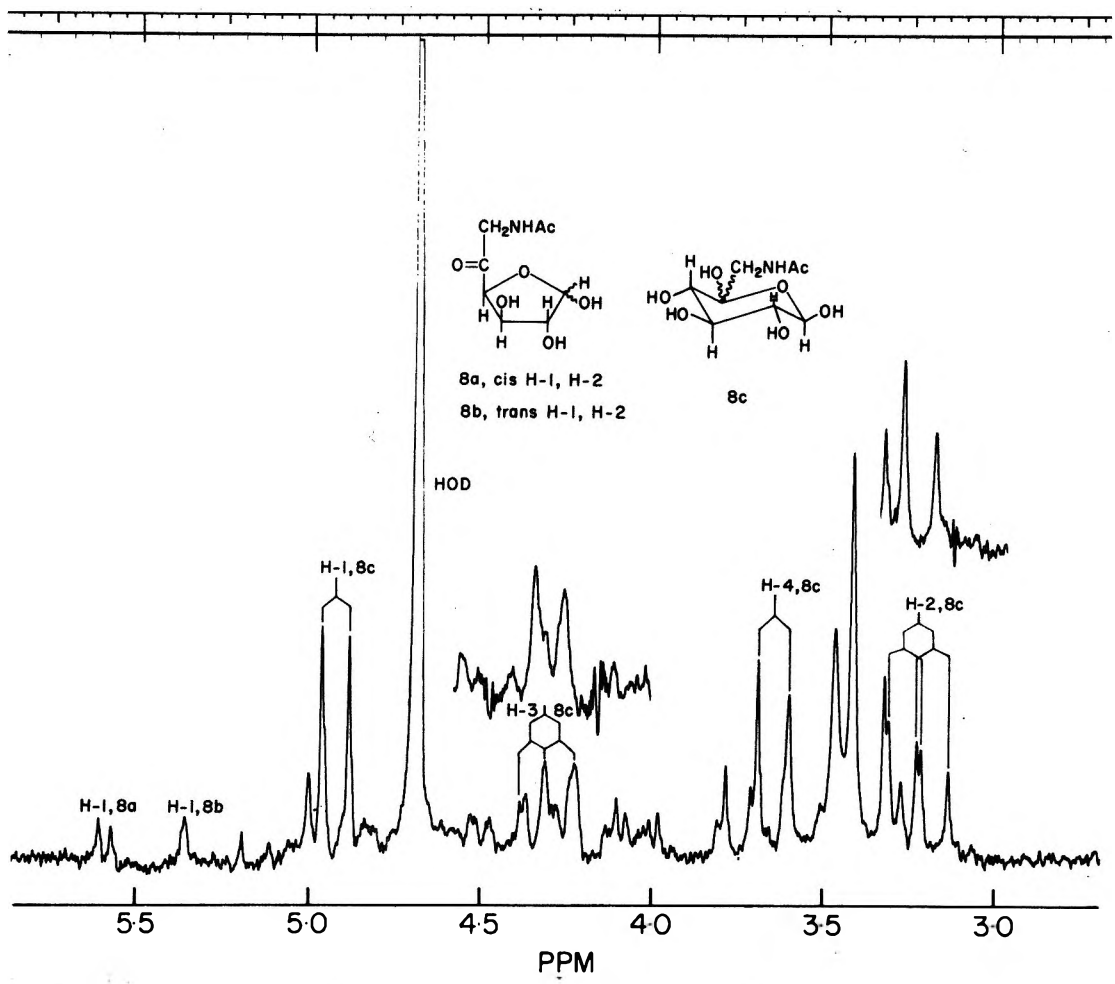


Figure 1. 100-MHz ^1H NMR spectrum of 8 (ring proton region) as a mixture of pyranose and furanose forms with decoupled signals at δ 3.27 and 4.28.

syrup. A solution of this material was decolorized (Norit) and concentrated in vacuo to give 3,6-anhydro-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal (**2**) as a colorless syrup, 0.22 g, 63%: $[\alpha]^{20}D$ +46° (c 1.17, chloroform); ir (Nujol) no N_3 absorption; NMR δ 5.98 (d, $J_{1,2}$ = 3.5 Hz, H-1), 4.60 (overlapping signals from H-2, H-3, and H-4), 3.95 and 3.57 (each d, J_{gem} = 10 Hz, C-6 protons), 3.42 and 3.30 [each s, $C(OCH_3)_2$], 1.48 and 1.33 [each s, $C(CH_3)_2$].

Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.53; H, 7.46.

6-Azido-6-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (4).[9] This compound was prepared by way of the known tosylate 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (**3**).[9,17] Crude 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[17] (2.11 g) was treated with *p*-toluenesulfonyl chloride (1.5 g) in the standard fashion, and the products separated by silica gel column chromatography. The monotosylate **3** was obtained chromatographically pure in 52% yield (1.65 g).

To a solution of **3** (1.6 g) in acetone (12 ml) was added 2 g of sodium azide in water (9 ml). After the reaction mixture was refluxed for 3 days, TLC [benzene–ether (1:1)] showed no unreacted starting material. The solvent was evaporated in vacuo and the residue was extracted with acetone (30 ml). Concentration of this solution in vacuo gave the organic product still contaminated with inorganic salts. This material was then successively extracted with acetone and chloroform to give the slightly yellow, chromatographically pure, syrupy **4**[9] (1.03 g, 86% from **3**), ir (neat) 2.87 (OH) and 4.74 μm (N_3). Saeki and Ohki described the conversion of **3** to **4** with sodium azide in methyl sulfoxide solution.[9]

Chromic Acid Oxidation of 4. Jones reagent (3 ml), prepared according to the method of Djerassi et al.,[4] was added to an ice-cold solution of **4** (1.8 g) in acetone (65 ml). The temperature of the reaction mixture was maintained at 0–5° and additional reagent (3-ml aliquots) was added after 1 and 2 hr, and again after 4 hr (2-ml aliquot). The reaction mixture, diluted with ether (400 ml), was washed with three 50-ml portions of water or until the organic layer was colorless. The ether solution was then dried ($MgSO_4$) and concentrated in vacuo to give a syrupy mixture (1.5 g) consisting mainly of the ketone **6**. The analytical sample of **6** was prepared by chromatographing a portion of the crude product (0.15 g) on a column of silica gel (8 g) with benzene–ether (92:8): yield 0.120 g of pure **6**; $[\alpha]^{20}D$ −121° (c 1.24, chloroform); ir (neat) 4.74 (N_3) and 5.75 μm (C=O); NMR δ 7.32 (m, $CH_2C_6H_5$), 6.07 (d, $J_{1,2}$ = 3.5 Hz, H-1), 4.77, 4.63, and 4.32 (each d, J = 3.5 Hz, three remaining ring protons), 4.66 and 4.45 (each d, estimated J_{gem} = 11 Hz, $CH_2C_6H_5$), 4.23 (s, CH_2N_3), 1.51 and 1.44 [each s, $C(CH_3)_2$].

Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.46; H, 5.64; N, 12.30.

6-Acetamido-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (7) from 5. Hydrogenolysis of the azide **4** (1.8 g), in acetic acid (100 ml), at 2 atm of hydrogen with 10% palladium on carbon (1.6 g) was complete after 18 hr as seen by TLC [ether–methanol (9:1)]. The mixture was filtered and the filtrate, then diluted with an equal volume of acetic anhydride, was kept at room temperature for 3 hr. The solution, after dilution with water (100 ml), was concentrated in vacuo (ca. 1 mmHg) at 38° and the residue was triturated with ethyl acetate to give **5** (0.245 g). A second fraction of **5** (0.320 g) was recovered by addition of petroleum ether to the ethyl acetate wash, yield 38% from **4**. Recrystallization of the crude product from ethyl acetate–petroleum ether gave pure **5**, mp 162–163° (lit.[10] mp 164–165°).

Acetone (25 ml) was added to crude **5** (0.245 g) and the mixture was stirred vigorously for several minutes until dissolution was almost complete. Jones reagent (0.65 ml) was added to the cooled (−5°) solution, the reaction mixture was maintained at −5° for 1 hr and warmed to 5°, and a second aliquot of reagent (0.35 ml) was added to it. After an additional 9 hr, 6 hr at 5° and 3 hr at 25°, the reaction mixture contained no starting material as detected by TLC [ether–methanol (9:1)]. Excess acid was neutralized with sodium hydrogen carbonate and the reaction mixture was concentrated. The blue residue was extracted with benzene (100 ml) and then benzene–methanol (100 ml, 9:1) and the combined extracts

were concentrated to a blue oil. This material was chromatographed on a column of silica gel (ca. 20 g) with ether–methanol (95:5) and the 20-ml fractions containing the major component (**7**) were pooled and concentrated: yield of **7**, 0.092 g (38% from **5** or 15% from 4); mp 114–115°; $[\alpha]^{20}D$ −102° (*c* 0.419, chloroform); ir (KBr) 5.75 (ketone C=O), 6.05 (acetamido C=O), and 6.45 μm (NH); NMR ($CDCl_3$) δ 6.72 (t, J_{NH,CH_2} = 5.0 Hz, NH, exchanged in D_2O), 6.12 (d, $J_{1,2}$ = 3.5 Hz, H-1), 4.8–4.5 (unresolved signals from ring protons), 4.28 (d, J_{NH,CH_2} = 5.0 Hz, C-6 protons, changed to s after addition of D_2O), 2.07 (s, NHAc), 1.50 and 1.35 [each s, $C(CH_3)_2$]; NMR (D_2O) δ 6.12 and 4.98 (each d, $J_{1,2}$ = 3.5 Hz, H-1 and H-2), 4.63 (HOD and remaining ring protons), 4.25 (s, C-6 protons), 2.05 (s, NHAc), 1.48 and 1.37 [each s, $C(CH_3)_2$].

Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96: H, 6.61; N, 5.40. Found: C, 50.75; H, 6.52; N, 5.25.

6-Acetamido-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (7) from 6. Crude **6** (1.45 g) in acetic acid (80 ml) was agitated for 18 hr at 2 atm of hydrogen with 10% palladium on carbon. The suspension, after being diluted with acetic anhydride (40 ml) and left to stand at room temperature for 2 hr, was seen by TLC [ether–methanol (9:1)] to contain one major product. The suspension was filtered, and the filtrate, after dilution with water (40 ml), was kept at 0° for 3 hr. The aqueous acetic acid was removed by lyophilization and the syrupy residue was chromatographed on a column of silica gel (ca. 60 g) with ether–methanol (95:5) to give white, crystalline **7**, mp 113–114°, yield 0.47 g (33% from 4).

6-Acetamido-6-deoxy-D-*xylo*-hexos-5-ulose (8). An acid form cation exchange resin (0.3 ml, AG 50W-X2, 200–400 mesh, Bio-Rad Laboratories, Richmond, Calif.) was added to an aqueous solution (1.5 ml) of **7** (10 mg). The reaction mixture was then maintained at 45°, without stirring, for 18 hr. Microcrystalline cellulose TLC [ethyl acetate–pyridine–water (2:1:2) upper phase[18]], in conjunction with the ammoniacal silver nitrate spray reagent,[19] showed that the hydrolysate was composed of a single reducing sugar (**8**), R_f 0.41. The resin was removed by filtration and after the aqueous wash (0.5 ml) was added to the filtrate. The filtrate was concentrated to a gum by freeze drying: ir (KBr) 2.97 (OH), 5.75 (ketone C=O), and 6.05 μm (acetamido C=O). A solution of the residual gum in deuterium oxide was prepared and after 1 hr at room temperature the solvent was removed by freeze drying. This process was repeated twice more in order to minimize the HOD peak in the NMR spectrum of the material: NMR (D_2O) δ 5.60 (d, *J* = 4.0 Hz, H-1, **8a**), 5.37 (s, H-1, **8b**), 4.93 (d, *J* = 8.0 Hz, H-1, **8c**), 4.69 (HOD), 4.28 (m over a q, H-3, **8c**, and unassigned signals), 3.65 (d, *J* = 9.2 Hz, H-4, **8c**), 3.48 and 3.40 (each s, H-6 protons), 3.27 (d of d, $J_{1,2}$ = 8.0 and $J_{2,3}$ = 9.2 Hz, H-2, **8c**), and 2.09, 2.06, and 2.03 (each s, NHAc, in the ratio of 1:5.5:8.7). Additional unresolved signals were observed at δ 5.11, 4.93 (under the H-1 signal of **8c**), 4.28, 4.11, and 3.80, but no signal was observed for an aldehyde proton. Lowering the temperature of the probe from the normal operating temperature (32°) to 7.5° shifted the HOD peak from δ 4.69 to δ 5.0, but no additional signals were seen at the higher frequency. Results from the decoupling experiments are described in the discussion section.

Compounds 9 and 10 from 7. Sequence A, by Way of 8. Sodium borohydride (13 mg) was added to the hydrolysate from **7** and the reaction mixture was left to stand at room temperature for 18 hr. The aqueous solution was treated with an acid form cation exchange resin until hydrogen evolution ceased, the resulting mixture was filtered, and the filtrate and aqueous washings were freeze dried. After the boric acid was removed from the residue as its volatile trimethyl ester, the remaining material was treated with a trimethylsilylating reagent[20] (800 μl). This reaction was brought almost to boiling and then left at room temperature for 2 hr. A sample of the mixture was analyzed by GLC giving a chromatogram with two major peaks (ratio ~ 9:1), retention times of 12.4 and 6.3 min, respectively. The larger peak was unsymmetrical and increased in size when the mixture was cochromatographed with the trimethylsilyl derivative of authentic **9**.

Sequence B, by Way of 12 and 13. Sodium borohydride (15 mg) was added to a solution of **7** (13.5 mg) in water (1 ml). The reaction mixture was kept at room temperature for 1 day and then worked up by the procedure described in sequence A. Silica gel TLC [ether–methanol (9:1)] showed a mixture of two components, R_f 0.35 and 0.20. The component of higher R_f value gave a spot indistinguishable from that of 6-acetamido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**). An authentic sample of the L-idose derivative **11** was not available for TLC comparison. The protecting isopropylidene groups were then removed from the two compounds in the mixture by resin-catalyzed acid hydrolysis. The hydrolysate contained two reducing sugars of R_f 0.33 and 0.43, as determined by microcrystalline cellulose TLC using the previously mentioned ethyl acetate–pyridine–water system. The component of R_f 0.33 gave a spot identical with that from 6-acetamido-6-deoxy-D-glucose (**12**), obtained by acid hydrolysis of pure **5**. The mixture was then treated with sodium borohydride and the reduction products were analyzed by GLC. The resulting chromatogram was essentially the same as that obtained via sequence A.

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Registry No.—**1**, 55701-71-8; **2**, 55701-72-9; **3**, 23313-03-3; **4**, 23313-05-5; **5**, 55298-36-7; **6**, 55701-73-0; **7**, 55701-74-1; **8**, 55701-78-5; **8a**, 55701-75-2; **8b**, 55701-76-3; **8c** isomer 1, 55701-77-4; **8c** isomer 2, 55701-79-6; **9**, 55780-31-9; **10**, 55780-32-0; **12**, 55701-80-9; **13**, 55701-81-0; 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose dimethyl acetal, 17231-21-9; *p*-toluenesulfonyl chloride, 98-59-9; 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose, 22529-61-9.

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On a Convenient Resolution Method for the Preparation of Isoleucine Optical Isomers

George Flouret* and Satoe Hase Nakagawa

Department of Physiology, Northwestern University McGaw Medical Center, Chicago, Illinois 60611

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Derivatives of the amino acids D-Ile and D-aIle for use in the synthesis of oxytocin isomers were prepared from epimeric mixtures of the derivatives by resolution with α-phenylethylamine (PEA). Epimerization of L-aIle with excess isobutyric anhydride and 4 *N* NaOH, followed by heating to 80°, led in a few minutes to an epimeric mixture of Ibu-D-Ile and Ibu-L-aIle, from which acid hydrolysis yielded the amino acids. The preparation of the (*S*)- and (*R*)-PEA salts of Z-L-Ile and Z-L-aIle made possible the knowledge of the melting points and crystallizing properties of all eight possible diastereoisomeric salts. With this knowledge, treatment of the Z derivative of the D-Ile and L-aIle epimeric mixture with (*S*)-PEA yielded (as predicted) the higher melting of the two possible diastereoisomeric salts, Z-D-Ile (*S*)-PEA. Similarly, the four diastereoisomeric salts of (*S*)- and (*R*)-PEA with Boc-L-Ile and Boc-D-aIle were made and, from these, the melting points of their four enantiomers were predicted. By the methodology used for L-aIle, L-Ile was converted to the epimeric mixture of D-aIle and L-Ile, and the latter derivatized to Boc-amino acids. Addition of (*S*)-PEA to the latter mixture gave (as predicted) the higher melting Boc-D-aIle (*S*)-PEA salt. The resolved salts were converted to the free amino acids D-Ile and D-aIle, each of which was subjected to amino acid analysis and found to be devoid of the epimer (L-aIle and L-Ile, respectively) under conditions where 0.1–0.3% of the latter could have been detected. Therefore, the routes described allow the rapid and direct preparation of useful synthetic derivatives of the unnatural amino acids D-Ile and D-aIle from which the free amino acids can also be prepared.

The need for D-isoleucine (D-Ile) and D-alloisoleucine (D-aIle) for the synthesis of D analogs of oxytocin,[1,2] as well as the erratic commercial supply of these unnatural amino acids, led us to develop practical and convenient resolution methods for certain useful derivatives of these diastereoisomers.

L-Ile has two assymetric centers so that inversion of its α carbon leads to an epimeric mixture of L-Ile and the diastereoisomer D-aIle. Therefore, epimerization of suitable derivatives of the more readily available L-Ile and L-aIle and resolution of the epimeric mixtures constitute convenient synthetic routes for the preparation of D-aIle and D-Ile, respectively. In earlier studies, the enzymatic resolution of *N*-isobutyryl (Ibu)-L-Ile (or Ibu-L-aIle) in an epimeric mixture was accomplished by formation of the anilide in the presence of papain.[3] However, this procedure was rather slow and tedious, and like most enzymatic procedures it leads first to L isomers and only after subsequent steps to D isomers. Alternative methods of resolution have been described but either involve lengthy enzymatic methods, or require special chromatographic equipment.[4]

In an extension of our earlier studies, we found that Ibu-L-Ile is epimerized cleanly and in excellent yield by treatment of its sodium salt in aqueous solution at 35–40° with excess of acetic anhydride.[5] Alternatively, treatment of the sodium salt of L-Ile with excess of isobutyric anhydride and warming leads directly to the epimeric mixture of Ibu-L-Ile and Ibu-D-aIle. In either case the rapid epimerization of the α carbon proceeds very likely through an azlactone intermediate.[5]

We decided to attempt the direct resolution of derivatives of D-Ile and of D-aIle by the general method of resolution by diastereoisomer salt formation.[6] The resolving agent selected, (*S*)- or (*R*)-α-phenylethylamine (PEA), was added to Ibu-L-Ile, to Ibu-L-aIle, and to the epimeric mixture of Ibu-L-Ile and Ibu-D-aIle in order to form the diastereoisomeric salts. However, the rates of crystallization of all salts were slow, and the derivatives obtained were low melting and poorly defined, and such attempt to resolve isobutyryl derivatives was discontinued. On the other hand, *N*-benzyloxycarbonyl Z-L-Ile as well as Z-L-aIle readily gave well-defined salts with both (*S*)- and (*R*)-PEA, so that the melting points and optical rotations for all possible diastereoisomeric salts could be either determined or predicted (Table I). In considering a model epimeric mixture of Z-L-Ile and Z-D-aIle, we predicted as well (and later verified) that (a) the addition of (*S*)-PEA, leading to diastereoisomeric salts of similar melting points, would not resolve isomers readily on account of the probably similar crystallization rates of their salts with this amine; (b) the addition of (*R*)-PEA would cause the relatively more rapid and selective crystallization of the higher melting diastereoisomer Z-L-Ile (*R*)-PEA salt, leaving the lower melting Z-D-aIle (*R*)-PEA in the mother liquor. It was also predicted that addition of (*S*)-PEA to an epimeric mixture of Z-D-Ile and Z-L-aIle would selectively yield the Z-D-Ile (*S*)-

Table I
α-Phenylethylamine (PEA) Salts of Z-Isoleucines

	(*R*)-PEA		(*S*)-PEA		Registry no.	
Z-Amino acid	Mp, °C	$[\alpha]^{25}D$, deg (*c* 2, EtOH)	Mp, °C	$[\alpha]^{25}D$, deg (*c* 2, EtOH)	(*R*)-PEA	(*S*)-PEA
Z-L-Ile	124–125	+10.4	134–136	+0.98	55723-44-9	55723-50-7
Z-D-aIle	108–109.5	−3.42[a]	140.5–141.5	−8.7[a]	55723-46-1	55723-51-8
Z-D-Ile	134–136	−0.98[a]	124–125	−10.4[a]	55723-47-2	55723-52-9
Z-L-aIle	140.5–141.5	+8.7	108–109.5	+3.42	55723-49-4	55723-53-0

[a] Predicted melting point and optical rotation.

Table II
α-Phenylethylamine (PEA) Salts of Boc-Isoleucines

Boc-Amino acid	(R)-PEA Mp, °C	(R)-PEA $[\alpha]^{25}D$, deg (c 2, EtOH)	(S)-PEA Mp, °C	(S)-PEA $[\alpha]^{25}D$, deg (c 2, EtOH)	Registry no. (R)-PEA	Registry no. (S)-PEA
Boc-L-Ile	144–145	+10.3	128–129	+4.3	55723-54-1	55723-57-4
Boc-D-aIle	142–143	−3.0	145–146	−14.2	55280-21-8	55780-91-1
Boc-D-ile	128–129	−4.3[a]	144–145	−10.3[a]	55723-55-2	55723-58-5
Boc-L-aIle	145–146	+14.2[a]	142–143	+3.0[a]	55723-56-3	55723-59-6

[a] Predicted melting point and optical rotation.

PEA salt. Therefore, the model epimeric mixture of Ibu-L-Ile and Ibu-D-aIle was hydrolyzed with 6 *N* HCl and the epimeric amino acid mixture was isolated and subsequently acylated with the more convenient Z group. When (*R*)-PEA was added to an epimeric mixture of Z-L-Ile and Z-D-aIle, Z-L-Ile (*R*)-PEA crystallized selectively and was found to be comparable to the sample prepared directly from pure Z-L-Ile and (*R*)-PEA. As predicted, (*S*)-PEA failed to yield selective crystallization of either isomer. Consequently, L-aIle was epimerized as an Ibu derivative and the epimeric amino acids were isolated and converted to the Z derivative. When (*S*)-PEA was added to the epimeric mixture of Z-D-Ile and Z-L-aIle, the Z-D-Ile (*S*)-PEA salt crystallized selectively.

In an attempt to develop a direct resolution route for D-aIle we also studied the salts of Boc-L-Ile and Boc-D-aIle with (*S*)- and (*R*)-PEA (Table II). As predictable from inspections of Table II, addition of (*S*)-PEA to the epimeric mixture of Boc-L-Ile and Boc-D-aIle caused the selective crystallization of the higher melting Boc-D-aIle (*S*)-PEA salt, from which Boc-D-aIle was readily prepared for use in solid phase peptide syntheses.[7] The Z and Boc groups of resolved isomers were removed by hydrogenolysis and by treatment with 25% TFA–CH_2Cl_2, respectively. The free amino acids were analyzed in a Durrum automatic analyzer capable of resolving isoleucines from alloisoleucines. Both D-Ile and D-aIle emerged as sharp single peaks, devoid of visible amounts of wrong epimers (L-aIle and L-Ile, respectively), under conditions where not less than 0.3% and perhaps as much as 0.1% of contaminating epimers should have been detectable.

The methods here described allow a convenient epimerization of any optical isomer of isoleucine and the rapid resolution of the resulting epimeric mixture into a derivative of either of the two resulting diastereoisomers. The procedures developed are adaptable to the preparation of large quantities of isomers. In contrast to enzymatic resolutions our methods are particularly useful for the direct resolution of derivatives of D-Ile and D-aIle which are suitable for synthetic work or for the preparation of the free amino acids.

Experimental Section

All melting points were determined in a Thomas-Hoover melting point apparatus and are corrected. Optical rotations were measured in 1-dm tubes with a Rudolph polarimeter with a precision of ±0.01°. The (*S*)- and (*R*)-α-phenylethylamine employed were respectively *l*-(−)-α-methylbenzylamine, $[\alpha]^{20}D$ −39° (neat), and *d*-(+)-α-methylbenzylamine, $[\alpha]^{20}D$ +39° (neat), supplied by Aldrich. Amino acid analyses were determined in a Durrum automatic amino acid analyzer. The following abbreviations were used: isoleucine, Ile; alloisoleucine, aIle; DCC, dicyclohexylcarbodiimide; Ibu, isobutyryl; PEA, α-phenylethylamine; Z, benzyloxycarbonyl; Boc, *tert*-butyloxycarbonyl; and DCHA, dicyclohexylamine.

Ibu-L-aIle. A solution of L-aIle (40 g, 0.30 mol) in 4 *N* NaOH (80 ml) was cooled (−10°) and isobutyryl chloride (48.5 g, 0.46 mol) and 2 *N* NaOH (80 ml) were added in several portions, maintaining the pH above 8 and the temperature of the reaction mixture below 0°. After the reaction was complete (5 min) the pH remained constant, and the reaction mixture was extracted with three 100-ml portions of $CHCl_3$. The aqueous layer was acidified with 6 *N* HCl and cooled in an ice bath. The crystalline material which precipitated was collected, washed with H_2O, and dried in vacuo over P_2O_5. Upon extraction with $CHCl_3$, the mother liquor yielded an additional crop, for a combined yield of 56.5 g (92%). A recrystallization afforded the analytical sample, mp 143–145°, $[\alpha]^{20}D$ +15.5° (c 4, EtOH).

Anal. Calcd for $C_{10}H_{19}NO_3$: N, 6.96. Found: N, 6.74.

Epimerization of Ibu-L-aIle. Ibu-L-aIle (56 g, 0.28 mol) was dissolved in 2 *N* NaOH (280 ml). To this solution was added H_2O (280 ml) and acetic anhydride (262 ml, 2.8 mol), and the mixture was incubated in an oven for 30 min at 50° when a clear solution resulted. The reaction mixture was cooled in ice and the crystalline mass which formed was filtered and washed three times with H_2O. The filtrate was extracted with four 50-ml portions of $CHCl_3$ and the combined extracts were washed once with H_2O, dried ($MgSO_4$), filtered, and evaporated to a residue which was combined with the crystalline product inasmuch as both crops had mp 174–176°, $[\alpha]^{20}D$ +2.9° (c 4, EtOH).

Ibu-L-Ile. This compound was obtained in 85% yield by the method described for Ibu-L-aIle, mp 152–153°, $[\alpha]^{19}D$ +9.62° (*c* 4, EtOH).

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.7; H, 9.52; N, 6.96. Found: C, 59.6; H, 9.49; N, 6.85.

Epimerization of Ibu-L-Ile. Method A. Ibu-L-Ile (4 g, 0.02 mol) was dissolved in 2 *N* NaOH (20 ml). To this solution was added H_2O (20 ml) and acetic anhydride (20.4 g, 0.2 mol). After 10 min the mixture became hot (62°), and 5 min later white plates began to appear. After a few minutes the reaction mixture was cooled in ice, and the product was collected, washed with H_2O, and dried in vacuo over P_2O_5, yielding 3.4 g of product, mp 175–177°; $[\alpha]^{20}D$ −2.96° (*c* 4.5, EtOH). From the mother liquor, extraction with $CHCl_3$ yielded 0.35 g of additional material (total yield 94%), lit.[3] mp 175–176°.

Method B. L-Ile (10.5 g, 0.08 mol) dissolved in 4 *N* NaOH (80 ml) was treated with isobutyric anhydride (84 ml, 0.5 mol) with stirring. After 1 min the temperature climbed to 52° and then began to decrease. At this point 4 *N* NaOH (25 ml) was added and the temperature was raised to 80° for 10 min, when the two phases of the reaction mixture cleared up. The solution was cooled in ice and acidified to pH 2 with 20% HCl and the crystals formed were collected, washed with H_2O, and dried over P_2O_5 in vacuo, yielding 13.2 g (82%), mp 173–175°; $[\alpha]^{24}D$ −2.6° (c 4, EtOH).

Hydrolysis of the Epimeric Mixture of Ibu-L-aIle and Ibu-D-Ile. The above epimeric mixture of acyl amino acids (25 g, 0.225 mol) was added to 20% HCl (250 ml) and the suspension was refluxed for 3 hr. The resulting solution was evaporated in vacuo to a solid residue to which H_2O (50 ml) was added and evaporation under vacuum was repeated, the latter process being repeated several times. The residue was dissolved in H_2O (100 ml) and the pH was adjusted to 6 with concentrated ammonium hydroxide. Crystallization took place at this stage, and it was completed by the addition of EtOH (800 ml). The amino acid epimerizate was allowed to crystallize overnight in a cold room (0°). The crystals obtained were filtered and washed with H_2O, H_2O–EtOH, EtOH, and Et_2O. Drying under vacuum over P_2O_5 and KOH pellets afforded 15.4 g (94.5%), $[\alpha]^{18}D$ 0° (c 1, 5 *N* HCl). This product was homogeneous on silica gel TLC with *n*-BuOH–H_2O–AcOH (4:1:5) and *n*-BuOH–EtOAc–AcOH–H_2O (1:1:1:1), with Cl_2–tolidine and ninhydrin color sprays, and was indistinguishable from Ile.

Z-L-Ile. This derivative was prepared from L-Ile by the proce-

dure of Bergman[8] for the preparation of Z-amino acids. In one occasion a preparation kept in a freezer for several weeks gave prisms, mp 51–54°, $[\alpha]^{24}D$ +13° (c 2, EtOH).

Z-L-aIle. This derivative was obtained as an oil, $[\alpha]^{18}D$ +15.2° (c 2, acetone) [lit.[9] $[\alpha]^{20}D$ +16.0° (c 2, acetone)].

Salts of PEA and Z-Ile Diastereoisomers. A solution of the corresponding Z-Ile or Z-L-aIle (0.5 g, 1.9 mmol) in EtOAc (2 ml) was treated with (*S*)- or (*R*)-PEA (0.23 g, 1.9 mmol), and the solution was allowed to stand overnight. The crystals collected were washed with EtOAc–pentane and pentane and finally dried. The melting points and optical rotations of all possible diastereoisomeric salts are shown in Table I.

Resolution of an Epimeric Mixture of Z-L-Ile and Z-D-aIle. The epimeric mixture of Ibu-L-Ile and Ibu-D-aIle prepared as described earlier was hydrolyzed with 20% HCl and the freed amino acid was converted to the Z derivative (oil) by the general method of Bergman. A solution of the resulting Z-L-Ile and Z-D-aIle mixture (1.15 g, 4.3 mmol) in EtOAc (1.6 ml) was treated with (*R*)-PEA (0.55 ml, 4.3 mmol). Crystals began to form slowly in clusters of needles, yielding 0.50 g (60%), mp 119–121°; $[\alpha]^{19}D$ +8.42° (*c* 2, EtOH). Three recrystallizations of the latter material from EtOAc gave Z-L-Ile (*R*)-PEA, mp 124–125°, $[\alpha]^{19}D$ +10.9° (*c* 2, EtOH).

Anal. Calcd for $C_{22}H_{30}N_2O_4$: N, 7.25. Found: N, 7.10.

Resolution of an Epimeric Mixture of Z-L-aIle and Z-D-Ile. The epimeric mixture of amino acids was converted to the Z derivatives by the general method of Bergman. The resulting oil (43.2 g, 0.163 mol) was dissolved in EtOAc (65 ml) and (*S*)-PEA (22.6 ml, 0.175 ml) was added all at once. The crystals which formed overnight were collected and washed with EtOAc, yielding 19.5 g (62%), mp 122–123°. Three successive recrystallization yielded Z-D-Ile (*S*)-PEA salt, 14.0 g (44%), mp 124–125°; $[\alpha]^{17}D$ −10.9° (*c* 2, EtOH).

A sample of the latter (79 mg, 0.20 mmol) was dissolved in 80% EtOH (10 ml) and the solution was treated with BioRex 70 (H^+). The resin was filtered and to the filtrate (20 ml) was added AcOH (0.1 ml) and 5% Pd/C (100 mg), and H_2 was bubbled gently for 2 hr at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. After drying overnight over P_2O_5 in vacuo the crystals were suspended in Et_2O, filtered, and dried, yielding 26 mg of the amino acid, $[\alpha]^{24}D$ −41.7° (*c* 1, 6 *N* HCl) [lit.[4] $[\alpha]^{19}D$ −41.6° (c 1, 6 *N* HCl)]. An amino acid analysis of this product, obtained in a Durrum automatic analyzer, showed one sharp single peak with the retention time corresponding to Ile. Although no aIle was detected, the presence of 0.3% to as low as perhaps 0.1% cannot be ruled out.

Epimeric Mixture of Boc-D-aIle and Boc-L-Ile DCHA Salts. The epimeric amino acid mixture of D-aIle and L-Ile (5.9 g, 45 mmol) was dissolved in a mixture of 2 *N* NaOH (45 ml) and dioxane (45 ml), and Boc-azide (10.0 g, 70 mmol) was added with stirring at room temperature while the pH of the mixture was adjusted to 10 by the occasional addition of 2 *N* NaOH. Excess Boc-azide was extracted with Et_2O, and the aqueous layer was carefully acidified to pH 2 wihh 20% HCl in an ice bath and extracted with EtOAc (100 ml). The organic layer was extracted and washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residual oil was dissolved in Et_2O and treated with DCHA (9 ml). The DCHA salt was collected, yielding 14.9 g (80%), mp 133–134°; $[\alpha]^{24}D$ 0° (*c* 1.5, DMF).

Boc-D-aIle DCHA Salt. Boc-D-aIle was prepared from D-aIle essentially by the methods described in the preceding experiment. Because Boc-D-aIle did not crystallize readily, it was isolated as the DCHA salt in 94% yield, mp 136–137°. Recrystallization from EtOAc–hexane gave the analytical sample, mp 138–139°, $[\alpha]^{24}D$ −11.3° (c 1.5, DMF).

Anal. Calcd for $C_{23}H_{44}N_2O_4$: C, 67.0; H, 10.8; N, 6.79. Found: C, 67.1; H, 10.8; N, 6.68.

Salts of PEA with Boc-Ile Diastereoisomers. These salts were prepared essentially as described for Z-Ile diastereoisomers and their melting points and rotations are shown in Table II. In the case of the combination of Boc-L-Ile and (*S*)-PEA, hexane had to be added to the EtOAc solution in order to force crystallization of the salt.

Resolution of Boc-D-aIle and Boc-L-Ile. The epimeric mixture of Boc-D-aIle and Boc-L-Ile DCHA salts (8.25 g, 20 mmol) was added to EtOAc (40 ml) and 1 *N* H_2SO_4 (40 ml), and the mixture was shaken in a separatory funnel until the salts dissolved. The EtOAc extract was washed with H_2O, dried (Na_2SO_4), and evaporated to an oil. The latter was dissolved in EtOAc (10 ml), (*S*)-PEA (2.58 ml, 20 mmol) was added, and the solution was kept at room temperature for 20 hr and then at 4° for 6 hr. The crystals which formed were collected, washed with 1:1 EtOAc–hexane (15 ml) and then hexane and finally air dried, yielding 2.83 g (80%), mp 142–143.5°. Two recrystallizations from EtOAc (15 ml) gave 2.4 g (70%), mp 145–146°, $[\alpha]^{24}D$ −14.5° (c 2, EtOH). Anal. Calcd for $C_{19}H_{32}N_2O_4$: C, 64.7; H, 9.15; N, 7.95. Found: C, 64.4; H, 9.27; N, 7.88.

A sample of Boc-D-aIle (*S*)-PEA (0.35 g, 1 mmol) was dissolved in CH_2Cl_2 and the solution was extracted with 0.1 *N* H_2SO_4 and then H_2O and finally dried (Na_2SO_4). To the CH_2Cl_2 solution (about 10 ml) was added trifluoroacetic acid (3 ml) and the solution was allowed to stand at room temperature for 30 min, when the solvents were removed in a rotatory evaporator. The residue obtained was extracted with Et_2O and dissolved in H_2O and the solution was treated with Rexyn AG3-X4 (AcO^-) and filtered. The filtrate was lyophilized and the powder obtained was triturated with EtOH and Et_2O and dried, yielding 80 mg of the amino acid, $[\alpha]^{24}D$ −38.9° (*c* 1, 6 *N* HCl) [lit.[4] $[\alpha]^{19}D$ −38° (c 1, 6 *N* HCl)]. A sample of the product was subjected to an amino acid analysis in a Durrum automatic analyzer, which revealed only one sharp single peak with the retention time corresponding to D-aIle. A contamination with Ile of 0.3% and perhaps as low as 0.1% would have been detectable.

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Registry No.—L-Alloisoleucine, 1509-34-8; *N*-isobutyl-L-alloisoleucine, 55723-60-9; *N*-isobutyrl-D-isoleucine, 55723-61-0; *N*-isobutyryl-L-isoleucine, 55723-62-1; *N*-isobutyryl-D-alloisoleucine, 55723-63-2; L-alloisoleucine, 73-32-5; DL-isoleucine, 443-79-8; *N*-benzyloxycarbonyl-L-isoleucine, 3160-59-6; *N*-benzloxycarbonyl-L-alloisoleucine, 55723-48-3; D-isoleucine, 319-78-8; D-alloisoleucine, 1509-35-9; *tert*-butyloxycarbonyl-L-isoleucine DCHA, 55723-64-3; *tert*-butyloxycarbonyl-D-alloisoleucine DCHA, 55780-92-2.

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Synthesis and Characterization of 3-Bromo-1,4-dihydroxy-2-butanone 1,4-Bisphosphate, a Potential Affinity Label for Enzymes That Bind Sugar Bisphosphates[1]

Fred C. Hartman

Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830

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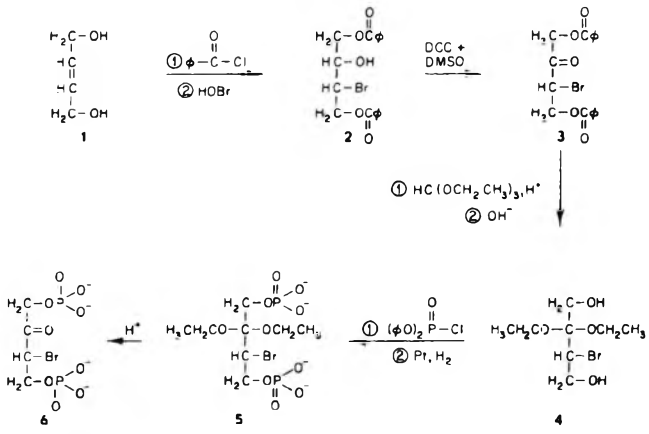
3-Bromo-1,4-dihydroxy-2-butanone 1,4-bisphosphate, a compound that can be considered a reactive analog of several sugar bisphosphates, has been synthesized as a potential affinity labeling reagent for enzymes whose substrates are sugar bisphosphates. The starting material for the synthesis is the commercially available *cis*-2-butene-1,4-diol. The immediate precursor to the reactive reagent, the corresponding diethyl ketal, is obtained as a crystalline triscyclohexylammonium salt. The stability of 3-bromo-1,4-dihydroxy-2-butanone 1,4-bisphosphate at pH 4–10 has been determined by measuring the release of both bromide and P_i. Even at pH 4.0 the reagent is unstable, and at pH 10.0 the release of bromide is complete within 3 hr. Studies with free amino acids, glutathione, and N-α-acetyl-L-lysine indicate that of the functional groups found in proteins, sulfhydryl is the most rapidly modified by bromobutanone bisphosphate. Modification of amino groups by the reagent has also been demonstrated, but at a much slower rate. The compounds resulting from the reactions of glutathione and N-α-acetyl-L-lysine have been reduced with tritiated sodium borohydride and hydrolyzed with 6 N HCl; the hydrolysates were analyzed on an amino acid analyzer to provide chromatographic markers for future studies involving bromobutanone bisphosphate as a protein reagent.

Affinity labeling is recognized as a powerful tool for the selective modification and subsequent characterization of the active sites of enzymes.[2] A major limitation of affinity labeling is the scarcity of reagents for any given enzyme; therefore, application of the technique usually necessitates designing reactive derivatives of the naturally occurring substrate. Reactive sugar bisphosphates should provide potentially versatile affinity labels, since there are a number of enzymes involved in carbohydrate metabolism whose substrates are sugar bisphosphates, e.g., phosphofructokinase, fructosebisphosphate aldolase, fructose bisphosphatase, glyceraldehyde 3-phosphate dehydrogenase, phosphoglucomutase, phosphoglyceromutase, phosphoglycerate kinase, ribulosebisphosphate carboxylase, and phosphopentokinase. To begin the development of a series of reactive bisphosphates, I have synthesized Br-butanone-P_2[3] (**6**) according to Scheme I and studied its stability and reactivity toward functional groups that are present in proteins. In a preliminary study[4] this reagent proved useful as an affinity label for ribulosebisphosphate carboxylase.

Scheme I



The overall yield of **6** was only 11%, but the first three intermediates are readily prepared in large quantities. Since Br-butanone-P_2 is quite unstable and therefore was not isolated from solution, efforts were made to obtain the immediate precursor, the diethyl acetal (**5**), in a highly purified form. Thus, the material to be phosphorylated (**4**) was purified to homogeneity by chromatography on Florisil. This diol is unstable and will decompose (elimination of bromine with tarring) during concentrating in organic solvents. Decomposition does not take place if the temperature is kept at 30° or below during concentration and if exhaustive drying is avoided. The phosphorylated ketal (**5**) was obtained as a crystalline triscyclohexylammonium salt which was slightly contaminated with P_i. Elemental analyses of this compound and the corresponding lithium salt, which was freed of P_i, agreed closely with theory. The formation of a tris- instead of a tetracyclohexylammonium salt of a bisphosphate ester is not without precedent. D-Erythrulose 1,4-bisphosphate also yielded a triscyclohexylammonium salt.[5]

Several lines of evidence confirm the formation of **6** from the free acid of the corresponding ketal upon incubation in aqueous solution. (1) The pure ketal is converted to a new phosphate ester without substantial appearance of P_i or bromide. (2) The phosphate ester formed is a reducing sugar. (3) The phosphate ester formed contains both base-labile bromide and phosphate.

Incubation of Br-butanone-P_2 in base results in the liberation of 1.0 molar equiv of bromide and about 1.15 molar equiv of P_i (Table I). On the basis of the previous observation that D-erythrulose 1-P is much more sensitive than the 4-P isomer to degradation by alkali,[6] it is assumed that the phosphate group in the 1 position (adjacent to the carbonyl) is the one in Br-butanone-P_2 that is base-labile. In the case of erythrulose 4-P, only 50% of the total phsophate was released as P_i, and it was postulated that some phosphate ester was formed in alkali that could not undergo phosphate elimination.[6] A similar phenomenon could account for the release of slightly more than 1 molar equiv of P_i upon incubation of Br-butanone-P_2 in alkali. Both phosphate groups of the bromo reagent were hydrolyzed by 1 N H_2SO_4 at 100° at about equal rates (half-time of 12 min), as was observed for erythrulose 1,4-P_2.[5] Both phosphate groups of D-ribulose 1,5-P_2 were also reported to be acid labile,[7] as confirmed in the present study. However, in contradiction to the earlier report,[7] I found only one of the two phosphate groups to be hydrolyzed by base. Thus, three related bisphosphates (erythrulose 1,4-P_2, ribulose 1,5-P_2, and Br-butanone-P_2) have similar stabilities in acid and base.

Table I
Phosphate and Bromide Analyses on Br-butanone-P_2 and Related Compounds[a]

Compd	Concn, m*M*					
	By weight	Phosphate				Base-labile bromide
		P_i	Total organic[b]	Acid-labile[b]	Base-labile[b]	
Br-butanone-P_2	25.0	4.1	48.1	48.7[c,d]	27.0	23.4
Br-butanone-P_2 diethyl ketal	25.0	1.1	47.5	47.7[c,d]	0	0
Ribulose 1,5-P_2	25.0	10.8	41.2	40.8	20.5[c]	

[a] Analyses performed as described in Experimental Section. [b] These concentrations obtained after subtraction of the P_i concentration. [c] These values obtained after an incubation period of 2 hr. [d] The half-time of phosphate release during the incubation in acid was 12 min.

The kinetics of P_i and bromide formation from Br-butanone-P_2 at pH 4–10 are complex. It seems apparent from data in Figure 1 that the bromine atom increases the lability of one phosphate group. This conclusion was supported by the detection of tetrulose bisphosphate (a tentative identification based on chemical and chromatographic properties) as a decomposition product after the release of P_i had virtually ceased. It also appears that a phosphate group (see data for pH 6.0 and 8.0 in Figure 1) increases the lability of the bromine atom. This could be a reflection of an intramolecular displacement of bromide by a phosphate anion.

To determine which amino acid residues in proteins would be the most likely sites of modification by Br-butanone-P_2, we studied its reaction with free amino acids. These studies revealed sulfhydryl and amino groups as the most reactive and therefore the reactions of **6** with the sulfhydryl group of glutathione and the amino group of N-α-acetyl-L-lysine were investigated in some detail. Although the products of modification of glutathione and N-α-acetyl-L-lysine by **6** have not been completely characterized, the prime objective of tagging them with a radioactive label that survives conditions used to hydrolyze proteins was achieved by reduction of the carbonyl group with NaB^3H_4. Hydrolysates of the derivatized acetyllysine and glutathione were chromatographed on the amino acid analyzer (Figures 2 and 3). The established elution positions of the cysteinyl and lysyl derivatives will serve as markers in the determination of whether in a given protein sulfhydryl and ϵ-amino groups react with the reagent. Sulfhydryl and

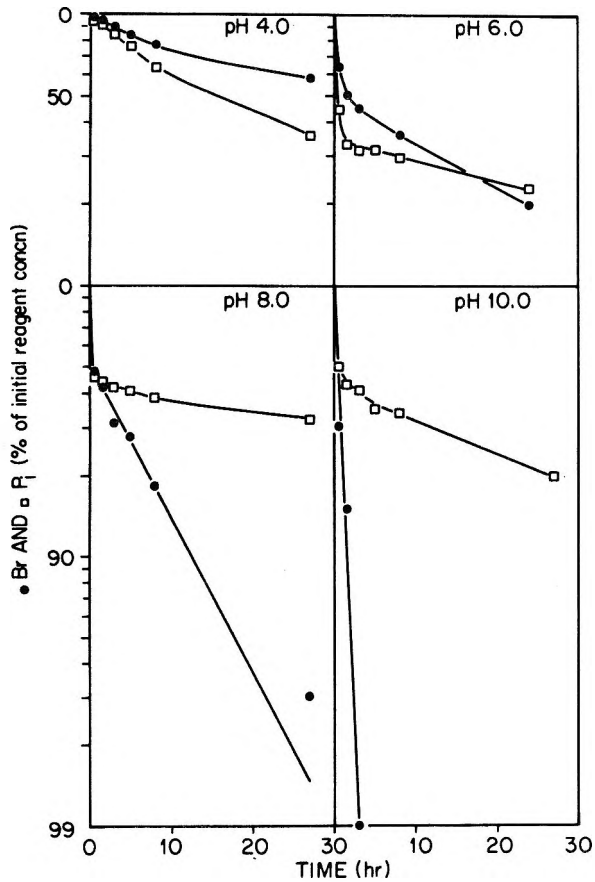


Figure 1. Release of P_i (□) and bromide (●) from Br-butanone-P_2 upon incubation in aqueous solution at pH 4–10.

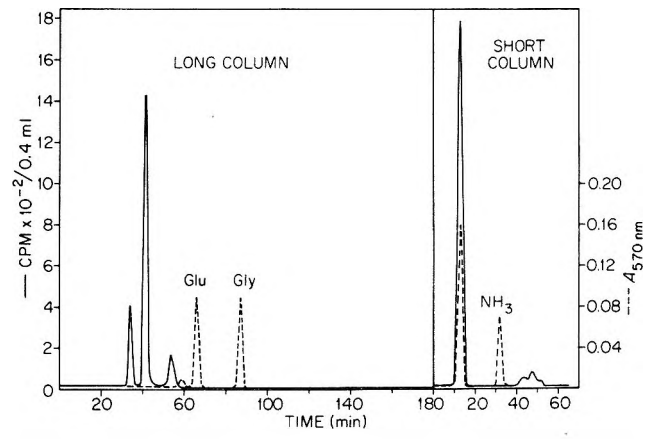


Figure 2. Amino acid analysis of a hydrolysate of the glutathione derivative obtained by reaction with Br-butanone-P_2 followed by reduction with [^{3}H]$NaBH_4$. Fractions (3 min from the long column and 1 min from the short column) were collected, and 0.4-ml aliquots of each were assayed for radioactivity.

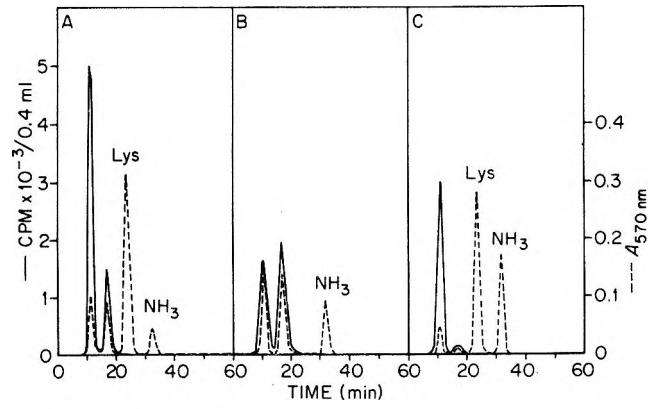


Figure 3. Chromatography (on the short column of the amino acid analyzer) of hydrolysates of N-α-acetyl-L-lysine that had been modified with Br-butanone-P_2 and reduced with [^{3}H]$NaBH_4$. Fractions (1 min) were collected, and 0.4-ml aliquots of each were assayed for radioactivity. (A) Hydrolysate of unfractionated reaction mixture. (B) Hydrolysate of the acetyllysine derivative after purification on Dowex 1. (C) Same hydrolysate as shown in B after incubation for 30 min at room temperature in 0.01 *M* sodium metaperiodate buffered with 0.1 *M* sodium bicarbonate (pH 8.6).

amino groups, by virtue of their nucleophilicity, presumably displace the bromine atom of the reagent and are thereby alkylated. However, reactions involving the carbonyl group of the reagent or even nucleophilic attack on the carbon atom bearing the base-labile phosphate group with alkyl–oxygen scission cannot be excluded. A similar reagent, bromoacetol phosphate,[8] is highly reactive toward sulfhydryls and forms a *S*-alkyl derivative of glutathione. Reaction of glutathione with Br-butanone-P_2 gives two major ninhydrin-positive phosphate esters, both of which lack a sulfhydryl group. The structural differences between these two compounds have not been elucidated.

N-α-Acetyl-L-lysine was treated with Br-butanone-P_2 and reduced with tritiated borohydride. After the product(s) was purified by ion-exchange chromatography, acid hydrolysates contained two radioactive components (Figure 3B). One of these could be a decomposition product formed during hydrolysis. Alternatively, two chemically distinct lysyl derivatives (e.g., mono- and dialkylated products) may not have been resolved by the chromatographic procedure used. Both compounds in the hydrolysate can be converted to lysine by periodate oxidation (Figure 3C), as was reported for the related compound, N^6-β-glyceryllysine.[9] This latter lysyl derivative was retarded on the short column of the amino acid analyzer and eluted before lysine in a position close to that observed for one of the derivatives reported here.[10]

The Br-butanone-P_2 synthesized and used in the present studies is a racemic mixture. Furthermore, the reduction of the reagent carbonyl to a hydroxyl group creates a second asymmetric center so that the derivatives of glutathione and lysine that were prepared are mixtures of diastereoisomers. The degree of separation obtained by paper chromatography of the glutathione derivatives and by ion-exchange chromatography of the hydrolyzed lysyl derivatives seems too great to represent resolution of diastereoisomers, but this possibility cannot be excluded.

Experimental Section

Materials. *cis*-2-Butene-1,4-diol, dicyclohexylcarbodiimide, triethyl orthoformate, diphenyl chlorophosphate, and DTNB were obtained from Aldrich Chemical Co. D-Ribulose 1,5-bisphosphate, glutathione, and *N*-α-acetyl-L-lysine were products of Sigma Chemical Co. Florisil was obtained from the Floridin Co., Tallahassee, Fla. Sodium [^{3}H]borohydride (4.3 mCi/mmol) was purchased from Amersham/Searle Corp. and diluted tenfold with unlabeled borohydride before use.

General Methods. Elemental analyses were performed by Stewart Laboratories, Inc., Knoxville, Tenn.

Melting points were taken with a Fisher-Jones apparatus and are uncorrected.

Thin layer chromatography was conducted on plastic sheets coated with silica gel containing a fluorescent indicator (MN-Polygram Sil N-HR sold by Brinkmann Instruments, Inc.). The solvent used was ether–petroleum ether (bp 30–60°) (1:1 v/v). Paper chromatography was conducted by the descending method using Whatman No. 1 paper. The solvent used was *n*-butyl alcohol–glacial acetic acid–water (7:2:5 v/v/v). Some compounds on the thin layer sheets could be visualized under ultraviolet light. Ketones were detected with 2,4-dinitrophenylhydrazine[11] or silver nitrate–sodium hydroxide.[12] Phosphate esters were detected with ammonium molybdate,[13] and amines were detected with ninhydrin–collidine.[14] Periodate–benzidine[15] was used to detect compounds containing vicinal hydroxyl groups. The periodate spray was 0.05% (w/v) sodium metaperiodate rather than a saturated solution of the potassium salt as reported earlier.

Inorganic bromide was measured with a bromide ion electrode (Orion Research Inc.) connected to a Digicord pH-millivolt meter (Photovolt Corp.). Base-labile bromide was determined as inorganic bromide after incubation of the sample for 20 min in 1 *N* sodium hydroxide at room temperature.

Inorganic phosphate was assayed by the method of Marsh.[16] Organic phosphate was determined as P_i after digestion of the phosphate ester for 2 hr with sulfuric acid (initial concentration of 1 *N*) at 180° on a sand bath. After the digestion period, water was added to the sample, which was then heated in a boiling-water bath for 20 min to hydrolyze the phosphoric acid anhydrides formed during digestion. Base-labile phosphate was determined as P_i after incubation of the sample for 20 min in 1 *N* sodium hydroxide at room temperature. Acid-labile phosphate was determined as P_i after incubation of the sample for 5–120 min in 1 *N* sulfuric acid in a boiling-water bath.

Radioactivity was assayed with a Packard 3003 liquid scintillation spectrometer. The scintillation fluid contained 4.6 g of 2,5-diphenyloxazole (PPO) and 115 mg of 1,4-bis[2-(5-phenyloxazolyl)]benzene (POPOP) dissolved in 1 l. of toluene–ethanol (4:3 v/v).

Amino acid analyses were performed on a Beckman Model 120C amino acid analyzer according to Spackman et al.[17] Samples were hydrolyzed at 110° for 21 hr in sealed, evacuated (<50 μmHg) tubes with 6 *N* HCl. Before analysis the samples were concentrated to dryness on a rotary evaporator.

***cis*-1,4-Di-*O*-benzoyl-2-butene-1,4-diol.** To a solution of 500 ml of $CHCl_3$ containing 44 g (0.5 mol) of *cis*-2-butene-1,4-diol and 121 ml (1.5 mol) of pyridine that was cooled to −5° in an ice–salt bath was added 140 ml (1.2 mol) of benzoyl chloride. This mixture was left in the ice–salt bath for 2 hr, then transferred to room temperature for 3 hr, at which time 20 ml of water was added. After remaining overnight at room temperature, the solution was washed in succession with two 500-ml portions of 1 *N* H_2SO_4, saturated sodium bicarbonate, and water. The chloroform layer was then dried over anhydrous sodium sulfate and concentrated to dryness at 40° on a rotary evaporator. Crystallization of the residue from 200 ml of ethyl alcohol gave 132 g (90%) of the dibenzoate, mp 64–65°. A value of 65–66° was reported previously.[18] Anal. Calcd for $C_{18}H_{16}O_4$ (296.33): C, 72.96; H, 5.44. Found: C, 73.02; H, 5.57.

1,4-Di-*O*-benzoyl-3-bromo-1,2,4-butanetriol (2). The above dibenzoate (100 g, 0.34 mol) was dissolved in dioxane (300 ml), and to this solution were added 71.2 g (0.4 mol) of *N*-bromosuccinimide and 50 ml of water. The resulting mixture was stirred until homogeneous (about 5 min). Within 1.5 hr the temperature of the reaction mixture rose from 24 to 33°. After the temperature decreased to 30° (total reaction time of 3.5 hr), the dioxane was removed by concentration. The residual liquid was mixed with 200 ml of $CHCl_3$; this solution was washed, dried, and concentrated as described above. The product was crystallized from 100 ml of isopropyl ether to give 56 g (42%) of material with mp 97–99°. Anal. Calcd for $C_{18}H_{17}BrO_5$ (393.25): C, 54.98; H, 4.35; Br, 20.32. Found: C, 55.27; H, 4.24; Br, 20.59.

1,4-Di-*O*-benzoyl-3-bromo-2-butanone (3). A solution containing 500 ml of ether, 20 ml (0.28 mol) of dimethyl sulfoxide, 3 ml (0.037 mol) of pyridine, 50 g (0.24 mol) of dicyclohexylcarbodiimide, and 48 g (0.122 mol) of the dibenzoylbromobutanetriol was cooled to 8°. The oxidation (a method of Pfitzner and Moffatt[19]) was initiated by the addition of 3 ml (0.04 mol) of trifluoroacetic acid. The temperature of the reaction mixture rose rapidly to 33°. Fifteen minutes after initiation, the reaction was terminated by the addition of powdered oxalic acid (15 g, 0.12 mol). The insoluble dicyclohexylurea was removed by suction filtration, and the filtrate was washed, dried, and concentrated as described above. Crystals (39 g, 82%) with mp 83–84° were obtained from 200 ml of isopropyl alcohol. Anal. Calcd for $C_{18}H_{15}BrO_5$ (391.26): C, 55.26; H, 3.86; Br, 20.43. Found: C, 55.28; H, 3.79; Br, 20.42.

3-Bromo-2-butanone-1,4-diol Diethyl Ketal (4). A solution of the above ketone (5 g), ethanol (16 ml), freshly distilled triethyl orthoformate (33 ml), and concentrated sulfuric acid (1.4 ml) was incubated in the dark at room temperature for 7 days. At this time thin layer chromatography showed approximately an 80% conversion of the ketone (R_f 0.40) to the ketal (R_f 0.56) (both compounds visualized under ultraviolet light). The reaction mixture was neutralized with 15 g of sodium bicarbonate. After the addition of 100 ml of ether, the mixture was filtered through Celite and concentrated to dryness at 60°. The residual liquid was dissolved in 150 ml of methyl alcohol, and to the solution was added 35 ml of 1 *N* NaOH. After 1 hr the methyl alcohol was removed by concentration, and the resulting aqueous mixture was extracted twice with 50-ml portions of ether. The extracts were dried and concentrated at 30° to yield 3.0 g of a slightly yellow, thin syrup. Thin layer chromatography showed this material to contain a fluorescent substance (R_f 0.61) tentatively identified as methyl benzoate and two 2,4-dinitrophenylhydrazine-positive (after heating the sprayed sheet at 100° for 5 min) components, a major one with R_f 0.24 and a minor one with R_f 0.47. The mixture was dissolved in 5 ml of cyclohexane and fractionated on a 2.5 × 23 cm column of Florisil

packed in cyclohexane. The column was washed in succession with 300 ml of cyclohexane (which eluted the methyl benzoate), 500 ml of cyclohexane–benzene (1:1) (which eluted the material with R_f 0.47), and 225 ml of benzene–ether (1:1) (which eluted the material with R_f 0.24 assumed to be the 3-bromo-2-butanone-1,4-diol diethyl ketal). Concentration of the benzene–ether washings at 30° gave 1.6 g (49% based on 5 g of the crystalline ketone) of chromatographically pure material as a colorless, slightly viscous liquid.

3-Bromo-1,4-dihydroxy-2-butanone 1,4-Bisphosphate Diethyl Ketal (5). To an ice-cold solution of 3-bromo-2-butanone-1,4-diol diethyl ketal (1.5 g, 5.9 mmol) in a mixture of pyridine (5 ml) and $CHCl_3$ (10 ml) was added diphenyl chlorophosphate (3.8 ml, 18 mmol). The reaction mixture was left overnight at 4°, and then a few chips of ice were added. After an additional 12 hr at 4°, more $CHCl_3$ (100 ml) was added to the mixture, which was then washed (with 1 *N* H_2SO_4 and saturated $NaHCO_3$), dried, and concentrated. The viscous syrup that was obtained was dissolved in 80 ml of ethyl alcohol; the resulting solution was filtered through Celite and hydrogenated in the presence of platinum black (0.5 g) at 50 psi on a Parr apparatus. Consumption of hydrogen was completed within 3 hr, at which time the catalyst was removed by filtration through Celite. The filtrate was neutralized to pH 8.0 with cyclohexylamine and concentrated to dryness. The residue was slurried in 100 ml of acetone, and the insoluble triscyclohexylammonium salt of Br-butanone-P_2 diethyl ketal (3.4 g, 71%) was collected by filtration. Paper chromatography revealed a single organic phosphate ester (R_f 0.53) and a slight contamination with P_i (R_f 0.36). The salt was recrystallized by dissolving it in 4 ml of 20% (v/v) aqueous cyclohexylamine followed by the addition to this solution of 300 ml of isopropyl alcohol. Crystallization occurred during 24 hr at room temperature to yield 2.6 g of the triscyclohexylammonium salt. Based on a molecular weight of 714, phosphate assays revealed 1.91 molar equiv of organic phosphate and 0.028 molar equiv of P_i. Anal. Calcd for $C_{26}H_{58}BrN_3O_{10}P_2$ (714.63): C, 43.70; H, 8.18; Br, 11.18; N, 5.88; P, 8.67; OCH_2CH_3, 12.61. Found: C, 43.95; H, 8.33; Br, 11.07; N, 5.87; P, 8.59; OCH_2CH_3, 12.35.

A sample (100 mg) of the bisphosphate ester was freed of P_i by subjecting it to anion-exchange chromatography on a 1.2 × 25 cm column of Dowex 1 (Cl^-). The column was equilibrated with 0.05 *M* LiCl–0.001 *N* HCl and eluted with a linear gradient consisting of 200 ml of the equilibration solution and 200 ml of 0.5 *M* LiCl–0.001 *N* HCl as the limit solution. The bisphosphate eluted at 0.32 *M* LiCl. The fractions in this region were pooled; the solution was then adjusted to pH 8.0 with 0.1 *N* LiOH and concentrated to dryness at 40°. Ethyl alcohol (100 ml) was added to the residue, and the insoluble product (49 mg, 88%) was collected by filtration. This material was dissolved in 0.5 ml of water and precipitated with 10 ml of ethyl alcohol. Anal. Calcd for $C_8H_{15}BrO_{10}P_2Li_4 \cdot H_2O$ (458.84): C, 20.94; H, 3.73; Br, 17.42; P, 13.50. Found: C, 20.67; H, 3.87; Br, 17.19; P, 13.46.

3-Bromo-1,4-dihydroxy-2-butanone 1,4-Bisphosphate (6). An aqueous solution (10 ml) containing 179 mg (0.025 *M*) of the triscyclohexylammonium salt of the diethyl ketal was swirled with 2 g of Dowex 50 (H^+) to remove cyclohexylammonium ions and then filtered. The resulting acidic solution was incubated at 40° for 3 hr. At this time paper chromatography followed by visualization with the molybdate spray revealed an essentially complete conversion of the ketal (R_f 0.53) to the ketone (R_f 0.23). The latter component gave an immediate positive response with the silver nitrate dip, whereas the ketal was not detected. Solutions of Br-butanone-P_2 (the free acid form) were stored in the freezer without appreciable decomposition during several months.

Stability of Br-butanone-P_2. A solution of Br-butanone-P_2 prepared from the corresponding ketal as described in the above paragraph was assayed for P_i, total organic phosphate, acid-labile phosphate, base-labile phosphate, and base-labile bromide (Table I). For comparison, samples of the ketal were subjected to the same analyses. The phosphate assays were also performed on commercial ribulose 1,5-bisphosphate because of the expectation that its phosphate groups might have stabilities similar to those of Br-butanone-P_2. The base labilities of the bromine atom and one of the two phosphate groups in Br-butanone-P_2, in contrast to their stabilities in the ketal, provide convenient methods for quantitating the concentration of the ketone in solution. The appearance of base-labile phosphate was used to follow the hydrolysis ($t_{1/2}$ = 40 min) of the ketal to the ketone. During this hydrolysis, less than 0.1 molar equiv of P_i and bromide are released.

The rates of release of bromide and P_i from Br-butanone-P_2 were determined as a function of pH (Figure 1). At pH 10.0, the release of bromide is rapid and approximates first-order kinetics. The initial rate of P_i appearance at this pH is similar to that of bromide; however, the rate decreases dramatically as the release of bromide appraoches completion and before 1 molar equiv of P_i is liberated. At pH 8 and 6 the kinetics of both bromide and P_i appearance are complex, with less than 1 molar equiv of P_i being released. At pH 4 the reagent is more stable, and the rate of P_i formation slightly exceeds that of bromide.

Decomposition Products of Br-butanone-P_2. The extent of P_i release during incubation of the reagent in 1 *N* NaOH or at pH 4–10 (1.1 molar equiv with the former and <1 with the latter) suggested that phosphate esters were the end products of decomposition. To verify this assumption, solutions of the reagent, after incubation in 1 *N* NaOH for 20 min or in 0.2 *M* $NaHCO_3$ (pH 8.0) for 24 hr, were inspected by paper chromatography. The untreated Br-butanone-P_2 (R_f 0.23) was detectable with both molybdate and silver nitrate but not with periodate–benzidine. After the reagent was treated with base, a single phosphate ester (R_f 0.36) was found that gave positive tests with silver nitrate and periodate–benzidine. On the chromatograms, this compound coincided with P_i but was nevertheless recognizable as a phosphate ester on the basis of color differentiation. P_i gives a yellow spot immediately upon spraying with the molybdate reagent; after drying the chromatogram and exposing it to ultraviolet irradiation, the spot becomes greenish-grey. The mixture of P_i and phosphate ester which coincided gave the expected yellow spot when sprayed, but upon irradiation a definite bluish-green spot was apparent.

The solution of reagent that was incubated at pH 8.0 contained two phosphate esters (R_f 0.25 and R_f 0.18). Both of these compounds were detectable with silver nitrate and periodate–benzidine. The compound with R_f 0.18 is assumed to be tetrulose 1,4-bisphosphate, since on the basis of the less than stoichiometric release of P_i some bisphosphate should remain. A compound that should have similar chromatographic properties, ribulose 1,5-bisphosphate, has an R_f of 0.16 and is detected by all three reagents. The compound with R_f 0.25 is probably tetrulose 4-phosphate. Solutions of ribulose 1,5-bisphosphate, after base treatment, contained a phosphate ester with R_f 0.27. This component was visualized with the periodate–benzidine sprays, but gave a very faint response with the silver nitrate dip.

Reaction of Br-Butanone-P_2 with Glutathione. The rate of reaction between glutathione and Br-butanone-P_2 was determined by measuring the decrease in sulfhydryl concentration with DTNB.[20] Reaction mixtures were prepared with 1.78 ml of 0.2 *M* buffer [sodium acetate (pH 4.0), Pipes (pH 6.0), potassium phosphate (pH 7.0), or Bicine (pH 8.0), all of which were 1 m*M* in EDTA], 0.02 ml of 0.1 *M* glutathione, and 0.2 ml of 0.02 *M* Br-butanone-P_2. Controls containing all ingredients except Br-butanone-P_2 were also prepared. Periodically, 0.2-ml aliquots of the reaction mixtures and controls were added to cuvettes containing 2.2 ml of 0.2 *M* potassium phosphate (pH 8.0) and 0.1 ml of DTNB (0.01 *M*). The sulfhydryl concentration was determined from the increase in *A* at 412 nm using an $\epsilon_{1\,cm}$ (1%) of 13,600.[20] Calculated second-order rate constants at pH 6.0, 7.0, and 8.0 were 0.68, 1.2, and 1.4 M^{-1} sec^{-1}, respectively. To prepare a quantity of modified glutathione sufficient for characterization studies, glutathione (20 μmol) and Br-butanone-P_2 (50 μmol) were incubated at room temperature for 30 min in 2 ml of 0.2 *M* $NaHCO_3$–1 m*M* EDTA (pH 8.0). The reaction was then terminated by acidification to pH 2.0 with 1 *N* HCl. Paper chromatography showed two ninhydrin-positive components (R_f 0.14 and R_f 0.22) that contained phosphate as demonstrated with the molybdate spray. From the relative intensities of the two components, there appeared to be about three times as much of the compound with R_f 0.14 as of the compound with R_f 0.22. A sample of the reaction mixture (equivalent to 0.2 μmol of glutathione present initially) was chromatographed on the long column of the amino acid analyzer. A major peak (0.17 μmol based on the constant for leucine) eluted essentially with the front (18 min), and a minor peak (0.017 μmol based on the constant for leucine) eluted at 39 min just before the position (42 min) at which glutathione emerges. The sample contained no glutathione but did contain oxidized glutathione (0.017 μmol) that elutes at 50 min. The oxidized glutathione must be considered a reaction product, since a glutathione control that was incubated under the same conditions for the same period of time did not contain oxidized glutathione. The peak that eluted at 18 min represents both ninhydrin-positive phosphate esters visualized by paper chromatography, since this peak was resolved into two by running the sample with the usual citrate buffer (pH 3.25) after adjusting its pH to 2.6 with 12 *N* HCl.

A sample of the reaction mixture was also hydrolyzed and then

subjected to amino acid analysis. About 5% less glutamic acid than glycine was found, and there was thus an indication of slight reaction of the N-terminal amino group with Br-butanone-P_2. The hydrolysate contained about 0.05 molar equiv of cystine, but did not contain significant quantities of other ninhydrin-positive compounds. Since the derivatives arising from the cysteinyl residue were apparently converted to ninhydrin-negative compounds during the hydrolysis procedure, some of the reaction mixture (1.0 ml) was treated with [^{3}H]$NaBH_4$ (0.1 *M* at pH 8.0 for 30 min) so as to reduce the carbonyl group of the glutathione derivative and thus provide a radioactive marker. The major glutathione derivative (4.0 μmol, 40%) was separated from the excess reagent on a 1.2 × 25 cm column of Dowex 50 (H^+) that was equilibrated and eluted with 0.05 *N* HCl. A hydrolysate of the derivative was chromatographed on the amino acid analyzer, and the effluent was monitored for radioactivity (Figure 2).

Reaction of Br-Butanone P_2 with *N*-α-Acetyl-L-Lysine. A solution of *N*-α-acetyl-L-lysine (40 μmol) and Br-butanone-P_2 (50 μmol) in 2 ml of 0.2 *M* $NaHCO_3$ (pH 8.0) was incubated in the dark at room temperature. Periodically, 0.05-ml aliquots were withdrawn and added to 0.95 ml of 0.1 *N* HCl. One-half of these diluted aliquots was analyzed on the long column of the amino acid analyzer by elution with the second buffer (pH 4.25) only (acetyllysine eluted at 64 min). The percentages of acetyllysine remaining at 0.5, 1, 2, 4, 24, and 48 hr were 94, 87, 77, 63, 51, and 49, respectively. After 48 hr a sample (1.0 ml) of the incubation mixture was reduced with [^{3}H]$NaBH_4$ as described for the glutathione derivative. A portion (0.1 ml) of the reduced reaction mixture was hydrolyzed and then inspected on the amino acid analyzer. The hydrolysate contained ninhydrin-positive components that eluted from the short column at 11 min (0.19 μmol based on the constant for leucine) and 18 min (0.26 μmol based on the constant for leucine) in addition to lysine (0.8 μmol) (Figure 3A). Much of the radioactivity coincident with the ninhydrin-positive peak at 11 min was assumed to be from unreacted reagent. The remainder of the reduced mixture was fractionated on a 1.2 × 25 cm column of Dowex 1 (Cl^-) using a linear gradient of LiCl (0–0.5 *M*) in 0.001 *N* HCl. The major radioactive lysyl derivative eluted at about 0.2 *M* LiCl and was obtained in a 39% yield. Hydrolysates of this material contained both of the ninhydrin-positive peaks found in the hydrolysate of the unfractionated reaction mixture (Figure 3A), and both were radioactive (Figure 3B). Both derivatives were converted to lysine upon treating the hydrolysate with sodium metaperiodate (Figure 3C).

Registry No.—**1**, 6117-80-2; **2**, 55759-07-4; **3**, 55759-08-5; **4**, 55759-09-6; **5** triscyclohexylamine, 55759-10-9; **5** tetralithium, 55759-11-0; **6**, 52084-24-9; *cis*-1,4-di-*O*-benzoyl-2-butene-1,4-diol, 55759-12-1; benzoyl chloride, 98-88-4; *N*-bromosuccinimide, 128-08-5; triethyl orthoformate, 122-51-0; diphenyl chlorophosphate, 2524-64-3; glutathione, 70-18-8; *N*-α-acetyl-L-lysine, 1946-82-3; ribuluse 1,5-P_2, 2002-28-0.

References and Notes

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Synthesis of the 2,5-Protoadamantanediols[1]

Roger K. Murray, Jr.,* and Thomas K. Morgan, Jr.[2]

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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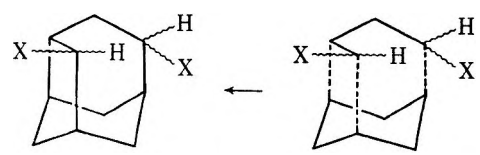
Acid-catalyzed conjugate additions to 8,9-dehydro-2-adamantanone provide a general route to 2-exo-substituted 5-protoadamantanones. 2-*exo*-Acetoxy-5-protoadamantanone, thus generated, is shown to be a useful precursor for the synthesis of 2-*exo*-5-*exo*-, 2-*exo*-5-*endo*-, and 2-*endo*-5-*endo*-protoadamantanediol. 2-*endo*-5-*exo*-Protoadamantanediol has been prepared by a reaction sequence which features the Lewis acid catalyzed regioselective ring cleavage of 3-oxatetracyclo[5.3.1.$0^{2,6}$.$0^{4,9}$]undecane. Thus, the four possible 2,5-protoadamantanediols have been synthesized.

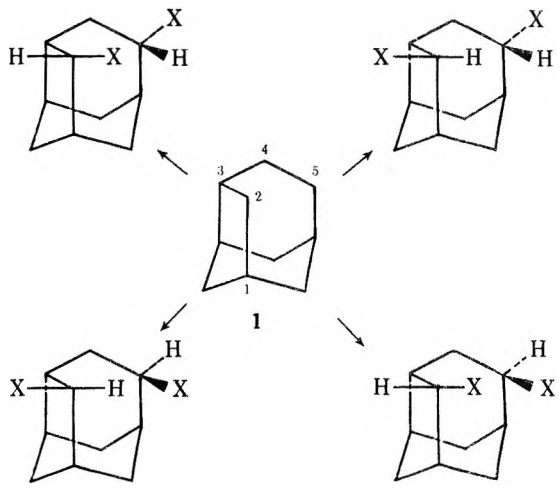
The chemistry of protoadamantane (1) and its derivatives has attracted significant attention.[3-5] However, although both 2-substituted[4] and 5-substituted[4a,5] protoadamantanes have been known for some time, no 2,5-disubstituted protoadamantanes have been reported. In principle, substitution of 1 at C-2 and C-5 with different substituent groups such that C-2 and C-5 remain sp^3 hybridized may lead to eight isomeric 2,5-disubstituted protoadamantanes. Of course, if the substituents are identical, only four isomeric 2,5-disubstituted protoadamantanes can be realized (Scheme I). We now wish to report the synthesis of the four 2,5-protoadamantanediols.

Results and Discussion

In terms of molecular architecture, a 2,5-disubstituted protoadamantane may be viewed as a 1,4-disubstituted butane that has been attached to the C-1, C-3, and C-5 axial positions of cyclohexane. Since it is well known that 1,4-disubstituted butanes may be prepared by acid-catalyzed



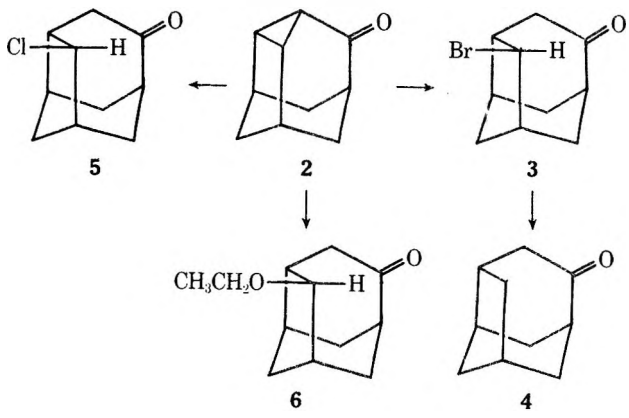
Scheme I



conjugate additions to cyclopropyl ketones,[6] we anticipated that 8,9-dehydro-2-adamantanone (2) might prove to be a useful precursor for the synthesis of 2,5-disubstituted protoadamantanes.

Treatment of 2[7] with hydrobromic acid in glacial acetic acid provides 2-*exo*-bromo-5-protoadamantanone (3) in ca. 95% yield (Scheme II). The skeletal framework of 3 and the

Scheme II

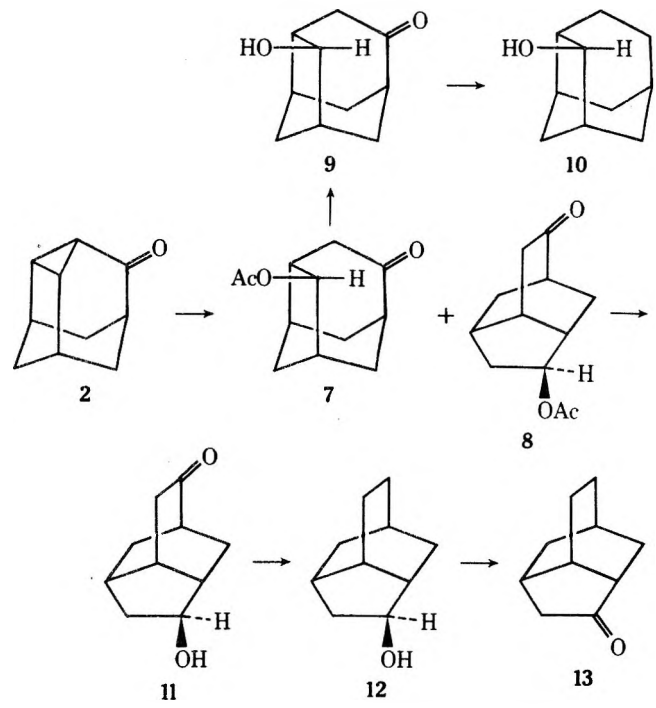


skeletal position of the carbonyl substituent in 3 were established by hydrogenolysis of 3 with palladium on calcium carbonate to give the known ketone, 5-protoadamantanone (4).[4a,5b,d] The assigned skeletal position and stereochemistry of the bromo substituent in 3 are consistent with the observation that treatment of 3 with alkali regenerates 2.

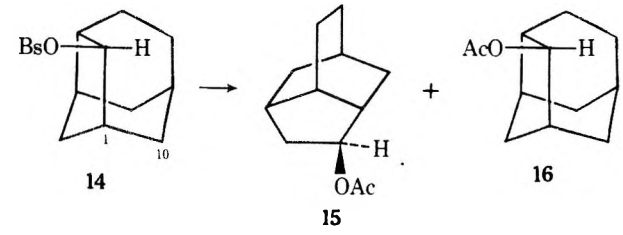
Other 2,5-disubstituted protoadamantanes can be prepared from 2 in good yield through analogous reactions. Thus, treatment of 2 with acetic acid which has been saturated with dry hydrogen chloride gas gives 2-*exo*-chloro-5-protoadamantanone (5) in ca. 85% yield. Refluxing an ethanolic solution of 2 in the presence of *p*-toluenesulfonic acid, followed by aqueous work-up, affords 2-*exo*-ethoxy-5-protoadamantanone (6) in ca. 80% yield.[8,9]

Perchloric acid catalyzed acetolysis of 2 gives not only 2-*exo*-acetoxy-5-protoadamantanone (7) in ca. 80% yield, but also 2-*exo*-acetoxy-7-isotwistanone (8)[12] in ca. 10% yield (Scheme III). The skeletal framework of 7 and the skeletal position and stereochemistry of the acetoxy substituent in 7 follow from the conversion of 7 to the known alcohol, 2-*exo*-protoadamantanol (10).[4d,13] Hydrolysis of 7 gives 2-*exo*-hydroxy-5-protoadamantanone (9) and Wolff–Kishner reduction of 9 provides 10. The skeletal framework of 8 and the skeletal position of the acetoxy substituent in 8 were established by the conversion of 8 to the known ketone, 2-

Scheme III



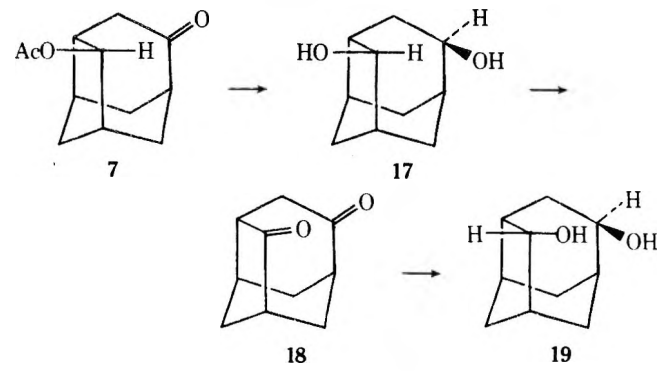
isotwistanone (13).[4d] Hydrolysis of 8 affords 2-*exo*-hydroxy-7-isotwistanone (11) and Wolff–Kishner reduction of 11 provides 2-*exo*-isotwistanol (12). Jones oxidation of 12 gives 13. The formation of 8 is not unexpected. Spurlock and Clark have reported that the major products resulting from the acetolysis of 2-*exo*-protoadamantyl brosylate (14) are 2-*exo*-isotwistyl acetate (15) and 2-*exo*-protoadamantyl acetate (16).[4d] The formation of 15 was accounted for by



anchimeric assistance of the C-1 to C-10 σ bond of 14 in the ionization process, accompanied by nucleophilic attack at C-1 of 14. The stereochemistry of the acetoxy substituent and the position of the keto substituent in 8 follow from a similar mechanism rationalizing the formation of 8.

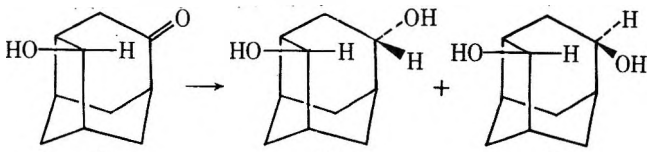
The synthesis of acetoxy ketone 7 permits the facile preparation of three of the 2,5-protoadamantanediols. Treatment of 7 with lithium aluminum hydride affords a single product to which we have assigned the structure of 2-*exo*-5-*endo*-protoadamantanediol (17) (Scheme IV). An

Scheme IV



examination of molecular models clearly shows that whereas there is no apparent steric hindrance to attack at the exo face of the C-5 carbonyl carbon in **7**, attack at the endo face of the C-5 carbonyl carbon should be significantly impeded by the endo hydrogen at C-2. Consistent with the structure assignment, Jones oxidation of **17** affords 2,5-protoadamantanedione (**18**), which shows carbonyl absorptions in the infrared at 1743 and 1721 cm^{-1}.[14] Sodium borohydride reduction of **18** provides 2-*endo*-5-*endo*-protoadamantanediol (**19**). Jones oxidation of **19** regenerates **18**.

Since 2-*exo*-5-*exo*-protoadamantanediol (**20**) is undoubtedly thermodynamically more stable than diol **17**, it was anticipated that **20** might be obtained from **17** via equilibration. However, treatment of **17** with aluminum isopropoxide in isopropyl alcohol[15] gave only recovered starting material. Boyd and Overton were similarly unsuccessful in equilibrating 5-*endo*-protoadamantanol.[5b] However, they did find that 5-*exo*-protoadamantanol could be obtained in ca. 70% yield by reduction of 5-protoadamantanone with lithium in ammonia.[5b] Diol **20** may be synthesized by means of an analogous reaction. Thus, treatment of **9** with a large excess of lithium in ammonia provides a 2:1 mixture of **20** and **17** in an overall yield of ca. 50%. The diols can be

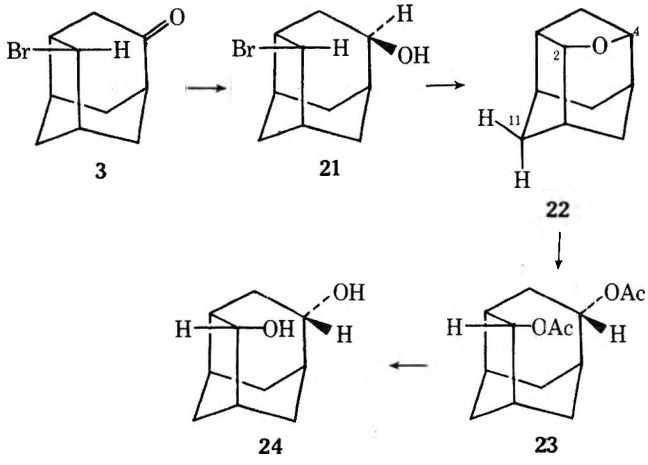


9 20 17

readily separated by GLC. As expected, Jones oxidation of **20** gives **18**.

In view of the conversion of **9** to **20**, it appears that 2-*endo*-5-*exo*-protoadamantanediol (**24**) might also be prepared from **9**.[16] However, we have developed an alternative

Scheme V



3 21 22 24 23

and less obvious synthesis of **24** (Scheme V). The key intermediate in this reaction sequence is cage ether **22**. 3-Oxatetracyclo[5.3.1.$0^{2,6}$.$0^{4,9}$]undecane (**22**) was prepared via an internal Williamson ether synthesis from 2-*exo*-bromo-5-*endo*-protoadamantanol (**21**) which, in turn, was obtained by sodium borohydride reduction of bromo ketone **3**. Refluxing **22** with a mixture of zinc chloride and acetic anhydride provides 2-*endo*-5-*exo*-diacetoxy protoadamantane (**23**) in ca. 85% yield.[17,18] Since treatment of **22** under these reaction conditions might well lead to both 2-endo-5-exo- and 2-exo-5-endo-disubstituted protoadamantanes, it is apparent that **22** → **23** is a strikingly regioselective reaction which proceeds by preferential attack at C-4 rather than at C-2 of **22**. From an examination of molecular models, it is tempting to suggest that this is the case because the equatorial hydrogen at C-11 of **22** sterically hinders attack at C-2. There is no apparent steric hindrance to attack at C-4 of **22**. Hydrolysis of **23** gives diol **24** in nearly quantitative yield. The skeletal framework of **24** and the skeletal positions of the substituent groups in **24** were confirmed by Jones oxidation of **24** to give dione **18**.

Aspects of the chemical and physical properties of the 2,5-protoadamantanediols are currently under active investigation.

Experimental Section

All melting points were obtained in sealed capillary tubes using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 180 or 337 spectrophotometers and proton magnetic resonance spectra were recorded with Varian A-60A or Perkin-Elmer R-12B 60-MHz spectrometers. Apparent splittings are given in all cases. Unless noted otherwise, yields were obtained by integration of appropriate signals in the ^1H NMR spectrum of the product(s) vs. the signal of a predetermined amount of added standard (generally trichloroethylene) and are regarded as being accurate to ca. ±10%. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del.

2-*exo*-Bromo-5-protoadamantanone (3). To a solution of 227 mg (1.53 mmol) of 8,9-dehydro-2-adamantanone (**2**)[7] in 20 ml of acetic acid was added 1 ml of a 30–32% solution of hydrobromic acid in acetic acid and the resulting solution was stirred for 1 hr at 80–100°. The reaction mixture was then quenched in aqueous sodium bicarbonate (250 ml) and extracted with ether (4 × 100 ml). The combined ether extracts were washed with water (2 × 50 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 327 mg of a tan solid which by ^1H NMR analysis contained a ca. 95% yield of **3**. Recrystallization of this material from heptane gave pure **3**: mp 127–127.5°; δ_{Me_4Si} ($CDCl_3$) 3.79 (d, J = 3.5 Hz, 1 H, CHBr), 3.3–1.5 (br m, 12 H); ν (CCl_4) 2960, 2885, 1725, 1455, 1425, 1400, 1310, 1250, 1240, 1145, 1065, and 1045 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}OBr$: C, 52.42; H, 5.72; Br, 34.87. Found C, 52.52; H, 5.70; Br, 34.96.

5-Protoadamantanone (4). A solution of 69 mg (0.3 mmol) of **3** in 25 ml of methanol was stirred with 250 mg of 5% palladium on calcium carbonate under an atmosphere of hydrogen for 21 hr. The reaction mixture was filtered to remove the catalyst and the methanol was then evaporated at reduced pressure to afford 37 mg (ca. 80% yield) of an off-white solid which GLC analysis (5 ft × 0.25 in. FFAP column, 160°) showed contained a single component. Purification of this compound by GLC (above conditions) gave pure **4**, whose physical and spectral properties were identical with those previously reported.[4a,5b]

Dehydrobromination of 3. A solution of 105 mg (1.85 mmol) of potassium hydroxide in 3 ml of methanol was added to a solution of 22 mg (0.1 mmol) of **3** in 2 ml of methanol and the resulting solution was refluxed for 0.5 hr. The reaction mixture was then quenched in water (100 ml) and extracted with ether (4 × 25 ml). The combined ether extracts were washed with water (3 × 10 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 21 mg of a yellow oil which GLC analysis (5 ft × 0.25 in. FFAP column, 190°) showed contained a single component. Isolation of this compound by GLC (above conditions) provided pure **2**, which was identified by comparison of its ir spectrum with that of an authentic sample.[7]

2-*exo*-Chloro-5-protoadamantanone (5). To 102 mg of **2** was added 4 ml of acetic acid which had been saturated with dry hydrogen chloride gas. The reaction mixture was refluxed for 1 hr and then quenched in water (50 ml). The resulting mixture was neutralized with solid sodium bicarbonate and extracted with ether (4 × 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure to afford 139 mg of an off-white solid which by ^1H NMR analysis contained a ca. 85% yield of **5**. Recrystallization of this material from chloroform–heptane gave pure **5**: mp 170–171°; δ_{Me_4Si} ($CDCl_3$) 3.68 (d, J = 1.5 Hz, 1 H, CHCl), 3.1–1.3 (br m, 12 H); ν ($CHCl_3$) 2950, 2865, 1710, 1475, 1460, 1450, 1420, 1345, 1270, 1240, 1150, 1120, 1070, 1045, and 1015 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}OCl$: C, 65.04; H, 7.10; Cl, 19.20. Found: C, 65.31; H, 7.15; Cl, 19.46.

2-*exo*-Ethoxy-5-protoadamantanone (6). A solution of 193

mg of *p*-toluenesulfonic acid monohydrate in 10 ml of benzene was refluxed for 20 min and the water was removed azeotropically. The remaining benzene was evaporated at reduced pressure and 93 mg of **2** and 10 ml of ethanol were added to the residue. The solution was refluxed for 10 hr, after which the mixture was poured onto 20 ml of 10% aqueous sodium bicarbonate. An additional 30 ml of water was added, and the solution was saturated with sodium chloride and then extracted with ether (5 × 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure to give 131 mg of a brown oil which by ^{1}H NMR analysis contained a ca. 80% yield of **6**. Isolation by GLC (5 ft × 0.25 in. FFAP column, 160°) gave pure **6**: δ_{Me_4Si} ($CDCl_3$) 3.36 (q, J = 7 Hz, 2 H, $-OCH_2CH_3$), 3.08 (d, J = 1.5 Hz, 1 H, $CHOCH_2CH_3$), 2.9–1.3 (br m, 12 H), and 1.14 (t, J = 7 Hz, 3 H, $-OCH_2CH_3$); ν ($CHCl_3$) 2925, 2870, 1715, 1470, 1445, 1375, 1360, 1340, 1150, 1120, 1085, and 1015 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.31; H, 9.53.

Perchloric Acid Catalyzed Addition of Acetic Acid to 2. A solution containing 100 mg (0.7 mmol) of **2** and 50 μl of 70% perchloric acid in 4 ml of acetic acid was stirred for 4 hr at 80–100°, then quenched in water and neutralized with solid sodium bicarbonate. The resulting mixture was extracted with ether (5 × 75 ml) and the combined ether extracts were washed with water (2 × 50 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 134 mg of yellow oil which GLC analysis (5 ft × 0.25 in. FFAP column, 190°) showed contained a major and a minor component. ^{1}H NMR and GLC analysis indicated that the products were obtained in ca. 80 and 10% yields, respectively. The reaction products were separated and purified by GLC (above conditions) to give, as the major product, **2-*exo*-acetoxy-5-protoadamantanone (7)**: mp 66–68°; δ_{Me_4Si} (CCl_4) 4.26 (d, J = 1.5 Hz, 1 H, $CHOCOCH_3$) and 2.6–1.2 (br m, 15 H, containing $CHOCOCH_3$ singlet at δ 1.93); ν (CCl_4) 2950, 2875, 1739, 1726, 1360, 1250, 1235, 1165, 1075, 1055, and 1030 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.18; H, 7.48.

2-*exo*-Acetoxyisotwistan-7-one (**8**) was obtained as the minor product: mp 79.5–80.5°; δ_{Me_4Si} (CCl_4) 4.87 (m, 1 H, $CHOCOCH_3$, an apparent ABX multiplet where J_{AX} = 6 and J_{BX} = 3.3 Hz) and 2.5–1.2 (br m, 15 H, containing $CHOCOCH_3$ singlet at δ 1.92); ν (CCl_4) 2945, 2870, 1738, 1728, 1395, 1375, 1355, 1240, 1170, 1140, 1080, 1045, and 1030 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.07; H, 7.92.

2-*exo*-Hydroxy-5-protoadamantanone (9). A reaction mixture containing 422 mg of **7**, 113 mg of sodium hydroxide, 6 ml of methanol, and 8 ml of water was refluxed for 2 hr and then quenched in water (100 ml). The resulting solution was saturated with sodium chloride and extracted with ether (4 × 100 ml). The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 389 mg of material which by ^{1}H NMR analysis contained a ca. 100% yield of **9**. Isolation of the product by GLC (5 ft × 0.25 in. FFAP column, 220°) afforded pure **9**: mp 244–246°; δ_{Me_4Si} ($CDCl_3$) 3.54 (d, J = 1 Hz, 1 H, CHOH) and 2.6–1.2 (br m, 13 H); ν (CCl_4) 3625, 3440, 2935, 2875, 1715, 1470, 1440, 1410, 1290, 1235, 1165, 1150, 1050, 1030, and 1000 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.21; H, 8.43.

2-*exo*-Protoadamantanol (10). A stirred solution containing 34 mg (0.2 mmol) of **9**, 130 μl (3.9 mmol) of 95% hydrazine, and 32 μl (0.5 mmol) of acetic acid in 2 ml of diethylene glycol was heated at 90° under a nitrogen atmosphere for 24 hr. At this point 275 mg (4.8 mmol) of potassium hydroxide was added and the reaction mixture was heated at 190° for an additional 5 hr. During this time, a white solid appeared on the condenser. The system was cooled and the material on the condenser was dissolved in pentane. The pot residue was quenched in water (50 ml) and extracted with pentane (4 × 25 ml). The pentane extracts from condenser and pot were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 21 mg of material which GLC analysis (5 ft × 0.25 in. FFAP column, 175°) showed contained a single component. Isolation of this compound by GLC (above conditions) gave pure **10**, mp 218–220°, which was identified by comparison of its ir spectrum with that of an authentic sample.[4d,13]

2-*exo*-Hydroxy-7-isotwistanone (11). A reaction mixture containing 55 mg of **8**, 13 mg of sodium hydroxide, 3 ml of methanol, and 4 ml of water was refluxed for 2 hr and then quenched in water (100 ml). The resulting solution was extracted with ether (5 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 44 mg of material which by ^{1}H NMR analysis contained a ca. 40% yield of **11**. Purification of the product by GLC (5 ft × 1.25 in. FFAP column, 215°) provided pure **11**: mp 61–62°; δ_{Me_4Si} ($CDCl_3$) 4.18 (m, 1 H, CHOH, an apparent ABX multiplet where J_{AX} = 5.5 and J_{BX} = 2.7 Hz) and 2.7–1.1 (br m, 13 H); ν ($CHCl_3$) 3610, 3450, 3005, 2940, 2865, 1715, 1400, 1350, 1325, 1235, 1130, 1125, 1045, and 1030 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.98; H, 8.30.

2-*exo*-Isotwistanol (12). By a procedure analogous to that employed for **9** → **10**, Wolff–Kishner reduction of **11** provided **12** in yields of 50–60%. Purification by GLC (5 ft × 0.25 in. FFAP column, 165°) gave pure **12**: mp 57.5–58.5°; δ_{Me_4Si} (CCl_4) 4.04–3.76 (br m, 1 H, CHOH), 2.80 (br s, 1 H), and 2.5–0.8 (br m, 14 H); ν (CCl_4) 3625, 3345, 2935, 2860, 1445, 1280, 1215, 1165, 1080, 1040, and 1025 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.10; H, 10.52.

2-Isotwistanone (13). To a stirred solution of 9 mg of **12** in 5 ml of acetone at 0° was added 40 μl of a freshly prepared solution of Jones reagent (2.8 g of chromic anhydride, 4.5 ml of sulfuric acid, and 12 ml of water). The reaction mixture was stirred for 4 hr and allowed to gradually warm to room temperature. The reaction was then quenched with 4 ml of 25% aqueous sodium bisulfite and the volume of the mixture was increased to 20 ml by the addition of water. The resulting solution was extracted with ether (4 × 25 ml) and the combined ether extracts were then washed successively with saturated aqueous sodium bicarbonate (2 × 10 ml) and saturated aqueous sodium chloride (2 × 10 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated at reduced pressure and the residue was purified by GLC (5 ft × 0.25 in. FFAP column, 175°) to give pure **13** whose physical (mp 112–114°) and spectral properties were identical with those previously reported.[4d]

2-*exo*-5-*endo*-Protoadamantanediol (17). To a solution of 187 mg (0.9 mmol) of **7** in 20 ml of freshly distilled dry ether at 0–5° was added 333 mg (8.8 mmol) of lithium aluminum hydride and the resulting reaction mixture was stirred at 0–5° for 1 hr and then at 25° for 12 hr. The reaction mixture was cautiously quenched with 10 ml of saturated aqueous ammonium chloride and the resulting precipitate was filtered. The filtrate was saturated with sodium chloride and extracted with ether (4 × 50 ml). The precipitate from the reaction was washed with several portions of ether and the ether extracts and washings were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 181 mg of material which by ^{1}H NMR analysis contained a ca. 70% yield of **17**. Isolation by GLC (5 ft × 0.25 in. FFAP column, 205°) provided pure **17**: mp 271–272°; δ_{Me_4Si} (CD_3OD) 4.13–3.84 (br m, 2 H, CHOH) and 2.5–1.0 (br m, 12 H); ν ($CHCl_3$) 3630, 3440, 3000, 2940, 2835, 1090, and 1020 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.56.

2,5-Protoadamantanedione (18). Oxidation of 56 mg of **17** with Jones reagent by the procedure described for **12** → **13** provided 59 mg of material which was purified by GLC (5 ft × 0.25 in. FFAP column, 200°) to give pure **18**: mp 264–267°; δ_{Me_4Si} ($CDCl_3$) 2.9–1.5 (br m); ν ($CHCl_3$) 3020, 2940, 2875, 1743, 1721, 1465, 1450, 1440, 1400, 1180, 1175, 1140, 1070, 1040, and 1020 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.90; H, 7.08.

2-*endo*-5-*endo*-Protoadamantanediol (19). Sodium borohydride (670 mg, 17.6 mmol) was added to a stirred solution of 145 mg (0.9 mmol) of **18** in 20 ml of methanol at 0–5°. The solution was stirred for 12 hr while it gradually warmed to room temperature. At this point 50 ml of saturated aqueous ammonium chloride was added and the solution was saturated with sodium chloride. The reaction mixture was extracted with ether (4 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 173 mg of crude diol which was purified by GLC (5 ft × 0.25 in. FFAP column, 200°) to give **19**: mp >290°; δ_{Me_4Si} (CD_3OD) 4.5–3.8 (br m, 2 H, CHOH) and 3.0–1.1 (br m, 12 H); ν (CCl_4) 3610, 3270, 2930, 2860, 1450, 1170, 1085, 1055, and 1015 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.30.

Oxidation of **19** with Jones reagent by the procedure described for **12** → **13** gave **18**.

2-*exo*-5-*exo*-Protoadamantanediol (20). To a stirred slurry of 381 mg (54.5 mmol) of lithium metal in ca. 100 ml of liquid ammonia was added 326 mg (2.0 mmol) of **9**. The stirred solution was refluxed for 1.5 hr, at which point ca. 8 g of ammonium chloride was carefully added and the ammonia was allowed to evaporate. Water (100 ml) was added to the reaction mixture and the resulting solution was saturated with sodium chloride and extracted with ether (4 × 100 ml). The combined ether extracts were washed successively with 5% hydrochloric acid (2 × 50 ml) and water (50 ml) and then dried over anhydrous magnesium sulfate. GLC analysis (5 ft × 0.25 in. QF-1 column, 200°) of the crude reaction mixture indicated the presence of two components: a minor product (which proved to be **17**) and a major product **20** (longer retention time). Evaporation of the solvent at reduced pressure gave 295 mg of material which by ^{1}H NMR analysis contained a ca. 50% yield of the two diols. The diols were separated by GLC (5 ft × 0.25 in. QF-1 column, 165°) to provide pure **20**: mp 235–236°; δ_{Me_4Si} (CD_3OD) 3.96–3.50 (br m, 2 H, CHOH) and 2.5–0.6 (br m, 12 H), ν ($CHCl_3$) 3625, 3300, 2925, 2860, 1155, 1030, 1010, and 995 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.48.

Oxidation of **20** with Jones reagent by the procedure described for **12** → **13** gave **18**.

2-*exo*-Bromo-5-*endo*-Protoadamantanol (21). To a stirred solution of 361 mg (1.73 mmol) of **3** in 25 ml of methanol at 0–5° was added 610 mg (16.0 mmol) of sodium borohydride. Over a period of 2 hr the reaction mixture was allowed to warm to room temperature and it was then quenched with water (50 ml). The resulting solution was saturated with sodium chloride and extracted with ether (4 × 25 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 306 mg of material which by ^{1}H NMR analysis contained a ca. 75% yield of **21**. Recrystallization of this material from chloroform–heptane gave pure **21**: mp 113.5–114.5°; δ_{Me_4Si} ($CDCl_3$) 4.51 (d, J = 1.6 Hz, 1 H, CHBr), 4.34–3.94 (br m, 1 H, CHOH), and 3.0–1.2 (br m, 14 H); ν ($CHCl_3$) 3615, 3450, 2950, 2870, 1465, 1450, 1435, 1085, 1040, and 1030 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}OBr$: C, 51.96; H, 6.54; Br, 34.57. Found: C, 52.06; H, 6.35; Br, 34.79.

3-Oxatetracyclo[5.3.1.0^{2,6}.0^{4,9}]undecane (22). A solution of 209 mg of **21** and 108 μl of water in 10 ml of methanol was added to a stirred solution of 293 mg of sodium in 20 ml of methanol and the reaction mixture was refluxed for 12 hr. At this point the solution was concentrated by evaporation of most of the methanol at reduced pressure and 50 ml of water was added. The solution was extracted with ether (4 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 168 mg of material which by ^{1}H NMR analysis contained a ca. 60% yield of **22**. Purification by GLC (10 ft × 0.25 in. Carbowax column, 150°) provided pure **22**: mp 238–239°; δ_{Me_4Si} ($CDCl_3$) 4.60–4.15 (br m, 2 H, CHOCH, containing an apparent triplet centered at δ 4.43) and 2.8–0.3 (br m, 12 H); ν ($CHCl_3$) 2985, 2860, 1470, 1450, 1340, 1315, 1180, 1145, 1125, 1100, 1030, 1000, 985, and 930 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.81; H, 9.22.

2-*endo*-5-*exo*-Diacetoxyprotoadamantane (23). To a stirred solution of 82 mg (0.55 mmol) of **22** in 7 ml of acetic anhydride was added 66 mg (0.49 mmol) of zinc chloride and the reaction mixture was refluxed for 10 hr and then quenched in 100 ml of ice–water. The resulting solution was neutralized with solid sodium bicarbonate and extracted with ether (4 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 194 mg of a brown oil which by ^{1}H NMR analysis contained a ca. 85% yield of **23**. GLC analysis (5 ft × 0.25 in. Carbowax column, 210°) indicated a single major reaction product and several minor products. Isolation of the major product by GLC (above conditions) gave pure **23** as an oil: δ_{Me_4Si} ($CDCl_3$) 5.11–4.75 (br m, 2 H, $CHOCOCH_3$) and 2.8–1.1 (br m, 18 H, containing $OCOCH_3$ singlets at δ 2.12 and 1.98); ν ($CHCl_3$) 2940, 2875, 1720, 1460, 1250, 1070, and 1025 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.52; H, 7.86.

2-*endo*-5-*exo*-Protoadamantanediol (24). Hydrolysis of 117 mg of **23** by the procedure described for **7** → **9** provided 127 mg of material which by ^{1}H NMR analysis contained a ca. 100% yield of **24**. The reaction product was sublimed and finally purified by GLC (5 ft × 0.25 in. Carbowax column, 235°) to give pure **24**: mp 286–288°; δ_{Me_4Si} (CD_3OD) 4.34–3.60 (br m, 2 H, CHOH) and 2.6–0.9 (br m, 12 H); ν ($CHCl_3$) 3610, 3360, 2925, 2865, 1455, 1260, 1095, and 1020 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.38; H, 9.31.

Oxidation of **24** with Jones reagent by the procedure described for **12** → **13** gave **18**.

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Registry No.—**2**, 10497-56-0; **3**, 32456-48-7; **5**, 55682-02-5; **6**, 55682-03-6; **7**, 50266-25-6; **8**, 50266-28-9; **9**, 50266-27-8; **11**, 50266-29-0; **12**, 50266-30-3; **17**, 55682-04-7; **18**, 55682-05-8; **19**, 55721-89-6; **20**, 55721-90-9; **21**, 55682-06-9; **22**, 55682-07-0; **23**, 55682-08-1; **24**, 55721-91-0.

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(16) Such a synthesis of **24** might involve the following sequence of reactions.

$$9 \xrightarrow[H^+]{HOCH_2CH_2OH} \xrightarrow[Py]{CrO_3} \xrightarrow[CH_3OH]{NaBH_4} \xrightarrow[H_2O]{H^+} \xrightarrow[NH_3]{Li} 24 + 19$$

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Panurensine and Norpanurensine, New Bisbenzylisoquinoline Alkaloids from *Abuta panurensis*

Michael P. Cava,* J. M. Saá, M. V. Lakshmikantham, and M. J. Mitchell

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19174

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Panurensine and norpanurensine, new bisbenzylisoquinoline alkaloids from *Abuta panurensis* Eichler, have been assigned structures 1 and 2, respectively, on the basis of spectroscopic and chemical evidence. They are the first examples of bisbenzylisoquinolines containing both a 5–7′ and an 11–12′ ether bridge.

Many plants of the family Menispermaceae have been shown to be a rich source of alkaloids of the benzylisoquinoline and benzylisoquinoline-derived types.[1] As part of a broad search for new anticancer alkaloids, we are studying a number of previously unexamined South American members of this family, especially species of the genus *Abuta*.[2] The Amazonian species, *Abuta panurensis*, has now been found to contain an alkaloid fraction exhibiting marked activity in the KB-nasopharynx tumor cell system. We wish to report here the isolation and structure determination of the two major constituents of this fraction, namely the new bisbenzylisoquinoline alkaloids panurensine (1) and norpanurensine (2).

Panurensine (1) was obtained as white needles, mp 156–158°, which readily become yellow on exposure to light and air. The composition $C_{37}H_{40}N_2O_6$ was determined by high-resolution mass spectrometry.

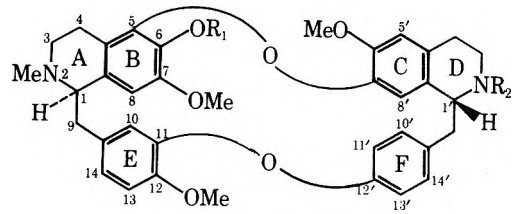
The infrared spectrum (KBr) of panurensine showed the absence of a carbonyl band, but a band at 3400 cm^{-1}, attributable to a nonassociated phenolic group, was observed.

The NMR spectrum of panurensine showed the presence of three aromatic methoxyls at δ 3.46, 3.82 and 3.92, as well as two methylimino groups at δ 2.40 and 2.55. Of the ten aromatic protons present, four were clearly discernible as singlets at δ 6.61, 5.82, 5.24, and 5.02. The high degree of shielding of the latter three protons certainly is the most striking feature of the spectrum.

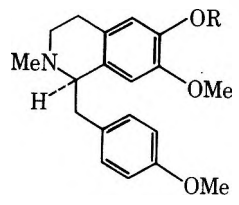
Treatment of panurensine with excess diazomethane afforded *O*-methylpanurensine (3), confirming the presence of one phenolic function in the parent alkaloid. The corresponding reaction of panurensine with deuteriodiazomethane in dioxane–deuterium oxide[3] yielded the corresponding *O*-trideuteriomethyl derivative 4. A comparison of the NMR spectra of 3 and 4 showed that the new methyl of the methyl ether 3 is represented by the normal methoxyl signal at δ 3.75. This result rules out the possibility that panurensine may be a normal head-to-head dimer having a C-7 hydroxyl, since a methoxyl at the corresponding position would be highly shielded.[4]

The mass spectrum of panurensine is typical of that of a bisbenzylisoquinoline alkaloid containing both head-to-head and tail-to-tail ether bridges.[5] Thus, weak peaks at M − 107, M − 121, and M − 137 occur in the spectra of both panurensine (1) and its methyl ether 3. These peaks are characteristic of a tail-to-tail diphenyl ether system containing one methoxyl substituent, and require that the phenolic group of 1 be located on one of the isoquinoline units. In accord with this general formulation, the base peak of panurensine, representing the linked isoquinoline units, is seen at *m/e* 381, a value which is shifted to 395 in the spectrum of methyl ether 3.

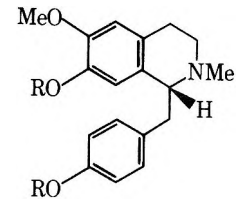
The mass spectrum of the trideuteriomethyl ether 4 further defines the environment of the original phenolic hydroxyl of 1. Loss of the CD_3 group from the head-to-head



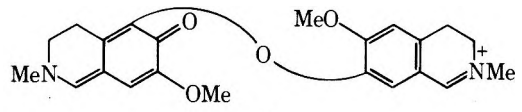
1, R_1 = H; R_2 = Me
2, R_1 = R_2 = H
3, R_1 = R_2 = Me
4, R_1 = CD_3; R_2 = Me
5, R_1 = Me; R_2 = H



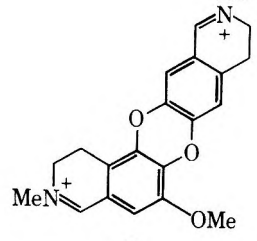
6, R = CD_3
7, R = Me



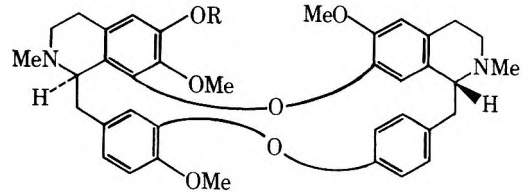
8, R = H
9, R = Et



10



11



12, R = H
13, R = Me

fragment of the molecule gives rise to an ion (10) at *m/e* 380, consistent with the loss of this group from a C-6 (or C-6′) position to give a stabilized *p*-quinonoid species. Furthermore, the same intense doubly charged dioxane fragment at *m/e* 175 (11) appears in the mass spectra of both the methyl ether 3 and the trideuteriomethyl analog 4, in-

dicative of the presence of an *o*-hydroxy-*o'*-methoxydiphenyl ether system in the top portion of panurensine itself.

Treatment of *O*-methylpanurensine (**3**) with sodium in liquid ammonia cleanly cleaved the molecule into nonphenolic and phenolic portions.[6] The nonphenolic product was identical with authentic (*R*)-*O*-methylarmepavine (**7**). The phenolic product was identified as (*R*)-*N*-methylcoclaurine (**8**) by comparison with an authentic sample of its enantiomer and by conversion to the known crystalline oxalate[7] of its *O,O*-diethyl ether (**9**). A similar reductive cleavage of *O*-trideuteriomethylpanurensine (**4**) afforded (*R*)-*N*-methylcoclaurine (**8**) and the deuterated nonphenolic base **6**. A comparison of the mass spectrum of **6** with that of (*R*)-*O*-methylarmepavine (**7**) established that the CD_3 group was in the isoquinoline unit (*m/e* 209 for the base peak), while a comparison of their NMR spectra showed that the deuterated compound still possessed the more shielded C-7 methoxyl group.

The above data are consistent only with two possible structures (**1** and **12**) for panurensine. Structure **12** is clearly ruled out, since its *O*-methyl derivative would be *l*-tetrandrine (phaeanthine, **13**), and the reported NMR values for tetrandrine[4] clearly distinguish it from *O*-methylpanurensine. Panurensine must therefore be assigned structure **1**.

The three highly shielded aromatic protons appearing in the NMR spectrum of panurensine are clearly assignable to protons at C-8, C-8', and C-10, since molecular models reveal these protons to lie over the centers of nearby aromatic rings. Acid-catalyzed deuteration[8] of *O*-methylpanurensine introduces two deuteriums into the molecule, neither deuterium having replaced one of the shielded aromatic protons. The mass spectrum of the deuterated product showed peaks indicative of one deuterium in ring C (*m/e* 175 and 191) and one in ring E (*m/e* 486); the deuterated positions must therefore be C-5' and C-13.

Thalmine (*S,S*), lauberine (*S,R*), dryadine (*R,S*), and dryadodaphnine (*R,S*) belong to a small group of bisbenzylisoquinoline alkaloids which arise biogenetically by the oxidative coupling of one coclaurine and one isococlaurine unit, all have a 5–7' ether bridge at the top and a 12–11' ether bridge at the bottom of the molecule.[9] The most shielded aromatic protons of this group appear only slightly upfield (δ 5.88–6.25) from the normal aromatic region.[10] Panurensine is biogenetically related to these alkaloids, but is the first example of a bisbenzylisoquinoline having 5–7' and 11–12' ether bridges. This structural feature is apparently responsible for the unusually high shielded (δ 5.02–5.82) aromatic protons of panurensine, a characteristic which should be of diagnostic value in the identification of further related alkaloids which may be isolated in the future.

Norpanurensine (**2**), mp 175°, formed white crystals from methanol, and had the empirical composition $C_{36}H_{38}N_2O_6$. N-Methylation of **2** with formalin and sodium borohydride afforded panurensine (**1**). The location of the secondary amine function was revealed by a study of the mass spectra of norpanurensine and its *O*-methyl derivative (**5**), both of which showed peaks at *m/e* 160 and 176, corresponding to the loss of the CD isoquinoline unit containing the unmethylated nitrogen. Structure **2** may therefore be unambiguously assigned to norpanurensine.

Experimental Section

Melting points are uncorrected. NMR spectra were determined in $CDCl_3$ solution with tetramethylsilane as internal standard using Varian A-60, HR-100, or 220-MHz instruments. Infrared, ultraviolet (ethanol solution), mass spectra and optical rotations (chloroform solution at room temperature) were determined using Perkin-Elmer Models 137, 202, 270, and 141 instruments, respectively. All preparative chromatography (PLC) was carried out on silica plates using 10:1 $CHCl_3$–MeOH (developer A) or 20:1 $CHCl_3$–MeOH (developer B). *Abuta panurensis* (*Prance 14973*) was collected by G. T. Prance on the Rio Cuieras basin of the lower Rio Negro, Amazonas, Brazil, and identified by B. A. Krukoff. A voucher specimen has been deposited at New York Botanical Garden and other institutions.

Isolation of Panurensine (1) and Norpanurensine (2) from *Abuta panurensis* Eichler. Ground stems of liana (1.67 kg) were extracted exhaustively first with aqueous ammonia–ether, and then with 4 *N* hydrochloric acid. The acid extract was basified with ammonia and extracted with ether. The combined ether extracts yielded 17.21 g of crude residue consisting of neutral and basic material. This material was subjected to gradient pH-countercurrent distribution (100 transfers) between chloroform and aqueous acid, starting with pH 6.5 citrate–phosphate buffer and ending with 3 *M* phosphoric acid. The acidic aqueous layers from tubes 28–41 and 48–61 yielded, upon basification and reextraction with chloroform, 2.2 and 3.3 g, respectively of crude norpanurensine (**2**) and panurensine (**1**). Panurensine crystallized from methylene chloride–hexane to yield pale yellow crystals, mp 155°. Further purification via PLC and recrystallization from methylene chloride afforded colorless crystals: mp 156–158°; $[\alpha]D$ −245.6° (c 0.5); ir (KBr) 3400 cm^{-1} (OH); uv λ_{max} (ε) 225 nm (24,000), 238 (35,400), 284 (16,800); λ_{max} (EtOH–NaOH) (ε) 225 nm (25,500), 240 (39,000), 288 (20,700); NMR (220 MHz) δ 2.40, 2.55 (s, 3 H each, 2 NMe), 3.46, 3.82, 3.92 (s, 3 H each, 3 OMe), 5.02 (s, 1 H), 5.24 (s, 1 H), 5.82 (s, 1 H), 6.61 (s, 1 H) (m, 6.42–7.26); mass spectrum *m/e* (rel intensity) 608 (M^+, 73), 607 (43), 501 (<1), 487 (1), 471 (2), 381 (100), 192 (7), 191 (78), 190 (16), 176 (10), 174 (15), 168 (17); high-resolution mass spectrum *m/e* 608.29067 ($C_{37}H_{40}N_2O_6$ requires *m/e* 608.28863).

Norpanurensine crystallized from methanol as needles: mp 175°; $[\alpha]D$ −250° (c 0.1); ir (KBr) 3400 (OH) and 3200 cm^{-1} (NH); uv λ_{max} (ε) 223 nm (11,000), 240 (20,000), 288 (12,600); NMR δ 2.42 (s, 3 H, NMe), 3.47, 3.83, 3.94 (s, 3 H each, 3 OMe), 5.08 (s, 1 H), 5.28 (s, 1 H), 6.08 (s, 1 H), 6.63 (s, 1 H), 6.50–7.24 (m, 6 H); mass spectrum *m/e* (rel intensity) 594 (M^+, 26), 593 (11), 487 (<1), 473 (1), 457 (2), 367 (100), 206 (11), 205 (15), 192 (8), 191 (10), 190 (23), 184 (92), 176 (14), 168 (5), 161 (26), 160 (7); high-resolution mass spectrum *m/e* 594.27120 ($C_{36}H_{38}N_2O_6$ requires 594.27298).

***O*-Methylpanurensine (3).** To a solution of **1** in methanol was added ethereal diazomethane in two portions during 2 days. The mixture was left in the dark. The usual work-up gave **3** as colorless prisms from EtOAc–hexane: mp 124–125°; $[\alpha]D$ −210° (c 0.05); NMR δ 2.48, 2.60 (s, 3 H each, 2 NMe), 3.44, 3.75, 3.93, 3.96 (s, 3 H each, 4 OMe), 5.15 (s, 1 H), 5.32 (s, 1 H), 5.82 (s, 1 H), 6.73 (s, 1 H), 6.40–7.31 (m, 6 H); mass spectrum *m/e* (rel intensity) 622 (M^+, 100), 621 (75), 515 (<1), 501 (1), 485 (2), 395 (74), 220 (4), 206 (6), 198 (96), 190 (22), 175 (81), 174 (15); high-resolution mass spectrum *m/e* 622.3075 ($C_{38}H_{42}N_2O_6$ requires 622.3042).

***O*-Trideuteriomethylpanurensine (4).** To a cooled solution of excess diazomethane in dioxane[3] (10 ml) and D_2O (1 ml) was added a solution of **1** (50 mg) in dioxane (2 ml) and D_2O (1 ml). After standing for 24 hr in the dark, the usual work-up afforded **4** as an oil (40 mg): NMR δ 2.47, 2.59 (s, 3 H each, 2 NMe), 3.44, 3.92, 3.94 (s, 3 H each, 3 OMe), 5.15 (s, 1 H), 5.32 (s, 1 H), 5.82 (s, 1 H), 6.72 (s, 1 H), and 6.50–7.21 (m, 6 H).

Acid-Catalyzed Deuteration[8] of 3. A solution of **3** (40 mg) in 3% DCl–D_2O (1.5 ml) was heated at 110° under nitrogen in a sealed tube. After 120 hr, the reaction mixture was worked up as usual to give the 5',13-dideuterio derivative as a pale yellow oil (36 mg): NMR δ 2.46, 2.58 (s, 3 H each, 2 NMe), 3.43, 3.74, 3.90, 3.93 (s, 3 H each, 4 OMe), 5.14 (s, 1 H), 5.32 (s, 1 H), 5.82 (s, 1 H), 6.71 (s, <1 H), 6.50–7.30 (5–6 H); mass spectrum *m/e* (rel intensity) 624 (M^+, 57), 623 (67), 622 (41), 517 (M − 107, <1), 486 (M − 138, 2), 386 (56), 198.5 (100), 193 (4), 192 (6), 191 (9), 176 (20).

Sodium–Ammonia Cleavage of 4. To liquid ammonia (400 ml) at −78° was added alternately, with stirring, small pieces of sodium (total of 1 g) and portions of a solution of **4** (400 mg) in dry dioxane, making sure that the color remained blue, prior to each addition of the alkaloid solution. Finally some extra pieces of sodium were added until the blue color persisted for 15 min. The ammonia was then allowed to evaporate overnight. The residue was extracted into methanol. The residue from the methanol was dissolved in water and extracted with ether to separate the nonphenolic fraction (130 mg).

From the aqueous fraction, after saturation with ammonium

chloride (pH 8–9) and extraction with ether (addition of a little $NaBH_4$ retarded air oxidation) was obtained the phenolic fraction (98 mg).

From the nonphenolic fraction, **6** was isolated by PLC (developer B) as an oil: $[\alpha]D$ −76° (c 0.075); NMR δ 2.53 (s, 3 H, NMe), 3.57, 3.77 (s, 3 H each, 2 OMe), 6.07 (s, 1 H), 6.58 (s, 1 H), 6.80 (d, 2 H, J = 8 Hz), 7.05 (d, 2 H, J = 8 Hz); mass spectrum *m/e* (rel intensity) 330 (M^+, 3), 329 (6), 209 (100), 121 (15). The oxalate of **6** crystallized from ethanol–ether, mp 124–125°, $[\alpha]D$ −70° (c 0.11).

From the phenolic fraction was obtained the amorphous **8**: $[\alpha]D$ −25.2° (c 0.21); NMR δ 2.42 (s, 3 H, NMe), 3.77 (s, 3 H, OMe), 5.90 (broad, s, 2 H, 2 OH), 6.52 (s, 1 H), 6.29 (s, 1 H), 6.60 (d, 2 H, J = 8 Hz), 6.90 (d, 2 H, J = 8 Hz); mass spectrum *m/e* (rel intensity) 299 (M^+, 2), 192 (100), 107 (9). The ir ($CHCl_3$) and NMR spectra of **8** were identical with those of an authentic sample of its enantiomer.

A portion of the phenolic fraction (25 mg) was treated with ethereal diazoethane. Work-up in the usual manner after two days yielded *O,O'*-diethyl-*N*-methylcoclaurine (**9**) (20 mg) as a pale yellow oil: NMR 1.31 (t, 3 H, J = 7 Hz), 1.38 (t, 3 H, J = 7 Hz), 2.53 (s, 3 H, NMe), 3.81 (s, 3 H, OMe), 3.68 (q, 2 H, J = 7 Hz), 3.98 (q, 2 H, J = 7 Hz), 6.13 (s, 1 H), 6.58 (s, 1 H), 6.74 (d, 2 H, J = 8 Hz), 7.00 (d, 2 H, J = 8 Hz). It was converted to the oxalate which crystallized from ethanol–ether as needles, mp 173–175°,[7] $[\alpha]D$ −115° (c 0.16).

Anal. Calcd for $C_{24}H_{31}O_7N$: C, 64.71; H, 6.96; N, 3.14. Found: C, 64.87; H, 7.22; N, 3.13.

Sodium–Ammonia Cleavage of 3. The sodium–liquid ammonia cleavage was carried out on **3** (200 mg) exactly as described earlier and the products were separated into nonphenolic and phenolic fractions. From the nonphenolic fraction, **7** was obtained after PLC (developer A) as a colorless oil (50 mg), NMR 2.52 (s, 3 H, NMe), 3.58, 3.77, 3.83 (s, 3 H each, 3 OMe), 6.08 (s, 1 H), 6.57 (s, 1 H), 6.80 (d, 2 H, J = 8 Hz), 7.05 (d, 2 H, J = 8 Hz); these values are identical with those reported for *O*-methylarmepavine.[11] The oxalate was obtained as needles from ethanol, mp 112°, $[\alpha]D$ −98° (c 0.061) (lit.[7] mp 112°), and found to be identical (ir, melting point, and $[\alpha]D$) with an authentic sample prepared from the *R* enantiomer of *O*-methylarmepavine. Work-up of the phenolic fraction afforded **8**.

N-Methylation of 2. To a solution of **2** (45 mg) in $CHCl_3$ (4 ml)–MeOH (4 ml) was added formalin with stirring. After 1 hr, the mixture was cooled in ice and treated with excess sodium borohydride in small portions. After stirring for an additional 1 hr, the solvent was removed and the residue was treated with water. The product was extracted into chloroform and purified via PLC (developer A) to give a product (35 mg), mp 156–158° from methylene chloride–hexane, $[\alpha]D$ −245° (*c* 0.5), identical in all respects (ir, melting point, mixture melting point, rotation, and mass spectra) with panurensine (**1**).

***O*-Methylnorpanurensine (5).** Treatment of **2** (50 mg) with ethereal diazomethane for 2 days in the dark followed by the usual work-up gave an oily residue (45 mg). Purification by PLC (developer A) gave **5** as an oil: NMR 2.45 (s, 3 H, NMe), 3.47, 3.77, 3.94, 3.97 (s, 3 H each, 4 OMe), 5.18 (s, 1 H), 5.31 (s, 1 H), 6.05 (s, 1 H), 6.72 (s, 1 H), 6.52–7.38 (m, 6 H); mass spectrum *m/e* (rel intensity) 6.08 (M^+, 65), 607 (28), 501 (1), 487 (2), 471 (3), 381 (97), 206 (9), 205 (18), 204 (22), 191 (100), 183 (13), 176 (6), 175 (10), 168 (37), 161 (10), 160 (7); high-resolution mass spectrum, *m/e* 608.28838 ($C_{37}H_{40}N_2O_6$ requires 608.28863).

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Registry No.—**1**, 55701-99-0; **2**, 55702-00-6; **3**, 55702-01-7; **4**, 55722-70-8; **5**, 55702-02-8; **6**, 55702-03-9; **6** oxalate, 55702-04-0; **7**, 5701-00-8; **7** oxalate, 55702-05-1; **8**, 5096-70-8; **9**, 6681-71-6; **9** oxalate, 55723-12-1; **5'**,13-dideuterio-o-methylpanurensine, 55722-71-9.

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A New Synthesis of 6-Substituted Benzo[a]pyrenes[1]

Melvin S. Newman* and Len-Fang Lee[2]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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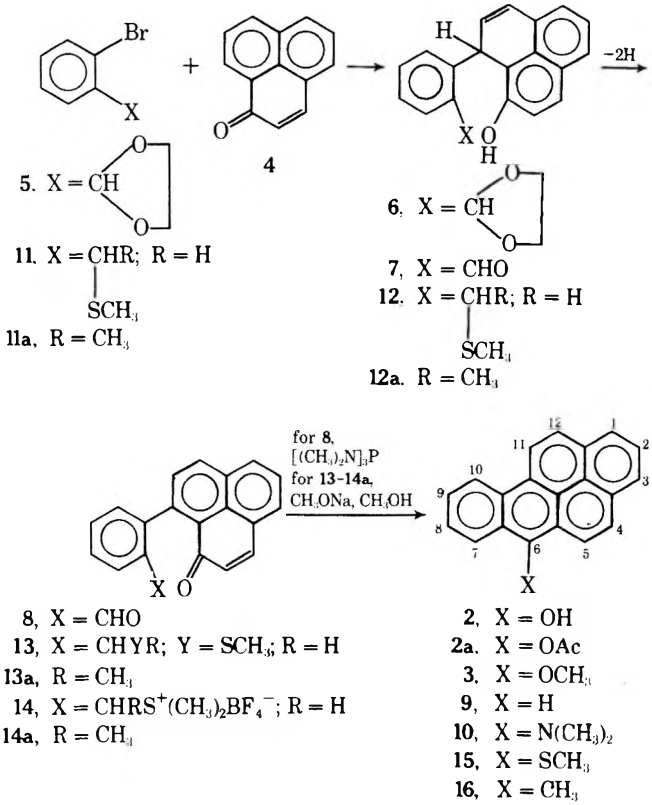
The synthesis of o-(9-phenalenonyl)benzaldehyde (8) from 2-o-bromophenyl-1,3-dioxolane (5) and phenalenone (4) is described. Treatment of 8 with tris(dimethylamino)phosphine yields small amounts of benzo[a]pyrene and 6-dimethylaminobenzo[a]pyrene (10). Treatment of 4 with lithio derivatives prepared from o-bromobenzyl methyl sulfide (11), and o-bromo-(1-methylthioethyl)benzene (11a) afforded (after oxidation of intermediate dihydro compounds) 9-[o-(methylthiomethyl)phenyl]phenalenone (13) and 9-[o-(1-methylthioethyl)phenyl]phenalenone (13a), respectively, both of which, by treatment with methyl iodide and the product with silver tetrafluoroborate, were converted into dimethyl[o-(9-phenalenonyl)benzyl]sulfonium tetrafluoroborate (14) and dimethyl[α-methyl-o-(9-phenalenonyl)benzyl]sulfonium tetrafluoroborate (14a), respectively. The reaction of 14 with sodium methoxide in methanol afforded mainly 6-acetoxybenzo[a]pyrene (2a) (on acetylation of the reaction mixture), together with smaller amounts of 6-methoxybenzo[a]pyrene (3) and 6-methylthiobenzo[a]pyrene (15).

In a preliminary communication[3] our efforts to prepare 5a,6-epoxy-5a,6-dihydrobenzo[a]pyrene (1) were outlined. Although 1 was not isolated, the formation of 6-hydroxybenzo[a]pyrene (2) and 6-methoxybenzo[a]pyrene (3) presumably involved 1 which was unstable under the reaction conditions. In this paper these and other efforts are described in more detail.

The desirability of preparing arene oxides and the methods which have been developed for their synthesis have been reviewed.[4] The importance of these epoxides in possible metabolic pathways of carcinogenic and noncarcinogenic aromatic hydrocarbons formed the subject of a symposium.[5] However, no analog of 1 has yet been isolated.

Our first attempt at synthesis of 1 is outlined in Scheme I. The details are given in the Experimental Section.

Scheme I



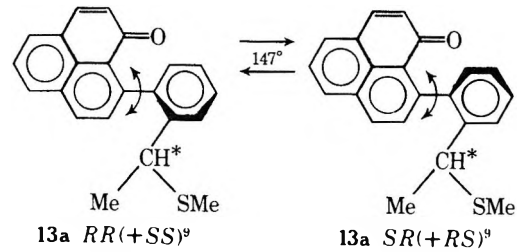
When 8 was treated with tris(dimethylamino)phosphine (TDP) in an attempt to extend the synthesis of epoxides previously developed here,[6] a small yield (32%) of benzo[a]pyrene 9 was obtained. Under slightly different conditions a small yield of 6-dimethylaminobenzo[a]pyrene 10 was obtained. No effort was made to improve either of these yields.

The next attempt to prepare 1 is outlined in Scheme I. The final ring closure was an attempt to apply a previous intermolecular epoxide synthesis[7] to an intramolecular situation.

In the reactions of the lithium derivative formed from 11 both dihydro product, 12, and oxidized product, 13, are produced. By an oxidative work-up (heating with quinone) all 12 can be converted into 13. As described previously,[3] when 14 was treated with methanolic sodium methoxide and the reaction product acetylated by treatment with acetic anhydride there were isolated 66% of 2a, 10% of 3, and 10% of 15. A rationalization for the formation of 2 and 3 involving the formation of the epoxide 1 has been presented.[3] When lithium methoxide was used in acetonitrile–methanol, 68% of 2a and 14% of 15 were isolated.

In the hope that an epoxide of type 1 might be more stable if the hydrogen in the 6 position were replaced by a methyl group, we prepared the series of compounds, 11a–14a, by starting from 11a. Interestingly, yields of 12a (17%) and 13a (52%) were obtained when reaction of the lithio derivative of 11a with 4 was carried out at −60 to −50°. However, when the reaction was run at 0° neither 12a nor 13a could be isolated from the mixture of products formed. A small yield of 6-methylbenzo[a]pyrene[8] (16) was the only crystalline product obtained.

In attempting to purify 13a by crystallization it was noted that a form, mp 146–147°, could be isolated. On melting and resolidification of this material the melting point fell to 131–135°. The higher melting point form showed only one doublet at δ 1.37 for a C-methyl group in the NMR, whereas the lower melting form showed two C-methyl doublets. We interpret these facts by assuming that the 146–147° form represents one of the two diastereomeric racemates possible, since there are two sources of chirality in the molecule: one due to the asymmetric carbon, and one due to biphenyl-type isomerism, as shown below. At the



melting point, rotation about the biphenyl bond results in the formation of a mixture of the two racemates.[10] We thank Dr. K. Mislow for providing the references cited.[10]

The 147° isomer of **13a** was readily converted into **14a** but all efforts to cyclize this to a derivative of benzo[a]pyrene gave such mixtures of products that work in this area was abandoned.

Experimental Section[11]

2-o-Bromophenyl-1,3-dioxolane (5). A mixture of 86 g of o-bromobenzaldehyde and 1 g of toluenesulfonic acid in 80 g of ethylene glycol and 200 ml of benzene was refluxed for 18 hr, water being removed as formed, to yield 74 g (81%) of **5**, bp 102–106° (0.5 mm) [lit.[12] bp 126–127° (5 mm)].

2-[(o-1*H*,9-Hydroxyphenalen-1-yl)phenyl]-1,3-dioxolane (6).* A Grignard reagent was prepared from 2.9 g of mg, 7.6 g of ethylene dibromide, and 19 g of **5** in 150 ml of THF. This Grignard reagent was cooled to −30° under N_2 and treated with a solution of 9.0 g (0.05 mol) of **4** in 50 ml of THF during 5 min. The mixture was held at −30 to −10° for 1 hr and then treated with excess saturated aqueous NH_4Cl. After a conventional work-up, crystallization from benzene–hexane afforded 11.5 g (70%) of **6**, mp 173–175°, suitable for further use. Additional recrystallization from benzene–hexane yielded the analytical sample: mp 176–177°; ir (KBr) 3280 cm^{-1}; NMR (DMSO-d_6) δ 4.05 (s, 4, $-CH_2-$). 5.52 (br, 1, CHCH=CH), 6.06 (d of d, 1, J = 10 and 5 Hz, CHCH=CH), 6.47 (s, 1, OCHO), 6.50–7.58 (m, 10, ArH and CHCH=CH), 9.60 (s, 1, OH). When a similar reaction was carried out in THF at reflux a mixture of many products was obtained from which only an 8% yield of benzo[a]pyrene (**9**), mp 176–177°, was isolated. The uv spectrum agreed with that given previously.[13]

In a reaction involving 3.4 g of **5** and 0.85 g of **4** in THF at −30 to −10° as above, hydrolysis with dilute HCl instead of NH_4Cl yielded 0.75 g (55%) of o-(1*H*,9-hydroxyphenalen-1-yl)benzaldehyde (**7**),* mp 171–174°, suitable for further work. The analytical sample, mp 173–174°, was obtained by recrystallization from benzene–hexane: ir (KBr) 3340 (OH), 1670 cm^{-1} (CO); NMR (DMSO-d_6) δ 5.97–6.49 (m, 2, CHCH=CH), 6.70 (d of d, 1, J = 10 and 1 Hz, CHCH=CH), 9.77 (s, 1, OH), 10.67 (s, 1, CHO).

o-(9-Phenalenonyl)benzaldehyde (8).* In a typical experiment, a mixture of 200 mg of **7**, 400 mg of benzoquinone,[14] and 10 ml of benzene was held at reflux for 30 min. After the usual work-up, which included washing with saturated $Na_2S_2O_4$ and with 10% NaOH, there was obtained 180 mg (90%) of yellow **8**, mp 125–126°. Recrystallization from benzene–EtOH yielded the analytical sample: mp 125.5–126.5°; ir (KBr) 1680, 1630 (CO), 1618 cm^{-1} (C=C), 5.95 μ; NMR ($CDCl_3$) δ 6.45 (d, 1, J = 10 Hz, CH=CHCO), 7.10–8.18 (m, 10, ArH, CH=CHCO), 9.79 (s, 1, CHO).

Benzo[a]pyrene (9) and 6-Dimethylaminobenzo[a]pyrene (10).* A mixture of 50 mg of **8**, 200 mg of tris(dimethylamino)phosphine (TDP), and 5 ml of benzene was refluxed for 1 hr and worked up as usual. The only crystalline product isolated by chromatography over alumina was **9** (3 mg, 6%), mp 176–178°, not depressed by mixing with authentic **9**. When a similar mixture was refluxed in o-dichlorobenzene for 24 hr a 32% yield of **9** was obtained. When 1.5 mmol each of **8** and TDP in o-dichlorobenzene were stirred for 7 days and refluxed for 24 hr, chromatography on alumina using benzene yielded a first fraction (R_f 0.75 on silica gel plate) as a yellow oil which afforded a brown picrate (14%), mp 170–172°. The picrate was chromatographed on alumina to yield a yellow solid which was unstable to heat in the presence of air. On the basis of elemental and mass spectral[15] analyses (exact mass, 295.1365, calcd for $C_{22}H_{17}N$, 295.1361) the structure **10** was assigned to this compound but no further attempts were made to improve the yield or derivatize.

1-(o-Methylthiomethyl)phenyl-1*H*-phenalen-9-ol (12) and 9-[o-(Methylthiomethyl)phenyl]phenalenone (13). To the solution of o-(methylthiomethyl)phenyllithium prepared from 117 ml of 2.2 *M* n-BuLi in hexane and 57 g of o-bromobenzyl methyl sulfide (**11**) as described[16] was added at 0° 10.0 g of **4** in portions under N_2. After 2 hr at 0° and 4 hr at room temperature the mixture was refluxed overnight. The mixture was treated with dilute HCl and worked up as usual. A benzene solution of the residue yielded crystals which were recrystallized from dimethylformamide (DMF) to yield 2.5 g (25%) of an orange solid, mp 250–251° dec, which elementary* and mass spectral analyses indicated to be a dimer of phenalenone (exact mass, 358.0998, calcd for $C_{26}H_{14}O_2$, 358.0994). The remaining product from the mother liquors was chromatographed on 1 kg of silica gel. Fraction 2 [benzene–petroleum ether (bp 30–60°) (1:4)] gave a mixture of a solid and an oil. Recrystallization from benzene–petroleum ether (bp 60–100°) yielded 3.0 g (17%) of **12:*** mp 147.0–148.5°; ir (KBr) 3200 cm^{-1}; NMR ($CDCl_3$) δ 2.09 (s, 3, SCH_3), 3.74 and 4.02 (AB q, 2, J = 16.7 Hz, CH_2), 5.51 (d of d, 1, J = 4 and 2 Hz, CHCH=CH), 5.93 (d of d, 1, J = 10 and 4 Hz, CHCH=CH), 6.55 (d of d, 1, J = 10 and 2 Hz, CHCH=CH), 6.50 (s, 1, OH), 6.90–8.20 (m, 9, ArH). Fraction 4 [benzene–petroleum ether (bp 30–60°) (4:1)] yielded 2.6 g (16%) of orange prisms of **13:*** mp 149–150°; ir (KBr) 1630 and 1618 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (s, 3, SCH_3), 3.41 and 3.52 (AB q, 2, J = 16 Hz, CH_2), 6.60 (d, 1, J = 10 Hz, COCH=CH), 7.02–8.25 (m, 10, COCH=CH, ArH).

A solution of 1.97 g of **12** and 4 g of benzoquinone in 40 ml of benzene was held at reflux for 20 min; the solution was washed with saturated sodium dithionate and 18% NaOH and worked up as usual. Recrystallization from benzene yielded 86% of **13**. In general it was better to chromatograph reaction mixtures obtained by reaction of o-(methylthiomethyl)phenyllithium with **4** *before* any attempt to oxidize the **12** present with quinone because chromatographic separation of **13** and **4** is difficult.

Dimethyl[o-(9-phenalenonyl)benzyl]sulfonium Tetrafluoroborate (14). After a solution of 1.00 g of **13** and 6.6 g of methyl iodide in 20 ml of acetonitrile was stirred at 20–25° for 30 min, 0.56 g of $AgBF_4$ was added and stirring was continued for 3 hr. The mixture was filtered and AgI was washed with solvent. After removal of about ⅔ of the solvent by rotary evaporation, addition of EtOH afforded 1.15 g (90%) of yellow **14**: mp 197–199° dec; ir (KBr) 1630 and 1618 cm^{-1}; NMR (DMSO-d_6) δ 2.71 and 2.80 [two s, 6, $(CH_3)_2S^+$], 4.46 and 4.62 (AB q, 2, J = 14 Hz, CH_2), 6.60 (d, 1, J = 10 Hz, COCH=CH), 7.05–8.60 (m, 10, COCH=CH, ArH). As **14** is unstable on heating it is best not to recrystallize before proceeding to the next step.

6-Acetoxybenzo[a]pyrene (2a), 6-Methoxybenzo[a]pyrene (3), and 6-Methylthiobenzo[a]pyrene (15). To the CH_3ONa solution prepared from 1.0 g of Na and 20 ml of MeOH was added a solution of 0.60 g of **14** in 10 ml of CH_3CN and 10 ml of benzene. The mixture was stirred under N_2 for 3 hr, when a TLC analysis on silica gel pretreated with triethylamine using benzene–EtOAc (1:9) showed a major spot (R_f 0.33), which corresponded to known 6-hydroxybenzo[a]pyrene (**2**). Since **2** is known to be somewhat unstable toward chromatography,[17] the crude mixture was treated with 10 ml of Ac_2O and the product was isolated as usual and chromatographed over 70 g of silica gel. Fraction 1 [ether–petroleum ether (bp 30–60°) (1:99)] on crystallization from petroleum ether (bp 60–100°) yielded 40 mg of **15,*** mp 168.5–169.0° (lit.[18] mp 169–170.5°). The second fraction, obtained with the same eluent, was rechromatographed over silica gel as above to yield an additional 8 mg of **15** (total yield 10%) followed by a fraction which yielded 45 mg (10%) of **3**, mp 173–174° (lit.[19] mp 174–175°). From the third fraction [ether–petroleum ether (bp 30–60°) (1:4)] was isolated 268 mg of pure **2a**, mp 208–209°, not depressed by mixing with an authentic sample.[8] When 0.62 g of **14** in 25 ml of CH_3CN and 40 ml of benzene was treated for 2 hr at 15–20° with MeOLi prepared by treating 0.5 g of Li with 40 ml of MeOH, a work-up similar to that described above yielded 14% of **15** and 67% of **2a**. The use of Me_2SO or CH_3CN in treatment of **14** with bases gave smaller yields of the same products.

o-Bromo(1-methylthioethyl)benzene (11a). A mixture of 96.5 g of o-bromoethylbenzene,[20] bp 68–70° (8 mm), 93 g of *N*-bromosuccinimide, 1 g of benzoyl peroxide, and 250 ml of CCl_4 was held at reflux for 2 hr. After a conventional work-up the residue was added to a solution made by treating 29 g of CH_3SH with the MeONa prepared by treating 12 g of Na with 250 ml of MeOH. After refluxing for 30 min and the usual work-up there was obtained 103 g (86%) of **11a,*** bp 84–85°, on fractionation through a 30-in. Widmer column topped with a total-reflux partial take-off head.

1-[o-(1-Methylthioethyl)phenyl]-1*H*-phenalen-9-ol (12a) and 9-[o-(1-Methylthioethyl)phenyl]phenalenone (13a). A solution of 13.0 g of **11a** in 30 ml of dry ether was added during 10 min to 23 ml of 2.2 *M* n-BuLi in hexane and 0°. After stirring at 0° for 30 min the solution was cooled to −60° and treated with 8.0 g of **4** in portions and the mixture was held at −60 to −50° for 40 min and poured into dilute HCl. After standing at 15–20° overnight, 3.3 g of a yellow solid, mp 170–178°, had separated and was collected. Crystallization from benzene–petroleum ether (bp 30–60°) yielded 2.5 g (17%) of light yellow **12a:** mp 177–179°; ir (KBr) 3300 cm^{-1} (OH); NMR (DMSO-d_6) δ 1.64 (d, 3, J = 7 Hz, $CHCH_3$), 1.93 (s, 3, SCH_3), 4.81 (q, 1, J = 7 Hz, $CHCH_3$), 5.59 (br,

1, CHCH=CH), 6.06 (d of d, 1, J = 10 and 5 Hz, CHCH=CH), 6.66 (d of d, 1, J = 10 and 2 Hz, CHCH=CH), and 6.85–6.70 (m, 9, ArH).

The filtrate from the above yellow solid and the mother liquors from recrystallization were combined and worked up as usual. The organic product was chromatographed over 400 g of alumina. From the second fraction eluted with benzene–ether (4:1) was obtained 7.6 g (52%) of orange solid, mp 121–128°. On recrystallization from benzene–petroleum ether (bp 60–100°) and four times from benzene–ethanol a portion of **13a**, mp 146.0–147.5°, ir (KBr) 1630, 1610 cm^{-1}, was obtained. However, after the melting point had been taken the remelting point was 131–135°. The NMR of the 147° form in $CDCl_3$ showed the following: δ 1.37 (d, 3, J = 6 Hz, $CHCH_3$), 1.83 (s, 3, SCH_3), 3.32 (q, 1, J = 6 Hz, $CHCH_3$), 6.60 (d, 1, J = 10 Hz, CH=CHCO), and 7.10–8.25 (m, 10, ArH, CH=CHCO). The lower melting samples of **13a** showed two doublets ($CHCH_3$) at δ 1.37 and 1.47, the remaining NMR spectrum being similar to that of the high-melting **13a**. When the lithio derivative of **11a** was treated with **4** at 0° only 45% of **16**[8] was isolated.

Dimethyl[α-methyl-*o*-(9-phenalenonyl)benzyl]sulfonium Tetrafluoroborate (14a). In a reaction of **13a** (820 mg) with CH_3I, etc., entirely similar to that for the conversion of **13** to **14**, except that the reaction with CH_3I was run for 2 hr, there was obtained 850 mg (80%) of **14a**,* mp 218–220° dec, having the expected ir and NMR spectra. All attempts to obtain benzo[*a*]pyrene derivatives by treatment of **14a** with CH_3ONa in MeOH failed to yield appreciable amounts of any pure substance.

Registry No.—**4**, 548-39-0; **5**, 34824-58-3; **6**, 55669-59-5; **7**, 55669-60-8; **8**, 55669-61-9; **9**, 50-32-8; **10**, 55669-62-0; **10** picrate, 55669-63-1; **11**, 19614-11-0; **11a**, 55669-64-2; **12**, 55669-35-3; **12a**, 55669-66-4; **13**, 52288-10-5; **13a** isomer 1, 55669-67-5; **13a** isomer 2, 55721-20-5; **14**, 52288-12-7; **14a**, 55669-69-7; ethylene dibromide, 106-93-4; tris(dimethylamino)phosphine, 1608-26-0; o-(methylthiomethyl)phenyllithium, 52288-09-2; phenalenone dimer, 55669-48-2; $AgBF_4$, 14104-20-2; *o*-bromoethylbenzene, 1973-22-4.

References and Notes

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Alkaline Hydrolysis of Cationic Di- and Trimethylthiopurines

Felix Bergmann,* Miriam Rahat, Uri Reichman, and Ilana Tamir

Department of Pharmacology, The Hebrew University—Hadassah Medical School, Jerusalem, Israel

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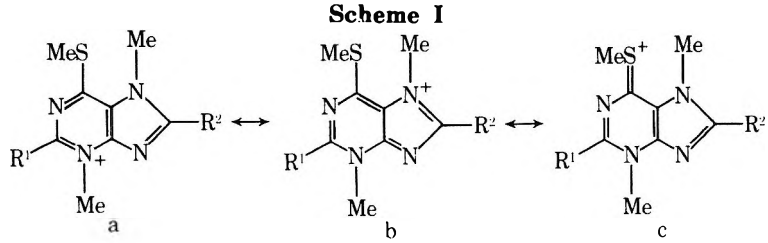
Di- and trimethylthiopurines, which bear two *N*-methyl substituents, exist as resonating cations in which the charge spreads over both rings. Alkali hydrolyzes the methylthio groups in a fixed order, which for 3,7-dimethyl-2,6,8-trimethylthiopurinium cation is 2, 6, 8. Hydrolysis of dimethylthiopurinium cations follows the same order.

In a previous study on di- and trimethylthiopurines it was found that those derivatives, which can form anions, are not attacked by alkali. On the other hand, the *N*-methyl homologs exist above pH 7 only as neutral molecules and thus can be hydrolyzed, the sequence of the reaction being determined by the position of the *N*-alkyl group.[1] It was assumed that the polarized form of the latter creates a positive center which directs the hydroxyl ion to the nearest SMe-substituted carbon atom.

Di- and trimethylthiopurines bearing two *N*-alkyl substituents are resonating cations (Scheme I), their structure being independent of pH in the range 0–14. Consider, for

Scheme I



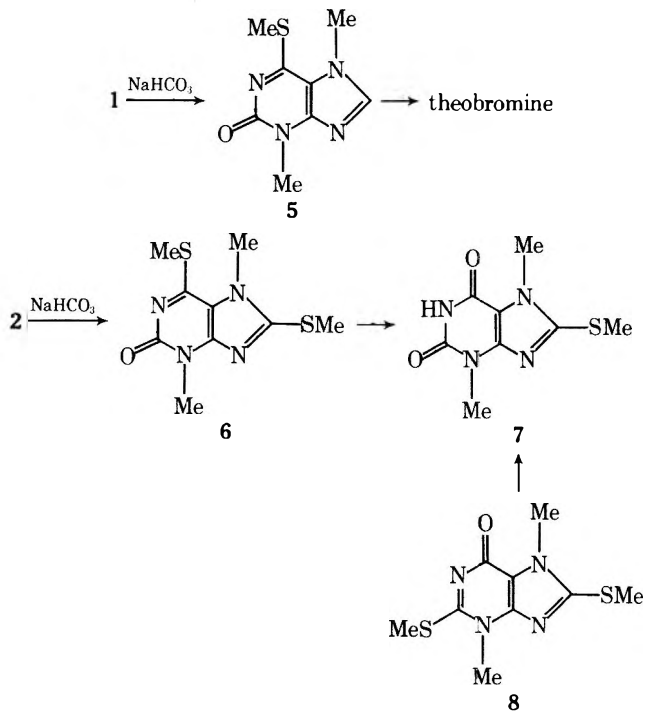
1, R^1 = SMe; R^2 = H
2, R^1 = R^2 = SMe
3, R^1 = H; R^2 = SMe

instance, the three mesomeric forms of 3,7-dimethyl-2,6,8-trimethylthiopurinium cation **2**. Form a would lead to alkaline hydrolysis of the 2-SMe group; in mesomer b, the 8-methylthio substituent should be replaced first; and in c attack should be directed toward position 6. Similarly in 3,7-dimethyl-2,6-dimethylthiopurinium cation **1**, OH^- should attack mesomer a at the 2–3 bond to cause hydrolysis of the 2-SMe group, while in form c nucleophilic substitution should involve position 6. In mesomer b of **1**, OH^- may be directed, inter alia, toward the 6–7 region and thus may again split off the 6-SMe group. This possibility is suggested by the observation that a 7-methyl group in 2,6-dimethylthiopurine directs attack to position 6.[1] Finally, in 3,7-dimethyl-6,8-dimethylthiopurinium cation **3** we may expect attack at position 8 for mesomer b and at C-6 for mesomer c (see Scheme I). However, in this case, predictions about mesomer a are ambiguous because of the remoteness of the positive center from the SMe-substituted positions.

The question arises whether nucleophilic attack will take simultaneously two (or three) different courses or whether a specific resonance form of the cations **1–3** will be preferred in the transition state.

We have observed that in compounds **1** and **2**, position 2 is attacked by alkali to yield **5** and **6**, respectively (Scheme II), indicating preference of mesomer a, containing an aromatic pyrimidine ring. In these two cases, very mild conditions had to be used to avoid further reactions. Thus in 2 *N* NaOH, **5** was converted to theobromine and **6** to the xanthine derivative **7**[2] (Scheme II).

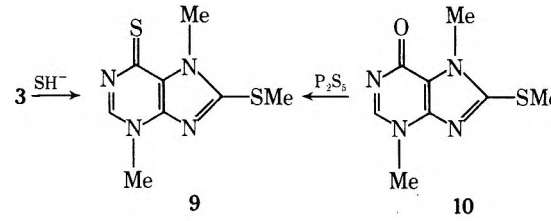
Scheme II



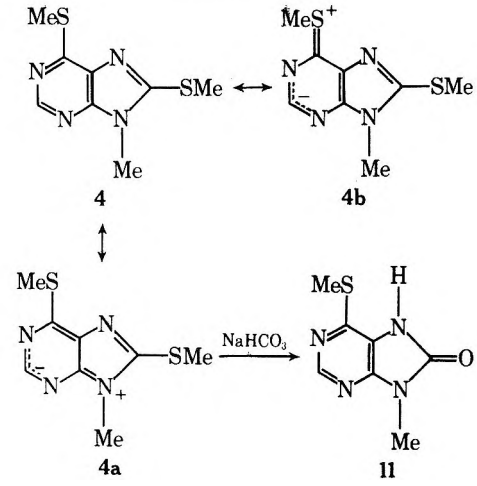
Hydrolysis of **3**, even under very cautious conditions, led to degradation products, presumably by ring opening. We have used instead thiohydrolysis, which converts **3** quantitatively into 3,7-dimethyl-8-methylthio-6-thioxopurine (**9**, Scheme III). Thus in **2**, the methylthio group at position 2 is most susceptible to nucleophilic attack. When this substituent is removed, as in **3**, then the 6-methylthio group exhibits the greater reactivity. Thus the overall sequence of reactivities in **2** is **2**, 6, 8, just as in 3-methyl-2,6,8-trimethylthiopurine.[1]

We have also found that in 9-methyl-6,8-dimethylthiopurine (**4**), the 8-methylthio group undergoes hydrolysis by hot sodium bicarbonate to yield **11**[3] (Scheme IV). This shows that attack at C-8 is definitely possible; the direction of nucleophilic attack is determined by the 9-methyl substituent, i.e. the mesomeric effect of the NMe group (**4a**) is more powerful than that of the SMe substituent (**4b**).

Scheme III



Scheme IV



Identification of Reaction Products. 3,7-Dimethyl-6-methylthio-2-oxopurine (**5**)[4] and 9-methyl-6-methylthio-8-oxopurine (**11**)[3] are known compounds. The structure of **6**[2] can be derived (a) from comparison of its uv spectrum with that of 3-methyl-6,8-dimethylthio-2-oxopurine[1] (Table I); and (b) from the fact that both **6** and its isomer, 3,7-dimethyl-2,8-dimethylthiohypoxanthine (**8**),[2] are hydrolyzed to the same xanthine derivative **7**[2] (Scheme II). Since the structure of **8** has been established before,[5] this conversion confirms the structure assigned to **6**. It should also be noted that introduction of a 2-oxo group shifts the 3-Me signal from 4.22 in **3** to 3.70 ppm in the cation of **6** (Table I), while the 7-Me substituent is shielded only little.

3,7-Dimethyl-8-methylthio-6-thioxopurine (**9**) was identical with the product resulting from thiation of 3,7-dimethyl-8-methylthiohypoxanthine (**10**)[6] (Scheme III).

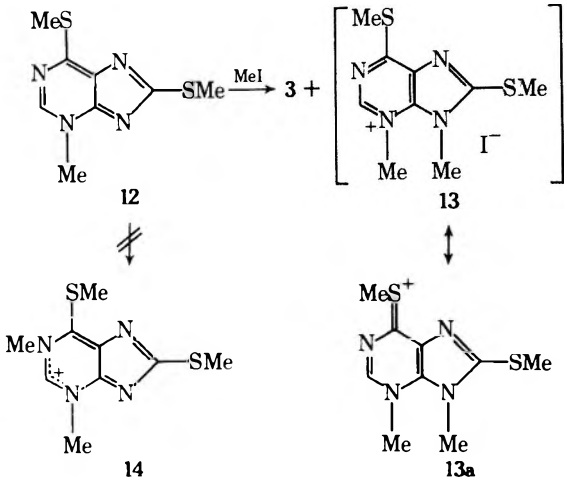
Observations on the Methylation of 3-Methyl-6,8-dimethylthiopurine (12). Methylation of **12** gave a mixture, from which pure **3** was isolated as the main product. The water-insoluble portion contained, inter alia, a small amount of an isomer, identified as the 3,9-dimethyl derivative **13** (Scheme V). The NMR spectrum of either compound showed two NMe and two SMe bands (Table I). Neither in **3** nor in **13** can the new *N*-methyl group be located at N-1 because formation of the "fixed cation" **14**[7] would move the 2-H signal downfield by about 1 ppm[8,9]. Such a large shift of the 2-H band is observed, e.g., for protonation of **9**, $\Delta\delta(\text{N–C})_{2H}$ = 0.99 ppm (see Table I and Scheme VI, **9d**). However the actual displacement of δ_{2H} for the transition **12** (neutral form) → **3** is only 0.33, and for the conversion **12** (neutral form) → **13**, 0.59 ppm. It should also be noted that protonation of **12** leads to $\Delta\delta$(N–

Table I
Comparison of Spectral Data for Structure Determination of Reaction Products

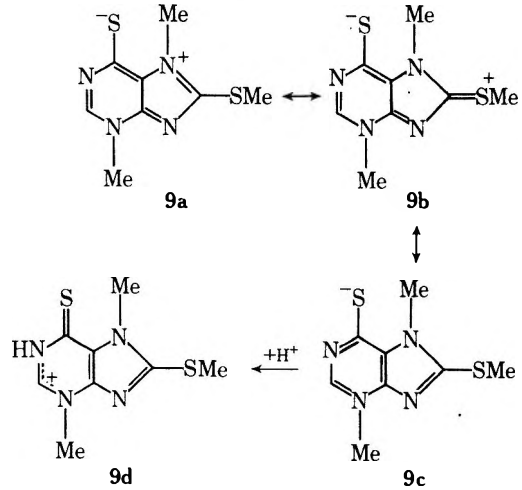
Compd	Molecular form used	λ_{max}, nm	2-H	δ, ppm[a] NMe		SMe		
A. 6,8-Dimethylthiopurines								
3-Methyl- (**12**)	N	259, 340	8.68	4.11		(6) 2.82	(8) 2.74	
	C	259, 285, 340	9.10	4.22		2.89	2.89	
9-Methyl- (**4**)	N		8.81	3.50		(6) 2.85	(8) 2.78	
	C	248, 331	9.02	3.97		2.95	3.12	
3,7-Dimethyl- (**3**)	C	258, 290, 343	9.01	(3) 4.22	(7) 4.02	(6) 2.89	(8) 2.84	
3,9-Dimethyl- (**13**)	C	*b*	9.27	(3) 4.54	(9) 4.24	(6) 2.94	(8) 3.15[c]	
B. 2,6-Dimethylthiopurines								
3,7-Dimethyl- (**1**)	C	332	8.88	(3) 4.27	(7) 4.16	(2) 2.99	(6) 2.99	
3,7-Dimethyl-8-methylthio- (**2**)	C	227, 294, 358		(3) 4.11	(7) 4.08	(2) 2.97	(6) 2.97	(8) 2.97
C. Oxo Derivatives								
3,7-Dimethyl-6-methylthio-2-oxopurine (**5**)	N	272, 319		(3) 3.56	(7) 4.06	2.69		
	C	258, 343		3.75	4.12	2.85		
3-Methyl-6,8-dimethylthio-2-oxopurine	N	342		3.52		(6) 2.65	(8) 2.61	
	C	279, 370		3.78		3.02	2.91	
3,7-Dimethyl-6,8-dimethylthio-2-oxopurine (**6**)	N	340		(3) 3.65	(7) 3.95	(6) 2.87	(8) 2.70	
	C	285, 373		3.70	3.96	2.92	2.88	
9-Methyl-6-methylthio-8-oxopurine (**11**)	N	224, 297.5	8.66	3.52		2.76		
	C	237, 320.5	8.96	3.63		2.93		
3,7-Dimethyl-8-methylthio-6-thioxopurine (**9**)	N	270, 357	8.44	(3) 3.94	(7) 4.33	2.88		
	C	273, 367	9.43	4.11	4.02	2.88		

[a] All measurements in D_2O at 70°. Figures in parentheses indicate the assignment of the signals to a specific methyl group. Assignment of the SMe signals is based on comparison with known compounds, in which unequivocal identification of these bands was possible, and is thus arbitrary. [b] This substance was not isolated in pure form. The NMR spectrum was determined with the impure product, containing small amounts of 3. [c] This assignment is based on the assumption that the neighboring 9-methyl substituent deshields the 8-SMe group as in the cation of 4. However, 13 cannot form a mesomer like 4B in Scheme VII. On the other hand, 13a (Scheme V) represents a possible resonance form of this cationic purine. Therefore the low-field signal of 3.15 ppm may actually belong to the 6-SMe group.

Scheme V



Scheme VI



$C)_{2H}$[10] = 0.42 (Table I), indicating again formation of a resonating cation, similar to forms a–c in Scheme I, by protonation at N-7. Thus alkylation and protonation of 12 take a similar course.

The above conclusions are supported by measurement of the nuclear Overhauser effect (NOE). Irradiation of 3 with the frequency of its 3-Me band (δ 4.22) causes a 40% increase in the area underneath the 2-H signal, while use of the 7-methyl frequency has no marked effect. For the same reason, only one NMe group (δ 4.54) in 13 can neighbor 2-H (NOE 50%). It is concluded that 3 and 13 can only be the 3,7- and 3,9-dimethyl derivatives. Since the structure of 3 is established by its thiohydrolysis to compound 9, 13 must be the 3,9 isomer. This assignment receives further support from comparison of the δ_{3Me} and δ_{9Me} values of 13 with those of its congeners 12 and 4 in their protonated forms (Table I). The two *N*-methyl signals are shifted downfield in 13 by 0.32 and 0.27 ppm, respectively, in accordance with earlier observations on other 3,9-dimethylated purines.[8,11] On the other hand, in the 3,7-dimethyl derivatives, the presence of a second NMe substituent has very little influence on the position of a given *N*-methyl band (compare, e.g., the δ_{3Me} values of 3 and of the cation of 12).

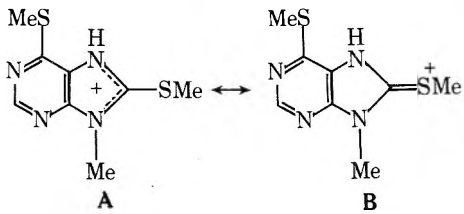
If the second methylation product of 12 were the fixed 1,3-dimethyl cation 14 (Scheme V), we should expect rapid H–D exchange of 2-H upon dissolution in D_2O.[12,13] The ab-

Table II
Alkaline Hydrolysis of Methylthiopurines and Physical Constants of the Products Formed

No.	Compd used	Alkaline hydrolysis[a] Time, min	Temp, °C	Product[b] formed	Mp or dec, °C	Solvent for crystn	Crystal form	R_f[c]	Fluorescence[d]
1	3,7-Dimethyl-2,6-dimethylthiopurinium cation	20	90	5[e]	300	Water	Needles		Violet
2	3,7-Dimethyl-2,6,8-trimethylthiopurinium cation	20	90	6	225–226	Ethanol	Needles	(B) 0.69	Violet
3	3,7-Dimethyl-6,8-dimethylthiopurinium cation[f]	30	0	9	295	Water	Rods	(A) 0.72 (B) 0.73 (C) 0.71	Yellow
4	9-Methyl-6,8-dimethylthiopurine	180	100	11[g]	272	1-Butanol	Rectangular plates	(B) 0.75 (C) 0.75	Light blue

[a] For the method used see Experimental Section. [b] The new compounds 6 and 9 gave satisfactory analyses of C, H, N, S. [c] For solvents A, B, and C see Experimental Section. [d] Under a Mineralight uv lamp. [e] See ref 14. [f] This compound underwent thiohydrolysis to 9. [g] See ref 3.

Scheme VII
Cation of 4



sence of such an effect is satisfactorily explained by the 3,9-dimethyl structure.

The steric interference between the two *N*-methyl groups in **13** presumably is responsible for the marked deshielding of the 8-SMe substituent (see Table I).

The relative proportion of **3** and **13**, resulting from methylation of **12**, shows that electrophilic attack at N-7 is much faster than at N-9, i.e., the combined steric effect of 3-Me and 8-SMe is much stronger than the combined influence of the 6- and 8-SMe substituents.

NMe and SMe Signals in the NMR Spectra (Table I). The NMR spectra of **3** and of the cation of **12** are very similar, indicating protonation of the latter at N-7, as mentioned above. In the cation of **12**, $\Delta\delta$(N–C) of 3-Me = 0.11 and 8-SMe = 0.15 ppm. **4** also attaches a proton at N-7, but this process displaces the 9-Me signal downfield by 0.47 ppm and the 8-SMe band by 0.34 ppm. As shown in Scheme VII, the cation of **4** bears a fixed charge in the imidazole ring. Here the resonance form B may be responsible for the considerable deshielding of the 8-methylthio group; a similar canonical form cannot be formulated for **13**.

In the cation **9d**, the 7-methyl signal is shifted *upfield* by 0.31 ppm. This surprising change may be explained by inspecting Scheme VI. Protonation at N-1 creates a fixed charge in the pyrimidine moiety and thus eliminates any participation of 7-NMe^+ (as, e.g., in **9a**) in the polarized forms of the neutral molecule.

Assignment of the 3- and 7-methyl signals in the compounds used was based on NOE, whenever the two signals were sufficiently apart. Furthermore, in **9**, the 3-methyl band was broader and of lower amplitude than the 7-methyl signal, both in the neutral form and in the cation. This effect is due to splitting of the 3-Me signal by the neighboring 2 hydrogen.

Experimental Section

All melting points are uncorrected. Microanalyses were performed by F. Strauss, Oxford, England. For chromatography on Whatman paper No. 1 by the descending method, the following solvents were used: A, 1-butanol–acetic acid–water (12:3:5 v/v); B, 2-propanol–DMF–concentrated ammonia (13:5:2 v/v); C, ethanol–DMF–water (3:1:1 v/v). Spots were located by their fluorescence under a Mineralight uv lamp (λ ~254 nm).

Uv spectra were measured on a Hitachi Perkin-Elmer Model 124 spectrophotometer, and NMR spectra on a Jeol MH-100 instrument, using TSP (sodium 3-trimethylsilylpropionate-*2,2,3,3-d*$_4$ of Merck Sharp and Dohme, Canada) as internal standard. Unless stated otherwise, NMR measurements were carried out in $(CD_3)_2SO$–D_2O (9:1) at 70°.

General Procedure for Hydrolysis of Methylthiopurines. A suspension of the purine was stirred and, if necessary, heated with an aqueous solution of sodium bicarbonate. The precipitate was removed by filtration and purified, as indicated in Table II; yield 80–90%. In the case of hydrolysis of **4**, the product **11** was soluble at pH 8 and was precipitated by addition of acetic acid.

Purines. The following compounds were prepared by known methods: **1**,[1] **2**,[1] **5**,[14] **7**,[2] **8**,[2] **11**,[3] and **12**.[9]

I. Synthesis of 3,7-Dimethyl-6,8-dimethylthiopurinium Cation 3 and Its 3,9-Dimethyl Isomer 13. A suspension of 3-methyl-6,8-dimethylthiopurine (**12**, 0.5 g) in acetonitrile (50 ml) was stirred and refluxed with methyl iodide (3 ml) for 3 hr. The solvent was removed in vacuo and the residue was stirred with water for 15 min.

A. The water-soluble portion was lyophilized and the residue was converted into the picrate of **3**: yellow cubes (ethanol); 0.5 g, mp 177°; λ_{max} (pH 0) 258, 290, 342 nm (log ϵ_{max} 4.33, 4.19, 4.61); R_f (A) 0.68, (C) 0.60.

Anal. Calcd for $C_{15}H_{15}N_7O_7S_2$: C, 38.4; H, 3.2; N, 20.9; S, 13.6. Found: C, 38.4; H, 3.2; N, 20.8; S, 13.4.

B. From the red, water-insoluble portion, a second product **13** was separated by paper chromatography. Its NMR spectrum was determined (Table I), but the amount was insufficient for purification and analysis.

Thiohydrolysis of 3 to 9. 3 (100 mg) was dissolved at 0° in concentrated ammonia that had been saturated with hydrogen sulfide; H_2S gas was bubbled through the solution for another 30 min. The precipitate (**9**) that had formed (50 mg, 80%), was purified by paper chromatography and then recrystallized from water as yellow rods, mp 295° (see Table II).

The chromatogram revealed the presence of small amounts of a second product, λ_{max} (pH 0) 250, 373 nm; (pH 6) 282, 372 nm; R_f (A) 0.30, (B) 0.60; orange fluorescence. The spectral data resemble those of 3-methyl-6,8-dithiopurine.[15] Therefore the by-product of the thiohydrolysis of **3** is most probably 3,7-dimethyl-6,8-dithioxopurine.

Synthesis of 3,7-Dimethyl-8-methylthio-6-thioxopurine (9).

A solution of 3,7-dimethyl-8-methylthiohypoxanthine (**10**,[6] 100 mg) and phosphorus pentasulfide (200 mg) in pyridine (10 ml) was refluxed for 30 min. The solvent was removed in vacuo and the residue was treated with boiling water for 30 min. The insoluble portion was recrystallized from water. The physical properties of this compound were identical with those of the product resulting from thiohydrolysis of **3** (see Table I).

II. Hydrolysis of 6 to 3,7-dimethyl-8-methylthioxanthine (7). A suspension of **6** in 2 *N* NaOH was stirred and refluxed for 20 min. The clear solution was acidified with acetic acid. The precipitate was identified by comparison with an authentic sample of **7**.[2]

9-Methyl-6,8-dimethylthiopurine (4). A. 9-Methyl-8-thiohypoxanthine. An intimate mixture of 5-amino-6-hydroxy-4-methylaminopyrimidine[16] (2 g) and thiourea (6 g) was heated to 250° for 45 min and then to 280° for 15 min. The cake was dissolved in dilute NaOH and the solution was neutralized with acetic acid. Repeated reprecipitation and finally recrystallization from water gave colorless needles (56%): mp >300° dec; λ_{max} (pH 1) 234 sh, 289 nm (log ϵ_{max} 4.30); R_f (B) 0.48, (C) 0.51; violet fluorescence.

Anal. Calcd for $C_6H_6N_4OS$: C, 39.6; H, 3.3; N, 30.8; S, 17.6. Found: C, 40.0; H, 3.1; N, 30.6; S, 17.3.

B. 9-Methyl-6,8-dithiopurine. A mixture of 9-methyl-8-thiohypoxanthine (5 g) and phosphorus pentasulfide (20 g) in pyridine (800 ml) was refluxed for 3.5 hr. Already after the first 20 min a homogeneous solution was obtained. After removal of the solvent in vacuo, the mixture was heated with water (150 ml) for 2.5 hr. The brown, insoluble portion was dissolved in 1 *N* NaOH and the product was precipitated by addition of glacial acetic acid. Final purification was by ammonia–acetic acid: yield 45%; mp >300° dec; λ_{max} (pH 1) 269, 357 nm (log ϵ_{max} 4.47, 4.42); λ_{max} (pH 8) 263, 337 nm (log ϵ_{max} 4.23, 4.39); R_f (B) 0.68, (C) 0.66; yellow fluorescence.

Anal. Calcd for $C_6H_6N_4S_2$: C, 36.4; H, 3.0; N, 28.3; S, 32.3; Found: C, 36.4; H, 3.1; N, 28.1; S, 32.35.

C. 9-Methyl-6,8-dimethylthiopurine (4). A solution of the foregoing dithio derivative (2 g) in 5% NaOH (30 ml) was stirred with methyl iodide (3 ml). After 5 min, a white precipitate formed as colorless needles (ethanol): mp 166°; yield 75%; λ_{max} (pH 0) 248, 331 nm; R_f (B) 0.83, (C) 0.75; sky-blue fluorescence.

Anal. Calcd for $C_8H_{10}N_4S_2$: C, 42.5; H, 4.4; N, 24.8; S, 28.3. Found: C, 42.5; H, 4.5; N, 25.0; S, 28.5.

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Registry No.—**1**, 55800-42-5; **2**, 55800-43-6; **3**, 55800-44-7; **3** picrate, 55800-45-8; **4**, 55800-46-9; **5**, 38759-27-7; **6**, 40848-24-6; **9**, 55800-47-0; **10**, 55800-48-1; **11**, 42930-79-0; **12**, 39008-31-6; **13**, 55800-49-2; 3-methyl-6,8-dimethylthio-2-oxopurine 39013-78-0; phosphorus pentasulfide, 1314-80-3; 9-methyl-8-thiohypoxanthine, 55800-50-5; 5-amino-6-hydroxy-4-methylaminopyrimidine, 45751-74-4; thiourea, 62-56-6; 9-methyl-6,8-dithiopurine, 55800-51-6.

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(6) Synthesis of this compound will be described in a separate publication.
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Solvolysis of *exo*- and *endo*-2-Bicyclo[3.2.0]hept-6-enyl Tosylates and the Corresponding 1,4,4- and 4,4,6-Trimethyl Derivatives. Steric and Conformational Effects on the Ring Enlargements of the Resulting Carbocations[1]

Burgess J. A. Cooke*[2]

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

Paul R. Story

Department of Chemistry, The University of Georgia, Athens, Georgia 30601

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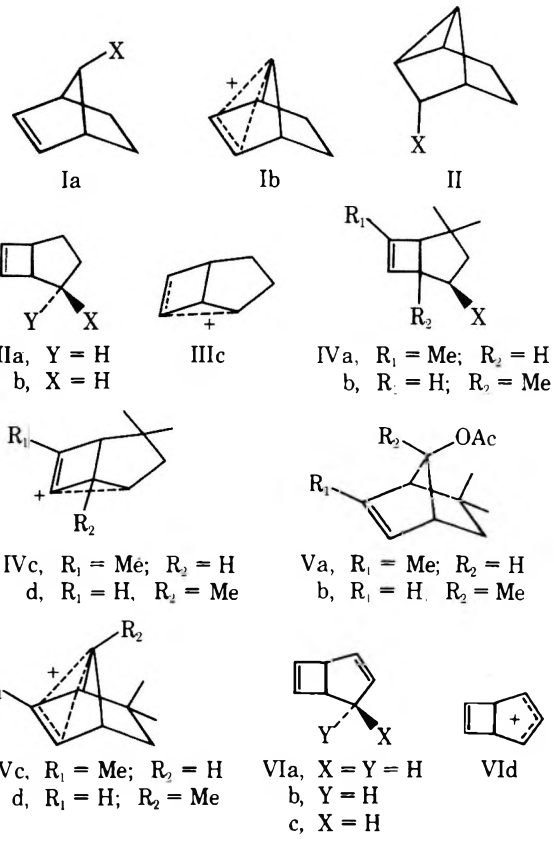
The kinetics of acetolysis and the products from solvolysis in acetic acid, aqueous acetone, and 4.0 *M* sodium methoxide in methanol of the title compounds were determined. An exo/endo rate ratio, corrected for the observed yield of products formed via a solvent-assisted pathway during acetolysis of the endo tosylate, of 2400 was observed. Solvolysis of the endo tosylate yields unrearranged exo-2-substituted and ring-enlarged products, with product ratios dependent on the nucleophilicity of the solvolysis medium. Solvolysis of the exo tosylate yields only products derivable from the ring-enlarged 7-norbornenyl cation. Acetolysis of the *exo*-1,4,4- and 4,4,6-trimethylbicyclo[3.2.0]hept-6-enyl tosylates has been shown to yield small amounts of the corresponding unrearranged exo 2-acetates. The differences in the rates for ring enlargement of the first formed cations from these solvolyses are explained in terms of steric and conformational effects.

Winstein[3] and Tufariello[4] have elegantly delineated two routes which result in direct formation of the 7-norbornenyl cation (Ib). The π route involves solvolysis of *anti*-7-norbornenyl tosylate (Ia, X = OTs)[3a,b] or treatment of the corresponding alcohol (Ia, X = OH) with fluorosulfonic acid (FSO_3H) at low temperatures.[3c,d] The other, termed the σ route, involves treatment of *endo*-tricyclo[3.2.0.0^{2,7}]hept-3-yl methyl ether (II, X = OMe) with dilute acid[3c] or FSO_3H



at low temperatures,[3d] and solvolysis of the corresponding aryl esters[3e,4] (II, X = OPNB, OPMB). In the preliminary communication[5] describing this work, we noted that SN1 solvolysis of *exo*-2-bicyclo[3.2.0]hept-6-enyl tosylate (IIIa, X = OTs) yields only products derivable from the 7-norbornenyl cation (Ib), furnishing an interesting alternate π route to this cation. Analysis of the appropriate kinetic data and relative energies of the substrates showed that the solvolytic transition states for acetolysis of IIIa and Ia, X = OTs, differ in energy by ca. 18–19 kcal/mol, showing that the new π route is not direct, and that bridged cation IIIc is probably involved as the first-formed intermediate.[5] We now present this more detailed report on the solvolysis of *exo*- and *endo*-2-bicyclo[3.2.0]hept-6-enyl tosylates (IIIa, X = OTs; IIIb, Y = OTs), noting that the data from acetolysis of the endo tosylate agrees well with those independently published by Coates[6a] and Svensson.[6b] Whitham[7] noted that acetolysis of *exo*-1,4,4- and -4,4,6-trimethylbicyclo[3.2.0]hept-6-en-2-yl tosylates (IVa, IVb, X = OTs) yields small amounts of the corresponding unrearranged exo acetates along with major proportions of the corresponding ring-enlarged acetates (Va and Vb, respectively), indicating that the exceedingly rapid ring enlargement (IIIc → Ib) noted during solvolysis of our exo tosylate (IIIa, X = OTs) is retarded by the methyl substituents to the extent that first-formed cations IVc and IVd can be trapped even in such a weakly nucleophilic medium as acetic acid before rearrangement is complete. The rather dramatic reactivity differences shown by these cations can be explained using the conformational arguments presented below.

Experimental Section

Melting points were determined using a Varian capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlabs, Inc.

Nuclear magnetic resonance (NMR) spectra were recorded using either a Varian HA-100 or A-60 nuclear magnetic resonance spectrometer on carbon tetrachloride (CCl_4) solutions (Me_4Si internal standard). Infrared (ir) spectra were recorded using either the Perkin-Elmer Model 621 or 257 recording infrared spectrophotometer. Mass spectra were recorded using a Hitachi Perkin-Elmer RMU-6E single focusing mass spectrometer.

Analytical and preparative gas chromatography (GC) separations were performed using either the Varian A-90-P3 or HiFi-III Model gas chromatographs. Columns packed with either Carbowax 20M or 1500 were found to be satisfactory for all separations described herein. Detector responses were determined prior to each analytical determination by injecting known volumes of standard solutions of *anti*-7-norbornenol (Ia, X = OH) or the corresponding acetate.

All solvents and reagents used were commercially available and not further purified, with the following exceptions. Methanol was purified by distillation from magnesium turnings, and *p*-toluenesulfonyl (tosyl) and *p*-bromobenzenesulfonyl (brosyl) chlorides were recrystallized from pentane. Pyridine was dried by distillation from barium oxide and stored over potassium hydroxide pellets.

Titrimetric rate constants for acetolysis were determined on weighed amounts of tosylates in 0.0753 *M* sodium acetate in 5% acetic anhydride in acetic acid by the ampoule method. The excess sodium acetate was back-titrated with 0.0156 *M* perchloric acid–acetic acid solutions to the Crystal Violet end point. Least-squares treatment of the data was used in the calculation.

***endo*-2-Bicyclo[3.2.0]hept-6-enyl tosylate (IIIb, Y = OTs)** was prepared in yields as high as 80% from samples of the corresponding alcohol[8] (IIIb, Y = OH) by treatment with tosyl chloride in pyridine, followed by aqueous work-up, mp 53.0–53.6° (hexane) (lit.[6a] mp 52.5–54°). Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10; S, 12.13. Found: C, 62.81; H, 6.39; S, 11.70. ν_{max}(neat) 3040, 1600, 1365, 1190, 1178, 752, 670 cm^{-1}; δ 7.47 (ab q, ArH), 4.50 (d of t, J = 6, 8 Hz), 3.09 (m, 2 H), 2.40 (s, 3 H, $ArCH_3$), 1.98 (m, 2 H), 1.40 (m, 2 H). Kinetic determinations on 100-mg samples (0.380 mmol) yielded the following values for the rate constants: $k = 1.11 \pm 0.1 \times 10^{-7}$ (50.0°), $3.60 \pm 0.1 \times 10^{-6}$ (75.03°), and $1.11 \pm 0.016 \times 10^{-4}$ sec^{-1} (106.8°).

***endo*-2-Bicyclo[3.2.0]hept-6-enyl brosylate (IIIb, Y = OBs)** was prepared in similar fashion, mp 75° (hexane) (lit.[6b] mp 76–77°). Anal. Calcd for $C_{13}H_{13}O_3BrS$: C, 47.43; H, 3.98; S, 9.74; Br, 24.27. Found: C, 47.47; H, 4.00; S, 9.85; Br, 24.50. $\nu_{max}(CCl_4)$ 3040, 1620, 1375, 1187, 1172, 718, 692 cm^{-1}. The NMR spectrum is very similar to that for the corresponding tosylate, and matches the published spectrum of Svensson.[6b]

***exo*-2-Bicyclo[3.2.0]hept-6-enyl tosylate (IIIa, X = OTs)** was synthesized in 82% yield by the same procedure used for the endo tosylate (IIIb, Y = OTs). The product was isolated as an oil. Attempts to induce crystallization from hydrocarbon failed, as did attempts to further purify the product by elution chromatography from silica gel or alumina, which resulted in bulk decomposition of the sample. The following spectral properties were noted: ν_{max}(neat) 3040, 1600, 1370, 1195, 1183, 704, 670 cm^{-1}; δ 7.46 (ab q, ArH, 4 H), 5.86 (2 H), 4.69 (d, J = 3 Hz, 1 H), 3.30 (1 H), 3.19 (1 H), 2.40 (s, 3 H), 1.2–2.1 (m, ca. 4 H). Samples of exo alcohol (IIIa, X = OH) used in this preparation were obtained by large-scale hydrolysis of exo tosylate (IIIa, X = OTs) in 50% aqueous acetone and purified by elution chromatography (silica gel, with pentane and pentane–diethyl ether mixtures as eluent). GC analysis showed these samples to be of 99% or higher purity.

Kinetic determinations were carried out on 61.5-mg (0.233 mmol) and 67.0-mg (0.254 mmol) samples of the tosylate at 50.0°. The following values were obtained for the rate constant: $k = 1.79 \pm 0.08$ and $1.99 \pm 0.13 \times 10^{-4}$ sec^{-1}.

***anti*-7-Norbornenyl tosylate (Ia, X = OTs)** was prepared in 50% yield according to the procedure of Winstein,[3a] and used without further purification.

Acetolysis of Endo Tosylate (IIIb, Y = OTs). A 264-mg sample (1 mmol) of endo tosylate was treated with 15 ml of 5% acetic anhydride–acetic acid and 0.25 g of sodium acetate in a sealed tube at 101° for 8 hr. The resulting slurry was extracted with three portions of methylene chloride, and the organic layer was dried (sodium sulfate) and concentrated to a known volume. GC analysis showed the presence of a ca. 72:28 mixture (56% yield) of *anti*-7-norbornenyl acetate (Ia, X = OAc), whose ir spectrum matched that of an authentic sample,[3a] and *exo*-2-bicyclo[3.2.0]hept-6-enyl-acetate (IIIa, X = OAc). Reduction of a portion of the crude acetate mixture with ethereal $LiAlH_4$ formed a 68:32 mixture (82% yield) of the corresponding alcohols, Ia, X = OH, mp 116–117° (lit.[3a] mp 117–118°), and IIIa, X = OH: ν_{max}(neat) 3340 (br), 3030, 1565, 1060, 738 cm^{-1}; δ 5.89 (two lines, separated by 2 Hz, 2 H),

3.94 (d, J = 3.5 Hz, 1 H), 3.26 (m, 1 H), 2.96 (m, 1 H), 1.2–2.1 (m, 4–5 H). Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 75.81; H, 9.22.

Hydrolysis of Endo Tosylate (IIIb, Y = OTs) in 50% Aqueous Acetone.[9] A 264-mg sample (1 mmol) of endo tosylate was treated with 252 mg of sodium bicarbonate and 20 ml of 50% (by volume) aqueous acetone in a sealed tube at 101° for 8 hr. After cooling, the contents were poured into saturated salt solution. The resulting slurry was extracted with three 30-ml portions of CH_2Cl_2. The organic layers were combined and washed with salt, sodium bicarbonate, and salt solutions, dried (sodium sulfate), and concentrated at reduced pressure for GC analysis, which showed the presence of a 57:43 mixture (91% yield) of anti alcohol (Ia, X = OH) and exo alcohol (IIIa, X = OH).

Basic Methanolysis of Endo Brosylate (IIIb, Y = OBs). A 100-mg sample (0.304 mmol) of endo brosylate was treated with 15 ml of 4.1 M sodium methoxide in methanol, prepared by dissolving the appropriate amount of sodium metal in methanol, in a sealed tube at 101° for 9 hr. The contents were subjected to aqueous work-up, and the resulting slurry was extracted with four 25-ml portions of hexane. Organic layers were separated and dried (sodium carbonate) and concentrated by distillation. GC analysis showed the presence of bicyclo[3.2.0]hepta-2,6-diene (VIa) (8% yield), identified by comparison of its ir spectrum with that of an authentic sample,[10] and *exo*-2-methoxybicyclo[3.2.0]hept-6-ene (IIIa, X = OMe) (78% yield): $\nu_{max}(CCl_4)$ 3030, 1100, 735 cm^{-1}; δ 5.92 (2 H), 3.48 (d, J = 3 Hz, 1 H), 3.26 (m, 1 H), 3.20 (s, 3 H), 2.98 (m, 1 H), 1.2–2.1 (m, ca. 4 H); m/e 124 (P^+), 123, 109 ($P - CH_3$), 91 (base peak).

Acetolysis of Exo Tosylate (IIIa, X = OTs). An 18.2-mg (0.069 mmol) sample of exo tosylate was treated with 20 mg of sodium acetate and 1.5 ml of 2% acetic anhydride in acetic acid under the conditions described above. GC and ir analysis of the crude product showed the presence of anti acetate (Ia, X = OAc) (81% yield) as the only GC volatile product.

Hydrolysis of Exo Tosylate (IIIa, X = OTs) in 50% Aqueous Acetone.[9] A 16.5-mg sample (0.065 mmol) of exo tosylate was treated with 50 mg of sodium bicarbonate and 1.3 ml of 50% aqueous acetone under the conditions described above for 12 hr. Analysis using GC and ir showed the presence of anti alcohol (Ia, X = OH) as the only GC volatile product (80% yield).

Basic Methanolysis of Exo Tosylate (IIIa, X = OTs). A 110-mg (0.418 mmol) sample of exo tosylate was treated with 10 ml of 4.3 M sodium methoxide in methanol at 50.0° for 8 hr. Work-up and GC analysis as described above showed the presence of four components, characterized as bicyclo[3.2.0]hepta-2,6-diene (VIa)[10] (10% yield), *anti*-7-methoxynorbornene (Ia, X = OMe) (39% yield), $\nu_{max}(CCl_4)$ 3050, 1114, 713 cm^{-1}, matching that of an authentic sample,[3c] *endo*-2-methoxybicyclo[3.2.0]hept-6-ene (IIIb, Y = OMe) (30% yield), $\nu_{max}(CCl_4)$ 3025, 1560, 1098, 734, 708 cm^{-1}, δ 5.95 (ab q, 2 H), 3.40 (q, J = 7.7 Hz, 1 H), 3.21 (s with 2 m, 5 H), 1.78 (m, 2 H), 1.36 (m, 2 H), m/e 124 (P^+), 123, 91 (base peak), and *endo*-6-methoxytricyclo[3.2.0.$0^{2,7}$]heptane (II, X = OMe) (20% yield), δ 3.66 (q, J = 3.8 Hz), matching that of an authentic sample.[3e] Yield ratio for Ia, X = OMe:II, X = OMe, is 65:35.

Basic Methanolysis of *anti*-7-Norbornenyl Tosylate (Ia, X = OTs). A 106.8-mg sample (0.405 mmol) of anti tosylate was treated with 10 ml of 4 M sodium methoxide in methanol at 50.0° for 2 hr. Usual work-up and analysis procedures showed the presence of an unidentified hydrocarbon (11% yield), *anti*-7-methoxynorbornene (Ia, X = OMe) (46% yield), and endo tricyclic ether II, X = OMe (27% yield). Yield ratio for Ia, X = OMe:II, X = OMe, is 63:37.

Results and Discussion

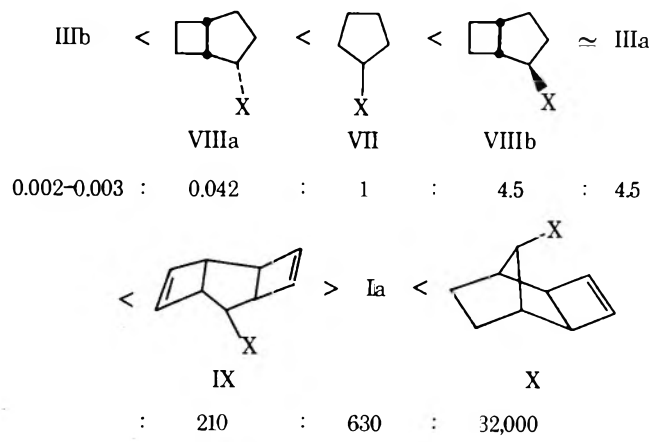
The kinetics of acetolysis of *endo*-2-bicyclo[3.2.0]hept-6-enyl tosylate (IIIb, X = OTs) were studied at three temperatures. The following results were obtained: 50.0°, k = $1.11 \pm 0.1 \times 10^{-7}$ sec^{-1}; 75.03°, k = $3.60 \pm 0.1 \times 10^{-6}$ sec^{-1}; 106.8°, k = $1.11 \pm 0.016 \times 10^{-4}$ sec^{-1}. This is in good agreement with the results of Coates[6a] (50°, k = 1.21×10^{-7} sec^{-1}; extrapolated from data at higher temperatures) and those of Svensson[6b] from the more reactive corresponding brosylate (50°, k = 4.45×10^{-7} sec^{-1}). Samples of the exo tosylate (IIIa, X = OTs) could only be obtained as oils despite extensive attempts at purification using column chromatography, and recrystallization from hydrocarbon solvents, so the kinetic results cannot be accepted without some reservation. It should be pointed out that high-purity (99% or better) samples of alcohol were used in its preparation. Also, the spectral results are consistent with the assigned structure, especially those from the NMR, which shows no extraneous signals, and integration peak heights in ratios expressable as integral numbers within experimental error. This is consistent with 95% or better purity. Also, first-order plots of the rate data did not deviate from linearity over at least 2 half-lives. Replicate determinations of the rate constant for acetolysis of the exo tosylate at 50.0° yielded the following average value: k = $1.9 \pm 0.1 \times 10^{-4}$ sec^{-1}. Thus, the exo tosylate undergoes acetolysis at a rate some 1600 times faster than does the endo epimer. Since at least 30% of the products from acetolysis of the latter appear to be formed via a solvent-assisted pathway, rather than unassisted ionization (see below), a corrected rate ratio of 2400 is probably a more accurate representation of the reactivity difference. Either ratio, being close to the corresponding rate difference (7600) in the dehydronorbornenyl system,[11] is consistent with homoallylic participation to form bridged cation IIIc, analogous in structure to the bridged 2-norbornenyl cation,[12] as the first-formed intermediate from solvolysis of exo tosylate IIIa. In a study of the solvolysis of *exo*- and *endo*-2-bicyclo[3.2.0]hepta-3,6-dienyl *p*-nitrobenzoates (VIb, X = OPNB, and VIc, Y = OPNB, respectively), we noted[14] that the allylic double bond in the five-membered ring levels the exo/endo rate ratio to unity and also swamps out homoallylic participation in the product-forming step. This indicates that homoallylic participation in the solvolysis of exo tosylate results in nonvertical[15] or distortional[16] stabilization in bridged cation IIIc. The rate data from acetolysis of the title compounds and some related substrates are presented in Table I. Consideration of the relative reactivities is informative in several respects.

Table I
Rate Constants for Acetolysis of Various Tosylates

Substrate	Temp, °C	k, sec^{-1}	Relative rate	Ref
VII, X = OTs[a]	50	4.23×10^{-5}	1	17
VIIIa, X = OTs[b]	50	2×10^{-6}	0.042	18
VIIIb, X = OTs[b]	50	1.9×10^{-4}	4.5	18
IIIb, Y = OTs[c,d]	50.0	$(1.11 \pm 0.1) \times 10^{-7}$	0.0027	*e*
	50[f,g]	1.21×10^{-7}		6a
	75.03[c,d]	$(3.6 \pm 0.12) \times 10^{-6}$		*e*
	100[f]	4.90×10^{-5}		6a
	106.8[c,d]	$(1.11 \pm 0.02) \times 10^{-4}$		*e*
IIIa, X = OTs[c,h]	50.0	$(1.9 \pm 0.1) \times 10^{-4}$	4.5	*e*
Ia, X = OTs[i]	50	2.7×10^{-2}	630	3a
IX, X = OTs[i]	50	9×10^{-3}	210	6a
X, X = OTs[j]	50	1.4	3.2×10^4	6a

[a] [NaOAc] = 0.117 M. [b] Calculated from rate data on the corresponding brosylate using a factor of 3 to relate the relative reactivities. [c] [NaOAc] = 0.0756 M. [d] Result of a single determination. Error is standard deviation. [e] This work. [f] [NaOAc] = 0.045 M. [g] Extrapolated from data at higher temperatures. [h] Average of two determinations. Error is average deviation. [i] Extrapolated from data at lower temperatures. [j] Calculated from the data on Ia, X = OTs, assuming that the reactivity ratio for hydrolysis of the corresponding *p*-nitrobenzoates (50, ref 6a) is applicable to acetolysis at 50°.

The endo tosylate (IIIb, Y = OTs) undergoes acetolysis some 300–500 times slower than does cyclopentyl tosylate



(VII, X = OTs).[17] That this difference is due in part to the electron-withdrawing powers of the double bond is shown by the fact that the corresponding reactivity difference for *endo*-2-bicyclo[3.2.0]heptyl tosylate (VIIa, X = OTs),[18] the saturated analog, is decreased to ca. 25. The exo tosylate (IIIa, X = OTs), on the other hand, reacts 4.5 times faster than VII, X = OTs, as does *exo*-2-bicyclo[3.2.0]heptyl tosylate (VIIIb, X = OTs),[18] the saturated analog. The latter observation would appear to argue against significant homoallylic participation in the solvolysis of exo tosylate IIIa, but the solvolysis of VIIIb, X = OTs, is itself thought to be anchimerically assisted ($k_{VIIIb}/k_{VIIIa} = 10^2$),[18] rendering it a poor model compound for comparisons of this type.

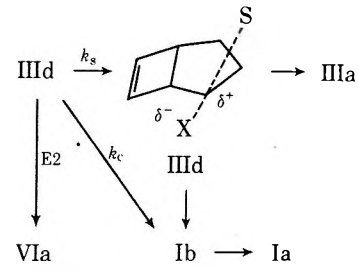
Svensson[6b] noted that attempts to prepare exo brosylate IIIa (X = OBs) resulted in mixtures of the desired compound and *anti*-7-norbornenol (Ia, X = OH) and made the reasonable proposal that exo brosylate, which partially hydrolyzed during work-up, was probably somewhat more reactive than anti 7-brosylate Ia (X = OBs), which survives such work-up intact. This seems plausible, since *anti*-tricyclo[5.2.0.0^{2,5}]nona-3,8-dien-6-yl tosylate (IX, X = OTs)[6a] undergoes acetolysis some 6.8×10^4 times faster than endo tosylate IIIb (X = OTs) at 25°. Our results show, however, that exo tosylate IIIa (X = OTs) is in fact some 140 times *less* reactive than *anti*-7-norbornenyl tosylate (Ia, X = OTs), and some 47 times less reactive than tricyclic tosylate IX (X = OTs). The latter compound exhibits a reactivity ca. 150 times slower than that projected for *exo-syn*-tricyclo[4.2.1.0^{2,5}]nona-3,7-dien-9-yl tosylate. Since exo tosylate and anti 7-tosylate (IIIa and Ia, X = OTs) are structurally related in the same fashion as the tricyclic tosylates (IX and X, X = OTs), the good agreement between the relative rates is probably significant, demonstrating that incorporation of an additional ethylenic bridge in exo tosylate and anti 7-tosylate (forming IX and X, respectively) results in a ca. 50-fold solvolytic rate enhancement ($k_{IX}/k_{IIIa} = 47$; $k_X/k_{Ia} = 50$[6a]).

The results from the product studies involving the endo tosylate IIIb are presented in Table II. Acetolysis and hydrolysis in 50% aqueous acetone produce mixtures of *exo*-2-bicyclo[3.2.0]hept-6-enyl and *anti*-7-norbornenyl derivatives (IIIa and Ia, X = OAc and OH, respectively). Our results from the acetolysis (IIIa:Ia, X = OAc 32:68) agree well with those of Svensson[6b] (IIIa:Ia, X = OAc 33:67). Hydrolysis in 50% aqueous acetone, a more nucleophilic medium, results in an increase in the ratio of yields of unrearranged to ring-enlarged products (IIIa:Ia X = OH 57:43). Methanolysis in 4 *M* sodium methoxide of the more reactive endo brosylate (IIIb, Y = OBs) yielded the corresponding exo methyl ether (IIIa), along with small amounts of bicyclo-[3.2.0]hepta-2,6-diene (VIa).

Table II
Products from Solvolysis of *endo*-2-Bicyclo[3.2.0]hept-6-enyl Tosylate (IIIb, X = OTs)

Solvolysis medium (temp, °C)	Products (relative yield)	Total yield, %
HOAc[a] (101)	IIIa, X = OAc (32); Ia, X = OAc (68)	82
HOAc[b] (75)	IIIa, X = OAc (33); Ia, X = OAc (67)	100
50% aqueous acetone[c] (101)	IIIa, X = OH (57); Ia, X = OH (43)	91
4 *M* NaOMe in MeOH[d] (101)	IIIa, X = OMe (90); VIa (10)	86

[a] Buffered with a ca. threefold excess of NaOAc; reaction time 8 hr. [b] Run in 0.07 *M* NaOAc for 170 hr (ref 6b). [c] Buffered with a ca. threefold excess of $NaHCO_3$; reaction time 8 hr. [d] Reaction carried out on corresponding brosylate (IIIb, Y = OBs); reaction time 8 hr.



The stereospecific Walden inversion observed in the formation of unrearranged products is more consistent with a solvent-assisted pathway (k_s) than with reaction of solvent with a "classical" cation, as observed[14] during the nonstereospecific solvolysis of the closely related *exo*- and *endo*-dienyl *p*-nitrobenzoates VIb and VIc (X and Y = OPNB, respectively), presumably involving allyl cation VId. We concur, therefore, with Svensson's view[6b] that the endo tosylate undergoes solvolysis at least in part via transition state IIId which collapses to form the exo products (IIIa, X = OAc, OH). Since nucleophilic solvent participation occurs to an extent sufficient to influence the stereochemistry, it also probably influences the reactivity of the endo substrate. The rearranged anti 7 products (Ia, X = OAc, OH) can arise either from unassisted ionization (k_c), with rearrangement to the more stable 7-norbornenyl cation (Ib) probably occurring within a tight ion pair before solvent can intervene, or solvent-assisted ionization via leakage from IIId to Ib.[6b] This ambiguity cannot be resolved using the data at hand, but disappears when 4 *M* sodium methoxide in methanol is employed; in this strongly nucleophilic medium, rearrangement is not observed, IIId becomes the classical SN2 transition state with little ionic character, and E2 elimination, forming VIa, occurs to a limited extent.

The results from product studies on the solvolysis of the exo tosylate are given in Table III. Hydrolysis of this substrate, *anti*-7-norbornenyl tosylate (Ia, X = OTs), and *endo*-tricyclo[3.2.0.0^{2,7}]hept-3-yl *p*-nitrobenzoate (II, X = OPNB) in 50% aqueous acetone produces anti 7-alcohol, with the latter substrate also furnishing some of the less reactive corresponding ester (Ia, X = OPNB). Thus, the 7-norbornenyl cation (Ib) appears to be the product-forming intermediate in the solvolysis of all three substrates. The latter two (Ia, X = OTs, and II, X = OPNB) are thought[3,4] to yield this cation directly. In our preliminary communication[5] of these results, we showed that the solvolytic transition state for the exo tosylate was ca. 18–19 kcal/mol higher in energy than that from anti tosylate, suggesting the involvement of another species, presumably bridged cation

Table III
Products from Solvolysis of
exo-2-Bicyclo[3.2.0]hept-6-enyl
Tosylate and Related Substrates in Various Media

Substrate	Solvolysis medium	Products (% yield)	Ref
Ia, X = OTs	50% aqueous acetone[a]	Ia, X = OH (100)	3b
II, X = OPNB	50% aqueous acetone[a]	Ia, X = OH (76); Ia, X = OPNB (23)	4
IIIa, X = OTs	50% aqueous acetone[b]	Ia, X = OH (80)	*c*
IIIa, X = OTs	4 *M* NaOMe–MeOH[d]	Ia, X = OMe (39); II, X = OMe (20); IIIb, X = OMe (30); VIa (10) (Ia:II 65:35)	*c*
Ia, X = OTs	4 *M* NaOMe–MeOH[e]	Ia, X = OMe (46); II, X = OMe (27) (Ia:II 63:37)	*c*

[a] Buffered by excess $NaHCO_3$. [b] Buffered by a threefold excess of $NaHCO_3$. [c] This work. [d] 50° for 6 hr. [e] 50° for 2 hr. An unidentified hydrocarbon (10% yield) was also detected.

Table IV
Products from Acetolysis of Various
exo-2-Bicyclo[3.2.0]hept-6-enyl Tosylates[a]

Substrate	Products (% yield)	Ref
IVa, X = OTs[b]	IVa, X = OAc (12); Va, X = OAc (82)	7
IVb, X = OTs[b]	IVb, X = OAc (11); Vb, X = OAc (83)[c]	7
IIIa, X = OTs[d]	Ia, X = OAc (80)	*e*

[a] Buffered by a threefold excess of NaOAc. [b] 98°. The crude product was reduced to the corresponding alcohols using $LiAlH_4$ prior to GC analysis. [c] Also detected in 5% yield was 7-methylene-5,5-dimethylbicyclo[2.2.1]hept-2-ene, bringing the total yield of ring-enlarged products to 88%. [d] 101°. [e] This work.

IIIc, as the first-formed intermediate,[19] which undergoes a very facile rearrangement.

Strong nucleophiles are often employed to trap[3e,20] rapidly rearranging cations; thus a study of the solvolysis of exo tosylate (IIIa, X = OTs) in 4 *M* sodium methoxide in methanol was undertaken. The products were found to be bicyclo[3.2.0]hepta-2,6-diene (VIa) (10% yield) and endo methyl ether IIIb (Y = OMe) (30% yield), formed via E2 and SN2 pathways, respectively, as well as a 65:35 mixture of *anti*-7-norbornenyl and *endo*-tricyclo[3.2.0.$0^{2,7}$]hept-3-yl methyl ethers (Ia and II, X = OMe, respectively) (59% yield). The latter products are known to arise from similar treatment of anti tosylate at 25° (as a 51:49 mixture)[3e]. As a control experiment, the latter reaction was studied at 50°, the conditions employed for the methanolysis of exo tosylate IIIa. A virtually identical (63:37) mixture of Ia and II was observed (73% yield).

Thus, the ring enlargement of bridged cation IIIc to the 7-norbornenyl cation is exceedingly rapid, being complete before reaction with solvent or added strong nucleophile occurs to a detectable extent. Whitham[7] found that acetolysis of exo-4,4,6- and -1,4,4-trimethylbicyclo[3.2.0]hept-6-en-2-yl tosylates (IVa and IVb, X = OTs, respectively) yields mixtures of the corresponding ring-enlarged acetates (Va and Vb, X = OAc) along with small amounts of the unrearranged exo acetates (see Table IV). Acetolysis of exo tosylate IIIa yields, as expected, only *anti*-7-norbornenyl acetate (Ia, X = OAc). The first-formed cations (IVc and IVd) from solvolysis of the exo trimethyl tosylates are, therefore, seen to be partially trapped even by the weak nucleophile, buffered acetic acid, showing that they undergo ring enlargement at a much slower rate than does cation IIIc. Comparison of the relative free energies of activation (calculated directly from the solvolytic product ratios) for ring enlargement vs. solvent capture for these cations (Figure 1) is instructive.

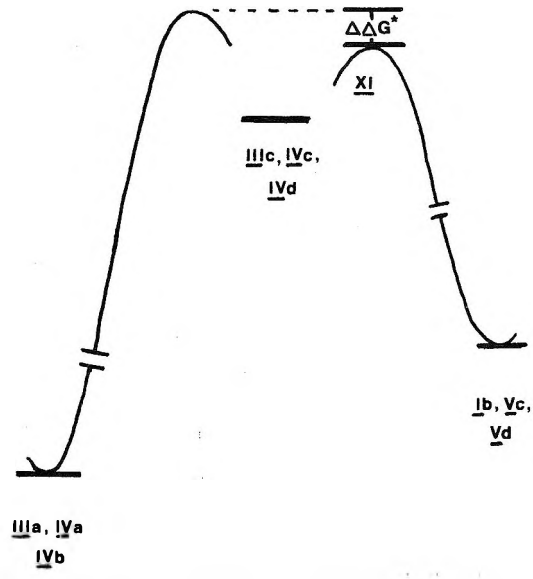


Figure 1. Relative free energies of activation for ring enlargement of various 2-bicyclo[3.2.0]hept-6-enyl cations vs. capture by solvent: $\Delta\Delta G^*_{IIIc} > 4$ kcal/mol, $\Delta\Delta G^*_{IVc} = 1.41$ kcal/mol, $\Delta\Delta G^*_{IVd} = 1.53$ kcal/mol.

For the 4,4,6-trimethylbicyclo[3.2.0]heptenyl cation (IVc), the transition state for solvent capture is higher in energy than that for ring enlargement ($\Delta\Delta G^*_{IVc}$) by 1.41 kcal/mol; the corresponding value ($\Delta\Delta G^*_{IVd}$) for the 1,4,4-trimethylbicyclo[3.2.0]heptenyl cation (IVd) is 1.53 kcal/mol. Since no unrearranged products were observed in the solvolysis of exo tosylate IIIa, an accurate value for the corresponding free energy difference ($\Delta\Delta G^*_{IIIc}$) is not available. A lower limit, however, can be assigned as follows: if, along with the 80% yield of anti 7-acetate (Ia, X = OAc), unrearranged products were formed in yields as high as 0.3–0.5%, but escaped detection, then this energy difference is at least ca. 4 kcal/mol, differing by ca. 2.5 kcal/mol from the value for both trimethyl derivatives.

In cation IVc, the methyl group at C-6 should have a similar stabilizing effect on the transition states for both solvent capture and ring enlargement (XI, $R_1 = R_2 = Me$; $R_3 = H$). The relative free energies for ring enlargement of cations IVc and IIIc should be similar. They are not. More significantly, the methyl group at C-1 in cation IVd should have little or no effect on the energy of the transition state for solvent capture (or the cation itself), but should significantly stabilize the ring-enlarged cation (Vd). Gassman[21] noted that substitution of a methyl group at C-7 enhances the rate of solvolysis of *anti*-7-norbornenyl tosylate (Ia, X = OTs) by a factor of 7600 (25°), corresponding to a 5.4 kcal/mol decrease in the free energy of activation with a similar enhancement in stability of the intermediate cation, closely related to Vd. The transition state for ring enlargement (XI, $R_1 = R_3 = Me$; $R_2 = H$) should be stabilized by a similar amount, rendering the relative free energy for ring enlargement vs. solvent capture for cation IVd ($\Delta\Delta G^*_{IVd}$) larger than for cation IVc ($\Delta\Delta G^*_{IVc}$). The predicted energy difference is observed ($\Delta\Delta G^*_{IVd} - \Delta\Delta G^*_{IVc} = 0.11$ kcal/mol), but is so small as to be insignificant. Thus, neither single methyl gives rise to the predicted effect. The retar-

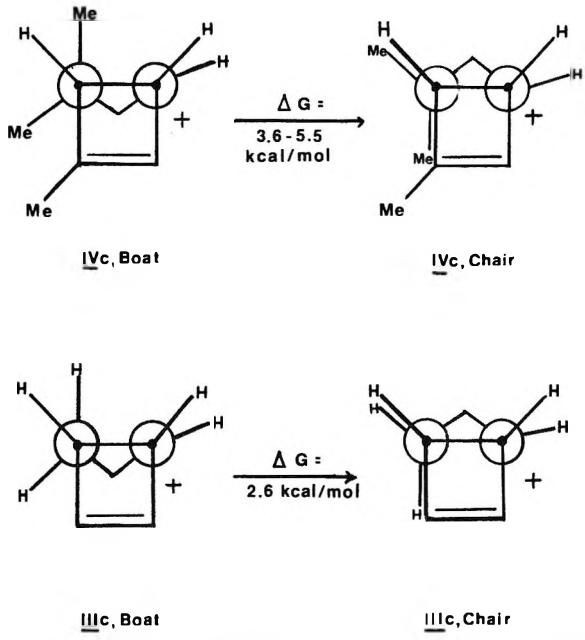
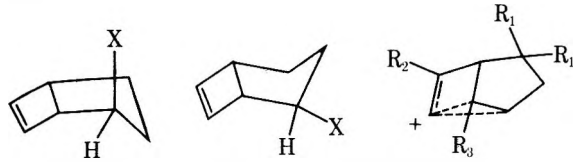


Figure 2. Chair- and boat-like conformations for the 2-bicyclo-[3.2.0]hept-enyl cation (IIIc) and the 4,4,6-trimethyl derivative (IVc).

dation is, therefore, probably best explained in terms of steric–conformational effects arising from the *gem*-dimethyl group at C-4.

Svensson[6b] noted that the NMR data on the endo brosylate (IIIb, X = OBs) are consistent with a boat-like conformation. We note in all *exo*-2-bicyclo[3.2.0]hept-6-enyl derivatives (IIIa) that the methine proton at C-2 gives rise to a doublet, J = 3.5 Hz [X (δ): OTs (4.69), OH (3.94), OMe (3.48)] with the splitting apparently due to the endo proton at C-3, with similar observations being made by Whitham[7] concerning trimethyl derivatives IVa and IVb. These observations are consistent with a boat-like conformation for the exo derivatives (IIIa, IVa, IVb) also. Inspection of molecular models of these derivatives shows that (a) orbital interactions between the developing positive charge and the homoallylic double bond are more favorable in the boat-like conformation than the chair, suggesting the former conformation for the first-formed cations (IIIc, IVc, IVd) also, and (b) ring enlargement must be concomitant with or preceded by ring flipping to the chair-like conformation.



IIIa, boat IIIa, chair XI

Examination of the Newman projections of cations IIIc and IVc (Figure 2) shows that in the latter case this ring flipping gives rise to eclipsing between C-6 and the endo methyl at C-4, and should be endothermic by ca. 3.6–5.5 kcal/mol, the energy difference between butane in the gauche and cisoid conformation.[22] The corresponding interaction in cation IIIc, involving the endo hydrogen at C-4, is less unfavorable; the ring flipping in this case should only be endothermic by ca. 2.6 kcal/mol, the energy difference between the gauche and lower energy eclipsed forms of butane.[22] Thus, a difference in the relative free energies of activation for ring enlargement between cations IIIc and IVc (as well as IVd) ($\Delta\Delta G^*_{IIIc} - \Delta\Delta G^*_{IVc}$) of ca. 1–3 kcal/mol would be expected. The reasonably good agreement between expectation and experiment ($\Delta\Delta G^*_{IIIc} - \Delta\Delta G^*_{IVc} \geq$ 2.5 kcal/mol) demonstrates the validity of these steric–conformational arguments.

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Registry No.—Ia (X = OTs), 13111-74-5; Ia (X = OH), 694-70-2; Ia (X = OMe), 13041-10-6; Ia (X = OAc), 13426-55-6; II (X = OMe), 38452-05-0; II (X = OPNB), 23211-61-2; IIIa (X = OTs), 53585-69-6; IIIa (X = OH), 52759-75-8; IIIa (X = OAc), 55682-01-4; IIIa (X = OMe), 54594-93-3; IIIb (Y = OTs), 41326-98-1; IIIb (Y = OH), 41398-41-8; IIIb (Y = OBs), 52743-48-3; IIIb (Y = OMe), 53934-56-8; tosyl chloride, 98-59-9; brosyl chloride, 98-58-8.

References and Notes

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Reactions of Substituted 5,5-Di(R)(Ar)-2-cyclohexenones. I. SN2 and SN2′ Reactions of 4-Bromoisophorone

H. Meislich* and S. Jasne†

Department of Chemistry, City College of the City University of New York, New York, New York 10031

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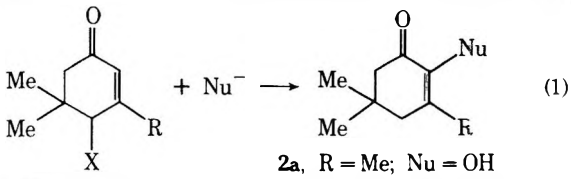
The reactions of 4-bromoisophorone (**1a**) with pivalate (Piv) salts in various solvents were studied. With AgPiv in HPiv, the nonconjugated SN2′ product, 2-pivaloxy-3,5,5-trimethyl-3-cyclohexenone, was obtained (25%). With KPiv in HPiv, 25% of **1a** reacted to give the reconjugated SN2′ product, 2-pivaloxyisophorone (**2b**). In DMF a 29% yield of **2b** and a 71% yield of the direct SN2 product, 4-pivaloxyisophorone (**1b**), were obtained; phenols were not formed. This was the first unequivocal instance of an uncatalyzed SN2 reaction of **1a**. A qualitative kinetic study with added triethylamine negated the intermediacy of a carbanion for the formation of this mixture of **1b** and **2b**. The absence of solvolysis products in the presence of a trace of base precludes a role for a solvent-separated ion pair. A negative salt effect opens to question the need to invoke a tight ion pair. The formation of **2b** may be consistent with a classical SN2′ mechanism. It is suggested that reactions of **1a** with strong bases such as HO^-, RO^-, and ArO^- which give C_2 substitution products and phenols may proceed through a carbanion intermediate. Under these conditions no C_4 substitution is observed. Furthermore, reactions of **1a** with soft bases such as I^-, ArS^-, and $ArSO_2^-$ may proceed initially by displacement on Br to give the C_4 carbanion.

Recently[1,2] 4-bromoisophorone (**1a**) was reported to react with nucleophiles to give 2-substituted 2-cyclohexenones (eq 1). It was asserted that these products were



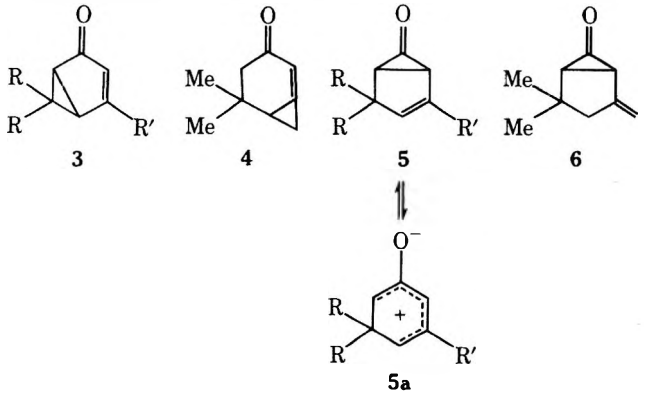
(1)

1a. R = Me; X = Br
b. R = Me; X = $OCOC(CH_3)_3$(Piv)
c. R = Me; X = OH
d. R = Ph; X = Br

2a, R = Me; Nu = OH
b, R = Me; Nu = Piv
c, R = Me; Nu = OCH_3
d, R = Ph; Nu = Piv

Nu^- = OH^-, I^-, 3,4,5- and 2,3,5-trimethylphenoxide, ArS^{2-}, $ArSO_2^{2-}$

formed by an SN2′ mechanism. However, this conclusion is equivocal because other mechanisms were overlooked. For example, a strong base such as OH^- could abstract a proton from C_6 or C_3 CH_3 and the resulting carbanion could then undergo an intramolecular displacement of Br^- to give any of several cyclopropyl intermediates (**3–5**) or their



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

5a

corresponding dipolar forms[3,4] (Favorskii-type reactions). These intermediates could aromatize to phenols and/or bond with nucleophiles at C_2 to give SN2′-like products such as **2a**. Nucleophilic attack is more likely at C_2 than at the more sterically hindered C_4 and C_6 positions. Intermediate 3 (R = R′ = CH_3) was postulated by Kosower and Wu[3] for the formation of phenols from the reaction of 6-chloroisophorone with $N(CH_3)_3$ and Ag^+. Zimmerman and Epling[4] implicated **5a** (R = Ph; R′ = H) in the formation of phenols during the reaction of 6-bromo-5,5-diphenyl-2-cyclohexenone with KO-*t*-Bu in *t*-BuOH. It is noteworthy that in neither case was C_2 substitution observed, possibly because sterically hindered bases were used. Structure **4** was postulated as an intermediate in the formation of 3,4,5-trimethylphenol from the reaction of 3-chloromethyl-5,5-dimethyl-2-cyclohexenone with triethylamine.[3] A cyclopropanone intermediate **6** similar to **5**, was suggested by Fort[5] in the reaction of 6-tosyloxyisophorone with methoxide ion. In this case, **2c**, 6-methoxyisophorone, and methyl trimethylcyclopentenecarboxylate were identified.

The aforementioned base-induced carbanion mechanisms are precluded in the reaction of **1a** with I^-. However **1a** has all of the structural requirements suggested by Jarvis and Saukaites[6] for a soft base[7] to displace on bromine, namely, a sterically hindered carbon and an ability to form a stabilized carbanion. The carbanion could react with the resulting IBr or I_2 at C_2 to give the observed product. α,β-Unsaturated enolates react with electrophiles such as H^+ and RX[8] at the α carbon, giving an unconjugated product isomerizable to the more stable conjugated isomer. This same type of reaction could account for the formation of C_2 substituted products when the soft nucleophiles ArS^- and $ArSO_2^-$ reacted with **1a**.[2b]

In an attempt to look for an unambiguous SN2′ reaction, we chose the pivalate (Piv) anion as the nucleophile because it is (a) not soft and therefore will not displace on Br, (b) a weak Brønsted base and therefore less likely to form carbanions easily, and (c) bulky and less likely to undergo direct SN2 attack at C_4.

Results and Discussion

When **1a** was treated with potassium pivalate (KPiv) in pivalic acid (HPiv), the only product isolated was 2-pivaloxyisophorone (**2b**) in 25% yield (Table I, expt 1); 75% of **1a** was unreacted. However, in the aprotic solvent dimethylformamide (DMF), a 29% yield of **2b** was obtained along with a 71% yield of 4-pivaloxyisophorone (**1b**), the direct substitution product (Table I, expt 2). In hexamethylphosphoramide (HMPA) only **1b** was detected (Table I, expt 3). *These are the first substantiated instances of an uncatalyzed formation of a C_4 substitution product from* **1a**. With silver pivalate (AgPiv) in pivalic acid a 10% yield of

† Taken from the Ph.D. Thesis of S. J. Jasne, City University of New York, 1973.

Table I
Reactions of 4-Bromoisophorone with Nucleophiles[a]

Expt	Reactants (equiv)	Solvent	Product(s) (yield, %)
1	KPiv (1.3)	Me_3CCOOH	2-Pivaloxyisophorone (2b, 25)
2	KPiv (1.3)	DMF	2b (29), 4-pivaloxyisophorone (1b, 71)
3	KPiv	HMPA	1b (95)
4	AgPiv	Me_3CCOOH	2b (10), 1a (65), 2-pivaloxy-3,5,5-trimethylcyclohex-3-enone (7a, 25)
5[b]	KPiv	DMF	5,5-Dimethyl-3-phenyl-2-pivaloxycyclohex-2-enone (>90)
6	KPiv (1.3), Et_3N (1.3)	DMF	2b (29), 1b (71)
7[c]	AgPiv (1.3), AgPiv (1.3)	Me_3CCOOH	No reaction
8[c]	KPiv (1.3), KBr (1.3)	DMF	No reaction
9	KPiv (1.3), $KClO_4$ (1.3)	HMPA	2b (20), 1b (80)
10	KPiv (1.3)	Dioxane–H_2O (1:1)	2b (8), 1a (92)

[a] 45°, 40.5 hr. [b] Substrate was 5,5-dimethyl-3-phenyl-4-bromocyclohex-2-enone. [c] Substrate was 1b.

2b and a 25% yield of the nonconjugated isomer 2-pivaloxy-3,5,5-trimethyl-3-cyclohexenone (7a) were obtained (Table I, expt 4). It is noteworthy that in none of these four reactions of 1a were phenols formed. The structure of 2b was proven by direct synthesis from 2-hydroxyisophorone (2a), pivalic acid, and trifluoroacetic anhydride. Compound 1b was similarly prepared from the corresponding alcohol 1c. Although 7a was not isolated as an analytically pure sample, its spectral data were consistent with the assigned structure, and in addition it rearranges exclusively to 2b in the presence of base and with KPiv in DMF.

Since pivalate anion may be sufficiently basic to form carbanions, it was necessary to examine whether intermediates 3–5 could be precursors for the C_2 substitution products, the so-called SN2′ products. The formation of 4 requires the removal of a proton from the C_3 CH_3 group of 1a. Since 1d, with a phenyl group instead of a CH_3 group at C_3, also afforded the SN2′-type product, 2d (Table I, expt 5), 4 is *not* a required intermediate for the formation of 2b.

Elimination of mechanisms initiated by carbanion formation at C_6 was more circuitous. Experiment 1 (Table I) is complicated by the possibility that the enol of 1a, formed from the C_6 carbanion, could be the substrate undergoing the displacement reaction, possibly by pivalolysis, to give 2b. We studied deuterium exchange of 1a using NaPiv in pivalic acid-*O*-*d*. NMR and mass spectral analysis showed that no more than a 5–6% exchange of deuterium in recovered 1a occurred at C_4, C_6, C_2, and C_3 CH_3. The percentage of exchange at each position was much less than the percent yield of 2b (25%). However, these data do not permit the drawing of an unequivocal conclusion about the intermediacy of a carbanion in the formation of 2b under these conditions. The data are consistent with a carbanion *not* being an intermediate; the mechanism of deuterium exchange could be independent of the mechanism for formation of 2b. Yet a carbanion could be a common intermediate for the H–D exchange and displacement reactions, if its return to deuterated 1a is slower than the steps leading to the formation of 2b. Although Bordwell[9a] ruled out this latter possibility in the Favorskii reaction of $ArCH_2COCH_2Cl$ and $ArCHClCOCH_3$ with CH_3O^- in CH_3OH because of the low concentration of enol in the strongly basic medium, it could be significant in our system because pivalate is a weaker base than methoxide and pivalic acid is a stronger acid than methanol. However, the observation of some deuterium exchange definitely mitigates against a concerted loss of H and Br[9a] during the displacement reactions.

The enol should not be a significant intermediate in expt 2 (Table I) because DMF is an aprotic solvent. This reaction is therefore better for studying whether the formation of 2b proceeds by a concerted SN2′ reaction or whether it requires the initial formation of a carbanion. Our premise was that the rate of any reaction initiated by carbanion formation should be increased by the addition of a supplementary base. Reactions not proceeding through a carbanion should be insensitive to the added base. In expt 2 (Table I) the added base should have no affect on the formation of 1b, which likely arises by direct SN2 displacement at C_4. If 2b arose via a carbanion, its rate of formation should be augmented by added base. If the foregoing situation prevails, the addition of triethylamine should alter the product distribution of 1b and 2b. Even if 1b and 2b were to arise from a common carbanion intermediate, the rates of their formation should increase on the addition of triethylamine.

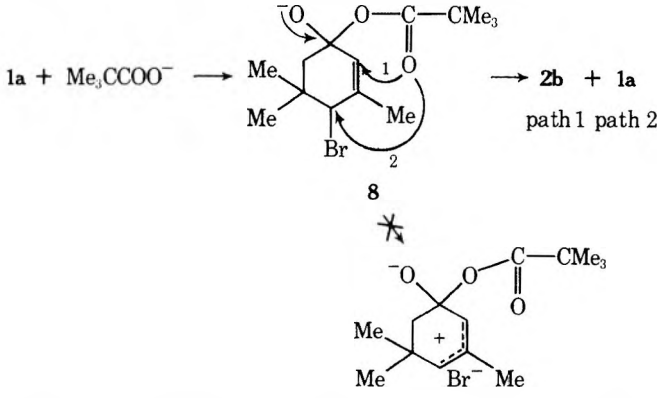
Identical reactions were run, treating 1a with KPiv, in DMF, except that 1.3 equiv of triethylamine was added to one of the reactions (Table I, expt 2 and 6). NMR analysis of aliquots taken periodically from the reaction mixture revealed that added base had no effect on either the product distribution or the rate of formation of these products. The relative amounts of 1b and unreacted 1a were determined by comparing the ratio of the areas of the C_2 vinylic (ca. δ 5.8 ppm) and the C_4 CHX protons of 1b (X = Piv, δ 5.48 ppm) and 1a (X = Br, δ 4.43 ppm). The relative yields of C_2 substitution products were usually determined by the differences in the expected as compared to the observed integration of the C_3 methyl, C_4 and C_6 methylene groups (δ 1.8–2.8), and the *gem*-dimethyl region (δ 0.8–1.3). Similar types of NMR analyses were done for all reactions in Table I. Apparently 1b and 2b do not arise from a C-6 carbanion. This conclusion is reinforced by the observation that the reaction of KPiv with 1a in HMPA, which gave only C_4 substitution product, also showed no product or rate change with added triethylamine.

Since Bordwell[9b] has criticized earlier assignments of SN2′ mechanisms because they did not consider one or more of the following pathways, (1) SN1, (2) SN2 followed by an SNi′, (3) SNi′ followed by an SN2, we addressed ourselves to these possibilities. Attempted ethanolysis of 1a afforded only 3,4,5-trimethylphenol. However, this is an auto-acid-catalyzed reaction, since with a trace of 2,6-lutidine no reaction occurs even at ten times the normal reaction time. In addition, no reaction occurs in dioxane–water

(1:1 v/v) or in HPiv. The lack of solvolysis rules out an SN1 mechanism and any mechanism proceeding through an intermediate solvent-separated ion pair. In typical allylic systems such as α- and γ-methylallyl chloride, SNi′ reactions proceed through tight ion pairs and are always accompanied by solvolysis.[10] Hence the absence of solvolysis products also precludes the SNi′–SN2 pathway for rearrangement of **1a** to 2-bromo-3,5,5-trimethylcyclohex-3-enone (**7b**). It should be noted that a C_4 carbonium ion is a vinylog of one α to a carbonyl group and would have a high energy.[11a,b] The SN2–SNi′ pathway involves initial formation of the C_4 direct substitution product followed by an internal allylic rearrangement. This pathway is untenable because **1b** is stable under the reaction conditions (Table I, expt 7 and 8).

To determine whether a tight ion pair precedes nucleophilic attack on C_2 and C_4, we looked for a positive salt effect as observed by Bordwell.[12] Whereas **1a** with KPiv in HMPA (Table I, expt 3) gave only **1b**, the addition of 1.3 equiv of $KClO_4$ gave 80% **1b** and 20% **2b** (Table I, expt 9) but at an overall *decrease* in rate of disappearance of **1a**. In the absence of $KClO_4$ the reaction was complete in 2.5 hr. With the salt in the same period of time 50% of **1a** was unreacted. This negative salt effect for the rate of formation of **1b** is expected for an SN2 reaction *not* proceeding through an ion pair.[12] Sneen[10] showed that competitive SN2 and SN2′ reactions follow from equilibrating intermediate tight ion pairs. Our system would be exceptional if the SN2 reaction proceeds from an un-ionized substrate while the SN2′ reaction occurs through a tight ion pair. It is more likely that *neither the SN2 nor SN2′ products arise from the intermediate tight ion pair of* **1a**. The yield of **2b** could increase on adding $KClO_4$ if the rate of formation of **1b** is decreased more than is the rate of formation of **2b**.

Since C_4 is adjacent to a quaternary carbon (C_5) the facile nucleophilic displacement leading to **1b** (in HMPA, 2.5 hr at 45°) is extraordinary. Rather than the displacements occurring directly on **1a**, it is possible that **8**, formed by attack of Piv on the carbonyl carbon, may be an intermediate.[13] **8** could rearrange to give either the SN2′ (path 1) or SN2 (path 2) product. The intramolecular SN2 reaction of **8**



would not be sterically hindered by the C_5 *gem*-dimethyl groups as would an intermolecular SN2 reaction. The intermediate **8** would not undergo an SN1-type reaction because no solvolysis products, e.g., Table I, expt 10, or phenols are obtained.

However, one argument against **8** being a *common* intermediate for **1b** and **2b** is the variation in product distribution on changing the solvent or on adding $KClO_4$ (Table I, expt 2, 3, 9). The validity of the intermediacy **8** is being tested by reacting **1a** with hard weakly basic anions which are incapable of bridging to C_4 from the carbonyl carbon.

In our hands the reaction of **1a** with I^- in Me_2SO gave, in addition to iodinated products, about 25% of isophorone recovered by preparative thick layer chromatography. This substantiates our suggestion that **1a** can react with soft nucleophiles by displacement on bromine. Markley[2] isolated only isophorone and ethyl disulfide when **1a** was treated with sodium ethylthiolate.

Conclusion

The several routes whereby **1a** can react with nucleophiles can be sorted out in terms of the distribution of products. Hard, moderate to strong bases such as OH^-, RO^-, and R_3N can initiate carbanion formation and displacement can then proceed through intermediates **3**, **4**, and/or **5**. Phenol formation always accompanies these pathways. We have not ruled out the possibility that some of these bases also react with **1a** directly at C_2. No C_4 substitution products occur from these intermediates. The absence of phenols in our reactions with pivalate anion argues against these pathways. With soft nucleophiles such as I^- displacement could occur initially at Br, giving only substitution at C_2, no phenolic products, and isophorone as a possible side product. With a hard, weakly basic nucleophile such as Piv in aprotic solvents, both direct SN2 and SN2′ reactions can occur giving C_4 and C_2 substituted products, respectively. In protic solvents only attack at C_2 occurs. In these cases phenols and isophorone do not form. The directly formed SN2′ product does not arise from a solvent separated ion pair because no solvolysis products are obtained.[10] The observance of a negative salt effect opens to question whether even a tight ion pair must be invoked. This reaction may indeed be of the concerted SN2′ type. More work is underway to test this hypothesis.

Experimental Section

Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, New York, N.Y. Melting points were determined using a Thomas-Hoover apparatus, in open capillary tubes, and are corrected; boiling points are uncorrected. Mass spectra were determined using a Varian CH5 mass spectrometer at 70 eV under direct sample inlet conditions and logarithmic mass scan. Infrared spectra were determined using a Perkin-Elmer 137 spectrophotometer and a Beckman IR 20A spectrophotometer. Absorption maxima are expressed in reciprocal centimeters. Proton magnetic resonance spectra were determined using a Varian A-60 spectrometer and a Jeolco C-60HL spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane (δ 0).

Preparation of 4-Bromoisophorone (1a).[14] Methylene chloride was substituted for carbon tetrachloride as the solvent. **1a** had mp 49.5–50.2° (lit.[14] mp 48–49.5°); NMR ($CDCl_3$) δ 5.66 (t, J = 1 Hz, 1 H, C=CH), 4.40 (d, J = 1 Hz, 1 H, CHBr), 2.37 (AB pattern, 2 H, CH_2), 2.13 (d, J = 1 Hz, 3 H, C=CCH_3), 1.30 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3); ir ($CHCl_3$ solution) 1675 (s, ketone).

Preparation of 3,5,5-Trimethylcyclohex-3-enone (7c). 4-Bromoisophorone (**1a**, 32.5 g, 0.15 mol) was added to 300 ml of 95% ethanol in a 500-ml flask fitted with a reflux condenser, drying tube, and mechanical stirrer. Zinc dust (65 g, 1 mol) was added and the reaction mixture was stirred rapidly for 14.5 hr at 41–45°. The reaction mixture was suction filtered and the solid was washed with 100 ml of diethyl ether which was combined with the filtrate and concentrated under reduced pressure at room temperature. The resulting solution was placed under a nitrogen atmosphere and stored in the freezer (4°). Fractional vacuum distillation gave cut 1, bp 34–37° (1.8 Torr); cut 2, bp >40° (2 Torr). A rough NMR analysis indicated that cut 1 contained the desired product contaminated with isophorone. There appeared to be a significant amount of liquid collected in the Dry Ice–acetone vacuum trap. Analysis of this material by NMR showed it to be mainly **7c** contaminated with ethanol. Diethyl ether (200 ml) was added to the material collected from the trap and this solution was extracted with three 200-ml portions of water, dried over $MgSO_4$, and concentrated at reduced pressure at room temperature. The resulting liquid was added to the material from cut 1 to yield a total of 4.78 g (23.1%) of **7c** [lit.[15] bp ca 70° (10 Torr)]; NMR ($CDCl_3$) δ 5.42 (broad, 1 H, C=CH), 2.65 (s, 2 H, C=CCH_2), 2.23 (s, 2 H, CH_2), 1.68 (d, J = 1 Hz, 3 H, C=CCH_3), 1.00 (s, 6 H, 2-CH_3); ir (neat) 1735 cm^{-1} (s, ketone).

Preparation of 3-Oxido-3,5,5-trimethylcyclohexanone. 3.5.5-Trimethylcyclohex-3-enone (**7c**, 0.50 g, 3.56 mmol) was dissolved in chloroform (10 ml) and placed in a three neck 25-ml flask fitted with a condenser, drying tube, and magnetic stirrer. Solid *m*-chloroperbenzoic acid (0.77 g, 3.8 mmol) was added in small portions to the stirred solution over an 8-min period. Chloroform (2 ml) was used to wash some solid from the side of the flask into the solution. The reaction mixture was stirred for 15 min and then allowed to stand for 70 min. The white solid, *m*-chlorobenzoic acid, was suction filtered. The filtrate was concentrated under reduced pressure at room temperature, yielding a white solid which was partially dissolved upon the addition of 10 ml of petroleum ether (bp 30–60°). The resulting solid was suction filtered and a second crop of crystals was suction filtered from the solution. The solution was concentrated under reduced pressure at room temperature to yield a colorless liquid which was used as is, immediately, for the following reaction: NMR ($CDCl_3$) δ 2.88 (s, 1 H, epoxy H), 2.67 (s, 1 H, epoxy CH), 2.60 (s, 1 H, epoxy CH), 2.13 (AB pattern, 2 H, H_2C–C=O), 1.38 (s, 3 H, epoxy CH_3), 1.17 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3); ir (neat) 1740 cm^{-1} (s, ketone).

Preparation of 4-Hydroxyisophorone (1c). The 3-oxido-3,5,5-trimethylcyclohexanone obtained from the above reaction was dissolved in 2 ml of diethyl ether and 2 ml of distilled water in a 10-ml flask fitted with a condenser, magnetic stirrer, and drying tube. The pH of the solution was brought to between 11 and 12 by the dropwise addition of 10% sodium hydroxide. The mixture was stirred at this pH, at room temperature, for 5.7 hr and diethyl ether was added when necessary to maintain a constant volume. The layers were separated and the ethereal solution was washed with two 10-ml portions of a saturated sodium chloride solution and dried over $MgSO_4$. The sodium hydroxide layer was extracted with two 15-ml portions of ether which were dried over $MgSO_4$, added to the previously recovered ethereal solution, and concentrated under reduced pressure at room temperature to yield 0.272 g (48%) of **1c**: NMR ($CDCl_3$) δ 5.87 (broad, 1 H, C=CH), 4.37 (broad, 1 H, OH), 4.03 (broad, 1 H, HCO), 2.32 (AB pattern, 2 H, H_2C–), 2.06 (broad s, 3 H, C=CCH_3), 1.08 (s, 3 H CH_3), 1.03 (s, 3 H, CH_3); ir (neat) 3400 (m, hydroxy group), 1670 (s, conjugated ketone).

Preparation of 4-Pivaloxyisophorone (1b). Method A. Crude 4-hydroxyisophorone (**1c**, 1.0 g, 6.6 mmol) and 10 ml of trifluoroacetic anhydride were placed in a 25-ml flask fitted with a condenser and magnetic stirrer. Pivalic acid (0.663 g, 6.6 mmol) was added and the reaction flask was stoppered lightly. After being stirred for 4 hr at room temperature the reaction mixture was diluted with 20 ml of benzene. The organic layer was then extracted with three 20-ml portions of 10% sodium hydroxide and two 20-ml portions of a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure at room temperature to yield 0.928 g of a yellow oil. This oil was divided into two parts and placed on two 20 × 20 cm thick layer silica gel chromatography plates, activated for ca. 15 min at 100°. After development in 1,2-dichloroethane three bands were observed. The silica gel between R_f 0.28 and 0.31 was scraped from the plates and the organic material was extracted from the adsorbent by addition of two 50-ml portions of acetone. The combined acetone solutions were concentrated under reduced pressure at room temperature to yield 0.472 g (27.8%) of **1b**: NMR ($CDCl_3$) δ 5.75 (broad, 1 H, C=CH), 5.48 (broad, 1 H, HCO), 2.33 (s, 2 H, CH_2), 1.87 (t, J = 1 Hz, 3 H, C=CCH_3), 1.27 [s, 9 H, $C(CH_3)_3$], 1.02 (s, 6 H, 2-CH_3); ir (neat) 1740 (s, ester), 1680 (s, conjugated ketone); mass spectrum *m/e* (rel intensity) 239 (7.4), 238 (47), 192 (15), 164 (56), 149 (15), 147 (16), 146 (16), 122 (14), 118 (12), 108 (73), 103 (24), 94 (95), 91 (16), 88 (11), 76 (14), 67 (14), 66 (100, base peak), 64 (12), 50 (78), 48 (22). A DNP derivative of this liquid was prepared (mp 146–147°). Anal. Calcd for $C_{20}H_{26}N_4O_6$: C, 57.40; H, 6.26; N, 13.38. Found: C, 57.81; H, 6.30; N, 13.19.

Preparation of 4-Pivaloxyisophorone (1b). Method B. 4-Bromoisophorone (**1a**, 15.19 g, 0.07 mol), silver pivalate (14.56 g, 0.07 mol), and 56 ml of pivalic acid were placed in a 250-ml flask fitted with a condenser, magnetic stirrer, and drying tube. The entire apparatus was covered with aluminum foil to prevent light-catalyzed decomposition of the silver salt. The reactants were heated at ca. 90–95° for 355 min. The precipitated silver bromide was suction filtered and triturated with 350 ml of diethyl ether. The ethereal layer was washed with 10% sodium bicarbonate until the washings were no longer acidic (1800 ml) and then dried over $MgSO_4$ and concentrated under reduced pressure at room temperature to yield 11.89 g of an orange oil.

The crude product was prepared for wet column chromatography. A column, 3.4 cm diameter, using Davidson silica gel (ca. 900 g), activity grade III, 100–200 mesh, was used. A slurry of silica gel to a height of 114 cm, in benzene, including 1 cm of glass wool packing and 2 cm of sand below the absorbant, was used. The entire quantity of orange oil was placed on the column using a minimal amount of benzene. Cuts of 100 ml were generally taken: solvent system for cuts 1–15, benzene; cuts 16–20, 2% ethyl acetate, 98% benzene; cuts 21–27, 5% ethyl acetate, 95% benzene; cuts 28–35, 8% ethyl acetate, 92% benzene; cuts 36–40, 10% ethyl acetate, 90% benzene; cuts 41–46, 33% ethyl acetate, 67% benzene; cuts 47–53, ethyl acetate. Cuts 1–33 were combined based on TLC analysis but were not fully analyzed because they contained less than 10% of the weight of the material placed on the column. Based on rough NMR analysis cuts 34–40 were combined to yield 6.39 g of an orange oil which appears to contain mainly, based on spectral analysis, 2-pivaloxy-3,5,5-trimethyl-3-cyclohexenone (**7a**). Cuts 43–50 were combined based on rough NMR analysis and were proved to be **1b** by comparison with a sample obtained using method A. A light yellow oil was recovered (3.6 g, 30.9%).

Isolation of 2-Pivaloxy-3,5,5-trimethylcyclohex-3-enone (7a). From the above reaction of 4-bromoisophorone (**1a**) with silver pivalate in pivalic acid one of the recovered products was 2-pivaloxy-3,5,5-trimethylcyclohex-3-enone (**7a**) as shown above. The spectral data for this compound follow: NMR ($CDCl_3$) δ 5.56 (broad, 2 H, C=CH, HCO), 2.41 (AB pattern, 2 H, CH_2), 1.67 (t, J = 1 Hz, 3 H, C=CCH_3), 1.23 [s, 9 H, $C(CH_3)_3$], 1.15 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3); ir (neat) 1750 (s, ester), 1740 (s, shoulder of 1740, unconjugated ketone); mass spectrum *m/e* (rel intensity) 239 (02), 238 (15), 154 (5.1), 153 (38), 138 (34), 137 (6.5), 136 (30), 125 (8.0), 121 (7.3), 112 (25), 111 (7.6), 109 (15), 98 (14), 91 (5.3), 85 (46), 79 (9.4), 77 (69), 69 (60), 67 (12), 58 (16), 57 (100, base peak), 56 (6.5), 55 (16), 53 (8.7), 43 (13), 42 (6.2), 41 (41).

Isomerization of 2-Pivaloxy-3,5,5-trimethylcyclohex-3-enone (7a) to 2-Pivaloxyisophorone (2b). Method A. In a 25-ml flask fitted with a magnetic stirrer, condenser, and drying tube, potassium hydroxide (0.149 g, 2.1 mmol), 0.275 g (1.17 mmol) of **7a**, and 10 ml of 95% ethanol were stirred at room temperature for 50 min. The reaction mixture was then diluted with diethyl ether (100 ml) and the ethereal layer was washed with three 100-ml portions of water. The aqueous layer was back extracted with one 75-ml portion of diethyl ether. The combined ethereal layers were washed with one 50-ml portion of a saturated NaCl solution, dried over $MgSO_4$, and concentrated at room temperature under reduced pressure to yield 0.185 g of a slightly yellow oil which was identical in all respects with **2b**.

Method B. Compound **7a** (0.191 g, 0.8 mmol), potassium pivalate (0.157 g, 1.2 mmol), and 2 ml of DMF were placed in a 20-ml flask fitted with a magnetic stirrer. The flask was lightly stoppered and the reaction mixture was stirred for 40.5 hr at ca. 45°. Diethyl ether (15 ml) was added to the reaction mixture and the organic layer was washed with two 25-ml portions of water, one portion (20 ml) of 10% sodium bicarbonate solution, and once (20 ml) with water, dried over $MgSO_4$, and concentrated at room temperature under reduced pressure to give 0.143 g of a slightly yellow oil whose spectral properties matched those of **2b**.

Method C. Into a 20-ml flask fitted with a magnetic stirrer, **7a** (0.157 g, 0.65 mmol), potassium pivalate (0.118 g, 0.845 mmol), and 1 g of pivalic acid were added. The reaction mixture was stirred in the corked flask for 40.5 hr at 45 ± 2°. Diethyl ether (20 ml) was added and the ethereal layer was washed with one 20-ml portion of water, two 20-ml portions of 10% sodium bicarbonate, and one 20-ml portion of a saturated sodium chloride solution, dried over $MgSO_4$, and concentrated under reduced pressure at room temperature to yield 0.108 g of a slightly yellow oil whose spectral properties showed it to be **2b**.

Preparation of 2-Pivaloxyisophorone (2b). A general method for the esterification of hindered acids was employed.[16] 2-Hydroxyisophorone (**2a**, 1.0 g, 65 mmol) and pivalic acid (0.663 g, 65 mmol) were added to 5 ml of trifluoroacetic anhydride in a 25-ml flask fitted with a magnetic stirrer. The reaction mixture was stirred at room temperature for 3.5 hr. Benzene (20 ml) was added and the benzene solution was washed with three 15-ml portions of 10% sodium hydroxide and once with a 20-ml portion of water, dried over $MgSO_4$, and concentrated under reduced pressure at room temperature. The resulting solution was distilled under reduced pressure to give 0.527 g (34.1%) of a colorless liquid, **2b**: bp 113–115° (2.5 Torr); NMR ($CDCl_3$) δ 2.33 (s, 2 H, CH_2), 2.27 (s, 2 H, CH_2), 1.78 (s, 3 H, C=CCH_3), 1.30 [s, 9 H, $C(CH_3)_3$], 1.08 (s, 6

H, 2-CH_3); ir (neat) 1748 (s, ester), 1685 cm^{-1} (s, conjugated ketone); mass spectrum *m/e* (rel intensity) 239 (1.2), 238 (5.5) 154 (41), 153 (100, base peak), 138 (47), 125 (20), 124 (17), 111 (36), 110 (13), 107 (5.5), 97 (42), 84 (13). 82 (19), 69 (38), 68 (24), 66 (8.8), 58 (8.3); mp of DNP derivative 181–182.5°. Anal. Calcd for $C_{20}H_{26}N_4O_6$: C, 57.40; H, 6.26; N, 13.38. Found: C, 57.68; H, 6.37; N, 13.29.

Preparation of 4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (1d). 5,5-Dimethyl-3-phenylcyclohex-2-enone[17] (1.34 g, 6.7 mmol), *N*-bromosuccinimide (1.2 g, 6.7 mmol), a trace of benzoyl peroxide, and 20 ml of carbon tetrachloride were introduced into a 50-ml flask fitted with a magnetic stirrer, condenser, and drying tube. The reaction mixture, irradiated with a long-wavelength uv lamp, was stirred at reflux for a total of 21.75 hr. The reaction flask was cooled in an ice bath and the solid present was suction filtered. The mother liquor was concentrated at room temperature under reduced pressure. The resulting solid was recrystallized from pentane to give 1.04 g (56%) of a white solid: mp 83–85°; NMR ($CDCl_3$) δ 7.50 (m, 5 H, ArH), 6.32 (s, 1 H, C=CH), 4.92 (d, J = 1 Hz, HCBr), 2.50 (AB pattern, 2 H, CH_2), 1.33 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3); ir (KBr disk) 1655 (s, conjugated ketone). Anal. Calcd for $C_{14}H_{15}BrO$: C, 56.98; H, 5.12; Br, 28.67. Found: C, 56.15; H, 5.22; Br, 28.11.

Preparation of 5,5-Dimethyl-3-phenyl-2-pivaloxycyclohex-2-enone. 4-Bromo-5,5-dimethyl-3-phenylcyclohex-2-enone (**1d**, 0.556 g, 2.0 mmol), potassium pivalate (0.364 g, 2.6 mmol), and DMF (5 ml) were added to a 25-ml flask fitted with a magnetic stirrer. The reaction mixture was stirred at 45° for approximately 13 days. The reaction mixture was then dissolved in diethyl ether (20 ml) and washed with two 20-ml portions of water, one 20-ml portion of 10% sodium bicarbonate solution, and one 20-ml portion of water, dried over $MgSO_4$, and concentrated under reduced pressure at room temperature to yield a slightly yellow solid (0.450 g, 75%). This solid was recrystallized four times from petroleum ether (bp 30–60°) to yield a white solid: mp 112–113°; NMR ($CDCl_3$) δ 7.34 (s, 5 H, Ph), 2.69 (s, 2 H, CH_2), 2.44 (s, 2 H, CH_2), 1.18 (s, 3 H, CH_3), 1.13 [s, 9 H, $C(CH_3)_3$], 1.11 (s, 3 H, CH_3); ir (CCl_4 solution) 1755 (s, ester), 1690 cm^{-1} (s, conjugated ketone); mass spectrum *m/e* (rel intensity) 301 (18), 300 (76), 286 (10), 285 (5), 232 (5.2), 218 (6.1), 217 (49), 216 (100, base peak), 215 (30), 188 (14), 160 (12), 145 (5), 132 (7), 103 (5). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.26; H, 8.33.

Preparation of Potassium Pivalate. Pivalic acid (21.0 g, 0.26 mol) was added to 20 ml of water in a 250-ml flask fitted with a magnetic stirrer. The stirred mixture was made basic to a phenolphthalein end point using a 10% KOH solution. After filtration, the solvent was evaporated under reduced pressure (ca. 85°), leaving a white solid which was washed with 200 ml of acetone and 100 ml of diethyl ether, air dried for 4 hr, and then vacuum dried (1 Torr) at room temperature for 18 hr. A white solid (27.4 g, 87.5%) was recovered.

Preparation of Silver Pivalate.[18] Pivalic acid (40.8 g, 0.4 mol) and 600 ml of water were placed in a 2-l. flask fitted with a magnetic stirrer. Sodium hydroxide (10%) was added dropwise until the solution was just basic to a phenophthalein indicator (163.8 ml). The reaction flask was covered with aluminum foil and 1 equiv of silver nitrate (68 g, 0.4 mol) in 50 ml of water was added. The resulting precipitate was suction filtered in the dark, washed with 800 ml of water, 463 ml of methanol, and 463 ml of diethyl ether, and dried under high vacuum (1 Torr) for 4 hr to yield 60.2 g (75%) of a slightly gray solid.

Reactions of 1a with Nucelophiles. Reactions were generally run in a stoppered flask fitted with a magnetic stirrer at 45 ± 2° for 40.5 hr unless otherwise noted. When silver salts were used, the reaction flask was covered with aluminum foil and the resulting filtered silver bromide was washed with diethyl ether. When the potassium salt was employed, the reaction mixture was diluted directly with diethyl ether. These organic solutions were washed with water, then with 10% sodium bicarbonate if acetic acid or pivalic acid was present; dilute hydrochloric acid if triethylamine was present; or water if water-soluble solvents, such as Me_2SO, dioxane, DMF, HMPA, etc., were used. The organic layer was then washed with water, or a sodium chloride solution if the layers did not separate readily, dried over $MgSO_4$, and concentrated. Analysis of the product distribution was usually performed by NMR.

Registry No.—**1a**, 16004-91-4; **1b**, 55723-01-8; **1b** DNP, 55723-02-9; **1c**, 14203-59-9; **1d**, 55723-03-0; **2a**, 4883-60-7; **2b**, 55723-04-1; **2b** DNP, 55723-05-2; **2d**, 55723-06-3; **7a**, 55723-07-4; **7c**, 471-01-2; 3-oxido-3,5,5-trimethylcyclohexanone, 41967-76-4; *m*-chloroperbenzoic acid, 937-14-4; pivalic acid, 75-98-9; 5,5-dimethyl-3-phenylcyclohex-2-enone, 36047-17-3; *N*-bromosuccinimide, 128-08-5; potassium pivalate, 19455-23-3; silver pivalate, 7324-58-5.

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Carbonylation Reactions of Ortho-Palladation Products of α-Arylnitrogen Derivatives

James M. Thompson and Richard F. Heck*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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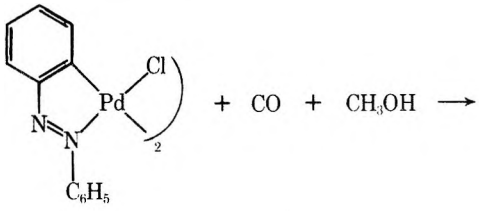
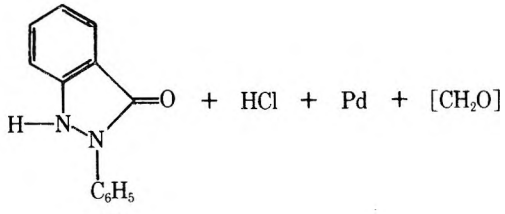
Ortho-palladation products of azobenzene, Schiff bases (two isomeric types), benzaldazine, acetophenone dimethylhydrazone, 1-methyl-1-phenylhydrazones, and tertiary benzylamines have been prepared and treated with carbon monoxide under mild conditions. A variety of unusual heterocyclic compounds have been obtained, often in good yields, from these reactions. Mechanistic patterns have appeared which should allow reaction products to be predicted from the carbonylations of the many other types of ortho-palladation products which probably can be prepared.

The formation of ortho-palladation products from numerous α-arylnitrogen derivatives and palladium salts is well known. For example, complexes with azobenzene,[1] Schiff bases,[2-5] tertiary benzylic amines,[6] oximes,[7-9] and appropriately substituted pyridines[10] and pyrazoles[11] are known. However, relatively little chemistry has been done with these readily obtainable, reactive complexes. The ortho-metalation reaction is ideally suited for use in the synthesis of heterocyclic compounds, since the metalated complexes can be made directly from monosubstituted aromatics. Previously, for example, in one of the few experiments carried out, the azobenzene–palladium chloride complex, I, was treated with carbon monoxide in methanol solution at 40 psi and room temperature and 2-phenyl-1*H*-indazolone (II) was formed, although only in 17% yield.[12] Much better yields were obtained at 100° under 150 atm pressure, however.[13]



I

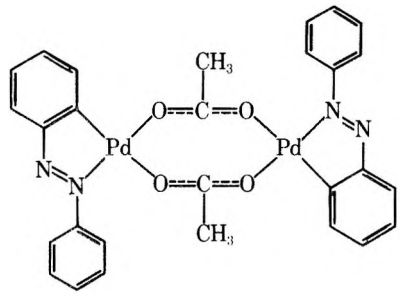


II

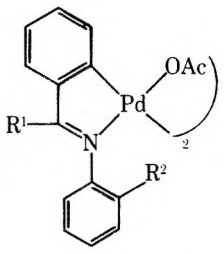
In the present paper we report the synthesis of several new ortho-palladated complexes and a study of the reactions of these and some previously known complexes with carbon monoxide.

Results and Discussion

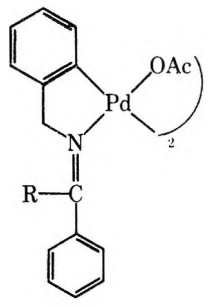
I. Palladium Complexes. Seven structurally different types of chelated, five membered ring, nitrogen-coordinated, ortho-palladated complexes were prepared for carbonylation by treating the parent aromatic compound with the appropriate palladium salt (chloride or acetate). The azobenzene–palladium chloride complex (I) was reinvestigated to determine the reason for the low yield of the carbonylation product found previously.[12] The related azobenzene–palladium acetate complex (III) was also prepared for comparison with the chloride. The higher reaction rates, better solubility, and higher yields of organic products obtained with the acetate derivative (results to be described) led us to investigate only the acetates of the other six structures. The known benzaldehyde–Schiff base–palladium acetate complexes, IV,[3] and the new type of complex from benzyl-



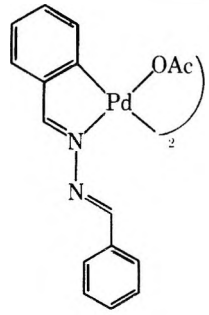
III



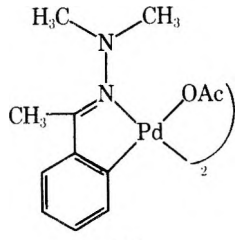
IVa. $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = CH_3$
c. $R^1 = CH_3$; $R^2 = H$



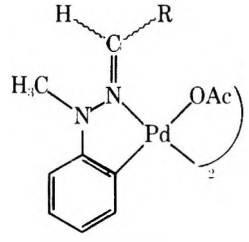
Va. R = H
b, R = CH_3



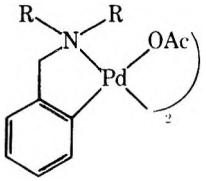
VI



VII

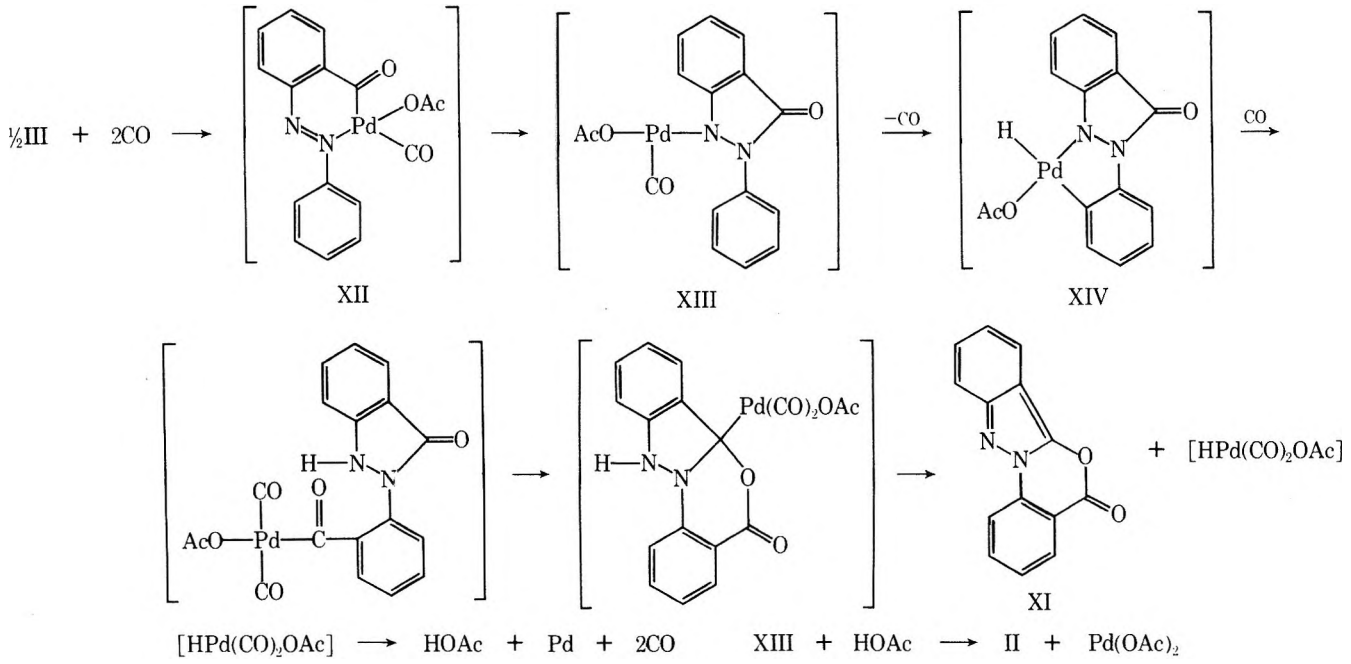


VIIIa, R = H
b. R = CH_3

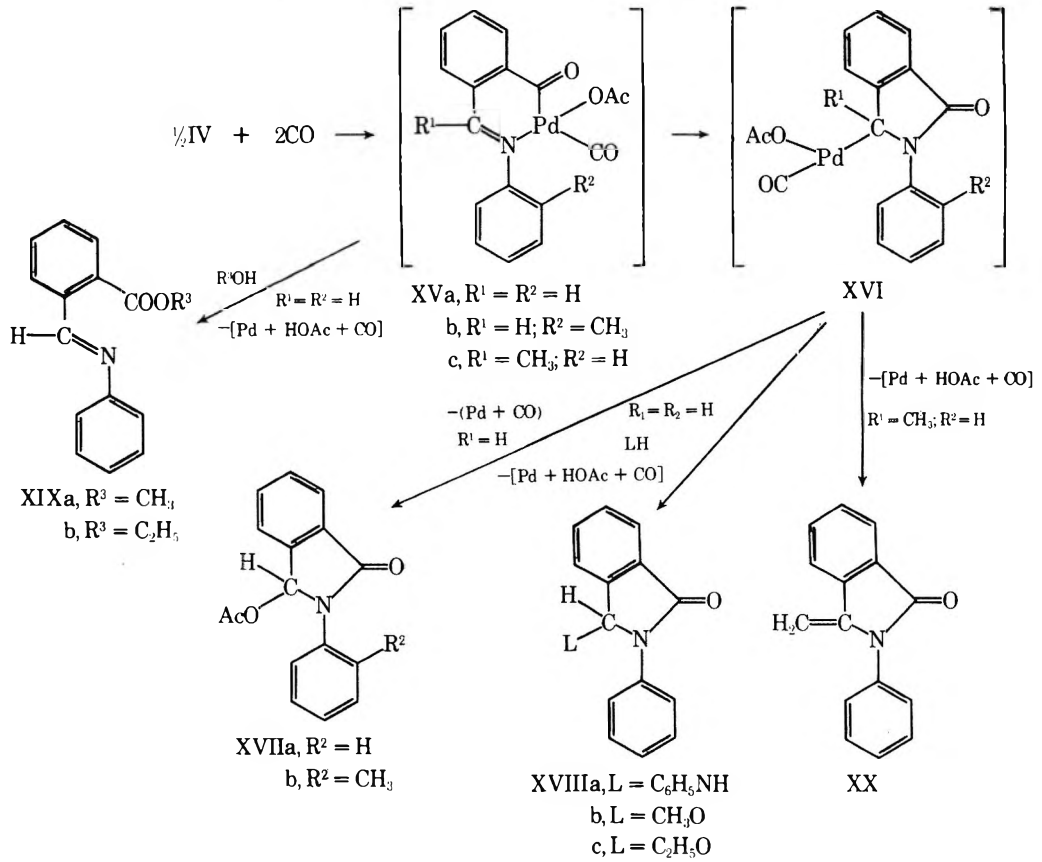


IXa. R = CH_3
b. R = C_2H_5
c. R-R = $(CH_2)_4$

Scheme I
Carbonylation of the Azobenzene–Palladium Acetate Complex



Scheme II
Carbonylation of Schiff Base–Palladium Acetate Complexes

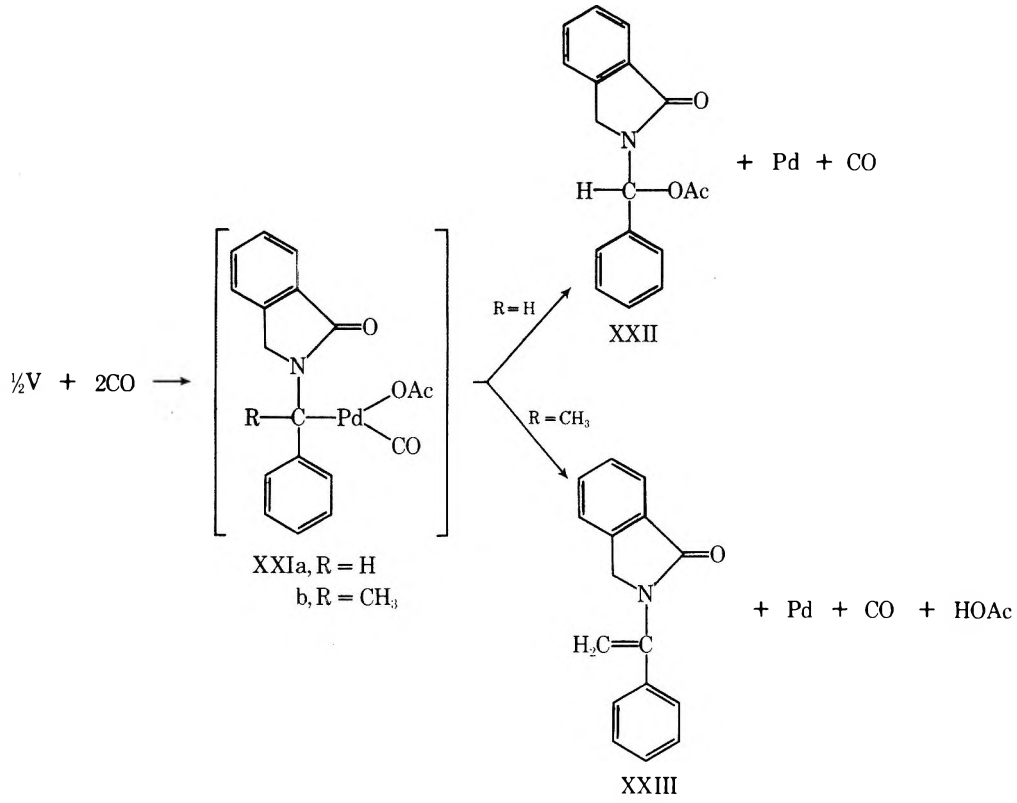


amine–Schiff bases, V, were similarly prepared by heating the Schiff bases with palladium acetate. While syn and anti isomers about the C–N double bond were possible, only one, presumably the anti isomer, was found in these complexes. Three varieties of hydrazone complexes were likewise prepared. Benzaldazine gave complex VI as bright red needles, acetophenone dimethylhydrazone gave complex VII, and 1-methyl-1-phenylhydrazones gave complexes of structure VIII.

Complex VIIIb was a mixture of syn and anti hydrazone complexes dimerized to both cis and trans isomers about the acetate bridges. The seventh type prepared was the palladium acetate complex with various *N,N*-dialkylbenzylamines. Palladium chloride derivatives of these ligands were already well known.[6] Three *N,N*-dialkylbenzylamines were used: the dimethyl, diethyl, and tetramethylene derivatives.

II. Carbonylation Reactions. A. Azobenzene Com-

Scheme III
Carbonylation of Benzylamine–Schiff Base–Palladium Acetate Complexes



plexes. The carbonylation of the azobenzene–palladium chloride complex (I) was examined in the inert solvent xylene at 100° under 1 atm of CO. About 4 equiv of CO per mole of dipalladium complex was absorbed and a dark purple precipitate formed (complex X). This material was insoluble in all solvents. It had ν_{CO} 1950 cm^{-1} indicative of terminal carbonyls. Analyses suggest the formula $C_7H_5NOClPd$, or more probably a polymer of this formula. The compound reacted with warm methanol with precipitation of palladium and formation of II in 77% yield. (See below.) If this formulation of X is correct, the material was obtained in 98% yield. Two other products were also formed in the carbonylation: the lactone XI, isolated in 25% yield, identical with the material obtained by the high-temperature carbonylation of azobenzene with nickel carbonyl,[14] and 9% of II.

The carbonylation of the azobenzene–palladium acetate complex (III) in chlorobenzene at 100° gave 15% II and 15% XI. The remainder of the material was insoluble and could not be separated from the palladium metal also formed.

Compounds XI and II probably are being formed in the azobenzene carbonylation as shown in Scheme I. An initial CO insertion, forming XII, and an addition of the acylpalladium group across the nitrogen–nitrogen double bond would give XIII. This complex could then either internally ortho palladate to give complex XIV or react with acetic acid (or water in the reaction of I) formed in subsequent reactions and produce II. Complex XIV would then undergo a hydrogen shift from palladium to nitrogen, insert CO, and cyclize by internal addition of the acylpalladium group to the amide carbonyl. A final 1,4-hydridopalladium acetate elimination would form XI. Apparently, the 6:5 ring closure observed is much more favorable than the symmetrical 5:5 closure which might have been expected.

Carbonylation of III in ethanol at 50° produces 44% of II, 21% of azobenzene, and 15% of a new compound, 2-ethoxycarbonylazobenzene. Apparently, the last compound is being formed by ethanolysis of XII. The origin of the azobenzene is not clear.

A catalytic synthesis of II from azobenzene using cobalt carbonyl as catalyst in an inert solvent at 190° and 150 atm pressure has been reported.[15] Cobalt[7] analogs of III, XII, and XIII with "$(CO)_3Co$" replacing "PdCl" are presumably involved in this reaction. The last complex could be reduced with $HCo(CO)_4$; the $Co_2(CO)_8$ formed would ortho metalate the azobenzene and the catalytic cycle would be complete.[12]

B. Schiff Base Complexes. The tendency for azobenzene to react at both aromatic rings complicated the carbonylation reaction. Carbonylations of the Schiff base complexes, IVa–c, were more straightforward. The benzalaniline–palladium acetate complex (IVa) carbonylated readily in xylene at 100° with 1 atm of CO, forming only one product, 3-acetoxy-3-phenylphthalimidine (XVIIa), in 65% yield. The *o*-methyl derivative IVb reacted analogously.

The carbonylation of IVa in the presence of nucleophiles led to incorporation of the nucleophile in the products. In the presence of aniline, 3-anilino-2-phthalimidine (XVIIIa) was formed in 63% yield rather than the acetate. The acetate was apparently not the initial product, since it did not react with aniline under these conditions. Similarly, in methanol solution 3-methoxy-2-phthalimidine (XVIIIb) was formed in 24% yield along with the uncyclized ester, XIXa, isolated in 55% yield. In ethanol the yields were reversed and 58% cyclization to XVIIIc occurred along with formation of 29% of "open chain" ester, XIXb.

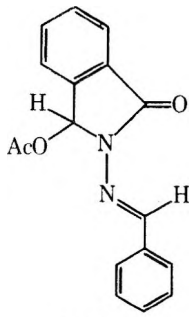
The methyl derivative, IVc, carbonylated in xylene at 100° to form exclusively the olefinic product XX in 86% yield rather than the tertiary acetate. These reactions may be explained by the equations shown in Scheme II. Initially, CO insertion and bridge breaking likely occur forming intermediate XV, which then has two possible reaction paths in alcohol solvents. The alcohol may either attack the carbonyl group and form noncyclicized ester XIX or the

compound may undergo an internal addition of the acylpalladium group to the nitrogen–carbon double bond to form XVI. The second path is the sole reaction course in xylene solvent. Complex XVI then has three possible reaction paths it may follow depending upon the substituents present and whether nucleophiles are in the reaction solution. A simple reductive elimination of product acetate, XVII from complex XVI, apparently occurs if R^1 is H. If R^1 is methyl (or presumably any other alkyl with an α-hydrogen substituent), metal hydride elimination is preferred and olefin XX is formed. When nucleophiles are present, at least when R^1 = H, the palladium group may also be replaced by the ligand minus a hydrogen.

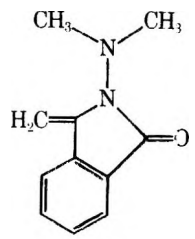
Schiff base–palladium acetate complexes of type V underwent carbonylation in xylene to form different cyclic products than type IV complexes because of the exocyclic double bond. See Scheme III. Carbon monoxide insertion followed by an internal addition of the acylpalladium group to the nitrogen–carbon double bond would produce complex XXI, which then may either reductively eliminate product acetate if R = H forming XXII (obtained in 48% yield at 100°), or eliminate metal hydride if R = CH_3 producing olefin XXIII (isolated in 49% yield after reaction in xylene at 130°. Complex XXIb did not carbonylate rapidly below 130°).

C. Azine and Hydrazone Complexes. The benzaldazine–palladium acetate complex (VI) carbonylated readily in xylene at 100°, producing a single product, isolated in 48% yield, 3-acetoxy-2-benzalimidophthalimidine (XXIV). This material is likely formed by a mechanism analogous to the one proposed for the carbonylation of IVa by Scheme II. The presence of the second carbon–nitrogen double bond apparently does not affect the reaction.

Carbonylation of the palladium acetate complex of the 1,1-dimethylhydrazone of acetophenone (VII) in xylene at 100° was similar to the corresponding reaction of IVc in Scheme II. A CO insertion, cyclization, and metal hydride elimination sequence was now followed forming XXV in 61% yield, since a tertiary palladium complex with β hydrogen substituents was the intermediate in the reaction.



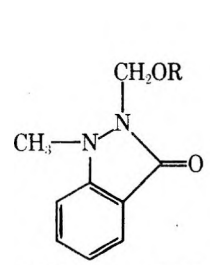
XXIV



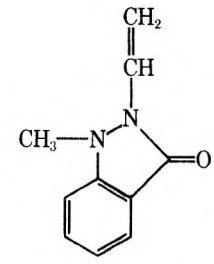
XXV

The above data led us to expect that the hydrazone–palladium acetate complexes VIIIa and VIIIb would behave analogously to complexes Va and Vb. Indeed this turned out to be correct. Complex VIIIa in xylene at 100° reacted readily with carbon monoxide, forming acetate XXVIa in 53% yield. Carbonylation in ethanol at room temperature formed 38% XXIXa, 28% formaldehyde 1-methyl-1-phenylhydrazone, and 13% XXVIb. Complex VIIIb carbonylated at room temperature in benzene, forming mainly olefin XXVII (68%) along with traces of what appeared to be the secondary acetate XXVIIIa.

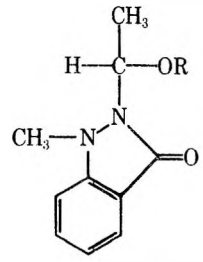
Carbonylation of VIIIb in methanol at room temperature gave mainly uncyclized methyl ester XXIXb (69%) and 20% of the cyclized methyl ether XXVIIIb. In ethanol, only the cyclized ethyl ether, XXVIIIc (68%), was obtained.



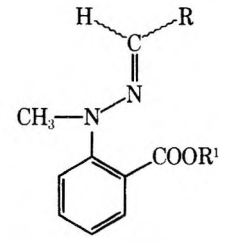
XXVIa, R = $COCH_3$
b, R = CH_2CH_3



XXVII



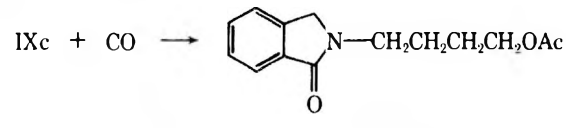
XXVIIIa, R = $COCH_3$
b, R = CH_3
c, R = C_2H_5



XXIXa, R = H; R^1 = C_2H_5
b, R = CH_3; R^1 = CH_3
c, R = CH_3; R^1 = C_2H_5

D. Tertiary Benzylamine Complexes. The carbonylation of the palladium acetate–tertiary benzylamine complexes (IXa and IXb) might have been expected to produce only mixed anhydrides and ketones as was observed in the carbonylation of simple arylpalladium acetate derivatives.[16,17] Ketones were not observed; hydrolysis products of the mixed anhydrides were, however. An unexpected third type of product was also formed. The third product, which was formed in both reactions, was a phthalimidine produced by cyclization and loss of one of the *N*-alkyl groups. Compound IXa, the *N,N*-dimethylbenzylamine complex, on carbonylation in xylene at 100° for 30 min gave 72% of the demethylated product, 2-methylphthalimidine (XXXa), along with 4.5% of acid (zwitterion) XXXIa, presumably formed by hydrolysis during isolation of an initially formed mixed anhydride with acetic acid. Similarly, complex IXb, the *N,N*-diethylbenzylamine complex, on carbonylation at 100° in xylene for 15 min gave 27% of 2-ethylphthalimidine (XXXb) and 36% of the acid XXXIb. There was also a trace of the ethyl ester of XXXIb formed. The last product was isolated in 24% yield when the reaction was carried out at 100° for 5 hr instead of for only 15 min. In this reaction 53% of XXXb was also formed. It is not clear how the ester was being produced, but obviously it was being formed in a secondary reaction since very little was formed in 15 min, by the time the palladium had all precipitated and the total amount of carbon monoxide had been absorbed. When the carbonylation of IXb was carried out at room temperature in benzene for 3 hr the only product formed was apparently the mixed anhydride, since a 63% yield of acid XXXIb was isolated after exposure to moist air.

We were not able to determine the fate of the second alkyl group in the reactions when esters of XXXI were not formed. We, therefore, investigated the carbonylation of IXc, the palladium acetate–*N*-benzylpyrrolidine complex, where the "second alkyl group" could not be lost as a low molecular weight fragment. The carbonylation of IXc gave only one significant product, 2-(4′-acetoxybutyl)phthalimi-

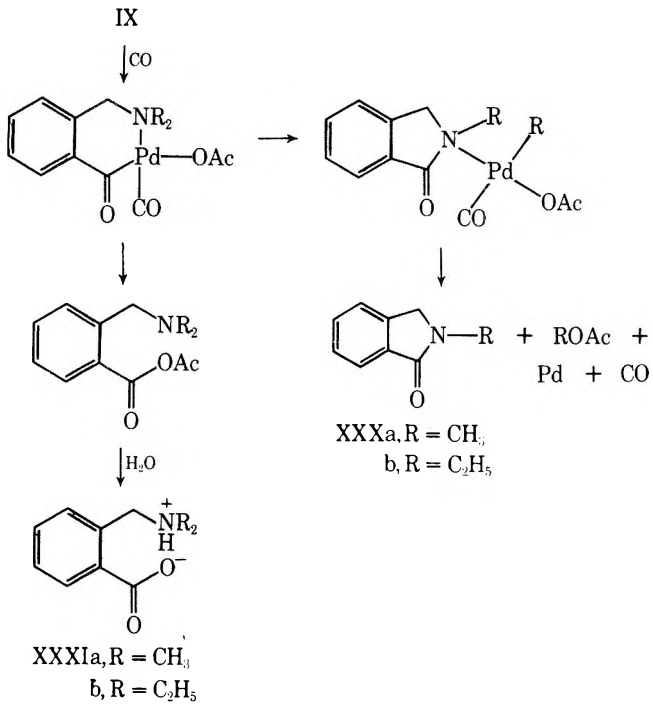


XXXII

dine (XXXII) showing that in this example, at least, the "alkyl group" was converted into the alkyl acetate.

The mechanism by which the carbon–nitrogen bond is cleaved is not certain, but it is probably a 1:2 shift of alkyl from nitrogen to palladium occurring with the ring closure. Plausible mechanisms for the ring closure and hydrolysis reaction are shown in Scheme IV.

Scheme IV
Carbonylation of *N,N*-Dialkylbenzylamine–Palladium Acetate Complexes



Conclusions

The carbonylation of isolable ortho-metalated palladium complexes has proved to be a general reaction capable of producing a variety of unusual five-membered ring heterocyclic and open-chain products. Mechanisms of reaction have been suggested which will allow prediction of products which can be obtained by carbonylation of the many related complexes which probably can be prepared.

Experimental Section

Reagents. Palladium chloride and palladium acetate were obtained from Engelhard Industries. They were generally used without further purification, although the purity of the palladium acetate varied significantly from batch to batch and particularly bad lots, as judged the amount of benzene-insoluble material (pure material is completely soluble), were recrystallized from acetic acid before use. Carbon monoxide (99.5%) was obtained from Matheson Gas Products. *N,N*-Dimethylbenzylamine was used as obtained from the Aldrich Chemical Co. *N,N*-Diethylbenzylamine and *N*-benzylpyrrolidine were prepared from benzyl chloride and the appropriate secondary amine.

Di-μ-chlorobis[*o*-(phenylazo)phenyl]dipalladium (I). This material was prepared by the method of Cope.[1]

Di-μ-acetatobis[*o*-(phenylazo)phenyl]dipalladium (III). A solution of 1.91 g (10.5 mmol) of azobenzene and 2.24 g (10.0 mmol) of powdered palladium acetate in 50 ml of anhydrous methyl alcohol was boiled for 1 hr. The mixture was concentrated under reduced pressure and cooled in Dry Ice. The crystals which formed were filtered and recrystallized from benzene–hexane. There was obtained 1.91 g (57%) of very dark red prisms, mp 208–210°.

Anal. Calcd for $C_{28}H_{24}N_4O_4Pd_2$: C, 48.51; H, 3.48; N, 8.08. Found: C, 48.82; H, 3.35; N, 7.99.

NMR ($CDCl_3$) τ 2.85 (multiplet, 18 aromatic protons), 7.96 (singlet, 6 acetate methyl protons), 7.77 and 8.82 (two singlet of low intensity, assigned to the nonequivalent acetate methyls of the cis dimer).

Di-μ-acetatobis[*o*-(*N*-phenylformimidoyl)phenyl]dipalladium (IVa). This complex was prepared by the procedure of Onoue and Moritani.[3]

Di-μ-acetatobis[*o*-(*N*-*o*-tolylformimidoyl)phenyl]dipalladium (IVb). The preparation of this complex has also been described by Onoue and Moritani.[3]

Di-μ-acetatobis[*o*-(*N*-phenylacetimidoyl)phenyl]dipalladium (IVc). Onoue and Moritani have previously prepared this compound.[3] We obtained the product in 85% yield after recrystallization from benzene–hexane.

Di-μ-acetatobis[α-(benzylideneamino)-*o*-tolyl]dipalladium (Va). A mixture of 2.24 g (10 mmol) of $Pd(OAc)_2$ and 2.05 g (10.5 mmol) of *N*-benzylbenzaldehyde imine in 50 ml of acetic acid was boiled for 50 min. After cooling, water was added and the solid formed was separated by filtration. After washing with water and air drying, the product was crystallized from benzene to give 3.00 g (80%) of golden yellow crystals; mp 194° dec; NMR ($DCCl_3$) τ 2.7 (m, 18 aromatic protons and 2 methine protons), 5.50 (AB quartet, 4 methylene protons), 7.8 (s, 6 acetate protons).

Anal. Calcd for $C_{32}H_{30}N_2O_4Pd_2$: C, 53.44; H, 4.20; N, 3.89. Found: C, 53.49; H, 4.18; N, 3.78.

Di-μ-acetatobis[α-[(α-methylbenzylidene)amino]-*o*-tolyl]dipalladium (Vb). This complex was prepared by heating 2.09 g (10 mmol) of *N*-benzylacetophenone imine with 2.24 g (10 mmol) of palladium acetate in 30 ml of acetic acid at reflux temperature for 1 hr. After cooling, water was added and the solid formed was separated by filtration. After air drying, the crude material was dissolved in methylene chloride and chromatographed on silica gel. The yellow eluate was concentrated and pentane was added. Yellow crystals, 1.63 g (44%), of the product were obtained: mp 245–249° dec; NMR ($DCCl_3$) τ 2.77 (m, 18 aromatic protons), 6.5 and 5.5 (AB doublets, methylene protons, J = 14.4 Hz), 7.82 (s, methyl protons), 8.2 (s, 6 acetate protons).

Anal. Calcd for $C_{34}H_{34}N_2O_4Pd_2$: C, 54.63; H, 4.58; N, 3.75. Found: C, 54.81; H, 4.62; N, 3.66.

Di-μ-acetatobis[α-(benzylidenehydrazono)-*o*-tolyl]dipalladium (VI). A mixture of 2.18 g (10.5 mmol) of benzaldazine and 2.24 g (10 mmol) of $Pd(OAc)_2$ in 50 ml of acetic acid was boiled for 45 min. After cooling, water was added and the solid formed was separated by filtration, washed thoroughly with water, and air dried. Recrystallization from benzene–hexane gave 2.86 g (77%) of bright red needles, mp 218–222° dec.

Anal. Calcd for $C_{32}H_{28}O_4N_4Pd_2$: C, 51.56; H, 3.78; N, 7.51. Found: C, 51.55; H, 3.61; N, 7.67.

NMR ($DCCl_3$) τ 1.25, 1.35, 1.95, and 2.20 (all s, 4 protons, methine protons, τ 1.25 and 1.95 signals were from the cis dimer and τ 1.35 and 2.20 from the trans dimer), 2.5 (m, 18 aromatic protons), 7.68, 7.70, and 7.90 (all s, 6 protons, τ 7.68 and 7.90 signals were from the nonequivalent acetate methyls in the cis dimer, and the τ 7.70 signal was from the trans dimer; from the relative intensities the solution was calculated to contain 66% of the trans isomer). Addition of a few drops of pyridine to the NMR solution removed the multiple peaks due to cis and trans dimers by converting the compounds to mononuclear species.

Di-μ-acetatobis[*o*-[1-(dimethylhydrazono)ethyl]phenyl]dipalladium (VII). A mixture of 1.70 g (10.5 mmol) of acetophenone dimethylhydrazone and 2.24 g (10 mmol) of palladium acetate in 50 ml of acetic acid was heated on the steam bath for 1 hr. After cooling and diluting with water, the product which precipitated was washed and air dried. Purification was achieved by chromatography over silica gel, elution with benzene, and recrystallization from benzene–hexane. There was obtained 2.08 g (61%) of pale yellow crystals, mp 230–235° dec. The material was dried at 90° to remove occluded benzene.

Anal. Calcd for $C_{24}H_{32}N_4O_4Pd_2$: C, 44.12; H, 4.94; N, 8.57. Found: C, 44.28; H, 4.79; N, 8.19.

NMR (C_6D_6) τ 3.10 (m, 8 aromatic protons), 7.65 (s, 12 *N*-methyl protons), 7.82 (s, 6 methyl protons), 8.30 (s, 6 acetate protons).

Di-μ-acetatobis[*o*-(1-methyl-2-methylenehydrazino)phenyl]dipalladium (VIIIa). A mixture of 0.85 g (6.3 mmol) of the 1-methyl-1-phenylhydrazone of formaldehyde and 1.42 g (6.3 mmol) of $Pd(OAc)_2$ with 50 ml of methylene chloride was heated to boiling for 45 min. A little decolorizing carbon was added and the reaction mixture was filtered. Evaporation of the solvent under reduced pressure and recrystallization from benzene by adding hexane three times below 35° gave 1.11 g (58%) of yellow crystals of the product, mp 193° dec.

Anal. Calcd for $C_{20}H_{24}N_4O_4Pd_2$: C, 40.22; H, 4.05; N, 9.38. Found: C, 39.98; H, 3.99; N, 9.22.

NMR ($DCCl_3$) τ 3.30 (m, 8 aromatic protons), 3.80, 4.60 (2 d, 4 methylene protons, J = 8 Hz), 7.40 (s, 6 *N*-methyl protons), 7.85 (6 acetate protons).

Di-μ-acetatobis[o-(2-ethylidene-1-methylhydrazino)phenyl]dipalladium (VIIIb). This complex was prepared by stirring a mixture of 0.81 g (5.5 mmol) of the 1-methyl-1-phenylhydrazone of acetaldehyde (ca. 55% anti:45% syn) and 1.12 g (5 mmol) of $Pd(OAc)_2$ with 50 ml of acetone at room temperature for 3 hr. The solution was treated with decolorizing carbon and filtered, and the solvent was removed under reduced pressure at room temperature. The crude product was then crystallized from benzene by adding hexane slowly at room temperature. There was obtained 0.77 g (45%) of greenish-yellow crystals, mp 138° dec.

Anal. Calcd for $C_{22}H_{28}N_4O_4Pd_2$: C, 42.26; H, 4.51; N, 8.96. Found: C, 42.12; H, 4.45; N, 8.76.

The spectrum in $CDCl_3$ was very complex because of the presence of at least three isomeric forms, presumably isomers, at the carbon–nitrogen double bond and cis–trans isomers about the acetate bridges. The spectrum was considerably simplified by the addition of a few drops of deuterated pyridine to the $CDCl_3$ solution. The pyridine breaks the dimeric bridges and reduces the number of isomers present to only two: the syn and anti isomers of the carbon–nitrogen double bond. NMR τ 3.5 (m, 4 aromatic protons and an olefinic proton), 7.5 (s, 3 *N*-methyl protons), 7.8 and 8.4 (2 d, 3 protons of the syn and anti methyl group, J = 5 Hz, for both isomers, 55% anti and 45% syn), 2.1 (s, 3 acetate protons).

Di-μ-acetatobis[α-(dimethylamino)-o-tolyl]dipalladium (IXa). To 150 ml of methanol was added with stirring 5.40 g (40 mmol) of *N,N*-dimethylbenzylamine and 4.48 g (20 mmol) of palladium acetate. After stirring for 3 hr at room temperature, the solution was filtered and the solvent was removed under reduced pressure at room temperature. The solid residue was dissolved in benzene and purified by chromatography over silica gel. Evaporation of the yellow eluate and recrystallization from benzene–hexane gave 2.86 g (47%) of yellow crystals of the product, mp 210–211°.

Anal. Calcd for $C_{22}H_{30}N_2O_4Pd_2$: C, 44.09; H, 5.04; N, 4.67. Found: C, 44.13; H, 5.09; N, 4.71.

NMR (C_6D_6) τ 3.00 (m, 8 aromatic protons), 6.80 (AB quartet, 4 methylene protons, J = 21.5 Hz), 7.61 and 8.02 (s, 12 *N*-methyl protons), and 7.94 (s, 6 acetate protons).

Di-μ-acetatobis[α-(diethylamino)-o-tolyl]dipalladium (IXb). This complex was prepared from *N,N*-diethylbenzylamine and palladium acetate as described for the *N,N*-dimethylbenzylamine reaction above. Recrystallization of the product from hexane gave a 66% yield of pale yellow crystals, mp 189–192° dec.

Anal. Calcd for $C_{26}H_{38}N_2O_4Pd_2$: C, 47.65; H, 5.84; N, 4.27. Found: C, 47.73; H, 5.90; N, 4.31.

NMR ($CDCl_3$) τ 3.15 (m, 8 aromatic protons), 6.27 (AB quartet, J = 13 Hz, 4 methylene protons), 7.30 (m, 8 methylene protons in ethyl groups), 8.30 (s, 6 acetate protons), and 9.40 (t, 12 methyl protons).

Di-μ-acetatobis(α-1-pyrrolidinyl-o-tolyl)dipalladium (IXc). A mixture of 0.40 g (2.24 mmol) of *N*-benzylpyrrolidine, 0.56 g (2.24 mmol) of $Pd(OAc)_2$, and 30 ml of benzene was stirred at room temperature for 48 hr. The benzene solution was concentrated under reduced pressure and chromatographed on silica gel. The yellow eluate was concentrated and the solid residue was crystallized from hexane to give 0.36 g (45%) of pale yellow crystals of product, mp 164° dec.

Anal. Calcd for $C_{26}H_{34}O_4N_2Pd_2$: C, 47.94; H, 5.26; N, 4.30. Found: C, 47.78; H, 5.18; N, 4.14.

NMR ($CDCl_3$–C_6D_6) τ 2.90 (m, 4 aromatic protons), 6.70 (m, AB quartet, 2 methylene protons, J = 14 Hz), 6.3, 7.2, and 8.5 (m, 8 methylene protons), 8.00 (s, acetate protons).

Carbonylation of the Azobenzene–Palladium Chloride Complex (I) in Xylene. In the previously described gasometric apparatus[18] was placed 0.50 g (0.77 mmol) of I, the apparatus was flushed with CO at 100°, and 10 ml of xylene was injected with magnetic stirring. In 2 hr, 3–4 equiv per mole of I had been absorbed and the reaction mixture was filtered hot to remove the purple solid present. The solid was rinsed several times with methylene chloride and the rinsings were added to the original filtrate. The insoluble purple product, 0.395 g (98%), complex X, did not have a sharp melting point, but decomposition began at about 120°. The complex in a Nujol mull showed a strong carbonyl absorption at 1950 cm^{-1}.

Anal. Calcd for $(C_7H_5NOClPd)_n$: C, 32.46; H, 1.95; N, 5.41. Found: C, 32.15; H, 1.67; N, 5.25.

On reaction with hot methanol, complex X decomposed, producing a precipitate of palladium metal and a solution from which a 77% yield of compound II was obtained by sublimation, mp 206–207° (reported mp 203–204°).[12] The molecular weight by mass spectroscopy was 210.079 (calcd 210.0793).

The soluble portion of the carbonylation reaction product was isolated by evaporation of the original filtrate. The mixture was separated by dissolving it in methylene chloride and chromatographing on silica gel. Methylene chloride eluted 0.029 g (9%) of compound II, mp 205–206° and ir spectrum identical with that of a known sample,[12] and methanol eluted 0.091 g (25%) of bright yellow lactone XI, mp 293–297° (reported mp 296°,[14] 300°[19]). The molecular weight by mass spectroscopy was 236.056 (calcd 236.0586).

Carbonylation of the Azobenzene–Palladium Acetate Complex (III). A. In Chlorobenzene Solution. Carbonylation of 1.70 g of complex III (2.45 mmol) in 15 ml of chlorobenzene at 100° under 1 atm of carbon monoxide was carried out as in the preceding experiment. In 3 hr, 169 ml of CO was absorbed and the reaction was complete. The precipitated palladium was separated by filtration and the solvent was evaporated from the filtrate under reduced pressure. The residue was separated by chromatography as in the preceding example. There was obtained 0.150 g of II (15%), mp 207–208°, ν_{CO} 1680 cm^{-1}, and 0.171 g (15%) of lactone XI, mp 293–297°.

B. In Ethanol Solution. The carbonylation of 0.300 g (0.43 mmol) of III in 10 ml of absolute ethanol was carried out at 50° as described in the preceding experiments. A total of 12.4 ml of CO was absorbed in 3 hr. The reaction mixture was then cooled and filtered, and the solvent was removed under reduced pressure. Hexane was added to the residue and the colorless crystals which formed were separated and recrystallized from aqueous ethanol. There was obtained in this manner 0.080 g (44%) of II, mp 203–205. The hexane solution obtained after filtration of II was concentrated and chromatographed on silica gel eluting with hexane. The first fraction eluted was azobenzene, 0.035 g (21%). This was followed by 0.032 g of red oil identified as 2-ethoxycarbonylazobenzene (15%): molecular weight by mass spectroscopy, 254.106 (calcd 254.1054); NMR ($CDCl_3$) τ 2.50 (m, 9 aromatic protons), 5.70 (q, 2 methylene protons), and 8.80 (t, 3 methyl protons).

Carbonylation of the Benzalaniline–Palladium Acetate Complex (IVa). A. In Xylene. Carbonylation of 1.0 g (1.45 mmol) of complex IVa in 10 ml of xylene at 100° was complete in 2.5 hr. Evaporation of the solvent and chromatography of the crude product on silica gel, eluting the product with benzene–ether, gave 0.50 g (65%) of colorless crystals of XVIIa, mp 84–85°, after crystallization from heptane. The ir spectrum showed a strong carbonyl absorption at 1730 cm^{-1}.

Anal. Calcd for $C_{16}H_{13}O_3N$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.87; H, 5.01; N, 5.28.

NMR ($CDCl_3$) τ 2.50 (m, 9 aromatic and 1 tertiary proton) and 7.95 (s, 3 acetate protons).

The product was readily hydrolyzed by boiling with aqueous alkali to give 2-phenyl-3-hydroxyphthalimidine: mp 170–171° (reported mp 171–172°);[20] molecular weight found by mass spectroscopy 225.081 (calcd 225.0790).

B. In Xylene with Aniline. Carbonylation of 3.0 g (4.3 mmol) of IVa in 20 ml of xylene containing 1.62 g (17.4 mmol) of aniline at 100° as above was complete in 2 hr. Evaporation of the solvent from the filtered reaction mixture and recrystallization of the residue from benzene–heptane gave 1.6 g (63%) of colorless crystals of XVIIIa: mp 166–167° (reported mp 162°);[21] molecular weight found by mass spectroscopy 300.127 (calcd 300.1263). There is a strong carbonyl absorption in the ir spectrum of the product at 1670 cm^{-1}; NMR ($CDCl_3$) τ 2.10 (m, 14 aromatic and 1 tertiary proton) and 5.00 (broad m, 1 amine proton).

C. In Methanol Solution. A solution of 0.50 g (0.71 mmol) of IVa in 10 ml of methanol was carbonylated at 50° in the usual manner. After 3.5 hr, 50 ml of CO had been taken up and the reaction stopped. The reaction mixture was filtered, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel. A small amount of benzaldehyde was apparently present judging by the odor of the first fractions eluted. Benzene–hexane eluted a pale yellow oil, 0.203 g (55%) of ester XIXa: molecular weight found by mass spectroscopy 239.096 (calcd 239.0946); NMR ($CDCl_3$) τ 0.81 (s, 1 tertiary proton), 2.50 (m, 9 aromatic protons), and 6.20 (s, 3 methyl protons).

The benzene eluate from the chromatography contained 0.087 g (24%) of XVIIIb, mp 77–79°. The molecular weight found by mass spectroscopy was 239.092 (calcd 239.095); NMR ($CDCl_3$) τ 2.70 (m, 9 aromatic protons), 3.70 (s, 1 tertiary proton), 7.20 (s, 3 methyl protons).

D. In Ethanol Solution. This carbonylation was carried out at 50° exactly as described for the reaction in methanol employing anhydrous ethanol in place of methanol. Chromatography separated a 29% yield of the yellow liquid ester, XIXb, and a 58% yield of 2-phenyl-3-ethoxyphthalimidine (XVIIIc), mp 74–76° after crystallization from aqueous ethanol.

The ester product, XIXb, had a strong carbonyl bond at 1715 cm^{-1}. The molecular weight found by mass spectroscopy was 253.112 (calcd 253.110); NMR ($CDCl_3$) τ 0.75 (s, methine proton), 2.50 (m, 9 aromatic protons), 5.60 (q, methylene protons, J = 8 Hz), 8.60 (t, methyl protons).

The phthalimidine product XVIIIc had a molecular weight of 253.113 by mass spectroscopy (calcd 253.110); NMR ($CDCl_3$) τ 2.50 (m, 9 aromatic protons), 3.52 (s, tertiary hydrogen), 6.85 (m, methylene group), 8.95 (t, methyl protons).

Carbonylation of IVb in Xylene. The carbonylation of IVb, 0.690 g (0.94 mmol), was carried out in 10 ml of xylene at 100° as described in the carbonylation of IVa. The reaction mixture was filtered to remove precipitated palladium, the solvent was evaporated under reduced pressure, and the residue was crystallized from benzene–hexane. There was obtained in 66% yield colorless crystals of compound XVIIb, mp 125–127°. The molecular weight found by mass spectroscopy was 281.105 (calcd 281.1052). The infrared spectrum showed a strong carbonyl absorption at 1720 cm^{-1}; NMR ($CDCl_3$) τ 2.50 (m, 8 aromatic and the tertiary proton), 7.65 (s, 3 acetate protons), 8.00 (s, 3 methyl protons).

Carbonylation of Complex IVc in Xylene. Carbonylation of 3.0 g (4.2 mmol) of complex IVc in 25 ml of xylene at 100° required 23 hr to reach completion. The crude product obtained after removal of the xylene under reduced pressure was purified by chromatography on silica gel. The only significant product was eluted with benzene–hexane. There was obtained 1.59 g (86%) of colorless crystals of XX, mp 97–98° (reported[21] mp 99–100°). The compound in chloroform solution had the expected infrared absorptions at 1730 and 1630 cm^{-1}. The molecular weight was found to be 221.084 (calcd 221.084); NMR ($CDCl_3$) τ 2.50 (m, 9 aromatic protons), 4.78 and 5.69 (2 d, J = 1.7 Hz, methylene protons).

Carbonylation of Complex Va in Xylene. The carbonylation of Va, 2.00 g (2.80 mmol), in 20 ml of xylene at 100° was complete in 10 hr. Filtration of the reaction mixture, evaporation of the xylene under reduced pressure, and two crystallizations of the residue from heptane gave 48% of compound XXII, mp 125–126°. The infrared spectrum showed a band at 1688 cm^{-1}. The molecular weight found was 281.104 (calcd 281.1052); NMR ($CDCl_3$–C_6D_6) τ 2.60 (m, 9 aromatic protons), 3.05 (s, tertiary proton), 5.30 (AB q, methylene group), 8.10 (s, 3 acetate protons).

Carbonylation of Complex Vb in Xylene. Carbonylation of 0.650 g (0.87 mmol) of Vb was carried out in 10 ml of xylene under 20 psi of carbon monoxide in a capped bottle at 130° for 2.5 hr. After cooling, the bottle was opened, the solvent was removed under reduced pressure, and the product was chromatographed on silica gel. Hexane–methylene chloride eluted 0.190 g (49%) of compound XXIII: mp 106–108°; molecular weight found 235.090 (calcd 235.100); NMR ($CDCl_3$–C_6D_6) τ 2.80 (m, 9 aromatic protons), 5.20 and 5.50 (2 d, J = 2.5 Hz, terminal methylene group), 5.30 (s, methylene protons).

Carbonylation of Complex VI in Xylene. One gram (1.34 mmol) of complex VI was carbonylated in 10 ml of xylene as usual at 100° in 5.5 hr. The product isolated by filtration and evaporation of the solvent was purified by two recrystallizations from heptane. There was obtained a 48% yield of compound XXIV, mp 102–103°. It had a carbonyl absorption at 1740 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.61, H, 4.79; N, 9.55.

NMR ($CDCl_3$) τ 0.81 (s, methine proton), 2.5 (9 aromatic protons), 7.87 (s, 3 acetate protons).

Carbonylation of Complex VII in Xylene. Carbonylation of 0.50 g (0.76 mmol) of VII in 10 ml of xylene was carried out at 100° in 3 hr, during which time 33 ml of carbon monoxide was absorbed. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel. Pentane–benzene eluted 61% of compound XXV, obtained as a viscous liquid. It had a strong carbonyl absorption at 1690 cm^{-1} in its infrared spectrum. The molecular weight observed was 188.094 (calcd 188.095); NMR (C_6D_6) τ 2.50 (m, 4 aromatic protons), 4.75 and 4.91 (2 d, J = 0.9 Hz, terminal methylene group), and 7.03 (s, 6 N-methyl protons).

Carbonylation of Complex VIIIa. A. In Xylene. Carbonylation of 0.50 g (0.84 mmol) of VIIIa in 10 ml of xylene for 6 hr at 100° was carried out as in the above examples. No reaction occurred at 25°. The product obtained after evaporation of the xylene, 0.282 g, was nearly pure XXVIa by NMR. Chromatography on silica gel, eluting with ether–benzene, gave a pure sample, 0.195 g (53%), of XXVIa as a pale yellow liquid. The infrared spectrum showed the expected carbonyl absorption at 1680 cm^{-1}. On standing the product solidified. Recrystallization from benzene–hexane gave colorless crystals, mp 160–161°.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.05; H, 5.63; N, 12.78.

NMR ($CDCl_3$) τ 2.60 (m, 4 aromatic protons), 4.10 (s, 2 methylene protons), 6.75 (s, 3 N-methyl protons), 2.00 (s, 3 acetate protons).

B. In Ethanol. Carbonylation of 0.22 g (0.37 mmol) of VIIIa was carried out at room temperature in 10 ml of absolute ethanol. The reaction was over in a few minutes after the absorption of about 8 ml of CO. The reaction mixture was filtered, the solvent was removed under reduced pressure, and the products were separated by chromatography on silica gel. Benzene eluted 0.028 g (28%) of formaldehyde 1-methyl-1-phenylhydrazone. Ether–benzene (20:80) eluted ester XXVIa, 0.057 g (38%), as a colorless liquid. Finally, 50:50 ether–benzene eluted 0.019 g (12.5%) of XXVIb as a viscous yellow liquid.

Ester XXVIa had a carbonyl absorption at 1730 cm^{-1} and a molecular weight of 206.105 (calcd 206.105); NMR ($CDCl_3$) τ 2.80 (m, 4 aromatic protons), 3.90 (s, 2 terminal vinyl protons), 5.30 (q, 2 methylene protons), 6.90 (s, 3 N-methyl protons), 8.70 (t, 3 methyl protons).

Ether XXVIb had a carbonyl band at 1680 cm^{-1} and a molecular weight of 206.103 (calcd 206.105); NMR ($CDCl_3$) τ 2.70 (m, 4 aromatic protons), 4.80 (s, 2 methylene protons), 6.35 (q, 2 methylene protons), 6.70 (s, 3 N-methyl protons), 8.85 (t, 3 methyl protons).

Carbonylation of Complex VIIIb (Mixture of Isomers). A. In Benzene. A solution of 0.300 g (0.52 mmol) of VIIIb in 10 ml of benzene at room temperature in the gasometric apparatus absorbed about 15 ml of CO in less than 2 min and the reaction stopped. The products were isolated by chromatography on silica gel after evaporation of the solvent. Benzene–ether eluted as a pale yellow oil, 68% of compound XXVII. The infrared spectrum showed a strong carbonyl absorption at 1684 cm^{-1} and the molecular weight was 174.077 (calcd 174.079); NMR (CCl_4) τ 2.60 (m, 4 aromatic protons, 1 vinyl proton), 5.22 and 5.34 (2 d, J = 16 and 10 Hz, 2 terminal vinyl protons), 6.85 (s, 3 N-methyl protons).

Elution of a second fraction with 1:1 ether–benzene gave a very small amount of a colorless solid which appeared to be compound XXVIIIa: NMR (CCl_4) τ 2.50 (4 aromatic protons plus 1 tertiary proton), 6.77 (s, 3 N-methyl protons), 9.85 (3 acetate protons), 8.40 (d, 3 methyl protons).

B. In Methanol. A solution of 0.600 g (1.04 mmol) of VIIIb in 10 ml of methanol was carbonylated in the gasometric apparatus at room temperature. About 41 ml of CO was absorbed in 10 min and the reaction stopped. Evaporation of the solvent under reduced pressure at room temperature and chromatography on silica gel separated two major products. Elution with 1:4 ether–benzene separated 0.275 g (69%) of liquid XXIXb. The material had an infrared band at 1740 cm^{-1} and a molecular weight of 206.111 (calcd 206.105); NMR ($CDCl_3$) τ 3.00 (m, 4 aromatic protons, and the methine proton), 6.20 (s, 3 ester methyl protons), 6.90 (3 N-methyl protons), 8.10 (d, J = 5 Hz, ethylidene methyl protons).

Elution with 2:3 ether–benzene gave 0.078 g (20%) of compound XXVIIIb as a pale yellow liquid. An infrared absorption at 1700 cm^{-1} was observed and the molecular weight found was 206.102 (calcd 206.105); NMR (CCl_4) τ 2.60 (m, 4 aromatic protons), 4.20 (q, tertiary proton, J = 6 Hz), 6.60 (s, 3 methyl protons), 6.70 (s, 3 methyl protons), 8.50 (d, J = 6 Hz, 3 methyl protons).

Elution with ether gave 0.004 g of colorless crystals of a compound of unknown structure, mp ~120°.

C. In Ethanol. The carbonylation of 0.160 g (0.26 mmol) of VIIIb in 10 ml of absolute ethanol at room temperature required about 2 hr to reach completion when about 2 equiv of CO had been absorbed. After filtration and evaporation of the ethanol there was obtained 0.130 g of a pale yellow oil, which by NMR was fairly pure XXIXc. Chromatography on silica gel with elution with benzene–ether gave 0.076 g (68%) of a pure sample of XXIXc. Its in-

frared spectrum showed a strong carbonyl band at 1728 cm^{-1} and the observed molecular weight was 220.119 (calcd 220.121); NMR ($CDCl_3$) τ 2.70 (m, 4 aromatic protons plus tertiary proton), 5.70 (q, J = 7.5 Hz, methylene protons), 6.80 (s, 3 N-methyl protons), 8.05 (d, J = 6 Hz, 3 methyl protons), 8.65 (t, 3 methyl protons).

Carbonylation of Complex IXa in Xylene. Carbonylation of 1.50 g (2.5 mmol) of IXa in 15 ml of xylene at 100° was complete in 0.5 hr with the absorption of 70 ml of CO. After removal of the xylene under reduced pressure the products were chromatographed on alumina. Benzene eluted 0.350 g of colorless crystals of XXXa (72%) (crystallized from hexane): mp 114–115° (reported[22] mp 114–116°); NMR ($CDCl_3$) τ 2.50 (m, 4 aromatic protons), 5.65 (s, methylene group), 6.80 (3 N-methyl protons). The molecular weight observed was 147.069 (calcd 147.068).

Elution with methanol gave acid XXXIa as a colorless solid which, after crystallization from benzene–hexane, weighed 0.020 g (4.5%): mp 123–125°; NMR ($CDCl_3$) τ 2.00 (m, 8 aromatic protons), 6.09 (s, 4 methylene protons), 7.45 (s, 12 N-methyl protons). The molecular weight found was 179.099 (calcd 179.095).

Anal. Calcd for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.27; H, 7.56; N, 7.39.

Carbonylation of IXb in Xylene. Carbonylation and purification was carried out exactly as in the preceding example. The reaction was complete in 15 min at 100°. Benzene elution in the chromatography gave a 27% yield of (liquid) 2-ethylphthalimidine (XXXb). The molecular weight by mass spectroscopy was found to be 161.085 (calcd 161.084); NMR ($CDCl_3$) τ 2.50 (m, 4 aromatic protons), 5.70 (s, methylene protons), 6.30 (q, J = 8 Hz, methylene protons), 8.80 (t, methyl protons). This was apparently the same compound prepared by Brewster et al.[22]

Elution with methanol and crystallization from benzene–hexane gave 36% of colorless crystals of acid XXXIb, mp 104–106°. A second recrystallization sharpened the melting point to 105–106° (reported[23] mp 105°); NMR ($CDCl_3$) τ 2.20 (m, 8 aromatic protons), 6.00 (s, 4 methylene protons), 7.10 (q, J = 6 Hz, 8 methylene protons), 8.70 (t, 12 methyl protons). The molecular weight observed was 207.124 (calcd 207.126).

When the above reaction was allowed to continue for 5 hr at 100° (CO absorption ceased in 15 min) and the products isolated as above, there was obtained from the chromatography a new fraction which was eluted with 1:1 benzene–hexane. This material was a colorless liquid with properties indicating that it was the ethyl ester of acid XXXIb. The molecular weight observed was 235.166 (calcd 235.157); NMR ($CDCl_3$) τ 2.40 (m, 4 aromatic protons), 5.60 (q, 2 methylene protons of the ethyl ester group), 6.70 (s, 2 benzylic protons), 7.40 (q, 4 methylene protons of N,N-diethyl group), 8.60 (t, 3 methyl protons in the ester ethyl group), 8.80 (t, 6 methyl protons in the N,N-diethyl group).

There was also eluted from the chromatography 53% of XXXb and 0.6% of XXXIb.

Carbonylation of IXb in benzene at room temperature was also carried out. The reaction was complete in about 3 hr. Filtration of the reaction mixture and addition of hexane gave a 63% yield of acid XXXIb, mp 103–106°. After recrystallization from benzene–hexane the melting point was 105–106° (reported[23] mp 105°).

Carbonylation of IXc in Xylene. The carbonylation of 0.400 g (0.61 mmol) of IXc was carried out in 10 ml of xylene at 100°. The reaction was over in about 10 min when 20 ml of CO had been absorbed. The products were isolated as in the carbonylation of IXa above. Benzene–ether eluted the major product, ester XXXII, in 51% yield as a pale yellow liquid. The infrared spectrum of the product had carbonyl absorptions at 1680 and 1730 cm^{-1}. The molecular weight found was 247.122 (calcd 247.121); NMR ($CDCl_3$) τ 2.50 (m, 4 aromatic protons), 5.70 (s, 2 methylene protons), 5.95 and 6.40 (2 t, 4 methylene protons), 8.00 (s, 3 acetate protons), 8.30 (m, 4 methylene protons).

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Registry No.—I, 54865-84-8; III, 55740-67-5; IVa, 39963-25-2; IVb, 55740-68-6; IVc, 39963-30-9; Va, 55740-69-7; Vb, 55740-70-0; VI, 55740-71-1; VII, 55740-72-2; VIIIa, 55740-73-3; VIIIb, 55740-74-4; VIIIb monomer, pyridine analog, 55740-75-5; IXa, 40243-08-1; IXb, 55740-76-6; IXc, 55740-77-7; XI, 3848-48-4; XVIIa, 55740-87-9; XVIIb, 55740-88-0; XVIIIa, 19339-69-6; XVIIIb, 52920-25-9; XIIIc, 25770-48-3; XIXa, 55740-89-1; XIXb, 52920-28-2; XX, 19339-67-4; XXII, 55740-91-5; XXIII, 55740-90-4; XXIV, 55740-92-6; XXV, 55740-93-7; XXVIa, 55740-94-8; XXVIb, 55740-95-9; XXVII, 55740-96-0; XXVIIIa, 55740-97-1; XXVIIIb, 55740-98-2; XXIXb, 55740-99-3; XXIXc, 55741-00-9; XXXa, 5342-91-6; XXXb, 23967-95-5; XXXIa, 55741-01-0; XXXIb, 55741-02-1; XXXIb ethyl ester, 55741-03-2; XXXII, 55741-04-3; azobenzene, 103-33-3; palladium acetate, 3375-31-3; N-benzylbenzaldehyde imine, 780-25-6; N-benzylacetophenone imine, 14428-98-9; benzaldazine, 588-68-1; acetophenone dimethylhydrazone, 13466-32-5; 1-methyl-1-phenylhydrazone of formaldehyde, 15754-28-6; methylene chloride, 75-09-2; 1-methyl-1-phenylhydrazone of acetaldehyde, 52163-09-4; acetone, 67-64-1; N,N-dimethylbenzylamine, 103-83-3; N,N-diethylbenzylamine, 772-54-3; N-benzylpyrrolidine, 29897-82-3; CO, 630-08-0; 2-ethoxycarbonylazobenzene, 18277-91-3.

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Rate Study on the Ozonolysis of Acetylenes

D. J. Miller, T. E. Nemo, and L. A. Hull*

Union College, Schenectady, New York 12308

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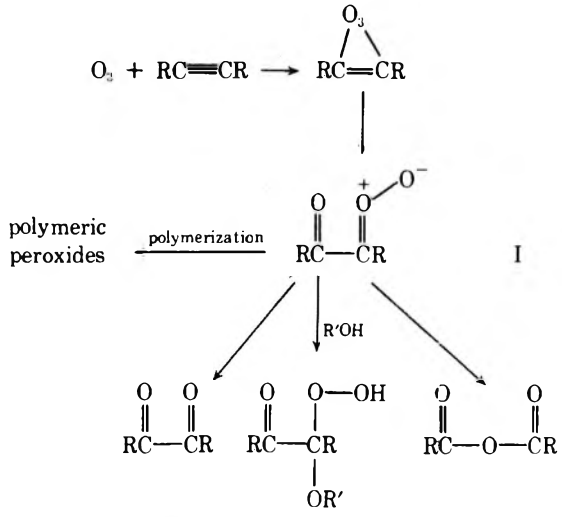
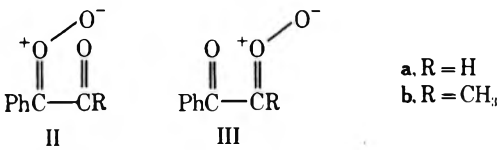
A kinetic study on the reaction of ozone with a series of propargyl compounds has been performed. Absolute rate data are included for the reaction of propargyl chloride in CCl_4 and propargyl acetate in a series of solvents of differing polarity. The absolute rate constants are relatively insensitive to solvent polarity. A relative rate study of several propargyl compounds in methylene dichloride has been made. The rates correlate well with the corresponding Taft substituent constant. From the linearity of the correlation and low ρ value, as well as the insensitivity of the reaction rate to solvent polarity, it is concluded that the initially formed species is a symmetrical nonpolar addition compound, most likely the five-membered ring cycloaddition product.

Compared to the number of mechanistic studies on the ozonolysis of alkenes, relatively little work has been done on the mechanism of the reaction of ozone and alkynes.[1] According to the Criegee–Lederer mechanism,[2] some initially formed species rearranges to an acylcarbonyl oxide, I, which can then react by any of several pathways, as shown below. The production of anhydrides and α-dicarbonyl

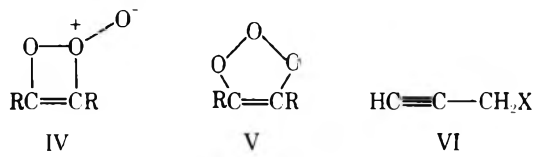


compounds is well known[1] and in addition to Criegee and Lederer, Bailey and coworkers[3] have identified the alkoxyhydroperoxide adducts in the ozonolysis of the two unsymmetrical alkynes, phenylacetylene and 1-phenylpropyne, in alcohol solution and found that of the two possible acrylcarbonyl oxides produced in either case (II, III) the



one with the carbonyl oxide adjacent to the benzene ring, II, was preferred by about 2:1. DeMore and Lin,[4] working at low temperatures in liquid CO_2, have recently directly observed by ir a thermally unstable intermediate in the ozonolysis of propyne and 1- and 2-butyne which they have identified as an acylcarbonyl oxide.

At present the nature of the precursor(s) to the acylcarbonyl oxide still remains in doubt. By analogy with either of the two currently cited mechanisms for the ozonolysis of alkenes, either IV[5a,b] or V[6] could be possible. In addition the observations of ozone–olefin π complexes[7,8] at low temperatures may imply a π complex precursor to either IV or V. In an effort to try to distinguish between either IV or V as an intermediate in the ozonolysis of acetylenes we undertook a kinetic study on a series of unsymmetrically substituted acetylenes of the type VI.



Experimental Section

Relative Rate Studies. An ozone–oxygen mixture produced by silent electric discharge in an oxygen stream was passed (at about 10^{-4} mol O_3/min) into a solution in methylene chloride (spectral grade) of the two compounds under study (0.1–0.01 *M* in each compound) and an unreactive internal standard (either dodecane or hexadecane, also 0.1–0.01 *M*) kept at 0° by immersion in an ice–water bath. The reaction was allowed to proceed to beyond 50% consumption of the more reactive component. Analyses of the remaining alkyne concentrations were performed on a P. E. 900 GPC using the flame ionization mode with either a 6-ft Carbowax 20M column or a 12-ft 1,2,3-tris(2-cyanoethoxy)propane column. The GPC response of the alkynes to that of standards was shown to be linear with their relative concentrations.

Propargyl alcohol, propargyl chloride, and propargyl bromide were all obtained commercially (Aldrich). Propargyl acetate was prepared from the alcohol, bp 122–125° (lit.[9] bp 124–125°). The *N,N*-dimethylpropargylamine was prepared from propargyl bromide and dimethylamine, bp 77–78° (lit.[10] bp 79–81°). The 1-decyne was prepared from 1,2-dibromodecane by dehydrohalogenation, bp 24–26° (0.5 mm).[11] The solvents used were spectral quality (Aldrich and Fisher).

Kinetic Studies. The apparatus used for the kinetic studies was an Aminco-Morrow stopped-flow apparatus whose amplifier output was fed into a Tektronix type 531A oscilloscope. The oscilloscope trace was photographed and the data analyzed. The light source was a Beckman DU monochromator and the photomultiplier tube had a type S-5 spectral response, uv transmitting glass, and maximum response at 340 nm.

The half-lives for ozone decay in the various solvents used in the study, in the apparatus, were >15 min.

The general procedure for a run involved first standardizing the instrument at the wavelength chosen (usually 290 nm) with a given solvent so that 1-V output was 10% transmittance. The reactant cylinders were then filled with the alkyne solution and the ozone solution. The reactant cylinders are made of Kel F, which is relatively inert to ozone. After several flushings the system was ready for use. To initiate reaction the drive plungers were forced down and the two reactant components mixed in the mixing chamber and flowed through the observation cell (made of Teflon with quartz windows oriented so the observation path length is 10 mm) and filled a storage cylinder forcing up the stopping plunger. The stopping plunger was forced against a trigger causing the flow to stop and triggering the oscilloscope. The two reactants reacted in the observation cell and the oscilloscope displayed the disappearance of the absorbing reactant (O_3) as a function of time, which was recorded by the camera. The time it took the solutions to go from the mixing chamber to the observation cell was about 4 msec.

For each concentration of acetylene at least three runs were made. The data were treated by a least-squares analysis and the resulting pseudo-first-order rate constants averaged.

Table I
Relative Rates of Reaction with Ozone and Taft σ* Constants

Substituent, X	Relative rate[a]	σ*
Cl	1	1.05
Br	1.3	1.00
O_2CCH_3	1.7	0.89
OH	5.5	0.55
$N(CH_3)_2$	8.5	0.22
$(CH_2)_6CH_3$	16.6	(−0.13)[b]

[a] Rate relative to propargyl chloride. [b] Estimated to be equal to that for n-C_4H_9.[9]

Table II
Products from Ozonolysis

Compd	Registry no.	Solvent	Products (after treatment with H_2O)
$HC{\equiv}CCH_2Cl$	624-65-7	CCl_4	HCO_2H, $ClCH_2CO_2H$
$HC{\equiv}CCH_2Br$	106-96-7	CCl_4	HCO_2H, $BrCH_2CO_2H$
$HC{\equiv}CCH_2O_2CCH_3$	627-09-8	$CHCl_3$	HCO_2H, $CH_3CO_2CH_2CO_2H$
$HC{\equiv}CCH_2OH$	107-19-7	CH_2Cl_2	$HCO_2CH_2CO_2H$, + some HCO_2H and $HOCH_2CO_2H$
$HC{\equiv}CCH_2N(CH_3)_2$	7223-38-3	CH_2Cl_2	HCO_2H, $(CH_3)_2NH^+CH_2CO_2^-$
$HC{\equiv}C(CH_2)_7CH_3$	764-93-2	$CHCl_3$	HCO_2H, $CH_3(CH_2)_7CO_2H$

Product Studies. An ozone–oxygen mixture was passed (about 10^{-3} mol O_3/min) into 10 ml of a 1 M solution of the alkyne in the indicated solvent (spectral grade) at 0° until a stoichiometric amount of O_3 had been added. An ir and uv of the product solutions was then taken. The solvent was removed under reduced pressure and the residue was treated with a few drops of H_2O or D_2O and taken up in D_2O or deuterioacetone, and the NMR was determined. For 1-decyne NaOD–D_2O was used as solvent. The products were identified either by comparison with genuine samples or from the spectrum itself.

Results

In a simple competition between two compounds A and B for O_3 the ratio of their rates of reaction, k_A and k_B, is given by

$$\frac{k_A}{k_B} = \frac{\log A_f/A_i}{\log B_f/B_i}$$

where A_i and B_i are initial concentrations and A_f and B_f are the final concentrations of A and B, respectively, if the reaction is first order in A and B.

Listed in Table I are the compounds studied and their rates of reaction relative to propargyl chloride in methylene chloride. Also listed are the Taft substituents constants, σ*, for each of the substituents.[12,13] The σ* constant for the n-heptyl group was estimated to be approximately equal to that for the n-butyl group.

In Table II are listed the products of ozonolysis of each of the compounds after aqueous work-up. A combination of ir and NMR was used to identify the products listed. Also from the lack of any significant absorption above 400 nm in the uv spectra of the product solutions it is concluded that in each case there was less than 0.1% of an α diketone produced. From the ir spectra of the product solutions before aqueous work-up it is apparent that there is an anhydride

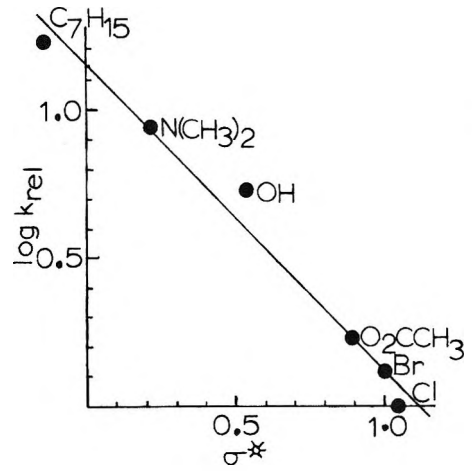


Figure 1. Plot of log k_{rel} vs. Taft substituent constant, σ*, for the reaction of ozone and various propargyl compounds of the type $HCCCH_2X$.

present as well as some carboxylic acid (possibly from adventitious water). The principal product from ozonolysis of propargyl alcohol listed is a formic acid ester and probably arises from attack of the alcohol OH group (of the starting acetylene or product hydroxy anhydride) on the initially formed anhydride product.

A plot of log k_{rel} vs. the Taft constant is given in Figure 1. The least-squares line is described by the equation

$$\log k_{rel} = (-1.02 \pm 0.2)\sigma^* + (1.15 \pm 0.1)$$

and has a linear correlation coefficient of 0.986.

In addition to the relative rate study a kinetic study was performed on propargyl chloride in CCl_4 and propargyl acetate in a series of acetic acid–water mixtures and methyl acetate. The reactions were monitored using stopped-flow techniques by following the disappearance of ozone in the uv. The ozone concentrations varied from 10^{-3} to 10^{-4} M with the concentration of alkyne between 0.5 and 0.01 M. Under the conditions employed the alkyne was always in vast excess and its concentration varied little over the course of the reaction.

In Figures 2 and 3 are plotted the negative logarithm of the absorbance of the ozone vs. time for varying concentrations of propargyl chloride in CCl_4 and propargyl acetate in 100% acetic acid, respectively, at 24 ± 1°. The disappearance of ozone is first order for >4 half-lives. In Figure 4 is a plot of the logarithm of the pseudo-first-order rate constants vs. the logarithm of the concentration of the alkyne substrate for the two aforementioned compounds under the specified conditions. From the slopes of the lines the order of reaction for propargyl chloride is 1.1 ± 0.1 and for propargyl acetate 0.93 ± 0.06, both of which are within reasonable agreement of 1.0. In Table III are listed the second-order rate constants for reaction of the two compounds with ozone in various solvents.

Discussion

From the product studies it is apparent that for these propargyl compounds the course of the reactions seems to proceed almost exclusively through formation of the anhydride.

The reaction appears to be clearly first order in both ozone and acetylene, implying either that ozone and the acetylene are involved in a rate-determining encounter, or in some prior equilibrium, perhaps involving a π complex.

From the data in Table III it is apparent that the rate of reaction is virtually insensitive to the polar or hydrogen-bonding nature of the solvent. On comparing the rate con-

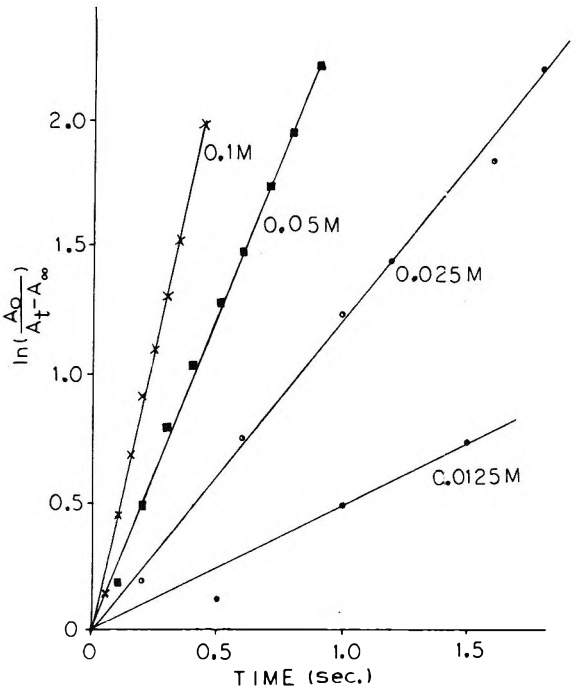


Figure 2. Plot of ln $A_0/(A_t - A_\infty)$ where A_0 is the initial absorbance, A_t is the absorbance at time t, and A_∞ is the absorbance at long reaction time vs. time for the reaction of ozone and propargyl chloride at various propargyl chloride concentrations under pseudo-first-order conditions, in CCl_4 at 24 ± 1° monitored at 290 nm.

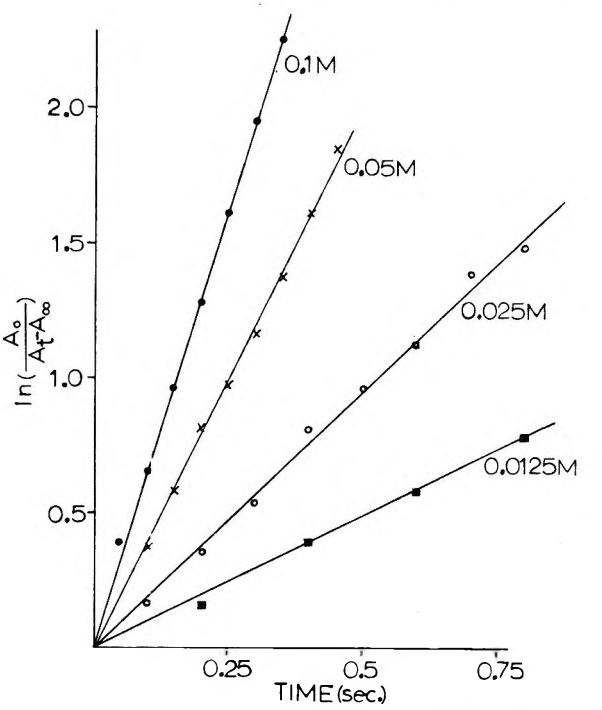


Figure 3. Plot of ln $A_0/(A_t - A_\infty)$ where A_0 is the initial absorbance, A_t is the absorbance at time t, and A_∞ is the absorbance at long reaction time vs. time for the reaction of ozone and propargyl acetate at various propargyl acetate concentrations under pseudo-first-order conditions, in CH_3CO_2H at 24 ± 1° monitored at 290 nm.

Table III
Rate Constant for Reactions with Ozone at 24 ± 1°

Compd	k, M^{-1} sec^{-1}	Solvent
$HC{\equiv}CCH_2Cl$	52 ± 12	CCl_4
$HC{\equiv}CCH_2O_2CCH_3$	74 ± 7	CH_3CO_2H
$HC{\equiv}CCH_2O_2CCH_3$	168 ± 3	75:25 CH_3CO_2H–H_2O
$HC{\equiv}CCH_2O_2CCH_3$	270 ± 47	50:50 CH_3CO_2H–H_2O
$HC{\equiv}CCH_2O_2CCH_3$	264 ± 18	25:75 CH_3CO_2H–H_2O
$HC{\equiv}CCH_2O_2CCH_3$	218 ± 8	H_2O
$HC{\equiv}CCH_2O_2CCH_3$	104 ± 40	$CH_3CO_2CH_3$

stant for ozonolysis of propargyl acetate in pure acetic acid with its rate constant for reaction in the various acetic acid–water mixtures one finds a variation by at most a factor of 3. Comparison of the rate constant for this same substrate in methyl acetate and acetic acid shows again no significant variation. This insensitivity of the rate constant to solvent polarity and the hydrogen-bonding nature of the solvent would indicate that the intermediate formed in any rate-determining step is unlikely to be polar or able to accept hydrogen bonds from the solvent, characteristics one would expect for an intermediate such as IV. For the situation in which there is a prior equilibrium it is possible for these to be mutually compensating effects. This latter explanation seems unlikely, however, since the π complex usually invoked in such a prior equilibrium is not likely to be very polar. Some polarity for such a species might explain the slight sensitivity to solvent polarity observed.

The relative rates of ozonolysis are linearly correlated with the Taft substituent constant. The implication of such a correlation is that either there is no significant steric and/or resonance effect or they are of a compensatory nature. Most likely because of the linear arrangement of atoms about the triple bond in VI the substituent is held rigidly away from the approaching ozone molecule, minimizing steric factors. The presence of the methylene group would

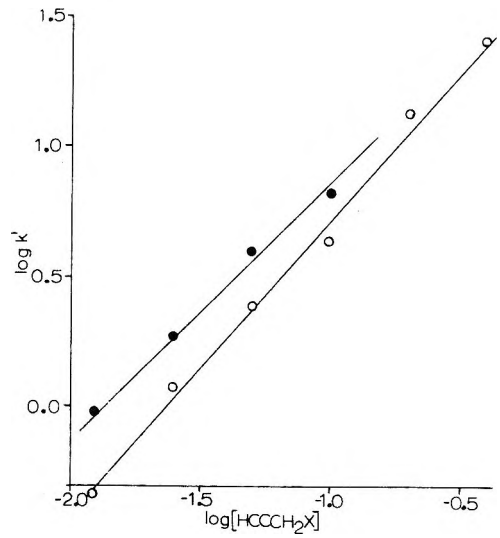


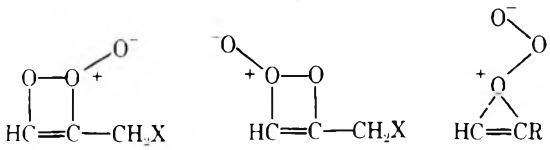
Figure 4. Plot of the log of the pseudo-first-order rate constant vs. log of the alkyne concentration for X = Cl (○) and for X = O_2CCH_3 (●) in CCl_4 and CH_3CO_2H, respectively, at 24 ± 1°.

prevent any resonance effect of the substituent from interfering. The predominant effect is therefore inductive.

The comparatively low slope (−1.02 ± 0.2) implies only a minimal sensitivity of the reaction to the polar nature of the substituent,[12] a characteristic of 1,3-dipolar cycloadditions.[14] The negative slope corresponds to increased rates for more inductively electron-donating substituents in line with and confirming the electrophilic nature of ozone.[15]

The low slope, or ρ value, as well as the good linear correlation of the relative rates is hard to understand in terms of the four-membered ring, Staudinger molozonide as an initially formed species. In the ozonolysis of unsymmetrical alkynes of the type VI, there are two conceivable orientations of a four-membered ring intermediate, VIIa and VIIb.

If the initially formed species were exclusively VIIb,



VIIa VIIb VIII

where the positive oxygen was three atoms away from the CH_2X group, the relative insensitivity of the reaction to varying inductive effects and the good linear correlation would not be unreasonable. However, it is unreasonable to expect that VIIb could possibly be the exclusive intermediate over the range of substituents used in this study and in light of the strongly supported intermediacy of the two possible acylcarbonyl oxides in Bailey's study.[3] The two acylcarbonyl oxides, II and III, could only arise from two four-membered ring precursors which differ in addition orientation, as in VIIa and VIIb. If varying proportions of VIIa and VIIb were formed, depending on the substituent, it would be highly unlikely that a linear correlation would exist; instead, as one went to more electron-donating substituents, VIIa would be favored, resulting in marked curvature up as one went to decreasing σ^* values, something that is not observed.

The initial rate-determining formation of a symmetrical π complex, or of a symmetrical three-membered ring of the type VIII, cannot be ruled out. However, the relative insensitivity of the rate of reaction to changing substituents and changing solvent polarity does tend to make it less likely that charge is developed in the transition state.

The above supports the intermediacy of a symmetrical intermediate of the type V whose cleavage could then be affected by the substitution pattern but whose formation would be only slightly affected by inductive and solvent effects, since no charge is developed.

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Registry No.—Ozone, 10028-15-6.

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Reaction of Diaminomaleonitrile with Acetaldehyde

John W. Thanassi

The Salk Institute for Biological Studies, San Diego, California 92112

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The reaction of diaminomaleonitrile with acetaldehyde in an aqueous buffer at pH 6.8 proceeds rapidly at 5° and leads to the formation of a product which results from the condensation of three molecules of acetaldehyde and one molecule of diaminomaleonitrile with the elimination of one molecule of water. The properties of the compound are consistent with a heterotricyclic ring system.

Diaminomaleonitrile,[1] a tetramer of hydrogen cyanide, has been implicated as an intermediate in the prebiotic synthesis of purines.[2] It has also been shown to be a very useful intermediate in the preparation of a variety of heterocyclic compounds containing from five to seven members in the rings.[3]

Except for the investigations concerned with chemical evolution, the synthetic procedures utilizing diaminomaleonitrile have largely employed nonaqueous solvents. This report deals with the reaction of diaminomaleonitrile with acetaldehyde in an aqueous buffer. The reaction proceeds rapidly under very mild conditions (pH 6.8, 5°) leading to an unexpected and unusual product. This is identified as a heterotricyclic system (structure **3**) resulting from the condensation of three molecules of acetaldehyde with one molecule of diaminomaleonitrile.

Results and Discussion

The crystalline product obtained from the reaction of diaminomaleonitrile with acetaldehyde was initially assumed to be a dihydroimidazole derivative (structure **1**, Scheme I). However, the proton magnetic resonance spectrum (Figure 1) revealed that three molecules of acetaldehyde had been incorporated into the product and that all three of the incorporated CH_3CH groups were in different chemical environments. That the three CH_3CH groups were each incorporated intact was shown by a spin-decoupling experiment in which the upfield methyl signals (integrating for nine protons) were irradiated, causing a collapse of the quartets in the δ 4–6 region of the spectrum. (The quartets integrated for three protons in a ratio of 1:1:1.) Addition of a small amount of D_2O to the Me_2SO-d_6 solution resulted in a disappearance of the two exchangeable NH signals at δ 7.96 and 8.22, each integrating for one proton. All of the incorporated acetaldehyde molecules were covalently bound because heating overnight at 100° under constant oil pump vacuum caused no significant loss of weight or change in the ir spectrum.

The low-resolution electron impact mass spectrum of the product is found in Figure 2. It can be seen that the spectrum is complex. In view of the fact that the product analyzed satisfactorily for $C_{10}H_{14}N_4O_2$ (mol wt 222) it is evident that the molecular ion is not sufficiently stable to appear in the low-resolution mass spectrum. However, a high-

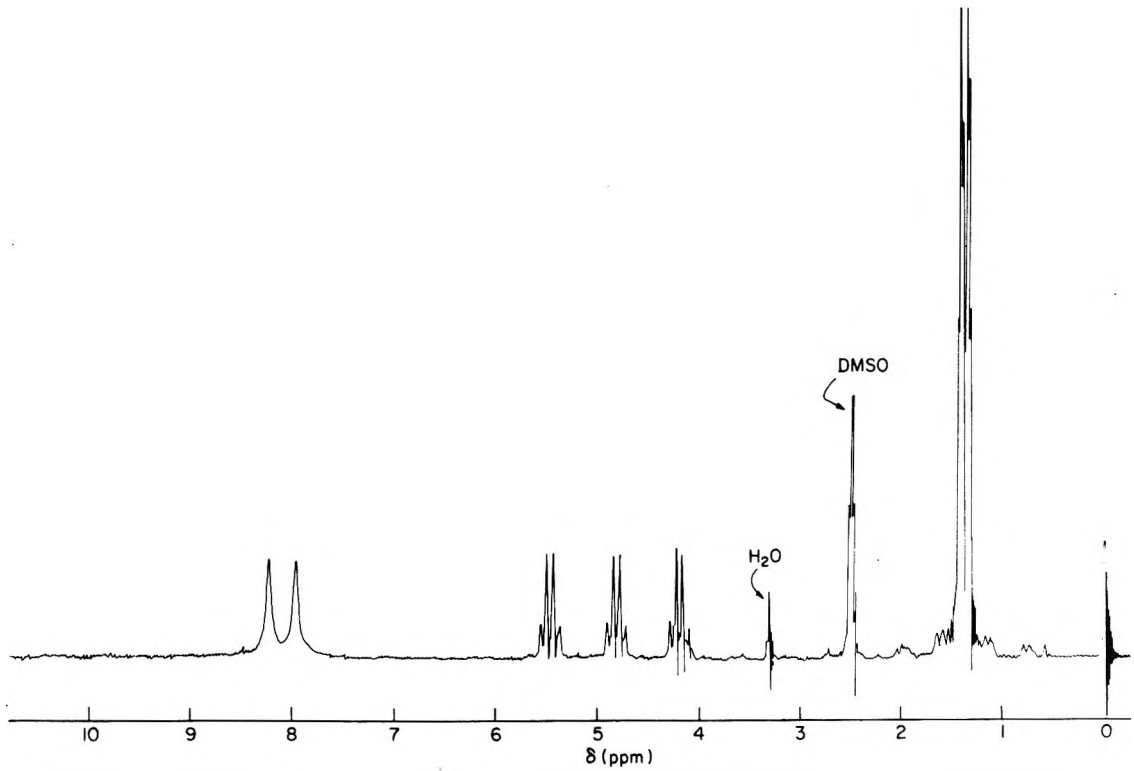
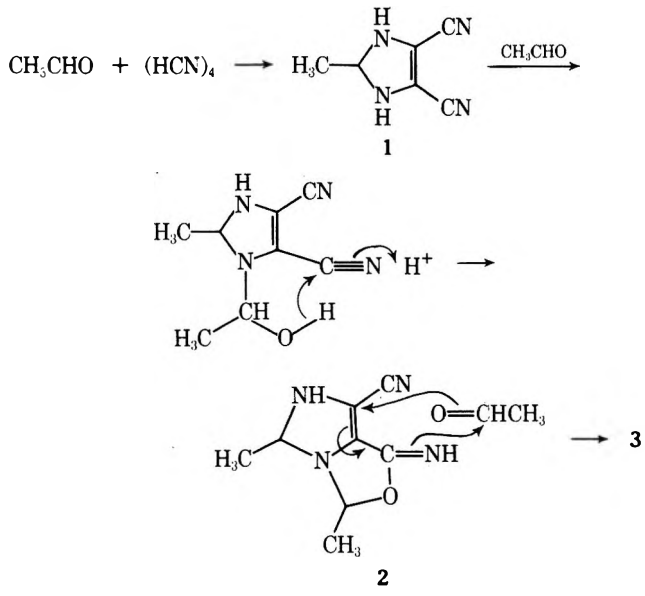
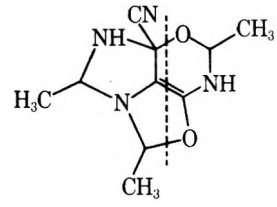


Figure 1. Proton magnetic resonance spectrum of the product of the reaction of acetaldehyde and diaminomaleonitrile. Solvent in Me_2SO-d_6; reference is Me_4Si; frequency, 100 MHz.

Scheme I



resolution mass spectrum of the compound also was obtained and it showed an ion at mass 222 providing that a very strong exposure was employed. A bar-graph spectrum constructed from the high-resolution data is identical, except for intensity differences, to the low-resolution spectrum provided in Figure 2. However, two other significant peaks are found in the high-resolution spectrum, namely peaks at 221 ($M - H^+$) and 196 ($M - CN$). The high-resolution data indicate that the signals at 180, 178, and 163 mass units can be explained by loss of methyl plus HCN, acetaldehyde, and acetaldehyde plus methyl, respectively. Of particular interest are the signals at 162 and 161 mass units. The high-resolution data can be accommodated only by the loss of $CH_3CH(NH)O$ plus one and two protons, respectively, and not by the loss of $CH_3CH(O)O$ plus zero and one proton. This particular fragmentation can reasonably be explained only from structure **3** and not from the alternative structure **4**. Loss of one and two protons is frequently found throughout the high-resolution spectrum, probably owing to formation of imidazole derivatives and/or loss of hydrogen from the six-membered ring. High-resolution analysis reveals that 25% of the signal at 135 can be accounted for by loss of $C_3H_5O_2N$. This is most readily explained by the fragmentation shown in **3**. A number of other signals in the low-resolution spectrum can be tentatively identified in combination with the high-resolution data. The base peak at 44 in the high-resolution mass spectrum consists almost entirely of signals for C_2H_4O, CH_2NO, and C_2H_6N. The electron impact mass spectrum is complemented by the chemical ionization mass spectrum. The $(M + 1)^+$ signal at 223 is very prominent in the chemical ionization mass spectrum, confirming the molecular weight of 222.



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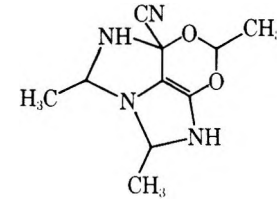

4

Ultraviolet spectroscopy of the product of the reaction of diaminomaleonitrile and acetaldehyde shows that the absorption maximum of the starting material at around 300 nm in ethanol has disappeared. Hence the double bond conjugated to the nitrile groups is no longer present. The infrared spectrum has in it a very weak CN absorption band at 2250 cm^{-1} which is consistent with the loss of the double bond.

At ambient temperatures, and under conditions where acetaldehyde is 0.15 M, diaminomaleonitrile is 6×10^{-5} M, and the buffer is 0.25 M each in NaH_2PO_4 and Na_2HPO_4,

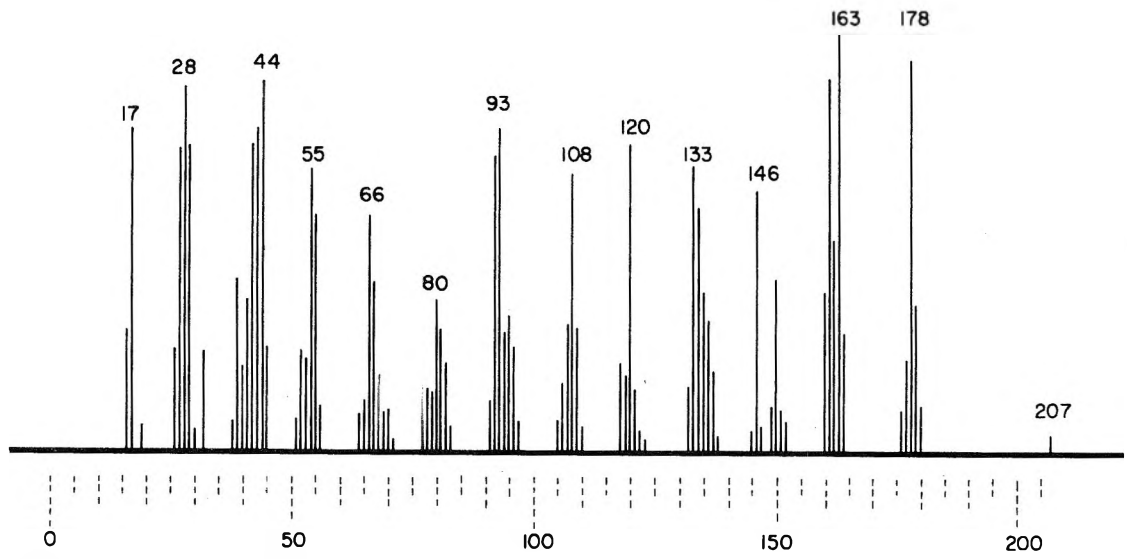

Figure 2. Low-resolution electron impact mass spectrum of **3**.

the pseudo-first-order rate constant for the disappearance of the double bond, determined spectrophotometrically, is 3.98×10^{-2} min^{-1}, corresponding to a half-life of 17.4 min. Under otherwise identical conditions, the absorbancy of diaminomaleonitrile at 295 nm does not decrease in the absence of acetaldehyde.

Synthesis of the above information leads to **3** as the structure of the product. A reasonable route for the formation of **3** is proposed in Scheme I.

The first step involves formation of a dihydroimidazole, followed by addition of acetaldehyde to one of the secondary amino groups. The resulting carbinolamine then converts the nitrile to the imide **2**. (A number of examples for the participation of neighboring OH in nitrile hydrolysis are available, e.g., ref 4–6.) The final step, leading to the heterotricyclic product **3**, is analogous to a Diels–Alder reaction in which a heterodienophile, acetaldehyde, reacts with a heterodiene.[7]

The facility of the formation of the compound isolated is perhaps surprising. The driving force may be its precipitation. Inspection of structure **3** shows that there are four potentially asymmetric carbon atoms in the product. However, the proton magnetic resonance spectrum shown in Figure 1 is a very clean spectrum and suggests that only one of the possible D, L stereoisomeric pairs has crystallized out of the aqueous solvent. An analogous reaction is not observed between diaminomaleonitrile and either formaldehyde or acetone under similar conditions.

Reaction of diaminomaleonitrile with a variety of aldehydes in methanol has been investigated by Bagland et al.[3] No reaction analogous to the one reported herein was found. Furthermore, Robertson and Vaughan[8] have reported that there is no reaction between diaminomaleonitrile and acetaldehyde in hot alcohol. Hence the chemistry of diaminomaleonitrile in aqueous solvents can be substantially different from that in organic solvents and, in view of its utility as a synthetic intermediate, merits further attention.

Experimental Section

Reaction of Diaminomaleonitrile with Acetaldehyde. Diaminomaleonitrile (4.4 g, 0.04 mol) was suspended with stirring in 750 ml of ice-cold pH 6.8 phosphate buffer (0.25 *M*). To this was added 35 ml of ice-cold acetaldehyde. Within 5 min, a clear solution was obtained. After approximately 20 min, a granular precipitate was evident. The reaction mixture was kept overnight in a refrigerator. The precipitate (4.84 g, 53% of theory) was filtered, washed with water, dried, dissolved in hot acetonitrile, and decolorized with Darco G-60 and Norit A. Recrystallization from acetonitrile yielded white crystals, mp 163–164° dec.

Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.08; H, 6.43; N, 25.49.

The ir spectrum (Nujol) was obtained on a Perkin-Elmer 237B spectrometer: 3430, 3310, 3230, 2250, 1705, 1650, 1620, 1200–1080, 910, 830 cm^{-1}. The uv spectrum (2×10^{-4} *M* in spectroquality acetonitrile) was taken manually on a Zeiss PMQII spectrophotometer and showed only a plateau around 225 nm ($\epsilon \sim 2500$) and trailing absorption.

The high-resolution electron impact mass spectrum was obtained with an instrument tolerance set at an upper limit of 2.2×10^{-3} amu. Calcd for $C_{10}H_{13}N_4O_2$, $C_9H_{11}N_4O_2$, $C_9H_{14}N_3O_2$, $C_8H_{10}N_4O$, $C_7H_7N_4O$, $C_8H_8N_3O$, $C_8H_7N_3O$, $C_7H_9N_3O$, and $C_7H_4N_3O$: *m/e* 221.10385, 207.08820, 196.10860, 178.08546, 163.06198, 162.06673, 161.05891, 151.07456, and 146.03543. Found: *m/e* 221.10487, 207.08712, 196.11015, 178.08676, 163.06196, 162.06596, 161.05891, 151.07495, and 146.03623. The chemical ionization mass spectrum had in it signals at 223 $(M + 1)^+$, 196 (base peak), 179, 152, and 135.

The low-resolution mass spectrum, NMR spectrum (solvent, Me_2SO-d_6), and chemical ionization mass spectrum were kindly provided by Drs. N. Ling, J. Rivier, and K. Kirk, respectively. The high-resolution mass spectral data were obtained from Drs. K. Biemann and C. Costello.

Acknowledgments. The author is indebted to the individuals cited in the Experimental Section for providing much of the data used in this investigation. This work was performed during the course of a sabbatical leave from the Department of Biochemistry, College of Medicine, University of Vermont, Burlington, Vermont, in the laboratory of Dr. Leslie E. Orgel, to whom the author is extremely grateful. This research was supported by NASA Grant NSG-07021.

Registry No.—**3**, 55759-62-1; diaminomaleonitrile, 1187-42-4; acetaldehyde, 75-07-0.

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Synthesis of Carbocamphenilone and Its 6,7-Dehydro Derivative[1]

Ryoji Noyori,* Toshiaki Souchi, and Yoshihiro Hayakawa

Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

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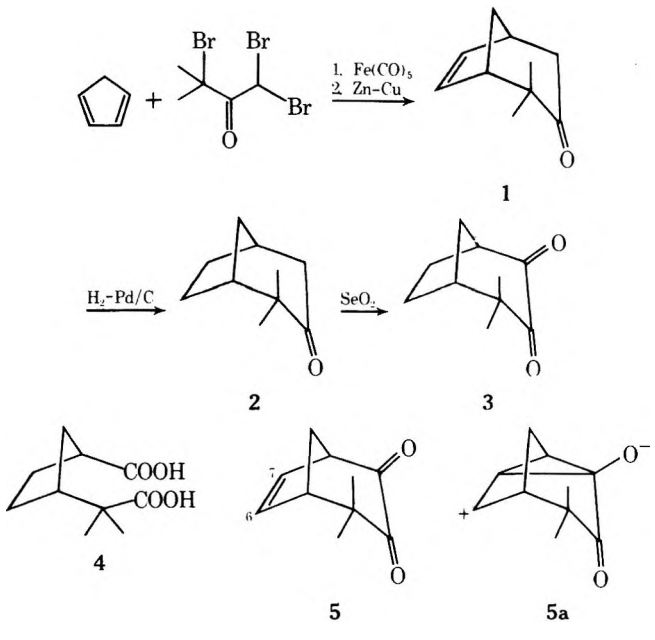
Carbocamphenilone (**3**) is a terpenic α diketone which has been of interest as a skewed glyoxal model.[2] Previously its syntheses have been achieved from camphene only in low yields and the diketone[3] or its synthetic precursors[4] were usually obtained by isolation from complex reaction mixtures. This note describes an effective, rational route to **3** which is based on the recently developed iron carbonyl promoted cyclocoupling between polybromo ketones and 1,3-dienes.[1,5,6]

Reaction of 1,1,3-tribromo-3-methylbutan-2-one and cyclopentadiene in the presence of iron pentacarbonyl followed by Zn–Cu couple reduction of the reaction mixture gave the bicyclic ketone **1** (83% yield by GLC, 66% yield after isolation). Catalytic hydrogenation of **1** on Pd/C afforded the saturated ketone **2**, which was oxidized with selenium dioxide in refluxing xylene to give the desired α diketone **3** quantitatively. Camphenic acid (**4**) can be obtained readily by potassium permanganate oxidation of **2**.[4d,7]

Oxidation of the unsaturated bicyclic ketone **1** with selenium dioxide led to 6,7-dehydrocarbocamphenilone (**5**) in 72% yield. Notably, for diketone **5** the carbon–carbon double bond and carbonyl moieties are situated such that interaction can occur and hence **5** serves as a new example of a homoconjugated α diketone.[8] As a consequence of the strong homoconjugation in an excited state,[9] **5** exhibits characteristic uv-visible absorptions, in marked contrast with the saturated analog **3**; see Figure 1. Diketone **3** shows absorptions due only to n–π^* transitions. The unsaturated ketone **1** does not give an unusual spectrum either [in isooctane, n–π^* band at 295 nm (ϵ 31)] [cf. **2** (isooctane) λ_{max} 298 nm (ϵ 23)]. The spectrum of the unsaturated diketone **5** shows a π–π^* band at 249 nm (ϵ 675) as well as the n–π^* bands which are shifted bathochromically with concomitant hyperchromic effect. Fine structure is observed in the 431-nm band.[9b,c] Interestingly, the C-6 vinylic proton of **5** exhibits a NMR signal at unusually low field, δ 6.54; this value should be compared with that of the C-7 vinylic proton, δ 5.97, as well as the chemical shift of the vinylic protons of the unsaturated monoketone **1**, δ 6.12. This deshielding could be explained by the ground-state homoconjugation effect; the conventional resonance description, **5** ↔ **5a**, could account for the electron deficiency at the C-6 position.



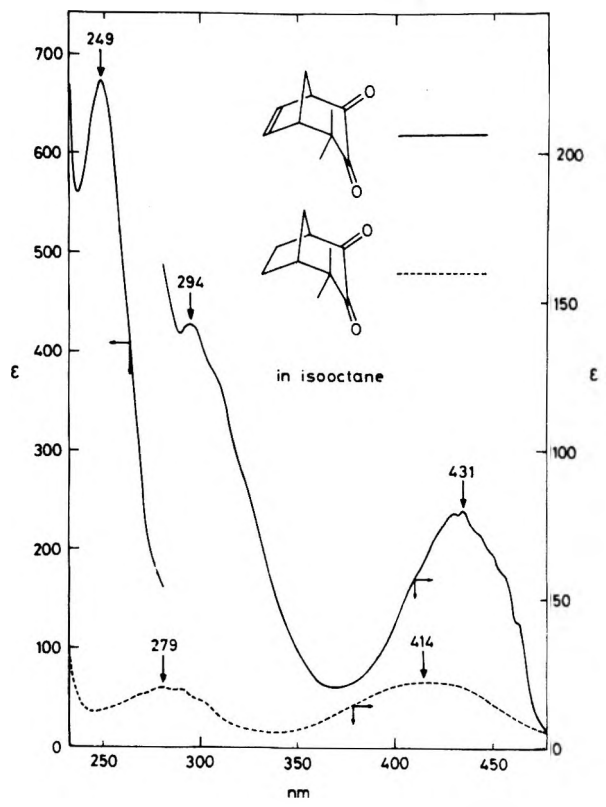


Figure 1. Electronic absorption spectra of carbocamphenilone (**3**) and the dehydro derivative **5**.

Experimental Section

All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on either a Varian HA-100D or JEOLCO C-60H instrument with tetramethylsilane as an internal standard. Infrared (ir) spectra were measured with a Nihon Bunko DS-402G spectrometer, and ultraviolet (uv)–visible spectra with a Hitachi Model 323 instrument. Mass spectra were determined on a Hitachi RMU 6C-2 spectrometer at 70 eV ionizing irradiation. Gas chromatographic analyses (GLC) were performed on a Hitachi 063 gas chromatograph equipped with a column of 5% poly(diethylene glycol succinate) on Neopak 1A (2 m, column temperature 100°). For column chromatography Merck Kieselgel 60 (70–230 mesh) was used.

2,2-Dimethylbicyclo[3.2.1]oct-6-en-3-one (1). To a mixture of freshly distilled cyclopentadiene (1.0 ml), iron pentacarbonyl (Strem, 0.78 ml, 1.17 g, 5.98 mmol), dry tetrahydrofuran (1.0 ml), and dry benzene (10.0 ml) stirring at 80° under argon was added dropwise a solution of 1,1,3-tribromo-3-methylbutan-2-one[10] (1.62 g, 5.00 mmol) in 1:1 cyclopentadiene–benzene (7.5 ml) over 25 min. The resulting mixture was stirred for an additional 45-min period

at the same temperature. After cooling, the reaction mixture was quenched by addition of methanol (12.0 ml) saturated with NH_4Cl and shaken vigorously with Zn–Cu couple[11] (3.80 g, 57.8 mg-atoms) for 20 min. The reaction mixture was diluted with methylene chloride (200 ml) and a saturated aqueous solution (100 ml) of ethylenediaminetetraacetic acid disodium salt. The insoluble materials were removed by filtration, and the filtrate was extracted twice with methylene chloride (50 and 30 ml). The combined organic layers were dried over sodium sulfate and concentrated to give an oily residue (2.16 g), whose GLC analysis showed the yield of the desired adduct 1 (retention time 8 min) to be 83%. The oil was dissolved in methylene chloride (20 ml) and added dropwise to vigorously stirred *n*-hexane (200 ml). The resulting insoluble precipitates were removed by filtration and the filter cake was washed thoroughly with *n*-hexane. The filtrate and washing were combined and evaporated to leave an oil (1.10 g), which was chromatographed on a silica gel column (15 mm diameter, 15.0 g). Elution with 1:1 benzene–*n*-hexane (110 ml) and 1:10 ethyl acetate–*n*-hexane (50 ml) and collecting 10-ml fractions gave an oily 1 (95% pure by NMR analysis, 520 mg, 66% yield) in fractions 9–15, which was identified by comparison of the NMR spectrum with the reported one.[12] Bulb-to-bulb distillation of this oil gave an analytical sample (375 mg), bp 70–120° (bath temperature) (2 mm), as colorless crystals, mp 45–48° (lit.[12] an oil).

2,2-Dimethylbicyclo[3.2.1]octan-3-one (2). Cycloadduct 1 (300 mg, 2.00 mmol) was stirred in ethyl acetate (5.0 ml) containing 10% Pd/C (30 mg) under atmospheric pressure of hydrogen at room temperature for 3 hr. The catalyst was removed by filtration and the filtrate was concentrated to give an oil (350 mg). Bulb-to-bulb distillation of the oil gave 2 (242 mg, 80% yield) as colorless crystals, bp 80–130° (bath temperature) (2 mm), mp 35–37° (lit.[3d] an oil), showing an NMR spectrum identical with the reported one.[3d] Its 2,4-dinitrophenylhydrazone melted at 117–118° (lit.[3d] mp 117.5–119.5°).

Carbocamphenilone (3). Selenium dioxide (90 mg, 0.81 mmol) and 2 (61 mg, 0.40 mmol) were mixed in dry xylene (1.2 ml) and the slurry was heated at 140° with stirring. After 4 hr the reaction mixture was subjected directly to column chromatography (8 mm diameter) on silica gel (2.0 g). The column was eluted with *n*-hexane followed by benzene. After concentration the fraction eluted with benzene yielded carbocamphenilone (3) (79 mg, quantitative yield) as yellow crystals. On recrystallization from *n*-pentane an analytical sample was obtained, mp 57–61° (lit. mp 49–52°,[2a] 59–60°,[2f] 50–53°,[3d] 58–59°,[4a] 56–59°,[4b] and 48–50° [4d]). Its ir and NMR spectra were identical with reported ones.[4d]

4,4-Dimethylbicyclo[3.2.1]oct-6-ene-2,3-dione (6,7-Dehydrocarbocamphenilone) (5). A mixture of 1 (136 mg, 0.90 mmol) and selenium dioxide (200 mg, 1.80 mmol) in dry xylene (2.5 ml) was stirred at 140° for 4 hr. The resulting mixture was chromatographed on a silica gel column (8 mm diameter, 4.0 g) with *n*-hexane (20 ml), benzene (75 ml), and 1:10 ethyl acetate–benzene (50 ml) and 5-ml fractions were collected. Fractions 14–21 gave a yellow, crystalline 5 (106 mg, 72% yield), which was recrystallized from *n*-pentane to afford an analytical specimen: mp 57–61°; ir (CCl_4) 1736 (weak) and 1720 cm^{-1} (C=O); uv-visible max (isooctane) 249 nm (ϵ 675), 294 (141), and 431 (77.7); NMR (CCl_4) δ 1.14 and 1.24 (s, 3 H each, CH_3), 2.40 (m, 2 H, CH_2), 2.58 [m, 1 H, $(CH_3)_2CCH$], 3.42 (m, 1 H, COCH), 5.97 (dd, 1 H, J = 2.3 and 6.0 Hz, $(CH_3)_2CCHCH$=), and 6.54 (dd, 1 H, J = 2.3 and 6.0 Hz, COCHCH=). The assignment of NMR signals was confirmed by double-resonance technique; irradiation at δ 3.42 changed the δ 5.97 signal into a doublet with J = 6.0 Hz, and irradiation at δ 2.58 gave a doublet with J = 6.0 Hz at δ 6.54.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.11; H, 7.37.

Registry No.—1, 22940-29-0; 2, 55682-09-2; 3, 27455-93-2; 5, 55682-10-5; cyclopentadiene, 542-92-7; 1,1,3-tribromo-3-methylbutan-2-one, 1578-05-8.

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Regioselectivity in the Reaction of $C_5H_5Fe(CO)_2(isobutylene)^+BF_4^-$ with Polyenes

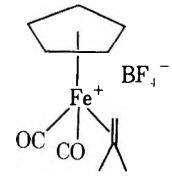
Peter F. Boyle and Kenneth M. Nicholas*

Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167

Received March 19, 1975

The recently demonstrated abilities of the $C_5H_5Fe(CO)_2^+$ (Fp^+) group to activate olefins toward nucleophilic attack[1] and to stabilize highly reactive alkenes (e.g., cyclobutadiene[2] and benzocyclobutadiene[3]) promise to be of considerable synthetic value. In connection with our evaluation of this organometallic moiety as a protecting group for the carbon–carbon double bond,[4] we have investigated the regioselectivity for the metalation of unsymmetrical polyenes with $Fp(isobutylene)^+BF_4^-$ (1).[5]

When 1,2-dichloroethane solutions of 1 were heated (65–70°, 10 min) in the presence of a tenfold excess of the

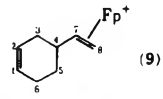
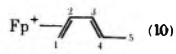
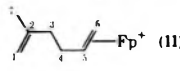
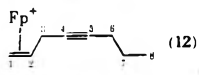
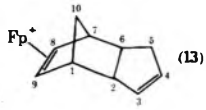
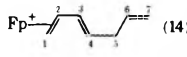
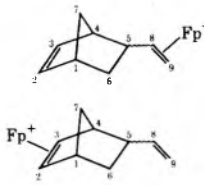


1

polyenes 4-vinylcyclohexene (2), *trans*-piperylene (3), 2-methyl-1,5-hexadiene (4), 1-octen-4-yne (5), *endo*-dicyclopentadiene (6), 1,3,6-heptatriene (7), and 5-vinyl-2-norbornene (8), 1:1 complexes formed as air-stable yellow solids in good yield.[6] The structures of the complexes 9–15 followed readily from their ^1H NMR spectra (Table I) since olefinic proton absorptions are generally shielded ca. 1.0–1.7 ppm upon coordination by Fp^+ whereas allylic proton absorptions are correspondingly deshielded ca. 0.4 ppm. For each substrate (except 8) only one positionally isomeric complex was detectable by NMR, indicating at least 90–95% regioselectivity. Additional support for the assigned structures was obtained by comparison of ^1H NMR spectra with model systems or by hydrogenation of the free unsaturation and comparison of the resulting complexes with authentic samples.[7]

Table I

Regioselectivity for $C_5H_5Fe(CO)_2$(isobutylene)$^+BF_4^-$ + Polyene ⟶ $C_5H_5Fe(CO)_2$(polyene)$^+BF_4^-$ + Isobutylene

Polyene	Complex	Yield, %[a]	NMR spectrum, δ (ppm)[b]
2	 (9)	76	5.7 (s, Cp, $H_{1,2}$), 5.0 (m, H_7), 3.9 (d, 9 Hz, H_{8cis}), 3.5 (dd, 15 Hz, H_{8trans}), 2.8–1.4 (bm, $H_{3,4,5,6}$)
3	 (10)	83	6.6 (m, H_3), 5.9 (m, H_4), 5.6 (s, Cp), 5.4 (m, H_2), 3.7 (d, 7 Hz, H_{1cis}), 3.5 (d, 14 Hz, H_{1trans}), 1.9 (d, 6 Hz, H_5)
4	 (11)	58	5.6 (s, Cp), 5.2 (m, H_5), 4.8 (bs, H_1), 4.0 (d, 8 Hz, H_{6cis}), 3.5 (d, 15 Hz, H_{6trans}), 2.4 (m, $H_{3,4}$), 1.8 (bs, H_7)
5	 (12)	65	5.9 (s, Cp), 5.3 (m, H_2), 3.6 (d, 9 Hz, H_{1cis}), 3.4 (d, 18 Hz, H_{1trans}), 2.9 (t, J = 8 Hz, H_3), 2.0–1.2 (m, $H_{6,7}$), 1.0 (t, 6 Hz, H_8)
6	 (13)	85	5.6 (s, Cp, $H_{8,9}$), 5.3 (bm, $H_{3,4}$), 3.4 (bm, H_2), 3.0 (bm, $H_{1,6,7}$), 2.3 (bm, H_5), 1.0 (d, 12 Hz, H_{10}), −0.1 (d, 12 Hz, H_{10})
7[c]	 (14)	58	6.7 (m, $H_{3,4}$), 5.9 (s, Cp), 5.8 (s, Cp), 5.8 (bm, $H_{2,6}$), 5.2 (bd, 6 Hz, H_{7cis}), 5.1 (bd, 13 Hz, H_{7trans}), 4.2 (d, 9 Hz, H_{1cis}), 3.9 (d, 8 Hz, H_{1cis}), 3.7 (d, 13 Hz, H_{1trans}), 3.6 (d, 14 Hz, H_{1trans}), 3.0 (bt, 7 Hz, H_5)
8[d]	 (15a)[d] ca. 65:35 (15b)[d]	65	6.2 (bm, $H_{2,3}$), 5.55 (s, Cp), 4.9 (m, H_8), 3.5 (m, H_9), 2.9 (bs, $H_{1,4,5}$), 2.5–0.9 (bm, $H_{6,7}$) 5.6 (s, Cp), 5.2 (m, $H_{2,3,8}$), 4.9 (bd, H_9), 2.9 (bs, $H_{1,4,5}$), ~2.2 (bm, H_6), 0.9 (bd, ~12 Hz, H_7) −0.1 (bd, ~12 Hz, H_7)

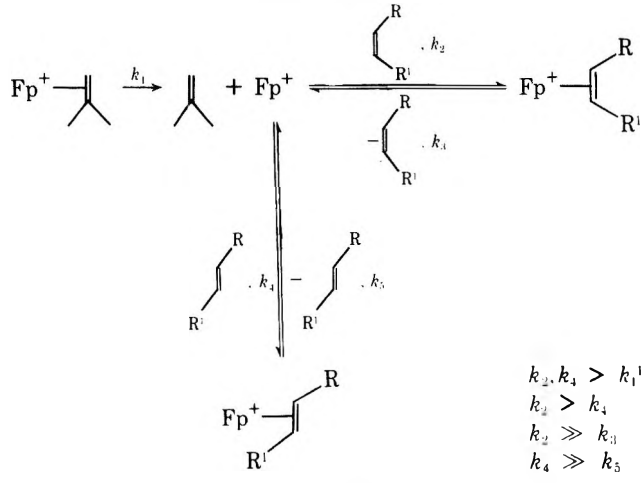
[a] No attempts were made to optimize yields. [b] Spectra of 9, 10, 11, 13, 15a, and 15b obtained in CD_3NO_2 solution; CD_3COCD_3 was the solvent for 12 and 14. [c] Mixture of cis and trans isomers. [d] Mixture of exo and endo vinyl derivatives. Complexes 15a and 15b were not separated but characteristic ^1H resonances for each were discernible in the spectrum of the mixture.

The observed regioselectivity for the exchange process generally parallels the stability trends of transition metal–alkene complexes.[8] It is thus possible to rationalize formation of **9**, **10** and **11** in terms of steric effects and of **13** on the basis of relief of strain.[9,10] Preferential coordination to the double bond of enyne **5** is not surprising in view of the apparent instability of Fp(alkyne)$^+$ salts.[11] The regiospecific formation of **14** is particularly noteworthy since, although dienes are generally more reactive toward electrophilic reagents, stability constants for Ag(I)-conjugated diene complexes are somewhat lower than for simple alkene complexes.[12]

While these products are probably the thermodynamically more stable, the exchange process appears to be kinetically controlled and essentially irreversible as indicated by the following experiments. ^1H NMR analysis of aliquots removed after 2, 5, 8, 12, and 15 min during the reaction of **1** with 10 equiv of a 1:1 mixture of *cis*- and *trans*-2-octene showed the ratio of cis/trans complexes (**17**, **18**), 2.5:1, to be essentially constant throughout the reaction period. Furthermore, when Fp(*trans*-2-octene)$^+BF_4^-$ (**18**) was heated (65°, 10 min) with 10 equiv of *cis*-2-octene, the recovered Fp(2-octene)$^+BF_4^-$ (30%) was mostly trans (ca. 67%). These results are consistent with the mechanism outlined in Scheme I.

Preferential binding of the Fp$^+$ moiety to less substituted or more strained double bonds and to conjugated diene units should allow activation of a single position in a polyene toward nucleophilic attack. This regioselectivity also provides a method for protection of the same double bonds during hydrogenations and electrophilic and certain other addition reactions.[4] We are currently exploring the above applications.

Scheme I



Experimental Section

NMR spectra were recorded on a Perkin-Elmer R-24 spectrometer with Me_4Si as internal standard. Ir spectra were obtained on a Beckman IR 10 spectrometer. The polyenes 2–8 and *cis*- and *trans*-2-octene were obtained commercially and used without further purification. The complex **1** was prepared according to the method of Giering and Rosenblum.[5]

Preparation of $C_5H_5Fe(CO)_2(h^2$-polyene)$^+BF_4$ Complexes (9–15). The general procedure is as described by Giering and Rosenblum.[5] The olefin (30 mmol), **1** (3.0 mmol), and 40 ml of 1,2-dichloroethane were placed in an erlenmeyer flask. A rubber septum fitted with a syringe needle and thermometer was secured to the flask and the mixture was heated at 65–70° for 10–15 min. After cooling to room temperature and filtering to remove any $C_5H_5Fe(CO)_3^+BF_4^-$, the solvent and excess polyene were removed by evaporation under reduced pressure. The residue was dissolved

in a minimum of acetone or nitromethane and filtered, and the filtrate was added dropwise to a large volume (100–200 ml) of ether with scratching to afford the complexes as yellow, air-stable precipitates. Purification was accomplished by reprecipitation from nitromethane–ether or acetone–ether.

Complex **7** was conveniently separated from a small amount (12%) of 1-6 bis-Fp^+ complex **16** by trituration of the reaction residue with several small portions of CH_2Cl_2. This bis complex was identified by its NMR spectrum (CD_3NO_2): δ 6.4–7.0 (m, 2 H, olefinic), 5.7 (s, 5 H, Cp), 5.6 (s, 5 H, Cp), 4.8–5.5 (m, 2 H, coordinated CH=CH_2), 3.5–4.2 (m, 4 H, coordinated CH=CH_2), 2 5 (bm, 2 H, allylic).

All new complexes exhibited prominent infrared absorptions (CH_3COCH_3) at 2055, 2020 (M-C≡O), and 1025 cm^{-1} (BF_4^-). NMR spectral data are presented in Table I. Satisfactory C and H analyses were obtained for all new compounds except **11** and **15**.

Hydrogenation of Fp(vinylcyclohexene)$^+BF_4^-$ (9). Complex **9** (0.186 g, 0.50 mol), 10 mg of 5% Pd/C, and 5 ml of trifluoroacetic acid were stirred at 25° under 1 atm of hydrogen until gas uptake ceased (ca. 15 min). The catalyst was removed by filtration and the filtrate was added dropwise to 100 ml of ether. The NMR spectrum of the resulting yellow precipitate (0.140 g, 75%) was identical with that produced from the reaction of **1** with vinylcyclohexane: δ (CD_3NO_2) 5.7 (s, 5 H, Cp), 5.1 (m, 1 H, CH=CH_2), 3.8 (d, J = 9 Hz, 1 H, CH=CH_2 cis), 3.5 (d, J = 16 Hz, 1 H, CH=CH_2 trans), 1.0–2.2 (6 m, 1 H, ring H).

Anal. Calcd for $C_{15}H_{19}BF_4FeO_2$: C, 48.18; H, 5.12. Found: C, 48.11; H, 5.09.

Fp(*cis*-2-octene)$^+BF_4^-$ (17). The reaction of **1** with *cis*-2-octene according to the general method (above) gave **17** (38%): NMR (acetone-d_6) δ 5.80 (s, 5 H, Cp), 5.3 (bm, 2 H, complexed CH=CH), 2.5–0.8 (bm, 14 H, CH_2, CH_3).

Anal. Calcd for $C_{15}H_{21}BF_4FeO_2$: C, 47.91; H, 5.64. Found: C, 47.89; H, 5.48.

$C_5H_5Fe(CO)_2$(h^2-*trans*-2-octene)$^+BF_4^-$ (18). *trans*-2-Octene and **1** gave **18** (66%); NMR (acetone-d_6) δ 5.85 (s, 5 H, Cp), 4.9 (bm, 2 H, complexed CH=CH), 2.5–0.7 (bm, 14 H, CH_2, CH_3).

Anal. Calcd for $C_{15}H_{21}BF_4FeO_2$: C, 47.91; H, 5.64. Found: C, 47.75; H, 5.46.

Monitored Competitive Reaction of 1 with *cis*- and *trans*-2-Octene. *cis*-2-Octene (30 mmol), *trans*-2-octene (30 mmol), **1** (6 mmol), and 60 ml of dichloroethane were heated in the usual fashion. Aliquots (10 ml) were withdrawn by syringe after 2.5, 5, 8, 12, and 15 min once the temperature reached 55° and transferred to separate flasks. The individual aliquots were filtered, the filtrates were added to ether, and the resulting precipitates were analyzed by NMR. Integration of the complexed olefinic proton absorptions indicated that the ratio of cis/trans complex, 2.5:1, was unchanged during the course of the reaction.

Reaction of $C_5H_5Fe(CO)_2$(*trans*-2-octene)$^+BF_4^-$ (18) with *cis*-2-Octene. *cis*-2-Octene (5.3 mmol), **18** (0.53 mmol), and 40 ml of dichloroethane were heated at 65–70° for 10 min and allowed to cool. The reaction mixture was filtered and the filtrate was added to 200 ml of ether. The resulting yellow precipitate (0.06 g, 30%) was found by NMR to be composed to ca. 67% trans complex **18** and 33% cis complex **17**.

Acknowledgment. The authors thank Professor M. Rosenblum for helpful discussions. Financial support provided by Boston College is also gratefully acknowledged.

Registry No.—**1**, 41707-16-8; **2**, 100-40-3; **3**, 2004-70-8; **4**, 4049-81-4; **5**, 24612-83-7; **6**, 1755-01-7; *cis*-**7**, 55758-72-0; *trans*-**7**, 44607-51-4; *exo*-**8**, 23890-32-6; *endo*-**8**, 25093-48-5; **9**, 55758-75-3; **10**, 55758-77-5; **11**, 55822-54-3; **12**, 55758-79-7; **13**, 55758-81-1; *cis*-**14**, 55758-83-3; *trans*-**14**, 55820-95-6; exo-**15a**, 55758-85-5; *endo*-**15a**, 55820-97-8; *exo*-**15b**, 55758-87-7; *endo*-**15b**, 55820-99-0; *cis*-**16**, 55758-89-9; *trans*-**16**, 55821-01-7; **17**, 55758-91-3; **18**, 55821-03-9; Fp(vinylcyclohexane)$^+BF_4^-$, 55758-93-5; *cis*-2-octene, 7642-04-8; *trans*-2-octene, 13389-42-9.

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(2) A. Sanders and W. P. Giering, *J. Am. Chem. Soc.*, **96**, 5247 (1974); **97**, 919 (1975).
(3) A. Sanders, C. V. Magatti, and W. P. Giering, *J. Am. Chem. Soc.*, **96**, 1610 (1974).
(4) K. M. Nicholas, *J. Am. Chem. Soc.*, **97**, 3254 (1975).
(5) W. P. Giering and M. Rosenblum, *Chem. Commun.*, 441 (1971).
(6) From triene **7** a 1,6-bis-Fp^+ complex (**16**) also formed (12%).
(7) For example, the protons syn and anti to Fp^+ in **13** absorb at δ −0.2 (d, J = 12 Hz) and 0.7 (d, J = 12 Hz) while the corresponding proton absorptions for Fp (h^2-norbornadiene)$^+BF_4^{-5}$ are at δ −0.1 (d, J = 12 Hz) and 1.0 (d, J = 12 Hz) (ref 8). Also, hydrogenation of **9** (19% Pd/C, TFA solvent) gave Fp(vinylcyclohexane)$^+BF_4^-$ which had a ^1H NMR spectrum identical with that prepared from Fp(isobutylene)$^+BF_4$ and vinylcyclohexane.
(8) F. R. Hartley, *Chem. Rev.*, **73**, 163 (1973).
(9) Coordination at the 8,9 position of *endo*-dicyclopentadiene by Au(I) and Cu(I) has also been reported: R. Huttel, R. Reinheimer, and H. Dietl, *Chem. Ber.*, **99**, 462 (1966); R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.*, **95**, 1889 (1973). Additionally, Ni-catalyzed hydrogenation of **6** proceeds selectively at the 8,9 position: C. A. Brown and V. K. Ahuja, *J. Org. Chem.*, **38**, 2226 (1973).
(10) Since back-bonding in the Fp(olefin)$^+$ complexes may not be extensive, coordination at the 8,9 position of dicyclopentadiene could be due to stronger forward (olefin–metal) donation. Since the energy of $\pi_{8,9}$ is higher than that of $\pi_{3,4}$, $\pi_{8,9}$ would interact with relatively high energy empty metal orbitals to form a lower energy bonding MO.
(11) S. Raghu and M. Rosenblum, *J. Am. Chem. Soc.*, **95**, 3060 (1973).
(12) M. A. Muhs and F. T. Weiss, *J. Am. Chem. Soc.*, **84**, 4697 (1962).
(13) Preliminary results indicate that the exchange reaction is first order in **1** and zero order in alkene: M. Rosenblum and N. Genco, personal communication.

Some Observations on the Interaction of Diarylamines and Arsenic Trichloride[1]

Leon D. Freedman* and Virgil L. Styles

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27607

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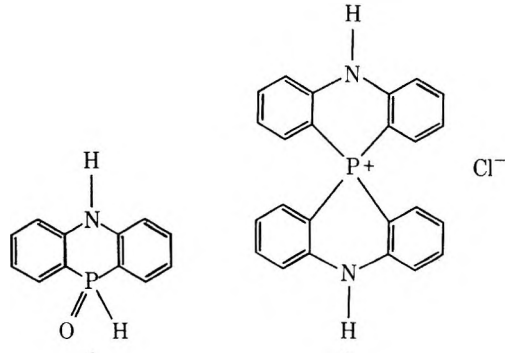
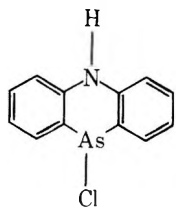
The reaction of diarylamines with phosphorus trichloride followed by treatment of the reaction mixtures with water has been found[2] to yield not only the expected heterocyclic phosphine oxides (i.e., **1** and its ring-substituted derivatives) but also the spirophosphonium chloride **2** and its derivatives. It seemed of interest to determine whether



1 **2**

the analogous spiroarsonium chlorides could be obtained via the interaction of diarylamines and arsenic trichloride. Wieland and Rheinheimer[3] reported in 1921 that the chloroarsine **3** (now often known as Adamsite) is formed in high



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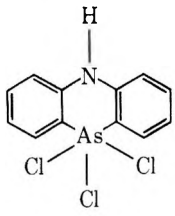
yield by refluxing a mixture of diphenylamine and arsenic trichloride for about 4 hr; and various ring-substituted derivatives of **3** have been prepared in a similar manner by a

number of investigators.[4] Although spiroarsonium halides have not been isolated from any of these reactions, it seemed possible to us that such compounds had been formed as by-products and had been missed. Accordingly, we have allowed several diarylamines (diphenylamine, di-*p*-tolylamine, and *N*-phenyl-1-naphthylamine) to react with arsenic trichloride under a variety of conditions. In every case we obtained a good yield of the expected heterocyclic chloroarsine (e.g., 89% of **3**). Attempts to isolate spiroarsonium chlorides by the methods previously used for the corresponding phosphorus compounds[2c] were, however, uniformly unsuccessful. Accordingly, we have concluded that spiroarsonium chlorides analogous to **2** are not produced in appreciable amounts (i.e., >0.5%) by the interaction of diarylamines and arsenic trichloride.

We have also tried to prepare a spiroarsonium chloride by the reaction of diphenylamine and the trichloride **4**. The latter substance, obtained as a red powder by allowing the arsinic acid **5** to react with thionyl chloride as described by



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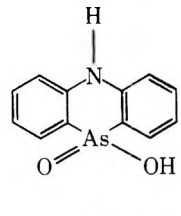

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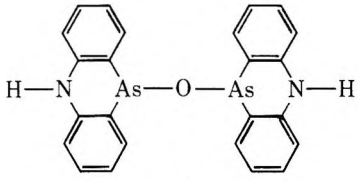
Gibson and coworkers,[5] was not purified but immediately after isolation was treated with a benzene solution of diphenylamine. The resulting reaction did not produce the desired spiroarsonium chloride but instead gave a green solid[6] that yielded on treatment with aqueous sodium hydroxide the trivalent arsenical **6**. It seems possible that the primary product of the reduction[7] was the amide **7**, which was hydrolyzed by the aqueous base to **6**. The hydrolysis of



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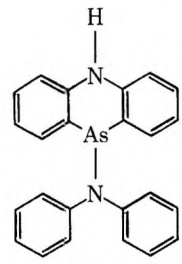

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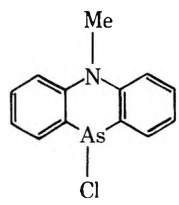
compounds containing the As–N bond to yield oxides of the type $(R_2As)_2O$ has been observed by Sommer.[8]

In addition to our attempts to obtain the spiroarsonium compounds discussed above, we have tried to clear up some puzzling reports in the literature dealing with the interaction of *N*-methyldiphenylamine and arsenic trichloride. Wieland and Rheinheimer[3] claimed that the reaction of these substances yielded the expected *N*-methyl compound **8** (0.75 g from 20 g of amine and 20 g of $AsCl_3$). In contrast,



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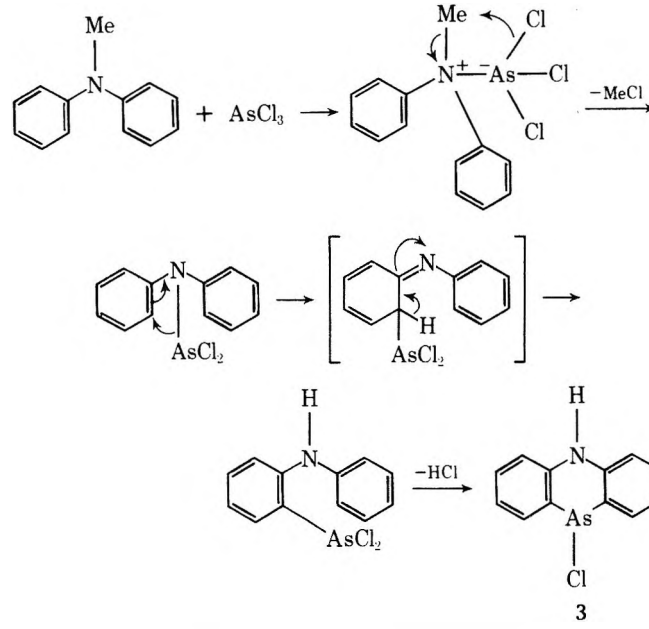
Burton and Gibson[9] reported that the product was the unmethylated chloroarsine **3**, and they were unable to prepare **8** by a number of indirect methods. We have allowed *N*-methyldiphenylamine to react with arsenic trichloride at 150–170° without solvent (as described by Wieland and Rheinheimer[3]) or in refluxing *o*-dichlorobenzene (as described by Burton and Gibson[9]). Under both sets of conditions we obtained a low yield (~2%) of a chloroarsine that was shown by its ir spectrum to be the unmethylated compound **3**. A larger yield of arsenical could be isolated by subjecting the reaction mixture obtained by the method of Wieland and Rheinheimer[3] to alkaline peroxide oxidation and subsequent acidification. In this way a 19% yield of the unmethylated arsinic acid **5** was obtained. As previously noted,[3] the major product formed by the interaction of *N*-methyldiphenylamine and arsenic trichloride is a dark blue-black resinous material that has not been further identified.

Although commercial *N*-methyldiphenylamine exhibits a weak N–H stretching vibration at 3400 cm^{-1}, the amount of diphenylamine present in this material was shown by GLC analysis to be only 0.1%. It is clear, therefore, that the unmethylated arsenicals **3** and **5** cannot arise solely from this impurity and that Burton and Gibson[9] were correct in concluding that demethylation must occur during the course of the interaction of *N*-methyldiphenylamine and arsenic trichloride. The following mechanism is suggested.



The above mechanism (somewhat similar to the one proposed[2c] for the reaction of diphenylamine with phosphorus trichloride) rationalizes the cleavage of the methyl group and the fact that only substitution ortho to the nitrogen is observed.

Ultraviolet Spectra. Earley and Gallagher[10] have reported that the electronic spectra of several trivalent dihydrophenarsazine derivatives have one or two moderately intense bands above 300 nm. Quaternization of the arsenic atom produced no profound changes in the spectra. In particular, the bands above 300 nm were still present; and, in some cases, there were small bathochromic shifts and slight increases in intensity. The results obtained on quaternization and the fact that diphenylamine and 5,10-dihydroacridine do not exhibit absorption bands above 300 nm prompted the authors[10] to suggest that the long-wavelength bands in the spectra of the arsenic compounds should be attributed to d_π–p_π bonding involving the lone pair of electrons on the nitrogen atom and empty d orbitals of arsenic. PMR data obtained by Earley and Gallagher appear to be consistent with this conclusion. It will be noted

Table I
Ultraviolet Absorption Maxima of Arsinic and Phosphinic Acids

Compd	λ_{max}, nm	ϵ_{max}
5,10-Dihydro-10-hydroxy-phenarsazine 10-oxide (5)	216	30,900
	238[a]	9,050
	273	19,600
	307	13,000
	330	6,500
5,10-Dihydro-10-hydroxy-phenophosphazine 10-oxide (11)	216	34,200
	238[a]	11,500
	274	21,800
	304	11,800
	330	6,440
5,10-Dihydro-2,8-dimethyl-10-hydroxyphenarsazine 10-oxide (9)	218	29,800
	240[a]	10,500
	277	23,900
	315	12,500
	342	6,300
5,10-Dihydro-2,8-dimethyl-10-hydroxyphenophosphazine 10-oxide (12)	218	28,600
	240[a]	11,300
	277	24,900
	312	9,050
	340	5,350
7,12-Dihydro-7-hydroxybenzo[c]phenarsazine 7-oxide (10)	225	51,000
	252	31,700
	266[a]	8,330
	288[a]	3,850
	300	6,630
	328[a]	16,900
	336	18,300
	353[a]	8,500
7,12-Dihydro-7-hydroxybenzo[c]phenophosphazine 7-oxide (13)	223	54,500
	252	29,600
	268[a]	10,500
	290[a]	3,830
	302[a]	5,920
	327[a]	15,300
	337	16,900
	352[a]	9,230

[a] Shoulder.

in Table I that the spectra of the arsinic acids **5**, **9**, and **10** also contain moderately intense bands above 300 nm. The spectra of the phosphinic acids **11**, **12**, and **13** exhibit similar bands and are indeed almost identical with the spectra of the corresponding arsenic compounds.[11] Presumably, then, these arsinic and phosphinic acids also exhibit conjugative interaction between the arsenic or phosphorus atom and the π-electron system of the aromatic rings. Extensive electron delocalization in the heterocyclic rings of the spirophosphonium chloride **2** has been suggested by an X-ray and ^{31}P NMR study of this compound.[2b]

Experimental Section

General. Melting points were determined with a Mel-Temp capillary melting point apparatus and are uncorrected. Ir spectra were obtained with a Perkin-Elmer Model 521 spectrophotometer. Uv spectra were determined in 95% ethanol with a Cary 14 Model 50 recording spectrophotometer with matched 1.0-cm silica cells. Analyses for carbon and hydrogen were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.; arsenic analyses were performed by Mrs. Dolores E. Knight through the courtesy of Dr. G. G. Long of this department. Authentic samples of the chloroarsine **3**,[3,9] the arsinic acids **5**,[3] **9**,[12] and **10**,[13] the oxide **6**,[3] and the phosphinic acids[2c] **11**, **12**, and **13** were prepared by methods described in the literature. The identity and purity of these compounds were confirmed by melting point, ir, and elemental analysis.

Reaction of Diphenylamine with 5,10-Dihydro-10,10,10-trichlorophenarsazine (4). The arsinic acid **5** (3.19 g, 0.012 mol) and 4.9 ml of thionyl chloride were allowed to react in 8.5 ml of dry benzene by the procedure of Gibson and coworkers.[5] Evaporation of the solvent and the excess thionyl chloride yielded a red powder, which was assumed to be the trichloride **4**. A solution of diphenylamine (11.6 g, 0.069 mol) in 25 ml of dry benzene was added to the red powder, whereupon a green reaction mixture was quickly formed. The green solid obtained by evaporation of the benzene was dissolved in about 250 ml of boiling acetone. Addition of 4 *N* aqueous NaOH to the acetone solution precipitated a yellow solid that was removed by filtration, washed with acetone, and then dried in vacuo, yield 2.86 g. The ir spectrum, which exhibited a strong peak at 740 cm^{-1} attributable to the As–O–As linkage,[14] indicated that the yellow solid was crude 10,10′-(5*H*,5′*H*-oxydiphenarsazine) (**6**). Recrystallization from pyridine gave greenish-white crystals, mp 349–350° (lit.[3] mp 350), shown by mixture melting point and ir to be identical with an authentic sample of **6**.[3]

Reaction of *N*-Methyldiphenylamine with Arsenic Trichloride. A mixture of *N*-methyldiphenylamine (20 g, 0.11 mol) and arsenic trichloride (20 g, 0.11 mol) was heated at 150–170° for 4 hr as described by Wieland and Rheinheimer.[3] The resulting blue-black resinous material was mixed with 100 ml of xylene and heated until the mixture was homogeneous. Addition of ether precipitated a dark solid, which was removed by filtration. The filtrate was then evaporated to 25 ml and cooled, whereupon yellow crystals separated from the solution. Recrystallization from CCl_4 gave 0.61 g (2%) of pure 10-chloro-5,10-dihydrophenarsazine (**3**) as shown by melting point, mixture melting point, and ir.

In another experiment, the reaction mixture obtained from *N*-methyldiphenylamine (18.3 g, 0.100 mol) and arsenic trichloride (18.1 g, 0.100 mol) was refluxed gently for 15 hr with a mixture of 200 ml of 2 *N* NaOH and 50 ml of 30% H_2O_2. The resulting mixture was extracted with two 100-ml portions of ether to remove an oily material, and the aqueous layer was added slowly with good stirring to an excess of 10% hydrochloric acid. The blue solid that precipitated was shown by its ir spectrum to be essentially pure 5,10-dihydro-10-hydroxyphenarsazine 10-oxide (**5**), yield 5.3 g (19%).

The above experiments were performed with unpurified *N*-methyldiphenylamine (Eastman Kodak No. 2098). Similar results were obtained, however, with *N*-methyldiphenylamine purified by distillation through a spinning band column and shown by ir and GLC to be free of diphenylamine.

Registry No.—**3**, 578-94-9; **4**, 55712-32-8; **5**, 4733-19-1; **6**, 4095-45-8; **9**, 55712-33-9; **10**, 5657-43-2; **11**, 472-43-5; **12**, 53798-60-0; **13**, 53798-62-2; diphenylamine, 122-39-4; thionyl chloride, 7719-09-7; *N*-methyldiphenylamine, 552-82-9; arsenic trichloride, 7784-34-1.

References and Notes

(1) Abstracted from the M.S. Thesis of V. L. Styles, North Carolina State University, Raleigh, N.C., 1972.
(2) (a) R. N. Jenkins, L. D. Freedman, and J. Bordner, *Chem. Commun.*, 1213 (1971); (b) *J. Cryst. Mol. Struct.*, **3**, 103 (1973); (c) R. N. Jenkins and L. D. Freedman, *J. Org. Chem.*, **40**, 766 (1975).
(3) H. Wieland and W. Rheinheimer, *Justus Liebigs Ann. Chem.*, **423**, 1 (1921).
(4) Cf. F. G. Mann, "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony and Bismuth", Wiley-Interscience, New York, N.Y., 1970, pp 506–522.
(5) C. S. Gibson, J. D. A. Johnson, and D. C. Vining, *Recl. Trav. Chim. Pays-Bas*, **49**, 1006 (1930).
(6) The arsenic-containing substance in the green solid could not be extracted with boiling CCl_4 and therefore could not have been the chloroarsine **3**, which is moderately soluble in hot CCl_4.
(7) Since W. Steinkopf and S. Schmidt, *Ber.*, **61**, 675 (1928), have reported that thionyl chloride can reduce certain arsonic acids and since the trichloride **4** has not been adequately characterized, we felt it was necessary to show that reduction had not occurred during the course of the reaction between thionyl chloride and the arsinic acid **5**. Accordingly, we allowed a sample of the trichloride **4** to react with water and found that a virtually quantitative yield of **5** was obtained.
(8) K. Sommer, *Z. Anorg. Allg. Chem.*, **383**, 136 (1971).
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(10) R. A. Earley and M. J. Gallagher, *J. Organomet. Chem.*, **20**, 117 (1969).
(11) The close resemblance of the uv spectra of corresponding organoarsenic and -phosphorus compounds has often been noted; cf. G. O. Doak, L. D. Freedman, and J. B. Levy, *J. Org. Chem.*, **29**, 2382 (1964), and references cited therein.
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(13) W. L. Lewis and C. S. Hamilton, *J. Am. Chem. Soc.*, **43**, 2218 (1921).
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A Simplified Method for the Titanium(II)-Induced Coupling of Allylic and Benzylic Alcohols

John E. Mc Murry* and Michael Silvestri

Thimann Laboratories, University of California, Santa Cruz, California 95064

Received April 15, 1975

Some years ago, van Tamelen and Schwartz introduced a conceptually elegant method, based on the thermal fragmentation of a titanium(II) dialkoxide, to effect the reductive coupling of allylic and benzylic alcohols.[1] Operationally, titanium tetrachloride was added to 2 equiv of alkoxide ion, and the resulting dichlorotitanium(IV) dialkoxide was reduced with molten potassium in refluxing benzene. After solvent removal, the resulting black residue of titanium(II) dialkoxide was heated to effect fragmentation and coupling. Benzyl alcohol, for example, coupled to bibenzyl in 51% yield based on recovered starting material.

$$2RO^- + TiCl_4 \longrightarrow TiCl_2(OR)_2 \xrightarrow{K} Ti(OR)_2$$

$$R\text{-}R \longleftarrow [2R\cdot] + TiO_2$$

Subsequently, a modification based on the use of titanium trichloride and methyllithium was introduced, simplifying the procedure considerably.[2]

We have been exploring the chemistry of a reagent derived by reaction of titanium trichloride with lithium aluminum hydride,[3] and we suggested in a recent review that this reagent might prove effective and convenient in the alcohol reductive coupling reaction.[4] We have now demonstrated this to be the case, and we wish to report our results.

Cautious addition of 1 molar equiv of $LiAlH_4$ to a slurry of 3 molar equiv[5] of $TiCl_3$ in dry dimethoxyethane (glyme) results in instantaneous evolution of hydrogen and formation of a black suspension [presumably containing Ti(II)]. Alternatively, addition to glyme of a 3:1 ball-milled premix of $TiCl_3$–$LiAlH_4$ prepared for us by Alfa Inorganics[6] gives the same black suspension. The major advantage of this premix is that it serves as a convenient one-bottle source of reagent.

Addition of 1 molar equiv of alcohol, followed by overnight reflux, then gives the coupled product in high yield. A summary of our results is presented in Table I.

As can be seen, both allylic and benzylic alcohols couple well, and steric bulk of the alcohol seems to have no deleterious effect, since 2-phenyl-2-propanol couples in 95% yield. The most interesting results in Table I are those of farnesol. As expected for a radical mechanism,[7] coupling occurs at both ends of the allylic system in the farnesyl radical, leading to a mixture of primary–primary and primary–tertiary coupled products in a 2:1 ratio. We were unable to find any tertiary–tertiary product. In addition, farnesyl radical abstracted hydrogen from solvent in significant amounts, leading to a mixture of allylically rearranged and unrearranged uncoupled hydrocarbons. We were unable to suppress this side reaction by changing solvents and conditions. Use of tetrahydrofuran, dioxane, or benzene–THF mixtures gave much more hydrogenolysis product.

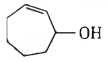
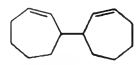
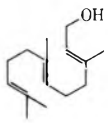
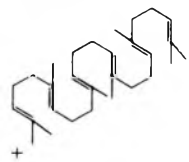
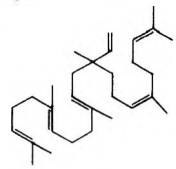
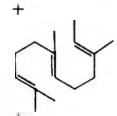
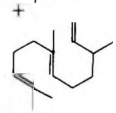
In summary, we feel that the efficiency and operational ease of the $TiCl_3$–$LiAlH_4$ mixture make it a desirable reagent choice for carrying out the reductive coupling of alcohols.

Experimental Section

General Reaction Procedure. A suspension of titanium(II) reagent was prepared in either of the following ways. A. Titanium

Table I
Reductive Coupling of Alcohols Using $TiCl_3$–$LiAlH_4$

$$ROH + TiCl_3\text{–}LiAlH_4 \longrightarrow R\text{–}R$$

ROH	Registry no.	R–R	Registry no.	Isolated yield, %
$PhCH_2OH$	100-51-6	$PhCH_2CH_2Ph$	103-29-7	78
$PhCH(OH)CH_3$	98-85-1	$PhCH(CH_3)CH(CH_3)Ph$	4613-11-0 (meso) 2726-2-8 (*dl*)	68
$PhC(OH)(CH_3)_2$	617-94-7	$PhC(CH_3)_2C(CH_3)_2Ph$	1889-67-4	95
	4096-38-2		55759-30-3	87
	4602-84-0		7683-64-9	33
		+ 	55759-31-4	15
		+ 	7681-88-1	8
		+ 	55759-32-5	13

trichloride (2.3 g, 15.0 mmol) was weighed under dry nitrogen in a glove bag and placed under nitrogen in a 100-ml three-neck flask with 70 ml of dry glyme. $LiAlH_4$ (190 mg, 5.0 mmol) was quickly added to the stirred $TiCl_3$ slurry, and the resulting black suspension was stirred for 10 min before use. **B.** Alternatively, a 3:1 $TiCl_3$–$LiAlH_4$ premix (effective mol wt 167, 2.50 g, 15.0 mmol) was weighed under nitrogen in a glove bag and added to 70 ml of dry glyme under nitrogen. The resulting black suspension was stirred for 10 min before use.

The substrate alcohol (5.0 mmol) in several milliliters of glyme was then added, and the reaction mixture was refluxed for 16 hr. After cooling, the reaction mixture was quenched by addition of dilute aqueous hydrochloric acid, then diluted with water and extracted with ether. The ether extracts were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated at the rotary evaporator. Crude products were then purified either by crystallization or distillation. In this manner, the following reactions were run.

Benzyl alcohol gave **bibenzyl,** 78%, mp 51–51.5° (lit.[8] mp 52°).

α-Phenethyl alcohol gave a liquid mixture of meso and *dl* forms of **2,3-diphenylbutane,** 68%. Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.59; H, 8.67.

2-Phenyl-2-propanol gave **2,3-dimethyl-2,3-diphenylbutane,** 95%, mp 117–118° (lit.[9] mp 118–119°).

2-Cycloheptenol gave **3-(2-cycloheptenyl)cycloheptene,** 87%. Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.14; H, 11.76.

Farnesol gave a mixture of products which was separated by high-pressure liquid chromatography on Porosil A[10] (16 ft × 0.25 in.). The results are shown in Table I. Identifications were made on spectroscopic grounds (100-MHz NMR and mass spectra) and were unequivocal.

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

Registry No.—Titanium trichloride, 7705-07-9; $LiAlH_4$, 16853-85-3.

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(2) K. B. Sharpless, R. P. Hanzlik, and E. E. van Tamelen, *J. Am. Chem. Soc.*, **90,** 209 (1968).
(3) J. E. Mc Murry and M. P. Fleming, *J. Am. Chem. Soc.*, **96,** 4708 (1974).
(4) J. E. Mc Murry, *Acc. Chem. Res.*, **7,** 281 (1974).
(5) This stoichiometry is chosen so that excess hydride [over the theoretical amount necessary to effect the Ti(III) → Ti(II) reduction] is present to react with substrate alcohol, thereby forming the necessary alkoxide ion.
(6) We thank Mr. Robert Wade, Alfa Inorganics, Beverly, Mass., for preparing this premix.
(7) E. E. van Tamelen, B. Akermark, and K. B. Sharpless, *J. Am. Chem. Soc.*, **91,** 1552 (1969).
(8) "The Merck Index", 8th ed, Merck and Co., Rahway, N.J., 1968, p 147.
(9) P. E. Verkade, K. S. de Vries, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas,* **82,** 637 (1963).
(10) Porosil A is a registered trademark of Waters Associates, Framingham, Mass.

Formation of a Stable Enol from a Michael Addition

J. M. Landesberg

Adelphi University, Garden City, New York 11530

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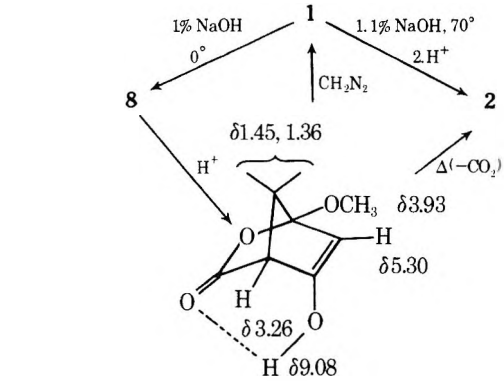
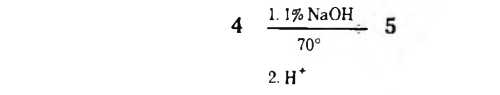
During the course of an earlier investigation,[1] difficulty was encountered in the hydrolysis of keto ester **1** (see Chart I). Base hydrolysis yielded only the enol ether **2** and not the corresponding acid **3**. This contrasted with the isomer **4**, which readily gave the acid **5** under similar conditions. Reinvestigation gave the γ-lactoenol **6**; evidence for the structure of this novel enol resulting from an internal Michael addition is presented here.

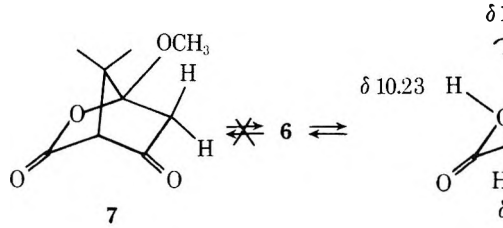
Chart I



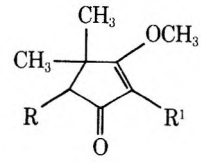
6 (1)



(2)



(3)



	R	R^1
1	CO_2CH_3	H
2	H	H
4	H	CO_2CH_3
5	H	CO_2H
8	CO_2^-	H

Saponification of **1** is effected by 1% sodium hydroxide at 0° and crystalline solid **6** precipitates on acidification. Treatment of this saponified product with diazomethane regenerates **1**. Elemental analysis shows that **6** is isomeric with **5**. On melting, mp 102° dec, **6** decomposes, a gas evolves, and oil **2** results (previously identified[1]).

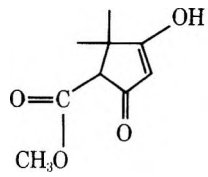
The infrared spectrum indicates, however, that **6** is *not* the carboxylic acid **3** but the γ-lactoenol **6**. A freshly prepared chloroform solution of **6** shows a strong absorption at ν 1780 cm^{-1}. This is characteristic of the five-membered lactone ring.[2,3] A solution of **6**, on standing at room temperature or on heating, undergoes changes in the infrared spectrum: the absorption at ν 1780 cm^{-1} decreases while an absorption at ν 1725 cm^{-1} increases; this would correspond to the formation of keto acid **3** by a retro-Michael; prolonged standing or heating finally yields the infrared spectrum of **2**. A methanol solution of **6** has only infrared absorptions which would be characteristic of **3** [ν 1725 (acid C=O), 1675 (α,β-unsaturated C=O), 1600 cm^{-1} (C=C)]. Thus, in solution **6** opens to give **3**, which eventually gives off CO_2 and leads to **2**. Attempts to isolate **3** only yield mixtures of **6** and **2**.

The nuclear magnetic resonance spectrum supports the above observations. In $CDCl_3$ **6** exhibits a chemical shift for the enolic proton at δ 9.08;[4] this is at higher magnetic field (δ 2.29 upfield) than the chemical shift of the carboxylic acid hydrogen of **5** (δ 11.37).[1] Heating the NMR solution (50°, 0.5 hr) brings about ring opening of **6** and the formation of **3**; a low-field absorption appears at δ 10.37[5] while the δ 9.08 signal decreases (and eventually disappears). No equilibrium with keto ester **7** is observed. NMR experi-

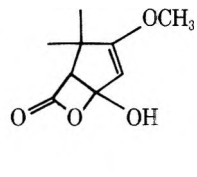
ments carried out in methanol-d_1 containing traces of acid (CF_3CO_2D) show no loss in intensity of the vinyl signal: the signal shows a change from δ 5.30 to δ 5.38 but the relative intensity of the signal to all other proton signals remains unity. Thus, equilibrium between **6** and **3** is the only one observed.

That the open form predominates in polar solvents is confirmed by the untraviolet spectrum: λ_{max} (95% ethanol) 239 mμ (ϵ 13,900). This absorbance is consistent with the chromophore -C(OCH$_3$)=C-C=O also found in **1** [λ_{max} (95% ethanol) 237 mμ (ϵ 13,900)], **2** [λ_{max} (95% ethanol) 237 mμ (ϵ 19,800)], and **4** [λ_{max} (95% ethanol) 240 mμ (ϵ 9900)].[1]

Two other structures, ester **9** and β-lactol **10**, may also be considered. However, compound **9** should show an ester ab-



9



10

sorption in the infrared spectrum as does compound **4**;[1] the absorption would not be expected to change with time in chloroform solution. Also, the ready loss of CO_2 on heating and on mass spectral analysis with formation of enol ether **2** would not be accommodated by **9**. While β-lactol formation to give **10** would parallel the observed behavior of phthalaldehydic acid,[6] one would expect infrared absorptions for the strained four-membered ring of structure **10** to be above ν 1800 cm^{-1}.[3] On this basis, the spectral and chemical evidence can be accommodated best by the γ-lactoenol **6**. This is a unique example of a stable enol[7] resulting from a Michael addition.

The γ-lactoenol forms by oxide attack on the δ carbon of the α,β-unsaturated cyclic ketone followed by H^+ addition to carbonyl oxygen. Survival of **6** results from the insolubility of **6** in aqueous acid medium and an equilibrium favoring **6** in the less polar organic solvents.[8] In more polar organic solvents strain relief derived by a retro-Michael is favored vs. keto–enol tautomerism.

Experimental Section[9]

Hydrolysis of 4,4-Dimethyl-3-methoxy-5-carbomethoxy-2-cyclopenten-1-one (1). Hydrolysis of compound **1** (0.50 g, 2.5 mmol) with 10 ml of 1% NaOH at 0° for 1 hr gave **6** (0.2 g, 50%) after acidification and extraction of the precipitated solid with ether. Recrystallization from 30–60° petroleum ether–ether solution gave white needles on cooling in Dry Ice–acetone, mp 102° dec.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.68; H, 6.57; mol wt, 184. Found: C, 58.83; H, 6.49; mol wt, 184 (mass spectrometry).

Treatment of **6** with excess diazomethane in ether gave **1** quantitatively.

A sample of **6** (0.1 g) was decomposed at the melting point; the infrared spectrum of the oil which resulted was identical in all respects with the infrared spectrum of 4,4-dimethyl-3-methoxy-2-cyclopenten-1-one (**2**).[1]

Attempts to isolate **3** from chloroform solutions using standard poedures for unstable compounds only resulted in the recovery of **2** and **6**.

The principal peaks in the mass spectrum of **6** are as follows: MS (75 eV) *m/e* (rel intensity) 184 (1), 151 (2), 141 (8), 140 (57), 139 (25), 126 (9), 125 (100), 111 (5).

This contrasts to the principal peaks in the mass spectrum of **5**:[1] MS (75 eV) *m/e* (rel intensity) 184 (95), 169 (84), 154 (31), 153 (100), 152 (31), 137 (44), 126 (48).

Acknowledgment. We thank Mr. D. Kellner for some preliminary experiments.

Registry No.—**1**, 17037-96-6; **6**, 55681-96-4.

References and Notes

(1) J. M. Landesberg and D. Kellner, *J. Org. Chem.*, **33**, 3374 (1968).
(2) For examples see A. McKillop, M. E. Ford, and E. C. Taylor, *J. Org. Chem.*, **39**, 2434 (1974).
(3) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Wiley, New York, N.Y., 1956.
(4) Band width at one-half peak height is 14 Hz.
(5) Band width at one-half peak height is 8 Hz.
(6) J. Kagan, *J. Org. Chem.*, **32**, 4060 (1967).
(7) (a) An example of a stable aliphatic enol is found in H. M. R. Hoffman and E. A. Schmidt, *J. Am. Chem. Soc.*, **94**, 1373 (1972). (b) E. A. Schmidt and H. M. R. Hoffman,, *J. Am. Chem. Soc.*, **97**, 7832 (1975).
(8) See E. S. Gould, "Mechanisn and Structure in Organic Chemistry", Henry Holt and Co., New York, N.Y., 1959, p 376 ff, for a discussion.
(9) General experimental details and procedures have been reported earlier.[1] Mass spectra were obtained on a Perkin-Elmer Hitachi Model RMU-6D mass spectrometer. The NMR spectra were determined on a Varian A-60 using tetramethylsilane as internal standard. All solvents for NMR determinations were obtained from Stohler Isotope Corp. and were used as received. Infrared spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer using ir transparent cells; bands in the carbonyl region were calibrated against the 1603 cm^{-1} band of polystyrene.

Photolysis of Dioxane

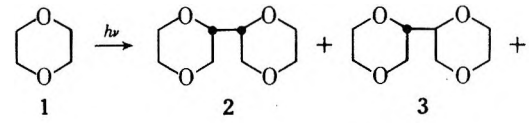
Paul H. Mazzocchi* and Michael W. Bowen

Department of Chemistry, University of Maryland, College Park, Maryland 20742

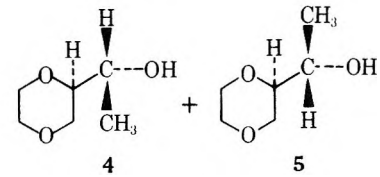
Received February 24, 1975

Dioxane has been a solvent of choice in many photochemical reactions owing to its excellent solvent properties and ultraviolet transparency. In the course of a series of photochemical reactions in dioxane we noted the presence of four products which were persistent in all of our photoreactions. In order to determine whether these products arose from irradiation of reactant, solvent, or both, we irradiated pure dioxane using a 450-W medium-pressure lamp through quartz in a nitrogen atmosphere. The reaction was monitored by GLC on a 20% Versmid column and indicated the slow formation of four products, in approximately equal amounts, over the period of irradiation.

Distillation, followed by preparative GLC, led to the isolation of the pair of diastereomeric dioxane dimers (**2** + **3**) which have been previously reported as products from the photolysis of dioxane,[1] and a pair of diastereomeric alcohols to which we assigned structures **4** and **5** on the basis of spectral and chemical evidence (vide infra).

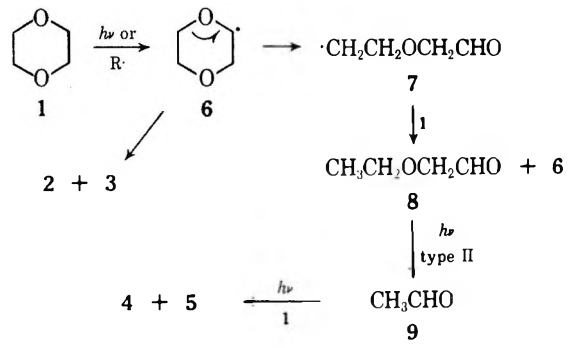


1 **2** **3**



4 **5**

The formation of **2** and **3** may be easily rationalized[1] as a simple dimerization of dioxyl radical **6** formed by photoinitiated hydrogen abstraction from dioxane.[2] The most reasonable route to **4** and **5** involves a β bond cleavage in **6** to give radical **7**, which hydrogen abstracts from dioxane in a chain propagation step to afford ethoxyacetaldehyde (**8**).[3] The ultraviolet spectrum of **8** is such that under the conditions used it should be immediately exposed to light undergoing an efficient Norrish II reaction to give 2 mol of acetaldehyde.[4] Acetaldehyde would then be expected to undergo an efficient photoreduction in dioxane to afford **4** and **5**.[5,6]



Although the presence of **2–5** does cause some problems during the work-up of preparative photochemical reactions, a major objection to the use of dioxane in quantitative or mechanistic studies is the presence of small steady-state concentrations of **8** and **9**, which could cause troublesome sensitization and/or quenching reactions.

Experimental Section

Infrared spectra were obtained on a Beckman IR-8, NMR spectra on a Varian A-60D spectrometer, and gas chromatographic work was carried out on Varian 1200 (flame ionization) and A-90 (thermal conductivity) instruments.

Photolysis of Dioxane. A sample of 200 ml of spectrograde dioxane was purged with nitrogen for 1 hr and then irradiated with a 450-W Hanovia type L lamp for a period of 200 hr. Aliquots were removed during the course of the reaction and analysis on a 6 ft × 0.125 in. 20% Versmid on 60–80 Chromosorb W column at 140° indicated the slow generation of four products with retention times of 8 (A), 12.5 (B), 23, and 31 min. Dioxane was removed by distillation and the residue was distilled to give a fraction, bp 100–120° (17 mm), enriched in the two short retention time peaks. The residue was rich in the two long retention time components and these were separated via preparative GLC on a 6 ft × 0.25 in. 15% DC550 on 80–100 mesh Chromosorb W column at 125°. Melting points and spectral data (ir, NMR, MS) indicated that these were the dimers **2** and **3**.[1]

The two early retention time peaks were isolated from the distillation fraction by preparative GLC on a 6 ft × 0.25 in 20% Versmid on 60–80 Chromosorb W column at 110°.

The material corresponding to peak A was identified as **4** (or **5**) on the basis of the following data: ν_{max} ($CDCl_3$) 3600, 2870, 2980, and 1120 cm^{-1}; NMR ($CDCl_3$) τ 8.87 (d, J = 6 Hz, 3 H, CH_3), 7.27 (broad s, 1 H, OH), 6.0–6.7 (broad m, 8 H, HCO); MS m/e (rel intensity) 132 (P, 4), 87 (100), 45 (98).

The material corresponding to peak B was identified as **5** (or **4**) on the basis of the following data: ν_{max} ($CDCl_3$) 3600, 2865, 2970, 1115 cm^{-1}; NMR ($CDCl_3$) τ 8.83 (d, J = 6.5 Hz, 3 H, CH_3), 7.72 (broad s, 1 H, OH), 5.9–6.6 (broad m, 8 H, HCO); MS m/e (rel intensity) 132 (P, 6), 87 (100), 45 (52).

Acknowledgment. We wish to thank the Center for Materials Research of the University of Maryland for partial support of this work.

Registry No.—**1**, 123-91-1; **4**, 55759-33-6; **5**, 55759-34-7.

References and Notes

(1) K. Pfordte, *Justus Liebigs Ann. Chem.*, **625**, 30 (1959).
(2) Although we would normally expect it to result from hydrogen abstraction processes, in the present case **6** probably arises via excitation of dioxane with 185-nm light. The formation of similar radicals in alcohols has been reported: N. C. Yang, D. P. C. Tang, D. M. Thap, and J. S. Sallo, *J. Am. Chem. Soc.*, **88**, 2851 (1966).
(3) N. L. Drake, H. M. Duvall, T. L. Jacovs, H. T. Thompson, and H. M. Sonnicksen, *J. Am. Chem. Soc.*, **60**, 73 (1938).
(4) The photochemistry of methoxyacetone has been studied. This material undergoes efficient Norrish II cleavage (quantum yield = $\bar{\phi}$ = 0.32) to give acetone and formaldehyde: R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 2475 (1962).
(5) Ketones are known to undergo photoreduction in the presence of dioxane: K. Shima and S. Tsutsumi, *Bull. Chem. Soc. Jpn.*, **36**, 121 (1963); G. O. Schenck, H. D. Becker, K. H. Schutte-Elte, and C. H. Krauch, *Chem. Ber.*, **96**, 510 (1963); W. Droste, H. D. Scharf, and F. Korte, *Justus Liebigs Ann. Chem.*, **724**, 71 (1969).
(6) We have carried out the photoreduction of acetaldehyde in dioxane and it does afford **4** and **5** efficiently.

Conformational Aspects of 1,4-Oxathiane *S*-Oxide by Carbon Magnetic Resonance Spectroscopy

Donna M. Frieze and Slayton A. Evans*

William Rand Kenan, Jr., Laboratories of Chemistry, University of North Carolina—Chapel Hill, Chapel Hill, North Carolina 27514

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Recently, considerable discussion has focused on the conformational preferences of the sulfinyl oxygen atom (S–O) in a variety of six-membered rings. For example, *trans*-1,4-dithiane 1,4-dioxide, possessing a diaxial oxygen conformation in the solid state,[1] appears to exist preferentially in the same conformation in solution.[2] This axial preference of the S–O group has been established for thiane *S*-oxide (**1**) by low-temperature ^1H NMR techniques[3] while an equilibrium mixture of anancomeric *cis*- and *trans*-4-*tert*-butylthiane *S*-oxides (**2** and **3**) exhibits a predominance of the cis isomer bearing the axial oxygen.[4] In contrast, the sulfinyl oxygen atom of 3,3-dimethylthiane *S*-oxide prefers the equatorial conformation (>95%).[5] The equatorial preference in the 3,3-dimethyl derivative is undoubtedly due to the repulsive 1,3-syn–axial methyl–sulfinyl oxygen atom interaction while the axial preference in **1** has been ascribed to an attractive interaction between the axial sulfinyl oxygen atom and the syn–axial C–H atoms.[6] In 1,3-dithiane *S*-oxide[7] and 1,3-oxathiane *S*-oxide[8] the sulfur oxygen atom favors the equatorial conformation in the former and the axial position in the latter. In view of the growing concern for those factors which influence (and possibly control) the conformations of sulfoxides in cyclic systems, we wish to report our results and conclusions regarding the conformations of 1,4-oxathiane *S*-oxide (**4**).

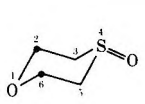
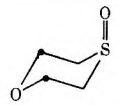
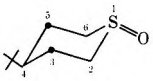
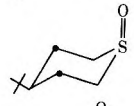
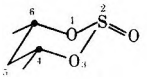
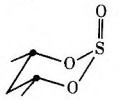
We have examined the conformational equilibria of 1,4-oxathiane *S*-oxide and the corresponding 3,3,5,5-tetradeuterio derivative **5** using ^{13}C NMR spectroscopy.

At −80° in CD_2Cl_2, two absorptions are observed for **5** while in a separate experiment four absorptions were visible for **4**. The carbons α to the ring oxygen and the ones α to the sulfinyl group were easily assigned since deuteration served to "mask"[9] only carbons adjacent to the sulfinyl group. Inspection of the low-temperature spectrum of **4** revealed two low-field absorptions of unequal intensity (δ 57.66 and 64.68 ppm) which exhibited a chemical shift difference of 7.02 ppm. A similar result was obtained for the high-field carbons α to the S–O group ($\Delta\delta$ = 7.42 ppm = 51.67 − 44.25). The conformer assignments for the two forms were made by comparison with the appropriate carbon shifts of other systems with established conformations as shown in Table I.

In all cases, it is apparent that the axial (sc) sulfinyl oxygen atom in a *chair conformation* engenders an upfield shift on the β carbons as compared to the equatorial (ap) sulfinyl oxygen atom.[10,11] From these data we conclude that the high-intensity absorptions (most populous conformer) correspond to the one with the *axial sulfinyl oxygen* atom (**4a**). This conclusion is in harmony with the one arrived at by Szarek et al.[15] from an examination of the ^1H NMR couplings and proton chemical shifts of **4** at ambient temperature. Calculation of the corresponding conformational free energy ($\Delta G°$) gave the data in Chart I.[16] The data on the conformational equilibrium of thiane *S*-oxide[3] are included for comparison.

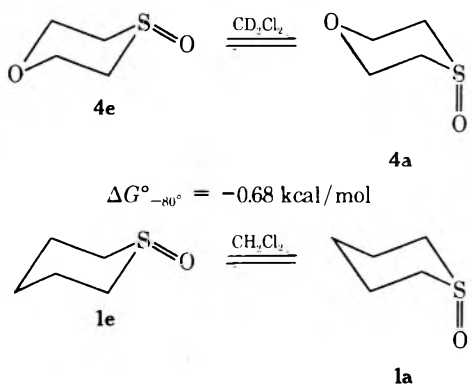
It is especially noteworthy that the $\Delta G°$ for **4** is more than three times that observed for thiane *S*-oxide under similar conditions ($\Delta G°_{-80°}$ = 0.68 ± 0.07 kcal/mol for **4** and $\Delta G°_{-90°}$ = 0.17 ± 0.03 kcal/mol[3] for **1**). Dreiding mo-

Table I
^{13}C NMR Shifts of β-Antiperiplanar (ap) and β-Synclinal (sc) Carbons in Six-Membered Ring Sulfoxides[a]

Conformer or diastereoisomer		Carbon chemical shift
ap	sc	difference ($\Delta\delta$), ppm[b]
		7.02[c,d]
		7.45[e]
		9.10[f]

[a] The ap and sc carbons relative to the sulfinyl oxygen atom are identified as darkened circles. [b] $\Delta\delta = \delta_{ap} - \delta_{sc}$. [c] Carbon shift difference measured at −80° in CD_2Cl_2 solution. [d] The shift difference for the appropriate carbons in 5 is identical with that observed for 4; however, the deuterium isotope effect caused a slight upfield shift for C-2 and C-6 relative to internal Me_4Si. Cf. D. Lauer, E. L. Motell, D. Traficants, and G. E. Maciel, *J. Am. Chem. Soc.*, **94**, 5335 (1972). [e] Data obtained from $CDCl_3$ solutions at ambient temperature. [f] G. W. Buchanan, J. B. Stothers, and G. Wood, *Can. J. Chem.*, **51**, 3746 (1973).

Chart I
Conformational Free Energy of 1,4-Oxathiane *S*-Oxide and Thiane *S*-Oxide



[a] J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966).

lecular models indicate that the distances between an axial sulfinyl oxygen atom and the 2,6-CH positions in 4 (2.75 Å) and the 3,5-CH positions in 1 (2.70 Å) are not significantly different. This, therefore, might suggest that spatial differences between these groups are only marginally reponsible for the disparity in conformational energy between 1 and 4. It would seem likely that an electrostatic interaction of the type described for the axial preference in 4-chlorocyclohexanone may, in part, be responsible for this additional stabilization of the axial conformer **4a** (as compared to **1a**).[17]

Experimental Section

The carbon FT NMR spectra were recorded on a Varian Model XL-100-12 NMR spectrometer controlled by a 620/f computer. Noise-decoupled and gated decoupled spectra[18] were obtained at ambient (30°) and low temperature (−80°) and the Fourier transforms were based upon 8K data points. The low temperature was measured by insertion of a thermometer directly into the 10-mm tube. Chemical shifts (δ) are reported in parts per million and measured as CD_2Cl_2 solutions downfield from internal tetramethylsilane (Me_4Si). Both ambient- and low-temperature spectra were obtained with pulse widths of $^6/_{14}$–$^{10}/_{14}$ μsec, acquisition time of 1.6 sec, and 400–1000 transients. Gated decoupled low-temperature spectra were obtained at PD + AD + AT = 30 sec and the number of transients was 400–600. The gated decoupling experiments gave averaged area ratios (K = 6.06 at −80°) consonant with those obtained by planimeterization and electronic integration (K = 5.82 at −80°) of the appropriate carbon signals.

1,4-Oxathiane *S*-oxide (**4**) was prepared by oxidizing 1,4-oxathiane with sodium metaperiodate in 50% aqueous methanol solution as previously described.[19]

3,3,5,5-Tetradeuterio-1,4-oxathiane *S*-Oxide (5). A solution of 4 (4.0 g, 32.5 mmol) in 20 ml of D_2O was added to a solution of NaOD (0.033 g-atom of Na) in 10 ml of D_2O and heated to reflux for 48 hr. The solution was cooled and extracted with CH_2Cl_2 (2 × 75 ml) and the organic layer was dried ($MgSO_4$) and concentrated to give an oil. Sublimation gave 500 mg of the desired sulfoxide (55°, 0.1 Torr). The proton and carbon spectra were consistent with the desired structure.

Acknowledgments. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the North Carolina Board of Science and Technology for support of this research. We also thank Dr. D. L. Harris for recording numerous ^{13}C NMR spectra related to this work and Drs. Dwight W. Chasar and Andrew L. Ternay for helpful comments and suggestions.

Registry No.—**2**, 937-08-6; **3**, 769-94-8; **4**, 109-03-5; **5**, 55758-73-1; NaOD, 14014-06-3.

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(1) H. M. Shearer, *J. Chem. Soc.*, 1394 (1959).
(2) C. Y. Chen and R. J. W. Le Fevre, *Aust. J. Chem.*, **16**, 917 (1963).
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(4) C. R. Johnson and D. McCants, Jr., *J. Am. Chem. Soc.*, **87**, 1109 (1965); **86**, 2935 (1964). See also J. C. Martin and J. J. Uebel, *ibid.*, **86**, 2936 (1964). This also appears to be the case in acidic media; see R. Curci, F. D. Furia, A. Levi, V. Lucchini, and G. Scorrano, *J. Chem. Soc., Perkin Trans. 2*, 341 (1975).
(5) J. B. Lambert, D. S. Bailey and C. E. Mixan, *J. Org. Chem.*, **37**, 377 (1972).
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(8) L. Van Acker and M. Anteunis, *Tetrahedron Lett.*, 255 (1974); K. Bergesen, M. J. Cook, and A. P. Tonge, *Org. Magn. Reson.*, **6**, 127 (1974).
(9) The carbon absorptions (CD_2) α to the sulfinyl group are surpressed from loss of the nuclear Overhauser effect, by being split into a pentet, and less efficient spin-lattice relaxation.
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(11) Although the γ-gauche effect is well documented[12] (particularly in six-membered rings[13]), we exercise some caution in defining this effect as purely steric[14] with regard to the sc CH/SO array.
(12) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(13) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 6612 (1967); **94**, 5318 (1972); T. Pehk and E. Lippmaa, *Org. Magn. Reson.*, **3**, 679 (1971).
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(15) W. A. Szarek, D. M. Vyas, A. M. Sepulchre, S. D. Gero, and G. Lukacs, *Can. J. Chem.*, **52**, 2041 (1974).
(16) See the Experimental Section.
(17) R. D. Stolow in "Conformational Analysis: Scope and Present Limitations", G. Chiurcoglu, Ed., Academic Press, New York, N.Y., 1971, p 251, and numerous references cited therein.
(18) R. Freeman, H. D. W. Hill, and R. Kaptein, *J. Magn. Reson.*, 7, 327 (1972).
(19) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, 27, 282 (1962); C. R. Johnson and J. E. Keiser, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 791.
(20) Note Added in Proof. After this manuscript was submitted for publication a report appeared [G. W. Buchanan and T. Durst, *Tetrahedron Lett.*, 1683 (1975)] which corroborated our findings on the chemical shift difference (7.5 ppm) of the 3,5 carbons in 2 and 3. In addition, the low temperature (−93°) ^{13}C NMR spectrum of 1 gave chemical shift results compatible with those observed for 4.

Preparation of a Substituted α-Methyleneoxetane by an Intramolecular Alkylation Reaction

Paul F. Hudrlik* and Mostafa M. Mohtady

School of Chemistry, Rutgers University, New Brunswick, New Jersey 08903

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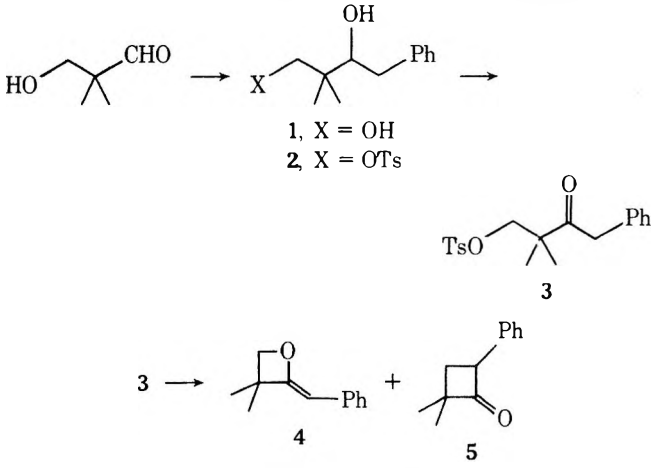
We have recently prepared α-methyleneoxetane by a retro-Diels–Alder reaction;[1] several substituted α-methyleneoxetanes have been prepared, primarily by cycloaddition reactions.[2] In connection with our interest in the use of α-methyleneoxetanes in organic synthesis,[1a,b] we have explored the possibility of generating these compounds by intramolecular O-alkylation reactions of ketone enolates.[3] This route would be potentially useful for the synthesis of a variety of substituted α-methyleneoxetanes which are not easily obtainable by existing methods. We report here an intramolecular alkylation reaction which yields a substituted α-methyleneoxetane (**4**) as the predominant product.



2,2-Dimethyl-4-phenyl-1,3-butanediol (**1**) was converted to the monotosylate **2** and oxidized to the keto tosylate **3**. When **3** was treated with potassium hydride[5] in THF, products of both O- and C-alkylation were isolated. 2-Benzylidene-3,3-dimethyloxetane (**4**) and 2-phenyl-4,4-dimethylcyclobutanone (**5**) were formed in estimated yields of 36 and 25%, respectively. The double bond of **4** most likely has the *Z* configuration, based on steric considerations and on the chemical shift (δ 5.07) of the olefinic hydrogen. From the reported chemical shifts of α-methyleneoxetane[1a,b] and a shielding increment of 1.38 ppm for phenyl,[6] the predicted chemical shifts for the *E* and *Z* isomers are δ 5.41 and 5.01, respectively.

Surprisingly, the ratio of **4** to **5** was rather insensitive to variations in cation (Na, K) or solvent (THF, THF–HMPA, or THF with dicyclohexyl-18-crown-6), varying only from about 2:1 to 1:2. The ratio of C- to O-alkylation of enolates is normally influenced strongly by changes in cation or solvent.[7] A model study of the intermolecular alkylation reactions of benzyl *tert*-butyl ketone with ethyl tosylate under comparable conditions showed large cation and solvent effects. We found that the proportion of O-alkylation varied from less than 5% (with NaH in THF) to more than 90% (with KH in THF–HMPA).

Compared to intermolecular alkylations of simple ketones in THF, the reaction **3** → **4** + **5** gives a high proportion of O-alkylation. This may be a consequence of the requirements for orbital overlap in the transition states leading to **4** and **5**.[8] If the transition state leading to the cyclobutanone **5** requires bond formation in a direction perpendicular to the plane of the enolate, it would be appreciably more strained than that leading to the oxetane **4**.[9] The product ratio may also be influenced by the stereochemistry (*E*, *Z*) of the starting enolate; for example, the *Z* enolate may cyclize predominantly to the oxetane **4**.

Intramolecular alkylation reactions are known in which cyclobutanones are formed from α,α-disubstituted ketones having a leaving group β to carbonyl.[10] These reactions, sometimes called homo-Favorskii reactions, normally produce a mixture of two isomeric cyclobutanones. Usually aqueous or alcoholic base has been employed, in contrast to the aprotic conditions used here. Although an α-methyleneoxetane was postulated as an intermediate in one case,[10e] such compounds have never before been isolated from these reactions.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium and benzophenone, pyridine was distilled from barium oxide, and hexamethylphosphoric triamide (HMPA) was distilled under reduced pressure from calcium hydride. Potassium hydride was obtained from Research Organic/Inorganic Chemical Corp., Belleville, N.J.; sodium hydride was obtained from Alfa Inorganics, Beverly, Mass. Elemental analyses were determined by Robertson Laboratory, Florham Park, N.J.

2,2-Dimethyl-4-phenyl-1,3-butanediol (1). Benzylmagnesium chloride was prepared by adding a solution of 12.6 g (0.10 mol) of benzyl chloride in 50 ml of ether to 2.4 g (0.10 mol) of magnesium in 60 ml of ether. To this was added a solution of 4.0 g (0.02 mol) of 3-hydroxy-2,2-dimethylpropanal[11] in 80 ml of ether with continuous stirring. After addition was complete, the reaction mixture was heated at reflux for 30 min, cooled to room temperature, and added to 40 ml of saturated NH_4Cl solution. The resulting mixture was extracted with three 30-ml portions of ether, and the combined ether extracts were washed with 10 ml of water and were dried (Na_2SO_4) and concentrated, yielding 8.5 g of a solid residue. This material was recrystallized once from hexane and three times from ether, yielding 7.1 g (93%) of **1** as white crystals: mp 95–96°; ir ($CHCl_3$) 2.85 (broad), 3.39, 6.25, 6.72, 6.82, 6.91, 9.55 μm; NMR ($CDCl_3$) δ 1.00 (s, 6 H), 2.5 (broad, OH) overlapping with 2.55 (doublet of doublets, J = 14, 10 Hz) (total 3 H), 2.96 (doublet of doublets, J = 14, 3 Hz, 1 H), 3.56 (broad s, CH_2OH) overlapping with 3.75 (doublet of doublets, J = 10, 3 Hz, CHOH) (total 3 H), 7.35 (broad s, 5 H); mass spectrum *m/e* 194 (M^+), 176, 103, 92, 91, 85, 65, 57, 56, 43.

Further recrystallization from ether provided the analytical sample, mp 96–96.5°. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.14; H, 9.60.

1-Phenyl-4-tosyloxy-3,3-dimethylbutan-2-ol (2). To a stirred, ice-cooled solution of 23 g (0.120 mol) of *p*-toluenesulfonyl chloride in 125 ml of pyridine was added 23 g (0.118 mol) of diol **1** in 125 ml of pyridine. After addition was complete, stirring was continued for 6 hr at room temperature. The reaction mixture was acidified with cold 2 *N* HCl and extracted with three portions of ether. The combined ether extracts were washed successively with dilute HCl, water, saturated $NaHCO_3$, and water, and were dried ($MgSO_4$) and concentrated. After volatile material was pumped off with a vacuum pump, 33 g of **2** remained as a pale yellow oil which solidified on cooling. This material was used without further purification in the next step.

Attempted recrystallization of this material was difficult. From a separate but similar experiment, **2** was obtained as a solid, mp 72–74°, ir ($CHCl_3$) 2.8 (broad), 3.37, 6.26, 7.40, 8.44, 8.53, 10.4 μm. The NMR spectrum ($CDCl_3$) showed three methyl singlets at δ 0.95, 1.04, and 2.45, and overlapping aromatic hydrogen absorptions at 7.2–8.0.

1-Phenyl-4-tosyloxy-3,3-dimethylbutan-2-one (3). To a solution of 30 g of the monotosylate **2** (from the above experiment) in 600 ml of acetone was added 79 ml of Jones reagent[12] with continuous stirring. The reaction mixture was allowed to stand overnight, 300 ml of saturated $NaHCO_3$ was added, the mixture was filtered, and the precipitate was washed with acetone. The combined filtrate was concentrated and extracted with five portions of ether. The ether extracts were washed successively with water, saturated $NaHCO_3$, and water, and were dried (Na_2SO_4) and concentrated, yielding 27.7 g of crude keto tosylate **3**. A portion (21.3 g) of this crude material was crystallized from CH_2Cl_2–hexane and recrystallized from ether, yielding 17.2 g of **3** as white crystals: mp

88–89°; ir ($CHCl_3$) 3.35, 5.84, 6.26, 7.37, 8.41, 8.50, 10.3 μm; NMR ($CDCl_3$) δ 1.20 (s, 6 H), 2.48 (s, 3 H), 3.80 (s, 2 H), 4.08 (s, 2 H), 7.2–8.0 (m, 9 H); mass spectrum *m/e* 346 (M^+), 291, 255, 227, 155, 91.

Further recrystallization from ether provided the analytical sample, mp 89–89.5°. Anal. Calcd for $C_{19}H_{22}O_4S$: C, 65.87; H, 6.40. Found: C, 66.10; H, 6.62.

Treatment of Keto Tosylate 3 with Potassium Hydride. Potassium hydride (400 mg of a ~50% slurry in oil, ~5 mmol) was stirred with several portions of pentane; the liquid from each portion was removed by pipet. THF (25 ml) was added to the residue, the mixture was cooled in an ice bath, and a solution of 640 mg (1.85 mmol) of keto tosylate 3 in 25 ml of THF was added. The resulting mixture was stirred for 1 hr, the ice bath was removed, and stirring was continued for 1 hr at room temperature. The mixture was then cooled in a Dry Ice–acetone bath and 10 ml of saturated NaCl was added. After warming to room temperature, the mixture was extracted with five 20-ml portions of ether, and the combined extracts were washed with saturated $NaHCO_3$ (two portions) and water and were dried (Na_2SO_4) and concentrated, giving 282 mg of residue, which was chromatographed on Florisil. Elution with 5–10% CH_2Cl_2 in hexane yielded 103 mg of oxetane 4 as an oil; VPC analysis (SE-30, 150°)[13a] showed one peak at a retention time of 3.5 min. Further elution with 20–50% CH_2Cl_2 in hexane yielded 94 mg of oil; VPC analysis (SE-30, 150°)[13a] showed two peaks at 2.5 (5) and 3.5 min (4), in a 6:1 ratio. The total yields of 4 and 5 are estimated to be 36 and 25%, respectively.

2-Benzylidene-3,3-dimethyloxetane (4) had the following spectra: ir (film) 3.39, 5.92, 7.44, 9.23, 9.45, 10.56, 14.42 μm; NMR ($CDCl_3$) δ 1.40 (s, 6 H), 4.60 (s, 2 H, CH_2O), 5.07 (s, 1 H, PhCH=C), 7.0–7.5 (m, 5 H). From a separate but similar experiment, a portion was purified by preparative VPC, followed by evaporative distillation: mass spectrum *m/e* 174 (M^+), 159, 144, 143, 129, 128, 118, 90, 89, 63, 51, 41, 39. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.71; H, 8.12.

A pure sample of 2-phenyl-4,4-dimethylcyclobutanone (5), obtained by preparative VPC, had the following spectra: ir ($CHCl_3$) 3.45, 5.63, 6.91, 8.71, 9.42, 9.66, 9.80, 11.56 μm; NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.34 (s, 3 H), 2.04 (doublet of doublets, J = 11, 9 Hz) overlapping with 2.40 (t, $J \approx 11$ Hz) (total 2 H), 4.61 (doublet of doublets, J = 10.5, 9 Hz, 1 H, PhCH), 7.30 (s, 5 H); mass spectrum *m/e* 174 (M^+), 173, 159, 146, 131, 118, 104, 103, 91, 90, 70. Purified samples of 5 decomposed and solidified after standing a few days in the refrigerator.

From 5 was prepared a 2,4-DNP derivative, mp 124–124.5° (from (EtOH). Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12. Found: C, 60.87; H, 5.27.

A series of similar reactions was carried out in the presence of hexadecane as an internal standard for VPC analysis (SF-96, 140°).[13b] Typical retention times were as follows: cyclobutanone 5, 7.5 min; oxetane 4, 11.0 min; hexadecane, 26.4 min. The yield of oxetane 4 was determined directly using the measured relative detector response; because of the lability of 5, its yield was estimated indirectly by using a detector response calculated by comparing the NMR and VPC of a mixture of 4 and 5. With NaH in THF–HMPA (4:1), or with KH in THF, in THF–HMPA (4:1), or in THF containing 0.005 equiv of dicyclohexyl-18-crown-6, 4 was formed in yields of 35–46% and 5 was formed in yields of 22–45%. Using NaH in THF, 4 and 5 were formed in yields of 24 and 50%, respectively.

Acknowledgments. We thank the National Science Foundation, the Research Corporation, the Research Council of Rutgers University, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support.

Registry No.—1, 55853-34-4; 2, 55853-35-5; 3, 55853-36-6; 4, 55853-37-7; 5, 55853-38-8; 5 2,4-DNP, 55853-39-9; 3-hydroxy-2,2-dimethylpropanal, 597-31-9; benzyl chloride, 100-44-7; *p*-toluenesulfonyl chloride, 98-59-9; potassium hydride, 7693-26-7.

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The Hydridotetracarbonylferrate Anion, a Convenient Desulfurization Reagent

Summary: Thioketones and thioamides react with $HFe(CO)_4^-$ in 1,2-dimethoxyethane to give hydrocarbons and amines, respectively, in good yield; use of $DFe(CO)_4^-$ as the reagent resulted in incorporation of two deuterium atoms in the product.

Sir: The hydridotetracarbonylferrate anion [$HFe(CO)_4^-$] is a useful reagent for effecting stereospecific dehalogenation of organic halides,[1] hydroacylation,[2] reductive alkylation,[3,4] amination,[5-7] and hydrogenation of an α,β-unsaturated carbonyl.[8] This communication reports a new, and important, use of the iron hydride as a desulfurization reagent.

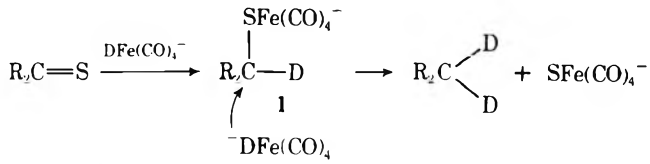
Treatment of an aliphatic or aromatic thioketone with 4 equiv of $HFe(CO)_4^-$ (generated in situ from a 3:1 mixture of KOH and iron pentacarbonyl) in refluxing 1,2-dimethoxyethane (8–12 hr) afforded the desulfurized hydrocarbon in 60–81% yield (Table I). Amines were obtained by use of thioamides as reactant thiones.

Table I
Products Obtained from Reactions of Organosulfur Compounds with $HFe(CO)_4^-$ (A) or $DFe(CO)_4^-$ (B)

Reactant	Iron hydride	Product[a]	Yield, %
$(C_6H_5)_2CS$	A	$(C_6H_5)_2CH_2$	60
$(4\text{-}CH_3C_6H_4)_2CS$	A	$(4\text{-}CH_3C_6H_4)_2CH_2$	61
$(4\text{-}CH_3OC_6H_4)_2CS$	A	$(4\text{-}CH_3OC_6H_4)CH_2$	77
$(4\text{-}CH_3OC_6H_4)_2CS$	B	$(4\text{-}CH_3OC_6H_4)_2CD_2$	74
$(4\text{-}(CH_3)_2NC_6H_4)_2CS$	A	$(4\text{-}(CH_3)_2NC_6H_4)_2CH_2$	81
Adamantanethione	A	Adamantane	74
Adamantanethione	B	2,2-Dideuterioadamantane	78
$C_6H_5CSNHC_6H_5$	A	$C_6H_5CH_2NHC_6H_5$	38
$CH_3CSNHC_6H_5$	A	$C_2H_5NHC_6H_5$	51

[a] Products were characterized by comparison of spectral data with that for authentic samples, as well as by mixture melting points (except for deuterium containing products where mass, NMR, and ir spectroscopy was used for structure elucidation).

Incorporation of two deuterium atoms readily occurred by reaction of 4,4′-dimethoxythiobenzophenone or adamantanethione with $DFe(CO)_4^-$ [from KOD and $Fe(CO)_5$)]. Attack of $HFe(CO)_4^-$ [or $DFe(CO)_4^-$] at the thione group of a thioketone to give **1** is probably the first step in the reaction. Addition of a second molecule of iron hydride



(or deuteride) would give the product and a sulfur iron carbonyl anion.

A Schiff base is a likely intermediate in the thioamide–$HFe(CO)_4^-$ reaction. The reduction of Schiff bases to amines by the related trinuclear hydride, $HFe_3(CO)_{11}^-$, has been described.[9]

The following procedure is typical. A mixture of $Fe(CO)_5$ (3.0 ml, 22.1 mmol), KOH (3.69 g, 66 mmol), and water (6.0 ml) was refluxed in 1,2-dimethoxyethane (90 ml) for 1.5 hr to generate $HFe(CO)_4^-$. To this solution was added 4,4′-dimethylthiobenzophenone (1.21 g, 5.35 mmol) in 1,2-dimethoxyethane (20 ml), and the resulting mixture was refluxed for 10 hr. The solution was cooled and filtered, and the filtrate was flash evaporated to a brown solid. The latter was treated with ether (200 ml) and filtered; the filtrate was washed three times with water (i.e., until the aqueous layer was colorless). The ether extract was dried ($MgSO_4$), filtered through a short column of Florisil, and concentrated to give 0.69 g (61%) of pure bis(*p*-tolyl)methane.

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Department of Chemistry **Howard Alper**
University of Ottawa
Ottawa, Ontario, Canada K1N 6N5

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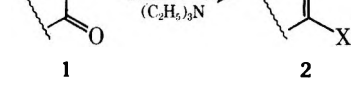
Reaction of Cyclic β-Halo α,β-Unsaturated Ketones with Cuprate Reagents. A New, Efficient Synthesis of β-Alkyl α,β-Unsaturated Ketones

Summary: Reaction of cyclic β-halo α,β-unsaturated ketones with various alkyl cuprate reagents produced the corresponding β-alkyl α,β-unsaturated ketones in high yield.

Sir: Recently, we reported[1] that the reaction of cyclic β diketones **1** with triphenylphosphine dihalides under appropriate conditions produced, in excellent yields, the corresponding β-halo α,β-unsaturated ketones **2**. We report



1 **2**

Table I
Conversion of β-Bromo α,β-Unsaturated Ketones into β-Alkyl α,β-Unsaturated Ketones

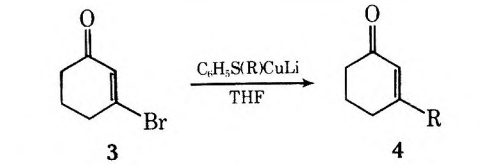
β-Bromo enone	Cuprate reagent[a]	Reaction temp, °C[b]	Yield of β-alkyl enone, %[c]
3	A	0	82
3	B	−20	84
3	C	−78	91
3	D	0	87
5	A	0	70
5	B	−20	87
5	C	−20	82
5	D	0	84
6	A	0	94
6	B	−20	93
6	D	0	89
7	D	22	95
8	A	0	83
9	D	0	89

[a] Reagent A, $C_6H_5S(CH_3)CuLi$; B, $C_6H_5S(n\text{-}C_4H_9)CuLi$; C, $C_6H_5S(sec\text{-}C_4H_9)CuLi$; D, $C_6H_5S(t\text{-}C_4H_9)CuLi$. In all of the experiments with reagent A, 2.0 equiv of cuprate was used; in the other cases, 1.5 equiv was employed. [b] The reaction time was 2.5 hr in each case. [c] Yield of distilled product. In some of the experiments, a small amount (generally <5%) of starting material (β-bromo enone) was recovered.

herein that the latter compounds **2** react smoothly with a variety of organocuprate reagents to produce efficiently the corresponding cyclic β-alkyl α,β-unsaturated ketones.[2]

Most of our experiments thus far have employed β-bromo enones as starting materials, although preliminary investigations have indicated that the corresponding chloro or iodo derivatives could also be used. In fact, in some cases, the best results were obtained from the appropriate iodo derivative. However, in general, the β-bromo enones appeared to be superior to the chloro compounds and, compared with the iodo derivatives, were more convenient to prepare[1] and were easier to handle experimentally. Furthermore, we have found that, although lithium dialkylcuprate reagents could be employed to convert the β-bromo enones into the corresponding β-alkyl enones, in most cases a more efficient and less cumbersome transformation could be achieved by use of lithium phenylthio(alkyl)cuprate reagents.[11,12]

Treatment of 3-bromo-2-cyclohexen-1-one (**3**) with 2.0 equiv of lithium phenylthio(methyl)cuprate in THF at 0° for 2.5 hr afforded, in 82% yield, 3-methyl-2-cyclohexen-1-one (**4**, R = CH_3).[13] In similar fashion, reaction of **3** with the corresponding *n*-butyl-, *sec*-butyl-, and *tert*-butylcuprates gave the enones **4** (R = *n*-C_4H_9, *sec*-C_4H_9, and *t*-C_4H_9, respectively) in high yield. Extension of these studies to the β-bromo enones **5–9**, inclusive, afforded comparable results, some of which are summarized in Table I.[13]



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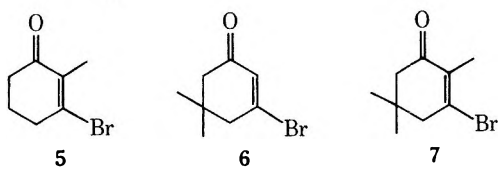

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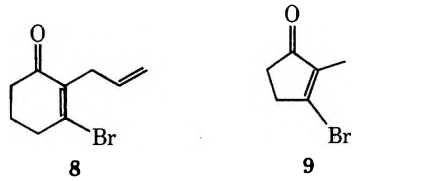

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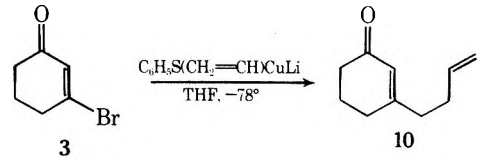
Although, in some of the experiments recorded in Table I, small amounts of starting material (<5%) were recovered along with the product, in no case were we able to detect any product resulting from further addition to the initially formed β-alkyl enone. It is also appropriate to emphasize the rather remarkable efficiency with which the β-*tert*-butyl enones were formed. Although some of the *tert*-butyl products had previously been prepared via entirely different synthetic processes, the yields were generally low.[14] In contrast, the present method not only provided high yields of product in each of these cases, but even the relatively highly hindered β-bromo enones **5** and **7** reacted smoothly with lithium phenylthio(*tert*-butyl)cuprate to provide the corresponding β-*tert*-butyl enones (previously unknown compounds[13]) in yields >80%.

Reaction of the β-bromo enone **3** with 1.3 equiv of lithium phenylthio(vinyl)cuprate in THF at −78° gave, in addition to starting material, the unsaturated ketone **10** (ratio ~7:2, respectively). Obviously, 1,6 addition of the cuprate reagent to the initially formed 3-vinyl-2-cyclohexen-1-one occurred at a rate faster than the original 1,4 addition to **3**. Treatment of **3** with 3.0 equiv of the vinylcuprate reagent afforded **10**[13] in 70% yield.

Finally, it should be mentioned that β,β-dialkylcycloalkanones can be prepared directly from the appropriate β-halo enone by reaction of the latter with an excess of lithium dialkylcuprate. For example, when 3-iodo-5,5-dimethyl-2-cyclohexen-1-one (**11**)[1] was allowed to react with 3.0 equiv of lithium dimethylcuprate in ether at 0°, 3,3,5,5-tetramethylcyclohexanone (**12**)[13] was formed in 84% yield.



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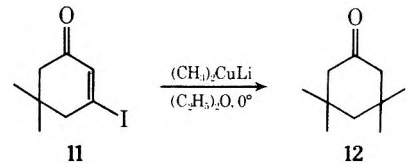

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A typical experimental procedure, involving conversion of **3** into **4** (R = *t*-C_4H_9), follows. To a stirred suspension of phenylthiocopper[12] (260 mg, 1.5 mmol) in 10 ml of dry THF at −20° was added dropwise 1.28 ml of 1.17 *M* *tert*-butyllithium in pentane. The resulting clear solution was stirred at −20° for 5 min and then cooled to −78°. After 3-bromo-2-cyclohexen-1-one (**3**, 175 mg, 1.0 mmol) had been added, the solution was allowed to warm to 0° and was kept at this temperature for 2.5 hr. During this time, the solution became dark green. Methanol (1.0 ml) and saturated aqueous ammonium chloride (0.5 ml) were added, followed after ~1 min by magnesium sulfate (4.0 g) and ether (10 ml). The resulting mixture was filtered through a short column of silica gel (10 g) and the column was eluted with an additional 100 ml of ether. The combined eluants were concentrated and the residual oil was distilled (air-bath temperature 75–85°, 9.0 Torr) to give 132 mg (87%) of 3-*tert*-butyl-2-cyclohexen-1-one: ir (film) 1680, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 9 H), 1.66–2.54 (diffuse, 6 H), 5.97 (s, 1 H).

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(13) All products exhibited spectral data (uv, ir, ^{1}H NMR) in full accord with the assigned structures. New compounds were fully characterized and gave satisfactory elemental analyses (±0.3%).
(14) For example: 3-*tert*-butyl-2-cyclohexen-1-one, 19%;[15] 3-*tert*-butyl-5,5-dimethyl-2-cyclohexen-1-one, 7%;[16] 3-*tert*-butyl-2-cyclopenten-1-one, 54%.[17]
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Department of Chemistry
University of British Columbia
Vancouver, Canada V6T 1W5

Edward Piers*
Isao Nagakura

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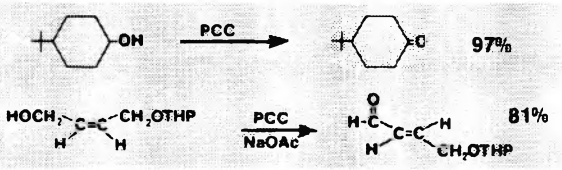
Oxidizing agents: Something old, something new

Pyridinium Chlorochromate

Corey and Suggs[1] have recently shown that **pyridinium chlorochromate (PCC)**, a stable crystalline reagent, readily oxidizes a variety of alcohols to the corresponding aldehydes and ketones in high yield under mild conditions. Yields of aldehydes and ketones obtained with 1.5 molar equivalents of **PCC** are equal or superior to those obtained with Collins reagent (using a five- or six-fold excess).[2]



The oxidation is performed by suspending **PCC** (1.5 mmol) in methylene chloride (*ca.* 2 ml) and adding the alcohol (1 mmol in 0.5 to 1.5 ml of CH_2Cl_2). After 1-2 hours the oxidation is complete as evidenced by a precipitate of the black reduced reagent. Dilution with five volumes of anhydrous ether, filtration of solid and evaporation of solvent give the product. Substrates containing acid labile groups may be oxidized by buffering the reaction mixture with powdered sodium acetate.

References:
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19,014-4 Pyridinium chlorochromate.....100g $7.00
500g $24.00

Lead Tetraacetate

Lead tetraacetate (LTA) is one of the most versatile oxidizing reagents known in organic chemistry because it reacts with a wide range of functional groups. The uses of **LTA** have been extensively reviewed.[1-4] A few highlights are presented below.

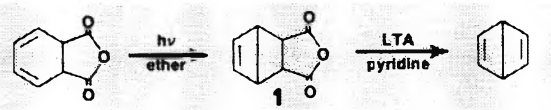
Cleavage Reactions

The classical cleavage of vicinal glycols by **LTA** to aldehydes and ketones has been used both for structure elucidation and for preparative purposes.[1] For example, *n*-butyl glyoxylate is obtained from the reaction of **LTA** and di-*n*-butyl D-tartrate.[5]

LTA also cleaves vicinal diamines, vicinal amino alcohols, α-hydroxyacids, α-hydroxyaldehydes, α-hydroxyketones, and oxalic acid.[1]

Oxidation of Carboxylic Acids

Vicinal dicarboxylic acids are oxidized to alkenes with **LTA** and pyridine in benzene as solvent at 50-60° or in dimethyl sulfoxide or dioxane at room temperature.[1] Dewar benzene has been prepared by oxidation of the anhydride **1**.[6]



Geminal diacids are oxidized to ketones *via* the intermediate *gem* diacetates.[1]

Oxidative decarboxylation of monocarboxylic acids affords mixtures of alkenes and acetates.[1] However, in the presence of cupric acetate, alkenes alone are obtained in good to excellent yield from primary and secondary acids.[2] The addition of lithium chloride or iodine results in halodecarboxylation.[1] Thus, cis- and *trans*-4-*t*-butylcyclohexanecarboxylic acid give mixtures of the 4-chloro isomers consistent with a free radical mechanism.

α-Acetoxylation of Carbonyl Compounds

Active methylene groups react with **LTA** in benzene to give acetoxy derivatives; the reaction of **LTA** with ketones is catalyzed by boron trifluoride etherate.[1] Half esters of malonic acid are easily oxidized to the α-acetoxy derivatives.[1]

Oxidation of Amides

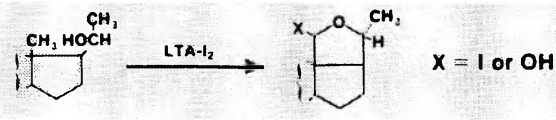
The oxidation of primary amides with **LTA** parallels the Hofmann reaction and offers an alternate route to isocyanates.[3]

Oxidation of Amines

Primary amines are oxidized to nitriles in yields up to 60% *via* an aldimine intermediate.[3] In contrast, tertiary amines containing one aromatic group are dealkylated to the secondary amine.[3]

Substitution of Methyl Groups

Oxidation of a steroid alcohol having a hydroxyl group strategically located for attack of an angular methyl group occurs with **LTA** in benzene or better with an **LTA**-iodine combination.[1]



Aliphatic alcohols react to give substituted furan or pyran derivatives.[4]

LTA has also been used to effect many other oxidations such as hydroquinones to quinones, thiols to disulfides or methyl sulfinates, and 1-aminobenzotriazole to benzyne.[1]

References:
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18,519-1 Lead tetraacetate... 100g $8.00; 500g $24.00