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THE JOURNAL OF Organic Chemistry®

VOLUME 41, NUMBER 1 JANUARY 9, 1976

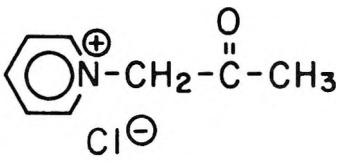
PYRIDINIUM ACTIVATED METHYLENES

THE NITROGEN YLID PRECURSORS

In the presence of base, **Pyridinium activated methylenes** are converted to uniquely stabilized yet highly reactive nitrogen ylids. In many respects these ylids are similar in reactivity and ease of formation to the more classical carbanions obtained from malonic esters, β-ketoesters, β-cyanoesters, β-diketones and malononitrile. Pyridinium stabilized carbanions participate in a wide variety of useful reactions such as: Aldol, Claisen, Claisen-Schmidt and Knoevenagel condensations; Mannich, Perkin, and Ehrlich-Sachs type reactions; Michael additions and alkylations. In these reactions the pyridinium moiety may be retained and subsequently reduced or incorporated into fused ring systems; elimination of the pyridinium moiety gives rise to sites of unsaturation; displacements with nucleophiles such as amines, phenoxides, alkoxides, hydroxide, cyanide and thiols further broaden the range of products available.

Pyridinium activated methylenes serve as convenient starting materials for such diverse products as: pyridinium ethanols, vinyl pyridinium salts, nitrones, α-cyanoanils, aromatic aldehydes, carboxylic acids, α-ketoacids, α-ketoaldehydes and anionocyanine dyes. Diverse ring systems such as pyridines, pyrimidines, quinoxalines, pyridopyrazines, pteridines, pyridotriazines, naphth[1,2-**d**]oxaxoles, benzo[f]-quinoxalines, benzimidazoles, indoles and indoloquinolizines are likewise easily obtained with **Pyridinium activated methylenes.**

Pyridinium activated methylenes are among the most versatile and interesting synthetic intermediates currently available with potential applications in nearly every area of organic synthesis. A variety of **Pyridinium activated methylenes** are now offered for use as intermediates in the synthesis of novel photographic dyes, pigments and indicators; drugs, cosmetics and pharmaceuticals; herbicides and pesticides; alkaloids and other natural products.



1039

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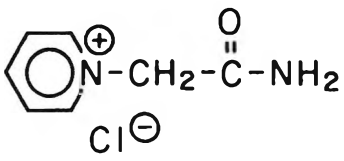

1029

1-(AMINOFORMYLMETHYL) PYRIDINIUM CHLORIDE

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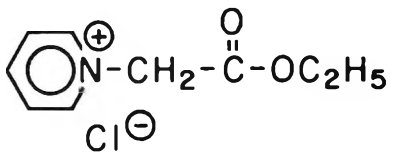

1044

1-(CARBETHOXYMETHYL) PYRIDINIUM CHLORIDE

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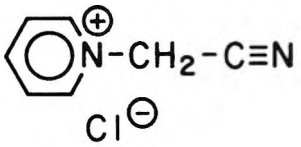

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1-(CYANOMETHYL) PYRIDINIUM CHLORIDE

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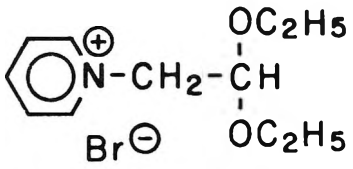

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1-(2,2-DIETHOXYETHYL) PYRIDINIUM BROMIDE

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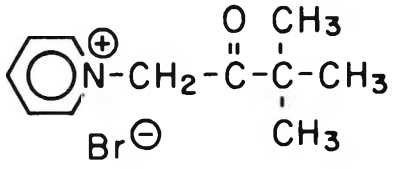

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1-(3,3-DIMETHYL-2-OXOBUTYL) PYRIDINIUM BROMIDE

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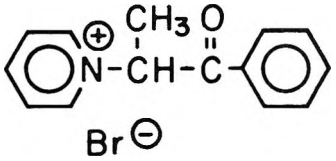

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1-(α-METHYLPHENACYL) PYRIDINIUM BROMIDE

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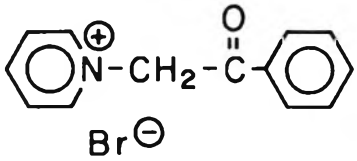

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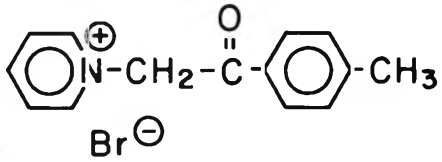

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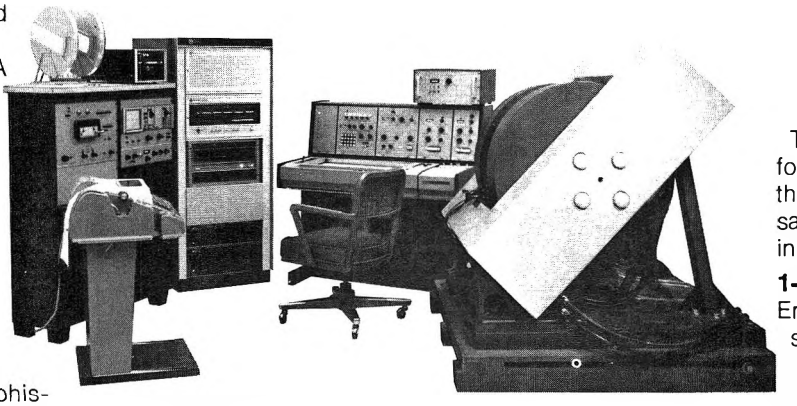

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We ran a 5-μg sample of gelsemine ($C_{20}H_{22}O_2N_2$) with the result you see here. We think the spectral quality speaks for itself.

Microgram sample capability, of course, is good news if you are involved in metabolite studies, biosynthetic research, flavors and fragrances — any field in which samples come from GLC or TLC, or are scarce for any other reason.

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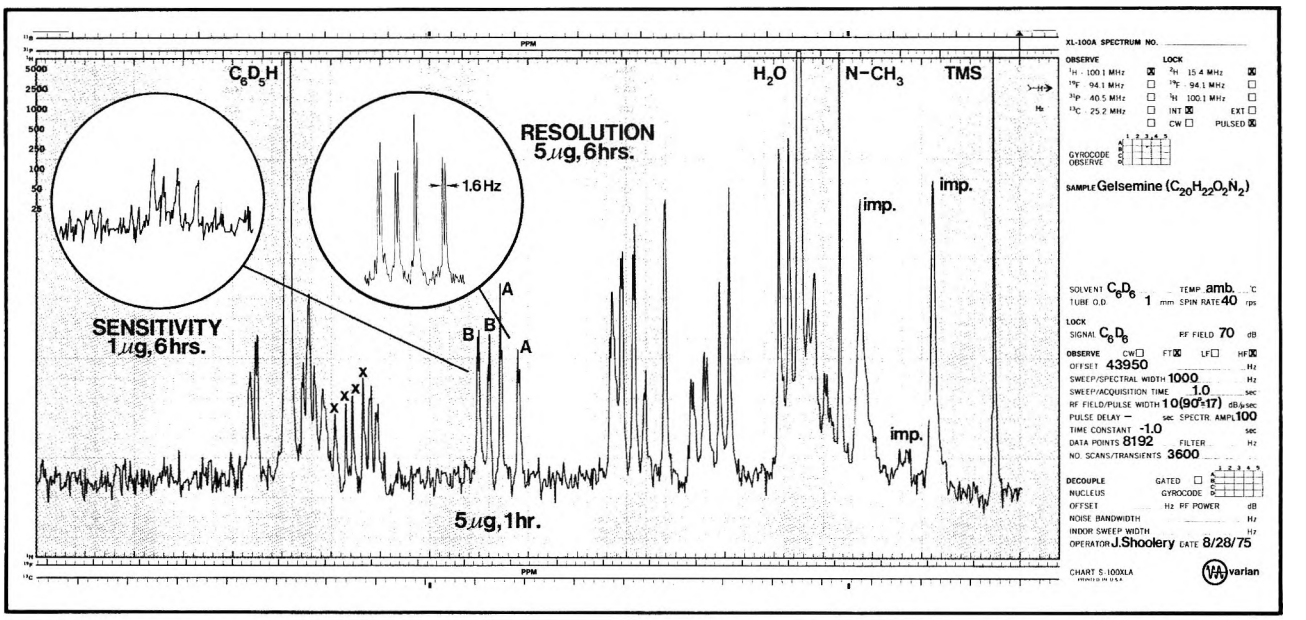

We dissolved 5 μg of gelsemine in 5 μl of C_6D_6 and pulsed it at one-second intervals for one hour, using a tip angle of 53° (10 μsec pulse) and a 2,500-Hz spectral width. Note the clear ABX pattern from the three vinyl protons and the excellent resolution of the 1.6-Hz geminal coupling! The spectral excerpts show two six-hour runs of 5-μg and 1-μg samples to demonstrate how resolution or sensitivity can be further enhanced at the expense of time.

COMMUNICATIONS

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

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

AUTHOR INDEX

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Papers in which the primary interest lies in the implications of new compounds for medicinal, polymer, agricultural, or analytical chemistry are generally considered to be published most appropriately in specialized journals, together with information on evaluation with respect to the original reason for synthesis.

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

Communications (see Editorial Notice, *J. Org. Chem.*, **37**, No. 13, page 4A, 1972) are intended to provide for rapid publication of important findings and will be handled as expeditiously as possible. The length is limited to 1000 words or the equivalent. Where appropriate, authors are encouraged to submit supplementary data (e.g., experimental procedures) for inclusion in the microfilm edition of the journal (see below). Each communication must have a *one-sentence* summary (informative, not simply indicative) placed at the beginning of the communication and a longer abstract, submitted on a separate sheet. The latter will not be printed but will be transmitted to *Chemical Abstracts* (see below).

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

Consideration by this journal of papers previously submitted to the *Journal of the American Chemical Society* may be facilitated by inclusion of the reviews along with a covering letter indicating the changes which have been made.

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

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

Titles and Abstracts.—Titles are of great importance for current awareness and for information retrieval. Words should be chosen carefully to provide information on the contents and to function as "points of entry" for retrieval purposes.

All manuscripts must be accompanied by an abstract. The abstracts, in general, are used directly in *Chemical Abstracts* (CA indexes are prepared from the full paper). The abstracts for notes and communications will not be printed in *The Journal of Organic Chemistry;* they should be submitted on a separate sheet for direct transmittal to *Chemical Abstracts* by this journal.

An abstract should state briefly the purpose of the research (if this is not contained in the title), the principal results, and major conclusions. Reference to structural formulas or tables in the text, by number, may be made in the abstract. For a typical paper, an 80–200-word abstract is usually adequate.

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

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

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

In lengthy papers, authors are encouraged to organize the manuscript so that the principal findings and conclusions are concisely presented in an initial section (Part A), with supporting data, experimental details, and supplementary discussion in a Part B [see *J. Org. Chem.*, **35** (11), 16A, 3591–3646 (1970)].

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worths, London, 1971; Sect. D, "IUPAC Information Bulletin No. 31," 1973; Sect. E (stereochemistry), *J. Org. Chem.*, **35**, 2849 (1970). For cyclic systems, see A. M. Patterson, L. T. Capell, and D. F. Walker, "Ring Index," 2nd ed, American Chemical Society, Washington, D.C., and Supplements I–III, 1963–1965. For rules of carbohydrate nomenclature, see *Biochemistry*, **10**, 3983 (1971); for steroid nomenclature, see *J. Org. Chem.*, **34**, 1517 (1969).

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Autoxidations of Cyclohexane and Its Autoxidation Products

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The rates, products, and mechanisms of t-Bu_2O_2-initiated oxidations of cyclohexane at 100° and *N,N'*-azobis(1-cyanocyclohexane)-initiated oxidations of cyclohexanone at 80° are described. The initial oxidation of cyclohexane gives mostly cyclohexyl hydroperoxide and gives cyclohexanol and cyclohexanone as chain termination products. On further reaction, much of the hydroperoxide is converted directly to ketone. Both cyclohexanol and cyclohexanone catalyze the decomposition of hydroperoxide into radicals, which increase the rate of oxidation. The further oxidation of cyclohexanone is complex, even at 80°. The major primary product is 2-hydroperoxycyclohexanone whose decomposition, also catalyzed by cyclohexanone, leads to other hydroperoxides, ε-caprolactone, adipic and glutaric acids, adipaldehyde acid, cyclohexane-1,2-dione, and δ-valerolactone. The oxidation of cyclohexanone is catalyzed by both cobalt and manganese, the latter giving high yields of adipic acid. Relative reactivities toward *tert*-butylperoxy radicals follow: cyclohexane, 1.0; cyclohexyl hydroperoxide, 56; cyclohexanol, 55; cyclohexanone, 13; and cyclohexyl acetate, 0.5. Rates of oxidation of pure compounds at the same rate of initiation at 100° follow: cyclohexane, 1.0; cyclohexanol, 40; and cyclohexanone, 27.

This paper describes some studies of high conversion oxidations of cyclohexane, in Pyrex glass, with special attention to (1) the relative reactivities of the compounds involved toward a common peroxy radical, (2) the role of thermal decomposition of the hydroperoxide, (3) the intermediates that lead to carbon–carbon cleavage, and (4) effects of cobalt and manganese salts. Cyclohexane was selected for study because of its symmetry, which leads to simpler products and makes it a useful model for oxidation of alkanes, and because its oxidation is industrially important. Our conclusions are summarized in the last section.

In low conversion experiments, cyclohexyl hydroperoxide is formed from air oxidation of cyclohexane in a sufficient yield for synthetic preparation of the hydroperoxide.[1] Cyclohexanol[2] oxidizes cleanly to an equilibrium mixture of cyclohexanone, hydrogen peroxide, and 1-hydroxycyclohexyl hydroperoxide. The oxidation of cyclohexanone[3] to adipic acid goes through 2-hydroperoxycyclohexanone and adipaldehyde acid with ε-caprolactone, valeric acid, and glutaric acid as by-products.

Most of the published work on oxidations of cyclohexane is in the Russian literature.[4] This work has usually been carried out without added initiator, and with markedly different results in glass and steel vessels. In glass, the rate is slightly slower than in steel, with an obvious induction period, and the maximum concentration of hydroperoxide attained is about three times that in steel.[5] In glass, addition of ^{14}C-labeled cyclohexanol to oxidizing cyclohexane at 155° showed that the alcohol is quantitatively converted to cyclohexanone (without cleavage) and that labeled adipic acid and some labeled CO_2 are eventually formed.[4,5] Whereas hydroperoxide is clearly the major primary product in glass, cyclohexanone is the major primary product in steel where the peroxide is apparently decomposed on the walls. Adding cyclohexyl hydroperoxide initially to a cyclohexane oxidation at 145° in steel had no significant effect on the reaction; however, if cyclohexanone is added in amounts found normally after about 10 hr of reaction, the reaction begins at the maximum rate that normally would be delayed for several hours.[4,6] Thus, in steel cyclohexanone appears to be more important in the initiation step than is the hydroperoxide.

Tanaka[7] recently described a cobalt-catalyzed oxidation of cyclohexane in acetic acid solution at 80–100°, with higher rates of reaction and higher yields of adipic acid at high conversions than have been reported previously, but the mechanism is obscure. A comparison with our own results shows that the rate of reaction in cyclohexane is markedly increased by cobalt, but the improvement in selectivity must arise from the effect of cobalt on the subsequent oxidation of oxygen-containing products.

In view of the Russian results, we have confined our own studies to glass vessels. After some preliminary investigations at 60–130°, 100° was chosen for most of our oxidations of cyclohexane.

Experimental Section

Chemicals. Cyclohexane and cyclohexanone from Matheson Coleman and Bell (Chromatoquality) and cyclohexanol from Eastman Chemical Co. (White Label) were distilled before use. Cyclohexyl hydroperoxide was made according to the procedure of Walling and Buckler.[8] Initiators were obtained through normal chemical suppliers and either distilled or recrystallized before use.

Reaction Procedures. Runs were made in a 100-ml Pyrex flask fitted with a glass break-seal. Reactants were introduced through a side arm and then degassed. The initiators *N,N'*-azobis(2-methylpropionitrile) (ABN) and *N,N'*-azobis(1-cyanocyclohexane) (ABC) were added in solvents that were then removed under vacuum. When di-*tert*-butyl peroxide was used, it was added through a septum from a tared syringe after the vessel had been degassed. The

Table I
Oxidations of Cyclohexane (RH), Cyclohexanol (ROH), and Cyclohexanone (R=O)

Charge	Concn, M	Initiator,[a] M	Reaction: Temp, °C	Reaction: Time, hr	$-\Delta\dot{O}_2$	Chain length[b]	Products, M: RO_2H	Products, M: Net ROH	Products, M: R=O	Products, M: Acid, as dibasic
RH	8.79	0.0105 (ABN)	60	17.1	0.016	2.8	0.0086	0.004	0.0017	0
RH	8.79	0.0312 (ABN)	60	20.0	0.056	3.0	0.0078	0.0088	0.0069	0
RH	8.67	0.0095 (ABN)	70	5.0	0.015	2.5	0.0069	0.0010	0.0016	0
RH	8.46	0.0109 (ABC)	91	14.3	0.046	2.4	0.0362	0.0053	0.0064	0
RH	8.33	0.0112	100	24.9	0.025	18	0.0163	0.0016	0.0005	0
RH	8.15	0.0108	130	15.0	0.042	28.4	0.0058	0.1487	0.110	0.0876
ROH	8.81	0.0151	100	2.0	0.089	596	0.0696		0.0616	0
ROH	8.81	0.010	100	4.0	0.152	720	0.127		0.200	0.0036
ROH	8.81	0.0154	100	220	0.355	220	0.0005		0.503	0.0085
ROH + RH	4.38 + 4.18	0.0094	100	24.0	0.087	66	0.0011		0.0080	0.0016
ROH + DCB[c]	3.58 + 3.53	0.0108	100	25.3	0.344	285	0.0430		0.332	0.0311
ROH + RH	0.19 + 8.15	0.010	100	24.0	0.012	10	0.0104	0.1639	0.0013	trace
R=O	9.04	0.010	100	2.0	0.045	440	0.0147			0.0151
R=O	9.04	0.0098	100	2.5	0.180	1520	0.0382	0		0.1085
R=O	9.04	0.519	100	15.0	0.388	99	0	0		0.356
R=O	9.04	0.098	100	24.0	1.893	150	0.0118			0.645
R=O + RH	0.17 + 8.17	0.010	100	38.0	0.065	57	0.0330	0.0260[d]	0.1541	0.0013

[a] Initiator is t-Bu_2O_2 except where indicated otherwise; at 100° $k_d = 6.0 \times 10^{-3}$ hr^{-1}. For ABN, $k_d = 0.035$ hr^{-1} at 60°, 0.14 hr^{-1} at 70°. For ABC, $k_d = 0.13$ hr^{-1} at 91°. [b] Moles oxygen per mole radical formed from initiator. [c] o-Dichlorobenzene. [d] Total ROH before correction for ROOH.

arm having the septum was sealed off; the oxygen was added through the other arm, which was connected to the vacuum line, and that arm was sealed off. The untransferred portion of the oxygen was measured using the same gas buret–Toepler pump that was used to measure the initial oxygen.

The runs were terminated by quickly cooling the flasks to 25°. After sealing the vessels on the vacuum line, flask contents were frozen at −195°; the seal was broken, and the noncondensable gases were measured using the gas buret–Toepler pump. The gas sample was then allowed to react in a Cu–CuO furnace at about 300° to convert oxygen to CuO and CO to CO_2. With the furnace trap at −195°, only N_2 and Ar are volatile and may be measured. CO is estimated as CO_2 by warming the furnace trap to −80° and measuring in the buret. Oxygen was estimated by difference of total noncondensables and CO_2. The reaction vessel was then warmed to −80° to release the CO_2, which was then measured.

Instead of vessels with glass break-seals, we also used vessels with a glass stem that is fitted with Swageloc fitting (Zytel ferrules) to a bellows-type stainless-steel valve (Whitey Research Tool Co.). This arrangement not only reduces the time required to prepare and analyze samples but also eliminates the possible hazard of sealing vessels containing oxygen and hydrocarbon mixtures.

Analyses. Hydroperoxide was then determined by refluxing a weighed sample (~1 ml) with 1 g of KI in 20 ml of 2-propanol (10% acetic acid) for 5–10 min, and then titrating with 0.02 N $Na_2S_2O_3$.

Acid was determined by dissolving the weighed sample in neutralized 95% EtOH and titrating with 0.05 N NaOH to a phenolphthalein end point.

Cyclohexanol and cyclohexanone were determined by first reducing the reaction mixture with a 100% excess of triphenylphosphine,[9] the amount being determined from hydroperoxide titration. Determinations were made on a chromatograph having a flame-ionization detector (Hewlett-Packard) and 10 ft of 0.125 in. column packed with 5% Carbowax 20M on Chromosorb G. p-Xylene was used as an internal standard. The "net ROH" is the difference between the total ROH found after reduction and the RO_2H found before reduction.

Oxidation products of cyclohexanone were determined first by direct GC analysis for ϵ-caprolactone and cyclohexane-1,2-dione. Then a second sample was reduced with triphenylphosphine, and after the volatile materials were removed, the residue was treated with methanol (1 ml) and boron trifluoride (several drops) to esterify the acids. The esters were then determined by GC.

In a third sample, after reduction with triphenylphosphine, the cyclohexanon-2-ol was esterified with acetic anhydride and pyridine catalyst at 80° for 3 hr and the ester was determined by GC.

Preparation of Cyclohexyl *tert*-Butyl Peroxide (CBP). CBP was prepared in a pressure bomb by decomposing 0.03 mol of *tert*-butylperoxy isopropyl carbonate (Pittsburgh Plate Glass Co., Chemical Division) at 115° for 16 hr in the presence of 0.02 mol of *tert*-butyl hydroperoxide and 200 ml of cyclohexane solvent. After most of the excess cyclohexane was removed by distillation at atmospheric pressure, the residue was fractionated at 20 Torr pressure on a spinning-band column to give 0.0058 mol (29%) of the desired product. The purity of the peroxide was easily determined by GC with 0.125-in. columns packed with 2% or 30% Carbowax 20M on Chromosorb P at 80°120°. The thermal decomposition of the peroxide was followed by the same method.

Results

Preliminary Oxidations. To determine the best conditions for studying the oxidation of cyclohexane, several exploratory runs were made between 60 and 130°. *N,N'*-Azobis(isobutyronitrile) (ABN) was used for the free-radical initiator at 60–70°, *N,N'*-azobis(1-cyanocyclohexane) (ABC) at 91°, and di-*tert*-butyl peroxide at 100 and 130°. Data are summarized in Table I. Below 100° kinetic chains are too short to study the chain oxidation of cyclohexane. Cyclohexanol and cyclohexanone were oxidized at 100° using di-*tert*-butyl peroxide. Cyclohexanol oxidizes 40 times as fast as cyclohexane under the same conditions; cyclohexanone is 27 times as fast. To determine how cyclohexanol and cyclohexanone affect the oxidation of cyclohexane, mixtures have been oxidized at 100° also. Cyclohexanol (2%) reduces the rate of oxidation of cyclohexane by ½; a similar amount of cyclohexanone accelerates the rate by a factor of 3.

Oxidation Products of Cyclohexane at 100°. Neat cyclohexane has been oxidized at 100° using 0.01 M di-*tert*-butyl peroxide as an initiator. Oxygen consumption was measured, hydroperoxide and acid were determined by titration, and cyclohexanol and cyclohexanone were determined by GC analysis after the hydroperoxide was reduced

Table II
Oxidations of Neat Cyclohexane (8.33 *M*) at 100°, 0.01 *M* t-Bu_2O_2 Initiator

Time, hr	$-\Delta O_2$, *M*	Products, *M*						Oxygen balance, %
		RO_2H	Total ROH	Net ROH	R=O	Acid	CO_2	
48A[a]	0.0428	0.0375	0.0388	0.0013	0.0020	0	0	94
72A	0.0690	0.0576	0.0666	0.0090	0.0072	0	0	100
96A	0.107	0.0822	0.101	0.0189	0.0158	0.001	0	103
144A	0.207	0.0876	0.137	0.0498	0.0638	0.006	0.001	93
169A	0.352	0.103	0.174	0.0708	0.0904	0.009	0.004	73[b]
192A	0.526	0.107	0.327	0.220	0.1844	0.006	0.009	108
48B[a]	0.0327	0.0238	0.0246	0.0007				79
72B	0.0610	0.0477	0.0540	0.0063	0.0016			87
96B	0.0956	0.0729	0.0834	0.0105	0.0037			87
144B	0.159	0.0967	0.156	0.0589	0.0409			117
192B[b]	0.276	0.105	0.205	0.100	0.0516			95[b]
216B	0.441	0.113	0.249	0.136	0.0392	0.0402		108
24	0.0200	0.0134	0.0136	0.0002				68
48.8	0.0350	0.0298	0.0302	0.0004				86
96	0.0667	0.0521	0.0552	0.0031	0.0190			109
96	0.0853	0.0590	0.0647	0.0051	0.0136	Trace		88
144	0.176	0.0621	0.0756	0.0135	0.0568	0.0100	0.0023	87
144	0.334	0.0867	0.144	0.0572	0.0776	0.0259	0.0085	77
192	0.414	0.0892	0.169	0.0796	0.105	0.0438	0.0138	86
192	0.360	0.130	0.184	0.0546	0.0844	0.0320	0.0193	95

[a] In the two six-part runs (labeled by A or B after time) with repeated additions of oxygen, product concentrations are cumulative. Reaction vessel was treated with EDTA solution before reaction. [b] After about 150 hr, a small heavy layer separates, probably mostly adipic acid and water. Since only the top layer was analyzed in the 169-hr A point and 192-hr B point, oxygen balances are low for these points.

with triphenylphosphine. Results are summarized in Table II. Initial experiments were carried out using all-glass vessels for each run; however, later experiments were run in a vessel with a valve that permitted several analyses during one reaction. Each time that the reaction was stopped and analyzed, it could be recharged with oxygen for oxidation. This technique eliminated some of the irregularities in conversion-time plots based on several experiments. In an attempt to improve reproducibility further, reaction vessels were washed with EDTA solutions to remove trace metal ions. Figure 1 shows oxygen consumed and products found vs. time for the oxidation of cyclohexane using data from the first series in Table II.

Oxidations of Cyclohexane. The products of oxidation of cyclohexanone are surprisingly complex. Careful GC analyses of the reaction mixtures after reduction of hydroperoxides with triphenylphosphine revealed δ-valerolactone, ϵ-caprolactone, cyclohexane-1,2-dione, and 2-cyclohexylidenecyclohexanone. Treating the reduced reaction mixture with acetic anhydride allowed determination of 2-hydroxycyclohexanone and 1-cyano-1-hydroxycyclohexane as their acetates. Treating the reduced reaction mixture with either diazomethane or methanol and BF_3-OEt_2 permitted determination of the acids: succinic, glutaric, adipic, and adipaldehyde. Because of complications, no attempt was made to detect the presence of monofunctional acids such as caproic or valeric acids. In all cases, identification was based on comparison of GC retention times with those of authentic samples and checked by NMR, ir, or mass spectroscopy of material isolated by GC.

Table III and Figure 2 summarize the oxidation of cyclohexanone at 80°. To determine the dependence of rate on initiator, ABC concentrations were varied from 0.01 to 0.10 *M*. Acetic acid (2 *M*), 0.01 *M* trifluoroacetic acid, or 0.1 *M* pyridine has little effect on rate or products in the ABC-initiated reactions. Oxidations in the presence of cobaltous or manganous acetates, in the presence of about 2 *M* acetic acid, are significantly faster than oxidations with 2 *M* acetic acid initiated with ABC.

The product analyses account for 76–82% of the oxygen consumed in ABC-initiated reactions, 86–102% in the Mn-catalyzed reactions. In the Co-catalyzed experiment, 91% of the oxygen was accounted for.

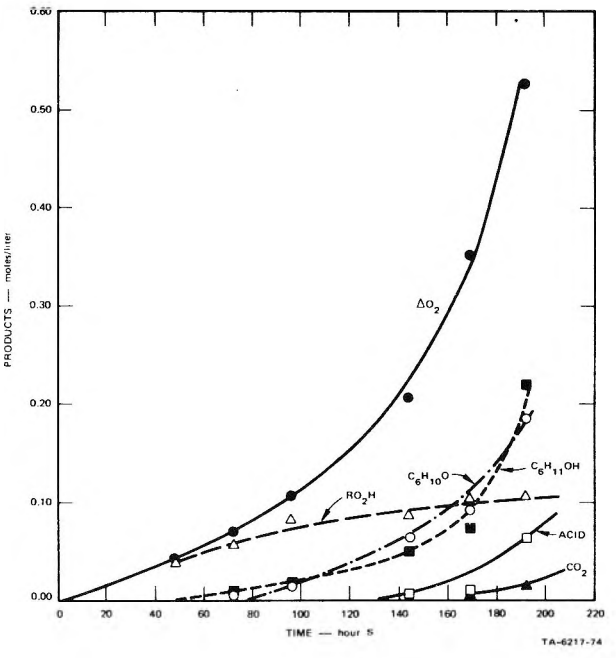


Figure 1. Oxidation of cyclohexane at 100°C in presence of 0.01 *M* t-Bu_2O_2 (A points in Table II).

Relative Reactivities toward *tert*-Butylperoxy Radicals. Cyclohexane, cyclohexyl hydroperoxide, cyclohexanol, cyclohexanone, cyclohexyl acetate, and tricyclohexyl borate were oxidized in the presence of 0.5 *M* *tert*-butyl hydroperoxide, with the results shown in Table IV. In each such oxidation the peroxy radicals corresponding to the substrate are rapidly converted by hydrogen transfer to *tert*-butylperoxy radicals that are responsible for both attack on substrate (k_p) and termination (k_t). Since the termination constant is known, the value for attack on substrate by *tert*-butylperoxy may be determined.[10] The expression for the rate of oxygen absorption (R_O) is

$$R_O = k_p[RH](R_i/2k_t)^{1/2} - R_i(1 - 2a)/2a \quad (1)$$

Table III
Oxidation of Cyclohexanone (8.97 *M*) at 80°

ABC, *M*	Time, hr	R_O, m*M*/hr	Products, m*M*										
			$-\Delta O_2$	RO_2H[a]	Acid, as dibasic	Dimethyl glutarate	Dimethyl adipate	Methyl adipaldehyde ester	2-Acetoxycyclohexanone	1-Acetoxy-1-cyanocyclohexane	Cyclohexane-1,2-dione	δ-Valerolactone	ε-Caprolactone
0.010	2.73	6.08	16.6	8.0	7.9				5.9				
0.010	8.98	6.48	58.3	21.9	28.9								
0.050	1.67	6.72	11.2	22.8	11.7								
0.10	1.67	2.20	36.7	16.1	15.0	1.7	2.5 (5.0)[b]	2.5	7.8				
0.10	5.0	20.6	103	38.8	22.6	6.9	9.4 (9.5)[b]	2.8	17.2	34.2	2.3	2.4	11.8
0.10	10.0	21.7	217	70.6	51.0	20.7	25.6 (38.1)[b]	5.3	34.2	34.2	2.8	3.6	19.0
0.10	15.0	22.5	337	73.1	93.5	29.4	35.3 (49.7)[b]	7.2	54.1	46.3	6.4	6.2	39.5
0.10	20.0	22.2	445	79.4	135	32.7	42.4 (54.4)[b]	14.2	73.0	64.5	8.3	7.6	61.3
0.10[c]	1.67	20.6	34.4	12.1	9.9	1.1	4.0	2.3	10.6				
0.10[d]	2.52	24.4	61.5	20	15		7.5		17.2				
0.10[e]	3.20	25.8	82.5	22	36		10.6		12.3				
Co[f]	0.53	488	259 ± 27	1.5	263	14.1 (14.4)[b]	84.5 (86.5)[b]	8.3 (8.3)[a]					
Mn[g]	0.35	1080	380	5.9	294	22.2	161				80.5		
Mn[h]	0.5	1240	621			21.8 (12.6)[i]	283 (292)[i]	29.2	129		13.1	7.3	4.4
Mn[h]	1.0	1020	1020			42 (est)	472	39.3	210		35.6	13.1	6.8
Mn[h]	2.1	903	1900			80.6 (108)[i]	811 (782)[i]	38.1 (46.7)	276		43.4	36.0	20.5
Mn[h]	3.1	1020	3150			131 (158)[i]	1230 (1225)[i]	39.1 (47.3)	341		62.2	54.5	43.3

[a] By titration; reduced compound appears as corresponding alcohol. [b] After esterification, sample transesterified with methanol–sodium methoxide; increase in ester value indicates presence of complex adipate. [c] 7.75 *M* cyclohexanone, remainder of reaction mixture is acetic acid. [d] 8.96 *M* cyclohexanone, 0.01 *M* trifluoroacetic acid. [e] 8.77 *M* cyclohexanone, 0.10 *M* pyridine. [f] 0.0057 *M* $Co(OAc)_2$, 8.00 *M* cyclohexanone, balance acetic acid. [g] 0.0037 *M* $Mn(OAc)_2 \cdot 4H_2O$, 7.99 *M* cyclohexanone, balance acetic acid. [h] 0.0043 *M* $Mn(OAc)_2 \cdot 4H_2O$, 7.8 *M* cyclohexanone, balance acetic acid. [i] Esterification by methanol and $BF_3 \cdot OEt_2$ rather than diazomethane.

Table IV
Oxidations of Cyclohexane and Derivatives at 80° with 0.1 *M* ABC and 0.5 *M* *tert*-Butyl Hydroperoxide in *tert*-Butylbenzene

Substrate	Concn, *M*	Initial $R_O \times 10^2$, *M*/hr	$k_p/(2k_t)^{1/2}$, $(M\ hr)^{-1/2}$		k_p, $(M\ sec)^{-1}$ [a]	Relative reactivity per C_6 group
None		−0.74				
C_6H_{12}	1.50	0.30	0.11			
C_6H_{12}	2.06	0.45	0.09	0.10[b]	0.175	1.0
C_6H_{12}	2.51	0.77	0.10			
C_6H_{12}	3.68	0.96	0.075			
$C_6H_{11}OH$	0.0099	−0.40	5.6		9.7	55
$C_6H_{11}OH$	0.048	0.27	3.4	5.6[b]		
$C_6H_{11}OH$	0.26	0.61	0.84			
$C_6H_{11}OH$	1.00	1.83	0.41			
$C_6H_{11}O_2H$	0.0098	0.25[c]	5.6[d]		9.8	56
$C_6H_{10}O$	0.098	−0.49	0.42		2.26	13
$C_6H_{10}O$	0.206	−0.45	0.23	~1.3[b,e]		
$C_6H_{10}O$	0.308	−0.31	0.23			
$C_6H_{11}OAc$	2.01	−0.03	0.058			
$C_6H_{11}OAc$	3.98	0.35	0.044	0.047[b]	0.082	0.5
$C_6H_{11}OAc$	5.92	0.69	0.039			
$(C_6H_{11}O)_3B$	0.99	0.73	0.081[f]		0.14	0.8

[a] Calculated from $k_p/(2k_t)^{1/2}$ using $k_t = 5.6 \times 10^3\ M^{-1}\ sec^{-1}$ and $R_i = 3.75 \times 10^{-3}\ M$/hr for 0.1 *M* ABC. [b] Preferred value based on plot of data. [c] Rate of formation of cyclohexanone. [d] Corrected for contribution of reaction 7 (see text). [e] Corrected for cyclohexanone as hydroperoxide adduct as determined by ir (see text). [f] Per C_6H_{11} group.

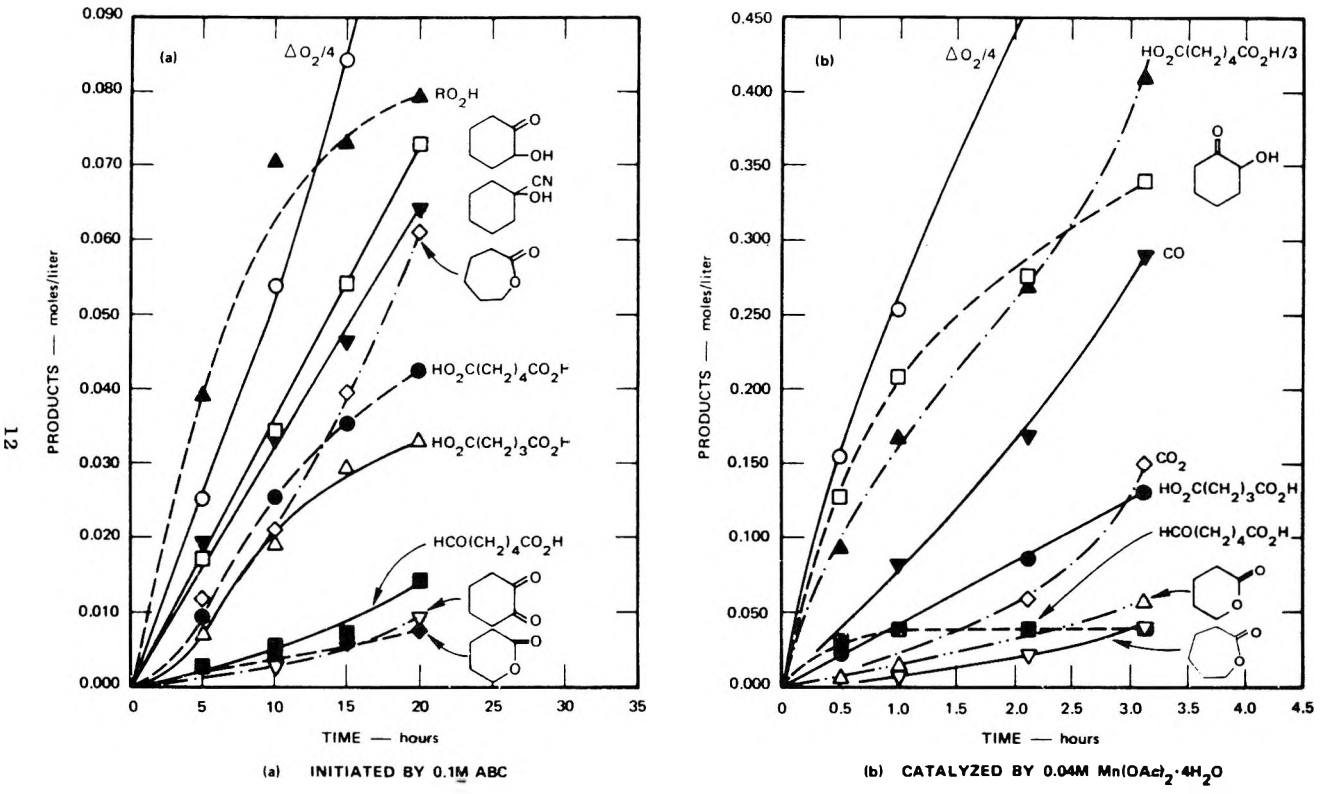
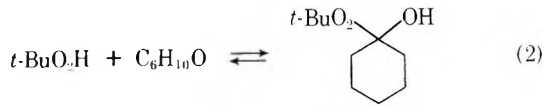


Figure 2. Oxidations of cyclohexanone at 80°C.

where R_i is the rate of initiation and a is the efficiency of termination in interactions of two *tert*-butylperoxy radicals. The negative term in eq 1 allows for evolution of oxygen and is evaluated from the decomposition of hydroperoxide in the absence of oxidizable substrate. The other term corresponds to oxygen consumed by chain propagation with substrate. There can be a net evolution of oxygen in the absence of sufficient substrate.

Although eq 1 predicts that values of $k_p/(2k_t)^{1/2}$ should remain constant as [RH] is increased, the data for cyclohexanol and cyclohexanone clearly show significant decreases. In the case of cyclohexanol, we attribute this decrease to incomplete reaction of hydroperoxy radicals with *tert*-butyl hydroperoxide and their participation in propagation and termination. Since the cross termination reaction between t-$BuO_2\cdot$ and $HO_2\cdot$ has a rate constant about 10^5 times that for 2 t-$BuO_2\cdot$,[11] relatively little $HO_2\cdot$ can have a large effect on the rate. The amount of $HO_2\cdot$ and its contribution to termination is expected to decrease as the concentration of cyclohexanol is decreased. Hence, the relative reactivity has been estimated from data at the lowest concentrations of cyclohexanol.

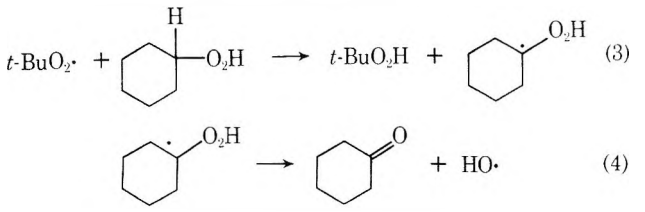
When hydroperoxide is added to cyclohexanone, and ir absorption of the carbonyl group decreases, indicating the



(2)

equilibrium in eq 2. The relative reactivities in Table IV were determined using the carbonyl absorption as a measure of free cyclohexanone.

Obtaining relative reactivity data for the oxidation of cyclohexyl hydroperoxide in the presence of *tert*-butyl hydroperoxide is more complicated, since reaction of this substrate does not result in oxygen consumption. Instead, α-attack of the hydroperoxide yields ketone by the reactions



(3)

(4)

Hence, if only *tert*-butylperoxy radicals participate in propagation and termination, the rate of formation of cyclohexanone measures the reactivity of cyclohexyl hydroperoxide in reaction 3.

$$d[C_6H_{10}O]/dt = k_p[C_6H_{11}O_2H](R_i/2k_t)^{1/2} \quad (5)$$

However, the cyclohexyl hydroperoxide which is present inevitably reacts with the propagating peroxy radicals,

$$t\text{-}BuO_2\cdot + c\text{-}C_6H_{11}O_2H \rightleftarrows t\text{-}BuO_2H + c\text{-}C_6H_{11}O_2\cdot \quad (6)$$

so that some cross-termination occurs:

$$t\text{-}BuO_2\cdot + c\text{-}C_6H_{11}O_2\cdot \rightarrow t\text{-}BuOH + c\text{-}C_6H_{10}O + O_2 \quad (7)$$

Since the latter reaction is 10^2–10^3 times as fast as termination by 2-t-$BuO_2\cdot$,[12] a small amount of c-$C_6H_{11}O_2\cdot$ can have a large effect on the rate of oxidation. If reaction 7 is unimportant, then added cyclohexyl hydroperoxide should have no effect on R_O in eq 1, since reactions 3 and 4 do not consume oxygen. However, if added hydroperoxide reduces R_O, the contribution of reaction 7 is equivalent to a corresponding reduction in rate of initiation. It was found necessary to work at concentrations of 2.0 M *tert*-butyl hydroperoxide and 0.01 M cyclohexyl hydroperoxide where the latter hydroperoxide retarded the rate of oxygen formation by only 50%. Since R_O is proportional to R_i under these conditions (eq 1) this amount of retardation indicates that reaction 7 accounts for ½ of the termination and that an amount of cyclohexanone is formed corresponding to ¼ the rate of initiation ($R_i = 3.75 \times 10^{-3}$ M/hr). Thus, the observed rate of formation of cyclohexanone from peroxy attack is 2.5×10^{-3} M/hr (from Table IV) $- 0.1 \times 10^{-3}$ M/hr $= 2.4 \times 10^{-3}$ M/hr. The value for $k_p/(2k_t)^{1/2}$ obtained by substitution of this value for $d[C_6H_{10}O]/dt$ in eq 5 must also be corrected for the effect of reaction 7 on the apparent value of k_t. Since R_O is reduced by 50% by the addition of cyclohexyl hydroperoxide, the apparent k_t is twice as fast as for the reaction of 2 t-$BuO_2\cdot$ (eq 1). Therefore the value of $k_p/(2k_t)^{1/2}$ (eq 5) was corrected for termination by only 2 t-$BuO_2\cdot$ by multiplying by $\sqrt{2}$.

Decompositions of Cyclohexyl Hydroperoxide. The rate of decomposition of cyclohexyl hydroperoxide has been investigated at 100° in the absence of both oxygen and added free radical initiator. First the decomposition was studied at 0.1 and 0.5 M in cyclohexane using 96% pure hydroperoxide containing about 2% each of cyclohexanol and cyclohexanone. The individual effects of about 0.1 M adipic acid, cyclohexanol, cyclohexanone, boric acid, and tricyclohexyl borate were determined on the decomposition

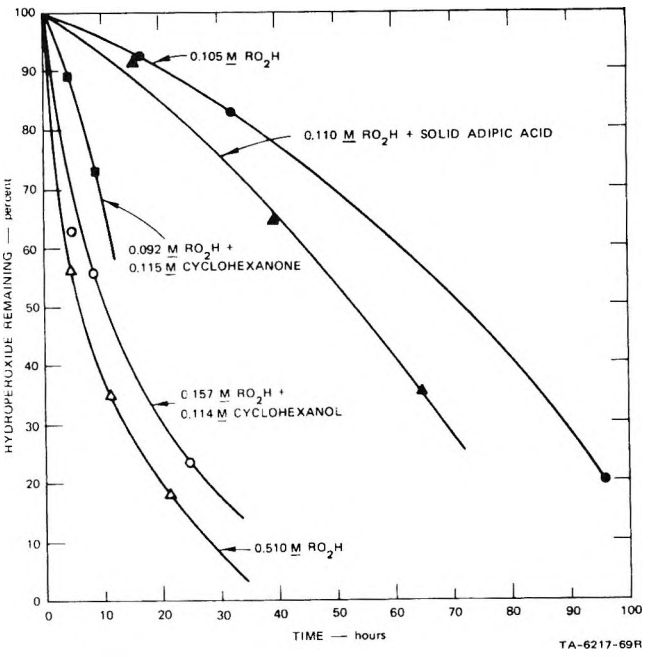
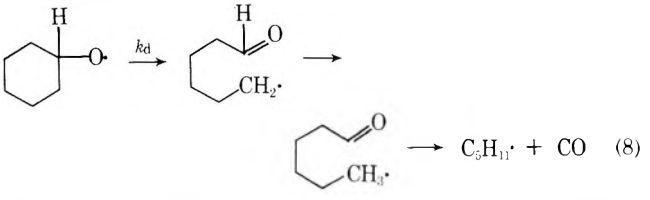


Figure 3. Effects of concentration and decomposition products on decompositions of cyclohexyl hydroperoxide (RO_2H) in cyclohexane at 100°.

of 0.1 M hydroperoxide. Concentrations of cyclohexanol and cyclohexanone were followed with conversion, but with limited success, although reproducibility per sample was usually within 5% for duplicate analyses. Data in Table V are plotted in Figure 3. The curves for 0.1 M hydroperoxide indicate autocatalysis up to >50% conversion. This relation is consistent with a faster reaction between hydroperoxide and one or more of the decomposition products. Cyclohexanol, cyclohexanone, and to a lesser extent adipic acid accelerate the decomposition of hydroperoxide. The magnitude of the effect indicates that the small amount of impurity in the 0.1 M hydroperoxide run is probably accelerating the decomposition initially. Since the initial rate of decomposition of 0.5 M hydroperoxide is ~70 times that for 0.1 M peroxide, the decomposition is not a simple unimolecular reaction.

Chemistry of the Cyclohexyloxy Radical. Cyclohexyl *tert*-butyl peroxide (CBP) was selected as the source of cyclohexyloxy radicals because of its ease of preparation and because, unlike secondary peroxides,[13] it cannot decompose to hydrogen and ketone.

CBP (0.0988 mmol) was heated with 1.0 ml of isopropyl acetate at 130° for 64 hr in a sealed tube. Analysis of the noncondensable products indicated formation of about 0.035 mmol of each of carbon monoxide and methane. Since the carbon monoxide results from cleavage of the cyclohexyloxy radical (reaction 8), at least 35% and possibly



(8)

all (since no cyclohexanol is found) of the cyclohexyloxy radicals cleave under the reaction conditions. The presence of carbon monoxide indicates that pentane or pentene should also be present. A GC analysis showed peaks with the necessary retention times, but positive identification has not been made.

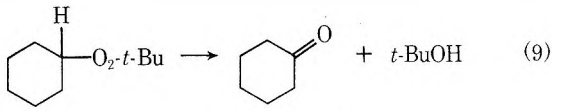
In a series of sealed tubes, 0.064 M CBP was decomposed

Table V
Decomposition of Cyclohexyl Hydroperoxide at 100°

Additive	Time, hr	Concn, M $C_6H_{11}O_2H$	$C_6H_{10}O$	$C_6H_{11}OH$	Yield decomposition products[a]
None	0	0.510	0.010	0.015	
	5.0	0.288	0.112	0.165	114
	11.5	0.177			
	22.3	0.093	0.205	0.331	122
None	0	0.105	0.002	0.003	
	16.0	0.098	0.004	0.002	
	32.0	0.087	0.013	0.009	113
	95.5	0.021	0.057	0.085	163
Cyclohexanone	0	0.092	0.115	0.003	
	4	0.082	0.135	0.014	
	8.5	0.067	0.134	0.011	108
Cyclohexanol	0	0.157	0.003	0.114	
	4.7	0.098	0.012	0.111	
	9.0	0.088	0.018	0.108	
	25.0	0.038	0.047	0.137	50
Adipic acid[b]	0	0.110	0.002	0.003	
	15.5	0.100	0.007	0.006	80
	39.5	0.071	0.023	0.020	97
	64.5	0.040	0.035	0.076	163
Boric acid[b]	0	0.105	0.002	0.003	
	3.0	0.071	0.004	0.014	
	5.25	0.048	0.009	0.014	
	8.25	0.030	0.012	0.030	54
	15.5	0.008	0.012	0.056	62
Tricyclohexyl borate (0.109 M)	0	0.113	0.002	0.003	
	4	0.104			
	20	0.057	0.046		
	28	0.022	0.072		

[a] (Increase in alcohol + ketone) × 100%/(decrease in hydroperoxide). [b] 1 mol/mol ROOH, insoluble in reaction mixture.

in cyclohexane for up to 2 hr at 140°, with the results in Table VI. This decomposition gives 8–9% cyclohexanone, probably in the cage reaction 9. Of the remaining free cyclohexyloxy radicals, 56% give cyclohexanol by hydrogen abstraction (reaction 10), and 44% is in unidentified and



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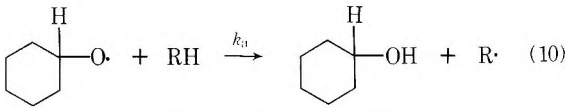


(10)

probably mostly acyclic products. The 44% includes products left after evolution of CO corresponding to about 8% of the cyclohexyloxy radicals that escape the initial cage.

Discussion

Oxidation of Cyclohexane at Low Conversion. The oxidation of cyclohexane at 100° initiated by 0.10 M di-*tert*-butyl peroxide gives about 0.5% conversion in 48 hr. At this conversion, hydroperoxide accounts for 87.5% of the oxygen consumed while cyclohexanol accounts for 1.4%, and cyclohexanone accounts for 4.7% (assuming 1 mol of water per mole of ketone). The missing oxygen corresponds to one molecule for every 14 molecules found as peroxide. The chain length averages 23 ($\Delta O_2/t$-BuO· formed). From the known amount of initiation, 0.00075 M each of cyclohexanol and cyclohexanone should be present if termination occurs by two cyclohexylperoxy radicals. Actually twice as much cyclohexanol and three times as much cyclohexanone are found. However, in the next 24 hours, 14 times as much cyclohexanol and 10 times as much cyclohexanone are found as expected from the calculated initiation and termination. Thus, during the first 0.1–0.3% of reaction only one molecule each of cyclohexanol and cyclohexanone appear to be formed per termination step. Since our CBP results showed that cyclohexyloxy radicals are readily converted to cyclohexanol in cyclohexane, the absence of excess cyclohexanol demonstrates that few or no free cyclohexyloxy radicals are formed either from nonterminating interactions of cyclohexylperoxy radicals or from reaction 11, suggested by Berezin et al.[14]

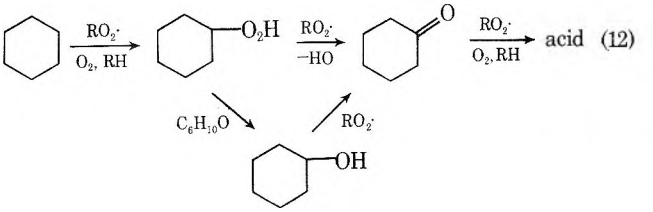
Table VI
Decomposition of CBP in Cyclohexane at 140.2°

Time, min	CBP mM	Products, mM[a] CO	$C_6H_{10}O$	$C_6H_{11}OH$	$(C_6H_{11})_2$
0	64	0	1.2	0.11	0.26
20	50	0.4	2.75	4.88	19.0
30	39	0.8	3.02	12.7	19.4
60	40	1.4	5.40	16.8	26.6
127	21	2.8	5.68	24.2	24.9
1200	0	4.4	6.64	33.2	21.9

[a] All values except for CO are averages of three replicate analyses by GC. Precision is generally better than ±5%.

$$RO_2\cdot + RH \rightarrow RO\cdot + ROH \qquad (11)$$

Oxidation of Cyclohexane at High Conversion. A simple sequence for the further oxidation of cyclohexane is the first line in reaction 12, although it neglects the presence of cyclohexanol in the products.



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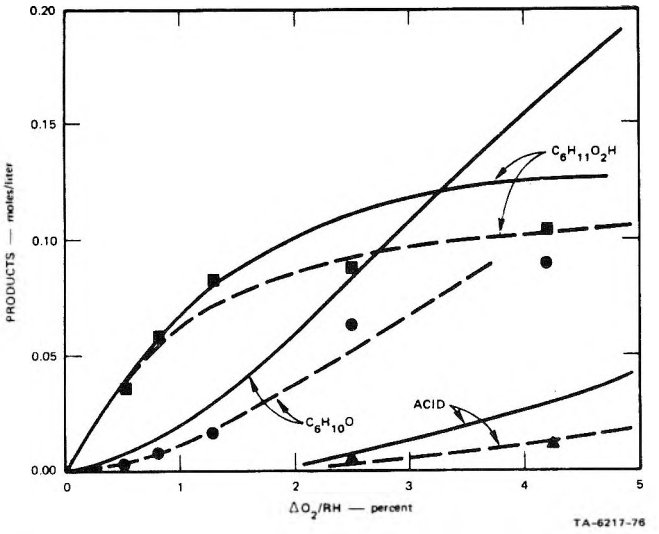
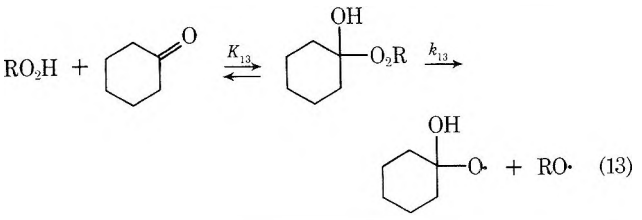


Figure 4. Formation of products in oxidation of cyclohexane at 100°C. Solid lines are calculated from independently measured relative reactivities; dashed lines and points are experimental.

If we assume that cyclohexane, cyclohexyl hydroperoxide, and cyclohexanone have the relative reactivities in Table IV and that these values do not change with conversion, it is possible to calculate the concentrations of hydroperoxide, cyclohexanone, and acid as the reaction proceeds, using the technique described by Benson,[15] which considers only the products formed in propagation. Figure 4 is a plot of the calculated concentration of products against conversion, with experimental points from the A series in Table II.

While there is qualitative agreement between the experimental and the calculated curve based on relative reactivities, all the calculated concentrations are too high, mostly because of neglect of cyclohexanol in the model and not because of neglect of termination products. Experimentally, cyclohexanol is present to about the same extent as cyclohexanone. We conclude that hydroperoxide is being converted to cyclohexanol by a partly nonradical reaction in addition to the radical attack that leads to ketone. Hence, the true relative reactivity of the hydroperoxide toward peroxy radicals may be smaller than the value used. The actual main sequence then requires incorporation of the second line in reaction 12.

The high strength of the O–O bond in ROOH (42 kcal/mol) precludes the conversion of hydroperoxide to alcohol by direct homolysis at 100°. One possible route is reaction 13, where R is cyclohexyl. Since such a reaction depends on



the accumulated ketone, it would be unimportant at low conversions, as observed. Further, this reaction predicts that the overall oxidation would be autocatalytic, as observed; after 6% conversion, the rate of oxygen absorption has increased tenfold (Figure 1). Little of this increase is caused by replacement of cyclohexane by more reactive products, since 2 mol % of cyclohexanol retards the rate of oxidation of cyclohexane and 2 mol % cyclohexanone only slightly accelerates the rate (Table I); however, the effects of these products on the decomposition of the hydroperoxide in cyclohexane (Figure 4) further supports occurrence

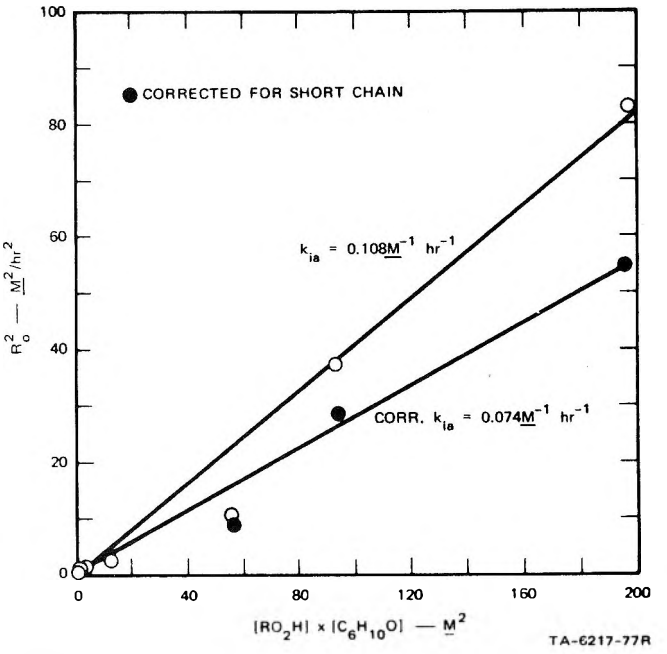


Figure 5. Autocatalytic initiation for oxidation of cyclohexane at 100°C.

of reaction 13 in the oxidation. Kazantseva and co-workers[16] have recently shown that 4-methylcyclohexanone not only increases the rate of radical production from cyclohexyl hydroperoxide but also increases the rate of the nonradical decomposition even more.

Equation 14 gives the rate of oxidation of cyclohexane with initiation from both the added *tert*-butyl peroxide and reaction 13, propagation by attack of cyclohexylperoxy radicals on cyclohexane, and termination by two cyclohexylperoxy radicals

$$R_O = \frac{k_p}{(2k_t)^{1/2}}[C_6H_{12}]\{2k_d[t\text{-}Bu_2O_2] + 2k_{ia}[RO_2H][C_6H_{10}O]\}^{1/2} - \{k_d[t\text{-}Bu_2O_2] + k_{ia}[RO_2H][C_6H_{10}O]\} \quad (14)$$

where k_{ia} ($= K_{13}k_{13}$) is the rate constant for the autocatalytic initiation and k_d is the rate constant for decomposition of initiator. If the second term on the right side of the equation is neglected (it is 2–5% of the total at low conversion but it could be as large as $R_O/2$ at high rates) and the equation is then squared, the two initiation terms can be separated.

$$R_O^2 = (k_p[C_6H_{12}])^2(2k_d[t\text{-}Bu_2O_2]/2k_t) + (k_p[C_6H_{12}])^2(2k_{ia}[RO_2H][C_6H_{10}O])/2k_t \quad (15)$$

Figure 5 plots R_O^2 (as determined from tangents at each point on the best curve of ΔO_2 vs. time in Figure 1) against the products of the concentrations of hydroperoxide and ketone. By combining the values of the intercept and slope, $k_{ia} = 0.108\ M^{-1}\ hr^{-1}$. If initiation occurs only by decomposition of di-*tert*-butyl peroxide and reaction 13, the actual rate of initiation may be calculated at each point. From these values, R_O^2 may be corrected using the second term on the right in eq 14 and a new value of k_{ia} determined; successive adjustment gives $k_{ia} = 0.074\ M^{-1}\ hr^{-1}$ (or $2.05 \times 10^{-5}\ M^{-1}\ sec^{-1}$). A reported value for the *tert*-butyl hydroperoxide–cyclohexanone decomposition is about $0.6 \times 10^{-5}\ M^{-1}\ sec^{-1}$.[17] The agreement between these values gives substantial support to the sequence in eq 12. However, as the rate increases, the termination reaction produces significant amounts of cyclohexanol and cyclohexanone. At the completion of the reaction in Figure 1, the actual chain

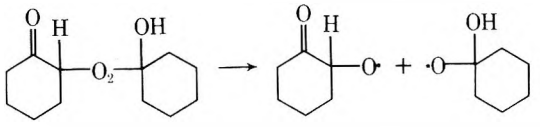
length appears to be about 4; therefore, as much as 25% of the consumed hydrocarbon could be in termination products.

At higher temperatures, 1-hydroxycyclohexyloxy radicals formed in reaction 13 apparently cleave to complicate the products,[18] but not in our work at 100°. Instead, cleavage is associated with oxidation of cyclohexanone, as shown in the following discussion.

Oxidation of Cyclohexanone. Although the free radical initiated oxidation of cyclohexanone was studied at 80° instead of the 100° used for cyclohexane, the products were more complex. At 0.7% conversion all products are present that are present at 4% conversion and in about the same proportions. The suggestion by Pritzkow[3] that an acid-catalyzed decomposition of the α-ketocyclohexyl hydroperoxide is responsible for the complex mixture of products may be ruled out, at least at our high rates of initiation, since the presence of acetic acid, trifluoroacetic acid, or pyridine does not have any large effect on rates, distribution of products, or the fraction of the oxygen appearing as hydroperoxide (Table III). Therefore, the intermediates must be largely free radical in nature. Apparently organic acids do shorten the induction period in uncatalyzed oxidations of cyclohexane, but the mechanism is obscure.[19] Acid does not accelerate the ABC-initiated reaction.

The α-hydroperoxy ketone must be an important intermediate since it accounts for a large fraction of the first products. We conclude that most of products result from decomposition of the hydroperoxide, although at least some of the products must arrive from chain termination reactions.

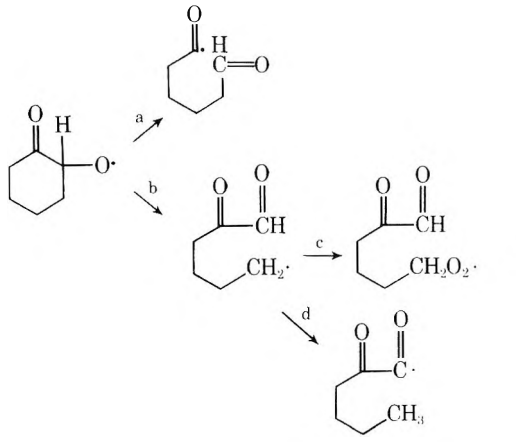
The cyclohexanone concentration is so high that a reaction like 13 must be the main route for decomposition of 2-hydroperoxycyclohexanone, as proposed by Berezin et al.[4]



(16)

At the temperature of our reaction, hydroxycyclohexyloxy radicals should initiate chains and be converted back to cyclohexanone (plus H_2O), although at higher temperatures cleavage of this radical may also be important.

The 2-ketocyclohexyloxy radicals formed in reaction 16 may abstract hydrogen or cleave. The amount of the alcohol thus formed is small since we find about the same amount of hydroperoxide before triphenylphosphine reduction as alcohol afterwards. Cleavage probably predominates and the competition between two possible routes explains the complexity of the observed products.



(17)

Route a leads easily to adipaldehyde acid, adipic acid, and monoperadipic acid, which can convert cyclohexanone to ε-caprolactone. Route b leads to glutaric acid and δ-valerolactone by route c and valeric acid related compounds by route d.

In the presence of cobalt or manganese, the rates are much faster than the ABC-initiated rates and much less hydroperoxide is found. With cobalt, the ratio of adipic to glutaric acid is about the same as found in the ABC-initiated reaction, suggesting that free-radical cleavage of the 2-ketocyclohexyloxy radical still predominates, although it is now formed by reaction of hydroperoxide with cobaltous salts. With manganese, much less glutaric acid is formed, which suggests that while some cleavage of 2-ketocyclohexyloxy radicals may occur, there is another important cleavage mechanism that produces less decarbonylation or decarboxylation. This mechanism may be similar to the ionic cleavage induced by the manganese which was proposed by Hertog and Kooyman.[20] Our rate and product results with cobalt and manganese have been confirmed and extended by Kamiya and Kotake,[21] who have shown convincingly that the rate-determining step in oxidations by manganic acetate is the enolization of cyclohexanone.

Conclusions

The di-*tert*-butyl peroxide initiated oxidation of cyclohexane at low conversions at 100° gives high yields of cyclohexyl hydroperoxide with cyclohexanol and cyclohexanone as chain termination products. On further oxidation, hydroperoxide is converted directly to cyclohexanone without much chain cleavage or by-product formation. The accumulating ketone also catalyzes the decomposition of hydroperoxide into radicals, increasing the rate of oxidation, regenerating ketone, and producing cyclohexanol, which is readily oxidized to more ketone. Cyclohexanol also accelerates decomposition of hydroperoxide. These conclusions are supported by thermal decompositions of hydroperoxide in the absence of oxygen. As these catalytic effects lead to faster oxidation, they also lead to shorter kinetic chains and higher proportions of chain termination products.

Relative rates of oxidation at the same rate of initiation at 100° follow: cyclohexane, 1; cyclohexanol, 40; and cyclohexanone, 27. Relative reactivities toward *tert*-butylperoxy radicals follow: cyclohexane, 1.0; cyclohexyl hydroperoxide, 56; cyclohexanol, 55; cyclohexanone, 13; and cyclohexyl acetate, 0.5.

Hydroperoxide appears to be converted to cyclohexanol by formation of the hemiperketal, which decomposes faster by O–O cleavage than the simple hydroperoxide. The cyclohexyloxy radicals formed react mostly by hydrogen abstraction at 100°, but more cleavage occurs at higher temperatures. Integration of data on peroxide decomposition and relative reactivities gives a satisfactory account of the observed rates and products of oxidation of cyclohexane to cyclohexanone at 100°.

The further oxidation of cyclohexanone is more complex, even where it was studied at 80°. The major primary product is 2-hydroperoxycyclohexanone and the decomposition of this compound, also catalyzed by cyclohexanone, leads to a variety of products. At 4% conversion, the oxidation gives about 30% hydroperoxide, 20% ε-caprolactone, 16% adipic acid, and 12% glutaric acid. The remaining 22% comprises adipaldehyde acid, cyclohexane-1,2-dione, and δ-valerolactone. The product mix depends on competing abstraction and cleavage reactions of alkoxy radicals and inter- and intramolecular hydrogen transfer and oxygen addition reactions of alkyl and acyl radicals formed by cleavage. The oxidation of cyclohexanone is catalyzed by both cobalt and manganese. The latter gives outstanding yields of adipic acid.

This investigation has brought out the relative simplicity of the oxidation of cyclohexane to cyclohexanone at 100°, and the variety of the subsequent reactions of cyclohexanone at 80°. It has also indicated what reactions should become important in the presence of metals and at higher temperatures. Therefore, it should provide an improved point of departure for study of oxidations of cyclohexane at higher temperatures and for other aliphatic hydrocarbons at all temperatures.

Registry No.—Cyclohexane, 110-82-7; cyclohexanol, 108-93-0; cyclohexanone, 108-94-1; cyclohexyl hydroperoxide, 766-07-4; cyclohexyl acetate, 622-45-7; tricyclohexyl borate, 2467-16-5; cyclohexyl-*tert*-butyl peroxide, 15619-54-2; *tert*-butylperoxy isopropyl carbonate, 2372-21-6.

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Cycloaddition of an Enamine to an Activated Cyclopropane

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The cycloaddition of *N*-pyrrolidinylcyclohexene (**5**) to 1,1-dicyano-2,2-dimethylcyclopropane (**9**) proceeded by an SN2 route (across the 1–3 bond) rather than by way of a zwitterionic intermediate (across the 1–2 bond). The adduct (**12**) rearranged upon partial hydrolysis to a spiro structure (**13**) which was further hydrolyzed to 2-oxo-4,4-dimethylcyclopentanepentanoic acid (**14**). This keto acid was synthesized.

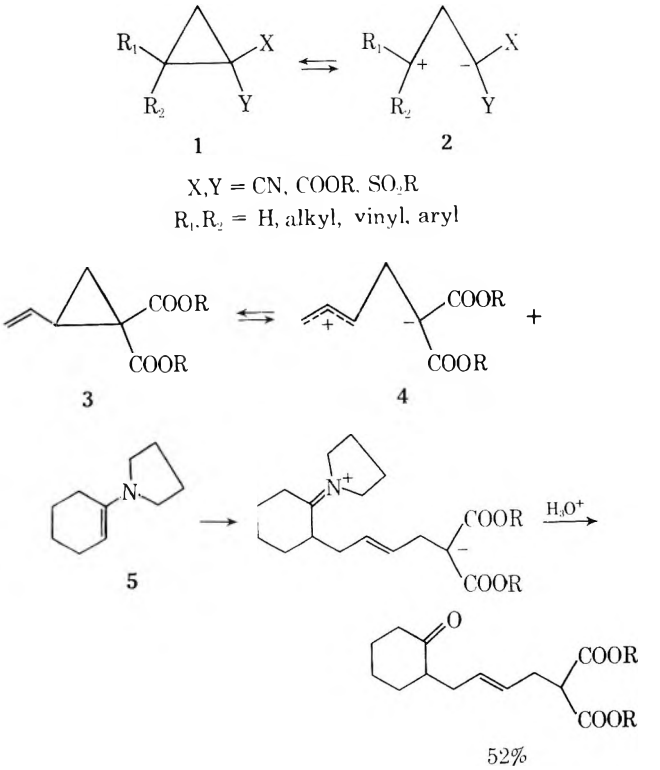
Considerable data now support the existence of zwitterionic intermediates (**2**) in the ring opening of suitably activated cyclopropanes (**1**). For instance, Cram[1] has demonstrated that nucleophiles, electrophiles, and polar solvents strongly increase the rate of racemization of such systems. In addition, both Cram[1] and Danishefsky[2] have shown that such systems suffer nucleophilic ring opening almost exclusively at the more highly substituted carbon (presumably by way of the more stable carbonium ion).

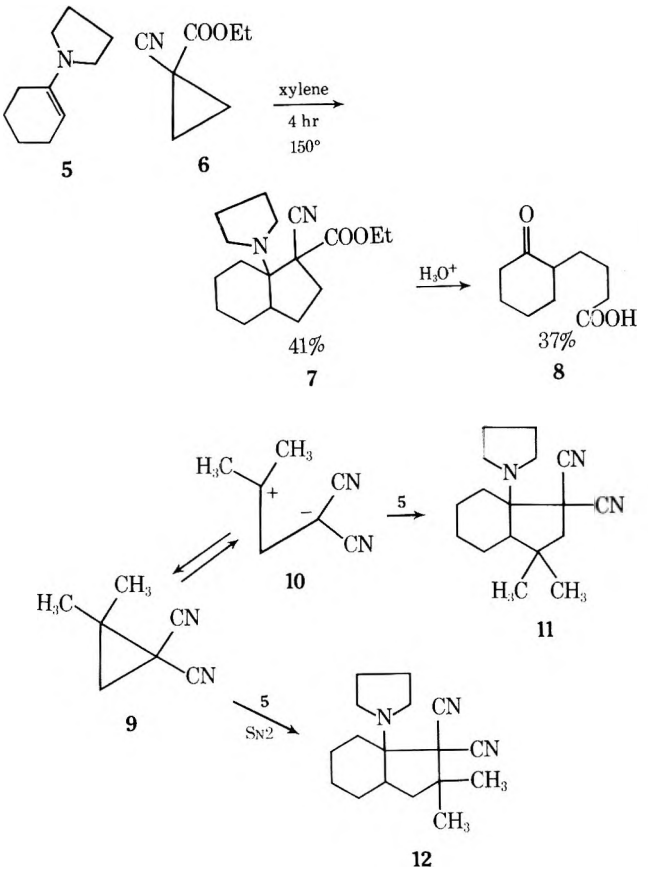
On the other hand, both authors have proven that nucleophilic attack occurs with *complete inversion*,[1,2a,b] leading to the conclusions that nucleophilic attack must be considerably faster than bond rotation and that racemization, at least in the presence of nucleophiles or polar solvents, probably involves a measure of nucleophilic participation as well (and also, perhaps, electrophilic aid).

Conversely, enamines attack **3** exclusively at the terminal carbon.[3] Danishefsky has suggested that the reaction involves zwitterionic intermediate **4**.

Where would an enamine attack cyclopropane **1**? Cycloaddition of enamine **5** to unalkylated cyclopropane **6** gave adduct **7** as shown by hydrolysis to keto acid **8**.[4]

We have examined the reaction of enamine **5** with 1,1-dicyano-2,2-dimethylcyclopropane (**9**).[5] A zwitterionic intermediate (**10**) would give **11**; SN2 attack would give **12**. In the event, **12** was produced in 47% yield. The results are summarized in Chart I.





Discussion

Adduct **12** showed a nitrile band at 2232 cm^{-1} in the ir; the NMR spectrum was characterized by two singlets at δ 1.38 and 1.45, attributable to the two methyl groups; the pyrrolidine group appeared in its characteristic form of an unresolved A_2B_2 multiplet. These data, and the lack of any ultraviolet absorption above 210 nm,[6] led us to formulate the cycloadduct as either **11** or **12**.

Recrystallization of **12** from hot 95% ethanol gave a crystalline product the formula of which denotes replacement of the pyrrolidinyl group by hydroxyl. Comparison of spectral bands with those of enaminonitrile **18**,[7] the presence of an additional ir band at 1701 cm^{-1}, two exchangeable protons (NMR), and the lack of a methine carbon (^{13}C NMR) convinced us that this hydrolysis product was **13** (position of the methyls still ambiguous). The hydrolysis and rearrangement of **12** to **13** is rationalized in Chart II.

Apparently the increased solvent polarity due to the presence of 5% water (**12** may be recrystallized without rearrangement from absolute alcohol) is sufficient to cause reopening of **12** to **19**.

Acid hydrolysis of both **12** and **13** gave keto acid **14** (which was synthesized as shown in Chart I), thereby fixing the position of the methyls as in **12** and not **11** (assuming that the structure shown for keto ester **16** is correct).

These results lead us to believe that terminal attack of enamine **5** on vinylcyclopropane **3** occurs by an SN2′ mechanism (in xylene). On the other hand, ring attack by pyrrolidine and other nucleophiles in *protic* solvents can be rationalized more readily in terms of solvent-, nucleophile-,

Chart I

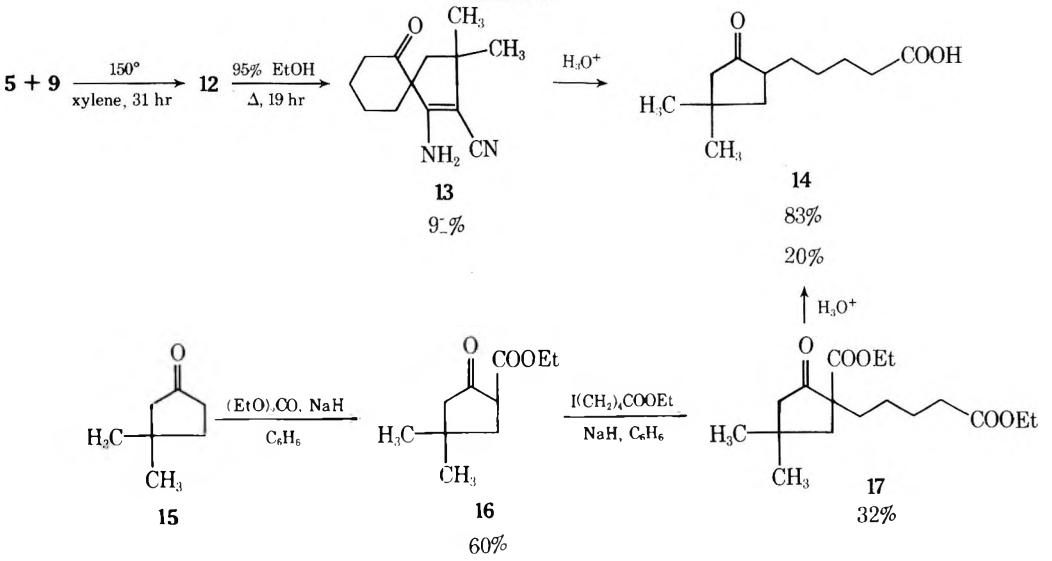
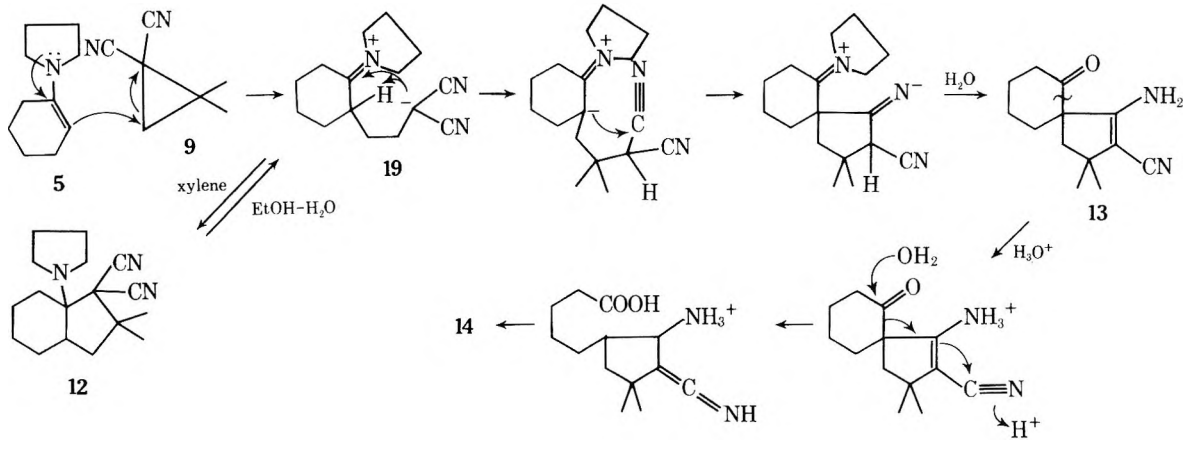


Chart II



or electrophile- (proton) assisted formation of a zwitterionic intermediate.

Experimental Section

Melting points (uncorrected) were determined on a Mel-Temp apparatus. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. GLC results were obtained on a Varian Aerograph A90-P3 thermal conductivity instrument. Infrared spectra were taken on a Perkin-Elmer 237-B or Beckman IR-20 grating spectrophotometer; ultraviolet spectra on a Cary 14; ^{1}H NMR spectra with a Varian A-60A or EM-360; ^{13}C NMR spectra with a Varian CFT-20 (Fourier transform); and mass spectra with a Varian MAT CH-7 (at 70 eV).

1,1-Dicyano-2,2-dimethyl-7a-(*N*-pyrrolidinyl)perhydroindene (Adduct 12). A solution of 35.0 g (0.292 mol) of 1,1-dicyano-2,2-dimethylcyclopropane (**9**)[5] and 67.0 g (0.445 mol) of 1-*N*-pyrrolidinylcyclohexene (**5**) (freshly distilled) in 300 ml of dry xylene (distilled from calcium hydride) was refluxed for 31 hr under an atmosphere of nitrogen. The disappearance of the cyclopropane was followed by GLC.[8] The mixture was then fractionated, giving 60.2 g (76%) of viscous yellow oil, bp 118–152° (0.05–0.07 mm), which partially solidified. This was recrystallized from warm (<45°) 95% ethanol, giving 36.0 g (45.6%) of white prisms, mp 78–79°, of adduct **12**.[9] The ir ($CHCl_3$) of this material exhibited a nitrile band at 2232 cm^{-1}; the NMR ($CDCl_3$) showed two methyl singlets at δ 1.38 and 1.45 and the typically unresolved pyrrolidinyl A_2B_2 multiplet centered at δ 3.10; the MS gave a parent ion at *m/e* 271. Adduct **12** showed no uv absorption above 220 nm (EtOH).

In addition, 2.80 g (4.4%) of enaminonitrile **13**, mp 164–165°, was obtained from the mother liquor.

1-Amino-2-cyano-3,3-dimethylspiro[4.5]decen-1-one-6 (13). A solution of 1.00 g of adduct **12** in 20 ml of 95% ethanol was refluxed for 19 hr. Concentration under reduced pressure left 710 mg (91%) of **13**, as shown by mixture melting point and ir. Recrystallization of crude **13** from 95% ethanol gave white prisms of **13**, mp 167–168.5°.[9] The enaminonitrile showed an ultraviolet absorption maximum (95% EtOH) at λ 264 nm (ϵ 11900); ir ($CHCl_3$) 3472, 3367, 2188, 1701, 1645, 1597 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 0.97, s, 3 H; 1.13, s, 3 H; 6.08, s, 2 H (D_2O labile); ^{13}C NMR[10] ($CDCl_3$) (downfield from Me_4Si) CH_3 20.6, 30.1; CH_2 21.6, 27.2, 38.3, 39.6, 48.4; CH, . . .; C 42.2, 63.3, 88.2, 117.4, 160.4, 219.4 ppm.

2-Oxo-4,4-dimethylcyclopentanepentanoic Acid (14). A mixture of 1.00 g (4.58 mmol) of enaminonitrile **13**, 25 ml of 85% phosphoric acid, and 25 ml of glacial acetic acid was refluxed (150°) for 71 hr, then poured onto 100 g of crushed ice. This mixture was extracted with four portions of ether which were combined, dried over magnesium sulfate, and concentrated under reduced pressure, leaving 1.60 g of brown oil. The oil was dissolved in benzene, washed with water, and again dried and concentrated, affording 801 mg (83%) of yellowish prisms, mp 80–83°. Recrystallization of the crude keto acid from benzene–hexane or ether gave white prisms of **14**, mp 84–85°.[9] The ir ($CHCl_3$) of **14** showed bands at 1730, 1712,[11] 2500–3500 cm^{-1} (br); NMR ($CDCl_3$) δ 1.06, s, 3 H; 1.18, s, 3 H; 11.05, s, 1 H (D_2O labile); MS *m/e* 112 > 42 > 56 > 57 > 97 > 69 > 83 > 40 > 46 > 67 > 54 > 70 > 81 > 68, parent ion *m/e* 212 (7.4% of *m/e* 112). A sample of this keto acid was proved identical with the product of acid hydrolysis of keto diester **17** (Chart I) by mixture melting point and comparison of ir, NMR, and mass spectra.

Keto acid **14** was also isolated in 14% yield from a similar phosphoric–acetic acid hydrolysis of adduct **12** (8 days reflux).

Ethyl 2-Oxo-4,4-dimethylcyclopentanecarboxylate (16).[12] To a refluxing suspension of 5.98 g (0.142 mol) of a 57% dispersion of sodium hydride in mineral oil in 70 ml of dry benzene and 11.81 g (0.10 mol) of freshly distilled diethylcarbonate was added, with stirring under a nitrogen atmosphere during 4 hr, a solution of 5.61 g (0.050 mol) of 3,3-dimethylcyclopentanone.[13] The reaction mixture was refluxed for an additional 0.5 hr, then cooled and cautiously acidified with a solution of 10 ml of acetic acid in 10 ml of benzene, followed by 35 ml of water. The aqueous layer was extracted with three portions of benzene. The combined organic layers were washed with several small portions of water, then dried over magnesium sulfate and concentrated by distillation. The concentrate was fractionated, giving 5.80 g (63%) of keto ester **16**, bp 99° (13 mm)–122° (16 mm) (>95% pure by GLC estimate[14]).

A sample of this material which was purified by GLC[14,9] showed ir (CCl_4) 1762, 1731, 1663, 1620 cm^{-1};[15] NMR (CCl_4) δ 1.06, s; 1.23, s; 1.27, t (*J* = 7 Hz) (combined 9 H); 2.10, s; 1.97–2.28, m (combined 4 H); 3.21, t, 1 H (*J* = 10 Hz; D_2O labile); 4.11, q, 2 H (*J* = 7.5 Hz); MS *m/e* 29 > 44 > 42 > 55 > 33 > 101 > 56 > 73 > 123 > 156 > 32 > 69 > 83 >39 > 184 > 169; parent ion *m/e* 184 (6.2% of *m/e* 29). Keto ester **16** gave a positive ferric chloride test, but no enolic H showed in the NMR.

Ethyl 1-Carbethoxy-2-oxo-4,4-dimethylcyclopentanepentanoate (17). To a suspension of 1.10 g (0.026 mol) of a 57% dispersion of sodium hydride in mineral oil in 25 ml of dry benzene was added, with stirring under nitrogen during 15 min, a solution of 3.68 g (0.020 mol) of keto ester **16** in 10 ml of dry benzene. Stirring was continued until hydrogen evolution ceased (5 min). To the white suspension of enolate salt was then added, during 10 min, a solution of 5.12 g (0.020 mol) of ethyl 5-iodopentanoate[16] in 15 ml of dry benzene. The resulting mixture was refluxed for 18.5 hr, then cooled and quenched with a solution of 5 ml of acetic acid in 20 ml of benzene, followed by 15 ml of water. The aqueous layer was extracted with two portions of benzene; the combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated by distillation. The concentrate was fractionated, affording 2.00 g (32%) of keto diester **17**, bp 139° (0.20 mm)–145° (0.28 mm) (>90% pure by GLC estimate[14]). A sample of **17** purified by GLC[9,14] showed ir (CCl_4) 1730, 1755 cm^{-1} (sh);[17] NMR (CCl_4) δ 1.11, s; 1.217, t (*J* = 7 Hz); 1.242, t (*J* = 7 Hz) (the upfield legs of both triplets are hidden under the *gem*-dimethyl singlet); 4.00 q (*J* = 7 Hz); 4.04, q (*J* = 7 Hz) (combined 4 H); MS *m/e* 184 > 41 > 55 > 81 > 56 > 43 > 109 > 83 > 67 > 39 > 138 = 95 > 42 > 137 = 45 > 53 > 69 = 77 = 79 > 123 > 193 (21% of *m/e* 184), parent ion *m/e* 312 (4% of *m/e* 184). Keto diester **17** gave a negative ferric chloride test.

Keto diester **17** (313 mg, 1.0 mmol) was hydrolyzed by refluxing with 18 ml of 20% hydrochloric acid for 27 hr. The mixture was then concentrated to dryness under reduced pressure. The residual oil was triturated with saturated aqueous sodium bicarbonate which was then extracted with ether and finally acidified with concentrated hydrochloric acid. The acid mixture was extracted with three portions of ether which were combined, dried over magnesium sulfate, and evaporated, leaving 104 mg of colorless oil which slowly crystallized. Recrystallization of this (benzene–hexane) gave 42 mg of keto acid **14**, mp 82–83.5°, which was identical with the keto acid isolated by hydrolysis of both adduct **12** and enaminonitrile **13** (mixture melting point, ir, MS, NMR).

1-Methylcyclohex-3-enecarboxaldehyde.[13] A practical improvement upon Pines' Diels–Alder procedure (autoclave, 150°) was obtained by the use of stannic chloride as a catalyst.[18]

To a solution of 77.88 g (1.00 mol) of methacrolein (90%, technical grade) in 500 ml of benzene at 3° was added a solution of 36.11 g (0.139 mol) of anhydrous stannic chloride in 50 ml of benzene. After the initial mild exotherm (the temperature rose to 18°), 1,3-butadiene was bubbled in subsurface with good stirring. The temperature was maintained at 20–30° with intermittent ice cooling (continuously at first) during 3 hr (cooling was rarely required after the first 1.5 hr). The reaction mixture (total volume 1 l.) was then poured into a mixture of 100 g of ice and 200 ml of water and shaken vigorously (much effervescence of dissolved butadiene). The organic layer was washed with dilute hydrochloric acid, 5% aqueous sodium chloride, and saturated aqueous sodium bicarbonate, then dried over magnesium sulfate and concentrated by distillation. The concentrate was fractionated (much foaming), affording 96.1 g (77%) of aldehyde: bp 74° (27 mm) (>99% pure by GLC estimate[19]); ir (CCl_4) 1732 cm^{-1} (no bands at 1600–1650 cm^{-1}); NMR (CCl_4) δ 1.03, s, 3 H; 1.33–2.65, m, 6 H; 5.57, s (crude triplet when expanded), 2 H; 9.30, s, 1 H; MS *m/e* 43 > 67 = 95 > 39 > 81 > 41 > 55 > 80 = 79 > 77 > 78, 91 = 109, parent ion *m/e* 124 (49% of *m/e* 43).

Semicarbazone: mp 173.5–174° (lit.[13] mp 170–172°).

The use of freshly distilled methacrolein or rigorously anhydrous conditions did not improve the yield of aldehyde. The use of anhydrous aluminum chloride as catalyst lowered the yield to 47%.

Acknowledgment. The authors gratefully thank the NIH for financial support of this project (NIH ROIAM11226).

Registry No.—**5**, 1125-99-1; **9**, 6904-09-2; **12**, 57091-01-7; **13**, 57091-02-8; **14**, 57091-03-9; **15**, 20500-49-6; **16**, 22773-08-6; **17**, 57091-04-0; diethyl carbonate, 105-58-8; 1-methylcyclohex-3-enecarboxaldehyde, 931-96-4.

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18

2189, 1645, 1605 cm^{-1}; uv λ 263 (ϵ 13000). **13**: ir ($CHCl_3$) 3472, 3367, 2188, 1645, 1597 cm^{-1}; uv λ 264 (ϵ 11900).
(8) A 10 ft × 0.38 in. column packed with Chromosorb coated with 20% by weight of SE-30 silicone gum was used.
(9) A satisfactory elemental analysis was obtained for this material.
(10) We are indebted to W. C. Jankowski of Varian for this spectrum.
(11) W. Herz, *J. Org. Chem.*, **22**, 630 (1957): 2-oxocyclopentanepentanoic acid ir 1730, 1710 cm^{-1}.
(12) (a) R. N. Chakravarti, *J. Chem. Soc.*, 1028 (1947); (b) S. Kagawa et al., *Tetrahedron Lett.*, 3913 (1969); neither reference reports physical data for **16**.
(13) M. Pines, F. J. Pavlik, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **73**, 5738 (1951).
(14) A 6 ft × 0.25 in. column packed with Chromosorb P coated with 30% by weight of SE-30 silicone gum was used.
(15) N. J. Leonard, H. S. Gutowsky, W. J. Middleton, and E. M. Petersen, *J. Am. Chem. Soc.*, **74**, 4070 (1952): 2-carbethoxycyclopentanone ir 1756, 1725, 1660, 1618 cm^{-1}.
(16) H. O. House and H. Babad, *J. Org. Chem.*, **28**, 90 (1963).
(17) W. Herz, *J. Am. Chem. Soc.*, **78**, 1485 (1956): ethyl 1-carbethoxy-2-oxocyclopentanepentanoate ir 1735, 1755 cm^{-1} (sh).
(18) A modification of the procedure of W. Kreiser, W. Haumesser, and A. Thomas, *Helv. Chim. Acta*, **57**, 164 (1974).
(19) A 4 ft × 0.25 in. column packed with Chromosorb W coated with 20% by weight of DC 200 silicone oil was used.

Mechanistic Studies on the Photochemical Reactions of Isoxazoles[1]

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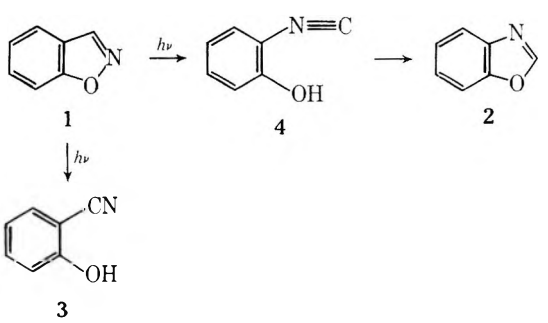
The mechanisms of the photochemical conversion of isoxazoles to oxazoles and ketoketenimines have been investigated. Isonitrile **14** was detected by an ir band at 2160 cm^{-1} in the photoconversion of **5** to **15** at −77°. Compound **14** was further identified by independent synthesis and by hydrolysis to formamide **17** in acid. Ir bands at 1690 and 1655 cm^{-1} are consistent with the hypothesis that azirine **13** is the precursor to isonitrile **14**. It is postulated that a vinyl nitrene is the immediate precursor to **13**. Photolysis of **10** at −77 or −196° resulted in the formation of an ir band at 2050 cm^{-1}. This band was assigned to ketoketenimine **23**. The structure of **23** was proved by independent synthesis and trapping with water. No intermediates in the photochemical conversion of **10** to **21** were detected by trapping or low-temperature ir studies. New syntheses of isoxazoles **5** and **10** were developed.

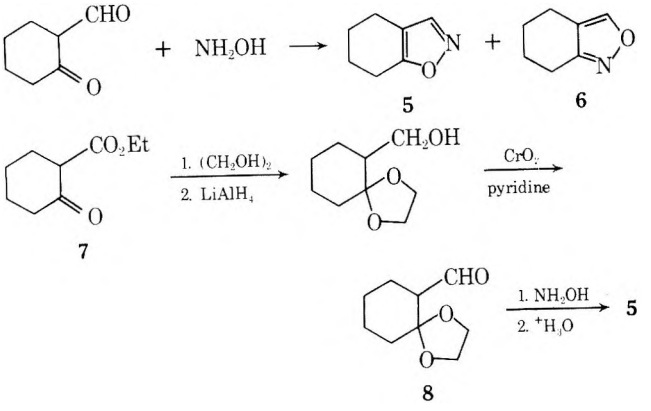
A study of the mechanisms of the photochemical rearrangement of indoxazene (**1**) to benzoxazole (**2**) and 2-cyanophenol (**3**) has been reported (Scheme I).[2] The isonitrile (**4**) was detected spectrally by trapping experiments and by independent synthesis. The present study was undertaken with the objective of learning more about the mechanism of the photochemical isomerization of isoxazoles to oxazoles.[3–5]

Scheme I

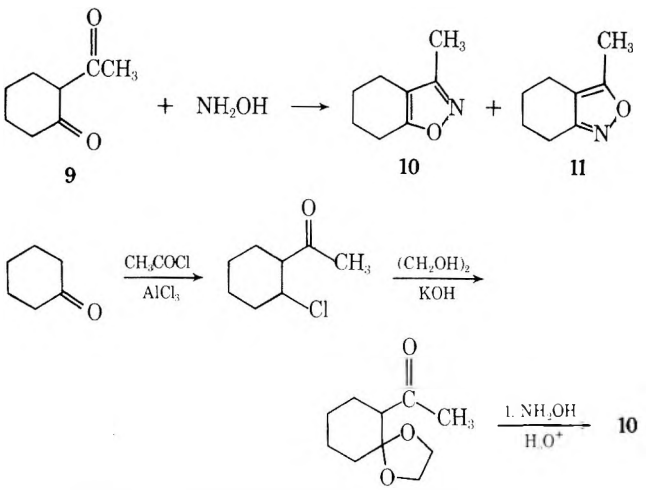


Results and Discussion

Synthesis of Isoxazoles. The reported synthesis of 4,5,6,7-tetrahydro-1,2-benzisoxazole (**5**) from 2-oxocyclohexanecarboxaldehyde was complicated by the formation of isomer **6**, which we were unable to separate from **5**.[6,7] A successful synthesis of pure **5** was devised starting from ethyl 2-oxocyclohexanecarboxylate (**7**) via aldehyde **8**.[8]



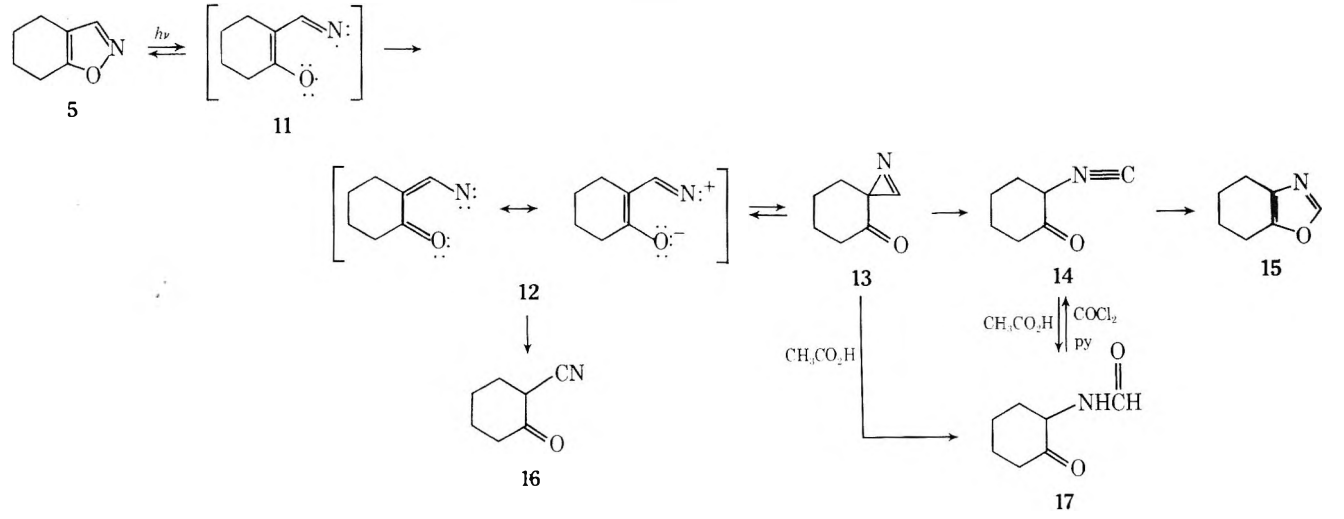
Attempted direct synthesis of 3-methyl-4,5,6,7-tetrahydro-1,2-benzisoxazole (**10**) from 2-acetylcyclohexanone (**9**) led to a 1:4 mixture of the desired isomer **10** and isomer **11**, respectively. A higher proportion (5:1) of **10** was obtained by preferential ketalization of the cyclohexanone carbonyl of **9** followed by its reaction with hydroxylamine and acid hydrolysis of the ketal. We succeeded in obtaining pure **10** starting from cyclohexanone and proceeding via 1-acetyl-2-chloro-1-cyclohexene.



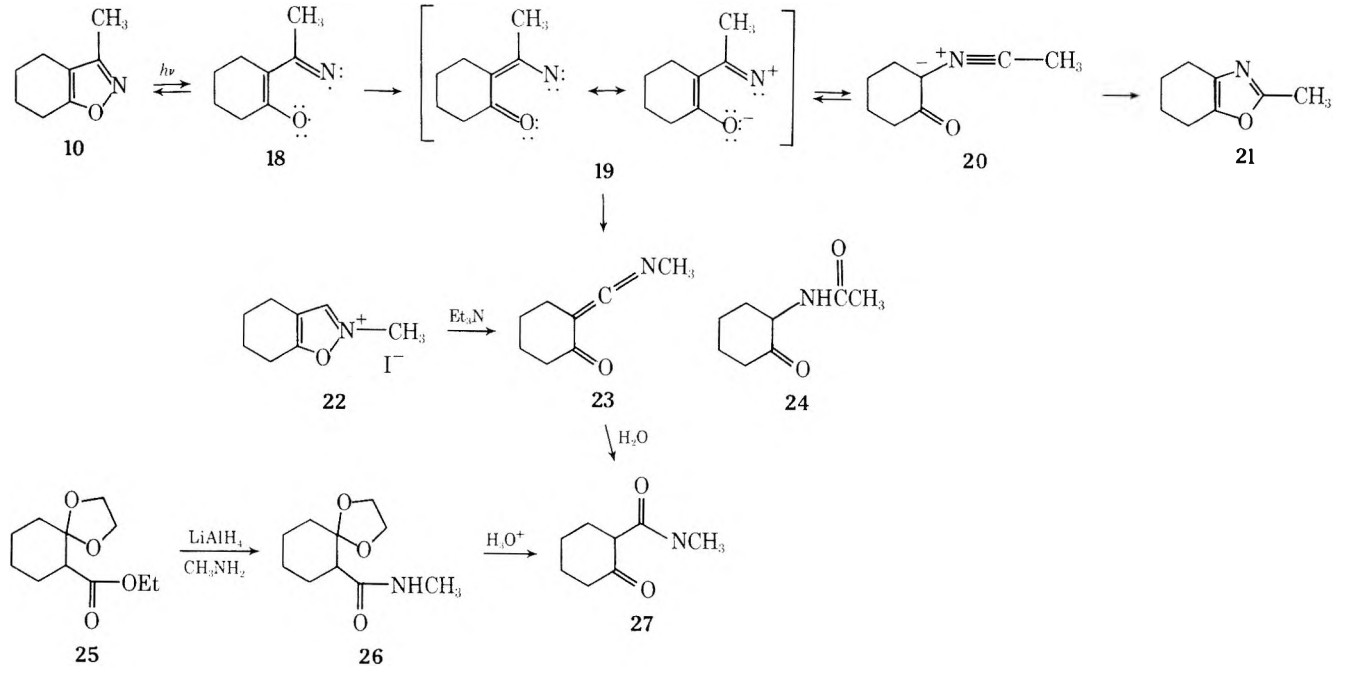
Photochemical Studies. The photochemical rearrangement of **5** to 4,5,6,7-tetrahydrobenzoxazole (**15**) proceeds in 99% yield in degassed ethanol (Scheme II). A 63% yield of **21** was obtained on irradiation of **10** in degassed ethanol (Scheme III). Other unidentified photoproducts were detected by TLC when the photolysis of **10** was performed in degassed methylcyclohexane. The photolysis of 2-oxocyclohexanecarbonitrile (**16**) gives a 2% yield of **15** in degassed aqueous solution; however, no **15** could be detected when the photolysis of **16** was performed in tetrahydrofuran or ethanol. None of the corresponding oxazole was detected when 2-oxocyclopentanecarbonitrile was photolyzed in a variety of solvents.

The mechanism of the photochemical rearrangements of **5** and **10** was first investigated by low-temperature ir techniques. Photolysis of a neat film of **5** at −77° resulted in the development of new ir bands at 2210, 1720, 1690, and 1655 cm^{-1}. The bands at 2210 and 1720 cm^{-1} were assigned to the ketonitrile **16** since they were also observed in the ir spectrum of an authentic sample of **16**. These ir bands did not change when the film was warmed to room temperature. The absorption bands at 1690 and 1655 cm^{-1} decrease when the film is warmed to room temperature and a new band develops at 2160 cm^{-1} together with intensified absorption in the 1720-cm^{-1} region. On continued standing at room temperature the infrared bands at 2160 and 1720 cm^{-1} decrease in intensity and absorption bands character-

Scheme II



Scheme III



istic of **15** appear. The presence of **15** in the liquid film was verified by TLC analysis.

The transitory ir absorptions at 1720 and 2160 cm^{-1} were assigned to the ketoisonitrile **14** (Scheme II) since identical bands were observed in the ir spectrum of an authentic sample prepared by the dehydration of the formamide **17**. The formation of oxazoles from β-ketoisonitriles has been reported.[9] The initially observed ir bands at 1690 and 1655 cm^{-1} are tentatively assigned to azirine **13**. The band at 1655 cm^{-1} is consistent with those reported for an azirine with no substituent in the 2 position.[10,11] The 1690-cm^{-1} absorption is consistent with a cyclohexanone carbonyl the frequency of which is shifted to longer wavelengths by conjugation with the spiroazirine group.[12,13] The azirine is probably formed from **5** via the vinyl nitrene **12**, since it has been suggested that vinyl nitrenes are in thermal equilibrium with azirines.[14] Vinyl nitrene **12** is also a likely precursor to ketonitrile **16**.[15,16]

Photolysis of 3-methyl-4,5,6,7-tetrahydro-1,2-benzoisoxazole (**10**) as a neat film at −77 or −196° resulted in the formation of a new ir band at 2050 cm^{-1}. This band disappeared on warming to room temperature. Absorption at 2050 cm^{-1} is characteristic of the ketenimine group in compound **23**. Ketenimines have been noted as photoproducts of isoxazoles[13b] and similar *N*-alkylketenimines are known to be stable at −77°.[8,17] No infrared bands characteristic of 2-methyl-4,5,6,7-tetrahydrobenzoxazole (**21**) were observed on warming the film to room temperature and only a trace of **21** could be detected by TLC analysis. The virtual absence of **21** when **10** was irradiated as a liquid film or in methylcyclohexane solution is due to the low polarity of the medium, since it has been observed that ketenimine and nitrile formation is favored when isoxazoles are irradiated in nonhydroxylic solvents.[2,5] However, the possibility of a greater temperature coefficient for the rate constant for the rearrangement of **10** to **21** as compared to **23** cannot be ruled out.

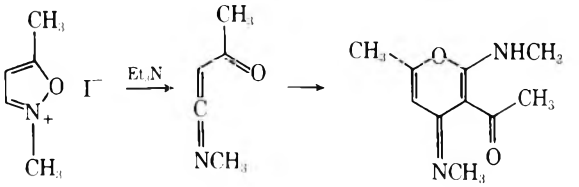
Trapping studies provided further evidence for the intermediates postulated as a result of the low-temperature experiments. Photolysis of **5** in glacial acetic acid resulted in a 50% yield of the corresponding formamide **17**. This product is probably formed by the acid hydrolysis of isonitrile **14**.[2] There is one report[15] of the acid hydrolysis of a 2-unsubstituted azirine to a formamide so the possibility exists that we are intercepting **13** as well as **14**. Only a 5% yield of **17** was obtained when **15** was photolyzed in acetic acid. This eliminates the possibility that **17** was formed after **5** had been converted to oxazole **15**.

A low yield (5%) of the acetamide **24** (corresponding to formamide **17**) along with **21** was obtained on photolysis of **10** in acetic acid. The low yield of **24** that was observed probably is not due to the trapping of a reaction intermediate, because a similar yield of **24** was obtained when **21** was irradiated for the same time period under the same reaction conditions. The absence of trapping by acetic acid suggests that neither azirine nor isonitrile type intermediates (e.g., **20**) are formed in the photochemical conversion of **10** to **21**. There does exist the possibility that intermediates of this type are formed but that they rearrange faster to **21** than they react with acetic acid.

The photochemically produced ketenimine **23** reacted with water in aqueous solution to give a 5% yield of amide **27** together with oxazole **21**. The low yield of **27** is probably due to the use of a polar solvent. It has been demonstrated that higher yields of amides are obtained when nonhydroxylic solvents containing 5% water or methanol are used.[5] There is one report of the predominant formation of a methanol adduct of the ketenimine formed by the photolysis of 3,5-disubstituted isoxazoles in methanol solution.[18]

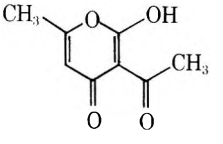
Direct comparison of the spectral and chemical properties of ketenimine **23** prepared synthetically with that prepared photochemically provides further evidence for its formation on irradiation of **10**. The ir spectrum of the reaction mixture formed by the treatment of methiodide **22** with Et_3N exhibited a band for the ketenimine chromophore at the same frequency (2050 cm^{-1}) as was observed in the ir spectrum of photolyzed **10**. Furthermore, addition of water to a solution of the ketenimine prepared from **22** resulted in the formation of the same amide (**27**) as was obtained by photolysis of **10**. Our sample of **27** prepared photochemically was identical in all respects with that prepared chemically but both samples exhibited a melting point that was considerable lower (64–70°) than that in the literature (82–84°).[8] An unambiguous synthesis of **27** from **25**, the ketal of 2-oxocyclohexanecarboxylate, resulted in the formation of a product that was identical with those samples prepared previously in our laboratory. The spectral properties of all our samples were identical with those of an authentic sample provided by Olofson.[8] The melting point of the sample provided by Professor Olofson decreased with time from 84° to the melting point we observed. Presumably this variation is due to different proportions of the two possible tautomeric forms of **27**.

In our initial studies on the chemical synthesis of ketenimines for comparison with those produced photochemically we synthesized ketenimine **29** from 2,5-dimethylisoxazolium iodide (**28**). Ketenimine **29** formed readily as shown



28 **29** **30**

by a band at 2075 cm^{-1} in the ir spectrum of the reaction mixture. However, treatment with water did not result in the expected amide but instead a dimer (**30**) was produced. Structure **30** is consistent with spectral studies and with the structure of dehydroacetic acid (**31**), a compound which



31

forms spontaneously from acetylketene.[19] Presumably the steric requirements of **23** mediate against its forming a similar dimer.

No tetrahydrosalicylamide was formed on irradiation of **5** in aqueous solution. This finding is consistent with the absence of the development of ketenimine absorption in the 2050–2090 cm^{-1} region when **5** was irradiated at −77 and −198°.

Attempts were made to trap the radical (e.g., **18**), or nitrenes (e.g., **19**) or nitrile ylides (e.g., **20**) derived from radicals using olefins.[20–22] Many of the olefins used previously to trap nitrile ylides absorb light at the same wavelengths as isoxazole **9**, so we were limited to the use of the weakly uv absorbing cyclohexene and norbornene as trapping agents. Considerable rearrangement of **10** to **21** was observed during the course of the photolysis of **10** in the presence of these olefins but there was no evidence of adduct formation. The failure to detect olefin adducts is not in conflict with the formation of **18**, **19**, or **20** as intermediates but instead suggests that the rate of the intramolecular re-

arrangement is much faster than the rate of the intermolecular reaction with the olefin.

Experimental Section

General Procedures. The same experimental procedures and instruments were used as described previously.[2] In addition some spectral measurements were performed on a Perkin-Elmer Model 337 ir spectrophotometer and a Varian HA-100 NMR spectrometer. Gas chromatography was performed on a F & M Model 810 equipped with a flame ionization detector and Aerograph Model A-700 equipped with a thermal conductivity detector. The liquid phase noted was supported on Chromosorb W. Samples for irradiation were degassed by at least three freeze–pump–thaw cycles. Thin layer chromatography (TLC) was conducted on Merck's precoated plates of silica gel (F-254) unless otherwise noted. Quantitative analysis was done visually with known amounts of standards chromatographed on the same plate. The accuracy is within ±10%.

The following compounds, prepared essentially by literature procedures, are listed together with the yields and physical constants we observed: 2-oxocyclohexanecarboxaldehyde,[23] 60%, bp 70–75° (7 mm); ethyl 2-oxocyclohexanecarboxylate,[24] bp 115–120° (22–25 mm); 2-aminocyclohexanone hydrochloride,[25] 60%, mp 159–160°, ir in agreement with the reported spectrum; *N*-methyl-5-methylisoxazolium iodide (**28**),[26] mp 125.5–126.5°; 4,5,6,7-tetrahydrobenzoxazole (**15**),[27] bp 67–69° (8 mm); NMR ($CDCl_3$) δ 7.7 (s, 1, aromatic H), 2.55 [m, 4, $(CH_2)_2$], and 1.75 [m, 4, $(CH_2)_2$].

Synthesis of 4,5,6,7-Tetrahydro-1,2-benzisoxazole (5) from 2-Oxocyclohexanecarboxaldehyde. The procedure of von Auwers et al.[6] was followed. The oil was distilled through a Vigreux column: 83%, bp 82–86° (7–8 mm) [lit. 90–95° (14 mm)]; NMR (neat) δ 8.15 (s, 1, aromatic H), 8.05 (s, 1, aromatic H), 2.55 [m, 4, $(CH_2)_2$], and 1.7 [m, 4, $(CH_2)_2$]. The signal at δ 8.05 was assigned to the aromatic proton of **5** while the one at δ 8.15 was assigned to the aromatic proton in **6**. A 6:1 ratio of **5** to **6** was obtained as determined from the NMR spectrum. Compound **6** was prepared previously.[28]

Synthesis of Ethyl 1,4-Dioxaspiro[4.5]decane-6-carboxylate (25). To 0.03 mol of ethyl 2-oxocyclohexanecarboxylate dissolved in 75 ml of benzene was added 0.03 mol of ethyl glycol, and a catalytic amount of *p*-toluenesulfonic acid. This solution was heated to reflux and after 10 hr 1 equiv of water was collected in a Dean-Stark trap. The solution was cooled and then poured into dilute aqueous sodium hydroxide and extracted three times with ether, and the combined ether phases were washed with water and then brine. The ether extract was dried over magnesium sulfate and concentrated in vacuo to an oil. The oil was distilled: bp 140–142° (19 mm); NMR (neat) δ 4.05 (q, 2, ester), 3.85 (s, 4, ketal), 2.75 (m, 1, $-CHCO_2Et$), 2.65 [m, 8, $(CH_2)_4$], and 1.2 (t, 3, ester); ir (neat) spectrum gives no evidence for starting material.

Synthesis of 6-Hydroxymethyl-1,4-dioxaspiro[4.5]decane. To a solution of 0.01 mol of lithium aluminum hydride in 150 ml of dry tetrahydrofuran (THF) was added dropwise 0.0317 mol of the ester **25** over a 10-min period at room temperature. The mixture was then heated to reflux for 9 hr and then allowed to stir overnight at room temperature. Water was added (4 ml) and then 12 ml of a saturated solution of sodium potassium tartrate was added to the mixture and it was stirred for an additional 1 hr. The solids were filtered and washed with THF and the filtrate was concentrated in vacuo to a yellow oil which was distilled: 70%; bp 136–145° (19–20 mm); ir (neat) 3460 cm^{-1} (s) (OH) and the carbonyl region (1760–1620 cm^{-1}) was blank.

Synthesis of 1,4-Dioxaspiro[4.5]decane-6-carboxaldehyde (8). The general oxidation procedure of Ratcliffe and Rodehorst was followed.[29] To a solution of 0.157 mol of dry chromium trioxide and 0.316 mol of dry pyridine in 450 ml of methylene chloride was added 0.26 mol of the above alcohol in a small volume of methylene chloride with vigorous stirring. The solution was stirred for 45 min and then decanted from the black solids. The filtrate was concentrated in vacuo to dryness. Ether was added to the residue and the ether was then washed with dilute aqueous potassium hydroxide. The basic aqueous phase was extracted three times with ether and the combined ether layers were washed once with water and two times with brine. The ether extract was dried over magnesium sulfate and concentrated in vacuo to a pale yellow oil which was distilled: 79%; bp 123–133° (20 mm); ir (neat) 2780 (w) (OCH) and 1720 cm^{-1} (s) (O=CH).

Synthesis of 4,5,6,7-Tetrahydro-1,2-benzisoxazole (5) from 1,4-Dioxaspiro[4.5]decane-6-carboxaldehyde (8). To 20 ml of 1:1 aqueous ethanol was added 0.01 mol each of hydroxylamine hydrochloride and potassium carbonate, then 0.01 mol of the above aldehyde (**8**) and the solution was stirred for 6 hr. The solution was acidified with 1 *N* HCl and then heated on a steam bath for 1.5 hr. The solution was then cooled and extracted four times with ether, and the combined ether layers were washed once with a small amount of water and then brine. The ether extract was dried over magnesium sulfate and concentrated in vacuo (20 mm) at 50° to an oil. The oil was distilled and the fraction of bp 102–105° (20 mm) was retained, affording a 72% yield of **5**: NMR (neat) δ 8.05 (s, 1, aromatic H), 2.5 [m, 4, $(CH_2)_2$], and 1.7 [m, 4, $(CH_2)_2$]. The peaks obtained in this NMR spectrum have the same chemical shifts as those peaks assigned to the major component present in the previous synthesis where a mixture of isoxazoles (**5** and **6**) was obtained.

Synthesis of 3-Methyl-4,5,6,7-tetrahydro-1,2- and -2,1-benzisoxazoles from 2-Acetylcyclohexanone. To a solution of 10 ml of ethanol, 20 ml of water, and 0.0359 mol of hydroxylamine hydrochloride was added 0.0350 mol of 2-acetylcyclohexanone (Eastman). The reaction mixture was heated to reflux for 1.5 hr, cooled, and made basic with potassium carbonate. The basic mixture was extracted three times with ether and the combined ether layers were washed twice with brine, dried with magnesium sulfate, and concentrated in vacuo to an oil which was distilled: bp 90–96° (8 mm); NMR ($CDCl_3$) δ 2.7 [m, 4, $(CH_2)_2$], 2.3 (s, 3, CH_3) (**11**, major), 2.2 (s, 3, CH_3) (**10**, minor), and 1.75 [m, 4, $(CH_2)_2$]; TLC analysis (ether–cyclohexane, 1:1) showed only one spot which was bright yellow when sprayed with iodoplatinate;[30a] VPC (5% Carbowax, 6 ft at 135°) showed two peaks with appreciable overlap in the ratio of 1:4, the one with the shortest retention time being 25% of the mixture.

Synthesis of 6-Acetyl-1,4-dioxaspiro[4.5]decane. To 0.03 mol of 2-acetylcyclohexanone in 50 ml of benzene was added 0.03 mol of ethylene glycol and 0.1 g of *p*-toluenesulfonic acid monohydrate and the mixture was heated to reflux for 20 hr. At the end of this time about 75% of 1 equiv of water was collected in a Dean-Stark trap. The solution was cooled, made basic by addition of a cold aqueous potassium carbonate solution, and extracted with ether, and the combined ether layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to a yellow oil which was then distilled. The fraction boiling at 112–118° (9 mm) was collected: ir (neat) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.9 [s, 4, $(CH_2)_2$], 2.75 (t, 1, methine), 2.2 (s, 3, CH_3), and 1.7 [m, 8, $(CH_2)_4$]. Minor peaks were observed at δ 2.1, 1.35, and 1.4 which indicate that about 85–95% of the ketalization took place on the ring carbonyl. The major peaks in the NMR are in agreement with the published spectrum.[31] The oil was redistilled before use at 130–132° (15 mm) [lit.[31] 119–120° (7 mm)].

Synthesis of 3-Methyl-4,5,6,7-tetrahydro-1,2-benzisoxazole (10) from the Crude 6-Acetyl-1,4-dioxaspiro[4.5]decane. To 40 ml of a 3:1 aqueous ethanolic solution of 0.004 mol of hydroxylamine hydrochloride were added 0.01 mol of sodium acetate and 0.004 mol of the above crude 2-acetylcyclohexanone ethylene ketal and the solution was stirred overnight. This solution was acidified with dilute aqueous HCl and heated to reflux on the steam bath for 2.5 hr. The solution was cooled, poured into water, and extracted three times with ether. The combined ether layers were washed successively with brine, dilute potassium hydroxide, and brine, dried over $MgSO_4$, and concentrated in vacuo to an oil which was distilled: bp 101–102° (11 mm); ir (neat) exhibited no bands in the 1700-cm^{-1} region; NMR ($CDCl_3$) δ 2.65 [m, 4, $(CH_2)_2$], 2.2 (s, 3, CH_3), and 1.8 [m, 4, $(CH_2)_2$]. A peak was observed at δ 2.3 (s, CH_3) which was assigned to isomer **11**. Based on the peak height at δ 2.2 (vs. δ 2.3) isoxazole isomer **10** represents about 85% of the isomer mixture.

Synthesis of 1-Acetyl-2-chloro-1-cyclohexane. The desired product was not obtained when the procedure of Kochetkov was followed exactly.[32] The procedure was modified by increasing the amount of aluminum chloride (11 g) by a factor of 13, i.e., 3 mol each of aluminum chloride and acetyl chloride per mole of cyclohexanone, which resulted in a satisfactory yield of the product, bp 92–108° (9 mm). Redistillation gave a water-white oil, bp 91–96° (7 mm) [lit.[32] 125–129° (30 mm)].

Synthesis of 6-Acetyl-1,4-dioxaspiro[4.5]decane from the Vinyl Chloride (1-Acetyl-2-chloro-1-cyclohexene). The procedure of Kochetkov et al.[32] was followed. Distillation of the oil, bp 115–119° (9 mm) [lit.[32] 121–122° (10 mm)], afforded a satisfactory yield of the above ketal: ir (neat) 1720 cm^{-1} (s); NMR ($CDCl_3$) δ 3.9 [s, 4, $(CH_2)_2$], 2.8 (t, 1, methine), 2.2 (s, 3, CH_3), and 1.65 [m, 8, $(CH_2)_4$]. This product was used directly in the following experiment.

Synthesis of the Oxime of 6-Acetyl-1,4-dioxaspiro[4.5]dec-

ane. To 0.01 mol of 6-acetyl-1,4-dioxaspiro[4.5]decane was added a solution of 0.01 mol of hydroxylamine hydrochloride, 0.02 mol of sodium acetate, 30 ml of water, and 15 ml of ethanol. The reaction mixture was stirred at room temperature for 18 hr. The crystals were collected by filtration and washed with water and air dried. White crystals were obtained after one recrystallization from cyclohexane: mp 115–117°; ir (KBr) 3320 (s) (OH), 2980 (s), 1680 (w), 1440 (m), 1160 (s), 1080 (s), 955 (s) (NO), and 930 cm^{-1} (s); NMR ($CDCl_3$) δ 8.65 (s, 1, OH), 3.85 [s, 4, $(CH_2)_2$], 2.5 (m, 1, methine), 1.95 (s, 3, CH_3), and 1.65 [m, 8, $(CH_2)_4$].

Synthesis of 3-Methyl-4,5,6,7-tetrahydro-1,2-benzisoxazole (10) from the Oxime of 6-Acetyl-1,4-dioxaspiro[4.5]decane. To 1 g of the above oxime were added 10 ml of ethanol and 25 ml of 1 *N* HCl. The reaction mixture was heated on a steam bath for 5 hr, cooled, poured into 40 ml of 1 *N* NaOH, and extracted three times with ether. The combined ether layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to an oil which was then distilled: bp 98–100° (10 mm); ir (neat) spectrum was superimposable on the spectrum of the product obtained by the monoketalization of 2-acetycyclohexanone; NMR ($CDCl_3$) was consistent with pure **10** since the δ 2.2 singlet peak assigned to **11** was absent. Analysis by VPC (5% Carbowax, 6 ft column) showed only one peak which corresponded to the major component (**10**) in the previous synthesis. Uv max (ethanol–methanol, 4:1 v/v) 226 nm.

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08. Found: C, 70.13; H, 8.31.

Synthesis of 2-Methyl-4,5,6,7-tetrahydrobenzoxazole (21). To 9.5 g (0.0834 mol) of adipoin were added 8.1 g (0.0825 mol) of concentrated H_2SO_4 and recrystallized acetamide (from methanol–ether) and the reaction mixture was then stirred on a steam bath for 3 hr. The mixture was then heated at 150° for 0.5 hr. The solution was then cooled, poured into ice water, made basic with KOH, and extracted three times with ether, the combined ether layers were washed once with water and then with brine and dried over $MgSO_4$, and the solvent was distilled. Distillation of the oily residue afforded a water-white oil: bp 74–76° (10 mm); NMR ($CDCl_3$) δ 2.45 [m, 4, $(CH_2)_2$], 2.4 (s, 3, CH_3), and 1.8 [m, 4, $(CH_2)_2$]; ir (neat) 2850 (s), 1670 (m) (C=N), 1585 (s), 1270 (s), and 1215 cm^{-1} (s); uv max (4:1 ethanol–methanol, v/v) 225 nm.

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08. Found: C, 70.03; H, 8.26.

Irradiation of 4,5,6,7-Tetrahydro-1,2-benzisoxazole in Ethanol. A 10^{-2} *M* ethanol solution of **5** was degassed and irradiated in a quartz cell at 254 nm for 2 hr. Analysis by VPC (10% SE-30, 6-ft column), using a 10^{-2} *M* ethanolic solution of the oxazole isomer **15** as a reference standard, indicated a 99% yield of the 4,5,6,7-tetrahydrobenzoxazole.

Photochemical Synthesis of 3-Methyl-4,5,6,7-tetrahydrobenzoxazole (21) from Isoxazole 5. A 10^{-2} *M* ethanolic solution of 3-methyl-4,5,6,7-tetrahydro-1,2-benzisoxazole (**10**) was degassed and irradiated at 254 nm for 0.5 hr. Analysis by VPC (5% Carbowax, 6-ft column) at 145°, using a 10^{-2} *M* ethanolic solution of the oxazole isomer **21** as a standard, indicated a 63% yield of the desired oxazole **21**; TLC (ether) further confirmed that only two materials were present, namely, unreacted starting material (**10**) and the oxazole **21**.

Photochemical Synthesis of 3-Methyl-4,5,6,7-tetrahydrobenzoxazole from 10 in Methylcyclohexane. A 10^{-2} *M* solution of **10** in methylcyclohexane was degassed and irradiated at 254 nm for 30 min. TLC analysis (ether) showed the major product to be the oxazole **21**, some starting material, and large amounts of polar substances at the origin of the TLC plate.

Irradiation of 2-Oxocyclohexanecarbonitrile (16). A 10^{-3} *M* aqueous solution of the 2-cyanocyclohexanone **16** was degassed and irradiated in a quartz cell using 254-nm lamps for 1 hr. A 10-ml sample was then concentrated in vacuo to an oil and analyzed by TLC using both ethyl acetate and ether. In both cases a spot corresponding to the 4,5,6,7-tetrahydrobenzoxazole (**15**) was observed which gave the same color test with iodoplatinate[30a] and the same R_f value as an authentic sample. From the TLC analysis (benzene–methanol, 95:5) using a known amount of the authentic oxazole **15**, it was estimated that the oxazole **15** was produced photochemically in a 2% yield. Analysis by VPC (6-ft column of 10% SE-30 at 130° and 6-ft column of 5% Carbowax at 160°) also indicated about a 2% yield of the oxazole isomer.

Photolysis of 4,5,6,7-Tetrahydro-1,2-benzisoxazole at −77°. The isoxazole **5** was irradiated at 254 nm as a neat film at −77° for several hours. New peaks formed at 2210 (w), 1720 (w), and 1690 (m) and shoulder at 1655 cm^{-1}. On slowly warming to room temperature, the 1690- and 1655-cm^{-1} peaks diminished and a 2160-cm^{-1} peak formed, and the 1720-cm^{-1} peak intensified. After 3 hr of such warming the 2160-cm^{-1} peak was sharply diminished and the 1720-cm^{-1} peak moderately diminished. Ir peaks corresponding to the oxazole isomer **15** were observed at 1705 (w), 1665 (w), 1110 (w), 1070 (w), and 905 cm^{-1} (w). The peak at 2210 cm^{-1} did not change in intensity. Its position corresponds with that of the nitrile moiety in 2-oxocyclohexanecarbonitrile. Analysis of this irradiated sample by TLC (cyclohexane–ether, 2:1) showed starting material (**5**), the oxazole isomer (**15**), and 2-oxocyclohexanecarbonitrile (**16**).

Synthesis of 2-Formamidocyclohexanone (17). The formylation procedure of Sheehan and Yang[33] was followed. To 9.2 g (0.057 mol) of the 2-aminocyclohexanone hydrochloride in 30 ml of 97–100% formic acid under a nitrogen cover at 0–5° was added 5 ml of dry pyridine with stirring followed by the slow addition of 20 ml of acetic anhydride. At the end of the addition of the acetic anhydride the ice bath was allowed to melt and the stirring was continued overnight. Ethanol was added to the reaction mixture and the solution was concentrated in vacuo to an oil. Ice was added to the oil and the mixture was extracted three times with chloroform, dried, filtered, and concentrated in vacuo. Distillation afforded a water-white oil: bp 108–109° (0.4 mm); ir (neat) 3330 (s), 3070 (w), 2960 (s), 1740–1650 (s and br), and 1530 cm^{-1} (s).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85. Found: C, 59.58; H, 7.90.

Synthesis of 2-Acetamidocyclohexanone (24). To 500 mg (0.00309 mol) of 2-aminocyclohexanone hydrochloride were added 15 ml of acetic anhydride and 260 mg (0.00317 mol) of anhydrous sodium acetate and the mixture was stirred at room temperature overnight. Methanol was added to the solution and it was stirred for an additional 4 hr and then concentrated to a small volume in vacuo (20 mm) while keeping the temperature at 30–40°. Dilute aqueous potassium carbonate was added to the solution and it was extracted with ether three times. The combined ether phases were washed with brine once, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue obtained was recrystallized from cyclohexane to afford white crystals: mp 91–92° (lit.[34] 92°); ir (KBr) 3320 (s) (NH), 1715 (s) (ketone), 1650 (s) (amide), and 1550 cm^{-1} (m).

Synthesis of 4,5,6,7-Tetrahydrobenzoxazole (15) from 2-Isocyanocyclohexanone (14). The general procedure of isonitrile synthesis by Ugi[35] was followed. To 1.4 g (0.01 mol) of 2-formamidocyclohexanone (**17**) in 50 ml of methylene chloride and 10 ml of triethylamine was bubbled in phosgene for about 5 min while allowing the temperature to rise to about 35°. The mixture was cooled and then nitrogen was bubbled through the solution to remove the excess phosgene; then ammonia was bubbled through the solution for about 20 min. After chilling the solution the salts were collected by filtration and the filter cake was washed with methylene chloride. The filtrate was concentrated at less than 30° (20 mm) to a light brown oil. Analysis by uv (ethanol) showed a strong max at 268 nm, and ir (neat) showed isonitrile peaks at 2160 (s) (keto) and 2130 cm^{-1} (w) (enol) (the enol is probably due to the base present). Distillation of the crude isonitrile at 7 mm afforded only one fraction: bp 55–62°; ir (neat) spectrum was identical with that of a sample of oxazole **15** made by a known procedure;[36] TLC analysis in two different systems also afforded the same R_f values and color (yellow) as **15** when sprayed with iodoplatinate reagent; the sample had the same retention time as an authentic sample of **15** by VPC (6-ft column of 10% SE-30).

Photolysis of 3-Methyl-4,5,6,7-tetrahydro-1,2-benzisoxazole at −77°. The trisubstituted isoxazole **10** was irradiated at 254 nm as a neat film at −77°. After 1 hr new peaks formed at 2050 (m), 1695 (w), and 1590 cm^{-1} (w). On slowly warming to room temperature for 0.5 hr the 2050-cm^{-1} band had completely disappeared and two new bands emerged at 3400–3500 (broad) and 1620 cm^{-1} which were thermally stable but do not correspond to the ir spectrum of the oxazole **21**. Analysis by TLC (ether) showed largely starting material (**10**), a smaller amount of the oxazole isomer (**21**) (same R_f value and yellow color when treated with the iodoplatinate reagent), and some unknown material at the origin.

Irradiation of 4,5,6,7-Tetrahydro-1,2-benzisoxazole in Glacial Acetic Acid. A 10^{-2} *M* solution of isoxazole **5** in acetic acid was degassed and irradiated in a quartz cell at 254 nm for 1 hr. Quantitative analysis of the reaction mixture by TLC (ethyl acetate) using a 10^{-2} *M* acetic acid solution of 2-formamidocyclohexanone (**17**) as a reference standard, indicated a 50% yield of the formyl compound (**17**). A 50% yield of 2-oxocyclohexanecarbonitrile (**16**) was also estimated by TLC.

Irradiation of 4,5,6,7-Tetrahydrobenzoxazole in Glacial Acetic Acid. In a control experiment to determine if **17** was a hydrolysis product of the oxazole **15** a 10^{-2} *M* solution of the oxazole **15** was degassed and irradiated in a quartz cell at 254 nm for 1 hr. A 5% yield of the formyl derivative (**17**) was detected by TLC analysis (ethyl acetate) of the reaction mixture using a 10^{-2} *M* acetic acid solution of 2-formamidocyclohexanone as reference standard.

Irradiation of 3-Methyl-4,5,6,7-tetrahydro-1,2-benzisoxazole in Glacial Acetic Acid. A 10^{-2} *M* solution of the isoxazole **10** in glacial acetic acid was degassed and irradiated in a quartz cell at 254 nm for 0.5 hr. The solution was concentrated in vacuo at less than 40° to an oil. Analysis by TLC (ethyl acetate) using chloroform–iodine and DNP spray reagents[30b] indicated a small yield of *N*-acetyl-2-aminocyclohexanone (**24**); TLC on alumina (chloroform–pyridine, 2:1) also afforded a spot corresponding in color and R_f value to amide **24**. Analysis by VPC (10% SE-30, 6-ft column) at 210 and 230° showed some starting material, the oxazole isomer **21**, and about a 5% yield of amide **24**; VPC (5% Carbowax, 6-ft column) at 210° gave identical results, but there were seven other unidentifiable peaks. In a control experiment where oxazole **21** was irradiated more than 5% of **24** was formed.

Irradiation of 3-Methyl-4,5,6,7-tetrahydro-1,2-benzisoxazole in Water. A 10^{-2} *M* solution of the isoxazole **10** in water was degassed and irradiated in quartz at 254 nm for 30 min. TLC analysis (ether–methanol, 95:5; ether) of the reaction solution showed the presence of starting material, 2-methyl-4,5,6,7-tetrahydrobenzoxazole, and *N*-methyl-2-oxocyclohexanecarboxamide. Ether was added to the reaction solution which was then extracted with 10% NaOH. The combined aqueous layers were washed once with ether and then acidified with 6 *N* HCl. The acidic aqueous solution was then extracted four times with methylene chloride and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. TLC analysis (ether) showed only the presence of *N*-methyl-2-oxocyclohexanecarboxamide (**27**); a yield of 5% was ascertained based on the uv absorption of **27** after elution from the TLC plate.

Synthesis of *N*-Methyl-4,5,6,7-tetrahydro-2,1-benzisoxazolium Iodide. To 500 mg of 4,5,6,7-tetrahydro-2,1-benzisoxazole (**6**) was added 5 ml of methyl iodide. This mixture was heated in a sealed tube at about 95° for 27 hr. Pale yellow crystals were collected from the cooled reaction mixture which were recrystallized from ethanol–ether (1:1) and again from 2-propanol: mp 120–121°; NMR ($CDCl_3$) δ 9.1 (s, 1, aromatic H), 4.5 (s, 3, CH_3), 3.3 (t, 2, CH_2), 2.8 (t, 2, CH_2), and 2.0 [m, 4, $(CH_2)_2$].

Synthesis of *N*-Methyl-4,5,6,7-tetrahydro-1,2-benzisoxazolium Iodide (22). To 1 g of isoxazole **5** was added 5 ml of methyl iodide. This mixture was heated in a sealed tube at about 95° for 22 hr and was then concentrated in vacuo to an oil. The oil crystallized from ethanol–ether (1:1) affording pale yellow crystals: mp 135–136°; NMR ($CDCl_3$) δ 10.4 (s, 1, aromatic H), 4.65 (s, 3, CH_3), 2.8 [m, 4, $(CH_2)_2$], and 2.0 [m, 4, $(CH_2)_2$].

Synthesis of the Ketoketenimine 23 and Its Hydrolysis Product (27) from *N*-Methyl-4,5,6,7-tetrahydro-1,2-benzisoxazolium Iodide (22). A solution of 1 g of **22** in 3 ml of methylene chloride at −77° was poured into 10 ml of a triethylamine–methylene chloride (1:2) solution at −77°. The chilled reaction solution was next poured into 15 ml of cold (−77°) *n*-hexane and the crystals of triethylamine hydriodide were collected by filtration. The ir spectrum of the filtrate exhibited a strong absorption at 2050 cm^{-1} (COC=C=N) (lit.[8] 2062 cm^{-1}). To the cold filtrate was added 50 ml of 1 *N* HCl and the acidic solution was then extracted four times with methylene chloride. The combined organic layers were washed once with brine, dried ($MgSO_4$), and concentrated to an oil which crystallized upon chilling in an ice bath: mp 59–64° and after one recrystallization from benzene–*n*-hexane (1:1) mp 68–70° (lit.[8] 82–84°) mixture melting point; ir (KBr) was superimposable with the spectrum of the *N*-methyl-2-oxocyclohexanecarboxamide prepared by the hydrolysis of *N*-methyl-1,4-dioxaspiro[4.5]decane-6-carboxamide (**26**).

Synthesis of *N*-Methyl-1,4-dioxaspiro[4.5]decane-6-carboxamide (26). The general procedure of Petit and Poisson was followed.[37] Methylamine was bubbled through a suspension of 0.0003 mol of $LiAlH_4$ in 50 ml of ether at −10°. To the solution was added 0.0002 mol of ethyl 1,4-dioxaspiro[4.5]decane-6-carboxylate (**25**) in 10 ml of absolute ether. The solution was stirred for 17 hr at room temperature. To the reaction solution was then added 0.5 ml of water with 1 ml of ethanol and then 1.5 ml of a saturated solution of sodium potassium tartrate. The reaction mixture was stirred for 30 min and filtered, and the filtrate was concentrated in vacuo to a clear oil which crystallized upon cooling to room temperature. The solid residue was crystallized from ether and the crystals were then washed with ether–*n*-pentane (1:1) to afford a 56% yield of amide **26**: mp 105.5–106.5°; ir (KBr) 3330 (s), 3130 (w), 2960 (s), 1640 (s) (amide C=O), 1565 (s), 1400 (m), 1250 (m), 1160 (s), and 1090 cm^{-1} (s); NMR ($CDCl_3$) δ 6.4 (br s, 1, NH), 4.0 [s, 4, $(CH_2)_2$], 2.8 (d, 3, methyl), 2.5 (t, 1, methine), and 1.65 [m, 8, $(CH_2)_4$]. After treatment with D_2O for 24 hr the doublet at δ 2.8 collapsed into a singlet and the broad singlet at δ 6.4 completely disappeared.

Synthesis of *N*-Methyl-2-oxocyclohexanecarboxamide (27). To 600 mg of *N*-methyl-1,4-dioxaspiro[4.5]decane-6-carboxamide (**26**) was added 7 ml of 6 *N* HCl and the resulting solution was allowed to stand for 48 hr at room temperature. The reaction solution was extracted four times with methylene chloride and the combined layers were then washed once with brine. The organic phase was then extracted three times with 10% NaOH and the combined aqueous layers were washed once with methylene chloride. The basic solution was acidified with 6 *N* HCl and then extracted four times with methylene chloride. The combined organic layers were then washed once with brine and dried ($MgSO_4$). Evaporation of the solvent afforded an oil which crystallized. White crystals (63%) were collected after one crystallization from benzene–*n*-pentane (1:1), mp 63–65.5°. The melting point of these crystals changed after a few hours to 58–70° (lit.[8] 82–84°); further recrystallizations of **27** did not appreciably change the melting point; ir (KBr) 3450 (s), 2990 (s), 1655 (s), 1620 (s), 1550 (s), 1370 (s), 1310 (s), 1225 (m), and 1160 cm^{-1} (s). This ir spectrum was superimposable with an ir spectrum taken from a sample obtained from Professor Olofson[8] whose sample was synthesized by a different procedure; NMR ($CDCl_3$) δ 14.2 (s, 0.5, OH), 7.1 (br s, 0.5, NH), 5.5 (br s, 0.5, NH), 3.1 (t, 0.5, methine), 2.8 (dd, 3, methyl), and 1.9 [m, 8, $(CH_2)_4$]; uv max (water) 256 nm (ϵ 100) and in 0.1 *N* NaOH 284 nm (ϵ 10400).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.92; H, 8.44. Found: C, 62.10; H, 8.43.

Synthesis of the Ketoketenimine 29 and Its Dimer 30 from *N*-Methyl-5-methylisoxazolium Iodide. A mixture of 0.5 g of quaternary salt **28** in 3 ml of methylene chloride at −77° was poured into 10 ml of triethylamine–methylene chloride (1:2) at −77°. The reaction mixture was then poured into 15 ml of cold (−77°) *n*-hexane and the triethylamine hydriodide crystals were collected by filtration. The filtrate exhibited a strong absorption at 2075 cm^{-1} (COC=C=N) in the ir. The filtrate was then poured into 50 ml of vigorously stirred water. After several hours white crystals precipitated from the reaction mixture, which were filtered to afford a 40% yield of the dimer **30**. The dimer was recrystallized from ethyl acetate and was not soluble in 1 *N* HCl nor 1 *N* NaOH: mp 176–178°; uv max (EtOH) 233 nm (ϵ 31600) and 315.5 (16200); ir (KBr) 3230 (m), 2950 (w), 1640 (s), 1610 (s), 1580 (sh), 1525 (s), and 1310 cm^{-1} (m); NMR ($CDCl_3$) δ 10.7 (s, 1, NH), 5.6 (s, 1, vinyl H), 3.4 (s, 3, C=NCH_3), 2.85 (d, 3, $NHCH_3$), 2.6 (s, 3, $COCH_3$), and 2.3 (s, 3, vinyl CH_3); mass spectrum *m/e* (rel intensity) 194 (43), 193 (7), 180 (12), 179 (100), 177 (12), 123 (6), and 56 (20).

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26. Found: C, 61.66; H, 7.16.

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Registry No.—**5**, 5626-82-4; **6**, 2305-78-4; **7**, 1655-07-8; **8**, 57091-28-8; **9**, 874-23-7; **10**, 24010-93-3; **11**, 29146-79-0; **15**, 40814-50-4; **16**, 4513-77-3; **17**, 40814-51-5; **21**, 33793-98-5; **22**, 57091-29-9; **23**, 27439-90-3; **24**, 17578-82-4; **25**, 13747-72-3; **26**, 57091-30-2; **27**, 27439-91-4; **28**, 57091-31-3; **30**, 57091-32-4; 2-oxocyclohexanecarboxaldehyde, 1193-63-1; 6-hydroxymethyl-1,4-dioxaspiro[4.5]decane, 23153-80-2; 6-acetyl-1,4-dioxaspiro[4.5]decane, 16111-99-2; 1-acetyl-2-chloro-1-cyclohexene, 16111-92-5; 6-acetyl-1,4-dioxaspiro[4.5]decane oxime, 57091-33-5; adipoin, 533-60-8; 2-aminocyclohexane HCl, 6946-05-0.

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Photochemical Conversion of Enaminonitriles to Imidazoles. Scope and Mechanism[1]

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The scope of the photolysis of enaminonitriles has been extended to include the conversions of cyclic five-, six-, and seven-membered enaminonitriles to imidazoles and the photochemical synthesis of imidazole-4-carbonitrile. Ketenimine intermediates were detected by ir bands at 2000–2020 cm^{-1} when the photolyses were performed at −77 and −195°. It was determined that pyrazoles are neither reaction intermediates nor products in the photolysis of aliphatic enaminonitriles. Similar rates were observed for the photochemical loss of the enaminonitrile **13b** and for the corresponding formation of imidazole **14b**, a result consistent with a monophotonic process with no buildup of uv-absorbing intermediates. It was not possible to detect excited state species by fluorescence measurements; however, the restricted geometry of these cyclic compounds established that the excited state does not have a trans geometry prior to cyclization to the imidazole.

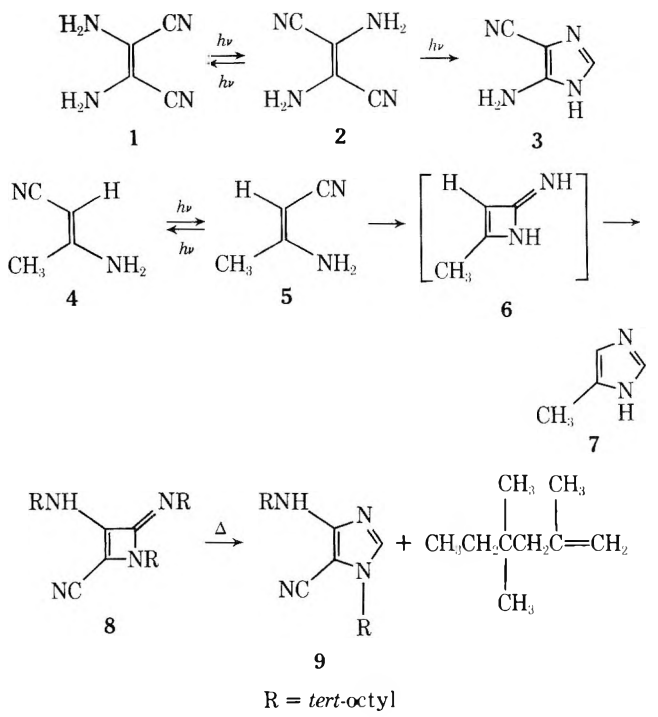
The photochemical conversion of the enaminonitrile diaminomaleonitrile (1) to 4-aminoimidazole-5-carbonitrile (3) is a key step in the proposed prebiotic formation of purines from HCN (Scheme I).[2] Previous studies established that the simpler enaminonitriles, β-aminoacrylonitrile and β-aminocrotononitrile (4), rearrange to imidazole and 4(5)-methylimidazole, respectively.[3,4] Since the trans isomer of β-aminocrotononitrile (5) must cyclize to 4(5)-methylimidazole (7), it was assumed that diaminofumaronitrile (2) is the photochemical precursor to 4-aminoimidazole-5-carbonitrile (3). This proposal was questioned by Becker, Kolc, and Rothman;[5] however, Koch and Rodehurst[6] have recently demonstrated that the excited diaminofumaronitrile (2) is the precursor to 3.

We proposed that an iminoazetine intermediate (e.g., 6, Scheme I) is formed photochemically and this rearranges to the corresponding imidazole in a thermal reaction.[4] The thermal conversion of iminoazetine 8 to imidazole 9 is consistent with this postulate.[7] Becker et al.[5] suggest that a stable intermediate is formed from 1 or 2 which is then photochemically converted to 3 (a two-photon process from 2). This possibility has been ruled out by the observation that the efficiency of the photoreaction is independent of light intensity.[6]

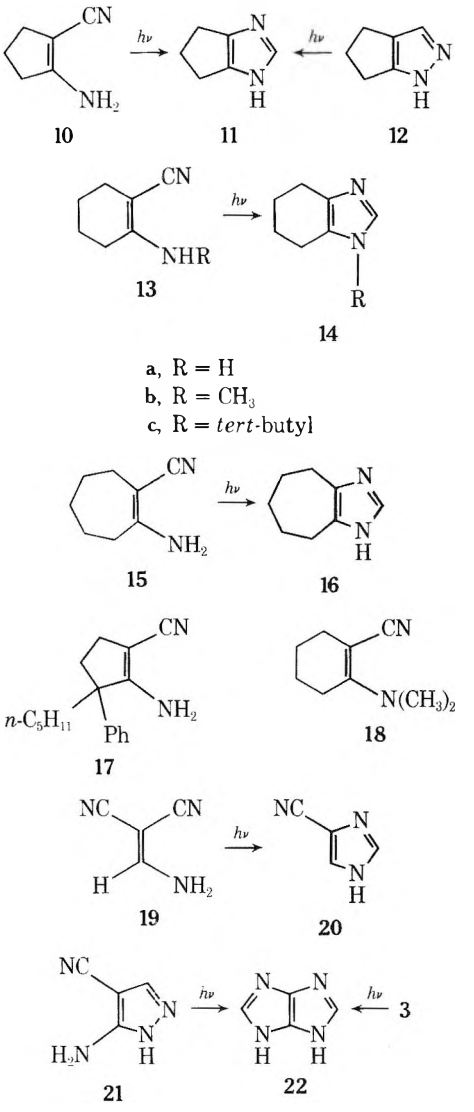
The present study was undertaken with the goal of providing further information concerning the scope and mechanism of this photochemical transformation.[8]

Scope. The photolysis of enaminonitriles provides a convenient and direct one-step synthesis of novel imidazoles (Scheme II). The cyclic enaminonitriles used as starting materials can be readily prepared by the base-catalyzed cyclization of the corresponding dinitriles. The N-substituted

Scheme I



Scheme II



enaminonitriles **13b**, **13c**, and **18** were prepared in high yield by the reaction of 2-oxocyclohexanecarbonitrile with the corresponding amine. Lower yields of imidazoles were observed when enaminonitrile concentrations greater than 10^{-2} *M* were used. Presumably this is due to the occurrence of bimolecular reactions in more concentrated solution. No imidazole products were detected on irradiation of the N,N-disubstituted enaminonitrile **18**.

The imidazole photoproducts were characterized by direct comparison with authentic samples prepared by other routes. The *N*-*tert*-butyl derivative **14c** was an exception since it was characterized by the close similarity of its uv spectrum and color tests with those observed for the *N*-methyl derivative **14b**. Imidazole-4-carbonitrile (**20**) had not been reported previously. A multistep chemical synthesis (Experimental Section) gave a product that was identical with the photoproduct of **19**. We were unable to effect the conversion of **19** to **20** previously[3] because we had not removed oxygen prior to photolysis.[4] It was not possible to prepare useful amounts of 2-aminocyclopentanone, an intermediate in the chemical synthesis of **11**, by the reported procedures.[9] Two alternative syntheses of 2-aminocyclopentanone were devised (Experimental Section) one of which gives a much higher yield than the published syntheses.[9] 1,6-Dihydroimidazo[4,5-*d*]imidazole (**22**) was prepared in the present work by the photochemical rearrangement of 3-aminopyrazole-4-carbonitrile (**21**). No chemical syntheses of **22** have been reported, but it was prepared previously by the photolysis of **3**.[2]

Mechanistic Studies. The enaminonitriles were photolyzed at −77 and −196° as liquid films[10] or in a KBr matrix[11] for 1 hr and their ir spectra were determined to detect reaction intermediates stable at low temperatures.[1,2] Compounds **10**, **13**, **15**, and **17** exhibited ir absorption at 2000–2020 cm^{-1} after irradiation characteristic of the ketenimine chromophore.[12] This absorption disappeared on warming. No ir absorption was detected in the 2000-cm^{-1} region when **18** was irradiated, demonstrating that at least one NH group is required for ketenimine formation. Two ketenimines (Scheme III, **23**, **26**) may be formed from a cyclic enaminonitrile. Ketenimine **26** was eliminated as a possibility because it would be impossible to form, without rearrangement, from the dialkyl-substituted enaminonitrile **17**.

The long-term (5 hr) photolyses of enaminonitriles **10** and **15** at −198° were investigated in an attempt to detect further intermediates. However, only one additional band was observed at 2260 cm^{-1} which did not disappear on warming. This absorption, characteristic of an aliphatic nitrile, was tentatively assigned to **24**, a compound which may be formed by the photolyses of **23**.

An attempt was made to trap the iminoketenimines (e.g., **23**) observed in low-temperature photolyses as amides by performing the photolysis in aqueous solution. In previous studies it was possible to trap the ketoketenimines formed by the photolyses of isoxazoles in this way.[1] However, photolyses of **13a** or **13b** in aqueous solution gave the imidazoles as the major photoproducts. It was not possible to detect any of the corresponding 2-oxocyclohexanecarboxamide either before or after acid hydrolysis of the reaction mixture (detection limit ~1% yield).

The absence of the formation of other definitive ir bands suggested that a pyrazole might be present, a structure which would not exhibit ir absorption above 1700 cm^{-1}. Previous experiments indicated that this intermediate was not likely;[4] however, the photochemical conversion of anthranilonitrile to indazole[2] suggested that this point should be reinvestigated. Photolyses of 3-methylpyrazole with

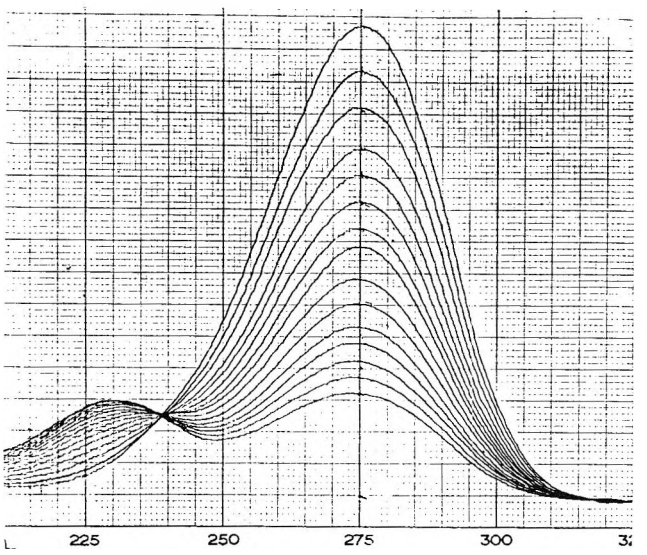


Figure 1. The photochemical conversion of enaminonitrile **13b** (uv max 276 nm) to imidazole **14b** (uv max 226 nm). Samples irradiated in a Rayonet reactor in degassed ethanol solution using lamps with principal emission at 300 nm. UV spectral measurements were made at 60-sec intervals.

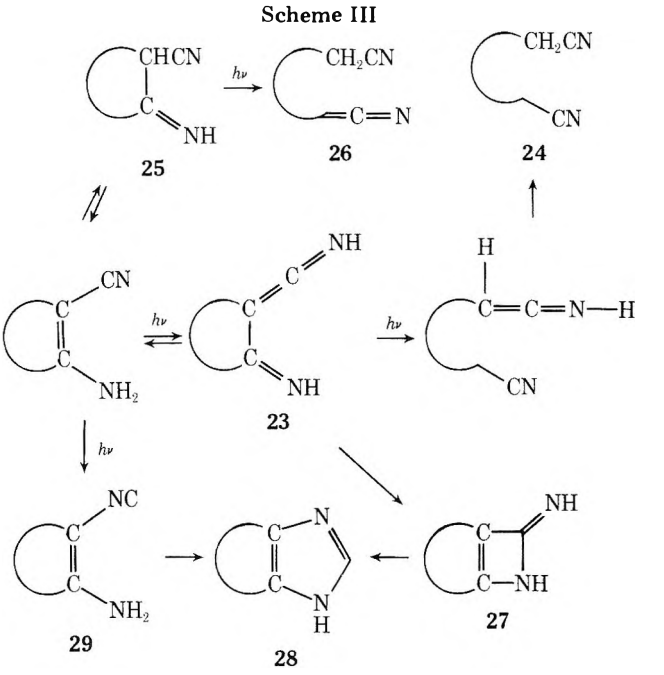
254- or 300-nm light sources resulted in the formation of both the 2-and 4(5)-methylimidazoles.[13] We found that this reaction is not sensitized by benzophenone.[13] Irradiation of β-aminocrotononitrile (**4**) under the same reaction conditions results in the formation of only 4(5)-methylimidazole.[4] In another experiment an attempt was made to detect pyrazole **12** on irradiation of **10**; however, it was not detected in the photolysis mixture. Finally, no new ir absorption bands could be detected in the 4000–1700-cm^{-1} region when pyrazole **12** or 3-methylpyrazole were irradiated at −77 or −195°. The differences observed in the photoproducts obtained from aliphatic enaminonitriles and the corresponding pyrazoles proves that pyrazoles are not formed nor are they intermediates in the photochemical rearrangement of aliphatic enaminonitriles to imidazoles.

The smooth conversion of enaminonitrile **13b** to imidazole **14b** was observed when the uv spectrum of the reaction mixture was monitored at 1-min intervals (Figure 1). The transformation proceeds without formation of a uv-absorbing intermediate as shown by the observation of a clean isosbestic point at 239 nm. In addition the rate of loss of **13b** paralleled the rate of formation of **14b.** The photochemical conversion of **13c** to **14c** proceeds in a similar fashion with an isosbestic point at 238 nm. These data are consistent with a monophotonic process with no buildup of uv-absorbing intermediates. The two or more photon process postulated by Becker et al.[5] would require the buildup of a uv-absorbing intermediate (no isosbestic point), more complex reaction kinetics, and a difference between the rate of the dissappearance of **13b** and the formation of **14b.** Our results require either the concerted formation of the imidazole from the enaminonitrile (no reaction intermediate) or the photochemical formation of a reaction intermediate which is rapidly converted to product and/or starting material by one or more thermal processes.

The photochemical formation of imidazoles from the cyclic enaminonitriles used in this study clearly demonstrates that the cis isomer is the precursor to the imidazole. It is not possible for these cyclic enaminonitriles to isomerize to the corresponding trans isomers. This would require that simple, noncyclic enaminonitriles such as diaminomaleonitrile (**1**) isomerize to the corresponding trans derivative **2** before rearranging to product **3**. This conclusion together with the monophotonic nature of the rearrangement is completely in accord with the conclusions drawn by Koch and Rodehurst[6] from their study of the photolysis of diaminonitrile (**1**).

The precise nature of the reaction intermediates (if any) formed on irradiation of enaminonitriles remains to be determined (Scheme III). The ketenimines (**23**) observed in

Scheme III



the low-temperature studies might thermally cyclize to azetines (**27**) which in turn thermally rearrange to the imidazoles (**28**).[4,7] The ketenimines do not appear to be likely precursors to azirines. Since it was not possible to detect the conversion of the ketenimines to product at low temperature, they may just revert back to the starting enaminonitrile. The observation of isonitrile intermediates on irradiation of isooxazoles[2] and the possible formation of the isonitrile on photolysis of 2-cyanophenol suggests the possibility of a direct conversion of the enaminonitrile to the corresponding isonitrile (**29**). Previous studies eliminated the possibility of tautomerization of the enaminonitrile to the β-iminonitrile (e.g., **25**), prior to the formation of the isonitrile;[4] however, the direct photochemical inversion of the nitrile to isonitrile **29** is a possibility. Finally, azirine intermediates must also be considered. The ir absorption of the 2-unsubstituted azirines in the 1650-cm^{-1} region[14] makes it difficult to detect these intermediates in low-temperature ir experiments.

Sensitization experiments have shown that the rearrangement proceeds from the singlet excited state, while cis–trans isomerization of the enaminonitrile proceeds via the triplet manifold.[4] Previous attempts to detect the excited state species formed from **1** or **4** were unsuccessful.[4] Presumably the absence of luminescence was due to a rapid vibrational relaxation of the excited state. It was anticipated that since the cyclic enaminonitriles possessed fewer degrees of freedom, it might be possible to detect emission from their singlet or triplet states. However, we could not detect luminescence from enaminonitriles **10** or **13a** or from imidazole **14a.**

Experimental Section[15]

Synthesis of 2-Methylamino-1-cyclohexene-1-carbonitrile (13b). To 1.23 g (0.01 mol) of 2-oxocyclohexanecarbonitrile[16] was added 0.25 ml of glacial acetic acid and 75 ml of benzene. Excess of methylamine was then bubbled through the solution and the reac-

tion mixture was then heated to reflux for 30 min and 0.01 mol of H_2O was collected in a Dean-Stark trap. The reaction solution was then concentrated in vacuo to a solid which was twice crystallized from cyclohexane to afford a 70% yield of white crystals: mp 66–67.5°; uv max (ethanol) 276 nm (ε 13200); ir (KBr) 3390 (m), 2190 (s, C≡N), and 1600 cm^{-1} (s, C=C); NMR ($CDCl_3$) δ 4.6 (s, 1, NH), 2.9 (d, 3, CH_3), 2.2 [m, 4, $(CH_2)_2$], and 1.65 [m, 4, $(CH_2)_4$]; the NH signal disappeared and the doublet collapsed to a singlet when D_2O was added.

Anal. Calcd for $C_8H_{12}N_2$: C, 70.54; H, 8.88. Found: C, 70.66; H, 8.90.

Synthesis of *N*-Methyl-4,5,6,7-tetrahydrobenzimidazole (14b). To 1.22 g (0.01 mol) of 4,5,6,7-tetrahydrobenzimidazole (**14a**) in 35 ml of benzene under nitrogen was added 0.0111 mol of NaH. To the vigorously stirred mixture was added 0.011 mol of methyl iodide and after 3 hr of stirring the reaction mixture was poured into 100 ml of ice water and the aqueous mixture was extracted three times with 50-ml portions of benzene. The combined organic layers were then washed once with 25 ml of water and then 25 ml of brine, dried over $MgSO_4$, and concentrated in vacuo to an oil. The oil was distilled to afford a 60% yield of product: bp 135–137° (10 mm) [lit.[17] 110–120° (4 mm)]; uv max (ethanol) 226 nm (ε 6100); NMR ($CDCl_3$) δ 7.3 (s, 1, aromatic H), 3.5 (s, 3, CH_3), 2.55 [m, 4, $(CH_2)_2$], and 1.9 [m, 4, $(CH_2)_2$]. The picrate had mp 219–220° (lit.[17] mp 219–220°).

Synthesis of 2-Dimethylamino-1-cyclohexene-1-carbonitrile (18). To 1.23 g (0.01 mol) of 2-oxocyclohexanecarbonitrile,[16] 0.25 ml of glacial acetic acid, and 20 ml of a 40% aqueous dimethylamine solution was added 50 ml of benzene. The reaction mixture was heated to reflux until no more water was collected in the Dean-Stark trap. The reaction solution was then concentrated in vacuo to an oil, 50 ml of 1 *N* NaOH was added, and the aqueous solution was then extracted three times with 50-ml portions of benzene. The combined organic layers were washed with 50 ml of brine, dried over $MgSO_4$, and concentrated in vacuo to an oil which was distilled to afford a 79% yield of **18**: bp 143–144° (10 mm); uv max (ethanol) 285 nm (ε 13800); ir (neat) 2960 (s), 2190 (s) (C≡N), 1585 (s) (C=C), 1385 (m), and 1115 cm^{-1} (m); NMR ($CDCl_3$) δ 3.05 (s, 6, CH_3), 2.25 [m, 4, $(CH_2)_2$], and 1.65 [m, 4, $(CH_2)_2$].

Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39. Found: C, 71.52; H, 9.24.

Synthesis of 2-*tert*-Butylamino-1-cyclohexene-1-carbonitrile (13c). To 1.23 g (0.01 mol) of 2-oxocyclohexanecarbonitrile[16] and 0.25 ml of glacial acetic acid was added 5 ml of *tert*-butylamine (freshly distilled from NaOH). The reaction mixture was sealed in an ampule and heated at 100° for 48 hr. The cooled reaction mixture was poured into 25 ml of 1*N* NaOH and extracted three times with 30-ml portions of benzene, and the combined organic layers were washed twice with water and once with brine, dried over $MgSO_4$, and then concentrated in vacuo to an oil. The oil was distilled to afford a 73% yield of product: bp 133–134° (9 mm); uv max (ethanol) 278 nm (ε 16200); ir (neat) 3430 (w), 2970 (s), 2195 (s) (C≡N), 1605 (s), 1385 (s), and 1230 cm^{-1} (s); NMR ($CDCl_3$) δ 4.65 (s, 1, NH), 2.4 [m, 4, $(CH_2)_2$], 1.6 [m, 4, $(CH_2)_2$], and 1.3 [s, 9, $(CH_3)_3$].

Anal. Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18. Found: C, 74.36; H, 10.25.

Irradiation of 2-Amino-1-cyclopentene-1-carbonitrile. A 250-ml solution of the enaminonitrile 10[18] (10^{-4} *M*, THF) was irradiated at 254 nm for 30 hr. Analysis by TLC (isopropylamine–methanol–benzene, 3:7:90) showed starting material and a substance which gave an R_f and DSA color corresponding to **11**. A 90% yield (based on recovered starting material) was obtained after column chromatography (isopropylamine–methanol–benzene, 1:2:97) on silica gel. The product was recrystallized from water–ethanol (95:5): mp 145.5–147° (lit.[9a] 150–151°); uv max (ethanol) 224 nm; ir (KBr) 2500–3100 (s and br), 1800 (w and br), 1600 (w), 1580 (m), 1420 (s), 1350 (w), 1270 (m), 1220 (s), 1210 sh (m), 1160 (m), 1070 (w), 980 (s), 920–930 (m and br), 785 (s), 715 cm^{-1} (m); NMR ($CDCl_3$) δ 2.6 (m, 6 H, methylene H's), 7.5 (s, 1, aromatic H), and 10.2 (s, 1, NH); mass spectrum *m/e* (rel intensity) 108 (89) (molecular ion), 107 (100), 81 (16), 80 (37), 54 (16), and 53 (24). The picrate was recrystallized from 2-propanol, mp 175–177° (lit.[19] 180–181°).

Irradiation of 2-Amino-1-cyclohexane-1-carbonitrile. A 250-ml solution (10^{-2} *M*, THF) of **13a**[19] was irradiated at 254 nm for 24 hr. Column chromatography (isopropylamine–methanol–benzene, 1:3:96) afforded an 81% yield of 4,5,6,7-tetrahydrobenzimidazole (**14a**). White crystals were obtained after one recrystallization from benzene–ether: mp 146–148° (lit.[17,20] 149–150°); ir (KBr) 3170–2630 (br and s), 1800 (br and w), 1615 (s), 1495 (m), 1490 (s), 1440 (s), 1295 (s), and 955 cm^{-1} (s); NMR ($CDCl_3$) δ 10.0 (s, 1, NH), 7.5 (s, 1, aromatic H), 2.55 [m, 4, $(CH_2)_2$], and 1.9 [m, 4, $(CH_2)_2$]. The picrate was also prepared, mp 191–192° (lit.[21] 189–190°).

Irradiation of 2-Methylamino-1-cyclohexene-1-carbonitrile. A 10^{-3} *M* solution of **13b** in ethanol was degassed and irradiated at 254 nm for 45 min. The product (**14b**) was identified by its uv max at 226 nm and by TLC in three solvent systems (benzene–ethanol–isopropylamine, 92:6:2, and ether–ethanol, 95:5, and ether). The R_f values and color reactions with DSA (orange) and iodoplatinate (yellow) were identical with an authentic sample. A 49% yield of the imidazole **14b** was determined from the extinction coefficient at 226 nm.

Irradiation of 2-Dimethylamino-1-cyclohexene-1-carbonitrile. A 10^{-4} *M* solution of **18** in ethanol was degassed and irradiated at 254 nm for 1 hr. No new peaks were observed in the uv spectrum and the intensity of the uv max of the enaminonitrile **18** diminished by about 50%.

Irradiation of 2-*tert*-Butylamino-1-cyclohexene-1-carbonitrile. 1. A 10^{-2} *M* solution of **13c** in ethanol was degassed and irradiated at 254 nm for 9 hr. The reaction solution was then concentrated in vacuo to an oil. TLC analysis (ether–methanol, 95:5; benzene–methanol–isopropylamine, 92:5:3) of the oil showed that a new product had formed which gave positive DSA (intense orange) and iodoplatinate (yellow) tests indicative of an imidazole formation. 2. A 10^{-4} *M* solution of **13c** in ethanol was degassed and irradiated at 254 nm at six 30-sec intervals. An isosbestic point at 237.5 nm and a new peak at 227 nm were observed. These data, in comparison with the data obtained from the photosynthesis of *N*-methyl-4,5,6,7-tetrahydrobenzimidazole (**14b**) from **13b**, provide a strong support for the *N*-*tert*-butyl-4,5,6,7-tetrahydrobenzimidazole (**14c**) as the photoproduct.

Irradiation of 2-Amino-1-cycloheptene-1-carbonitrile. A 10^{-2} *M* solution of 2-amino-1-cycloheptene-1-carbonitrile (**15**)[22] was prepared in 250 ml of freshly distilled THF. The solution was purged with nitrogen for 25 min and irradiated at 254 nm for 48 hr in a stoppered quartz tube. The solution was concentrated in vacuo to an oil which was chromatographed on 40 g of silica gel and eluted with a solution of isopropylamine–methanol–benzene (1:2:97). A 56% yield of pentamethyleneimidazole (**16**) was achieved based on isolated imidazole. White crystals were obtained on crystallization from benzene after prior treatment with decolorizing charcoal: mp 197–199° (lit.[23] 199°); uv max (methanol) 219 nm (ε 9500); ir (KBr) 2640–3140 (br and s), 1880 (br and s), 1600 (m), 1470 (s), 1440 (s), 1240 (s), 1080 (m), 965 (s), 814 (m), and 796 cm^{-1} (m); mass spectrum *m/e* (rel intensity) 136 (100 (molecular ion), 135 (45), 108 (32), 107 (86), 81 (34), 80 (21), 54 (18), and 53 (23).

Irradiation of Aminomethylenemalononitrile (19). A 10^{-3} *M* acetonitrile (purified) solution of compound **19**[24] [uv max (CH_3CN) 266 nm (ε 17100) and 346 nm (ε 750)] was degassed and irradiated in a quartz cell at 254 nm for 40 hr. Analysis of the product by TLC (ethyl acetate–methanol–isopropylamine, 90:7:3) showed a small amount of starting material (**19**) at the top of the plate (uv visible), the expected 4-cyanoimidazole (**20**) (DSA, dark red) at the center, and some unknown material at the origin. When the irradiation was conducted in water, methanol, dioxane, or unpurified acetonitrile no DSA positive spot was detected.

Synthesis of Imidazole-4-carboxaldehyde Oxime. The procedure of Hubball and Pyman[25] gave a 53% yield of the oxime: mp 181–184° (lit.[25] 183–184°); uv max (ethanol) 247.5 nm (lit.[26] 248 nm); ir (KBr) 2700–3350 (br and s), 1670 (s) (C=N), 1530 (s), 1450 (s), 1220 (s), 1110 (s), 1000 (s), 960 (s), 925 (s), and 825 cm^{-1} (br and s); NMR (acetone-d_6) δ 7.7 (s, 1, aromatic H) and 7.4 (s, 1, aromatic H).

Synthesis of Imidazole-4-carbonitrile (20). To 50 mg of imidazole-4-carboxaldehyde oxime was added 3 ml of acetic anhydride and the mixture was heated at reflux for 2 hr. To the reaction mixture was added 10 ml of cold aqueous 6 *N* HCl and the mixture was washed with ether. The aqueous solution was made basic with excess potassium carbonate, extracted with methylene chloride, and concentrated in vacuo to a small amount of a solid: ir (KBr) 3120 (br and s), 2235 (s) (C≡N), 1665 (m), 1550 (m), and 1400 cm^{-1} (s); NMR (acetone-d_6) 8.0 (s, 1, aromatic H) and 7.9 (s, 1, aromatic H); uv max (ethanol) 237 nm. When this solid was compared to the product obtained by photolysis of **19**, by TLC (ethyl acetate–methanol–isopropylamine, 90:7:3, and chloroform), both were found to have identical R_f values and reaction with DSA

(dark red). The tosylate salt of **20** was recrystallized from 2-propanol: mp 174–175°; ir (KBr) 2245 cm^{-1} (s).

Anal. Calcd for $C_4H_3N_3 \cdot C_7H_8SO_3$: C, 49.80; H, 4.18. Found: C, 49.72; H, 4.15.

Synthesis of 6-Amino-1,4-dioxaspiro[4.4]nonane. To 0.01 mol of 6-phthalimido-1,4-dioxaspiro[4.4]nonane[9a] in 50 ml of ethanol was added 0.01 mol aqueous 64% hydrazine and the stoppered solution was allowed to stand at room temperature overnight. The solution was concentrated at less than 50° (20 mm) to dryness, 50 ml of benzene was added, and the reaction mixture was then dried over magnesium sulfate and concentrated in vacuo to a pale yellow oil: bp 25–26° (0.3 mm) (a water-white oil) (76%); ir (neat) 3430 (m) (NH_2), 2960 (s), 2900 sh (s), 1600 (s and broad), 1470 (m), 1315 (s), 1205 (s), 1125 (s), 1035 (s), and 945 cm^{-1} (s).

Synthesis of 2-Aminocyclopentanone. A. Acid Hydrolysis of 6-Amino-1,4-dioxaspiro[4.4]nonane. To 186 mg of the ketal was added 5 ml of 1 *N* hydrochloric acid and the mixture was heated in a sealed ampule at 50° for 12 hr. The solution was cooled, filtered, and concentrated in vacuo to an oil. The oil was dissolved in a small amount of 2-propanol and triturated with ether to yield 74 mg (40%) of white crystals: mp 139–141° (lit.[9b] 146–147°); ir (KBr) identical with the published spectrum of 2-aminocyclopentanone hydrochloride.[9b] No attempts were made to optimize the yield.

B. Reaction of Cyclopentanone Oxime *p*-Toluenesulfonate with Sodium Alkoxide. To 60.5 g (0.239 mol) of cyclopentanone oxime *p*-toluenesulfonate[9a] in 100 ml of absolute ethanol at 0° was added a solution of 25.8 g (0.578 mol) of sodium methoxide in 200 ml of absolute ethanol over a period of 1 hr. The reaction mixture was kept under a nitrogen atmosphere at 0° for another 1 hr and then the temperature was allowed to rise to room temperature. Stirring was continued for 2 days. The white solids formed were collected by filtration and washed with absolute alcohol. The filtrate was poured into 300 ml of ice-cold 2 *N* HCl and extracted with 600 ml of ether and the ether extract was then washed with 300 ml of 2 *N* HCl. The combined acidic aqueous ethanolic solutions were treated with Norit and filtered. The filtrate was concentrated in vacuo to a semisolid which was dissolved in 2-propanol (hot), the insolubles were filtered, and white crystals were obtained from the filtrate on cooling: mp 145–146° (lit.[9b] 146–147°); 61%; ir (KBr) identical with the published spectrum.[9b]

Isolation of 1,6-Dihydroimidazo[4,5-*d*]imidazole from the Irradiation of 3-Aminopyrazole-4-carbonitrile. A 250-ml solution of 10^{-2} *M* pyrazole **21** in dioxane was degassed and irradiated at 254 nm for 77 hr. The solution was concentrated in vacuo to a solid and the residue was chromatographed on 50 g of silica gel (benzene–methanol, 95:5). The fractions which gave a blue color with DSA were combined and concentrated in vacuo to a solid. The product exhibited uv and ir spectra identical with those of an authentic sample of **3**.[2]

Irradiation of 2-Methylamino-1-cyclohexene-1-carbonitrile in Aqueous Ethanol. A 10^{-2} *M* solution of the enaminonitrile **13b** in aqueous ethanol (4:1) was degassed and irradiated in quartz at 254 nm for 17 hr. TLC analysis (ether–methanol, 95:5) showed the major product to be *N*-methyl-4,5,6,7-tetrahydrobenzimidazole (**14b**) together with smaller amounts of starting material plus some additional unknown products. The reaction mixture (10 ml) was then hydrolyzed with 5 ml of 6 *N* HCl at room temperature for 24 hr. (These reactions conditions were found in control experiments to hydrolyze the enaminonitrile to 2-oxocyclohexanecarbonitrile but they did not hydrolyze the amide moiety of *N*-methyl-2-oxocyclohexanecarboxamide.) The acidic solution was then extracted four times with methylene chloride, and the methylene chloride extract was washed once with water, dried over $MgSO_4$, and concentrated in vacuo to an oil. TLC analysis (ether–methanol, 95:5) did not reveal even a 1% yield of the desired 2-oxocyclohexanecarboxamide by uv absorption or characteristic purple color with $FeCl_3$.

Irradiation of 2-Amino-1-cyclohexene-1-carbonitrile in Aqueous Ethanol. A 10^{-2} *M* solution of the enaminonitrile **13a** in aqueous ethanol (4:1) was degassed and irradiated in quartz at 254 nm for 9.5 hr. TLC analysis (benzene–methanol–isopropylamine, 92:6:2) showed the major product to be the imidazole **14a** and the minor products to be starting material plus three other unknown compounds. 2-Oxocyclohexanecarboxamide was not detected when an aliquot of the reaction mixture was subjected to acid hydrolysis as described above.

Synthesis of 1,4-Dioxaspiro[4.5]decane-6-carboxamide from Ethyl 1,4-Dioxaspiro[4.5]decane-6-carboxylate.[1] The general procedure of Petit and Poisson was followed.[27] White crystals were obtained which crystallized from *n*-pentane–benzene (1:1): mp 138–140°; ir (KBr) 3380 and 3180 (m) (NH), 2940 (m), 1650 (m) (C=O), 1435 (m), 1155 (m), 1080 (s), and 1030 cm^{-1} (m); NMR ($CDCl_3$) δ 6.7–5.6 (br s, 2, NH_2), 4.0 [s, 4, $(CH_2)_2$], 2.55 (m, 1, methine), and 1.65 [m, 8, $(CH_2)_4$].

Synthesis of 2-Oxocyclohexanecarboxamide. To 170 mg of 1,4-dioxaspiro[4.5]decane-6-carboxamide was added 6 ml of 6 *N* HCl and the mixture was stirred at room temperature for 20 hr. The reaction solution was then extracted four times with 20-ml portions of methylene chloride and the combined organic layers were washed with 25 ml of brine, dried over $MgSO_4$, and concentrated in vacuo to a white residue. The residue was crystallized from 2-propanol: mp 130–132° (lit.[28,29] 131–132°); ir (KBr) 3430 (s), 3330 (w), 3190 (m), 2940 (m), 2840 (m), 1650 (s), 1635 (s), 1585 (m), 1450 (m), 1335 (m), 1225 (m), and 1135 cm^{-1} (m).

Kinetics of the Photoisomerization of 2-Methylamino-1-cyclohexene-1-carbonitrile (13b). Degassed 10^{-4} *M* solutions of **13b** were irradiated at 300 nm in ethanol for 60- or 120- sec time periods and the concentrations of reactant and product (**14b**) were monitored by their uv absorption at 276 and 215 nm, respectively. The absorption of **14b** was not followed at its maximum at 226 nm because of overlapping absorption with **13b**. A 300-nm light source was used in place of the usual 254-nm source to avoid photodecomposition of the imidazole product. The rate of loss of **13b** and formation of **14b** agreed within 15%. An isosbestic point was observed at 239 nm.

Photolysis at Low Temperatures. Photolysis of 2-Amino-1-cyclopentene-1-carbonitrile. Irradiation of the title compound in KBr pellet or Nujol mull using a Rayonet reactor equipped with a 254-nm light source for 1 hr at −195° resulted in the formation of an ir band at 2000 cm^{-1} which disappeared on warming. Irradiation at −77° resulted only in the development of weak bands at 2260, 1080, 820, and 765 cm^{-1}. These bands are not found in the ir spectrum of the imidazole **11** although a small amount of this product was detected by TLC after irradiation at −77°.

Photolysis of 2-Amino-3-n-pentyl-3-phenyl-1-cyclopentene-1-carbonitrile (17). Irradiation of **17** as a neat film at 254 nm at −196° for 1 hr resulted in the formation of a new peak at 2020 cm^{-1} which disappeared on warming.

Photolysis of 2-Amino-1-cyclohexene-1-carbonitrile (13a). Irradiation of **13a** in KBr with a 254-nm light source at −195° for 1 hr resulted in the formation of a new band at 2000 cm^{-1}. The absorption disappeared on warming to room temperature.

Photolysis of 2-Methylamino-1-cyclohexene-1-carbonitrile (13b). Irradiation of **13b** in KBr with a 254-nm light source for 1 hr at −195° resulted in the formation of a new band at 2010 cm^{-1}. This absorption disappeared on warming to room temperature.

Photolysis of 2-Dimethylamino-1-cyclohexene-1-carbonitrile (18). No change was observed in the ir spectrum when a neat film of **18** was irradiated with a 254-nm light source for 1 hr.

Photolysis of 2-*tert*-Butylamino-1-cyclohexene-1-carbonitrile (13c). A new band was observed in the ir at 2015 cm^{-1} when a neat film of **13c** was irradiated at −195° for 1 hr with a 254-nm light source. The absorption disappeared when the sample was warmed to room temperature.

Photolysis of 2-Amino-1-cycloheptene-1-carbonitrile (15). A new ir band was observed at 2000 cm^{-1} when a KBr pellet of **15** was irradiated at −195 or −77° for 1 hr. An additional band formed at 2260 cm^{-1} after irradiation for 3 hr. The 2000-cm^{-1} band disappeared on warming while the band at 3260 cm^{-1} was stable to heat. No peaks corresponding to imidazole **16** were observed when the pellet was warmed to room temperature, although a small amount was detected by TLC.

Photolysis of 3-Methylpyrazole. No change in the ir spectrum was observed when a melt of 3-methylpyrazole was irradiated at 254 nm at −196° and −77° for 2 hr.

Photolysis of 1,4,5,6-Tetrahydrocyclopentapyrazole (12). No change in the ir was observed when a KBr pellet of the pyrazole **12** was irradiated at −77° at 254 nm for 5 hr.

Acknowledgment. This investigation was supported by Public Health Service Research Grant CA-14511 from the National Cancer Institute and a Career Development Award G. M. 6380 (to J.P.F.) from the National Institutes of Health.

Registry No.—**10**, 2941-23-3; **11**, 10442-94-1; **12**, 15409-55-9; **13a**, 15595-71-8; **13b**, 57090-85-4; **13c**, 57090-86-5; **14a**, 3752-24-7; **14b**, 1837-49-6; **15**, 14798-99-3; **16**, 10493-90-0; **17**, 15324-06-8; **18**, 57090-87-6; **19**, 672-25-3; **20**, 57090-88-7; **20** tosylate, 57090-89-8;

21, 16617-46-2; 2-oxocyclohexanecarbonitrile, 4513-77-3; imidazole-4-carboxaldehyde oxime, 57090-90-1; 6-amino-1,4-dioxaspiro[4.4]nonane, 57090-91-2; 6-phthalimido-1,4-dioxaspiro[4.4]nonane, 10442-96-3; cyclopentanone oxime *p*-toluenesulfonate, 10442-97-4; 1,4-dioxaspiro[4.5]decane-6-carboxamide, 57090-92-3; ethyl 1,4-dioxaspiro[4.5]decane-6-carboxylate, 13747-72-3; 2-oxocyclohexanecarboxamide, 22945-27-3; 3-methylpyrazole, 1453-58-3.

References and Notes

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Thallium in Organic Synthesis. XLI. Synthesis of 1-Substituted 2(1*H*)-Pyridones. A New Synthesis of Unsymmetrical Biphenyls via Photochemical N–O Bond Cleavage of 1-Aroyloxy-2(1*H*)-pyridones[1,2]

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Reaction of the thallium(I) salt of 1-hydroxy-2(1*H*)-pyridone with alkyl iodides, arylsulfonyl chlorides, and aroyl chlorides gave a series of 1-alkoxy-, 1-arylsulfonyloxy-, and 1-aroyloxy-2(1*H*)-pyridones. A similar series was prepared from the thallium(I) salt of 1-hydroxy-3,5-dinitro-2(1*H*)-pyridone. Irradiation of the 1-aroyloxy-3,5-dinitro-2(1*H*)-pyridones in benzene gave unsymmetrical biphenyls in moderate yield. It is suggested that these stable, crystalline pyridone derivatives may be generally useful as sources of aryl radicals.

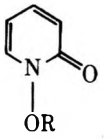
We have recently described a convenient, high-yield synthesis of 1-acyloxy-2(1*H*)-pyridones by reaction of the thallium(I) salt of 1-hydroxy-2(1*H*)-pyridone (1) with acyl halides in ether suspension.[4] Intrigued by the utility of these active esters for peptide synthesis,[4–6] we have examined the preparation and reactivity of a number of other 1-substituted 2(1*H*)-pyridones which were similarly prepared.

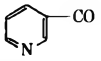
Although 1 was unreactive toward alkyl halides at room temperature in ether suspension, reaction was quantitative when 1 was heated under reflux with an excess of the alkyl halide.[7] Lower boiling halides and secondary halides needed longer reaction times, and not surprisingly, iodobenzene proved unreactive. 1-Phenoxy-2(1*H*)-pyridone was, however, readily prepared in 90% yield by stirring 1 with 1 equiv of diphenyliodonium chloride in *tert*-butyl alcohol for 16 hr at 30°.

1-Aroyloxy-2(1*H*)-pyridones were similarly prepared from 1 and the appropriate aroyl halide at room temperature in ethyl acetate suspension. The various 1-alkoxy- and 1-aroyloxy-2(1*H*)-pyridones prepared in this study, along with pertinent physical data and yields, are summarized in Table I.

An analogous series of 1-alkoxy and 1-aroyloxy derivatives was prepared from the thallium(I) salt of 1-hydroxy-3,5-dinitro-2(1*H*)-pyridone (2). As expected, 2 was weakly nucleophilic and proved to be relatively sluggish in its reac-

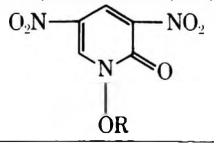
Table I
1-Substituted 2(1*H*)-Pyridones[a]

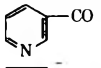
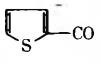


Registry no.	R	Reaction time, hr	Temp, °C	Ir carbonyl, cm^{-1} Pyridone	Ester	% yield	Mp or bp, °C (mm)
40775-55-1	CH_3	18	42	1665		98.5	87–90 (0.04)
56960-56-6	$CH_3CH_2CH_2$	3	101	1665		99.5	105–108 (0.08)
32846-47-2	$(CH_3)_2CH$	18	89	1665		97	90–94 (0.1)
4377-30-4	$CH_2{=}CHCH_2$	1	102	1670		99	*d*
5279-98-1	$CH_3CH_2CH_2CH_2$	1	130	1665		98	*d*
56960-57-7	CH_2CH_2Br	4	131	1670		93[b,e]	
56960-58-8	C_6H_5[c]			1660			
886-27-1	C_6H_5CO	1	20	1670	1780	86	139–141 (ref 6)
56960-59-9	*o*-ClC_6H_4CO	3	20	1660	1785	86	100–101
5037-55-8	*m*-BrC_6H_4CO	1	20	1670	1790	88	138–140 (ref 6)
5037-58-1	*m*-$NO_2C_6H_4CO$	1	20	1680	1790	93	136–138 (ref 6)
5037-59-2	*p*-$NO_2C_6H_4CO$	1	20	1670	1785	90	156–157 (ref 6)
56960-60-2	*m*-$CH_3C_6H_4CO$	1	20	1660	1770	78	94–95
5033-24-9	*p*-$CH_3OC_6H_4CO$	2	20	1660	1770	82	116–118 (ref 6)
56960-61-3		1	20	1660	1785	91	110–112

[a] Satisfactory microanalytical data for all new compounds listed in the table (except as noted) were submitted for review. [b] This compound decomposed upon distillation. [c] See Experimental Section. [d] L. A. Paquette, *Tetrahedron*, 22, 25 (1966). [e] Anal. Calcd for $C_7H_6BrNO_2$: C, 38.60; H, 3.67; N, 6.43. Found: C, 41.40; H, 4.31; N, 6.99.

Table II
1-Substituted 3,5-Dinitro-2(1*H*)-pyridones[a]



Registry no.	R	Reaction time, hr	Temp, °C	Ir carbonyl, cm^{-1} Pyridone	Ester	% yield	Mp, °C
56960-62-4	CH_3			1720		57	146–147
56960-63-5	CH_3CH_2	7 days	72	1720		96	123–124
56960-64-6	$CH_3CH_2CH_2$	3 days	101	1720		90	85–86
56960-65-7	$CH_3CH_2CH_2CH_2$	2 days	130	1715		82	92–93
56960-66-8	CH_3CO	3	20	1740	1820	95	148–150
56960-67-9	C_6H_5CO	1	20	1725	1775	89	148–149
56960-68-0	*o*-ClC_6H_4CO	3	20	1735	1810	85	170–171
56960-69-1	*m*-BrC_6H_4CO	3	20	1730	1785	89	167–168
56960-70-4	*m*-$NO_2C_6H_4CO$	2.5	20	1730	1795	64	171–172
56960-71-5	*p*-$NO_2C_6H_4CO$	1	20	1730	1800	51	190–191
56950-72-6	*m*-$CH_3C_6H_4CO$	3	20	1725	1795	86	173–174
56960-73-7	*p*-$CH_3OC_6H_4CO$	3	20	1725	1780	84	192–193
56960-74-8		3	20	1725	1790	76	171–172
56960-75-9		3	20	1725	1785	69	146–147

[a] Satisfactory microanalytical data for all new compounds reported in the table were submitted for review.

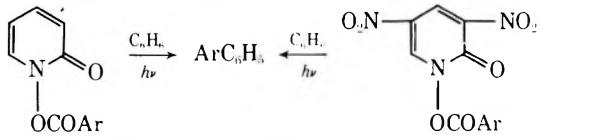
tions. For example, 1 reacted with benzenesulfonyl chloride within 1 hr to give 1-benzenesulfonyloxy-2(1*H*)-pyridone, but reaction with 2 was only partially complete after 12 days. Similarly, unreacted 2 was quantitatively recovered when 2 was heated under reflux in methyl iodide for 1 week. On the other hand, reaction of 1 with refluxing methyl iodide was complete in less than 1 day. 1-Methoxy-3,5-dinitro-2(1*H*)-pyridone could be obtained, however, by reaction of 1-hydroxy-3,5-dinitro-2(1*H*)-pyridone with diazomethane.[8] The various 1-alkoxy- and 1-aroyloxy-3,5-dinitro-2(1*H*)-pyridones prepared in this study, along with appropriate yield data and physical properties, are summarized in Table II.

It appears to be well documented that increased reactivity in nucleophilic reactions involving carbonyl groups is paralleled by a marked shift of the ir absorption of the carbonyl band toward shorter wavelengths.[9,10] In accordance with these observations, the reactive 1-acyloxy-2(1*H*)-pyridones exhibit a carbonyl band in the region between 1700 and 1800 cm^{-1}. Since the corresponding 3,5-dinitro derivatives show carbonyl absorptions at even shorter wavelengths (1790–1820 cm^{-1}), it was anticipated that these latter derivatives would be even more useful as active esters for peptide synthesis. We were thus surprised to discover that their reaction with nucleophiles, contrary to prediction, was much slower. For example, although 1-acetoxy-

2(1*H*)-pyridone was completely hydrolyzed within 1 hr at room temperature in aqueous solution, 1-acetoxy-3,5-dinitro-2(1*H*)-pyridone required 30 min of reflux for complete hydrolysis. 1-Aroyloxy-3-nitro- or 5-nitro-2(1*H*)-pyridones appear to be of intermediate activity, since they are reactive enough to form amides and esters upon reaction with amines and alcohols, respectively.[11] It would appear that, contrary to the generalization made in the past, the position of the ir active ester carbonyl band is not a reliable criterion of reactivity.

There are many precedents for both thermal and photolytic homolysis of the N–O bond in various hydroxylamine derivatives,[12–15] including 1-alkoxy-2(1*H*)-pyridones.[16] We have now found that photolysis of either the 1-acyloxy-2(1*H*)-pyridones or the 1-acyloxy-3,5-dinitro-2(1*H*)-pyridones in benzene results in the formation of unsymmetrical biphenyls in low to moderate yield. This reaction presumably involves homolysis of the N–O bond to give a carboxylate radical which then loses carbon dioxide to give an aryl radical.[17–20] This then reacts with the solvent benzene to give the observed biphenyl (see Table III).[21] Consistent

Table III
Unsymmetrical Biphenyls from Photolysis in Benzene of 1-Aroyloxy-2(1*H*)-pyridones



Method A Method B

Ar	Product	% yield[a] from A	% yield[a] from B	Registry no.
C_6H_5	Biphenyl	40[b]	57	92-52-4
o-ClC_6H_4	o-Chlorobiphenyl	27[c]	48[d]	2051-60-7
m-BrC_6H_4	m-Bromobiphenyl	30[e]	56[f]	2113-57-7
m-$NO_2C_6H_4$	m-Nitrobiphenyl	15[g]	40[h]	2113-58-8
p-$NO_2C_6H_4$	p-Nitrobiphenyl	17[i]	36[j]	92-93-3
m-$CH_3C_6H_4$	m-Methylbiphenyl	44[k]	57[l]	643-93-6
p-$CH_3OC_6H_4$	p-Methoxybiphenyl	9[m]	20[n]	613-37-6
3-Pyridyl	3-Phenylpyridine	26[o]	42[p]	1008-88-4

[a] Yield determined by GLC. [b] + 20% benzoic acid. [c] + 3% biphenyl, 2% chlorobenzene, 35% o-chlorobenzoic acid. [d] + 3% biphenyl. [e] + 3% biphenyl, 2% bromobenzene, 28% m-bromobenzoic acid. [f] + 1% biphenyl, 22% m-bromobenzoic acid. [g] + < 1% biphenyl, < 1% nitrobenzene, 35% m-nitrobenzoic acid. [h] + 6% biphenyl, < 1% nitrobenzene, 43% m-nitrobenzoic acid. [i] + < 1% biphenyl, < 1% nitrobenzene, 12% p-nitrobenzoic acid. [j] + 5% biphenyl, 1% nitrobenzene, 48% p-nitrobenzoic acid. [k] + 2% biphenyl, 2% toluene, 19% m-toluic acid. [l] + 2% biphenyl. [m] + 25% biphenyl. [n] + 7% biphenyl, 4% anisole. [o] + 2% biphenyl, 2% pyridine, 28% nicotinic acid. [p] + 2% biphenyl.

with this interpretation is the observation that the photolysis of 1-(thiophene-2-carbonyloxy)-3,5-dinitro-2(1*H*)-pyridone gave a mixture of biphenyl and phenyl thiophene-2-carboxylate. Unlike most aroyloxy radicals, the thiophene-2-carbonyloxy radical is known to be relatively stable, presumably because of stabilization of the odd electron by sulfur.[22] Also consistent with the above mechanistic interpretation is the observation that substantially improved yields of unsymmetrical biphenyls are obtained utilizing the 3,5-dinitro-2(1*H*)-pyridone intermediates, in line with the known ability of electron-withdrawing groups to promote homolytic N–O bond scission by stabilizing the odd electron fragments.[12,23]

It is interesting to compare this procedure for the phenylation of arenes with the classical one involving thermolysis of a diaroyl peroxide.[20,24,25] Both methods start with the corresponding aroyl chloride, but our new procedure possesses the distinct advantage of utilizing the intermediate 1-acyloxy-2(1*H*)-pyridones which, in contrast to the thermally unstable diaroyl peroxides, are indefinitely stable (even to heat), crystalline compounds. Furthermore, it is significant that, in contrast to the peroxide route to aryl radicals,[26] phenyl aroates were not generally observed as by-products in the photolytic decomposition of 1-aroyloxy-2(1*H*)-pyridones in benzene. We suggest, therefore, that the reaction pathway involving the conversion of an acid chloride to a 1-aroyloxy-3,5-dinitro-2(1*H*)-pyridone, followed by photolysis in benzene, provides a useful synthetic complement to the classical procedure involving the intermediacy of diaroyl peroxides. We are currently investigating other synthetic applications of this new procedure for the generation of aryl radicals.

Experimental Section[27]

Thallium(I) Salt of 1-Hydroxy-3,5-dinitro-2(1*H*)-pyridone (2). Thallium(I) ethoxide (10 g, 0.04 mol) was added to a vigorously stirred solution of 1-hydroxy-3,5-dinitro-2(1*H*)-pyridone[28] (8.04 g, 0.04 mol) in 350 ml of absolute ethanol. The orange salt which immediately precipitated was collected by filtration, washed with ethanol, and dried to give 16.0 g (99.5%) of analytically pure **2**, mp >195° dec.

Anal. Calcd for $C_5H_2N_3O_6Tl$: C, 14.85; H, 0.50; N, 10.15. Found: C, 14.92; H, 0.46; N, 9.92.

1-Alkoxy-2(1*H*)-pyridones. The thallium(I) salt of 1-hydroxy-2(1*H*)-pyridone (9.42 g) was suspended in 20 ml of the appropriate alkyl halide and then heated gently under reflux for the period of time specified in Table I. The insoluble thallium(I) halide was removed by filtration and washed thoroughly with ethyl acetate. The combined filtrates were then evaporated, the last traces of alkyl halide removed under high vacuum, and the crude product distilled. Yields and properties of the various compounds prepared by this procedure are listed in Table I.

1-Alkoxy-3,5-dinitro-2(1*H*)-pyridones. The same procedure was employed as described above except that the thallium(I) salt of 1-hydroxy-3,5-dinitro-2(1*H*)-pyridone was employed. However, the products in this series are solids and could be separated directly from the distillation residue by suspension in petroleum ether (bp 30–60°)–ethyl acetate followed by filtration. Recrystallization from the same solvent mixture then gave the products listed in Table II.

1-Methoxy-3,5-dinitro-2(1*H*)-pyridone. To a solution of 1.0 g of 1-hydroxy-3,5-dinitro-2(1*H*)-pyridone in 150 ml of anhydrous ether and 50 ml of anhydrous ethyl acetate was added an excess of ethereal diazomethane. Evaporation of the solvents then gave 0.61 g (57%) of 1-methoxy-3,5-dinitro-2(1*H*)-pyridone, mp 140–143°. The product was obtained as colorless needles, mp 146–147°, upon recrystallization from petroleum ether–ethyl acetate.

1-Aroyl-2(1*H*)-pyridones and 1-Aroyl-3,5-dinitro-2(1*H*)-pyridones. General Procedure. A suspension of the thallium(I) salt of 1-hydroxy-2(1*H*)-pyridone or 1-hydroxy-3,5-dinitro-2(1*H*)-pyridone in anhydrous ether or anhydrous ethyl acetate was treated with 1 equiv of the appropriate aroyl chloride, and the mixture was stirred at room temperature (see Tables I and II). The precipitated thallium(I) chloride was then removed by filtration through Celite, the filtrate evaporated to about half its volume, and petroleum ether added to cloudiness. Refrigeration then resulted in separation of the product which was collected by filtration and recrystallized from the appropriate solvent (see Tables I and II).

1-Phenoxy-2(1*H*)-pyridone. A suspension of 3.14 g (0.01 mol) of the thallium(I) salt of 1-hydroxy-2(1*H*)-pyridone and 3.17 g (0.01 mol) of diphenyliodonium chloride in 30 ml of *tert*-butyl alcohol was stirred for 16 hr at 30°, and the white precipitate of thallium(I) chloride which had separated was collected by filtration and washed with ethyl acetate. The combined filtrates were then evaporated under reduced pressure and the residual tan solid washed with *n*-hexane (to remove iodobenzene). The residual solid weighed 1.68 g (90%), mp 99–101°. Recrystallization from ethyl acetate–*n*-hexane raised the melting point to 102–103°.

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.37; H, 4.80; N, 7.37.

***m*-Bromobiphenyl.** A solution of 1.92 g (0.005 mol) of 1-*m*-bromobenzoyloxy-3,5-dinitro-2(1*H*)-pyridone in 300 ml of benzene

was placed in a 500-ml quartz photolysis vessel and the stirred solution purged with nitrogen for approximately 15 min. The vessel was then fitted with a reflux condenser, and the solution was photolyzed in a Rayonet photochemical reactor with 300-nm light for 18 hr. The dark orange solution was evaporated under reduced pressure and the residue dissolved in 50 ml of chloroform and washed with 25 ml of saturated aqueous sodium bicarbonate. The bicarbonate layer was then separated and extracted with another 25-ml portion of chloroform. The combined chloroform extracts were then washed with distilled water, dried (anhydrous $MgSO_4$), and evaporated to dryness. The residual red oil was chromatographed on a 10-g column of silica gel using *n*-hexane–ether (3:1 v:v) as the eluent. Evaporation of the solvent then gave 0.65 g (56%) of *m*-bromobiphenyl and 1% of biphenyl. Acidification of the aqueous sodium bicarbonate layer above, extraction with two 25-ml portions of ether, and evaporation of the ether extracts gave 0.22 g (22%) of *m*-bromobenzoic acid.

The other unsymmetrical biphenyls listed in Table III were similarly prepared by photolysis of the appropriate 1-aroyloxy-2(1*H*)-pyridone or 1-aroyloxy-3,5-dinitro-2(1*H*)-pyridone in benzene.

Registry No.—**1**, 23595-81-5; **2**, 56960-55-5; thallium(I) ethoxide, 20398-06-5; 1-hydroxy-3,5-dinitro-2(1*H*)-pyridone, 822-89-9; diazomethane, 334-88-3; benzoyl chloride, 98-88-4; o-chlorobenzoyl chloride, 609-65-4; *m*-bromobenzoyl chloride, 1711-09-7; *m*-nitrobenzoyl chloride, 121-90-4; *p*-nitrobenzoyl chloride, 122-04-3; *m*-methylbenzoyl chloride, 1711-06-4; *p*-methoxybenzoyl chloride, 100-07-2; 3-pyridinecarbonyl chloride, 10400-19-8; diphenyliodonium chloride, 1483-72-3.

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Mechanism in Organophosphorus Chemistry. II.[1] Reaction of Trialkyl Phosphite Esters with *N*-Methylol Carboxamides and Sulfonamides. Trapping of an Intermediate

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N-Methylol carboxamides and sulfonamides react uniquely with trialkyl phosphite esters to produce dialkylphosphonomethyl derivatives **2** and **7**, respectively. Although the product functionality observed is the same for both substrates, the contrasting reaction conditions observed suggests a difference in mechanistic behavior. Prior investigations offer convincing evidence for a transesterification–rearrangement sequence for the carboxamide system. The present study reports evidence for the sulfonamide substrate proceeding via an elimination–addition sequence. Trapping of a zwitterion intermediate, manifested as a 4-alkyl(aryl)sulfonyl-2,2,2-trialkoxy-1,4,2-oxazaphospholane, is demonstrative.

In general, trialkyl phosphite and triaryl phosphite esters react with aliphatic alcohols at temperatures in excess of 100°C to give transesterified esters and mixed esters in accordance with eq 1.[2,3]

$$P(OR)_3 + R'OH \rightleftharpoons P(OR)_2OR' + ROH$$
$$P(OR)_2OR + R'OH \rightleftharpoons P(OR')_2OR + ROH \quad (1)$$
$$P(OR')_2OR + R'OH \rightleftharpoons P(OR')_3 + ROH$$

However, for *N*-methylol carboxamide systems, reaction with trialkyl phosphites (eq 2)[4] takes a uniquely different

$$\underset{\mathbf{1}}{R'CNHCH_2OH} + P(OR)_3 \xrightarrow{>100°C} \underset{\mathbf{2}}{R'CNHCH_2P(OR)_2} + ROH \quad (2)$$

course, realizing dialkylphosphonomethyl carboxamides (**2**) and no detectable mixed esters.

An investigation of the reaction mechanism by Ivanovet al.[4,5] offers strong support for a transesterification–rearrangement pathway (Scheme I, sequence a) and rules out the alternate Michales–Arbusov type displacement[6] consideration (Scheme I, sequence b). The evidence for these conclusions is as follows.

(a) Alkoxymethyl analogues of **1** (i.e., structures **3** where R′ = CH_3, C_2H_5, n-C_3H_7) show inert activity to conditions

$$\underset{\mathbf{3}}{RCNHCH_2OR'}$$

of eq 2.[7] Since an alkoxy group has similar leaving group ability to hydroxide,[8] a displacement mechanism (b) would dictate similar behavior of substrates **1** and **3**.

(b) Reaction of **1** with diethyl phosphorochloridite (**4**) at ambient temperature (eq 3) realizes no detectable quantity

$$RCNHCH_2OH + Cl—P(OC_2H_5)_2 \xrightarrow[Et_3N:]{20–25°} \left[RCNHCH_2—OP(OC_2H_5)_2\right] \longrightarrow RCNHCH_2P(OC_2H_5)_2 \quad (3)$$

5

of the undoubtedly formed mixed ester **5**. Only product **2** (R′ = C_2H_5) supportive of a rearrangement mechanism was isolated.

The present investigation reports the behavior observed for the reaction of *N*-hydroxymethyl sulfonamide substrates with trialkyl phosphites. By contrast to the carboxamide systems **1**, the sulfonamide analogues **6** react under extremely mild conditions, producing the expected dialkylphosphonomethyl products **7** in excellent yields (Table I).

Particular note is made of the base-accelerating and acid-retarding influence on the reaction. In general, these catalytic conditions have little effect on the carboxamide substrates,[4] i.e., no significant reaction at ambient temperature and no change in reaction time, temperature, or yields at elevated temperatures (Table II).

Further, reasonable reactivity under neutral and base catalysis and pronounced acid retardation to preclusion of reaction was observed for the alkoxymethylsulfonamide system (Table III). The fully functionalized *N,N*-bis(methoxymethyl)methanesulfonamide (**8**), on the other hand, was found to be inert to the reaction conditions of Tables I and III. Only under extremes of temperature (110°C) with acid catalysis and prolonged reaction times did reaction occur (eq 4).

Scheme I

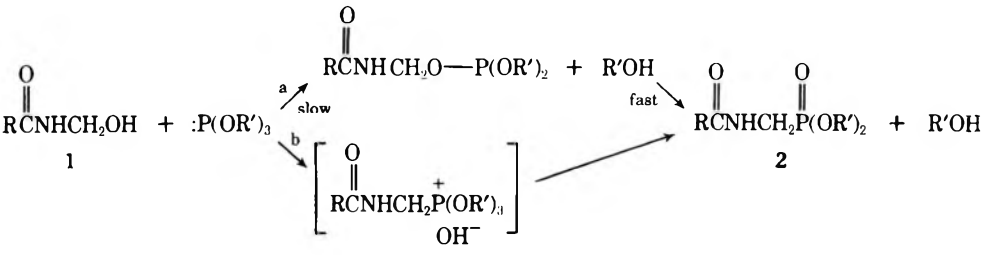


Table I[a]
Reaction of *N*-(Hydroxymethyl) sulfonamides with Trialkyl Phosphite Esters

$$\underset{\mathbf{6}}{RSO_2NHCH_2OH} + :P(OR'')_3 \longrightarrow \underset{\mathbf{7}}{RSO_2NHCH_2P(=O)(OR'')_2} + R''OH$$

R	R''	Catalyst[b]	Temp, °C	Solvent[c]	Time, hr	% yield[d]
CH_3	CH_3		25	CH_3OH	12	95%
CH_3	CH_3		50	CH_3OH	2.0	93
CH_3	C_2H_5		25	C_2H_5OH	15.5	72
CH_3	CH_3	$NaOCH_3$	25	CH_3OH	0.5	90
CH_3	CH_3	NaOH	25	CH_3OH	0.5	94
CH_3	CH_3	AcOH	25	CH_3OH	24	<10[e]
p-Ts[f]	CH_3		25	CH_3OH	13.5	78
p-Ts	CH_3		50	CH_3OH	2.0	75
p-Ts	CH_3	$NaOCH_3$	25	CH_3OH	1.0	75
p-Ts	C_2H_5		25	C_2H_5OH	15.0	65

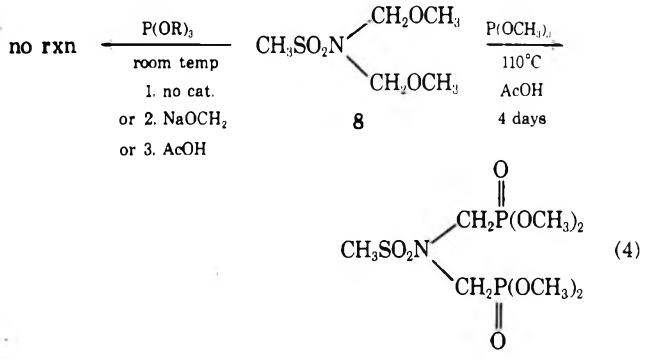
[a] Reactions run on 0.1-mol scale with 10% excess $P(OR'')_3$. [b] pH adjustment to 8.0 with $NaOCH_3$ and to 6.0 with AcOH. [c] 50 ml. [d] Adjusted yields based on purity of starting material (see Experimental Section). [e] >90% starting material recovered. [f] *p*-Ts = *p*-$CH_3C_6H_4SO_2$.

Table II
Reaction of *N*-Hydroxymethylacetamide with Trimethyl Phosphite[a]

$$CH_3C(=O)NHCH_2OH + P(OCH_3)_3 \longrightarrow CH_3C(=O)NHCH_2P(=O)(OCH_3)_2$$

Catalyst[b]	Temp, °C	Solvent	Time, hr	% yield
	25	CH_3OH	48	0
	70	CH_3OH	48	<10
$NaOCH_3$[c]	25	CH_3OH	48	<10
$NaOCH_3$[c]	70	CH_3OH	48	30
	105		1.5	73
$NaOCH_3$	105		1.5	75
AcOH	105		1.5	70

[a] The methyl ether derivative found unreactive to all conditions except acetic acid at elevated temperature (see ref 5). [b] pH adjustment to 8.0 for NaOCH, 6.0 for AcOH. [c] Notable retrograding to acetamide.



Discussion

The differences in behavior observed for the sulfonamide substrates (**6**) when compared with the carboxamide analogues (**1**) is an apparent consequence of the acidity inherent in the N–H proton of the respective systems. The pK_a (acidity constants)[9] for N-substituted sulfonamides (pK_a = 9–10) contrasted with that of carboxamides (pK_a = 16–18) offers support for N–H proton removal by alkoxide and hydroxide (pK_a = 14–15 for conjugate acids) in the former but not likely in the latter as a suspected part of the reaction mechanism.

If a direct displacement Arbusov-type reaction were operative for the sulfonamide systems at ambient temperature, reaction should be facilitated by acid protolysis on the hydroxy or alkoxy group rendering better leaving group ability; base would be expected to exert no enhanced rate over the uncatalyzed reaction. Further, a direct displacement mechanism would not be expected to be influenced by the N,N-bis substitution demonstrated in eq 4. Here again, the expected observations would be acid acceleration and no significant effect by base.

In keeping with all observed data, the following mechanism is suggested (Scheme II).

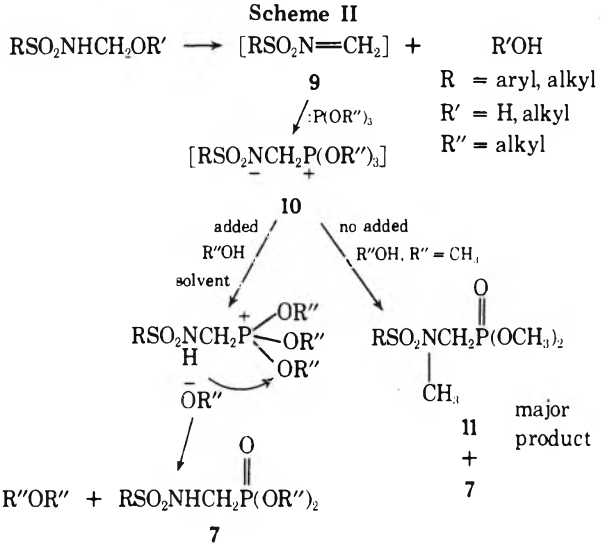
Table III[a]
Reaction of *N*-(Methoxymethyl)methanesulfonamide with Trimethyl Phosphite

$$CH_3SO_2NHCH_2OCH_3 + P(OCH_3)_3 \longrightarrow CH_3SO_2NHCH_2P(=O)(OCH_3)_2$$

Catalyst[b]	Temp, °C	Solvent	Time, hr	% yield
	25	CH_3OH	72	75
	50	CH_3OH	24	90
$NaOCH_3$	25	CH_3OH	1.0	93
$NaOCH_3$[c]	25		1.0	40
AcOH[d]	25	CH_3OH	168.0	0
AcOH	50	CH_3OH	164.0	20

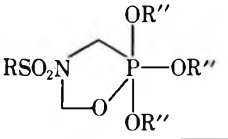
[a] Reactions run on 0.1-mol scale with 10% excess $P(OCH_3)_3$. [b] pH 8.0 for $NaOCH_3$, 6.0 for AcOH. [c] Predominant product (50–60%) $CH_3SO_2N(CH_3)CH_2P(=O)(OCH_3)_2$. [d] Quantitative recovery of starting material.

Scheme II



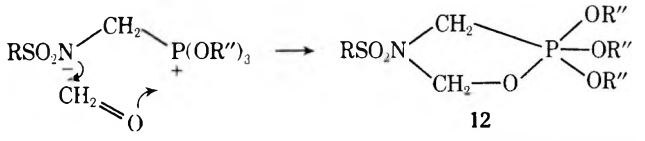
Support for this proposal was obtained from a trapping experiment in which an added equivalent of formaldehyde was placed in contact with the hydroxymethyl or alkoxymethyl sulfonamide system(s) before treatment with trialkyl phosphite. Monitoring the course of reaction by ^1H NMR (benzene as an internal standard and R = CH_3) revealed the formation of a component bearing P–OR functionality but differing significantly in overall structure from phosphonate **7**. This component was found to increase directly at the expense of starting material. At total conversion, the reaction mixture was stripped, realizing the newly produced material isolated in 70–75% purity. Although most derivatives prepared (four in number) could not be purified owing to extreme hydrolytic sensitivity, the system where R = *p*-Ts and R'' = C_2H_5 was stable enough to recrystallization to enable full unequivocal characterization as a cyclic phosphorane **12**. This adduct, produced via suggested formal 1,3-dipolar addition[10] of transient intermedi-

Table IV
^{31}P amd ^{1}H NMR Parameters for 1,4,2-Oxazaphospholanes (12)



R	R″	% yield[a]	^{31}P ($CDCl_3$)	^{1}H (δ_{CDCl_3})[b] P–CH_2N	P–OCH
CH_3	CH_3	70	+30.8	3.38 ($J_{P\text{-}CH}$ = 13 Hz, 2H)	4.72 ($J_{P\text{-}OCH}$ = 17 Hz, 2 H)
CH_3	C_2H_5	80	+32.6	3.35 ($J_{P\text{-}CH}$ = 12 Hz, 2 H)	4.65 ($J_{P\text{-}OCH}$ = 17 Hz, 2 H)
p-Ts	CH_3	90	+30.3	3.25 ($J_{P\text{-}CH}$ = 13 Hz, 2 H)	4.70 ($J_{P\text{-}OCH}$ = 17 Hz, 2 H)
p-Ts	C_2H_5	95	+33.6	3.26 ($J_{P\text{-}CH}$ = 13 Hz, 2 H)	4.68 ($J_{P\text{-}OCH}$ = 17 Hz, 2 H)

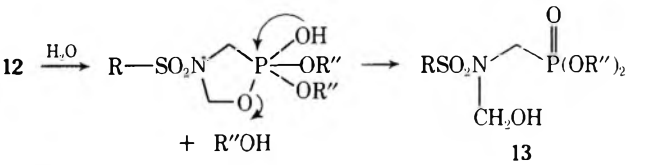
[a] The remainder of the product mix consists of hydrolysis product 13 and 7 from reaction before trapping. [b] For ^{1}H NMR support of chemical shifts and coupling constants, see ref 14–16.



12

ate 10 across the carbon–oxygen double bond of formaldehyde, was characterized as follows. In accordance with five-membered phosphorane ring systems prepared and rigorously studied by Ramirez et al.,[11,12] ^{31}P NMR proves diagnostic for the C–P–O–C (30.0–35.0 ppm) relationship within the ring; that is, the chemical shift for this atomic relationship is distinct from others (e.g., O–P–O, 48–55 ppm).[13] ^{1}H NMR shows further consistency with the proposed structures, in that the ring methylene protons are clearly distinguished and manifest the expected chemical shifts.[14–16] For structures 12 where R = CH_3 and *p*-Ts, the P–CH_2N proton chemical shift was obscured by the P–OCH_3 resonance. Determination of this shift was made from preparation of the perdeuteriomethoxyl system (R″ = CD_3), the ^{1}H NMR spectrum of which clearly revealed these protons. Pertinent data are reported in Table IV.

Additional support for structures 12 was obtained from identification of the hydrolysis product from treatment with 1 equiv of water. Compounds 13 were isolated in near quantitative yield based on purity of 12. These products



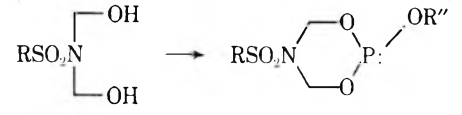
+ R″OH 13

are in keeping with the hydrolysis behavior that was observed for the 1,4,2-dioxophospholanes studied by Ramirez.[12] Appropriate identification parameters are found in the Experimental Section.

In summary, a difference in mechanism for the reaction of *N*-hydroxymethyl sulfonamide systems vs. carboxamide analogues with phosphite esters is suggested. An elimination–addition pathway is in keeping with the former and a transesterification–rearrangement consistent with the latter. Although the transesterification route may prevail to some degree for the sulfonamides as indicated by the slightly greater reactivity of the *N*-hydroxymethyl vs. the *N*-alkoxymethyl derivatives, the major pathway is undoubtedly as described for the following reasons.

(a) In general, heat >90–100°C is required for facile transesterification of alkyl phosphite esters by alcohols.[2,3] At ambient temperature, reaction is too slow to compare with observations made in this investigation.

(b) Formation of 1,4,2-oxazaphospholanes (12) from trapping experiment. If transesterification was the accepted pathway, six-membered 1,3,5-dioxazaphosphorinanes (14) would be the expected products (not observed) from the reaction with excess formaldehyde.



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(c) Transesterification processes show some response to catalytic activity by acid[2] (retardation observed in sulfonamide systems 6).

(d) For the system where R″ = CH_3 in Scheme II, N-methylation (11) of substrate occurs in the absence of excess R″OH. This process is not amenable to a transesterification process.

One further comment regards the minor response of *N*-(hydroxymethyl)carboxamides to base catalysis at low temperature (Table II). Since the alkoxymethyl analogue (3) exhibits no similar response, an elimination–addition mechanism in accordance with Scheme II is unlikely. A better explanation, emphasized by noted retrograding to amide substrate, is conversion of 1 to alkoxide 15 which fa-

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cilitates the transesterification rearrangement reaction with phosphite ester. Further evidence against the carboxamide systems engaging in elimination–addition reactions is the inability to trap phospholane intermediates similar to the sulfonamides.

Experimental Section

Materials. Methanesulfonamide (mp 91–93°) and *p*-toluenesulfonamide (mp 136–138°) were purchased from Eastman Organic Chemicals and were used without further purification. Trimethyl phosphite (bp 111–112°) and triethyl phosphite (bp 156°) were purchased from Aldrich Chemical Co., Inc., and were fractionally distilled through a 12-in. glass helices (0.125 in.) column several times before use. Column chromatography was conducted on Baker Analyzed Reagent silica gel, powder, 60–200 mesh.

General Information. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on Varian Models T-60 and HA-100 MHz spectrometers. Infrared spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. In vacuo strippings were carried out on a Buchler Instruments Flash-Evaporator.

***N*-(Hydroxymethyl)methanesulfonamide.** To a solution of 9.5 g (0.10 mol) of methanesulfonamide in 100 ml of anhydrous methanol was added 3.3 g (0.11 mol) of paraformaldehyde. The suspension was adjusted to pH 8–9 with sodium methoxide (Matheson Coleman and Bell) and then heated to 45–50°C for 2 hr. After cooling to room temperature, the reaction solution was neutralized to pH 7 with acetic acid (glacial) followed by stripping in vacuo to constant weight as an amber oil, weight of crude product 12.3 g (98.4%).

In general, the *N*-methylol sulfonamides proved too unstable to conventional purification by recrystallization, distillation, and column chromatography. Retrograding to starting sulfonamides was observed. Proof of structure was made on the basis of consistent spectral properties (infrared and ^{1}H NMR) and additional support for hydroxyl absorption through H–D exchange (D_2O treatment of NMR samples in $CDCl_3$). The degree of purity of *N*-(hydroxymethyl)methanesulfonamide was further assessed by degree of conversion to its methyl ether derivative (see below): ir ν_{max} (film) 3550 (OH), 3280 (NH), 1450, 1330 (SO_2), 1145 (SO_2), 1055, 965, 920, 830, 790 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 3.08 (3 H, CH_3SO_2–), 4.20 (broad singlet, 1 H, –OH), 4.95 (broad singlet, 2 H, NCH_2O), 6.60–7.20 (baseline integration for 1 H, NH). NMR signals at δ 4.20 and 6.60–7.20 disappear upon treating the sample with several drops of D_2O.

***N*-(Methoxymethyl)methanesulfonamide.** To a fresh solution of 6.25 g (0.05 mol) of *N*-(hydroxymethyl)methanesulfonamide in 100 ml of anhydrous methanol was added 8 drops of concentrated HCl (aqueous). Stirring at room temperature for 5 hr was followed by careful neutralization to pH 7 with sodium methoxide and stripping in vacuo. The clear, colorless oil (6.9 g, >99%) was chromatographed on silica gel ($CHCl_3$ as elution solvent): ir ν_{max} (film) 3275 (NH), 1340, 1150, 1075, 940, 790 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 3.08 (singlet, 3 H, CH_3SO_2–), 3.38 (singlet, 3 H, –OCH_3), 4.60 (doublet, J = 7 Hz, 2 H, NCH_2O). 6.18 (broad triplet, J = 7 Hz, 1 H, NH).

Anal. Calcd for $C_3H_9NO_3S$: C, 25.90; H, 6.47; N, 10.07. Found: C, 25.67; H, 6.31; N, 9.92.

***N*-(Hydroxymethyl)-*p*-toluenesulfonamide.** The procedure for preparing *N*-(hydroxymethyl)methanesulfonamide was utilized. From 17.10 g (0.1 mol) of *p*-toluenesulfonamide and 4 g (0.13 mol) of paraformaldehyde, 20.0 g (99.5%) of crude product was obtained from exhaustive stripping in vacuo. The clear, colorless, glassy solid exhibited the same instability to purification as noted for the methanesulfonamide system. Structure identification and degree of purity was determined by ^{1}H NMR (90%): ir ν_{max} (film) 3500 (OH), 3250 (NH, broad doublet), 1590, 1450, 1330, 1155, 1070, 900, 820, 740, 665 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) inter alia (trace amounts of methyl ether) 2.4 (singlet, 3 H, aromatic methyl), 4.78 (broad singlet, ca. 2 H, NCH_2O), 5.40 (singlet, 1 H, OH), 7.50 (AB quartet, J = 8 Hz, 5 H, four aromatic protons, one proton due to N–H broad peak under the resonance). The N–H and O–H signals disappeared upon treatment of the sample with several drops of D_2O.

General Procedure for Preparing *N*-(Dialkylphosphonomethyl)sulfonamides. Method A. To a solution of 0.10 mol of *N*-(hydroxymethyl)methane(*p*-toluene)sulfonamide in 50 ml of anhydrous methanol (ethanol for triethyl phosphite runs) was added 0.11–0.13 mol of trialkyl phosphite. Stirring and external heat was applied. When the temperature reached 35–45°C, exotherming was noted and moderating was accomplished with an ice–water bath. Temperature was maintained at 50°C for 1–2 additional hr followed by cooling to room temperature and stripping in vacuo to remove all volatiles. The residue was dissolved in a small portion of chloroform and chromatographed on silica gel ($CHCl_3$ as elution solvent). See characterization data below.

Method B. The above procedure can be conducted in one flask starting with parent sulfonamide substrates and preparing *N*-hydroxymethyl derivatives in situ.

Methanesulfonamide (9.5 g, 0.10 mol) was dissolved in 50 ml of anhydrous methanol. The pH was adjusted to 8–9 with sodium methoxide and 3.3 g (0.11 mol) of paraformaldehyde was added. Upon heating to 50°C, solution was obtained. After 1 hr the reaction flask was cooled to room temperature, at which time 13.6 g (0.11 mol) of trimethyl phosphite was added. Heat was applied; exotherming set in at 35°C. Reaction was maintained at 50°C for 1 hr followed by stripping in vacuo on a rotary evaporator (50°C, 0.5 mm). The crude *N*-(dimethylphosphonomethyl)methanesulfonamide (21.6 g, 99.5%) was shown to be of high purity (>95%) by ^{1}H NMR analysis. Part of this material was chromatographed on silica gel ($CHCl_3$) and recovered as a water-white oil. Attempted distillation led to decomposition. Characterization data for all systems prepared is given in the following.

***N*-(Dimethylphosphonomethyl)methanesulfonamide:** ir ν_{max} (film) 3200 (NH), 1320 (SO_2), 1240 (P=O), 1150 (SO_2), 1030 (P–O), 830 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −24.7; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 3.03 (singlet, 3 H, CH_3SO_2), 3.55 (doublet of doublets, J_{P-CH_2} = 12, J_{NH-CH_2} = 6 Hz, 2 H, NCH_2P=O), 3.82 (doublet, J = 12 Hz, 6 H, $POCH_3$'s), 6.42 (broad triplet, J = 6 Hz, 1 H, NH).

Anal. Calcd for $C_4H_{12}NO_5PS$: C, 22.10; H, 5.53; N, 6.46; P, 14.29. Found: C, 21.80; H, 5.91; N, 6.13; P, 14.50.

***N*-(Diethylphosphonomethyl)methanesulfonamide** was chromatographed on silica gel ($CHCl_3$): ir ν_{max} (film) 3140 (NH), 1325 (SO_2), 1240 (P=O), 1155 (SO_2), 1020–1050 (P–O), 970, 800 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −21.3; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.35 (triplet, J = 7 Hz, 6 H, ethyl ester CH_3's), 3.02 (singlet, 3 H, CH_3SO_2), 3.48 (doublet of doublets, J_{P-CH_2} = 12, J_{NH-CH_2} = 6 Hz, 2 H, NCH_2P=O), 4.15 (quintet, J = 7 Hz, 4 H, ethyl ester CH_2's), 6.45 (broad triplet, J = 6 Hz, 1 H, NH).

Anal. Calcd for $C_6H_{16}NO_5PS$: C, 29.39; H, 6.53; N, 5.71; P, 12.65. Found: C, 29.19; H, 6.47; N, 5.64; P, 12.80.

***N*-(Dimethylphosphonomethyl)-*p*-toluenesulfonamide** was recrystallized from $CHCl_3$–hexane: mp 117–119°C; ir ν_{max} (Nujol) 3100 (NH), 1330 (SO_2), 1250 (P=O), 1162 (SO_2), 1030–1050 (doublet, P–O), 880, 828, 805 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −23.6; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 2.40 (singlet, 3 H, aromatic CH_3), 3.25 (doublet of doublets, J_{P-CH_2} = 12, J_{NH-CH_2} = 6 Hz, 2 H, NCH_2P=O), 3.72 (doublet, J_{P-OCH_3} = 11 Hz, 6 H, $POCH_3$'s), 6.70 (broad triplet, J = 6 Hz, 1 H, NH), 7.53 (AB quartet, J = 8 Hz, 4 H, aromatic protons).

Anal. Calcd for $C_{10}H_{16}NO_5PS$: C, 40.96; H, 5.46; N, 4.77; P, 10.60. Found: C, 40.60; H, 5.70; N, 4.60; P, 10.52.

***N*-(Diethylphosphonomethyl)-*p*-toluenesulfonamide.** Crude product was recrystallized from $CHCl_3$–hexane: mp 83–85°C; ir ν_{max} (Nujol) 3100 (NH), 1332 (SO_2), 1300 (doublet), 1245 (P=O), 1205, 1160 (SO_2), 1100, 1025 (P–O), 978, 925, 800 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −20.2; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.30 (triplet, J = 7 Hz, 6 H, ethyl CH_3's), 2.23 (singlet, aromatic CH_3), 3.25 (doublet of doublets, J_{P-CH_2} = 14, J_{NH-CH_2} = 6 Hz, 2 H, NCH_2P=O), 4.18 (quintet, J = 7 Hz, 4 H, ethyl CH_2's), 6.0 (broad triplet, J = 6 Hz, 1 H, NH), 7.50 (AB quartet, J = 8 Hz, 4 H, aromatic protons).

Anal. Calcd for $C_{12}H_{20}NO_5PS$: C, 44.86; H, 6.23; N, 4.36; P, 9.66. Found: C, 44.77; H, 6.18; N, 4.14; P, 9.80.

***N*-(Hydroxymethyl)acetamide.** A solution of 5.9 g (0.1 mol) of acetamide in 8.1 g of 37% aqueous formalin was treated with 5% aqueous sodium hydroxide to a pH 8–9. A slight exotherm to 30°C was observed. After stirring at room temperature for several hours, reaction was neutralized to pH 6 with dilute aqueous HCl followed by stripping in vacuo to a colorless oil which solidified on standing. Recrystallization from dioxane realized 8.0 g of *N*-(hydroxymethyl)acetamide representing an 89% yield: mp 50–52° (lit.[17] 50–52°); ir ν_{max} (Nujol) 3300 (broad OH, NH), 1660 (C=O), 1540, 1285, 1090, 1030 cm^{-1}; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 2.00 (singlet, 3 H, CH_3CO), 4.65 (doublet, J = 7 Hz, 2 H, NCH_2O), 5.50 (singlet, 1 H, OH), 8.10 (broad triplet, J = 7 Hz, 1 H, NH).

***N*-(Dimethylphosphonomethyl)acetamide.** To 25 g (0.20 mol) of trimethyl phosphite (TMP) preheated to 105°C was added 13.3 g (0.15 mol) of *N*-(hydroxymethyl)acetamide portionwise over 15 min. Exotherm to 110° was noted during the addition. The reaction was then held at 105°C for 1.5 hr, followed by cooling to room temperature and stripping in vacuo. The oily residue was chromatographed on silica gel employing benzene as eluent, yield 13.2 g, as a colorless oil, representing a 73% yield: ir ν_{max} (film) 3290 (NH), 1685 (C=O), 1460, 1250 (P=O), 1040 (P–O), 890, 820 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −25.6; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 2.02 (singlet, 3 H, CH_3C=O), 3.65 (doublet, J_{P-CH_2} = 12 Hz, 2 H, NCH_2P), 3.78 (doublet, J_{P-OCH_3} = 11 Hz, 6 H, $POCH_3$'s), 7.60 (broad, 1 H, NH).

Anal. Calcd for $C_5H_{12}NO_4P$: C, 33.15; H, 6.63; N, 7.73; P, 17.13. Found: C, 32.91; H, 6.42; N, 7.81; P, 17.10.

Relative Rate Studies. All experiments were carried out on a 0.10-mol basis and conducted in accordance with the conditions indicated in Tables I–III. Reactions were monitored to exhaustive conversion (no further change) at varying intervals; i.e., 2–4 hr for long-term conversions, 15 min for short-term conversions. Aliquots were withdrawn at these times, stripped in vacuo, and qualitatively analyzed by ^{1}H NMR integration of P–OR″ and P–CH_2N resonances of product vs. diminution of –CH_2OH(–CH_2OCH_3) resonances of starting material.

***N,N*-Bis(methoxymethyl)methanesulfonamide.** A solution of 9.5 g (0.10 mol) of methanesulfonamide and 32.4 g (0.40 mol) of 37% aqueous formalin in 100 ml of distilled water was treated with

10% aqueous NaOH to pH 9 and allowed to stir at room temperature for 15 hr. The aqueous solvent was stripped in vacuo (20 mm, 50°C) and the residue redissolved in 200 ml of anhydrous methanol. Several drops (8–10) of concentrated hydrochloric acid were added followed by stirring at room temperature for an overnight period. The reaction was neutralized with sodium methoxide and stripped of methanol solvent. Chromatography on silica gel with chloroform as eluent realized 9.2 g of a colorless oil representing a 50% yield of product: ir ν_{max} (film) 1345 (SO_2), 1150 (SO_2), 1075, 930, 790 cm^{-1}; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 3.07 (singlet, 3 H, CH_3SO_2), 3.40 (singlet, 6 H, OCH_3's), 4.80 (singlet, 4 H, NCH_2O's).

Anal. Calcd for $C_5H_{13}NO_4S$: C, 32.75; H, 7.10; N, 7.66. Found: C, 32.68; H, 7.08; N, 7.54.

***N,N*-Bis(dimethylphosphonomethyl)methanesulfonamide.** To 50 g of trimethyl phosphite (TMP) were added 5 g (0.027 mol) of *N,N*-bis(methoxymethyl)methanesulfonamide and 1 ml of glacial acetic acid. External heat was applied and the flask contents taken to reflux. Reaction was monitored by ^1H NMR analysis of stripped aliquots taken twice daily. Owing to eventual consumption of AcOH through reaction with TMP, 1 additional ml of AcOH was added each day. After 4 days, reaction progressed no further. The flask contents were stripped in vacuo (1 mm, 50°C) followed by chromatography on silica gel ($CHCl_3$): yield of colorless oil 3.6 g (40%); ir ν_{max} (film) 1320 (SO_2), 1240 (P=O), 1145 (SO_2), 1030 (P–O), 800 cm^{-1}; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 3.03 (singlet, 3 H, CH_3SO_2), 3.58 (doublet, J_{P-CH_2} = 11 Hz, 4 H, NCH_2's), 3.75 (doublet, J_{P-OCH_3} = 12 Hz, 12 H, $POCH_3$'s).

Anal. Calcd for $C_7H_{19}NO_8PS$: C, 27.27; H, 6.17; N, 4.55; P, 10.06. Found: C, 27.13; H, 5.92; N, 4.43; P, 10.14.

General Procedure for Trapping Zwitterion Intermediates (10). Preparation of 4-Alkyl(aryl)sulfonyl-2,2,2-trialkoxy-1,4,2-oxazaphospholanes. A solution of 0.1 mol of *N*-(hydroxymethyl)methanesulfonamide or the *p*-toluenesulfonamide analogue in 100 ml of anhydrous methanol was treated with 1 equiv of paraformaldehyde (pH 8) at room temperature. When solution was obtained, the methanol solvent was stripped at 25° with a water aspirator. The residue was dissolved in excess trialkyl phosphite (ca. 100 ml total) and was agitated at room temperature. Reaction was monitored by ^1H NMR analysis of stripped aliquots withdrawn at 30-min intervals and was complete in 1–2 hr. All completed reactions were stripped exhaustively of excess phosphite ester at 30–35° (0.5 mm).

For those systems (R″ = CH_3) where ring proton NMR resonance was obscured by P–OCH_3 resonance, perdeuteriotrimethyl phosphite[18] was employed for complete characterization. Additional data not contained in Table IV in support of the oxazaphospholanes are given as follows.

4-Methanesulfonyl-2,2,2-trimethoxy-1,4,2-oxazaphospholane. Crude material was isolated as a colorless oil: estimated purity ca. 60–70%; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 2.83 (singlet, 3 H, CH_3SO_2), 3.38 (doublet, *J* = 13 Hz, 2 H, PCH_2N), 3.60 (doublet, *J* = 12 Hz, 9 H, $POCH_3$'s), 4.72 (doublet, *J* = 17 Hz, 2 H, $POCH_2$).

4-Methanesulfonyl-2,2,2-triethoxy-1,4,2-oxazaphospholane. Crude material was isolated as a colorless oil: purity: ca. 75–80%; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 1.20 (triplet, *J* = 8 Hz, 9 H, Et methyls), 2.80 (singlet, 3 H, CH_2SO_2), 3.35 (doublet, *J* = 12 Hz, 2 H, PCH_2N), 3.90 (pentuplet, *J* = 8 Hz, 6 H, Et methylenes), 4.65 (doublet, *J* = 17 Hz, 2 H, $POCH_2$ ring protons).

4-*p*-Toluenesulfonyl-2,2,2-trimethoxy-1,4,2-oxazaphospholane. Crude material was isolated as a white solid in estimated purity of >90%; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 2.43 (singlet, 3 H, aromatic CH_3), 3.30 (doublet, *J* = 12 Hz, 9 H, $POCH_3$'s), 3.25 (doublet, *J* = 13 Hz, 2 H, PCH_2N), 4.70 (doublet, *J* = 17 Hz, 2 H, $POCH_2$ ring protons), 7.50 (AB quartet, *J* = 8 Hz, 4 H, aromatic protons).

4-*p*-Toluenesulfonyl-2,2,2-triethoxy-1,4,2-oxazaphospholane. Crude material was isolated as a white solid in 95% yield and recrystallized as colorless needles from $CHCl_3$–hexane: mp 115–117°C. ir ν_{max} (Nujol) 1340 (SO_2), 1155 (SO_2), 1100, 1040–1080 (P–O), 975, 925, 834, 780, 710, 675 cm^{-1}; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 1.07 (triplet, *J* = 7 Hz, 9 H, Et CH_3's), 2.43 (singlet, 3 H, aromatic CH_3), 3.26 (doublet, *J* = 13 Hz, 2 H, PCH_2N), 3.63 (pentuplet, *J* = 7 Hz, 6 H, Et CH_2's), 4.68 (doublet, *J* = 17 Hz, 2 H, $POCH_2$ ring protons), 7.55 (AB quartet, *J* = 8 Hz, 4 H, aromatic).

Anal. Calcd for $C_{15}H_{26}NO_6PS$: C, 47.49; H, 6.86; N, 3.69; P, 8.18. Found: C, 47.12; H, 6.83; N, 3.72; P, 8.33.

Hydrolysis of 4-Alkyl(aryl)sulfonyl-2,2,2-trialkoxy-1,4,2-oxazaphospholanes. A 2-g sample of phospholane derivative was dissolved in 10 ml of tetrahydrofuran and the solution treated with 1 equiv of water. After stirring for 10–15 min at room temperature, a small portion of $MgSO_4$ was added followed by filtration and stripping in vacuo. The product (13) was purified by chromatography or recrystallization. The following data are germane.

***N*-(Dimethylphosphonomethyl)-*N*-(hydroxymethyl)methanesulfonamide.** Crude material isolated as a colorless oil was chromatographed on silica gel ($CHCl_3$): yield 95% based on purity of starting material; ir ν_{max} (film) 3300 (OH), 1340 (SO_2), 1230 (P=O), 1150 (SO_2), 1030 (P–O), 970, 865, 800 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −24.2; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 3.05 (singlet, 3 H, CH_3SO_2), 3.75 (doublet, *J* = 10 Hz, 2 H, NCH_2P), 3.83 (doublet, *J* = 11 Hz, 6 H, $POCH_3$'s), 4.97 (singlet, 2 H, NCH_2O), 5.25 (broad singlet, 1 H, OH).

Anal. Calcd for $C_5H_{14}NO_6PS$: C, 24.29; H, 5.67; N, 5.67; P, 12.55. Found: C, 24.12; H, 5.49; N, 5.65; P, 12.36.

***N*-(Diethylphosphonomethyl)-*N*-(hydroxymethyl)methanesulfonamide.** Crude material isolated as a colorless oil (93% pure) was chromatographed on silica gel ($CHCl_3$): ir ν_{max} (film) 3290 (OH), 1340 (SO_2), 1230 (P=O), 1150 (SO_2), 1030 (P–O), 970, 850, 780 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −21.3; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 1.38 (triplet, *J* = 7 Hz, 6 H, Et CH_3's), 3.03 (singlet, 3 H, CH_3SO_2), 3.75 (doublet, *J* = 10 Hz, 2 H, NCH_2P), 4.17 (pentuplet, *J* = 7 Hz, 4 H, Et CH_2's), 5.00 (singlet, 2 H, NCH_2O), 5.46 (broad singlet, 1 H, OH).

Anal. Calcd for $C_7H_{18}NO_6PS$: C, 30.55; H, 6.55; N, 5.09; P, 11.27. Found: C, 30.52; H, 6.33; N, 5.19; P, 10.89.

***N*-(Dimethylphosphonomethyl)-*N*-(hydroxymethyl)-*p*-toluenesulfonamide.** Crude product (98% purity) was recrystallized from toluene–hexane: mp 120–122°C; ir ν_{max} (Nujol) 3300 (OH), 1335 (SO_2), 1260 (P=O), 1165 (SO_2), 1030 (P–O), 955, 864, 810 (doublet), 740, 665 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −23.5; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 2.43 (singlet, 3 H, aromatic CH_3), 3.75 (two doublets superimposed, determined from O=$P(OCD_3)_2$ derivative: *J* = 10 Hz, 2 H, NCH_2P; *J* = 11 Hz, 6 H, $POCH_3$'s), 4.20 (singlet, 1 H, OH), 5.03 (singlet, 2 H, NCH_2O), 7.58 (AB quartet, *J* = 8 Hz, 4 H, aromatic protons).

Anal. Calcd for $C_{11}H_{18}NO_6PS$: C, 40.87; H, 5.57; N, 4.33; P, 9.60. Found: C, 41.03, H, 5.63; N, 4.27; P, 9.73.

***N*-(Diethylphosphonomethyl)-*N*-(hydroxymethyl)-*p*-toluenesulfonamide.** Crude product (>95% purity) was recrystallized from $CHCl_3$–hexane: mp 86–90°C; ir ν_{max} (Nujol) 3300 (OH), 1340 (SO_2), 1258 and 1220 (P=O), 1168 (SO_2), 1040 (P–O), 950, 857, 740, 660 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −20.3; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 1.30 (triplet, *J* = 7 Hz, 6 H, Et CH_3's), 2.41 (singlet, 3 H, aromatic CH_3), 3.68 (doublet, *J* = 11 Hz, 2 H, NCH_2P), 4.10 (pentuplet, *J* = 7 Hz, 4 H, Et CH_2's), 4.40 (broad singlet, 1 H, OH), 5.00 (singlet, 2 H, NCH_2O), 7.50 (AB quartet, *J* = 8 Hz, 4 H, aromatic protons).

Anal. Calcd for $C_{13}H_{22}NO_6PS$: C, 44.44; H, 6.27; N, 3.99; P, 8.83. Found: C, 44.53; H, 6.37; N, 3.96; P, 8.94.

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Registry No.— 1 (R = Me), 625-51-4; 2 (R = R′ = Me), 20495-30-1; 6 (R = Me), 52089-33-5; 6 (R = *p*-Ts), 23666-91-3; 7 (R = R″ = Me), 52089-34-6; 7 (R = Me; R″ = Et), 53376-16-2; 7 (R = *p*-Ts; R″ = Me), 28447-27-0; 7 (R = *p*-Ts; R″ = Et), 57049-65-7; 8, 23069-55-8; 12 (R = R″ = Me), 57049-66-8; 12 (R = Me, R″ = Et), 57049-67-9; 12 (R = *p*-Ts; R″ = Me), 57049-68-0; 12 (R = *p*-Ts; R″ = Et), 57049-69-1; 13 (R = R″ = Me), 57049-70-4; 13 (R = Me; R″ = Et), 57049-71-5; 13 (R = *p*-Ts; R″ = Me), 57049-72-6; 13 (R = *p*-Ts, R″ = Et), 57049-73-7; methanesulfonamide, 3144-09-0; methanol, 67-56-1; *N*-(methoxymethyl)methanesulfonamide, 57049-74-8; *p*-toluenesulfonamide, 70-55-3; acetamide, 60-35-5; formalin, 50-00-3; trimethyl phosphite, 121-45-9; *N,N*-bis(dimethylphosphonomethyl)methanesulfonamide, 53376-14-0; triethyl phosphite, 122-52-1.

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Kinetic Solvent Deuterium Isotope Effects on the Micellar-Catalyzed Hydrolysis of Trisubstituted Phosphate Esters[1]

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Functional micelles of hexadecyl(2-hydroxyethyl)dimethylammonium bromide (I) are better catalysts than hexadecyltrimethylammonium bromide (CTABr) for the alkaline hydrolysis of diethyl and di-*n*-hexyl *p*-nitrophenyl phosphate (IIIa,b). The kinetic solvent deuterium isotope effects for reactions catalyzed by CTABr are very similar to those for reaction in water, but for reaction of IIIb in the presence of I the inverse isotope effect gradually disappears with increasing concentration of hydroxide ion. These results show that the inverse isotope effect is due to the ionization of I to its zwitterion II at high pH. They are consistent with nucleophilic attack by the alkoxide moiety in II but not with general acid or base catalysis.

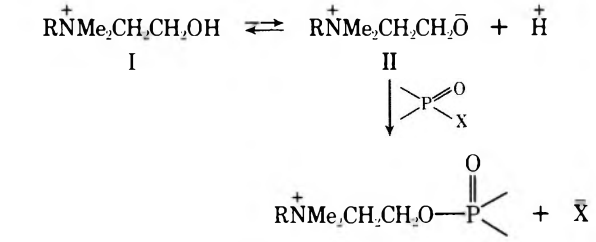
Micelles catalyze (or inhibit) many bimolecular reactions in aqueous solvents.[3] The catalysis can be explained in terms of the ability of the micelle to bring the reagents together at its surface in an environment which is favorable to reaction with stabilization of the transition state and avoidance in part of the unfavorable entropy effects caused by forming an activated complex from two or more reagents.[8] In general the catalysis is greater if one reagent is chemically incorporated into the surfactant, by analogy with the greater ease of intra- as compared with intermolecular reactions.[8] Most functional surfactants have contained amino or thiol groups and the former could act as nucleophiles or general bases,[4–6] but we have used quaternary ammonium ions derived from ethanolamine as reagents in reactions of phosphate esters[9,10] and acyl phosphates. Our evidence is consistent with the surfactant (I) generating the zwitterion (II) which reacts as a nucleophile. These micellized surfactants are effective reagents toward saturated and carbonyl carbon, and it was suggested that here they acted by increasing the nucleophilicity of hydroxide ion.[11]

Micelles of I can be regarded as models of protein bond serine, whose nucleophilicity is important in many enzymic reactions,[12] so that it is important to distinguish between the possible modes of catalysis in reactions catalyzed by micelles of I and related surfactants.

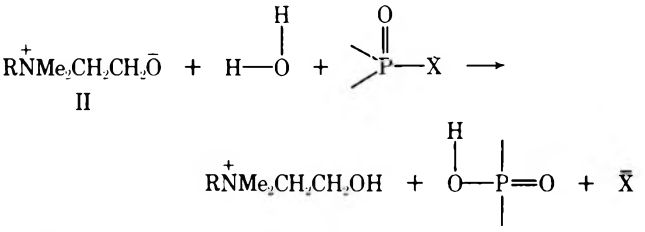
There are four reasonable mechanisms (1–4) by which micelles of I could speed reactions. They are shown for reaction at a phosphoryl group, but similar paths can be written for some of the reactions at carbon.

The fact that micelles of I are no better catalysts than micelles of cetyltrimethylammonium bromide (CTABr) for attack of fluoride ion upon *p*-nitrophenyl diphenyl phosphate[10] argues against 3 and 4, but either 1 or 2 are consistent with the evidence.

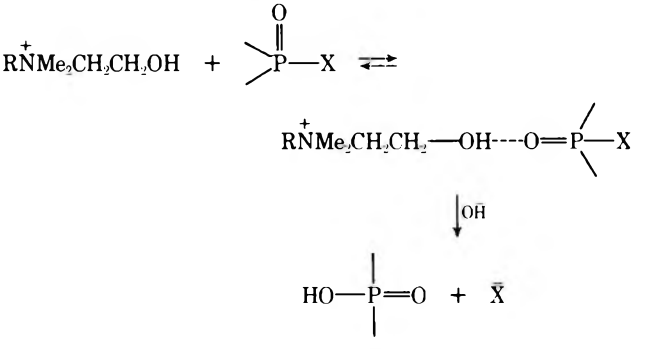
(1) Nucleophilic attack.[9,10]



(2) General base catalysis, cf. ref 13.



(3) General acid catalysis.



(4) By increasing reactivity of hydroxide ion.[11]

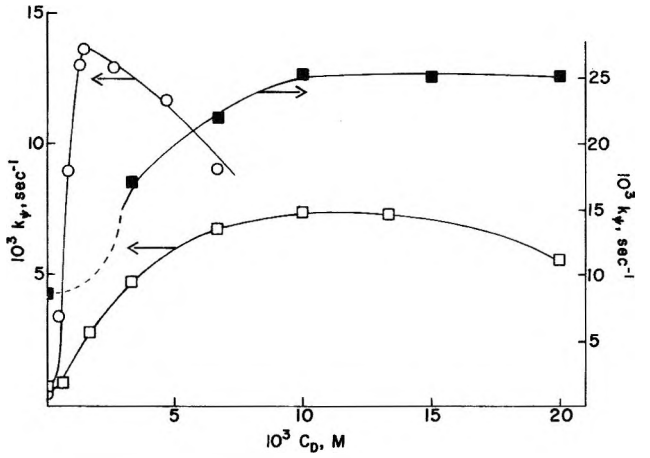
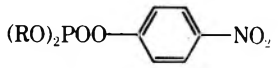


Figure 1. Reactions of *p*-nitrophenyl phosphate esters in 0.01 *M* NaOH at 25.0°. The open symbols are for reactions in CTABr in 0.01 *M* NaOH and the closed for reactions in the hydroxyethyl surfactant I in 0.1 *M* NaOH. Reactions of ■, □, diethyl (IIIa); ○, di-*n*-hexyl (IIIb).

Kinetic deuterium solvent isotope effects should distinguish between these mechanisms,[14] because those involving general catalysis should show relatively large effects with $k_{H_2O}/k_{D_2O} > 2$.[13,16,17] If the micelle merely increased the reactivity of hydroxide ion the solvent isotope effect should be typical of nucleophilic attack by that ion, but mechanism 1 predicts that the isotope effect will vary with hydroxide ion concentration, because of the changing equilibrium between I and II, although the overall isotope effect should not be large.[18]

In earlier work we used *p*-nitrophenyl diphenyl phosphate as substrate and followed the reaction using a stopped flow spectrometer,[9,10] but here we used the less reactive diethyl and di-*n*-hexyl *p*-nitrophenyl phosphate (IIIa,b) so that the rates in D_2O could be measured conventionally.



III

(IIIa, b, R = Et, *n*-Hex, respectively)

Experimental Section

Materials. The preparation and purification of the substrates and surfactant followed standard methods.[9,19] Redistilled and deionized water was used in the rate measurements.

Kinetics. The slower reactions were followed spectrophotometrically at 25.0° using Gilford spectrophotometers with water jacketed cell compartments,[9,10] and the faster reactions were followed in a Durrum stopped flow spectrophotometer with a Biomation 805 data acquisition unit. The substrate concentrations were ca. 10^{-5} *M*.

The kinetics were first order and the observed first-order rate constants, k_ψ, are in sec^{-1}, at 25.0°. In the figures we denote the surfactant (detergent) concentration as C_D.

Results

Micellar effects upon the reactions of *p*-nitrophenyl diphenyl phosphate but not of IIIa,b have been examined.[9,10,20]

It was difficult to follow the reaction of *p*-nitrophenyl di-*n*-hexyl phosphate (IIIb) in water in the absence of surfactant because of its low solubility, and using 1.8×10^{-6} *M* substrate in 0.1 *M* NaOH the initial part of the first-order plot was curved, but from the final linear part we calculated $k_\psi \sim 7.5 \times 10^{-4}$ sec^{-1}; with 5 vol % dioxane there was less bending and the linear part of the curve gave $k_\psi \sim 7.7 \times 10^{-4}$ sec^{-1} and in 12 vol % dioxane a good first-order plot

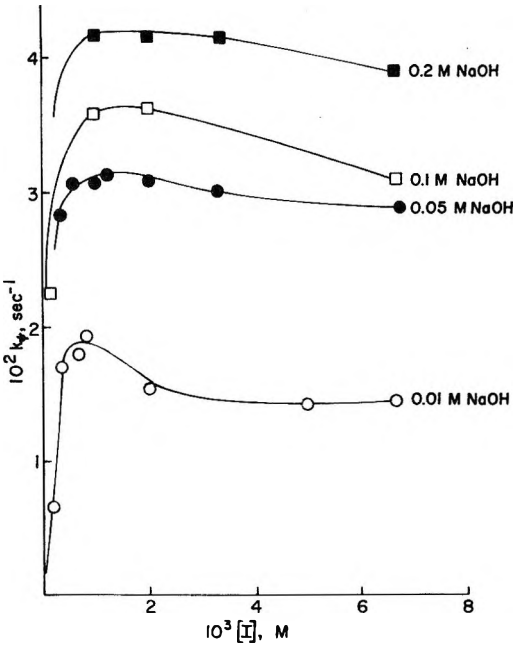


Figure 2. Effect of hydroxide ion on reaction of *p*-nitrophenyl di-*n*-hexyl phosphate (IIIb) in the presence of the hydroxyethyl surfactant I.

was obtained with $k_\psi = 7.7 \times 10^{-4}$ sec^{-1}. The initial curvature was probably due to the low solubility of the ester, so that first-order kinetics were not observed until all the ester was in solution, and it and the diethyl compound have similar reactivities in the absence of surfactant.

Relatively small amounts of dioxane have little effect on the reaction rate, and for reaction of *p*-nitrophenyl diethyl phosphate in 0.01 *M* NaOH at 25.0°, $10^5 k_\psi$ = 8.5, 8.7, 8.8, and 8.6 sec^{-1} in water and 5, 8, and 12% dioxane by volume, respectively. Addition of organic solvents can assist bimolecular nucleophilic attack because of decreased hydration of the nucleophile.[21] Probably the absence of rate enhancement here is related to a decrease in the activity coefficients of the hydrophobic substrates which offsets the normal solvent effect, and dioxane retards reaction of IIIb.

Micellar Effects. Cationic micelles of the nonfunctional surfactant, CTABr, catalyze reactions of IIIa,b and the rate constant–surfactant profile (Figures 1 and 2 and Table I) is similar to that for the hydrolysis of *p*-nitrophenyl diphenyl phosphate.[9,10] The less hydrophobic ester bonds less to micelles and more surfactant is needed to reach rate maxima in reactions of the diethyl as compared with the di-*n*-hexyl phosphate.[4-7] The maximum rates in micelles of CTABr are different for the two esters, with the more hydrophobic dihexyl compound being the more reactive (Table I). In many micellar-catalyzed reactions both reagent–micelle binding and the rates in the micelle increase with increas-

Table I
Micellar Effects upon Reactions of Phosphate Triesters[a]

Substrate	Surfactant				
	CTABr	I			
[OH$^-$], *M*	0.01	0.01	0.05	0.1	0.2
Diethyl	9			3	
Di-*n*-hexyl	18	256	84	49	28
Diphenyl[b]	12	310	104	58	

[a] Values of the rate enhancement at 25.0° and surfactant concentration at the rate maximum. In the absence of surfactant the second-order rate constants are respectively diethyl, 8.5×10^{-3}; di-*n*-hexyl, 7.5×10^{-3}; diphenyl, 0.49 l. mol^{-1} sec^{-1}. [b] Reference 20.

Table II
Deuterium Solvent Isotope Effects in Reactions of Phosphate Esters [a]

Substrate	Surfactant	$[\bar{O}H]$, M [b]	$10^3 k_{H_2O}$	$10^3 k_{D_2O}$	k_{H_2O}/k_{D_2O}
Diethyl		0.01	0.0853	0.0982	0.87
Diethyl	10^{-2} M CTABr	0.10	5.43	5.78	0.94
Diphenyl		0.01	4.86	4.43	1.10
Diphenyl	1.5 mM CTABr	0.01	96.2	75.7	1.27
Diphenyl	1.5 mM CTABr	0.05	263	231	1.14
Di-*n*-hexyl	1.5 mM CTABr	0.01	3.02	3.23	0.93
Di-*n*-hexyl	2 mM I	0.01	15.4	20.4	0.75
Di-*n*-hexyl	2 mM I	0.10	36.0	40.6	0.89
Di-*n*-hexyl	2 mM I	0.15	39.1	41.0	0.95
Di-*n*-hexyl	2 mM I	0.20	41.6	41.6	1.00

[a] At 25.0°; $[\bar{O}D]$ in D_2O.

ing hydrophobicity of the reagent, which would be expected if drawing the reagents deeper into the Stern layer of the micelle increases beneficial Coulombic interactions with the charged head groups.[4-7,22] The dependence of micellar catalysis with substrate hydrophobicity is often much larger than that seen here, suggesting that reaction occurs in a water-rich region at the micellar surface, with interactions between water and the anionic transition state, which is consistent with the observation that nonionic micelles strongly inhibit reactions of *p*-nitrophenyl diphenyl phosphate with hydroxide or fluoride ion.[20]

The hydroxyethyl surfactant (I) is a considerably better catalyst than CTABr, in agreement with earlier evidence, and the variation of the maximum values of k_ψ with hydroxide ion concentration is similar to that observed earlier and can be explained in terms of an equilibrium between I and II.[10]

At similar pH micelles of the hydroxyethyl surfactant (I) which are converted partially into the zwitterion II are considerably better reagents than hydroxide ion in CTABr, and functional micelles are generally better catalysts than nonfunctional micelles, because of the more favorable entropies of activation. However, in the absence of micelles the cholinate ion is also a better nucleophile than hydroxide ion,[10] suggesting that the quaternary ammonium centers in micellar and nonmicellar systems interact favorably with the anionic moieties in the transition state (cf. ref 23).

Kinetic Deuterium Solvent Isotope Effects. Because of differences in D_2O and H_2O as solvents,[15b] there could be an isotope effect on the properties of the micelles and their interactions with solutes. However, where kinetic solvent isotope effects have been measured in the presence of micelles, for example in acid-catalyzed reactions,[24] the isotope effects have been similar to those expected by analogy with measurements in the absence of micelles. The kinetic solvent isotope effects upon reactions of diethyl and *p*-nitrophenyl diphenyl phosphate in water and CTABr are similar (Table II), suggesting that here too the isotope effect depends on mechanism rather than on micellar properties.

In many reactions of lyate ion, there is a small inverse deuterium isotope effect,[18] because OD^- is a better nucleophile than OH^- as well as being a stronger base. Our results with *p*-nitrophenyl diethyl phosphate accord with these observations, but there is a small normal isotope effect on the reaction of *p*-nitrophenyl diphenyl phosphate, probably owing to differences in solvation, although the fastest of these reactions was only just within the range of measurement by conventional methods.

The mechanistically distinctive observations are on the reactions of *p*-nitrophenyl di-*n*-hexyl phosphate (IIIb). In CTABr the isotope effect is the same for this reaction and that of the diethyl compound (Table II). (We did not attempt to measure k_{H_2O}/k_{D_2O} for reaction of IIIb in water because of its low solubility.) In the presence of micellized hydroxyethyl surfactant I the inverse isotope effect gradually disappears with increasing concentration of lyate ion (Table II).

The equilibrium between I and the zwitterion II should move in favor of the latter with a change of solvent from protium to deuterium oxide, leading to the inverse deuterium solvent isotope effect. With increasing stoichiometric concentration of lyate ion this conversion should increase and as it becomes complete the observed kinetic solvent isotope effect will not depend upon the acid–base equilibrium between I and II, but only upon the kinetic isotope effects on the reaction of the alkoxide moiety in II with the substrate and any effects caused by differences in properties of the micelles in H_2O and D_2O, and to a first approximation these effects should not change with the stoichiometric concentration of lyate ion.

Therefore for nucleophilic catalysis the solvent deuterium isotope effect k_{H_2O}/k_{D_2O} should be inverse and close to unity, and increase to a constant value with increasing hydroxide ion concentration.

This change in the kinetic solvent isotope effect is fully consistent with mechanism 1 and it does not fit mechanisms involving general acid or base catalysis. For example, in reactions of *p*-nitrophenyl diphenyl phosphate catalyzed by functional micelles derived from histidine[13] or imidazole,[25] we observe $k_{H_2O}/k_{D_2O} \sim 2.5$, which is consistent with the imidazole moiety acting as a general base, and small isotope effects are observed when histidine or imidazole acts as a nucleophile.

We have no model on which to predict the solvent isotope for mechanism 4 although it is difficult to see how it could explain the systematic change in the isotope effect with increasing hydroxide ion concentration.

Registry No.—I, 20317-32-2; IIIa, 311-45-5; IIIb, 57016-65-6; *p*-nitrophenyl diphenyl phosphate, 10359-36-1.

References and Notes

(1) Support of this work by the Arthritis and Metabolic Diseases Institute of the U.S. Public Health Service is gratefully acknowledged.
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Micellar Effects on the Hydrolysis of *p*-Nitrobenzoyl Choline and the Related *N*-Hexadecyl Ester[1]

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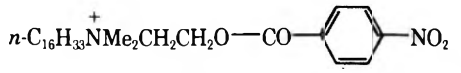
The reaction of hexadecyl(2-hydroxyethyl)dimethylammonium bromide *p*-nitrobenzoyl ester (n-$C_{16}H_{33}N^+Me_2CH_2CH_2OCOC_6H_4NO_2Br^-$, I) with hydroxide ion is catalyzed to similar extents by cationic micelles of hexadecyltrimethylammonium bromide (CTABr) or hexadecyl(2-hydroxyethyl)dimethylammonium bromide (n-$C_{16}H_{33}NMe_2CH_2CH_2OHBr^-$, II), suggesting that the greater catalytic efficiency of II in other reactions is due to nucleophilic attack by the zwitterion generated by II at high pH. Saponification of the more hydrophilic *p*-nitrobenzoyl choline (III) is not micellarly catalyzed. In the absence of surfactant I is slightly more reactive than III in aqueous dioxane and the reactions slow as the solvent becomes more aqueous, but there is a rate minimum in reactions of I at ca. 95 mol % water, and the rate increases in more aqueous solvents owing to association of I.

The biological importance of acetyl choline makes choline esters interesting substrates for mechanistic work[2] and a systematic study has been made of substituent effects upon reactions of hydroxide ion with benzoyl cholines.[3] We have kinetic evidence for the intermediacy of a related ester, hexadecyl(2-hydroxyethyl)dimethylammonium bromide *p*-nitrobenzoyl ester (I), in reactions of *p*-nitrobenzoyl phosphate in dilute alkali catalyzed by micelles of the choline derivative (II),[4] and we were therefore interested in the hydrolysis of I.

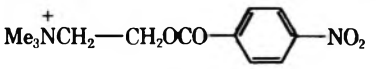


I

II

Micelles of II are effective catalysts of phosphate ester hydrolysis,[9] and of SN2 and E2 reactions at saturated carbon, and of reactions of carboxylic esters and amides.[10]

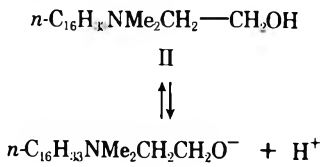
We also compared the reactivity of I with that of *p*-nitrobenzoyl choline (III), because self-micellization of I could make it more reactive than III toward anionic nucleophiles.



III

There has been considerable work on the reactions of esters of long-chain *n*-alkane carboxylic acids with *n*-alkyl amines and related compounds.[11-14] Comicellization has been shown to be of great importance in many of these reactions, and both the overall reaction rate and the kinetic form changes when the reactants are micellized.[11,12] Substrate micellization is also of great importance in hydrolysis of monoalkyl sulfates in both acidic and basic media.[15] Many biological reactions occur at interfaces, and the use of chemically inert micelles and micellized reactants can give evidence on the role of these microscopic medium effects;[5-8,16] for example, the hydroxyethyl head group of II can be regarded as a model for the corresponding group in serine which is implicated as a nucleophile in many enzymic reactions.[17]

In this work we compare reactivities of I and III in the presence of micelles of the cationic surfactants (detergents), hexadecyltrimethylammonium bromide (CTABr) and II. At high pH micelles of the choline-derived surfactant II are effective reagents for the decomposition of di- and trisubstituted phosphate esters, and it was suggested that the alkoxide moiety of the zwitterion IV attacked the phosphoryl group.[9b]



II

IV

Although in nucleophilic reactions involving II[10,18] the alkoxide moiety could act as a nucleophile, other reasonable mechanisms can be postulated.[9,10] For example, the hydroxyl moiety could act as a general acid and assist attack of hydroxide ion, or the alkoxide moiety in IV could act as a general base and activate a water molecule (cf. ref 19), and it has also been suggested that micelles of II activate hydroxide ions.[10] The kinetic form of the reaction and its pH–rate profile do not distinguish between these possibilities.

Nucleophilic attack by IV upon I gives no chemical change, and in that event micelles of II should be no better catalysts than micellized CTABr. However, if II is more ef-

Table I
Reaction of p-Nitrobenzoyl Choline Iodide[a]

H_2O, wt %	H_2O, mol %	k_ψ, sec^{-1}
100	100	0.126
95	98.9	0.133
90	97.8	0.167
80	95.1	0.229
70	91.9	0.341
60	88.0	0.576
50	83.0	0.931

[a] At 25.0° and 0.01 *M* NaOH.

fective than CTABr, it would appear that it is acting in some other way than as a nucleophile; cf. ref 9, 10.

Experimental Section

Materials. p-Nitrobenzoyl choline (III) was prepared as the iodide from MeI and 2-dimethylaminoethyl p-nitrobenzoate,[3] and was recrystallized from 85% EtOH–H_2O. It had mp 238–239° dec (lit.[3] 238–239° dec). It was bright yellow as a solid or in Me_2SO, but it was colorless in H_2O, EtOH, and Me_2CO. However, this difference may be due in part to its low solubility in some of these solvents. It was converted into its nitrate by treatment with $AgNO_3$ in MeOH, which after recrystallization (95% EtOH), gave fine, colorless needles, mp 211–213° dec.

The NMR spectra (60 MHz) of the iodide and nitrate were very similar in Me_2SO-d_6, as was that of the nitrate in Me_2CO-d_6 or D_2O. Because of low solubility only a poor NMR spectrum was obtained in D_2O, and Me_2SO was the only solvent which could be used with the iodide. The NMR spectra in Me_2SO-d_6 (60 MHz) had the following τ values: 1.76, partially resolved pair of doublets (4); 5.27, multiplet (2); 6.13, multiplet (2); 7.66 (9). The relative peak areas are in parentheses.

The uv and visible spectra were examined in Me_2SO. For both the iodide and the nitrate λ_{max} 260 nm [ϵ 11200 (nitrate) and 11500 (iodide)]. There was no maximum in the visible region, but when the spectra were measured using 0.027 *M* ester in 0.1-mm cells, the absorbance of the iodide was considerably higher than that of the nitrate in the region 280–350 nm. This difference disappeared when the concentration was reduced to 10^{-2} *M*, so that the color apparently depends on an interaction between p-nitrobenzoyl choline and iodide ions in the solid or in relatively concentrated solution.

Hexadecyl(2-hydroxyethyl)dimethylammonium bromide p-nitrobenzoyl ester (I) was prepared by reaction of p-nitrobenzoyl chloride with II in dry pyridine for 12 hr (cf. ref 14a). The pyridine was removed in vacuo, and recrystallization (twice) from CCl_4–$CHCl_3$ removed the pyridine salts; I was obtained largely as the bromide, but slightly contaminated with the chloride. Another sample prepared from 1-bromohexadecane and 2-(dimethylamino)ethyl p-nitrobenzoate in refluxing $CHCl_3$ for 24 hr had mp 122–124° after recrystallization from $CHCl_3$–CCl_4. (Anal. Calcd: C, 59.6; H, 8.7; N, 5.2; Br, 14.7. Found: C, 59.3; H, 9.0; N, 5.3; Br, 14.5.) The samples had the same chemical properties.

The NMR spectrum of I at 60 MHz in $CDCl_3$ had the following τ values: 1.79, singlet (4); 5.10, multiplet (2); 5.67, multiplet (2), 6.30, multiplet (2); 5.67 multiplet (2); 6.30, multiplet (2); 6.47, singlet (6); 8.78 (31). The relative peak areas are in parentheses.

The preparation and purification of the surfactants have been described.[9] A purified sample of 8-anilinonaphthalenesulfonic acid (ANSA) was provided by Professor H. W. Offen and Mr. C. Mastrangelo. Dioxane was refluxed over Na and redistilled under N_2. The mixed solvents were made up by weight using redistilled deionized water.

Critical Micelle Concentration. The critical micelle concentration (cmc) of I in neutral water–dioxane (95:5 w/w) was determined using a fluorescent dye, and by light scattering.[20] The fluorescence spectra of 10^{-6} *M* ANSA were measured over a range of concentrations of I in a Perkin-Elmer MPF3 spectrometer, with excitation at 365 nm. There was a sharp increase in the intensity of the fluorescence emission beginning at 2×10^{-5} *M* I.[20a,b] This method tends to give low cmc values because the hydrophobic dye can induce micellization,[20c] and light scattering from I was measured on a Sofica Photo Goniodiffusometer, Model 42000 using incident light at 546 nm for solutions of I. The solutions were centrifuged before measurement to remove dust particles, and there was a sharp increase in the 90° scattering (and at 45° and 60°) at 3.5×10^{-5} *M* I, and the scattering became constant at concentrations > 4×10^{-5} *M*. [We could not obtain transparent solutions of I greater than 6×10^{-5} *M*, because of its low solubility in water–dioxane (95:5 w/w).]

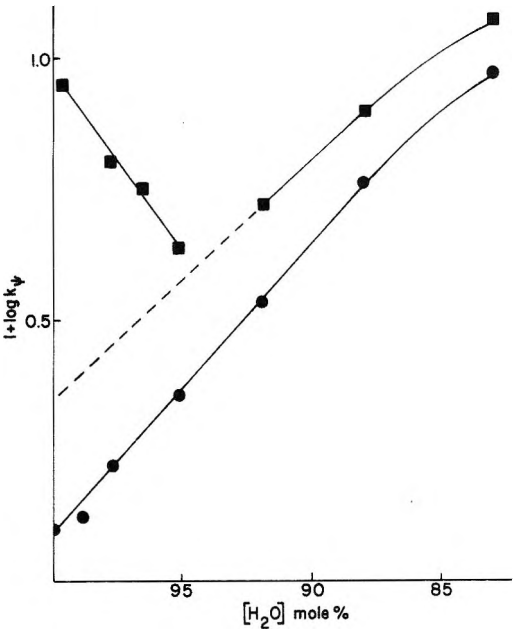


Figure 1. Reaction of p-nitrobenzoyl choline (●) and hexadecyl(2-hydroxyethyl)dimethylammonium bromide p-nitrobenzoyl ester (I) (■) with 10^{-2} *M* NaOH in aqueous dioxane at 25.0°.

Kinetics. The slower reactions were followed at 262 nm using a Gilford spectrophotometer with water-jacketed cells at 25.0°. The faster reactions were followed at 25.0° on a Durrum stopped flow spectrophotometer with a logarithmic amplifier and a Biomation 805 Waveform recorder for data acquisition. This equipment allowed us to follow the small changes in absorbance during reaction with low substrate concentrations. In the absence of surfactant we generally used 3×10^{-5} *M* substrate and obtained an absorbance change of ca. 0.3, and in some of these experiments we deliberately used higher concentrations of the ester I in order to observe effects due to its association. Surfactants were in at least 50-fold excess over substrate. The first-order rate constants, k_ψ, are in sec^{-1}, and the surfactant concentration is designated C_D. All reactions of I in the absence of surfactant were in aqueous dioxane because of its very low solubility in water.

Good first-order rate plots were obtained over about 3 half-lives except for some of the reactions of I in solvents of high water content in the absence of surfactant for which the plots were curved. We believe that this curvature is due to substrate association, which is discussed in the Results and Discussion section, and we quote initial rate constants for these reactions.

Most of the reactions were followed in 10^{-2} *M* NaOH, but more dilute alkali was used in a few experiments with I in water–dioxane (95:5 w/w) and in the presence of surfactant. We did not use buffers, because of their possible effects as electrolytes. In comparing the two sets of results we calculated the second-order rate constants as $k_\psi/[OH]$ with $[OH]$ being calculated from the pH of the more dilute alkali.

Results and Discussion

Reactions with Hydroxide Ion in the Absence of Added Surfactant. The rate constants for reaction of p-nitrobenzoyl choline iodide (III) in 0.01 *M* NaOH increase steadily with decreasing water content of the solvent (Table I) and a plot of log k_ψ against the mole percent of water is approximately linear (Figure 1). This solvent effect is consistent with the qualitative solvent theory of Hughes and Ingold,[21] but increased hydration of hydroxide ion in the more aqueous solvents is almost certainly important (cf. ref 22).

The solvent effect upon reaction of the hexadecyl derivative I is more complex. In solvents of relatively low water content the rate constant increases with dioxane content of

Table II
Reaction of I in the Absence of Added Surfactant[a]

H_2O, wt %	H_2O, mol %	k_ψ, sec^{-1}
80	95.1	0.43
75	93.6	0.47
70	91.9	0.53
60	88.0	0.79
50	83.0	1.18

[a] At 25.0° with 0.01 *M* NaOH.

the solvent (Table II and Figure 1), as for hydrolysis of *p*-nitrobenzoyl choline, but there is a minimum in a plot of log k_ψ against solvent composition (Figure 1). This figure only qualitatively represents the relation between rate constant for reaction of I and solvent composition, because for the four most aqueous solvents the concentrations of I differed slightly and were 0.026, 0.037, 0.040, and 0.035 m*M* for 95, 90, 85, and 80 wt % water, respectively. With the more aqueous solvents the first-order rate constants increase with increasing substrate concentration, but this dependence of rate on substrate concentration disappears as the water content of the solvent decreases (Figure 2). Therefore the rate minimum at water–dioxane (80:20 w/w) (95 mol % of water) in reactions of I probably arises from substrate self-association which should markedly assist attack of hydroxide ion (cf. ref 15), but even at relatively high dioxane concentrations I is slightly more reactive than *p*-nitrobenzoyl choline (by a factor of ca. 1.25). A hydrophobic solute such as I should micellize in solvents of high water content, although addition of solvents such as dioxane increases the cmc of cationic surfactants, and normal micelles do not form in solvents of high dioxane content.[20a,23] The rate increase with increasing [I] begins at concentrations well below the cmc (Experimental Section), suggesting that the substrate is forming submicellar aggregates which are more reactive than monomeric substrate. There is extensive kinetic and other evidence for the formation of submicellar aggregates, usually between solute and surfactant.[5–7,24]

Most of the runs with I were done using 0.01 *M* NaOH, but with this concentration the faster runs were in the range requiring use of a stopped flow spectrometer. The maximum usable concentration of I was then halved during mixing and because of the low solubility of I we could not use a large concentration range. Therefore some experiments were done with more dilute alkali using a Gilford spectrometer and we then were able to use a concentration of I large enough to observe a considerable rate enhancement, but we did not reach a concentration high enough to give the rate plateau which should be found when a substrate is wholly micellized (Figure 2).

One consequence of substrate association is that the reactions of I are not first order under all conditions. If an associated substrate reacts more rapidly than monomeric substrate, the instantaneous first-order rate constants will decrease during reaction because the relative amount of self-associated substrate will decrease as the total substrate concentration decreases. To avoid this difficulty we estimated initial first-order rate constants for the reactions of I in the more aqueous solvents where we found curved first-order rate plots, i.e., for the reactions in 95 wt % water. There was no curvature of the first-order rate plots for reactions of *p*-nitrobenzoyl choline (III) or for reactions of I in the less aqueous solvents or when the substrate concentration was low.

The self-association of I and its low solubility prevents our measuring directly the first-order rate constant for reaction of monomeric I in aqueous alkali, but we estimate it

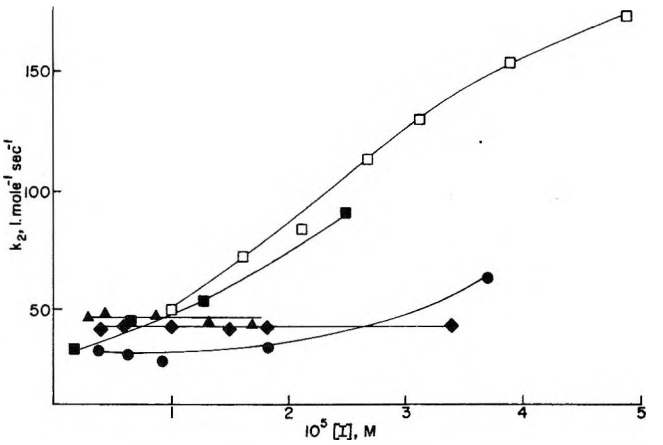


Figure 2. Variation of second-order rate constant for reaction of I in alkaline aqueous dioxane. Solid points, 10^{-2} *M* NaOH; open points, pH 11. □ ■, 95; ●, 90; ◆, 80; ▲, 75 wt % water.

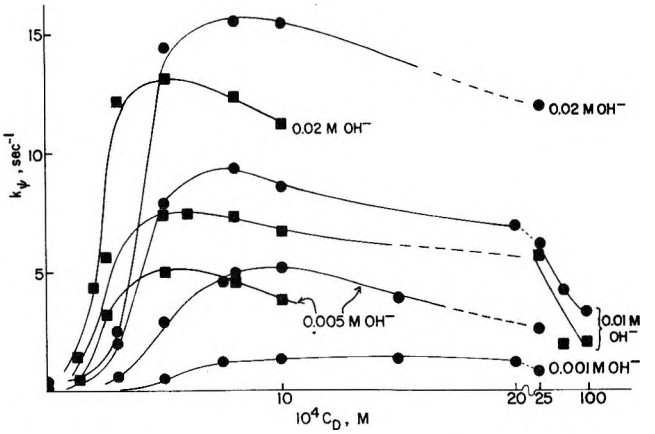


Figure 3. Reactions of I in CTABr (●), and in hexadecyl(2-hydroxyethyl)dimethylammonium bromide (II) (■) in aqueous alkali at 25.0°.

in two ways. (1) If the relative reactivities of *p*-nitrobenzoyl choline (III) and the analogous (monomeric) hexadecyl derivative I are approximately the same in water and 95 mol % water, we can correct the value of k_ψ = 0.43 sec^{-1} (Table II) by the factor of 0.12/0.23, which is given by the relative rates of reaction of *p*-nitrobenzoyl choline in the two solvents (Table I), giving $k_\psi \sim 0.24$ sec^{-1} for reaction of monomeric I in 10^{-2} *M* NaOH in water; or (2) we can extrapolate log k_ψ to zero dioxane (Figure 1), also giving $k_\psi \sim 0.23$ sec^{-1}. There is considerable uncertainty in this value because of the nature of the extrapolations.

Reactions with Hydroxide Ion in the Presence of Added Surfactant. Cationic micelles of either CTABr or the choline derivative II do not catalyze the reaction of *p*-nitrobenzoyl choline (III) with hydroxide ion, almost certainly because this cationic substrate is insufficiently hydrophobic to be incorporated into the cationic micelles and in aqueous 0.01 *M* sodium hydroxide k_ψ = 0.126 sec^{-1}, and 0.118 sec^{-1} with 10^{-3} *M* CTABr and 0.132 sec^{-1} with 10^{-3} *M* II. However the reaction of the hexadecyl derivative I in water is catalyzed by micelles of CTABr and of II (Figure 3). The plots of k_ψ against surfactant concentration show the maxima typical of bimolecular micellar-catalyzed reactions.[5–8,25] There was no curvature in the first-order rate plots when surfactant was present.

The micellar catalyses (k_{rel}) given in Table III are calculated using the estimated value of k_ψ = 0.23 sec^{-1} for reaction in water. These rate enhancements are similar to those found for micellar-catalyzed hydrolyses of esters of aliphat-

Table III
Micellar Rate Enhancements of Reaction of I[a]

	Surfactant	
$[\overline{OH}]$, *M*	CTABr	n-$C_{16}H_{33}\overset{+}{N}Me_2CH_2CH_2OH\ Br^-$
0.005	45 (10)	43 (5)
0.01	41 (8)	33 (5)
0.02	34 (8)	29 (5)

[a] At 25.0°; and calculated using k_ψ = 0.23 for reaction in 10^{-2} *M* NaOH in water. The values in parentheses are the concentrations (m*M*) of surfactant at the rate maxima.

ic alcohols,[5-8,26] and they decrease slightly with increasing hydroxide ion concentration as is often found for bimolecular micellar-catalyzed reactions.

The key point is that micellized II is no more effective than CTABr in catalyzing the hydrolysis of the hexadecyl derivative I, although in bimolecular reactions of phosphate esters,[9] acyl phosphates,[27] and alkyl halides, carboxylic esters, and amides[10] micellized surfactants carrying a choline-related head group are much better catalvsts than the corresponding tetraalkylammonium ions. We therefore conclude that micelles of I are not acting as general acids or bases and are not activating hydroxide ions, and therefore by inference the high reaction rates in the presence of I involve nucleophile attack upon the substrate by the alkoxide moiety of the zwitterion IV. This conclusion is supported by observation of formation of an intermediate in reactions of 2,4-dinitrochloro- and fluorobenzene in the presence of II.[28]

The simplest explanation of all the high reaction rates is in terms of nucleophilic attack by the alkoxide moiety. We could also assume that attack is by the hydroxyl group of I with IV or hydroxide ion acting as a general base. All these mechanisms lead to the same rate dependence on pH, but those involving proton transfer to a general base should generate a kinetic solvent deuterium isotope effect which is not observed in phosphate ester reactions in the presence of I.[29]

Cationic micelles increase the nucleophilicity of amines toward halonitrobenzenes and the 2,4-dinitrophenyl phosphate dianion,[30] but addition of 10^{-4} *M* dodecylamine to 1.5×10^{-3} *M* CTABr reduces the rate of reaction of I with 10^{-3} *M* hydroxide ion by 30%, presumably because the amine behaves as an inert organic solute in reducing the catalytic efficiency of the micelle (cf. ref 5b and 31), and there is no indication of any concerted action of hydroxide ion and the amine under these conditions.

Registry No.—I, 57016-81-6; II, 20317-32-2; III iodide, 28080-49-1; III nitrate, 57016-82-7; $AgNO_3$, 7761-88-8; *p*-nitrobenzoyl chloride, 122-04-3; 1-bromohexadecane, 122-82-3; 2-(dimethylamino)ethyl *p*-nitrobenzoate, 38152-22-6.

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Reactions of Carbocations with a Nucleophilic Surfactant and Related Alkoxide Ions[1]

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Micelles of 1-hydroxyethyl-2-dimethylhexadecylammonium bromide (I) are effective reagents for the decomposition of malachite green (MG^+) at high pH, giving approximately 600-fold rate enhancement over the hydroxide ion reaction. The decomposition of the tri-*p*-anisylmethyl cation (R^+) at high pH is also strongly catalyzed by micelles of I. This catalysis can be explained in terms of nucleophilic participation by the alkoxide zwitterion of I. At high pH, in the absence of micelles, 2,2,2-trifluoroethanol, propargyl alcohol, and choline are more effective reagents than expected from their dissociation constants, and the reactivities of the alkoxide ions, relative to hydroxide ion follow: $CF_3CH_2O^-$, 2.7 (2.6); $HC{\equiv}CCH_2OH$, 16 (10); $Me_3N^+CH_2CH_2O^-$, 13 (7). The values in parentheses are for reactions of R^+.

Micellar effects upon the equilibrium constants of the reaction of triarylmethyl carbocations with hydroxide ion were rationalized in terms of Coulombic interactions by Hartley and co-workers,[2] and Duynstee and Grunwald showed that the forward reaction was catalyzed by cationic and inhibited by anionic micelles,[3] e.g., for malachite green [bis(4-dimethylaminophenyl)phenylmethyl cation]

$$MG^+ + OH^- \rightleftarrows MGOH$$

More recently the effects of added salts and changes in the lengths of the alkyl group of the surfactant upon the reaction of crystal violet [tris(4-dimethylamino)phenylmethyl cation] have been examined.[4] Micellar catalysis is discussed in ref 5–8.

Functional micelles of surfactants which contain reactive groups are effective nucleophilic or basic reagents,[5–10] but they generally have been used for reactions of organic or inorganic esters. Micelles of surfactants containing a hydroxyethyl head group are effective reagents in reactions of di- and trisubstituted phosphate esters,[10] and our aim was to examine rate enhancements due to micelles of 1-hydroxyethyl-2-dimethylhexadecylammonium bromide (I) because choline is converted into its zwitterion at high pH with $pK_a = 13.9$,[11] and I should give the zwitterion, II.[10,12]

$$n\text{-}C_{16}H_{33}N^+Me_2CH_2{-}CH_2OH \rightleftarrows$$
I

$$n\text{-}C_{16}H_{33}N^+Me_2CH_2CH_2O^- + H^+$$
II

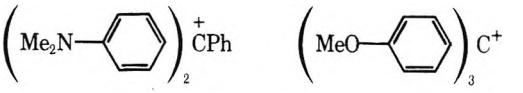
In addition we were interested in the nucleophilicity of the zwitterion (III) of choline and of alkoxide ions of propargyl alcohol and 2,2,2-trifluoroethanol toward carbocations.[13] The rates of nucleophilic attack upon relatively unreactive dye cations have been used to formulate the N^+ scale of nucleophilicity.[14]

$$Me_3N^+CH_2CH_2OH \rightleftarrows Me_3N^+CH_2CH_2O^- + H^+$$
III

Despite the cationic center, III is a good nucleophile toward phosphate esters[10] and halonitrobenzenes.[17] Bulky alkoxide ions are much better reagents than hydroxide ion in deacylations,[18,19] although in these reactions the partitioning of a tetrahedral intermediate could depend on the nature of the nucleophile, but this is not a problem for an association reaction with a carbocation.

As carbocations we used malachite green (MG^+) and the trianisylmethyl cation, R^+.

In the original work with the relatively stable dye cations, e.g., MG^+, both the rate and equilibrium constants for reaction with hydroxide ion were determined.[3,4] We measure only the forward rate constants because the zwitterion, II, is generated at high pH, where the equilibria are wholly toward MGOH and ROH. The reaction of R^+ with hydroxide ion is only weakly catalyzed by cationic micelles of CTABr, which do not affect the reaction with water.[20]



MG^+ R^+

Micelles of I in alkali effectively speed S_N2[21] and E2[22] reactions at saturated carbon, and it was suggested that this reaction was of hydroxide ions activated by the micelle,[21] but the evidence is equally consistent with II acting as a nucleophile or a general base, and evidence on deacylations catalyzed by micelles of I strongly supports nucleophilic attack by II, although in this system the substrate was in large excess over the surfactant, so that it could control the micellar structure.[23]

Experimental Section

Materials. The alcohols were commercial samples and were crystallized or redistilled before use, and the surfactant was prepared as described.[10] All rate measurements were made using deionized and redistilled water which had been degassed before use for the experiments on the stopped flow spectrophotometer. Choline was added as its chloride and I as its bromide.

Kinetics. The reactions were followed spectrometrically by following the absorbances at 480 nm of R^+ and at 616 nm for MG^+. Gilford spectrophotometers were used for the slower reactions and a Durrum stopped flow spectrophotometer with a Biomation 805 data acquisition unit was used for the faster reactions. Solutions of MG^+ were added at pH 4 and those of R^+ in 0.1 *M* HCl.[15] All reactions were followed at 25.0°. Our values of the second-order rate constants for reactions of R^+ and MG^+ with OH^- are in reasonable agreement with earlier results.[14,15a]

For reactions of R^+ with the surfactant it was generally in one syringe with NaOH and R^+ in HCl was in the other.[15a,20]

Products. Several tests were used to show that the initial products are ethers.

(1) Immediately after complete reaction of MG^+ with 0.1 *M* choline chloride + 0.05 *M* OH^- the pH of the solution was reduced to 7.1 with HCl, and the absorbance due to MG^+ increased from zero to ca. 40% of the initial absorbance and then gradually decreased to an equilibrium value (ca. 25% of the initial absorbance).

Similar observations were made on the products of the reactions of MG^+ with trifluoroethanol and propargyl alcohol, showing that the initially formed ethers gradually decomposed to give the carbocation and then the alcohol under thermodynamic control.

We have similar spectroscopic evidence for ether formation in the reaction of MG^+ with 6×10^{-3} *M* I in 10^{-2} *M* NaOH. After complete reaction the pH was reduced to 7 and the absorbance slowly increased from zero to 10% of that of the original MG^+ and then slowly fell toward the equilibrium value of ca. 2%. The differences in the magnitude of the absorbance changes in this reaction

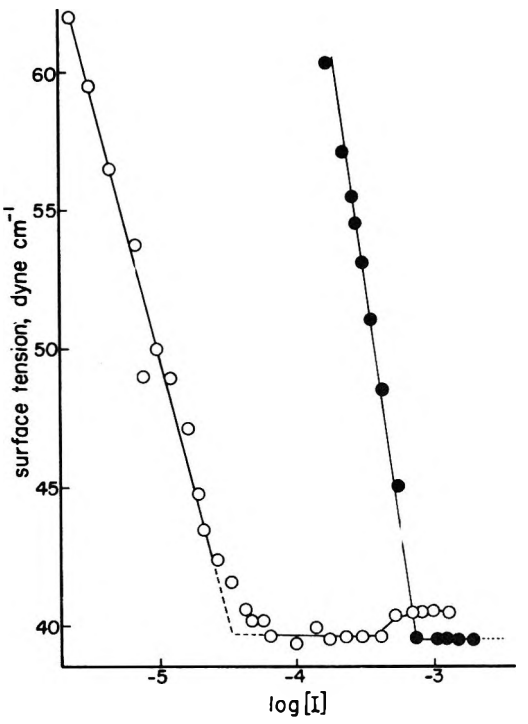


Figure 1. The variation of surface tension with concentration of 1-hydroxyethyl-2-dimethylhexadecylammonium bromide (I): ●, in water; ○, in 0.1 *M* NaOH.

and the corresponding one with choline are due to the effects of the micelle in slowing dissociation of the initially formed ether, n-$C_{16}H_{33}N^+Me_2CH_2CH_2OMG$, and speeding the subsequent reaction of MG^+ with OH^-, and in changing the equilibrium between MG^+ and MGOH (cf. ref 3 and 4).

(2) The reaction mixture of MG^+ with 0.1 *M* choline chloride and 0.05 *M* NaOH was spotted, after complete reaction, onto a silica gel plate and the plate was eluted with acetone–H_2O (50:50 v/v), giving a large spot with R_f 0.11 and a small spot at R_f 0.45, which were blue after acidification. After varying periods of time the reaction mixture was reexamined, and the spot with R_f 0.11 gradually decreased in intensity and the other increased, and after 4 hr only the spot with R_f 0.45 was left. This spot was coincident with that of MGOH, and we assume that the spot with the low R_f was that of $Me_3N^+CH_2CH_2OMG$.

A similar experiment was done using R^+ in 0.1 *M* HCl and 0.16 *M* choline chloride and 0.19 *M* NaOH. The mixture was extracted with Et_2O after complete reaction and spotted onto a silica gel plate and the plate was eluted with acetone–H_2O (50:50 v/v). Two yellow spots were observed after acidification, one with R_f 0.05 and a smaller one with R_f 0.93. This second spot was coincident with that of ROH. The ether extraction did not remove all the choline ether from the aqueous reaction mixture, and the yellow color of R^+ developed when this residual water layer was acidified. A control test showed that ROH is wholly extracted by water under these conditions, and addition of 0.3 *M* Me_4NCl did not affect the extraction, so that the material left in the aqueous layer after ether extraction must have been the choline ether.

Critical Micelle Concentrations. The critical micelle concentration of I (as its bromide) in water at 24° was determined from the variation of surface tension with surfactant concentration and a plot of surface tension against log [I] gave a linear plot with a sharp break (Figure 1), and the critical micelle concentration was 8 × 10^{-4} *M*. This value is, as expected, very close to the cmc of CTABr for which values range from 8 to 10 × 10^{-4} *M*.[24] Typically cmc's for similarly charged surfactants are dependent more on the length of the long hydrophobic chain than on the structure of the head group. For the chloride corresponding to I, cmc = 1.2 × 10^{-3} *M* in water at 30°, and this value is close to that of 1.3 × 10^{-3} *M* for CTACl.[24]

The value of the cmc of I was also measured in 0.1 *M* NaOH at 24°, and under these conditions cmc = 3.5 × 10^{-5} *M*. However, a plot of surface tension against log [I] did not give a sharp break (Figure 1), and there was considerable curvature in the plot at concentrations just above the cmc. This curvature is understandable because the composition of the micelle will be changing because of the equilibrium between the cationic surfactant (I) and its zwitterion. This marked decrease is understandable because conversion of I into its zwitterion should markedly reduce the head group repulsions which tend to disrupt a micelle. Our kinetic estimate of pK_a = 12.4 for micellized I suggests that conversion into the zwitterion should be extensive in 0.1 *M* NaOH.[10] Added salts decrease cmc, but effects as large as those we observe with NaOH would not be expected if there was no chemical change because hydrophilic counterions generally have only small effects on micellization.[5-8,24]

Results and Discussion

Reactions in the Absence of Surfactant. Choline, propargyl alcohol, and 2,2,2-trifluoroethanol increase the rates of disappearance of malachite green (MG^+) and the tri-*p*-anisylmethyl cation (R^+) in alkali (Tables I and II). Various effects have to be separated in estimating the reactivities of the choline zwitterion (III) or the alkoxide ions toward the carbocations, because allowance has to be made for the concurrent reactions with hydroxide ion and water.[14-16] Conversion into an alkoxide or zwitterion decreases the hydroxide ion concentration as shown for choline (eq 1), and the concentrations of the alkoxide nucleophiles are estimated using pK_a = 13.9 for choline,[11] 13.55 for propargyl alcohol, and 12.4 for 2,2,2-trifluoroethanol.[25]

$$Me_3N^+CH_2CH_2OH + OH^- \rightleftharpoons \underset{\text{III}}{Me_3N^+CH_2CH_2O^-} \quad (1)$$

Attack by nucleophilic anions and water upon R^+ is retarded by most electrolytes, although quaternary ammonium halides in low concentration only slightly retard these reactions but in high concentration speed them.[15,16] However, we neglect these electrolyte effects because of the low

Table I
Reaction of MG^+ in the Presence of 2,2,2-Trifluoroethanol, Propargyl Alcohol, or Choline[a]

R'OH	10^2 [R'OH]$_0$, *M*	10^2 [OH^-]$_0$, *M*	10^3 [RO^-], *M*	$10^2 k_\psi$, sec^{-1}	$10^2 k_\psi^N$, sec^{-1} [b]	k_2^N, l. mol^{-1} sec^{-1}
CF_3CH_2OH	2.0	1.73	6.2	4.30	2.5	4.0
	12	1.73	14.2	6.97	6.5	4.5
	20	1.73	15.4	7.41	7.1	4.6
$HC{\equiv}CCH_2OH$	1.0	1.75	0.46	3.85	1.1	23
	2.0	1.75	0.90	4.95	2.2	25
	6.3	1.75	2.45	9.12	6.7	27
	12.1	1.75	4.33	14.4	12.2	28
	20.1	1.75	6.20	17.2	15.3	25
$Me_3\overset{+}{N}CH_2CH_2OH$	2.5	4.16	1.21	9.59	3.0	25
	5.0	4.16	2.35	11.3	4.9	21
	10.0	4.16	4.47	14.3	8.2	18
	10.0	0.83	0.92	3.06	1.9	20
	10.0	2.08	2.3	7.28	4.3	19

[a] At 25.0°. [b] Calculated using k_2^{OH} = 1.64 l. mol^{-1} sec^{-1}.

Table II
Reaction of R^+ in the Presence of 2,2,2-Trifluoroethanol, Propargyl Alcohol, or Choline[a]

R'OH	10^2 [R'OH]$_0$, M	10^2 [R'O$^-$], M	k_ψ, sec^{-1}	k_ψ^N, sec^{-1} [b]	10^{-4} k_2^N, l. mol^{-1} sec^{-1}
CF_3CH_2OH	3.0	0.94	252	170	1.8
	6.0	1.33	288	232	1.7
	10	1.57	298	257	1.6
$HC{\equiv}C{-}CH_2OH$	1.0	0.052	188	48	~9
	3.0	0.15	233	99	6.6
	6.0	0.28	286	161	5.8
	10.0	0.43	412	296	7.0
$Me_3\overset{+}{N}CH_2CH_2OH$	10.0[c]	0.27	234	108	4.0
	10.0[d]	0.33	299	177	5.4

[a] At 25.0° with 0.02 M stoichiometric hydroxide ion unless specified. [b] Calculated using k_2^{OH} = 6580 l. mol^{-1} sec^{-1}, and k^{H_2O} = 12 sec^{-1}. [c] With 0.025 M stoichiometric hydroxide ion. [d] With 0.03 M stoichiometric hydroxide ion.

concentration of choline chloride (Tables I and II); for example, 0.5 M tetramethylammonium chloride reduces the rate of attack of hydroxide ion upon R^+ by ca. 30%.[15] (The rate increases at higher concentrations of the salt.) The cholinate zwitterion and anions of 2,2,2-trifluoroethanol and propargyl alcohol are good nucleophiles toward the carbocations. The first-order rate constants for the overall reactions are in Tables I and II, and the first- and second-order rate constants (k_ψ^N and k^N) for reactions of the alkoxide nucleophiles are calculated using pK_a values after allowing for the contributions of the reactions with water and hydroxide ion. In all these reactions we assume that the hydroxide ion and the other nucleophile, the zwitterion (III) or an alkoxide ion, do not affect each other's reaction (eq 2).

$$k_\psi = k_\psi^{H_2O} + k_2^{OH}[OH^-] + k_2^N[N] \qquad (2)$$

(where N = $Me_3N^+CH_2CH_2O^-$; $CF_3CH_2O^-$; $HC{\equiv}C{-}CH_2O^-$)

The contribution of the water reaction ($k_\psi^{H_2O}$) can be neglected for the reaction of MG^+. The values of k_2^N are reasonably independent of reagent concentrations, but they inevitably depend upon the pK_a values.

The nucleophilicities toward MG^+ (and R^+ in parentheses) relative to those of hydroxide ion follow: $CF_3CH_2O^-$, 2.7 (2.6); $HC{\equiv}C{-}CH_2O^-$, 16 (10); $Me_3N^+CH_2CH_2O^-$, 13 (7).

The overall rate differences for reactions of hydroxide ion and the alkoxide ions are similar to those found for attack upon p-nitrophenyl esters.[19] However, this similarity is not general for all oxyanions; for example, phenoxide ions are very effective nucleophiles toward R^+,[26] but show no unusual reactivity toward p-nitrophenyl acetate.[19]

The low nucleophilicities of hydroxide ion, and of other high charge density alkoxide ions such as methoxide, relative to their basicity are not unusual. They can be rationalized in terms of hard and soft reagents,[27] and we could also assume that hydroxide and small alkoxide ions merely have unusually high basicities, perhaps because of the ease with which they can transfer protons through a Grotthius chain, and strong solvation of these ions should decrease nucleophilicity more than basicity. However, the bulky organic residues may also act by modifying the solvent structure around the reaction center, or by interacting through dispersive or hydrophobic forces with the organic residues of the substrates.[6,15,16]

The results in Tables I and II, and the evidence for ether formation (Experimental Section), show that the cholinate zwitterion and the alkoxide ions of propargyl alcohol and 2,2,2-trifluoroethanol react as nucleophiles and not as general bases with the carbocations. The ethers are unstable (Experimental Section) and gradually revert to the alcohols, which are the thermodynamically controlled products, presumably by a slow formation of the carbocation, as shown for the choline ether. However, the initial reaction

$$Me_3\overset{+}{N}CH_2CH_2O^- + MG^+ \rightleftharpoons Me_3\overset{+}{N}CH_2CH_2OMG \xrightarrow{OH^-} MGOH$$

goes wholly to the ether, because the absorbance of the solution disappears in the course of the reaction.

Our rate measurements show that the quaternary ammonium moiety does not markedly reduce the nucleophilicity of the cholinate zwitterion (III), whose slightly lower reactivity than the anion of propargyl alcohol may be due to steric effects. Formation of an ion pair intermediate has been postulated in the reactions of relatively stable triarylmethyl carbocations with anions,[14] and it is therefore a little surprising that the cationic center in III has little or no effect on its nucleophilicity toward carbocations. However, there is extensive evidence for the relative unimportance of charge–charge interactions in nucleophilic reactions of charged reactants,[28] which leads us to believe that Coulombic interactions are not especially important in many carbocation–nucleophilic recombinations in aqueous solvents, even though there is evidence for ion pairs, or similar intermediates, in these reactions (cf. ref 15, 16, 26).

Micellar Reactions. Micelles of the hydroxyethyl surfactant effectively speed reactions of the carbocations, and the variations of k_ψ with surfactant concentration are typical of micellar catalysis,[3-8] as shown in Figure 2 for the reaction of MG^+. Very low concentrations of I do not affect

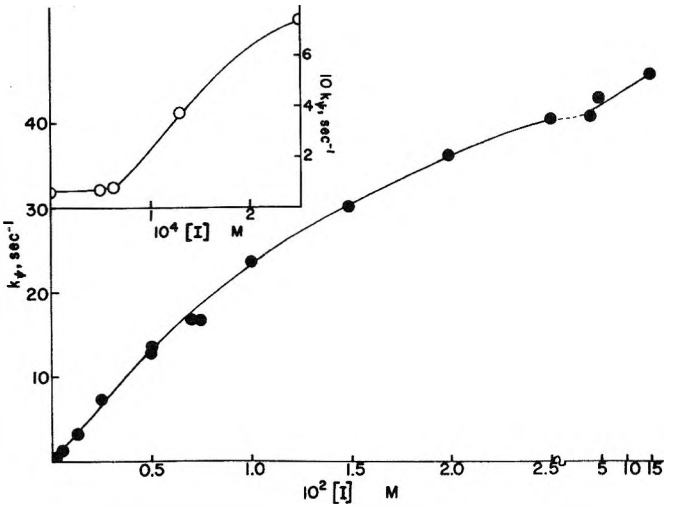


Figure 2. Catalysis of the reaction of MG^+ in 0.042 M NaOH at 25.0° by micelles of I. The inset shows the overall first-order rate constants, k_ψ, at low surfactant concentration.

Table III
Reaction of MG^+ in Micelles of I[a]

	$10\,k_\psi$, sec^{-1}	
10^3 [I], M	0.005 M OH^-	0.042 M OH^-
	0.083	0.70
0.30	0.79 (9.5)	9.5 (14)
0.60	1.97 (24)	19 (27)
3.00	5.83 (70)	81 (115)
6.00	23.3 (280)	156 (223)
30.0	39.2 (470)	400 (570)
50.0	47.1 (570)	427 (610)

[a] At 25.0°; MG^+ was added at pH 4. The values of k_ψ in 0.042 M OH^- are interpolated where necessary. The values in parentheses are the rate enhancements relative to reaction in the absence of surfactant.

Table IV
Reaction of R^+ in Micelles of I[a]

	10^2 [OH^-], M			
10^3 [I], M	0.03	0.5	2	5
	13.9	43.8	140	326
0.05			143	
0.10			188	328
0.10				319[b]
0.30	14.3	96		
0.50			630	
0.60		206		
1.0			~900	~950
1.2		337		
6.0	28		$>10^3$	$>10^3$
50	49			
110	120			

[a] Values of k_ψ, sec^{-1}, at 25.0°. [b] In this experiment the surfactant (I) was in both syringes.

the rate, but the rate increases at surfactant concentrations well below the cmc, suggesting that reaction is occurring in submicellar aggregates of MG^+ and the surfactant, or that MG^+ sharply lowers the cmc of the surfactant. Similar behavior was found for reactions of crystal violet with hydroxide ion catalyzed by nonfunctional cationic micelles.[4] We did not reach a rate plateau or maximum in reactions of MG^+, suggesting that the surfactant concentration was not high enough for the carbocations to be taken up wholly by the cationic micelles. A rate plateau was found for the reaction of crystal violet with hydroxide ion catalyzed by CTABr,[4] but crystal violet is probably more hydrophobic than MG^+.

The relation between rate and surfactant concentration can be interpreted qualitatively, and occasionally quantitatively, for micellar catalysis in terms of the distribution of substrate between micelle and bulk solvent,[29,30] although for bimolecular reactions there is a complication due to the distribution of the reagent, which is often a hydrophilic ion, between micelle and bulk solvent.[31] The situation is more complicated for these carbocation reactions where the cationic surfactant (I) is converted into the zwitterion (II) at high pH,[10] because incorporation of the cationic substrate into a cationic micelle requires that the favorable hydrophobic and dispersive interactions overcome the Coulombic repulsions, and these Coulombic repulsions decrease with increasing conversion of I into its zwitterion. Thus more substrate should be taken up into the micelle as the pH increases. At the same time the micelle itself should grow because Coulombic repulsions between the cationic head groups should decrease.

However, decreasing micellar charge is not the only reason for the high reaction rates in micelles of I as compared with CTABr, because the rate enhancements of reactions of MG^+ are similar in 5×10^{-3} and 4.2×10^{-2} M NaOH (Table III), and the main differences are at low surfactant concentrations where the effect of hydroxide ion on the cmc (Figure 1) is important.

As is generally found, these functional micelles of the hydroxyethyl surfactant (I) are much better catalysts than nonfunctional micelles of CTABr. For reaction of MG^+ with hydroxide in the presence of CTABr the rate enhancement was by a factor of 20,[3] although slightly larger rate enhancements were found for the reaction of crystal violet.[4] There is almost no catalysis by micellized CTABr of the attack of anions upon the less hydrophobic tri-*p*-anisylmethyl carbocation.[20]

The 600-fold rate enhancement of the reaction of MG^+ by micellized I (Table III) actually underestimates the nucleophilicity of the alkoxide moiety of the zwitterion (II) relative to hydroxide ion in water, because only some of the hydroxyethyl groups are converted into alkoxide.[10]

As noted earlier the cholinate zwitterion is a better nucleophile than hydroxide ion, and so much of the high reaction rates in micelles of I at high pH can be ascribed to the high nucleophilicity of the alkoxide moiety in II.[10,23]

As for the nonmicellar reactions with the cholinate and alkoxide nucleophiles, there is no complication due to partitioning of a tetrahedral intermediate in these reactions of the carbocations and micellized I. We could not examine the reaction of R^+ in the presence of micelles of I over a wide range of conditions because with increasing surfactant concentration the reaction became too fast to be followed. Micellized I is an effective reagent toward R^+ (Table IV), and this observation contrasts sharply with the absence of catalysis by micellized CTABr of the reactions of R^+ with hydroxide or azide ion.[20] It is generally assumed that the chemical processes are much slower than incorporation of reagents into the micelle. We tried to test this assumption for reaction of R^+ by having surfactant in both syringes. Unfortunately, cationic micelles sharply decrease the equilibrium formation of R^+, so that we could only do this experiment with low concentrations (10^{-4} M) of I and 0.05 M OH^-, where there is very little micellar catalysis. Although we could not observe rate plateaus in these reactions of R^+, the results in Figure 3 indicate that there is almost no catalysis in very dilute alkali, where the micelle is almost wholly cationic, cf. ref 20, but that it increases sharply as the zwitterionic surfactant (II) is formed with increasing hydroxide ion concentration.

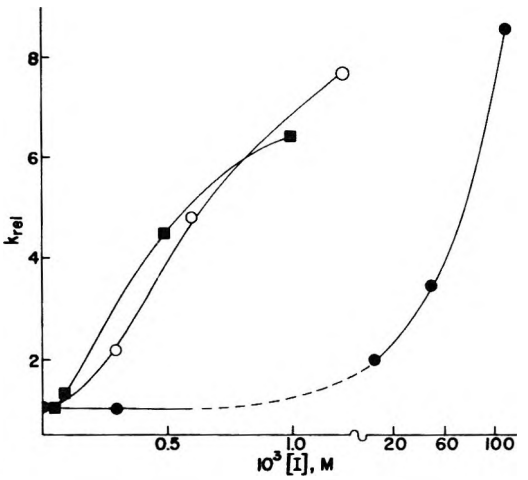


Figure 3. Catalysis of the reaction of R^+ by micelles of I: ●, 3×10^{-4} M OH^-; ○, 5×10^{-3} M OH^-; ■, 2×10^{-2} M OH^-. k_{rel} is relative to k_ψ in the absence of surfactant.

Registry No.—I, 24705-21-3; malachite green, 14426-28-9; trifluoroethanol, 75-89-8; propargyl alcohol, 107-19-7; choline, 62-49-7; tri-*p*-anisylmethyl cation, 14039-13-5.

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Influence of the *o*-Nitro Group on Base Catalysis in Nucleophilic Aromatic Substitution. Reactions in Benzene Solution[1]

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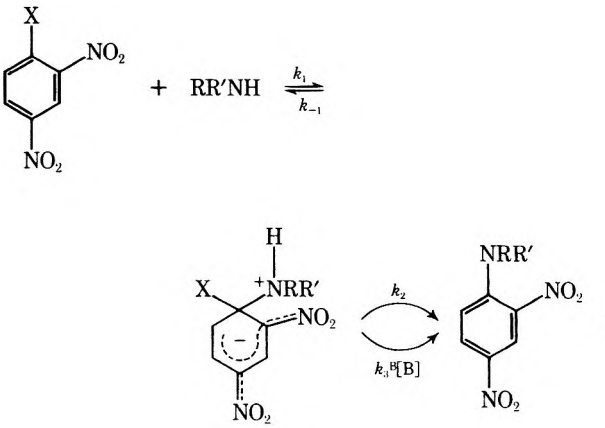
There exist two explanations why nucleophilic aromatic substitutions by secondary amines are frequently more prone to base catalysis than analogous reactions with a primary amine of comparable pK_a. Both are based on the intermediate complex mechanism of eq 1. The first invokes a steric acceleration of the k_{-1} step in the case of secondary amines which reduces k_2/k_{-1} (and k_3^B/k_{-1}) compared to primary amines. The second explanation, initially based on the observation that practically all known examples involved o-nitro substituted substrates, invokes intramolecular hydrogen bonding to the *o*-nitro group. Its effect is to lower k_{-1} about equally for primary and secondary amines, but to lower k_2 more for secondary than for primary amines, thus making k_2/k_{-1} larger for primary amines than for secondary amines. Kinetic data on reactions of *n*-butylamine and of piperidine with 1-fluoro-2,4-dinitrobenzene, 1-fluoro-4-nitronaphthalene, and 1-fluoro-4,5-dinitronaphthalene in benzene are presented which support the hydrogen bonding theory. The data are also shown to be most consistent with the SB–GA mechanism of base catalysis in this solvent.

It is well known that some nucleophilic aromatic substitution reactions involving amines as nucleophiles are subject to base catalysis whereas others are insensitive to the addition of base.[3] This has been rationalized in terms of the intermediate complex mechanism where the intermediate may be transformed into products either directly (k_2) or by a base-catalyzed route (k_3^B); eq 1 is representative for the most frequently studied type of substrates, viz., 1-substituted 2,4-dinitrobenzene derivatives. When the product-forming steps are much faster than the reversion of the intermediate to reactants ($k_2 + k_3^B[B] \gg k_{-1}$), intermediate formation (k_1) is rate determining and no base catalysis can be observed. When the rate of the product-forming steps is slower or at least does not greatly exceed the rate of reversion ($k_2 + k_3^B[B] \lesssim k_{-1}$), the net reaction is susceptible to base catalysis.



(1)

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The same conclusions follow from eq 2 which is derived for system 1 on the basis of the steady state assumption.

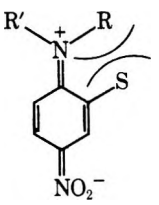
$$\frac{\text{rate}}{[\text{ArX}][\text{RR'NH}]} = k_A = \frac{k_1k_2 + k_1k_3^B[B]}{k_{-1} + k_2 + k_3^B[B]} \quad (2)$$

Whether in a given reaction $k_2 + k_3^B[B] \gg k_{-1}$, or $k_2 + k_3^B[B] \lesssim k_{-1}$, depends on a variety of factors which have been discussed recently.[3a] From the manner in which k_A depends on base concentration one may be able either to evaluate the ratios k_2/k_{-1}, k_3^B/k_{-1} and k_3^B/k_2, or at least to set low or high limits on these ratios.[3a]

The phenomenon of present concern is the frequent observation that the ratios k_2/k_{-1} and k_3^B/k_{-1} are considerably higher for primary amines than for secondary amines of comparable basicity in otherwise identical reactions. Experimentally this manifests itself in two ways. First a number of reactions with secondary amines are base catalyzed ($k_2/k_{-1} < 1$)[3a] whereas the same reaction with a primary amine is not ($k_2/k_{-1} \gg 1$).[3a] Second, reactions involving primary amines sometimes show a curvilinear dependence on base concentration ($k_3^B[B]/k_{-1} < 1$ at low [B], $k_3^B[B]/k_{-1} > 1$ at high [B])[3a] whereas the response is linear when the reaction is with a secondary amine ($k_3^B[B]/k_{-1} \ll 1$ over the entire range of [B]).[3a]

In principle, the smaller k_2/k_{-1} and k_3^B/k_{-1} ratios for secondary amines could be the consequence of smaller k_2 and k_3^B, or of larger k_{-1}, or a combination of both. An attractive explanation, offered by Bunnett and Garst.[4] invokes a steric compression (between amine and aromatic ring plus ortho substituents) in the intermediate in the case of secondary amines. Release of the steric strain enhances k_{-1} and thereby reduces k_2/k_{-1} and k_3^B/k_{-1} for secondary amines.

Another possible steric factor which has the effect of reducing k_2 and k_3^B is the hindrance, by an ortho substituent, of the developing resonance in the product (2). Which



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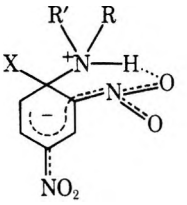

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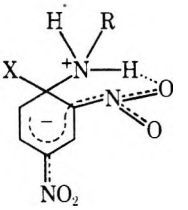

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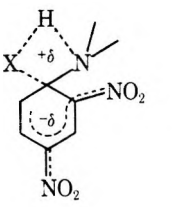
of these steric effects are potentially more important greatly depends on how close the respective transition states are to the intermediate, a question which is difficult to answer. Since both types of steric effects lead to a lowering in k_2/k_{-1} and k_3^B/k_{-1}, we shall not distinguish between them in the following discussions but simply refer to them as "the steric effect".[5]

It appears to us that the steric effect almost certainly plays a role in discriminating between primary and secondary amines, but it may not be the only factor. In a recent review[3a] we pointed out that practically all rate data which permit a comparison of k_2/k_{-1} and k_3^B/k_{-1} ratios for primary and secondary amines involve substrates with an *o-nitro group*. This fact and a number of other observations[3a] led us to suggest that intramolecular hydrogen bonding in the zwitterionic form of the intermediate, as shown in **3** and **4**, might be an additional significant factor in this discrimination, particularly in nonpolar solvents.

The argument, briefly restated, runs as follows. Intramolecular hydrogen bonding stabilizes the intermediate with the following consequences. (1) There is a decrease in k_{-1} because breaking the C–N bond requires also breaking of the hydrogen bond, and therefore some extra activation energy. This effect is presumably about equal for primary or secondary amines of equal basicity.

(2) The mechanism of the k_2 step involves a transfer of an ammonio proton to the leaving group in concert with leaving group departure (transition state **5**).[3a] In the case of



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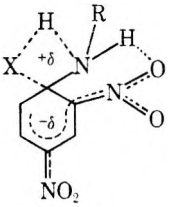

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secondary amines there is only one such proton available and it is tied up in the hydrogen bond to the *o*-nitro group in the intermediate (**3**). To make it available for catalysis in **5** the hydrogen bond has first to be broken which adds to the activation energy of the k_2 step and thus reduces k_2 in a similar way as it reduces k_{-1}. In the case of *primary* amines there is a nonhydrogen bonded proton available (**4**) and thus, in a first approximation no hydrogen bond needs to be broken in going to **5**, and k_2 remains unaffected. This is of course not exactly true since transferring the *available* proton to the incipient anion X^- reduces the acidity of the *bonded* hydrogen in **4** and thus reduces the stabilization through hydrogen bonding. However this is in turn partially compensated by an increase in acidity due to transformation from an aliphatic to an aromatic amine. To put it another way, the transition state of the k_2 step for primary amines (**6**) would benefit somewhat from intramolecular hydrogen bonding but not as much as the intermediate **4**. However, since there is absolutely no such stabilization in the transition state of the k_2 step for *secondary* amines, the net effect of introducing an *o*-nitro group is to make k_2/k_{-1} larger for primary than for secondary amines.

(3) The effect on k_3^B and thus on k_3^B/k_{-1} is more difficult to predict because the details of the mechanism of the k_3^B step in nonpolar solvents are not settled.[3a,6] Though it is obvious that the acidic proton in the zwitterion is removed during the reaction this could happen in different ways, such as (a) rate-limiting proton transfer to the base followed by rapid leaving group expulsion, (b) rapid equilibrium deprotonation followed by slow leaving group expulsion, catalyzed by the conjugate acid of the catalyst (SB–GA mechanism[3a]), (c) concerted proton transfer and leaving group expulsion, perhaps with a cyclic transition state where the amine acts as a bifunctional catalyst. In mechanisms a and c deprotonation of the intermediate is the, or part of the, rate-limiting process. Hence k_3^B should be similarly affected by an *o*-nitro group as k_2. For the SB–GA mechanism the situation is different; here the proton is removed in a rapid equilibrium step which for both types of amines involves a conversion of a zwitterion, stabilized by an intramolecular hydrogen bond, into a nonstabilized anionic intermediate (this implies that intramolecular hydrogen bonding to the ortho group is minimal in the anionic form of the intermediate in the case of a primary amine). Hence the *o*-nitro group should not have a discriminating influence on k_3^B (and with it on k_3^B/k_{-1}) between primary and secondary amines if the SB–GA mechanism prevails.[7]

It should be pointed out that the idea of intramolecular bonding to the *o*-nitro group is not new. For example, Bunnett and Morath[8] explained the stronger activation of an *o*-nitro group compared to a *p*-nitro group in reactions with amines by a stabilizing effect on the transition state of the k_1 step; they called the effect "built-in solvation" which

Table I
Reactions of 1-Fluoro-2,4-dinitrobenzene with Piperidine in Benzene at 25°[a]

10^3 [piperidine], M	k_ψ, sec^{-1}	k_A,[b] M^{-1} sec^{-1}
0.306	0.00026	0.85
1.02	0.00152	1.49
2.04	0.00388	1.90
3.06	0.00770	2.52
5.10	0.0175	3.44
10.2	0.067	6.57
20.4	0.259	12.7
50.0	1.13	22.6
100	3.60	36.0
200	10.26	51.3
300	18.6	62.1
400	27.7	69.2
500	38.1	76.1

[a] $[Substrate]_0 = 1.5–4.0 \times 10^{-5}$ M; runs at $[pip] \leq 3.06 \times 10^{-3}$ M measured on conventional spectrophotometer, runs at $[pip] \geq 5.10 \times 10^{-3}$ M measured by the stopped-flow technique. [b] $k_A = k_\psi/[amine]$ where k_ψ is the pseudo-first-order rate coefficient.

was visualized as either electrostatic or as a hydrogen bonding interaction. Bernasconi et al.[9] found that the rate of deprotonation by OH^- of certain zwitterionic σ complexes is slower than expected for a diffusion controlled process, indicating intramolecular hydrogen bonding.

More relevant to the present paper are recent suggestions by Pietra et al.,[10] by Kavalek et al.,[11] and by Chapman et al.[12] Pietra et al.[10] point out that plots of k_A vs. amine concentration have finite intercepts (k_1k_2/k_{-1}) in reactions of primary and secondary amines with 1-fluoro-2,4-dinitrobenzene, but zero intercepts in the reactions of *n*-butylamine with 1-fluoro-4,7-dinitronaphthalene and of imidazole with 1-fluoro-2,4-dinitrobenzene (attack by the tertiary nitrogen atom of imidazole is assumed). Since the reactions for which there is a possibility of intramolecular hydrogen bonding are also the ones which lead to a finite intercept, while those where hydrogen bonding is impossible were the ones with a zero intercept, Pietra et al.[10] believe that hydrogen bonding *enhances* k_2, thus making k_1k_2/k_{-1} more comparable to $k_1k_3^B/k_{-1}$ and thus more easily detectable.

Kavalek et al.[11a] also suggest that intramolecular hydrogen bonding may be particularly effective in stabilizing the transition state of the k_2 step, thereby increasing the contribution of the noncatalyzed pathway in the reactions of piperidine with 4-substituted 2-nitrofluorobenzenes. Chapman et al.[12] believe that the relatively small k_3^B/k_2 ratios in reactions with *o*-nitro-substituted substrates can be explained by a reduction in k_3^B and an increase in k_2 due to hydrogen bonding.

We note that all these suggestions are contrary to our own theory; they call for an *increase* in k_2 while ours calls for a *decrease* in k_2 due to hydrogen bonding.

In an earlier paper, Kavalek et al.[11a] attempted to explain why the reaction of 1-fluoro-2,4-dinitrobenzene with *N*-methylaniline is not catalyzed by *N*-methylaniline, despite evidence which suggests that $k_2/k_{-1} \ll 1$, whereas the reaction of the same substrate with aniline *is* catalyzed by aniline. Their rationalization was that in **3** there is only one acidic hydrogen which is not easily available to the base catalyst due to the hydrogen bond, thus making $k_3^B[B] \ll k_2$, while in **4** the base can attack the easily available nonbonded proton, thus making $k_3^B[B] > k_2$. This interpretation, which includes some ingredients of our own theory, fails to take into consideration that k_2 should also be re-

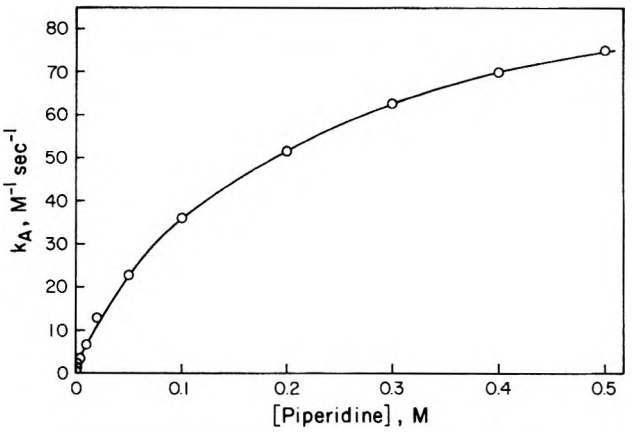


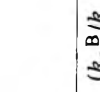
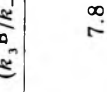
Figure 1. Dependence of k_A on amine concentration in reaction of piperidine with 1-fluoro-2,4-dinitrobenzene.

Table II
Reactions of Fluoronitronaphthalenes with *n*-Butylamine and Piperidine in Benzene at 25°[a]

[Amine], M	10^7 k_ψ,[b] sec^{-1}	10^6 k_A,[b] M^{-1} sec^{-1}
A. Reaction of 1-Fluoro-4-nitronaphthalene with *n*-Butylamine		
0.024	0.0838	0.35
0.049	0.361	0.74
0.099	1.50	1.52
0.158	3.96	2.50
0.198	6.44	3.25
0.238	9.52	4.00
0.317	17.4	5.50
0.396	29.9	7.54
B. Reaction of 1-Fluoro-4-nitronaphthalene with Piperidine		
0.01	0.281	2.81
0.02	1.06	5.30
0.03	2.46	8.20
0.04	4.38	10.9
0.05	6.77	13.5
0.06	10.1	16.8
0.10	25.8	25.8
C. Reaction of 1-Fluoro-4,5-dinitronaphthalene with *n*-Butylamine		
0.01004	0.237	2.36
0.0151	0.460	3.05
0.020	0.875	4.38
0.040	3.34	8.35
0.079	14.6	18.4
0.099	22.6	22.8
0.129	37.7	29.2
0.158	56.9	36.0
0.198	103	52.0
0.238	144	60.7
D. Reaction of 1-Fluoro-4,5-dinitronaphthalene with Piperidine		
0.00196	0.57	29.0
0.00304	1.10	36.1
0.00402	1.76	43.7
0.0059	2.91	49.3
0.00812	5.20	64.1
0.010	7.77	76.9
0.020	26.3	132
0.030	58.3	194
0.040	111	276
0.050	151	303
0.060	224	374
0.080	395	494
0.100	627	627

[a] $[Substrate]_0 = 1.3–5 \times 10^{-4}$ M. [b] $k_A = k_\psi/[amine]$.

Table III
Dissection of Rate Coefficients

Substrate	Amine	k_1k_2/k_{-1}, M^{-1} sec^{-1}	$k_1k_3^B/k_{-1}$, M^{-2} sec^{-1}	k_1, M^{-1} sec^{-1}	k_2/k_{-1}	k_3^B/k_{-1}, M^{-1}	k_3^B/k_2, M^{-1}	$(k_2/k_{-1})_{Bu}/(k_2/k_{-1})_{Pip}$	$(k_3^B/k_{-1})_{Bu}/(k_3^B/k_{-1})_{Pip}$
	*n*-BuNH$_2$[a]	0.17[a]	35.5[a]	0.71[a,b]	0.24[a,b]	50[a,b]	210[a]	32	7.8
	Piperidine	0.72[c]	609[c]	95	0.0075	6.4	850		
	*n*-BuNH$_2$	$\leqslant 3 \times 10^{-7}$	2.28×10^{-4}		$\leqslant 0.005$	$\leqslant 4$	$\geqslant 760$	$\leqslant 2.1$[c]	5.33
	Piperidine	1.9×10^{-5}	6.16×10^{-3}		$\leqslant 0.02$	$\leqslant 10$	325		
	*n*-BuNH$_2$	$\leqslant 5 \times 10^{-8}$	1.62×10^{-5}		$\leqslant 0.015$	$\leqslant 5$	< 324		
	Piperidine	$\leqslant 2 \times 10^{-7}$	2.74×10^{-4}		$\leqslant 0.007$	$\leqslant 10$	< 1360		

[a] Reference 15. [b] Calculated from rate data of ref 15 by Bernasconi.[3a] [c] $k_1k_2/k_{-1} = 0.5$ and $k_1k_3^B/k_1 = 615$ in ref 14.

duced by hydrogen bonding. *In fact our theory predicts that k_2 should be affected by hydrogen bonding about as much as k_3^B if mechanisms a or c for base catalysis prevail, but be reduced more than k_3^B if the SB–GA mechanism prevails.*

We now report data on reactions of some fluoronitroaromatics with piperidine and with *n*-butylamine, in benzene solution. They lend support to our hydrogen bonding theory and to the SB–GA mechanism for base catalysis. We shall also show that the above phenomena[10–12] are easily fitted into the present framework.

Results and Discussion

The reactions of 1-fluoro-2,4-dinitrobenzene both with piperidine[13,14] and with *n*-butylamine[15] have long been known to be base catalyzed by the respective amine nucleophile. Dependence on amine concentration was found to be linear in the case of piperidine[13,14] ($k_2 + k_3^B[B] \ll k_{-1}$ and thus $k_A = k_1k_2/k_{-1} + k_1k_3^B[B]/k_{-1}$) whereas it is curvilinear in the case of *n*-butylamine[15] ($k_2/k_{-1} = 0.24$,[3a] $k_3^B/k_{-1} = 50$[3a]). These two reactions thus epitomize the general findings discussed in the introduction.

Owing to the high rate, the piperidine reaction had only been investigated at piperidine concentrations $\leq 1.43 \times 10^{-2}$ M.[13] It was conceivable that curvature in the plot of k_A vs. piperidine concentration would be obtained at higher concentrations, thus enabling one to calculate the values for k_2/k_{-1} and k_3^B/k_{-1}. Employing the stopped-flow method we have now measured k_A at piperidine concentrations up to 0.5 M. The results are summarized in Table I. A plot of k_A vs. concentration is in fact curvilinear as shown in Figure 1; using standard procedures[4,16] we calculate $k_1 = 95$ M^{-1} sec^{-1}, $k_2/k_{-1} = 0.0075$, $k_3^B/k_{-1} = 6.4$ M^{-1}. Comparing these values with those of the *n*-butylamine reaction (Table III) we note that k_2/k_{-1} is 32-fold larger for *n*-butylamine whereas k_3^B/k_{-1} (B = *n*-butylamine) is 7.8-fold larger than k_3^B/k_{-1} (B = piperidine).

In order to check whether the ratios $(k_2/k_{-1})_{Bu}/(k_2/k_{-1})_{pip}$ and $(k_3^B/k_{-1})_{Bu}/(k_3^B/k_{-1})_{pip}$ would change in the absence of an o-nitro group, the reactions of the two amines with 1-fluoro-4-nitronaphthalene and with 1-fluoro-4,5-dinitronaphthalene were investigated. In these substrates the steric requirements of the second benzene ring (peri hydrogen) are only slightly smaller than those of an o-nitro group and thus the steric effect should be nearly constant for our purposes.

The results are summarized in Table II. All plots of k_A are linear up to at least 0.1 M amine[17] and thus conform to eq 3.

$$k_A = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3^B[B]}{k_{-1}} \qquad (3)$$

The intercept (k_1k_2/k_{-1}) in the reaction of piperidine with 1-fluoro-4,5-dinitronaphthalene is appreciable and easily determined. In the other reactions it is very small and cannot be distinguished from zero because the rates become too slow at the amine concentrations which would be low enough for measurements close to the intercept. We have nevertheless estimated an upper limit for k_1k_2/k_{-1} by setting the standard deviation of the intercept equal to this upper limit. They are summarized in Table III, along with the slopes ($k_1^Bk_3/k_{-1}$). By taking the ratios of slope/intercept, k_3^B/k_2 or lower limits thereof can also be calculated.

Furthermore, our data allow upper limits for k_2/k_{-1} and k_3^B/k_{-1} to be estimated as follows. Since the plots of k_A vs. amine concentration do not curve down even at the highest amine concentration ($[B]_{max}$), one can infer $k_3^B[B]_{max}/k_{-1} \ll 1$ or $k_3^B/k_{-1} \ll 1/[B]_{max}$. From $k_2/k_{-1} = (k_3^B/k_{-1})/(k_3^B/k_2)$ one then finds the upper limits of k_2/k_{-1}.

Let us now first focus on the change in k_2/k_{-1} when going from 1-fluoro-2,4-dinitrobenzene to the naphthalene derivatives. We note that k_2/k_{-1} is strongly reduced for both amines. Since, compared to 1-fluoro-2,4-dinitrobenzene, the naphthalenes are (1) slightly less hindered, (2) less activated electronically, and (3) lack the *o*-nitro group, the change in k_2/k_{-1} could in principle be due to any one or a combination of these factors.

Steric Effect. If there is a steric effect at all, it would lead to an *increase* in k_2/k_{-1} for the reaction of piperidine with the naphthalene derivatives. The data show that k_2/k_{-1} decreases, indicating that other, much more important factors, overcompensate whatever steric effect there is.

Electronic Effects. One has to distinguish two electronic effects. The first is the well-known "activating effect" of electron-withdrawing substituents in nucleophilic aromatic substitution, which enhances k_1 but reduces k_{-1} and k_2. The second results in a greater acidity of the ammonio proton in the intermediate, thereby making it a better acid catalyst for leaving group departure, i.e. stabilizing the transition state (5) of the k_2 step. Since the two effects on k_2 are in opposite directions, and thus tend to make the net effect on k_2 rather small, it is conceivable that the reduced electronic activation in the naphthalene derivatives enhances k_{-1} much more than it does k_2 (Hammett ρ value larger for k_{-1} than for k_2) leading to very small k_2/k_{-1} ratios for both amines.

This, however, would be in contradiction to the recent findings by Kavalek and Štěrba[11a] that k_2/k_{-1} is relatively insensitive to changes in the 4 substituent in reactions of piperidine with 4-substituted 2-nitrofluorobenzenes in benzene solution. Extrapolating their data to our situation, a reduction of k_2/k_{-1} by a factor of 20–50 is the most to be expected (it is probably less) from the smaller electronic activation in the 1-fluoro-4,5-dinitronaphthalene compared to the 1-fluoro-2,4-dinitrobenzene reactions. This contrasts with our *n*-butylamine reactions where k_2/k_{-1} is reduced from 0.24 to $\ll$ 0.005, i.e., probably at least 10^3-fold and possibly more.

Hydrogen Bonding to o-Nitro Group. The hydrogen bonding theory, in the case of *n*-butylamine, easily accounts for that part in the reduction of k_2/k_{-1} which cannot be explained by the electronic effects. Thus the first prediction of the hydrogen bonding theory is verified, viz., that the o-nitro group significantly reduces k_{-1}. The second prediction, viz., that hydrogen bonding also reduces k_2, but more so for secondary amines, remains to be proven.

Support for this second assertion comes from a somewhat different analysis of the data in Table III. One may estimate the ratio $(k_2/k_{-1})_{Bu}/(k_2/k_{-1})_{pip}$ for 1-fluoro-4,5-dinitronaphthalene by assuming that the relative nucleophilic reactivities of the two amines toward 1-fluoro-4,5-dinitronaphthalene are about the same as toward 1-fluoro-2,4-dinitrobenzene, i.e., $(k_1)_{Bu}/(k_1)_{pip} \approx 0.0075$. This provides $(k_2/k_{-1})_{Bu}/(k_2/k_{-1})_{pip} \leq 2.1$, which is $\geq$15 times lower than with 1-fluoro-2,4-dinitrobenzene. This shows that removal of the o-nitro group indeed reduces $(k_2/k_{-1})_{Bu}$ more (large increase in k_{-1} *not* compensated by equivalent increase in k_2) than it reduces $(k_2/k_{-1})_{pip}$ (large increase in k_{-1} partially compensated by comparable increase in k_2), as predicted.

Strictly speaking the above considerations still do not constitute an absolute proof of the hydrogen bonding theory because the steric theory also predicts that $(k_2/k_{-1})_{Bu}$ and $(k_2/k_{-1})_{pip}$ become more similar to each other the less steric hindrance there is. However, it is doubtful whether the small reduction of steric crowding in the naphthalene derivative could account for a $\geq$15-fold change. More compelling evidence on this point comes from a comparison of the k_3^B/k_{-1} ratios.

The steric theory predicts that $(k_3^B/k_{-1})_{Bu}$ and $(k_3^B/k_{-1})_{pip}$ should become more similar to each other in the less crowded compound, by a similar amount as the k_2/k_{-1} ratios. Incidentally, the hydrogen bonding theory, coupled with mechanism a or c for base catalysis, leads to the same prediction. However, if the SB–GA mechanism is assumed to prevail instead, the hydrogen bonding theory predicts that $(k_3^B/k_{-1})_{Bu}$ and $(k_3^B/k_{-1})_{pip}$ should not change *relative* to one another.[18] Our data bear this out: the ratio $(k_3^B/k_{-1})_{Bu}/(k_3^B/k_{-1})_{pip}$ is practically independent of substrate.

Thus the combined data on k_2/k_{-1} and on k_3^B/k_{-1} support the hydrogen bonding theory as well as the SB–GA mechanism for base catalysis.

Interpretation of Phenomena Reported by Other Investigators. The phenomena, mentioned in the introduction, which led other investigators[10-12] to propose hydrogen bonding theories different from ours, can either be fitted into the framework presented here or explained by other well-known effects. For example, the negligible intercept in the k_A vs. amine concentration plot for the reaction of *n*-butylamine with 1-fluoro-4,7-dinitronaphthalene[10b] is similar to our findings with 1-fluoro4-nitronaphthalene and 1-fluoro-4,5-dinitronaphthalene and thus can be explained similarly. Or, the negligible intercept in the reaction of imidazole (attack by tertiary nitrogen atom) with 1-fluoro-2,4-dinitrobenzene probably arises from the fact that no proton whatever (hydrogen bonded or not) is available to assist fluoride ion expulsion in the k_2 step.

Or, the greater increase in k_3^B/k_{-1} compared to k_2/k_{-1} with increasing electronic activation in reactions of piperidine with 4-substituted 2-nitrofluorobenzenes[11a] is consistent with the SB–GA mechanism for the k_3^B step. This is because in the k_3^B step the intermediate is deprotonated in an equilibrium reaction and thus the full acidifying effect of electron-withdrawing 4 substituents on the proton is felt in k_3^B, while in the k_2 step the same proton is only partially transferred in the transition state and thus k_2 is less sensitive to the acidifying effect of an electron-withdrawing substituent. Or, the absence of catalysis by *N*-methylaniline in the reaction of *N*-methylaniline with 1-fluoro-2,4-dinitrobenzene[11b] (which contrasts with the observation of catalysis by aniline of the reaction of aniline with the same substrate) is probably most easily rationalized by a steric hindrance to the access of the catalyst, a well-known phenomenon with bulky bases.[3a]

Experimental Section

Materials. 1-Fluoro-2,4-dinitrobenzene (Aldrich) and 1-fluoro-4-nitronaphthalene (Aldrich) were recrystallized from ethanol, mp 25–26 and 79–80°, respectively. 1-Fluoro-4,5-dinitronaphthalene was prepared from 1-chloro-4,5-dinitronaphthalene[19] by the method of Pietra et al.[20] used for 1-fluoro-4,7-dinitronaphthalene, yield 20%, mp 192–193°.

Anal. Calcd for $C_{10}H_5N_2O_4F$: C, 50.86; H, 2.13; N, 11.86. Found: C, 50.72, H, 2.13; N, 11.76.

N-(4-Nitronaphthyl)piperidine [mp 74–75°, λ_{max} in benzene 395 nm (ϵ 8900)], *N*-(4-nitronaphthyl)-*n*-butylamine [mp 158–159°, λ_{max} in benzene 409 nm (ϵ 15700)], *N*-(4,5-dinitronaphthyl)piperidine [mp 159–160°, λ_{max} in benzene 390 nm (ϵ 7550)], and *N*-(4,5-dinitronaphthyl)-*n*-butylamine [mp 197°, λ_{max} in benzene 420 nm (ϵ 10500)] were prepared by adapting the method of Bunnett and Randall[21] used for *N*-methyl-2,4-dinitroaniline; the elementary analyses were all excellent. Reagent grade benzene was refluxed over Na–K alloy for 24 hr and distilled immediately before use. Piperidine and *n*-butylamine (both Mallinckrodt) were refluxed over sodium for 12 hr and distilled under nitrogen.

Rate Measurements. The general photometric procedure of Bernasconi and Zollinger[14] was used for the slow reactions. All re-

actions were run in the dark. The reactions with the naphthalene compounds gave only good first-order plots and quantitative yields when run under a nitrogen atmosphere. The reaction of 1-fluoro-4-nitronaphthalene with *n*-butylamine was extremely slow at low amine concentrations and the determination of an infinity value or even an evaluation by the Guggenheim method became impractical. In these runs the reaction was only followed during the first few percent and the infinity value calculated under the assumption of a quantitative yield. The stopped-flow experiments for the reaction of 1-fluoro-2,4-dinitrobenzene with piperidine were carried out on a Durrum[22] stopped-flow spectrophotometer.[23]

The evaluation of the curvilinear plot of k_A vs. amine concentration, to provide k_1, k_2/k_{-1}, and k_3^B/k_{-1}, was according to standard procedures[4,16] in the reaction of piperidine with 1-fluoro-2,4-dinitrobenzene.

Acknowledgments. This work was supported by the Alfred P. Sloan Foundation. We also thank Professor J. F. Bunnett for criticism of the manuscript.

Registry No.—1-Fluoro-2,4-dinitrobenzene, 70-34-8; 1-fluoro-4-nitronaphthalene, 341-92-4; 1-fluoro-4,5-dinitronaphthalene, 52385-37-2; *N*-(4-nitronaphthyl)piperidine, 34599-45-6; *N*-(4-nitronaphthyl)-*n*-butylamine, 57091-55-1; *N*-(4,5-dinitronaphthyl)-piperidine, 57091-56-2; *N*-(4,5-dinitronaphthyl)-*n*-butylamine, 57091-57-3; piperidine, 110-89-4; *n*-butylamine, 109-73-9.

References and Notes

(1) Presented, in part, at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Abstracts, No. ORGN-55.
(2) (a) Alfred P. Sloan Fellow, 1971–1973; (b) Facultad de Ciencias Quimicas, Universidad Nacional de Córdoba, Córdoba, Argentina; part of this work was carried out at Córdoba.
(3) For recent reviews see (a) C. F. Bernasconi, *MTP Int. Rev. Sci., Org. Chem. Ser. One, 1973*, **3**, 33 (1973); (b) F. Pietra, *Q. Rev., Chem. Soc.*, **23**, 504 (1969); (c) J. Miller, "Aromatic Nucleophilic Substitution", American Elsevier, New York, N.Y., 1968; (d) T. J. de Boer and I. P. Dirkx in "The Chemistry of the Nitro and Nitroso Groups", Part I, H. Feuer, Ed., Interscience, New York, N.Y., 1969, p 487; (e) S. D. Ross, Prog. Phys. Org. Chem., 1, 31 (1963).
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(22) Durrum Instruments, Palo Alto, Calif.
(23) We thank Mrs. H. S. Cross for technical assistance in these experiments.

Electronegativity, Hybridization, and Properties of the Carbonyl Group. I. Lewis Basicity

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The basicity of a series of lactams, $\underline{C(O)N(CH_3)(CH_2)_n}$, lactones, $\underline{C(O)O(CH_2)_n}$, cyclic ureas, $CH_3\underline{NC(O)N(CH_3)(CH_2)_n}$, and cyclic carbonates, $\underline{OC(O)O(CH_2)_n}$, $n = 2$ to $n = 5$, was studied with respect to the acids phenol and 1,1,1,3,3,3-hexafluoro-2-propanol. The enthalpies of reaction (measured by infrared spectroscopy, $\Delta\nu_{CO}$) increased in every case: four-membered rings < five-membered rings < six-membered rings ≤ seven-membered rings. The results are explained in terms of the charge capacity of the methylene groups (inductive effect), the effect of ring size upon hybridization and electronegativity, and steric inhibition of resonance from ring strain in small rings.

Although the Lewis basicity of the carbonyl group has been widely studied,[2–5] the factors contributing to the base strength have never been adequately clarified. In this paper we report experiments which indicate that previous workers may have overemphasized certain contributions and minimized other, equally important ones.

It has long been known that the carbonyl group in amides is more basic than that in ketones[2f,6] when measured in nonpolar solvents. Furthermore, the basicity of esters is only slightly less than that of ketones[2f] despite the inductive effect of the electronegative amido and alkoxy groups in the carboxylic acid derivatives. More recently, a limited number of gas-phase proton affinities have been determined. The proton affinity of acetamide is about 37 kcal/mol more exothermic than that of acetone and esters are at least as basic as acetone.[7]

We have undertaken the study of the basicity of a series of cyclic bases in nonpolar solvents. We here report the basicities of several lactones, cyclic carbonates, lactams, and cyclic ureas toward phenol and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as measured by infrared spectroscopy ($\Delta\nu$ of the OH band[4]). We use the term *basicity* in its broadest sense, the ability of an electron donor to donate electron density to an electron acceptor,[8a] which is conveniently measured operationally by the enthalpy of reaction. Ideally, of course, the gas-phase proton affinities are desirable,[8b] but in view of the interesting effects and some controversy arising from hard–soft interactions[8c,9] or, alternatively, electrostatic–covalent effects,[8d,10] we feel that restricting the definition of basicity to proton affinities is undesirable and will simply require that a neologism be invented to replace the old term.

Experimental Section

Reagents. All solvents were Eastman spectrograde. All bases were of the highest purity commercially available and used without further purification (liquids were kept over molecular sieves) except for the following.

1-Acetylpiperidine, γ-butyrolactone, ε-hexanolactone, 1-methyl-δ-valerolactam, and tetramethylurea were purchased as practical or technical grades from Aldrich and Eastman and distilled under reduced pressure (9–15 mm).

Ethylene Carbonate. Eastman practical grade was recrystallized from a mixture of equal parts of benzene and chloroform (mp 38–40°).

***N,N*-Dimethylaminoacetone.** Aldrich technical grade was distilled at reduced pressure [bp 27° (9 mm)]. The colorless pure compound becomes yellow and then brown after a few hours; a freshly distilled sample was used each time.

Pyridine. This was distilled at atmospheric pressure (bp 115.5°).

δ-Valerolactone. This compound shows a marked tendency to polymerize even at room temperature. The method of Saatome and Kodaira[11] was used to convert the partially polymerized material into the monomer. The mixture was treated above 200° and distilled under reduced pressure [bp 130° (19 mm), n^{20}D 1.4500]. The pure lactone was used immediately and also kept over phosphorus pentoxide, remaining unpolymerized for several weeks.

***N,N*-Dimethylethyleneurea** was prepared by the Eschweiler–Clarke reaction[12,13] from a mixture of 43.0 g (0.50 mol) of ethyleneurea, 90.8 ml (1.21 mol) of 3 aqueous formaldehyde, and 187.2 ml (1.50 mol) of 99% formic acid refluxed on a steam bath for 48 hr. The solution was evaporated to approximately one-half of its original volume, 140 ml of 6 *M* NaOH was added, and the mixture was extracted with eight 200-ml portions of ether. The ether was evaporated and the residue was distilled under reduced pressure (15 mm). The fraction (14.6 g) boiling at 106–108° was collected. It was neutralized with 10 ml of 1 *M* HCl and extracted with six 15-ml portions of ether. The evaporation and distillation were repeated, yielding 10.62 g (18.2% yield) of a pale yellow oil [bp = 107–108° (15 mm)]. Other physical constants: mol wt (by mass spectroscopy), 114.073 (calcd, 114.079); n^{27}D 1.4690; nuclear magnetic resonance spectrum, δ_{CH_2} 3.24 ppm from Me_4Si (reported[29] 3.24), δ_{CH_3} 2.74 ppm from Me_4Si (reported[14] 2.75).

***N,N*-Dimethyltrimethyleneurea.** The Eschweiler–Clarke reaction was used as above on a mixture of 50 g (0.5 mol) of trimethyleneurea, 100 ml (3.61 mol) of 3 aqueous formaldehyde, and 187.2 ml (5 mol) of 99% formic acid. The fraction of extracted product boiling at 114–115° (10 mm) was collected, proved to be neutral to litmus, and was redistilled, yielding 29.42 g (43.1%) of product. Since the compound is light sensitive and hygroscopic it was kept over phosphorus pentoxide in the dark. Other physical constants: mol wt (by mass spectroscopy) 128.096 (calcd, 128.095); n^{25}D 1.4852; nuclear magnetic resonance spectrum, δ_{CH_2} 1.98, 3.26 ppm from Me_4Si (reported[29] 1.98, 3.25); δ_{CH_3} 2.88 ppm from Me_4Si (reported[14] 2.92).

The reference Lewis acids were Eastman 1,1,1,3,3,3-hexafluoro-2-propanol, used as received and kept over molecular sieves, and phenol. The latter was purified according to the procedure of Draper and Pollard:[15] 88 g of phenol, 12 g of water, 0.1 g of aluminum turnings, and 0.05 g of sodium bicarbonate were distilled until all the azeotrope was driven off (bp ≤99°). Then the pure phenol was distilled at reduced pressure [bp 114–115° (10 mm)]. The 66.19 g (0.703 mol) of phenol that was recovered was dissolved in 100.00 ml of spectrograde CCl_4, giving 170.9 ml of a 4.114 *M* solution that was kept over phosphorus pentoxide in the dark. The dilute solutions used were prepared from this stock solution. In the absence of light this solution stayed unaltered for several weeks. Periodic purity checks were made by nuclear magnetic resonance.

Equipment. All the infrared spectroscopy was carried out using a Digilab FTS-14 Fourier transform spectrophotometer and the cells used had sodium chloride windows with 0.1- or 1.0-mm spacers. The number of scans for each sample varied according to need and ranged from 80 to 300.[16] Two parallel investigations were undertaken, viz., the interaction of several bases with phenol and with 1,1,1,3,3,3-hexafluoroacetone.

Procedure. Pure phenol was prepared as described above. Dilutions of the stock solutions to concentrations of 0.055 and 0.563 *M* were made. Several dilute solutions of each base were prepared using the phenol solution as the solvent.[16] The infrared spectra of these solutions show a band due to the phenol–base interaction. Triangulation of this band yielded the frequency shift between the free OH group and the hydrogen-bonded OH group. Each spectrum was recorded several times (in general, six times[16]) and the frequency shifts measured with a pair of calipers and averaged. The measurements were found to be reproducible to ±5 cm^{-1}. A linear regression of base concentration vs. frequency shift was computed by the method of least squares for each system. Extrapolation gave the frequency shifts at infinite base dilution.[17]

Several solutions of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were prepared and a 0.0637 *M* solution in CCl_4, used throughout the whole experiment, was found to be free of intermolecular hydrogen bonding. The infrared spectrum of HFIP shows two sharp peaks at 3610 and at 3575 cm^{-1}. The 3610-cm^{-1} peak was used to compute the frequency shifts.[18] The procedure used in the phenol studies was repeated with HFIF and the reproducibility was the same.

Table I

Base	$-\Delta H_{calorim}$, kcal/mol	$\Delta\nu_{OH}$, cm^{-1} (this work)	$\Delta\nu_{OH}$, cm^{-1} (lit. values)
	Acid: Phenol		
CH_3CN	4.6[a]	155	178,[b] 150[c]
CH_3COOCH_3	4.8[d]	160	171,[e] 164[f]
CH_3COCH_3	5.1[a]	202	193[b]
$[(CH_3)_2N]_2CO$	6.6[d]	331	338[f]
$CH_3CON(CH_3)_2$	6.8[a]	345	345[b]
$(CH_3)_2SO$	6.9[e]	350	359,[b] 366[e]
	Acid: HFIP		
CH_3CN	5.9[g]	198	208 ± 10[g]
CH_3COCH_3	6.7[g]	222	280 ± 10[g]
$CH_3CON(CH_3)_2$	8.5[g]	410	428 ± 10[g]
$(CH_3)_2SO$	8.7[g]	402	449 ± 10[g]

[a] Reference 4d. [b] K. F. Purcell and R. S. Drago, *J. Am. Chem. Soc.*, 89, 2874 (1967). [c] Reference 17. [d] Reference 4c. [e] Reference 2f. [f] Private communication from H. F. Henneike reported in ref 2f. [g] Reference 4b.

Table I shows the values of $-\Delta H$ and $\Delta\nu_{OH}$ used in determining the equations relating the two experimental variables in the systems under study. Least-squares repressions were calculated for the data presented in Table I. The resulting equations follow.

(a) for systems with phenol as the acid

$$-\Delta H = 0.0114\Delta\nu_{OH} + 2.88 \quad (1)$$

(with a correlation coefficient, $r = 0.998$)

(b) for systems with HFIP as the acid

$$-\Delta H = 0.0119\Delta\nu_{OH} + 3.8 \quad (2)$$

(with a correlation coefficient, $r = 0.984$)

Results and Discussion

Figure 1 is a least-squares plot of $(\Delta\nu_{OH})_{PhOH}$ vs. $(\Delta\nu_{OH})_{HFIP}$. The straight line indicates a relationship between the two sets of data given by the equation

$$(\Delta\nu_{OH})_{HFIP} = 1.131(\Delta\nu_{OH})_{OH} + 13.840 \quad (3)$$

The high correlation coefficient ($r = 0.979$) for the linear relationship between the two methods of estimating base strength from infrared frequency shifts indicates that the two methods are self-consistent and give equivalent results.

The results of the measurements are given in Table II (phenol) and Table III (HFIP) for both cyclic and acyclic compounds. The interactions of π bonding and inductive effects can readily be determined. In their simplest form they can be seen in the simple acyclic ketones, esters, and amides. Substitution of electron-withdrawing substituents lowers the basicity: acetone > alkyl acetates > dialkyl carbonates. In contrast, the substitution of an amido group *increases* the basicity: acetone < dimethylacetamide. The enhanced basicity of amides is ascribed to delocalization of the nitrogen lone pair into the carbonyl π system.[6] We have found that insertion of a methylene group between the nitrogen atoms and the carbonyl group results in a decrease

Table II
OH Frequency Shift and Enthalpies of Phenol–Base Hydrogen Bonding Calculated from Spectrophotometric Data

Base	Registry no.	$\Delta\nu_{OH}$, cm^{-1}		$-\Delta H$, kcal/mol	
		This work	Lit. values	This work	Lit. values
Acetone	67-64-1	202	193[a]	5.2	5.1[b]
Acetonitrile	75-05-8	155	178,[a] 150[c]	4.7	4.6[b]
1-Acetylpiperidine	618-42-8	314		6.5	
Bis(pentamethylene)urea	57031-52-4	302		6.3	
γ-Butyrolactone	96-48-0	169		4.8	
Diethyl carbonate	105-58-8	156		4.7	
N,N-Dimethylacetamide	127-19-5	345	345[a]	6.8	6.8[b]
Dimethylaminoacetone	15364-56-4	215		5.3	
Dimethyl carbonate	616-38-6	151		4.6	
N,N-Dimethylethyleneurea	3715-67-1	311		6.4	
N,N-Dimethylpropionamide	758-96-3	282		6.1	
Dimethyl sulfoxide	67-68-5	350	359,[a] 366[d]	6.9	6.9[d]
N,N-Dimethyltrimethyleneurea	57031-53-5	352		6.9	
Ethylene carbonate	96-49-1	159		4.7	
ε-Hexanolactone	502-44-3	225		5.5	
Methyl acetate	79-20-9	160	171,[d] 164[e]	4.7	4.8[f]
N-Methylbutyrolactam	872-50-4	336		6.7	
N-Methylvalerolactam	931-20-4	360		7.0	
Neopentylene carbonate	3592-12-9	210		5.3	
β-Propiolactone	57-57-8	146		4.5	
Propylene carbonate	108-32-7	156		4.7	
Pyridine	110-86-1		465 ± 10[g]		8.0[f]
Tetramethylurea	632-22-4	331	338[e]	6.7	6.6[f]
δ-Valerolactone	542-28-9	222		5.4	

[a] K. F. Purcell and R. S. Drago, *J. Am. Chem. Soc.*, 89, 2874 (1967). [b] Reference 4d. [c] Reference 17. [d] Reference 2f. [e] Private communication from H. F. Henneike reported in ref 2f. [f] Reference 4c. [g] Private communication from H. F. Henneike reported in ref 4d.

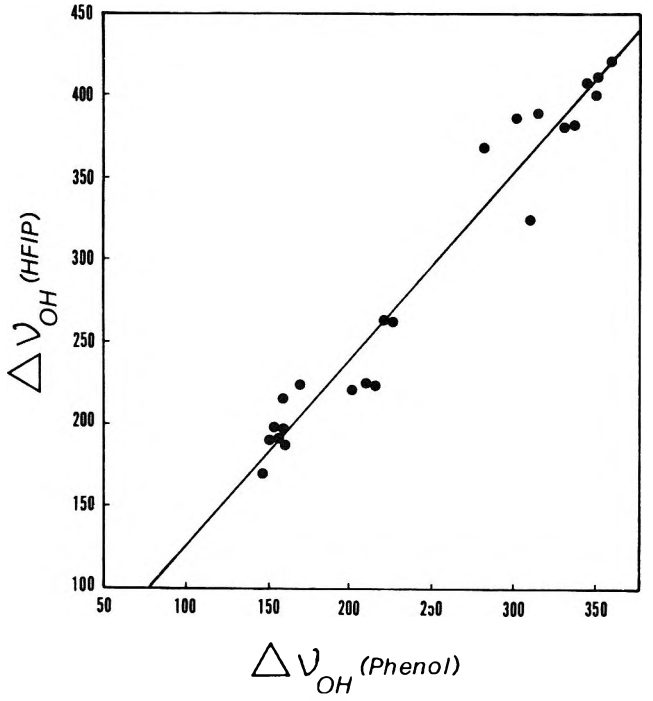
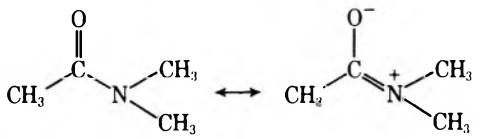


Figure 1. Correlation between $(\Delta\nu_{OH})_{HFIP}$ and $(\Delta\nu_{OH})_{phenol}$.

in enthalpy of adduct formation by about 1.5–2.2 kcal/mol which tends to confirm the importance of resonance as shown by **1a** and **1b**. Thus with phenol we obtain enthalpy

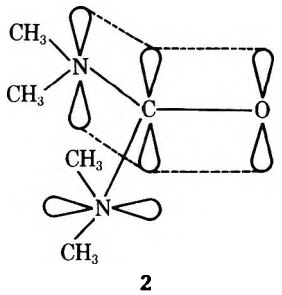


1a **1b**

values of −6.8 (DMA) compared to −5.3 (*N,N*-dimethylaminoacetone) and with HFIP we obtain values of −8.7 and −6.5, respectively.

Now the concept of resonance or its equivalent molecular orbital delocalization requires that the six (or five) atoms composing the amide (or ester)[19] group be planar or nearly so.

Molecular orbital calculations[21] show that the charge on the oxygen of acetone is 0.12 unit less negative than that on the oxygen of the amide. Since urea is known to be planar,[22] it is reasonable to assume that similar compounds like *N,N*-dimethylamide and tetramethylurea are also planar unless steric effects prohibit it. Based on this assumption, Middaugh, Drago, and Niedzielski[23] calculated that the electron density on the oxygen atom of tetramethylurea (2) should be 0.08 charge unit more negative than that of the oxygen atom in *N,N*-dimethylacetamide (1). Therefore, TMU should be more basic than DMA, but the opposite is observed experimentally. This surprising result has been explained[23] on the basis of the steric requirements of resonance described above. If the methyl groups of TMU interact sufficiently to prevent planarity, the increased delocalization expected in TMU will not obtain, and the basicity will be of the same extent as in DMA.



2

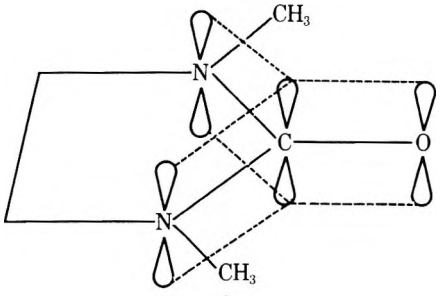
We have therefore tested a series of cyclic compounds in which the geometry of the amide linkage is known or can be approximated fairly well. Although the formation of a planar or quasi-planar ring system should reduce such steric inhibition of resonance, our results show that in every case the basicity of the cyclic compound is either the same as or

Table III
OH Frequency Shift and Enthalpies of HFIP–Base Hydrogen Bonding Calculated from Spectrophotometric Data

Base	$\Delta\nu_{OH}$, cm^{-1}		$-\Delta H$, kcal/mol	
	This work	Lit. values	This work	Lit. values
Acetone	222	280 ± 10[a]	6.4	6.7[a]
Acetonitrile	198	208 ± 10[a]	6.2	5.9[a]
1-Acetylpiperidine	391		8.4	
Bis(pentamethylene)urea	387		8.4	
γ-Butyrolactone	224		6.5	
Diethyl carbonate	197		6.1	
N,N-Dimethylacetamide	410	428 ± 10[a]	8.7	8.5[a]
N,N-Dimethylaminoacetone	223		6.5	
Dimethyl carbonate	190		6.1	
N,N-Dimethylethyleneurea	326		7.7	
N,N-Dimethylpropionamide	370		8.2	
Dimethyl sulfoxide	402	449 ± 10[a]	8.6	8.7[a]
N,N-Dimethyltrimethyleneurea	414		8.7	
Ethylene carbonate	189		6.1	
ϵ-Hexanolactone	263		6.9	
Methyl acetate	216		6.4	
N-Methylbutyrolactam	384		8.4	
N-Methylvalerolactam	423		8.8	
Neopentylene carbonate	225		6.5	
β-Propiolactone	170		5.8	
Propylene carbonate	191		6.1	
Tetramethylurea	383		8.4	
δ-Valerolactone	264		6.9	

[a] Reference 4b.

less than that of the open-chain compound. Particularly important in this regard is *N,N'*-dimethyleneurea (**3**), in



3

which the nitrogen p orbitals are optimally aligned for delocalization, in contrast to the sterically favored staggered arrangement of **2**. However, our results show that toward phenol the cyclic compound yields a reaction enthalpy 0.3 kcal/mol *less* than dimethylacetamide and towards HFIP the enthalpy is 0.7 kcal/mol less. In the corresponding carbonates there is no significant difference in the cyclic and acyclic compounds. In contrast, in the *nonplanar*[24] six-membered rings, the basicity is increased for all compounds studied. We therefore conclude that whether a *second* nitrogen (or oxygen) atom has its p orbital parallel or nonparallel to the first has little or no effect on the basicity of the carbonyl group.

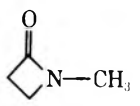
Our data thus show the importance of the delocalization of the nitrogen lone pair (in the decreased basicity of those compounds in which the delocalization is interrupted by insertion of a methylene group) in amides and its relative unimportance in the case of urea compounds (where steric inhibition of resonance seems to be unimportant). We believe that this apparent paradox can be rationalized by considering the importance of *charge capacity*.[25] Small atoms such as oxygen and fluorine have a relatively low ability to accept charge and can be readily "saturated" by a good electron-donating group.[26-30] In such cases, the addition of a second donating group is not expected to increase the charge density on the oxygen or fluorine to any great extent.

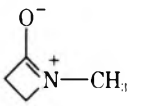
An important trend that may be observed in the data is that in all of the series studied, the basicity increases: four-membered ring < five-membered ring < six-membered ring < seven-membered ring. This order of basicity for the lactones has been reported previously by Tsuda et al.,[31] though the factors involved have not been thoroughly elucidated. We interpret these data in terms of three factors particularly important in cyclic compounds: the inductive effect (charge capacity), hybridization, and steric inhibition of resonance. With respect to the inductive effect, larger rings will exhibit a greater charge capacity of the methylene groups to donate electron density through the σ system to the carbonyl group.

The second factor is the change in hybridization, and hence in electronegativity, of the carbonyl carbon as the ring size is varied. The smaller the ring, the more p character must be utilized in the intraring bonding and the more s character is directed toward the exocyclic oxygen atom. Since electronegativity increases with increasing s character,[26,32] the smaller the ring, the more electronegative the carbonyl carbon will appear to the exocyclic oxygen. Thus more electron density is withdrawn from the latter making it less basic. Similar effects have been observed in the acid–base properties of biphenylene,[33] quinoxalines,[34] and phosphinic acids.[35] Further evidence that the effect is inherent in the ring size and is not due to solvation effects comes from the gas-phase proton affinities of cyclic ketones,[36] which follow the order reported here.

It is noteworthy that the changes in carbonyl basicity in cyclic compounds parallel similar changes in the infrared stretching frequencies, and the latter can be quantitatively related to rehybridization and electronegativity effects.[37] We thus feel that these two independent approaches to the electronic structure of the carbonyl group serve to substantiate each other. The idea that carbonyl basicity and stretching frequencies should be related is not new,[38] but it has been suggested[39] that this effect does not extend to cyclic compounds.

Finally, delocalization in small rings will suffer from steric inhibition of resonance since added strain energy of canonical form **4b** will reduce its contribution to the reso-


4a


4b

nance hybrid. This effect, like the hybridization of the carbonyl carbon atom, will always be affected by the bond angle and strain and therefore the two effects will always work in concert. Thus, although this latter effect may be involved in the basicity of cyclic compounds, it is of little heuristic value and we therefore discount its importance in this regard.

Our order of basicity confirms the one reported by Tsuda et al., who investigated the donor abilities toward deuteriomethanol in benzene. They also reported the pK_b's of those bases as

β-propiolactone	$pK_b = 10.05$
γ-butyrolactone	$pK_b = 6.12$
δ-valerolactone	$pK_b = 5.10$
ϵ-hexanolactone	$pK_b = 5.31$

This is the order one would expect based on inductive effects if solvation effects appear for the bulky last compound in the series and then only in aqueous solution. The corresponding lactones (and carbonates) are less basic than their nitrogen counterparts for the obvious reason that the oxygen in the ring is such a poor π donor. Whereas the π-bonding ability of nitrogen is very marked, that of oxygen is virtually nil.

We conclude, therefore, that although our data are consonant with the delocalization of π electrons, the constraints of cyclic compounds reveal important σ effects such as charge capacity and hybridization which may be more important than some π effects such as minor changes in geometry or addition of a second heteroatom donor. Such effects are presumably also present, though to a lesser degree and less clearly delineated, in the more relaxed acyclic systems. Furthermore, although none of the explanations presented here is novel, we believe that our data allow the evaluation of the predominant influence of hybridization and concomitant electronegativity effects on the acid–base properties of cyclic systems. Further supportive data and discussion will be presented in a forthcoming publication.[40]

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Supplementary Material Available. A listing of the phenol, HFIP, and base concentrations, cell path length, number of scans, and experimental values of $\Delta\nu$ described in this paper (8 pages) will appear following these pages in the microfilm edition of this volume of the journal.

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Electrolyte Effects upon the Polarographic Reduction of Alkyl Halides in Dimethyl Sulfoxide

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The polarographic half-wave potentials of a variety of alkyl halides are shown to be sensitive to the nature of cation of the supporting electrolyte. As the size of the tetraalkylammonium cation increases, the polarographic wave moves to more negative potentials. Because this change can be very substantial, polarographic waves are not observable at all for some halides when large electrolyte cations are employed; it is suggested that this phenomenon may be of analytical and synthetic value. The phenomenon is due in part to a decrease in the rate constant for electron transfer as the electrolyte cation increases in size; this was shown by measurements of a number of such rate constants.

A number of studies have demonstrated that the polarographic behavior of alkyl halides is dependent upon the experimental conditions employed, and one of the significant variables is known to be the nature of the supporting electrolyte.[1] Our interest in this problem was aroused as a result of investigations into the polarographic behavior of *trans*-15,16-dimethyldihydropyrene (DMDHP) and other aromatic compounds,[2] and of cyclooctatetraene (COT).[3] We observed[2] that the spacing between the two polarographic waves of DMDHP, 9,10-diphenylanthracene, and pyrene was dependent upon the nature of the supporting electrolyte, and, with others, we interpreted[2,3] the observed changes as being associated with ion pairing between the electrolyte cation and the aromatic radical anion and dianion, particularly the latter. We observed, however, a different phenomenon with COT.[3] While the same ion-pairing effects appear to operate, and indeed even dominate the observed polarographic behavior of COT, we also noted, using ac polarography, that the relative *rates* of electron transfer to COT appear to depend upon the nature of the R group in the tetraalkylammonium ion $R_4N^+X^-$ used as electrolyte: as R increased from methyl through heptyl, electron transfer to COT became progressively slower as shown by increasingly irreversible appearance of the ac (and dc) polarograms. We theorized[3] that the same effect may be operating with aromatic hydrocarbons, but would be experimentally unobservable because of the intrinsically high rates of electron transfer to these substances. On the other hand, employing the same reasoning, electrolyte effects ought to be pronounced in the case of cathodic processes in which electron transfer is very slow. One prominent class of compounds for which the latter requirement is met is that of alkyl halides, for which electron transfer is totally irreversible by all of the common criteria.[4] With this in mind, we carried out a study of the dependence of the polarographic behavior of a number of alkyl halides (comprising a variety of structural types) on the nature of the supporting electrolyte. Of particular interest was the question whether rates of heterogeneous electron transfer to alkyl halides are affected by the electrolyte, and, if so, the magnitude of this effect. The results of that study, described herein, promise to be of synthetic and analytical interest.

Experimental Section

Polarograms were measured using an all-glass jacketed cell (J. R. Tacussel Co.) and a Princeton Applied Research Model 170 electrochemistry system. The reference electrode was a saturated calomel electrode with porous Vycor barrier to prevent solvent flow into the reference.

The solvent reagent grade dimethyl sulfoxide (Matheson Coleman and Bell) was used without further purification. Supporting electrolytes were dried, after the indicated purification, in an Abderhalden drying pistol for 6–10 hr at 100° and 2 mm pressure.

A. Tetramethylammonium Hexafluorophosphate (Me_4NPF_6 or TMAHP). Tetramethylammonium hexafluorophosphate (Ozark-Mahoning Co.) was used without further purification.

B. Tetraethylammonium Bromide (Et_4NBr or TEAB). Tetraethylammonium bromide (5.7 mmol, Aldrich Chemical Co.) was dissolved in 36 ml of ethanol and recrystallized by slow addition of 108 ml of anhydrous ethyl ether. The precipitate was filtered under vacuum and dried as indicated above.

C. Tetra-*n*-propylammonium Tetrafluoroborate (n-Pr_4NBF_4 or TPAFB). Tetra-*n*-propylammonium tetrafluoroborate (Ozark-Mahoning Co.) was used without further purification.

D. Tetra-*n*-butylammonium Perchlorate (Bu_4NClO_4 or TBAP). Tetra-*n*-butylammonium perchlorate (Matheson Coleman and Bell) was used as supplied.

E. Tetra-*n*-heptylammonium Iodide (THpAI or Hp_4NI). Tetra-*n*-heptylammonium iodide (Eastman Organic Chemicals) was purified by the same procedure used for TEAB.

The dried salts were stored in a vacuum desiccator over phosphorus pentoxide.

Except where noted, the electroactive substances to be examined by polarography were purchased from commercial sources and used without further purification. 1-Iodo-1-chloroneopentane (2) was prepared by a published procedure; 1-bromonorbornane (1) was supplied by Professor J. W. Sease, who had obtained it from Professor K. B. Wiberg; 1,1-dichloroneopentane (3) was prepared by the procedure below. Except for diphenylanthracene, used as a saturated solution in Me_2SO, and 1-iodo-1-chloroneopentane (used as a 0.5 stock solution in Me_2SO), stock solutions of all compounds were 1.0 *M* in decane. After the polarographic background had been recorded, a quantity of the stock solution sufficient to afford a final concentration of 0.001 *M* was injected into the polarographic cell, and the polarogram was then recorded.

Synthesis of 1,1-Dichloro-2,2-dimethylpropane (3). A finely powdered suspension of 69.4 g (0.33 mol) of phosphorus pentachloride in 200 ml of carbon tetrachloride was cooled to −10°C. A solution of 35 ml of freshly distilled pivalaldehyde in 15 ml of carbon tetrachloride was then added dropwise to the cold, vigorously stirred suspension. The system was maintained under nitrogen throughout. The reaction mixture was carefully poured onto crushed ice, washed several times with water, and finally neutralized with aqueous potassium carbonate and dried over anhydrous magnesium sulfate. After the carbon tetrachloride was removed by distillation, the crude product was obtained in 87% yield. NMR spectroscopy showed this material to contain a substantial quantity of rearranged dichloride (2,3-dichloro-2-methylbutane). Pure 1,1-dichloroneopentane was obtained by vacuum distillation (60–67°, 127 mm) and then preparative gas chromatography (20 ft × 0.25 in. column packed with 10% Carbowax 20M on Chromosorb Pat 135°). The NMR spectrum consisted of two singlets at τ 4.5 and 8.9, relative areas 1:9, respectively.

Results and Discussion

The polarographic reduction of the following 16 organic compounds, 14 of them organic halogen compounds, was studied in dimethyl sulfoxide (Me_2SO) in the presence of up to five different quaternary ammonium salts as supporting electrolytes: *n*-pentyl bromide; isobutyl bromide; neo-

Table I
Electrolyte Effects on the Polarographic Half-Wave Potentials of Some Organic Compounds

Registry no.	Electroactive substance	R (in R_4N^+)	$-E_{1/2}$, V[a] Me[b]	Et[c]	n-Pr[d]	n-Bu[e]	$\Delta E_{1/2}$, V[f]
110-53-2	*n*-Pentyl bromide		2.09	2.21	2.34	2.56	0.47
78-77-3	Isobutyl bromide		2.14	2.28	2.51	2.65	0.51
630-17-1	Neopentyl bromide		2.23	*g*	2.58	>2.8[h]	≥0.6
39927-70-3	*sec*-Pentyl bromide		2.12	2.27	2.41	2.53	0.41
507-19-7	*tert*-Butyl bromide	E_1	1.91	1.94	1.99	2.08	0.17
		E_2	2.18	2.28	2.39	2.46	0.28
106-93-4	1,2-Dibromoethane		1.35	*g*	*g*	1.47	0.12
13474-70-9	1-Bromonorbornane		2.38	>2.6[h]	>2.7[h]	>2.8[h]	≥0.5
108-86-1	Bromobenzene		2.07	2.23	2.45	2.58	0.51
99-90-1	*p*-Bromoacetophenone	E_1	1.60	*g*	*g*	1.60	0
		E_2	1.95	*g*	*g*	1.94	0.01
		E_3	2.34	*g*	*g*	>2.8	≥0.47
108-90-7	Chlorobenzene		2.56	2.58	*h*	*h*	*g*
29559-54-4	1,1-Dichloroneopentane		2.31	*g*	*g*	~2.8[i]	~0.5
10199-24-3	1-Iodo-1-chloroneopentane	E_1	1.08	1.12	1.22	1.26	0.18
		E_2	1.37	1.32	1.43	1.45	0.08
591-50-4	Iodobenzene		1.59	1.64	1.74	1.82	0.23
589-87-7	*p*-Bromoiodobenzene	E_1	1.50	*g*	*g*	1.66	0.16
		E_2	2.06	*g*	*g*	2.54	0.48
98-86-2	Acetophenone	E_1	1.96	*g*	*g*	*g*	*g*
		E_2	2.34	*g*	*g*	*g*	*g*
1499-10-1	9,10-Diphenylanthracene	E_1	1.83	*g*	*g*	1.82	−0.01
		E_2	2.29	*g*	*g*	2.35	0.06

[a] Polarographic half-wave potential, vs. SCE. [b] Tetramethylammonium hexafluorophosphate. [c] Tetraethylammonium bromide. [d] Tetra-*n*-propylammonium tetrafluoroborate. [e] Tetra-*n*-butylammonium perchlorate. [f] ($E_{1/2}$, R = Me[b]) − ($E_{1/2}$, R = Bu[e]). [g] Not measured. [h] Polarographic wave not observed before the solvent decomposition potential. [i] $E_{1/2}$ coincides with the solvent decomposition potential.

pentyl bromide; 1,2-dibromoethane; 2-bromopentane; *tert*-butyl bromide; 1-bromonorbornane (**1**); 1-iodo-1-chloroneopentane (**2**); 1,1-dichloroneopentane (**3**); iodobenzene;

1

$(CH_3)_3CCHCl$
|
X

2, X = I
3, X = Cl

bromobenzene; chlorobenzene; *p*-bromoacetophenone; *p*-bromoiodobenzene; acetophenone; and 9,10-diphenylanthracene. The data are presented in Table I. A number of generalizations may be made based upon the data in Table I. First, the polarographic half-wave potentials of all alkyl halides studied underwent a progressive displacement to more negative potentials (and became more drawn out) as the cation of the supporting electrolyte was increased in size progressively from tetramethylammonium through tetrabutylammonium. This behavior is quite dissimilar from that exhibited by polycyclic aromatic compounds, where the potential of the first wave is essentially independent of the nature of the supporting electrolyte.[2,3] (The behavior of cyclooctatetraene is, as expected, intermediate, with $\Delta E_{1/2}$ = 0.05.)[3] The one apparent exception among the alkyl halides is *p*-bromoacetophenone, but reduction of this compound presumably follows a different mechanism involving electron injection into the π system followed by carbon–halogen bond breakage,[4,5] whereas the other halides are reduced by direct cleavage of the carbon–halogen bond.[4] The behavior of *p*-bromoacetophenone thus is similar to the aromatic hydrocarbons, which also undergo electron injection by the electrode into their π systems.

The range of potentials over which polarographic measurements can be made is limited by E_d, the decomposition potential of the supporting electrolyte. This potential moves slowly negative with increasing size of the electrolyte cation: Me_4N^+, −2.65 V;[5] Et_4N^+, −2.74 V; Pr_4N^+, −2.86 V; Bu_4N^+, −2.88 V; Hp_4N^+ (Hp = *n*-heptyl), −2.96 V.[6] This, along with the observed large shifts of half-wave potentials for the alkyl halides, gives rise to a striking effect: for a number of alkyl halides (neopentyl bromide, 1-bromonorbornane, and 1,1-dichloroneopentane) and also for the third wave of *p*-bromoacetophenone, the polarographic wave cannot be observed when electrolytes are used which have the most negative E_d's, yet can be seen clearly using electrolytes with more positive E_d's! This behavior, associated with the differential shifts of $E_{1/2}$ and E_d, is in contrast with intuition and the usual generalization that one selects large tetraalkylammonium ions, usually tetrabutylammonium, in order to obtain the widest accessible potential range for reduction processes. We suspect that this latter generalization is true only for substrates undergoing rapid electron transfer, and that the converse may often be true, as it clearly is here, with processes involving slow electron transfer. We believe that the phenomenon is of considerable potential utility in synthetic or analytical electrochemistry, since one may use it to shift reduction waves of carbon–halogen bonds in or out of accessible regions, or to separate closely spaced reduction waves. Dramatic examples are provided by 1,1-dichloroneopentane (**3**), whose reduction potential is cleanly resolved from background in the presence of tetramethylammonium ion, yet almost indistinguishable from background when the electrolyte cation is tetrabutylammonium,[8] and by 1-bromonorbornane, whose polarographic wave disappears merely upon changing the electrolyte cation from tetramethylammonium to tetraethylammonium!

Some other features of the data deserve comment. The progressively negative shift of the half-wave potential proceeding from *n*-pentyl to isobutyl to neopentyl bromide is an example of the known steric effect upon ease of alkyl halide reduction,[7] and presumably accounts for the difficulty with which 1,1-dichloroneopentane is reduced. Also, note that *tert*-butyl bromide and 1-iodo-1-chloroneopentane exhibit two polarographic waves, unlike the other alkyl halides studied. The wave heights show that both of these compounds undergo reduction by two one-electron

Table II
Relative Rates of Electron Transfer to Alkyl Halides as a Function of Supporting Electrolyte

Halide	$-E$, V[a]	$k_{f,h,Me} \times 10^4$, cm sec^{-1} [b,d]	Relative electron transfer rates[c,d] Me	Et	Pr	Bu	Hp
Isobutyl bromide	2.14	7.8	1	0.16	0.025	0.015	0.0015
tert-Butyl bromide	1.91	6.8	1	0.73	0.44	0.19	0.018
Bromobenzene	2.07	6.6	1	0.062	0.046	0.024	0.015
Iodobenzene	1.59	3.9	1	0.24	0.026	0.010	0.0075

[a] Potential at which relative rates were measured. [b] Heterogeneous electron-transfer rate in the presence of tetramethylammonium ion. [c] Relative to the rate in presence of tetramethylammonium ion as unity. [d] For definition of Me, Et, Pr, and Bu, see footnotes *b*–*e* of Table I; Hp = tetra-*n*-heptylammonium iodide.

transfers, unlike most other halides, which are reduced in a single two-electron step. The cause of this split into two discrete steps is probably different for each halide. The mechanism of reduction of alkyl halides is now generally accepted as consisting of two one-electron steps, involving initial formation of a free radical R· and subsequent reduction of R· to a carbanion, i.e.,

$$RX \xrightarrow[E_1]{e,\ -X^-} R\cdot \xrightarrow[E_2]{e} R:^-$$

The potential E_2 at which R· is reduced is generally positive of that (E_1) necessary to effect the first electron transfer, hence normally one observes a single two-electron wave. With a few halides, the two waves have been resolved.[4] In the present examples, the observance of two waves for 1-iodo-1-chloroneopentane presumably arises because for this compound E_1 occurs at a very positive potential, owing to the fact that this compound is both an alkyl iodide and a geminal dihalide. With *tert*-butyl bromide, on the other hand, separation is achieved not because E_1 is exceptionally positive, but rather because E_2 is unusually *negative*, owing to the difficulty of reducing a *tert*-butyl radical to the corresponding carbanion. *tert*-Butyl iodide has in fact previously been observed to exhibit two polarographic waves.[10a] In that study *tert*-butyl bromide was found to exhibit a single two-electron wave in tetrahydrofuran. Apparently in Me_2SO one or both waves are shifted sufficiently to permit their resolution. The sensitivity of the second wave of *tert*-butyl bromide and the third wave of *p*-bromoacetophenone to the nature of the electrolyte is presumably because these waves, involving anionic species, reflect ion-pairing and solvation effects (see footnotes 9 and 11 in ref 3).

With the observation in hand that polarographic half-wave potentials are sensitive to the nature of the supporting electrolyte, we were next interested in establishing to what extent the observed changes are related to changes in the rate of heterogeneous electron transfer to the two substrates, as opposed to, e.g., a shift in the location of the outer Helmholtz plane (OHP) with changes in the size of the electrolyte. The latter effect is undoubtedly also involved, although the necessary electrocapillary data to assess its magnitude is not available. In order to measure relative electron-transfer rates, we turned to a method developed by Koutecky.[11] He showed that the polarographic current for a totally irreversible electrochemical process can be written in terms of two parameters, χ and $F(\chi)$

$$\frac{i_{irrev}}{i_{rev}} = F(\chi) \quad (1)$$

$$\chi = \frac{ak_{f,h}t^{1/2}}{D_0^{1/2}} \quad (2)$$

where $a = (12/7)^{1/2}$, $k_{f,h}$ = rate constant for heterogeneous electron transfer, t = polarographic drop time, D_0 = diffusion coefficient of the electroactive species, and $F(\chi)$ is the computed ratio of the polarographic current for the irreversible (slow) electron transfer to the corresponding current for a rapid reversible electron transfer at the same potential. Koutecky computed values of $F(\chi)$ for various values of χ and presented the results in tabular form. To obtain the heterogeneous electron-transfer rate constant, $k_{f,h}$, at any point on the rising portion of the polarographic wave, one measures the ratio of the current at that potential to the polarographic diffusion current, i_d; this ratio is numerically equal to $F(\chi)$.[12] From Koutecky's tabulation, one obtains the corresponding value of χ, and thence $k_{f,h}$, by substitution of the drop time at that potential and an estimated value of the diffusion coefficient into eq 2. The diffusion coefficient may be estimated from model compounds[13] with acceptable accuracy (e.g., for isobutyl bromide in Me_2SO we estimate $D_0 = 2.5 \times 10^{-6}$ cm^2 sec^{-1}). In practice, the most useful way to present the data is as *relative* rates of electron transfer to a given halide in the presence of different electrolytes, thus eliminating any error involved in the estimates of the diffusion coefficient. What was done was to measure $k_{f,h}$ for a given alkyl halide in the presence of various electrolytes, at a potential corresponding to the half-wave potential in the presence of tetramethylammonium ion, and to calculate relative rates referred to the rate in the presence of this ion as unity. The data are presented in Table II. The rates do clearly depend upon the nature of the electrolyte to a substantial degree. At least part of the difference is likely due to a shift in the location of the OHP with changes in the nature of the cation, but this cannot be the whole cause of the observed changes, because the log-plot slopes[14] also change substantially with electrolyte, indicating changes in the nature of the electron-transfer process.

Table III
Relative Rates of Electron Transfer to Alkyl Halides in the Presence of a Common Electrolyte

Alkyl halide	$-E$, V[a]	Relative electron transfer rate
Tetramethylammonium Hexafluorophosphate		
Isobutyl bromide	2.00	1
Bromobenzene	2.00	3.8
tert-Butyl bromide	2.00	46.7
Tetrabutylammonium Perchlorate		
Isobutyl bromide	2.04	1
Bromobenzene	2.04	4.2
tert-Butyl bromide	2.04	39.6

[a] Potential (vs. SCE) at which relative rates were measured.

Because of the clear differences in values of $\Delta E_{1/2}$ for different substrates (Table I), it was of interest to measure relative rates of electron transfer to the various substrates in the presence of a single electrolyte. To do this, a potential was selected for each electrolyte such that the polarographic waves for bromobenzene and isobutyl and *tert*-butyl bromides were rising at that potential. The value of

$k_{f,h}$ at this potential was measured for each bromide and divided by $k_{f,h}$ for isobutyl bromide to obtain relative electron-transfer rates. The data are displayed in Table III. The high relative rate of cleavage of the carbon–bromine bond of *tert*-butyl bromide is probably associated with the stability of the resulting tertiary radical manifesting itself in the transition state for electron transfer.[10b] It is possible that reduction of bromobenzene involves initial electron injection into the π system of the aromatic ring,[4,5] rather than direct bond breakage in the electron-transfer step, but as one of us has argued previously,[4] we regard this as unlikely because of the very negative potential necessary to reduce benzene directly.

Conclusions

The changes in half-wave potential of alkyl halides as the supporting electrolyte is varied could in principle be taken advantage of in a variety of ways, both synthetic and analytical, because they offer a way to improve the resolution of closely spaced voltammetric waves. The caution must be repeated here again that when dealing with highly irreversible systems it is not necessarily true that the supporting electrolyte with the most negative reduction potential ought to be selected; on the contrary, the converse may be true.

Acknowledgment. Financial support was provided by the National Science Foundation. Professors Sease and Wiberg kindly provided the sample of 1-bromonorbornane.

Registry No.—TMAHP, 558-32-7; TEAB, 71-91-0; TPAFB, 15553-52-3; TBAP, 1923-70-2; THpAI, 3535-83-9; pivalaldehyde, 630-19-3.

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Response of Homo- and Benzhomobarrelenes to Uniparticulate Electrophilic Attack. Effect of a Lateral Cyclopropane Ring on the Direction and Stereochemistry of Chlorosulfonyl Isocyanate Addition[1]

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On reaction with chlorosulfonyl isocyanate, homobarrelene (1) afforded two isolable β-lactams, a γ-lactam, and a γ-lactone. All arise by electrophilic attack at the anti double bond with strong preference for endo approach. The site exclusivity was confirmed by ^{1}H NMR studies with unlabeled and 6,7-dideuterio-1. By way of contrast, the lone double bond in *syn*-benzohomobarrelene (2) experienced addition preferentially from the exo direction; two β-lactams and a γ-lactam were isolated in this instance. *anti*-Benzohomobarrelene (3) proved unreactive to chlorosulfonyl isocyanate under conditions where 1 and 2 reacted readily. Product structural assignments were made chiefly on the basis of spectral data, with extensive utilization of europium pseudocontact shifting. The mechanistic implications of these findings are discussed.

The rigid geometry and special three-dimensional π-electron character of barrelene has prompted experimental scrutiny of its capability to enter into molecular rearrangements.[2,3] High levels of interaction between the adjacent olefinic bridges are seen, but the symmetry properties of barrelene are such that stereochemical tests cannot be applied. To gain such information, some structural perturbation becomes necessary. In this paper, we report the first examples of electrophilic addition to homobarrelene (tricyclo[3.2.2.0^{2,4}]nona-6,8-diene, 1) and its isomeric benzo derivatives 2 and 3. Molecules other than 1 can in principle be

1

2

3

selected to address the stereochemical issue, but none of these share with homobarrelene the unique features imparted by the cyclopropane ring. Brown's examination of the steric effect caused by 7,7-dimethyl substitution at the

bridge carbon in norbornene has revealed a reversal in the customary exo direction of reaction in some, but not all, cases.[4] A comparable assessment of the influence of a cyclopropane ring laterally fused to a (necessarily homologous) bicyclo[2.2.2]octatriene frame has not been made. In addition to the purely steric factor, preferential interaction of the internal cyclopropane σ orbital with the C_6–C_7 π bond can gain importance. The possibility of selective stabilization of this type gains support from the photoelectron spectral behavior of 1.[5] In benzologues **2** and **3**, the available site for reaction is predetermined on structural grounds and only in one of these (**2**) is possible σ–π interaction attainable. The prevailing steric situations in **2** and **3** are also obviously quite different.

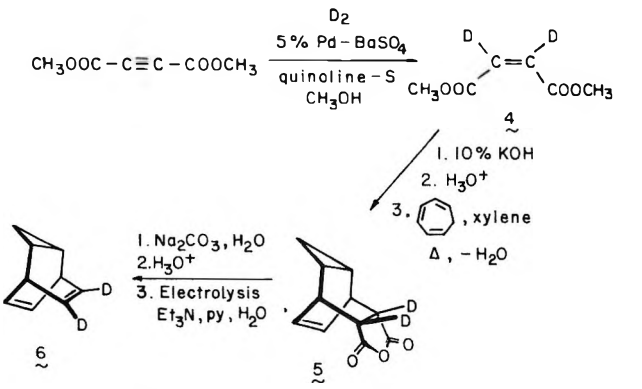
For these reasons, we have undertaken to study the comparative behavior of **1**–**3** toward chlorosulfonyl isocyanate (CSI). Use of this reagent was predicated on its recognized high reactivity, uniparticulate electrophilic character,[6] stereospecificity,[7] and appreciable steric requirements.[8] Furthermore, the *N*-chlorosulfonyl β-lactams which are formed initially under conditions of kinetic control are frequently rearrangement prone and sometimes experience ring opening–isomerization processes of mechanistic importance.

Results

Homobarrelene (1). The preparation of **1** was achieved by electrolytic decarboxylation[9] of the diacid obtained by aqueous hydrolysis of the cycloheptatriene–maleic anhydride adduct.[10] In agreement with earlier reports,[11,12] **1** was found to exhibit a ^{1}H NMR spectrum showing nearly degenerate secondary cyclopropyl protons (δ 0.60, m, 2), tertiary protons of the cyclopropane (1.10, m, 2) and bridgehead variety (3.60, m, 2), and two distinctive sets of olefinic proton pairs (5.90 and 6.45, q, 2 each). When **1** was treated with an equimolar quantity of CSI in purified deuteriochloroform solution and the progress of reaction monitored by NMR spectroscopy at ordinary probe temperatures, reduction of the intensity of the δ 6.45 signal to nil was noted during 15 min. The second olefinic quartet was somewhat reduced in area and some minor alteration in chemical shift was apparent as reaction progressed. A companion infrared study revealed the rapid appearance of a carbonyl band at 1825 cm^{-1} indicative of *N*-(chlorosulfonyl) β-lactam formation. With the passage of time, this peak was gradually (although never completely) supplanted by an absorption at 1790 cm^{-1}.

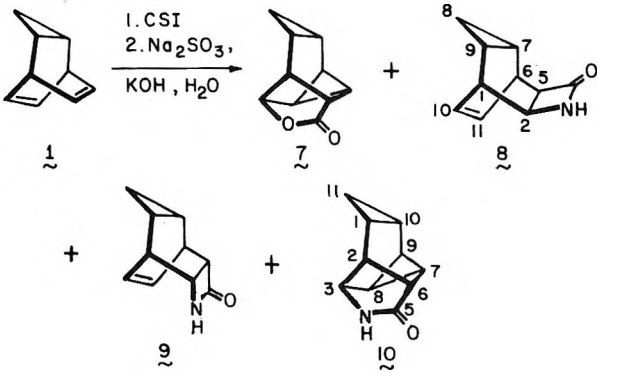
Using diamagnetic anisotropy arguments,[13] Rhodes and his co-workers[12] attributed the high-field olefinic quartet of **1** to H_8, H_9. Although support for the assumed selective shielding was gained by direct spectral comparisons with *syn*- and *anti*-tricyclo[3.2.2.0^{2,4}]non-6-ene, the difficulties sometimes encountered in determining the magnitude of long-range cyclopropane shielding effects[14] and possible anisotropic contributions of one double bond upon the other prompted us to establish the accuracy of these assignments in completely unequivocal fashion. To this end, the synthesis of homobarrelene specifically labeled with deuterium atoms at positions 6 and 7 was accomplished (Scheme I). Modified Lindlar reduction[15] of dimethyl acetylenedicarboxylate with deuterium gas gave dimethyl maleate-2,3-d_2 (**4**), the ^{1}H NMR spectrum of which consists of a sharp singlet at δ 3.75.[16] This diester was saponified and the resulting dideuteriomaleic acid was condensed directly with cycloheptatriene in refluxing xylene from which water was azeotropically removed. Subsequent hydrolysis and electrolytic decarboxylation of resulting anhydride **5** afforded **6** in low yield. The ^{1}H NMR and mass spectra of this hydrocarbon confirmed greater than 90% incorporation of two deuterium atoms. More specifically, the labeled diene almost completely lacked the downfield quartet centered at δ 6.45. With the knowledge that cycloheptatriene enters into Diels–Alder cycloadditions to give adducts having an anti cyclopropane orientation relative to the entering dienophile,[17] **6** is necessarily the 6,7-d_2 derivative and Rhodes' original assignments are fully confirmed.

Scheme I



These preliminary findings suggested that electrophilic attack on **1** occurs with total or near exclusivity at the anti double bond. Because the NMR spectra of the unpurified reaction mixtures were complex (several adducts were clearly in hand), product characterization was necessarily preceded by reductive dechlorosulfonylation and column chromatography. The latter separation was unavoidably deleterious to the resulting lactone and lactams with the result that high overall yields of pure materials were not realizable. Conversions to unpurified product mixtures were invariably quantitative. The addition proceeds to give four adducts (Scheme II), the relative proportions of which change with the duration of the experiment (Table I).

Scheme II



The availability of both β-lactam isomers facilitated the stereochemical assignments. The less dominant of these products [**8**, ν_{max} ($CHCl_3$) 1747 cm^{-1}] was shown by ^{1}H NMR analysis to have retained the high-field olefinic multiplet and to be of unrearranged structure (see Experimental Section). Appropriate Eu(dpm)$_3$-induced chemical shift studies established the proximal orientation of the amide functionality to the tertiary cyclopropyl hydrogens. For example, the relevant ΔEu values[18] for H_7 and H_9, determined to be −11.8 and −3.7, respectively, reveal the carbonyl oxygen to be the preferred site of lanthanide complexation. It follows that H_5 (−15.6) and H_6 (−9.5) should be affected to a greater extent than H_2 (−6.5) and H_1 (−2.8), and that the remaining olefinic protons should also be minimally but differently perturbed (H_{10}, −2.7; H_{11}, −3.8). In contrast, the tertiary cyclopropyl hydrogens in **9** (ν_{max} 1754 cm^{-1}) are characterized by small ΔEu shifts (H_7, H_9, −1.8).

Table I
Product Distribution after Chromatographic Separation of the CSI-Homobarrelene Adducts Formed at Various Reaction Times in Dichloromethane Solution (25°)

Reaction time, hr	Yield, %			
	7	8	9	10
0.5	1.5	1.5	9.1	1.0
5	2.3	3.2	8.3	2.6
24	*a*	*a*	9.0	28.0

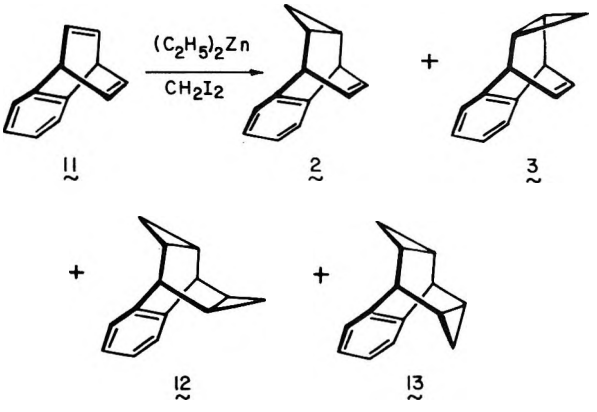
a Percent yield not determined.

That **10** is a γ-lactam follows from its intense carbonyl stretching frequency of 1700 cm^{-1}. The ^1H NMR spectrum is characterized by the absence of olefinic signals and the appearance of three new cyclopropyl protons. The presence of a total of seven such hydrogens is revealed by the array of multiplets appearing at 1.45–1.83 (1 H), 1.18–1.43 (2 H), 0.42–1.18 (2 H), 0.02–0.38 (1 H), and −0.08 to −0.37 ppm (1 H). The relative orientation of the lactam and cyclopropane groups was established by lanthanide shifting. The effect of added $Eu(fod)_3$ was most pronounced at H_6 (−10.8), H_7 (−5.1), and H_2 (−4.7) as well as at the >NH site (−11.1).

The most rapidly eluted adduct (**7**) was a γ-lactone (ν_{max} 1775 cm^{-1}), the ^1H NMR spectrum of which was very similar to that of **10** (see Experimental Section). As the direct result of lactam supplantation by lactone, downfield shifting of the three low-field multiplets [4.55–4.75 (1 H), 2.85–2.98 (1 H), and 2.52–2.79 ppm (1 H)] is observed. Both the basic structure and stereochemical disposition of the lactone unit were clear from this spectrum.

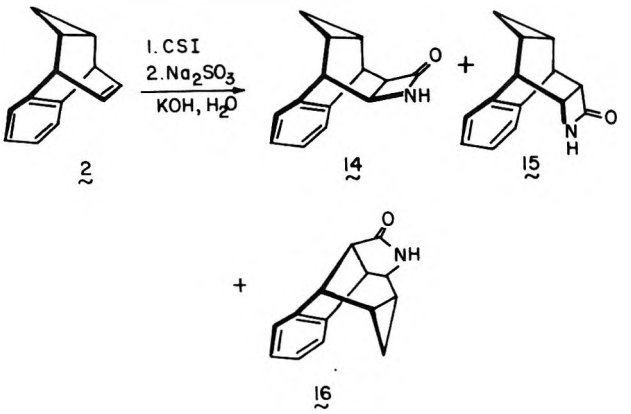
Benzohomobarrelenes 2 and 3. Reaction of benzobarrelene (**11**) with the Simmons–Smith reagent[19,20] gave a four-component mixture consisting of pairs of mono and bis adducts (Scheme III). Increased reliability and somewhat improved yields resulted from the use of diethylzinc[21] and this method was therefore preferred. Chromatography on silica gel–silver nitrate permitted isolation of the individual hydrocarbons in pure form. A distinction between syn and anti isomers in the monocyclopropanated products is reliably founded on ^1H NMR spectral data. The through-space shielding effect of the three-membered ring in **3** results in appearance of its olefinic protons at substantially higher field (δ 5.97–6.30) than those for **2** (6.68–6.90). Also, the secondary cyclopropyl protons in **2** (0.18–0.58; −0.26 to −0.53) appear upfield relative to those in **3** (1.03–1.40; 0.38–0.95) as a consequence of the diamagnetic anisotropy of the proximal benzene ring in the syn isomer. As concerns the bis adducts, the symmetry in **13** follows convincingly from the pairing of its proton signals. Definitive evidence for its syn,syn stereochemistry includes aromatic shielding of the individually resolvable secondary cyclopropyl protons (0.13 and −0.77). The aryl hydrogens of **13** are at approximately the same chemical shift as those of **12** but are split into a well-resolved AA'BB' multiplet.[22] The aryl protons of **12** appear as a narrow, unresolved multiplet. Hydrocarbon **12** lacks symmetry and is therefore uniquely reconcilable with prevailing syn,anti stereochemistry because of the four different secondary cyclopropyl resonances.

Scheme III



Chlorosulfonyl isocyanate reacted with **2** at room temperature to give three lactams (Scheme IV) which could again be separated by silica gel chromatography, but with appreciable loss of product. The major component to be isolated from this mixture was β-lactam **14** (16%), the exo configuration of which was deduced by pseudocontact shifting of its ^1H NMR spectrum with $Eu(fod)_3$ (see Experimental Section). Its carbonyl stretching frequency in chloroform solution (1748 cm^{-1}) differed insignificantly from that of endo isomer **15** (1752 cm^{-1}) which was next eluted (4.0% isolated). The major distinguishing characteristic of these [2 + 2] adducts is the chemical shift difference of tertiary cyclopropyl protons H_7 and H_9, which appear more upfield in **15** (δ 1.00–1.37) than in **14** (1.67–1.83). The ΔEu values of these protons in **14** (−6.6, −2.4) conform expectedly to their closer proximity to the lactam functionality than is possible in **15** (−2.5, −1.9).

Scheme IV



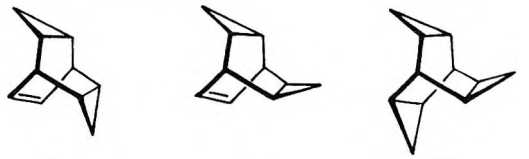
The minor (1.3%) product which accompanies the two β-lactams is assigned structure **16** on the basis of its intense absorption at 1700 cm^{-1} and key ^1H NMR signals at δ 4.15–4.33 (2 H) due to the protons flanking the amide group, 3.55–3.93 (2 H) arising from the benzylic bridgehead protons, and −0.1 to 0.9 (series of four one-proton multiplets) attributable to the individually distinctive cyclopropyl hydrogens. The precise alignment of the amide unit relative to the remainder of the molecular framework cannot be conclusively established from these data because the two adjoining methine protons (4.15–4.33) appear at chemical shifts sufficiently similar to preclude revealing double resonance studies; rather, this detail follows from mechanistic reasoning (vide infra).

Attempts to add chlorosulfonyl isocyanate to **3** under conditions where other analogous compounds reacted quite rapidly proved uniformly unsuccessful.

Discussion

Fusion of a cyclopropane ring to barrelene obviously exerts large effects upon the direction and stereochemistry of chlorosulfonyl isocyanate addition. The presence of the bulky three-membered ring modifies the steric environment such that electrophilic attack at the syn double bond lacks kinetic importance. The present results reveal further that a directive effect operates at the anti olefinic site, dif-

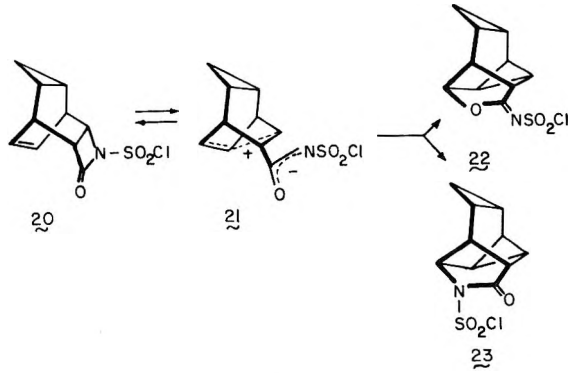
ferentiation arising in favor of endo attack, i.e., preferred addition from that direction proximal to the second double bond. This preference is not maintained during cuprous chloride promoted diazomethane addition to **1** where **17**, **18**, and **19** are reported to be formed in yields of 46, 25, and



17 **18** **19**

27%, respectively.[23] It is our thesis that the smaller steric requirements of the latter reagent, coupled with its probable impingement upon the center rather than termini of the π bond, may allow for a lesser degree of selectivity. However, owing to the low material balance in the CSI reaction with **1**, full assessment of the stereospecificity of electrophilic attack is beclouded.

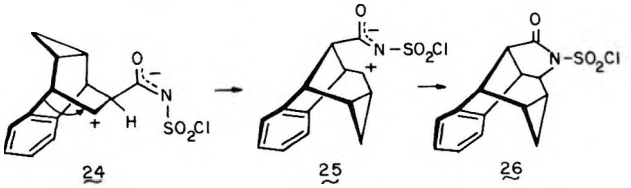
Once *N*-(chlorosulfonyl) β-lactam formation occurs from the endo direction the [2 + 2] adduct arising from endo capture (**20**) can experience ring opening with formation of zwitterion **21**. Alternatively, if bonding occurs in stepwise fashion, **21** would be formed initially. This centrally important dipolar species can, of course, cyclize to **20**; with involvement of the neighboring double bond, the possibility for more remote C–N and C–O closure with formation of **22** and **23** is also possible and does operate.[24]



20 **21** **22** **23**

An analogous zwitterion is likely formed from the related exo [2 + 2] adduct since double bond participation in this instance should be more facile. However, its further rearrangement (e.g., 1,2-vinyl shift) might be unfavorable, thus leading to **8** as the unique end product of this reaction pathway. Alternatively, the possibility that an isomerized lactam does result and is subsequently decomposed or consumed by further reaction with CSI cannot be dismissed.

The presence of the added benzene ring in **2** does not lend itself to comparably facile delocalization. However, isolation of **16** points up the real possibility for 1,2-phenyl migration in **24** with transient intervention of **25**.



24 **25** **26**

Replacement of the 8,9 double bond in **1** by a benzene ring can be expected to increase the level of steric interaction on the endo surface. The predominance of β-lactam **14** in the product mixture supports this contention, although the isolation of **15** reveals that chlorosulfonyl isocyanate bonding to **2** from the endo direction is not completely impeded. The total lack of reactivity of **3** under comparable conditions serves to emphasize the adverse effects engendered by the combination of the fused benzo substituent and a syn-oriented cyclopropane ring.

In conclusion, cycloaddition to homobarrelene and its syn benzologue via a process which may involve a cyclic $[\pi 2_a + \pi 2_s]$ four-membered transition state[7,8] is seen to proceed chiefly from the anti-endo and anti-exo directions, respectively. The effect of the cyclopropane ring is to deter attack at the syn double bond in **1** and the remaining double bond in **3**. It would appear therefore that such rigid bicyclic systems as **1–3** may prove to be sensitive mechanistic probes of cyclic and noncyclic addition processes.

Experimental Section

Proton magnetic resonance spectra were obtained on Varian A-60A, Varian HA-100, and Jeolco MH-100 spectrometers; apparent splittings are given in all cases. Infrared spectra were determined on Perkin-Elmer Model 137 and 467 instruments. Mass spectra were recorded on an AEI-MS9 spectrometer at an ionizing potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Maleic Acid-*2,3-d*$_2$. The sulfur–quinoline poison was prepared by heating 1.0 g of sulfur in 6.0 g of pure synthetic quinoline at the reflux temperature for 5 hr, dilution with 50 ml of xylene, and filtration to remove insolubles. A mixture of 4.00 g (28.2 mmol) of dimethyl acetylenedicarboxylate, 100 ml of absolute methanol, and 0.40 g of 5% palladium on barium sulfate was treated with 8 drops of the poison and subjected to an atmosphere of deuterium gas at atmospheric pressure. After 4.5 hr of vigorous magnetic stirring, the mixture was rid of catalyst by filtration and the filtrate was evaporated under reduced pressure. The resulting yellow oil was dissolved in diethyl ether and remaining coagulated material was separated by filtration. The organic phase was extracted with 5% hydrochloric acid solution until yellow color was no longer removed and dried. Vacuum distillation gave 2.70 g of colorless liquid, bp 85–95° (2.5 mm), the ^{1}H NMR spectrum of which showed the material to consist of maleate (65%) and succinate (35%). This ratio was confirmed by VPC methods and comparison with undeuterated authentic samples.

A 2.38-g sample of this mixture was heated at reflux with 40 ml of 10% aqueous potassium hydroxide for 4 hr. The pH of the cooled solution was adjusted to 5 with concentrated hydrochloric acid. Continuous ether extraction (14 hr) furnished 30 mg of succinic acid, mp 182–186°. The pH was now adjusted to 3 and continuous ether extraction was resumed (2 days). From the dried organic extracts, there was obtained 800 mg of pale yellow solid, mp 120–180°. Adjustment to pH 1 and final extraction afforded 1.0 g (80% based upon estimate of 4 originally present) of maleic acid-*2,3-d*$_2$, mp 132–134.5°. Recrystallization from ether with charcoal decolorization gave pure product, mp 137–138°.

Tricyclo[3.2.2.0^{2,4}]nona-6,8-diene-*6,7-d*$_2$ (6). A mixture of maleic acid-*2,3-d*$_2$ (640 mg, 5.42 mmol), 10.0 g (0.108 mol) of distilled cycloheptatriene, and 10 ml of xylene was carefully heated to reflux (foaming!) in a 100-ml round-bottomed flask fitted with a Dean-Stark trap. After 1 day at 120°, the solvent was evaporated under reduced pressure. The residual anhydride (**5**) and 2.0 g of sodium carbonate in 50 ml of water were heated to reflux for 1 hr, cooled, adjusted to pH 6, and evaporated in vacuo. Of the 4.57 g of residue obtained in this manner, 4.2 g was dissolved in a small amount of hydrochloric acid (pH 1) and the volume reduced under reduced pressure until crystals began to form. The entire mixture was then extracted with ether (2 × 200 ml) to give 560 mg (49%) of crude diacid, mp 159–167° (with gas evolution).

This diacid (560 mg, 2.66 mmol) was dissolved in 100 ml of 10% aqueous pyridine containing 1.25 ml of triethylamine and the solution was electrolyzed at 100 V and 7–19° for 3 hr. The resulting brown solution was poured into 200 ml of water and extracted with pentane (5 × 100 ml). The combined pentane extracts were washed with 5% hydrochloric acid (4 × 50 ml) and saturated sodium carbonate solution (100 ml), dried, and reduced in volume to 2 ml by careful fractional distillation. The hydrocarbon product was isolated by preparative VPC on a 6 ft × 0.25 in. 10% FFAP column (105°). There was obtained 30 mg (9.4%) of **6**: δ_{Me_4Si} (CCl_4) 6.50–6.67 (m, 0.10 H, residual H_6, H_7), 5.82–6.12 (m, 2, H_8, H_9), 3.45–3.75 (m, 2, H_1, H_5), 0.98–1.32 (m, 2, H_2, H_4), and 0.28–0.78 (m, 2, H_3); MS *m/e* 121 (3.8), 120 (41.8), 119 (100.0), 118 (34.3), and 117 (19.7).

Addition of Chlorosulfonyl Isocyanate to 1 with Stirring for 5 Hr. A SOLUTION OF 45] MG (3.81 mmol) of 1 in 10 ml of dry dichloromethane was stirred at 20° under nitrogen while 5.40 mg (3.81 mmol) of freshly distilled chlorosulfonyl isocyanate in 1 ml of the same solvent was introduced via syringe. After 5 hr, 50 ml of anhydrous ether was added and the solution maintained at 5° while 10 ml of 25% aqueous sodium sulfite and 1 ml of 10% potassium hydroxide solution were slowly added. After 1 hr at room temperature, the organic phase was separated and combined with an ether extract of the residual aqueous solution. After being washed successively with water (50 ml), 2% hydrochloric acid (50 ml), saturated sodium bicarbonate solution (50 ml), brine (50 ml), and water, the organic layer was dried and evaporated to leave 160 mg of pale yellow oil. Chromatographic separation was achieved on silica gel (Baker) using incrementally higher percentages of ethyl acetate in hexane as eluent.

The first substance to elute proved to be lactone 7 (14 mg, 2.3%), which was obtained as white crystals, mp 88.5–89.5°, after sublimation (50°, 0.02 mm) and recrystallization from ether–pentane: ν_{max} ($CHCl_3$) 1775 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 4.55–4.75 (m, 1, >CHO–), 2.85–2.98 (m, 1, >CHCO–), 2.52–2.79 (m, 1, bridgehead), 1.60–2.20 (m, 3, tertiary cyclopropyls), 0.77–1.52 (m, 2, tertiary cyclopropyls), 0.46–0.72 (m, 1, anti secondary cyclopropyl), and 0.12 to −0.17 (m, 1, syn secondary cyclopropyl).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22. Found: C, 73.88; H, 6.23.

The second substance isolated was β-lactam 8 (20 mg, 3.2%), white crystals, mp 150–151°, after sublimation (80°, 0.02 mm) and recrystallization from ether: ν_{max} ($CHCl_3$) 3250 and 1747 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 6.33 (br s, 1, >NH), 5.77–6.05 (m, 2, olefinic), 3.44–3.68 (m, 1, >CHN<), 2.85–3.23 (m, 3, >CHCO– and bridgeheads), 0.77–1.42 (m, 2, tertiary cyclopropyls), and 0.02–0.33 (m, 2, secondary cyclopropyls); *m/e* (calcd) 161.0841, (obsd) 161.0843.

The ΔEu values as determined with $Eu(dpm)_3$ in $CDCl_3$ solution follow: H_1 (−2.8), H_2, (−6.5), H_3 (−11.7), H_5 (−15.6), H_6 (−9.5), H_7 (−11.8), H_{8a} (−2.7), H_{8b} (−1.4), H_9 (−3.7), H_{10} (−2.7), and H_{11} (−3.8).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88. Found: C, 74.44; H, 6.89.

The third component was identified as β-lactam 9 (51 mg, 8.3%), white crystals, mp 111.5–112.5°, from ether–pentane: ν_{max} ($CHCl_3$) 1745 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 6.45 (br s, 1, >NH), 5.62 (m, 2, olefinic), 3.40–365 (m, 1, >CHN<), 3.12–3.33 (m, 1, >CHCO–), 2.73–3.10 (m, 2, bridgehead), 0.60–1.00 (m, 2, tertiary cyclopropyl), and 0.05–0.33 (m, 2, secondary cyclopropyl).

The ΔEu values as determined with $Eu(fod)_3$ in $CDCl_3$ solution follow: H_1 (−1.5), H_2 (−2.7), H_3 (−6.4), H_5 (−7.7), H_6 (−5.2), $H_{7,9}$ (−1.8), H_{8a}, H_{8b} (−1.3), H_{10} (−1.4), and H_{11} (−3.2).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.70; H, 6.85; N, 8.53.

The last product eluted was characterized as γ-lactam 10 (16 mg, 2.6%), colorless crystals, mp 134–135°, from ether: ν_{max} ($CHCl_3$) 1700 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 7.00 (br s, 1, >NH), 3.28 (br s, 1, >CHN<), 2.40 (br s, 1, >CHCO–), 2.13 (m, 1, bridgehead), 1.45–1.83 (m, 1, tertiary cyclopropyl), 1.18–1.43 (m, 2, tertiary cyclopropyl), 0.42–1.18 (m, 2, tertiary cyclopropyl), 0.02–0.38 (m, 1, secondary cyclopropyl), and −0.08 to −0.37 (m, 1, secondary cyclopropyl).

The ΔEu values as determined with $Eu(fod)_3$ in $CDCl_3$ solution follow: H_1, H_{10} (−2.1), H_2 (−4.7), H_3 (−3.0), H_4 (−11.1), H_6 (−10.8), H_7 (−5.1), H_8, H_9 (−1.9), H_{11anti} (−1.3), and H_{11syn} (−1.6).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.53; H, 6.85; N, 8.69.

Cyclopropanation of Benzobarrelene (11). A solution of benzobarrelene (11, 3.47 g, 22.5 mmol)[25] in 50 ml of anhydrous ether containing 7.0 ml (70 mmol) of diethylzinc was stirred mechanically under a dry nitrogen atmosphere at room temperature while 6.20 g (25.0 mmol) of diiodomethane in 10 ml of dry benzene was introduced dropwise. Upon completion of the addition, the mixture was heated at reflux for 10 hr. An additional 4.0 g (15.0 mmol) of diiodomethane in 5 ml of benzene was again added and heating was continued for 24 hr. Hydrochloric acid (5%, 50 ml) was slowly introduced with ice cooling and the hydrolyzed reaction mixture was poured into 300 ml of ether. The organic phase was washed with 5% hydrochloric acid and these washings were extracted with ether. The combined organic layers were shaken with saturated sodium carbonate (300 ml) and sodium chloride solutions (300 ml), dried, and evaporated to leave 4.15 g of yellow oil.

This oil was chromatographed on silica gel–silver nitrate (10%); elution was performed with increasing amounts of ether in hexane. The first component to elute was identified as *syn,syn*-9,10-benzoquadricyclo[3.3.2.$0^{2,4}$.$0^{6,8}$]dec-9-ene (13, 130 mg, 3.2%). Sublimation (70°, 50 mm) afforded colorless needles: mp 129–130°; ν_{max} (CCl_4) 3020, 3005, and 2938 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 6.75–7.25 (AA'BB', 4, aromatic), 3.47 (five-line m, 2, bridgehead), 1.08–1.53 (m, 4, tertiary cyclopropyl), 0.13 (d of t, J_{gem} = 5.6 Hz, J_{cis} = 7.4 Hz, 2, anti secondary cyclopropyl), and −0.77 (d of t, J_{trans} = 3.8 Hz, 2, syn secondary cyclopropyl); *m/e* (calcd) 182.1095, (obsd) 182.1098.

Anal. Calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.02; H, 7.81.

The next hydrocarbon proved to be bis adduct 12, rhombic crystals (from hexane) which were isolated in 6.1% yield (250 mg). Sublimation (70°, 50 mm) gave material of mp 91–92°; ν_{max} (CCl_4) 3075, 3010, and 2930 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 7.04 (narrow m, 4, aromatic), 3.37 (five-line m, 2, bridgehead, 1.79) (six-line m, 1, secondary cyclopropyl), 0.53–1.27 (m, 5, one secondary and four tertiary cyclopropyl), −0.27 (d of t, J_{gem} = 5.5, J_{cis} = 7.2 Hz, 1, secondary cyclopropyl), and −1.05 (d of t, J_{trans} = 3.8 Hz, 1, secondary cyclopropyl); *m/e* (calcd) 182.1095, (obsd) 182.1098.

Anal. Calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.23; H, 7.76.

The third component was a colorless oil (1.12 g, 29.6%) identified as *anti*-6,7-benzotricyclo[3.2.2.$0^{2,4}$]nona-6,8-diene (3): δ_{Me_4Si} ($CDCl_3$) 6.87–7.38 (m, 4, aromatic), 5.97–6.30 (m, 2, olefinic), 3.80–4.12 (m, 2, bridgehead), 1.03–1.40 (m, 2, tertiary cyclopropyl), and 0.38–0.95 (m, 2, secondary cyclopropyl).

Anal. Calcd for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.45; H, 7.20.

The last product was the corresponding syn isomer (270 mg, 7.1%) which likewise was a colorless oil: δ_{Me_4Si} ($CDCl_3$) 6.92–7.08 (narrow m, 4, aromatic), 6.68–6.90 (m, 2, olefinic), 3.82–4.20 (m, 2, bridgehead), 1.23–1.60 (m, 2, tertiary cyclopropyl), 0.18–0.58 (m, J_{cis} = 7 Hz, 1, secondary cyclopropyl), and −0.26 to −0.53 (d of t, J_{gem} = 5.8, J_{trans} = 3.8 Hz, 1, secondary cyclopropyl).

Anal. Calcd for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 93.06; H, 7.21.

Finally, 1.45 g (41.8%) of benzobarrelene was recovered unchanged.

Addition of Chlorosulfonyl Isocyanate to 2. To a solution of 2 (300 mg, 1.78 mmol) in 6.0 ml of dry dichloromethane was added with stirring under nitrogen 257 mg (1.82 mmol) of freshly distilled chlorosulfonyl isocyanate via syringe. The mixture was maintained at 25° for 72 hr before dilution with ether (20 ml) and introduction at 0° of 25% sodium sulfite solution (5 ml) and 10% potassium hydroxide (0.5 ml) followed by 10 ml of water. After 30 min at room temperature, the contents were poured into ether (100 ml) and the organic phase was washed with 5% hydrochloric acid (25 ml), saturated sodium carbonate (50 ml), and saturated brine solutions (50 ml). The organic layer was dried and evaporated to leave a yellow oil (409 mg) which was chromatographed on silica gel (elution with increasing amounts of ether in hexane).

Initially, there was recovered 60 mg (20%) of 2. This was followed by β-lactam 14 (60 mg, 16.0%) which was obtained as small white needles: mp 238–239° (from ether–hexane); ν_{max} ($CHCl_3$) 1748 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 6.87–7.30 (m, 4, aromatic), 6.37 (br s, 1, >NH), 3.37–3.90 (m, 3, >CHN< and bridgeheads), 2.98–3.28 (m, 1, >CHCO–), 1.67–1.83 (m, 2, tertiary cyclopropyl), −0.12 to 0.28 (m, 1, secondary cyclopropyl), and −0.68 to −0.93 (m, 1, secondary cyclopropyl).

The ΔEu values as determined with $Eu(fod)_3$ in $CDCl_3$ solution follow: H_1, −2.0; H_2, −4.0; >NH, −8.0; H_5, −9.9; H_6, −6.2; H_7, −6.6; H_{8a}, −0.9; H_{8b}, −0.2; H_9, −2.4; H_{12}, −2.2; and H_{13-15}, −1.5.

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.22; H, 6.37; N, 6.71.

The second product to elute was found to be β-lactam 15 (15 mg, 4.0%), off-white crystals: mp 164.5–166° (from ether); ν_{max} ($CHCl_3$) 1752 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 6.80–7.38 (m, 4, aromatic), 5.43 (br s, 1, >NH), 3.77–4.06 (m, 1, >CHN<), 3.38–3.72 (m, 3, >CHCO– and bridgeheads), 1.00–1.37 (m, 2, tertiary cyclopropyl), 0.07–0.47 (m, 1, secondary cyclopropyl), and −0.45 to −0.70 (m, 1, secondary cyclopropyl); *m/e* (calcd) 211.0997, (obsd) 211.1000.

The ΔEu values as determined with $Eu(fod)_3$ in $CDCl_3$ solution follow: H_1, −1.9; H_2, −2.5; >NH, −6.0; H_5, −7.5; H_6, −5.3; H_7, −2.5; H_{8a}, −1.4; H_{8b}, −1.9; H_9, −1.9; H_{12}, −3.5; and H_{13-15}, −1.3.

Lastly, there was isolated 5 mg (1.3%) of 16 as white needle clusters: mp 170.5–171° (from ether); ν_{max} ($CHCl_3$) 1700 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 6.80–7.32 (m, 4, aromatic), 6.22 (br, s, 1, >NH), 4.15–4.33 (m, 2, >CHCO– and >CHN<), 3.55–3.93 (m, 2, bridgehead), 0.8–0.9 (m, 1, tertiary cyclopropyl), 0.4–0.7 (m, 1, tertiary cyclopropyl),

−0.1 to 0.1 (m, 1, secondary cyclopropyl), and −0.5 to −0.7 (m, 1, secondary cyclopropyl); *m/e* (calcd) 211.0997, (obsd) 211.1000.

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Registry No.—**1**, 7092-05-9; **2**, 56960-48-6; **3**, 57029-75-1; **4**, 41411-75-0; **6**, 57029-76-2; **7**, 56960-49-7; **8**, 56960-50-0; **9**, 57029-77-3; **10**, 56960-51-1; **11**, 7322-47-6; **12**, 56960-52-2; **13**, 57029-78-4; **14**, 56960-53-3; **15**, 57029-79-5; **16**, 56960-54-4; maleic acid-2,3-d_2, 24461-33-4; dimethyl acetylenedicarboxylate, 762-42-5; succinic acid, 110-15-6; cycloheptatriene, 544-25-2; diacid, mp 159–167°, 57029-80-8; chlorosulfonyl isocyanate, 1189-71-5; diiodomethane, 75-11-6.

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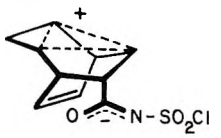

i

no isolated products require this intermediate although its transformation to **21** remains indeed an open possibility.
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Direct Determinations of *R/S* Enantiomer Ratios of Citronellic Acid and Related Substances by Nuclear Magnetic Resonance Spectroscopy and High Pressure Liquid Chromatography

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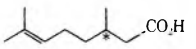
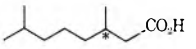
Two methods are described for direct determination of the enantiomer ratios of optically active 3,7-dimethyl-6-octenoic acid (citronellic acid), 3,7-dimethyloctanoic acid, and the homologous 3,7,11-trimethyldodecanoic acid. The first method is based on analysis of the C_3 methyl signal in the NMR spectra of methyl esters obtained in CS_2 in the presence of a chiral europium shift reagent. The second method is based on analytical separations by high pressure liquid chromatography of diastereomeric amides obtained by reaction of (*R*)-(+)-α-methyl-*p*-nitrobenzylamine with, e.g., citronellic acid. Both methods give directly *R/S* enantiomer ratios on samples of citronellic acid and epimer ratios on 3,7,11-trimethyldodecanoic acid. Using these methods citronellic acid samples from natural citronellal and (+)-pulegone have been shown to be respectively 80 and 96–98% excesses of the (3*R*)-(+) enantiomer.

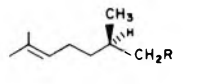
Citronellal is a relatively inexpensive chiral substance which is found in over 50 essential oils,[1] typically as a mixture of *R* and *S* enantiomers with one predominating. Citronellal obtained from its most important source, Java citronella oil,[2] has been assigned the (3*R*)-(+)-1 configuration[3] but is known to be only about 75% optically pure.[4,5] This paper describes two convenient methods for direct determination of the enantiomeric composition of citronellic acid (**2**) which is readily derived from citronellal. One method involves analysis of NMR spectra of **3** obtained in the presence of the chiral shift reagent Eu(dcm)$_3$, **4**.[6] The other involves analytical separation by high pressure liquid chromatography of diastereomeric amides **6** obtained from reaction of **5** with excess (*R*)-(+)-α-methyl-*p*-nitrobenzylamine.[7]

Both methods have been used to determine the enantiomeric compositions of samples of **2** and **7** obtained from racemic citronellol, from natural citronellal having $[\alpha]^{25}$D

Table I
Enantiomeric Compositions of C_{10} and C_{15} Substrates by NMR and HPLC Methods

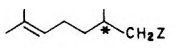
Substrate		$[\alpha]^{25}D$	*R/S* determinations of esters by NMR	Percentage of *R* and *S* enantiomer amides by HPLC	Percent enantiomeric excess[d]
	rac-2	0° (*c* 5.0, $CHCl_3$)	*R/S* = 1	54.4% *R*, 45.6% *S*	~0
	nat-2[a]	+7.73° (*c* 5.3, $CHCl_3$)	*R/S* = 9	90.2% *R*, 9.8% *S*	80.4
	pin-2	+8.70° (*c* 5.0, $CHCl_3$)	*R/S* = 12	92.5% *R*, 7.5% *S*[b]	85
	(*R*)-2	+10.3° (*c* 5.0, $CHCl_3$)	*R* only	99% *R*, 1% *S*	98
	rac-7	0°	*R/S* = 1	50.0% *R*, 50.01 *S*[b]	~0
	nat-7	+5.50° (*c* 5.0, $CHCl_3$)	*R/S* = 9	90.8% *R*, 9.2% *S*	82
	pin-7	+8.70° (*c* 5.0, $CHCl_3$)	*R/S* = 12	91.5% *R*, 8.5% *S*[b]	83
	(*R*)-7	+7.0° (c 5.0, $CHCl_3$)	*R* only	96.6% *R*, 3.4% *S*	93
					
(3*R*,7*R*(phytol))-14		+5.43° (c 5.0, $CHCl_3$)	3*R*,7*R* only	100% 3*R*	100 (C_3), 100 (C_7)
(3*R*(nat),7*RS*)-14		*c*	3*R*/3*S* ≃ 9, 7*R*/7*S* ≃ 1	90.5% 3*R*, 9.5% 3*S*	81 (C_3), 0 (C_7)
(3*R*(*R*),7*RS*)-14		+6.05° (c 5.0, $CHCl_3$)	3*R* only, 7*R*/7*S* = 1	98.3% 3*R*, 1.7% 3*S*	96 (C_3), 0 (C_7)
(3*RS*,7*RS*)-14		0°	3*R*/3*S* = 7*R*/7*S* = 1	49.4% 3*R*, 50.6% 3*S*[b]	0 (C_3), 0 (C_7)
(3*RS*,7*R*(nat))-14		*c*	Not determined	51.2% 3*R*, 48.8% 3*S*	0 (C_3), 80 (C_7)

[a] Natural citronellal, $[\alpha]^{25}D$ +12.00° (neat), was used to prepare nat-2. [b] Multiple determination. Typical precision limits ±0.5%. Other values are based upon single determinations. [c] Not obtained on free acid. [d] In the case of 14, numerical values given refer to the excess of *R* epimer over *S* epimer at C_3 or C_7 (i.e. % *R* epimer − % *S* epimer).



3R(+)-1 R = CHO

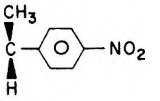
3R(+)-2 R = CO_2H



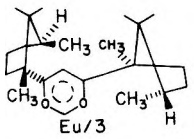
2 Z = CO_2H

3 Z = CO_2CH_3

5 Z = COCl

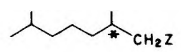
6 Z = CONH 

16 Z = CH_2OH



Eu/3

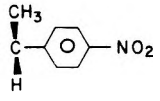
4



7 Z = CO_2H

8 Z = CO_2CH_3

9 Z = COCl

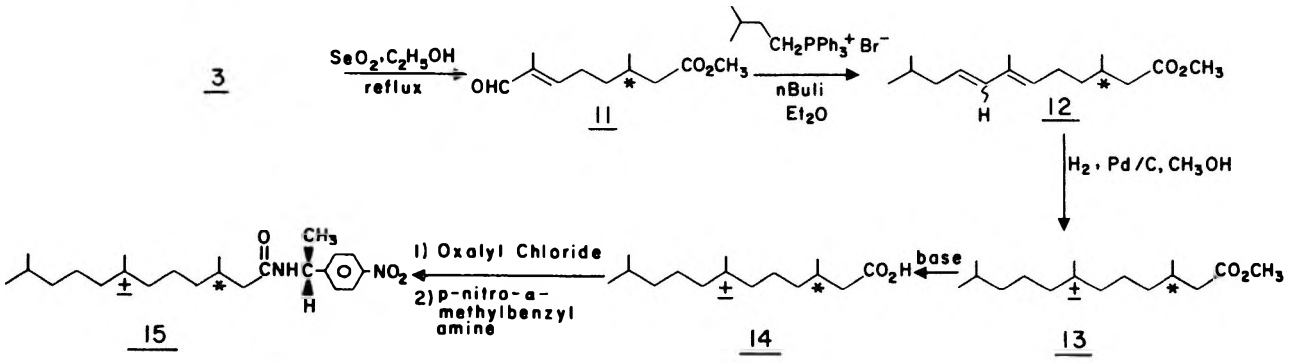
10 Z = CONH 

+12.00° (neat), from pulegone[8] and from (+)-citronellol derived from (−)-β-pinene obtained from U.S. sulfate turpentine.[9] These samples are herein designated as rac-2, nat-2, (*R*)-2, and pin-2, respectively, and are shown below to be respectively 0, 80–82, 96–98, and 84–86% enantiomeric excess of (3*R*)-(+)-2 or (3R)-(+)-7. The *R/S* epimer ratios at both C_3 and C_7 in the homologous C_{15} acid **14** were determined by NMR on **13** and HPLC on **15**. A sample of (3*RS*,7*RS*)-**14** was obtained from addition of triethyl phosphonoacetate to 6*RS*,10-dimethylundecan-2-one[12] followed by hydrogenation and hydrolysis; samples of (3*R*,7*RS*)-**14** were obtained both from nat-3 and (*R*)-3 as shown in Scheme I and a sample of (3*RS*,7*R*)-**14** was obtained from natural citronellal by reaction with methyl diethyl phosphonosenecioate. Properties of all these substances are given in Table I.

Determination of the enantiomeric composition of **3** or **8** by NMR was accomplished by integration of the pair of C_3 methyl group signals observed at 4.2 ppm on solutions of the ester and 1.2 equiv of **4** in CS_2 and Me_4Si. The procedure given in the Experimental Section was optimized with respect to which ester of **2** was used, the molar ratio **4/3**, the solvent, and the probe temperature, to obtain best analytical results on a Varian T-60 spectrometer with T-6057 lock/decoupler. The recommended conditions produce an enantiomeric shift difference ($\Delta\Delta\delta$) of the C_3 methyl group signals for **3** of ca. 0.015 ppm, sufficient to allow semiquantitative determination of *R/S* ratios in the range $1/9 < R/S < 9/1$ and to permit detection of ca. 3–5% of a minor enantiomer when suitable reference samples are available. Typical spectra are shown in Figures 1a–c which show respectively that rac-**8** is a 1:1 mixture of enantiomers, that nat-**3** is a 9:1 *R*:*S* mixture, and that no *S* enantiomer was detected in (*R*)-**3**.

Application of the NMR method to (3*RS*,7*RS*)-**13** gave the interesting C_3 methyl group signals shown as Figures 2a and 2b which were obtained at 60 and 100 MHz, respectively. These complex C_3 methyl group signals arise because

Scheme I



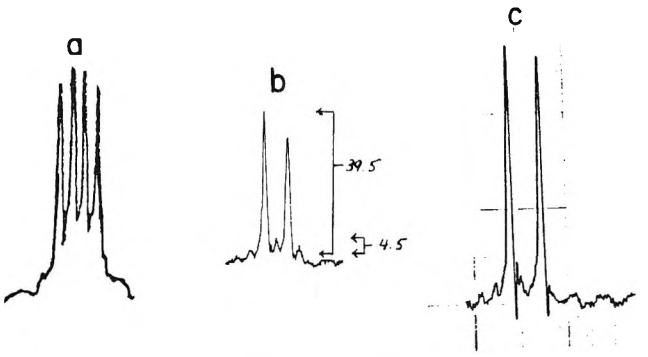


Figure 1. C_3 methyl group signals from 3 and 8 in the presence of $Eu(dcm)_3$: a, rac-8; b, nat-3; c, (*R*)-3.

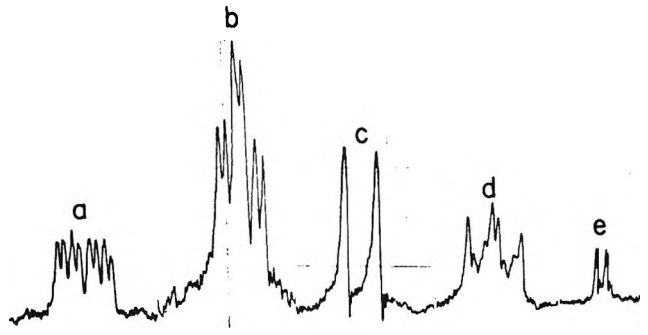
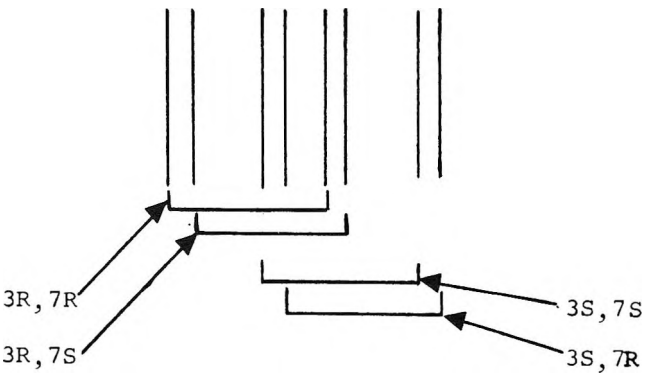


Figure 2. C_3 methyl group signals from 13 in the presence of $Eu(dcm)_3$: a, 3*RS*,7*RS* at 60 MHz; total width 11 Hz; b, same at 100 MHz; total width 15 Hz; c, 3*R*,7*R* (60 MHz); d, 3*RS*,7*R*(nat) + 3*RS*,7*RS* at 60 MHz; e, 3*R*(nat),7*RS* at 60 MHz. Sweep width is 250 Hz for a, c, d and 500 Hz for b, e.

$\Delta\Delta\delta$ is different for each of the four components of (3*RS*,7*RS*)-**13**: (3*R*,7*R*)-**13**, (3*R*,7*S*)-**13**; (3*S*,7*S*)-**13**, and (3*S*,7*R*)-**13**, listed in order of decreasing δ observed in the presence of $Eu(dmc)_3$. Full assignment of the spectrum as indicated in Figure 3 was made based on the appearance of spectra obtained for samples: (a) of (3*R*,7*R*)-**13** (Figure 2c); (b) of (3*RS*,7*R*)(nat)-**13** and (3*RS*,7*RS*)-**13** (Figure 2d); (c) of (3*R*(nat),7*RS*)-**13** (Figure 2e). These spectra can be used analytically to determine the *R*/*S* ratio at C_3 with roughly the same limits of accuracy as for C_{10} systems and to estimate the *R*/*S* ratio at C_7. The limit of detectability of a minor epimer at C_7 using 60-MHz spectra with reference compounds lies between 5 and 10%.

A somewhat more complicated but inherently more accurate and sensitive determination of *R*/*S* ratios in **2** and **7** and at C_3 (but not C_7) in **14** can be made by analytical HPLC of amides **6, 10,** and **15,** prepared by reaction of the appropriate acid chlorides with excess (*R*)-(+)-α-methyl-*p*-nitrobenzylamine.[7] The crude amide was analyzed to avoid possible epimeric fractionations. Data obtained on a variety of C_{10} and C_{15} systems are given in Table I. In the cases, e.g., of racemic **10** and of **15** which was known from its method of synthesis to be a 1:1 epimer mixture at both C_3 and C_7, repeated analyses on the same sample revealed two well-separated component peaks with areas in the ratio $3R = 50.0 \pm 0.6$ and $3S = 50.0 \pm 0.6$.

Analysis of (3*R*(nat),7*RS*)-**15** gave two peaks in about 9:1 ratio while analysis of (3*RS*,7*R*(nat))-**15** gave two peaks in ca. 1:1 ratio. Hence, one peak of **15** is due to those diastereomers containing 3*R* epimers (i.e., 3*R*,*R* and 3*R*,7*S*) and the other peak is due to those diastereomers containing 3*S* epimers (i.e., 3*S*,7*R* and 3*S*,7*S*). Analysis of (3*R*,7*R*)-**15** from natural phytol[8] revealed no 3*S* compounds. Since the limit of detectability of the HPLC method is probably below 0.5% of minor components, the last result demonstrates that the (*R*)-(+)-α-methyl-*p*-nitrobenzylamine used was essentially pure (*R*)-(+) enantiomer and that the 3*R* chiral center derived from phytol was also epimerically pure. Analogous results were obtained on the C_{10} derivatives **6** and **10.** Analyses of **6, 10,** and (3*R*,7*RS*)-**15** from natural citronellal all indicated about 90–91% of *R* and 9–10% of *S* enantiomer in the natural material. Analyses of **6** and **10** from (−)-β-pinene indicated about 92.5 parts *R* and 7.5 parts *S* enantiomer. Analyses of **6, 10,** and **15** from pulegone indicated that (3*R*)-(+)-**2** from pulegone contained 1–2% of the *S* enantiomer. Thus, samples of **2** from natural citronellal, from (−)-β-pinene, and from pulegone are respectively 80–82, 84–86, and 96–98% enantiomeric excesses of (3*R*)-(+)-**2.**



$\Delta\Delta\delta$ =		Hz
	3R,7R vs 3R,7S	1.3
	3R,7R vs 3S,7S	3.0
	3R,7R vs 3S,7R	4.5
	3R,7S vs 3S,7S	1.7
	3R,7S vs 3S,7R	3.2
	3S,7S vs 3S,7R	1.5

$J_{HC-CH_3} = 6.5$ Hz

Figure 3. Schematic representation of the C_3 methyl group signal of (3*RS*,7*RS*)-**13** at 60 MHz in the presence of $Eu(dcm)_3$.

It is unfortunate that natural citronellal and citronellol from (−)-β-pinene are not pure enantiomers because these otherwise useful chiral intermediates are not easy to transform into pure (3*R*)-(+)-**1** derivatives. The NMR and LC methods described here should be useful in connection with attempts to obtain enantiomerically pure citronellyl derivatives. For instance, the highest rotation previously reported for (+)-citronellol, **16,** is $[\alpha]_D$ +5.2° (neat) on a sample obtained by pyrolysis of *cis*-pinane.[13,14] The sample of **16** obtained in this work from pulegone had $[\alpha]_D$ +5.37° (neat) and it contains measurable amounts of (3*S*)-(−) enantiomer. Applications of NMR and HPLC methods similar to those described here are possible to determination of enantiomeric excess in a wide variety of aliphatic carboxylic acids derivable from C_5, C_{10}, and C_{15} chiral substances. A study of a number of α-methyl carboxylic acids and shift reagents recently appeared;[15] and many similar applications should be possible.

Experimental Section

Citronellal [$[\alpha]^{25}D$ +12.00° (neat)] from Java citronella oil was oxidized to citronellic acid, nat-**2,** using silver oxide. A sample of

(+)-citronellol obtained from (−)-β-pinene in a technical scale synthesis was obtained from Mr. B. J. Kane of Glidden-Durkee. A commercial sample of racemic citronellol was oxidized to racemic citronellal using CrO_3–pyridine. Conversion of **2** to **3** was accomplished with CH_2N_2 or acidic methanol.

Preparation and Analysis of (*R*)-(+)-*p*-Nitro-α-methylbenzylamides by HPLC. The acid (0.50 mmol) and oxalyl chloride (1.50 mmol) were refluxed for 30 min in 5 ml of benzene. Solvent and excess oxalyl chloride were removed at 45° and 20 mm. The crude acid chloride was dissolved in 5 ml of ether and cooled in an ice bath. A solution of (*R*)-(+)-α-methyl-*p*-nitrobenzylamine,[7] $[\alpha]^{25}D$ +17.7° (neat) (2.0 mmol), in 3 ml of ether was added in small portions. The mixture was stirred for 1 hr at 0–5° and then diluted with 100 ml of ether, washed successively with 1 *N* HCl, saturated $NaHCO_3$, and water, and dried over $MgSO_4$. Crude amide, obtained by evaporation of the ether, was analyzed by HPLC without further purification.

Six microliters of a 1% solution of the crude amide in ethyl acetate (5 mg in 0.5 ml) was injected into a 4 mm i.d. × 100 cm chromatographic column obtained by connecting, in series with minimum volume fittings, two 50-cm stainless steel columns which had been slurry packed with 10 μm silica gel (Partisil 10 from H. Reeve Angel & Co., Inc.). The mobile phase was 20% v/v tetrahydrofuran (distilled in glass from Burdick and Jackson) in spectral grade *n*-heptane pumped at a flow rate of 1.5 ml min^{-1}. The column effluent was monitored at 254 nm (Model 1222 uv monitor from Laboratory Data Control) and quantitative results were obtained from peak area measurements. The HETP values for all components ranged from 0.17 mm to 0.23 mm. Corrected elution volumes ($V_R{}^1 = \bar{V} - V_m$) and capacity ratios (k^1) for the diastereoisomers were as follows.

Compd	Confign,	$V_R{}^1$, ml	k^1	Confign,	$V_R{}^1$, ml	k^1
6	*RR*	108.5	7.2	*SR*	121.0	8.1
10	*RR*	94.0	6.3	*SR*	114.0	7.6
15	*RRR*	77.0	5.1	*RSR*	95.0	6.3
	SRR			*SSR*		

Analysis of 3, 8, or 13 for Enantiomeric Excess by NMR. In a dry tube under argon were combined 170 mg of $Eu(dcm)_3$, 0.35 ml of CS_2, and then 0.023 g of **3** or 8 or 0.028 g of **13**. The solution was filtered through a cotton plug into a Wilmad Glass Co. 507PP NMR tube and ca. 0.05 ml of Me_4Si was added. The NMR spectra of solutions prepared as above were taken within 30 min on a Varian T-60 spectrometer equipped with a T6057 lock-decoupler. It was preferred to lock the spectrometer on Me_4Si, whose signal was the strongest in the spectrum. The C_3 methyl doublets analyzed were found at ca. 4.2 ppm (for **3** and 8) and ca. 3.95 ppm (for **13**) downfield from the Me_4Si beat signal. Careful adjustment of the resolution was necessary to obtain good spectra. Aged solutions gave poor spectra.

Preparation of Methyl (3*R*)-7-Formylcitronellate [(*R*)-11]. A solution of 5.2 g of (*R*)-**3** and 6.3 g of SeO_2 in 565 ml of ethanol was refluxed for 12 hr, cooled, filtered, and concentrated under reduced pressure at 30°. The residue was dissolved in 50 ml of ether, filtered, and cautiously treated with 3 × 50 ml of saturated $NaHCO_3$ solution. The ether layer was washed with 2 × 50 ml of H_2O, dried over $MgSO_4$, and evaporated under reduced pressure to give a red oil which was quickly distilled under vacuum, then fractionated to give 3.0 g (54%) of the 7-formyl ester as a colorless oil: bp 80–84° (0.03 mm); ν_{CO} 1688, 1738 cm^{-1} ($CHCl_3$). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.46; H, 9.20. $[\alpha]^{25}D$ +10.67° (*c* 5.0, $CHCl_3$).

Treatment of nat-**3** in the same way gave nat-**11** in 58% yield, $[\alpha]^{25}D$ +8.55° (*c* 5.0, $CHCl_3$). Anal. Found: C, 66.47; H, 9.31.

Methyl (3*R*,7*RS*)-3,7,11-Trimethyldodecanoate (13). Following the general procedure of Inhoffen et al.,[16] 0.0051 mol of 3-methylbutyltriphenylphosphorane[16] was condensed with 0.0025 mol of (*R*)-**11**, giving after work-up 1.6 g of a mixture of methyl (3*R*)-3,7,11-trimethyldodeca-6*E*,8*EZ*-dienoate and triphenylphosphine oxide. This was taken up in ether cooled in dry ice–acetone, most of the phosphine oxide was removed by filtration, and the filtrate was chromatographed on 20 g of silica gel from which the ester was eluted with 3:1 benzene–hexane and vacuum distilled on the Kugelrohr, bp 107° (0.12 mm). The yield was 0.5 g (79%). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.34; H, 11.26. The (3*R*)(nat),7*RS* analogue was prepared similarly: $[\alpha]^{25}D$ +8.13° (*c* 5.0, $CHCl_3$); ν_{CO} 1730 cm^{-1} ($CHCl_3$). Anal. Found: C, 76.28; H, 11.33. Hydrogenation of the dienoate over Pd/C in methanol gave methyl (3*R*,7*RS*)-3,7,11-trimethyldodecanoate [(3*R*,7*RS*)-**13**]: $[\alpha]^{25}D$ +5.13° (*c* 5.0, $CHCl_3$); ν_{CO} 1745 cm^{-1} ($CHCl_3$). Anal. Calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 74.83; H, 12.71. Similarly, we obtained ((3*R*)(nat),7*RS*)-**13**: $[\alpha]^{25}D$ +4.25° (*c* 5.03, $CHCl_3$); ν_{CO} 1745 cm^{-1} $(CHCl)_3$. Anal. Found: C, 74.66; H, 12.77.

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Registry No.—rac-**2**, 57030-77-0; (*R*)-**2**, 18951-85-4; (*S*)-**2**, 2111-53-7; rac-**3**, 57030-78-1; (*R*)-**3**, 20425-48-3; (*S*)-**3**, 56994-89-9; (*RR*)-**6**, 56994-90-2; (*SR*)-**6**, 56994-91-3; rac-**7**, 57030-79-2; (*R*)-**7**, 32531-52-5; rac-**8**, 57030-80-5; (*RR*)-**10**, 56994-92-4; (*SR*)-**10**, 56994-93-5; (*R*)-**11**, 56994-94-6; (3*R*,7*R*)-**13**, 13955-72-1; (3*R*,7*S*)-**13**, 56994-95-7; (3*S*,7*S*)-**13**, 56994-96-8; (3*S*,7*R*)-**13**, 13852-95-4; (*RR*)-**14**, 13955-73-2; (*RS*)-**14**, 57030-81-6; (*SR*)-**14**, 13852-96-5; (*SS*)-**14**, 42763-75-7; (*RRR*)-**5**, 56994-97-9; (*SRR*)-**15**, 57030-82-7; (*RSR*)-**15**, 57030-83-8; (*SSR*)-**15**, 57030-84-9; oxalyl chloride, 79-37-8; (*R*)-(+)-α-methyl-*p*-nitrobenzylamine, 22038-87-5.

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(9) We are grateful to Mr. B. J. Kane of Glidden-Durkee for supplying us with a sample of (+)-citronellol from (−)β-pinene. This sample of citronellol was obtained from (−)-3,7-dimethyl-1,6-octadiene by reaction with diisobutylaluminum hydride, oxidation, hydrolysis and distillation. The (−)-3,7-dimethyl-1,6-octadiene had been prepared on a commercial scale from U.S. sulfate turpentine (ref 10).
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Spectral and Chemical Characterization of Fungal Metabolite LL-N313ζ

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The spectral characteristics of LL-N313ζ, including ^{13}C NMR, ^{1}H NMR, ir, uv, and CD studies, are used to elucidate the structure and stereochemistry of this metabolite as I. The behavior of I under a variety of degradative conditions is examined by subjecting the resultant derivatives to intensive spectral investigation. These studies confirm structure I. A suggestion is also made as to the polyketide origin of this the seventh crystalline metabolite obtained from *Sporormia affinis*.

The fungus *Sporormia affinis* yielded crude fermentation extracts which showed pronounced antifungal activity against *Microsporum canis* infections in animals. Isolation work revealed the presence of six crystalline metabolites, respectively named, LL-N313α, -β, -γ, -δ, -ε, and -η.[1] The major metabolite and also the one exhibiting the most potent antifungal activity was LL-N313β. The other components, with the possible exception of LL-N313α, were found in minor quantities. In later fermentations still another metabolite was detected in isolable quantities. This material, designated LL-N313ζ (I), while it is itself inactive as an antimicrobial agent, may be readily converted to products which have marked antifungal activity. The structure of I, based largely on spectral data, has been briefly reported.[2] The purpose of this paper is to elaborate on that communication and to outline some chemical studies on this metabolite.

Compound I was isolated by subjecting filtered fermentation beer of *Sporormia affinis* to batch carbon adsorption followed by acidic aqueous acetone elution of the carbon bed. The concentrated eluate was chromatographed over silica gel to obtain virtually pure I which crystallizes readily from ethyl acetate. The ir of this material shows a strong carbonyl band at 1680 cm^{-1} which shifts to 1703 cm^{-1} upon formation of a monoacetate consistent with the relationship of the hydroxyl and ketone in I. Three *C*-methyl groups are indicated by the ^{1}H NMR curve with two tertiary methyls at δ 1.08 and 1.23 and a secondary methyl at δ 1.02. A diene system is indicated by the AB pair at δ 6.20 and 5.47 (J = 9.5 Hz) and a virtual singlet at δ 5.72 in conjunction with a strong uv maximum at 242 nm (ε 19900). Borohydride reduction of I gives the dihydro II (no carbonyl in the ir) which has essentially an unchanged uv absorption from that of I. Thus the carbonyl is nonconjugated with the olefinic region of the molecule.

Spin-decoupling studies interrelated protons on carbons 1, 2, 3, 4, 6, 7, and 10. In addition the splitting constants suggested the relative stereochemistry at these centers. The appropriate chemical shifts and J values are summarized in Table I. The protons of C_{12} and C_{13} are closed off from the rest of the molecule and consist of an ABXY system with AB and XY geminal pairs. Extensive spin-decoupling experiments were necessary to resolve these relationships with the result that the two C_{12} protons can be assigned to multiplets at δ 2.86 and 2.11 and the C_{13} pair at δ 3.95 and 4.10. The J values in hertz were determined to be as follows: $J_{12\text{-gem}}$ = 14.6, $J_{13\text{-gem}}$ = 11.5, $J_{12,13}$ = 11.2, 9.0, 1.2, and 3.5.

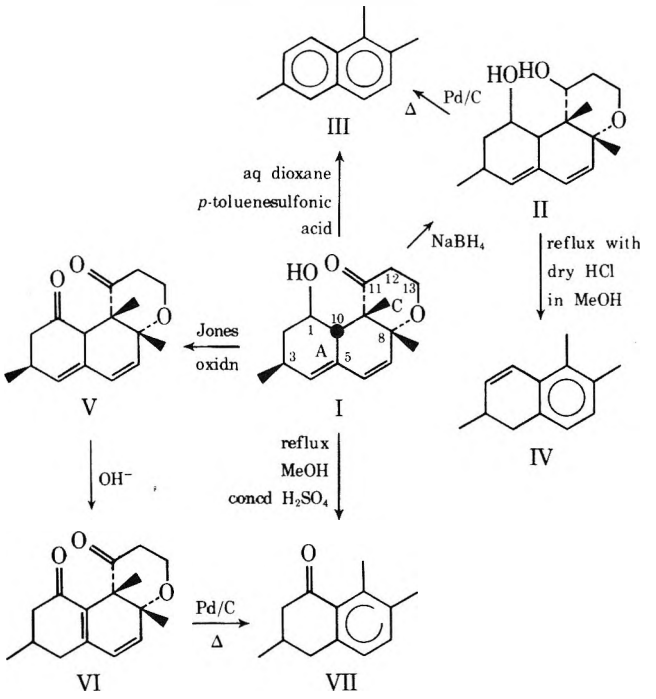
The information so far coupled with the knowledge that carbons 11–13 are removed under a variety of conditions (see below) to give the 1,2,6-trimethyldecalin system in various states of oxidation points strongly to structure I. This structure was confirmed by ^{13}C NMR. The proton noise decoupled 22.6-MHz PFT ^{13}C NMR spectrum of I shows clearly the 16 carbons of LL-N313ζ. Based on the ^{13}C shift data obtained in $CDCl_3$[3] there is only one carbonyl atom in I at 195.5 which is C_{11}. The olefinic resonances at 135.5, 132.1, 130.0, and 128.2 ppm are clearly those associated with the diene. One at least, because of its singlet nature, can be unequivocally assigned to C_5, that is, the C atom with a shift value at 130.0. The carbon with the chemical shift value similar to C_5, that at 132.1, is than logically C_6 because of its comparable situation in the diene system. Of the remaining two carbons of the diene system, C_7 can be assigned the 135.5 signal because of the adjacent alkoxyl grouping at C_8. Singlet multiplicity associated with lines at 78.7 and 57.0 ppm reveals quaternary C atoms, the first of which accounts for C_8 because of its direct link with oxygen and hence the other is due to C_9. The doublets connected with lines at 66.8, 41.7, and 25.3 ppm describe methine C atoms and may be assigned to C_1 which carries a hydroxyl group, C_{10} allylic to a double bond and adjacent to a carbon bearing an oxygen, and C_3 which is simply allylic to a double bond. The methylene carbons with triplet multiplicities at 60.0, 39.3, and 30.6 ppm describe C_{13}, C_{12}, and C_2, respectively, based on proximity to electronegative functionality. Finally the methyl carbons, quartets by off-resonance decoupling with shift values at 21.1, 20.7, and 13.0 ppm, may be tentatively assigned to the methyls at C_8, C_9, and C_3, respectively. There is little doubt that the lowest value is connected with the C_3 methyl but the other two assignments are not so certain.

Table I
^{1}H NMR Data on Protons of Carbons 1, 2, 3, 4, 6, 7, and 10 in I

Proton	Chemical shift	Coupling constants, Hz
H_1	3.95 bm	$J_{1,2e}$ = 2.0, $J_{1,2a}$ = 4.5
H_{2e}	2.0 m	J_{gem} = 13.0, $J_{2e,4}$ = 1.5
H_{2a}	1.23 m	$J_{2a,3}$ = 11.5
H_3	2.5 bm	J_{3,CH_3} = 7.0, $J_{3,2e}$ = 5.0
H_4	5.72 bs	$J_{10,4}$ = 3.0
H_6	6.20 d	$J_{6,7}$ = 9.5
H_7	5.47 d	
H_{10}	3.42 q	$J_{1,10}$ = 4

Compound I contains a transoid heteroannular diene system with an allylic oxygen function. According to Beecham[4,5] the chirality of the C=C–C–O determines the sign of the Cotton effect observed with such a system. This is particularly so if the diene system is almost flat, as Dreiding models of I reveal it to be. Burgstahler and Barkhurst, on the other hand, have correlated the chirality of this kind of system with asymmetric perturbation of the double-bond components by allylic axial bonds.[6] Both approaches are attributing the activity primarily to the influence of allylic chirality rather than to the inherent dissymmetry of the chromophore itself. As Beecham points out, it is difficult to see why allylic hydrogens or methyls should outweigh allylic oxygen. Hence, in our communication we

Scheme I
Reactions Resulting in Excision of C Ring from 1 or Related Compounds



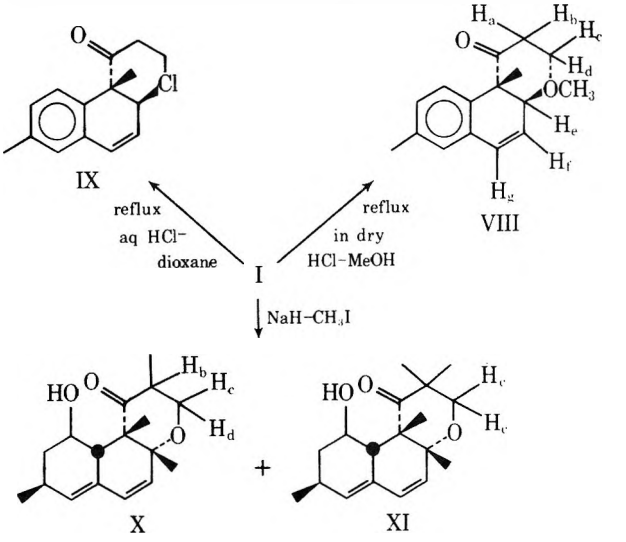
followed Beecham's ideas and since the CD curve of I is a double-humped curve with $\Delta\epsilon_{242.5}$ −21.9 and $\Delta\epsilon_{212.5}$ +21.9, we assigned left-handed chirality to the oxygen-forming helix. An ORD curve on this material shows the following values: ϕ_{267} 0, ϕ_{258} -6.82×10^3, ϕ_{254} 0, ϕ_{229} $+8.29 \times 10^4$, ϕ_{207} 0, ϕ_{203} $+6.82 \times 10^3$, and ϕ_{198} 0.

Examination of the CD and ORD curves shows that they exhibit the symmetry, location, and magnitude of a rotatory couplet, a characteristic form of dispersion which arises when two Cotton effects of equal but opposite strength lie less than a bandwidth apart.[7] While Beecham's ideas concerning allylic oxygen allow us to assign chirality on the basis of CD data, they do not explain the rotatory couplet. Burgstahler's notion of the influence of axial hydrogen or methyl would provide the requisite two chromophores for the couplet. However, both of them in I are skewed in the same direction and hence they would not meet the criterion of oppositeness.

When the Horeau procedure[8] was carried out on I, the recovery of (−)-α-phenylbutyric acid indicated that the configuration of C_1 is *S*. It is also known that the C_1 proton and the C_{10} proton are both cis (J = 4 Hz). The net effect of these facts is strong support for the Beecham interpretation of the CD results. By observing the deshielding shift of δ 0.15 of the C_3 proton in pyridine as opposed to chloroform, we conclude that this proton is 1,3-diaxial relative to the hydroxy group[9] and the secondary methyl is equatorial and hence the complete stereochemistry of I is defined.

As illustrated in Scheme I, when the dihydro derivative II is heated in the presence of palladium on charcoal, the known 1,2,6-trimethylnaphthalene (III) is obtained. The relatively mild procedure of refluxing I in aqueous dioxane in the presence of *p*-toluenesulfonic acid also yields III. When II is refluxed with dry HCl in methanol, IV is obtained. This oil is identified by its spectral data with uv maxima at 223 nm (ε 33500) and 267 (12000). The mass spectrum has a molecular ion peak at *m/e* 172 and metastables at *m/e* 143.3* and 128.4* indicating methyl fragmentations from ions *m/e* 172 and 157, respectively. The ^{1}H NMR spectrum shows a split methyl signal at δ 1.07 and three-proton singlets at δ 2.20 and 2.22 for the virtually

Scheme II
Reactions of I Involving C-Ring Opening or Substitution



equivalent aromatic methyls. The methine proton and benzylic pair are represented by a multiplet centered at δ 2.58. The vinyl protons are an AB pair at δ 5.88 and 6.70 (J = 10 Hz). The signals at δ 5.88 are further split by the methine proton ($J \sim 2$ Hz). The nearly equivalent aromatic protons are given by sharp lines at δ 6.78 and 6.80.

Scheme I illustrates another series of reactions which result in the elimination of the C ring from I. Careful Jones oxidation of I yields V which in the presence of hydroxide ion rearranges to the dienone VI. Despite the fact that VI was obtained chromatographically pure and could be recrystallized to a sharp-melting material, the ^{1}H NMR curves of several preparations always showed minor impurities which hindered interpretation of decoupling studies. Nevertheless we had good evidence for the proposed structure. The uv curve is typical for a conjugated dienone with maximum adsorption at 300 nm (ε 7150); the ir has bands at 1665 cm^{-1} for the conjugated carbonyl and at 1718 cm^{-1} for the pyranone carbonyl. In the ^{1}H NMR curve the tertiary methyls are observed at δ 1.0 and 1.26 while the secondary methyl is a poorly defined doublet at δ 1.10. A multiplet at δ 2.40 integrates for seven protons and the ether methylene pair appears as another multiplet at δ 3.88. The olefinic protons are observed as doublets at δ 5.92 and 6.22 (J = 9.5 Hz).

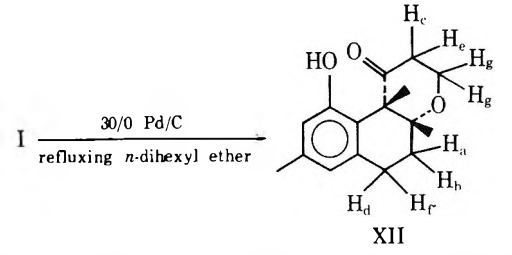
When VI is heated with palladium on charcoal, the tetralone VII is obtained. This oil was also isolated when I was refluxed in dry methanol containing concentrated sulfuric acid. It shows uv maxima at 247 nm (ε 8200) and 298 (2050) and a carbonyl band in the ir at 1675 cm^{-1}. The ^{1}H NMR shows a split methyl at δ 1.08 and an aromatic methyl at δ 2.22 which is where the corresponding methyl signals of IV are located. The other aromatic methyl of VII is shifted to δ 2.40 by virtue of its situation relative to the deshielding cone of the carbonyl. The five protons of the saturated ring are clustered as a broad multiplet around δ 2.40. The two aromatic protons are represented by a narrow AB pair at δ 6.82 and 7.40 (J = 7 Hz).

In Scheme II are illustrated some reactions of I where the C ring is opened or alkylated. In refluxing dry methanolic HCl I yields the oil VIII. The uv of VIII is styrenelike with maxima at 224 nm (ε 25000) and 264 (7000). The ir curve lacks absorption above 3000 cm^{-1} and has a strong carbonyl band at 1712 cm^{-1}. The ^{1}H NMR spectrum shows a split methyl at δ 0.86 (J_{b,CH_3} = 7.5 Hz), a tertiary methyl at δ 1.30, an aromatic methyl at δ 2.32, and a methoxyl singlet at δ 3.25. The H_a and H_b pair are multiplets at δ 2.16

and 2.55 while the ether methylene pair is a multiplet at δ 3.40. Decoupling experiments revealed the coupling constants in hertz for this system: J_{ab} = 17.4, J_{ac} = 5.9, J_{ad} = 6.7, J_{bd} = 7.0, and J_{cd} = 10.0. Proton H_e is a multiplet at δ 2.85 (J_{e,CH_3} = 7.5, J_{ef} = 4.8, and J_{eg} = 1.3 Hz). Vinyl proton H_g appears as four lines at δ 5.90. Upon irradiation of H_e, these four lines coalesce to two lines and the split methyl signal collapses to a singlet. The other vinyl proton is a doublet of doublets at δ 6.28 (J_{gf} = 9.5 and J_{ge} = 1.3 Hz). The aromatic protons are given by one-proton singlets at δ 6.88, 7.02, and 7.04. When I is refluxed in dioxane with aqueous hydrochloric acid, the oil IX is obtained. This relatively unstable β-halo ketone analyzes for $C_{16}H_{19}OCl$ and its uv and ^1H NMR spectra are very similar to those of VIII except of course that the methoxy signal at δ 3.25 in the ^1H NMR spectrum is missing. Compounds VII and IX exhibit good in vitro antimicrobial activity.[11]

We wished to observe the behavior of I under acidic conditions with the hydroxyl group protected as the methyl ether. Treatment of I with sodium hydride and methyl iodide in DMF yields instead of the expected ether the crystalline products X and XI. Mass spectral molecular ions are observed at *m/e* 276 and 290, respectively, and each spectrum exhibits a large metastable peak at *m/e* 143.3* (also observed in spectrum of IV) relating mother and daughter peaks at *m/e* 172 and 157. Both compounds retain the uv chromophore of I and their ^1H NMR spectra have much in common with that of I with diagnostic differences. The spectrum of X has an extra split methyl signal at δ 1.04. H_a is part of a complex signal at δ 2.8 integrating for two protons while H_b and H_c are represented by three lines at δ 3.46 (J = 12 Hz) and four lines at δ 3.96 (J = 8 Hz). Compound XI has two extra methyl signals at δ 0.99 and 1.01. The multiplet at δ 2.8 now integrates for one proton since H_b is missing and the ether methylene pair is represented by two doublets at δ 3.56 and 3.78 (J = 12 Hz).

Under the relatively drastic conditions of Scheme I, the B ring of I or both A and B rings are aromatized along with excision of the C ring. By the milder treatment of Scheme II the A ring is aromatized with loss of oxygen function accompanied by opening of the C ring. In one reaction[12] shown below, the A ring is aromatized without loss of the

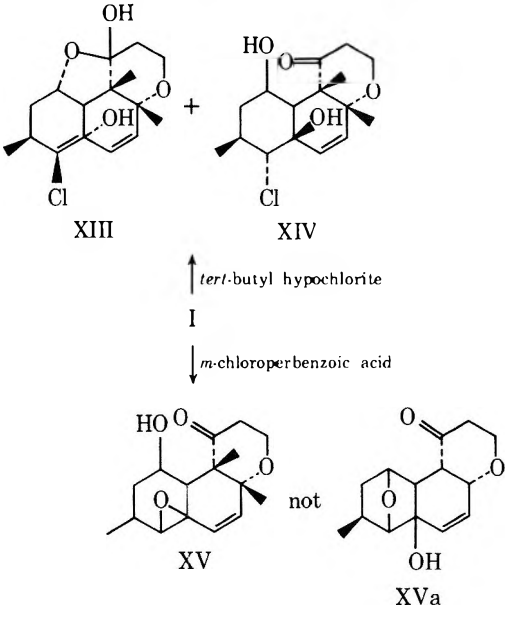


XII

oxygen by removal of hydrogen followed by prototropic shift transfer of the B ring double bond. The mass spectrum of XII shows a molecular ion at *m/e* 260 with peaks of great abundance at *m/e* 188 and 173 and a metastable at *m/e* 159.2*. The ir spectrum shows the carbonyl band at 1695 cm^{-1} while the uv is typical for a phenolic compound with maxima at 215 nm (ε 5400), 278 (1700), and 284 (1800) with a characteristic shift to 293 nm (ε 3000) in alkaline solution. The ^1H NMR spectrum of XII has six readily identifiable signals including the tertiary methyls at δ 1.19 and 1.22, the aromatic methyl at δ 2.21, the exchangeable phenolic proton at δ 5.69, and the two uncoupled aromatic proton singlets at δ 6.43 and 6.56. The remaining signals are complex multiplets, the interpretation of which requires extensive decoupling studies. They account for eight protons consisting of two independent systems H_a, H_b, H_d, and H_f on the B ring and H_c, H_e, and two H_g on the C ring. H_a and H_b are given by two multiplets at δ 1.85 and 1.95, H_d is a doublet multiplet at δ 2.72 and 2.85, while H_f is centered at about δ 3.20. The following coupling constants in hertz for this system were determined: J_{af} = 8.4, J_{ad} = 2.2, J_{bd} = 5.0, J_{bf} = 10.9, and J_{df} = 16.9. The C-ring system is relatively simpler since the ether methylene protons are magnetically equivalent and since there is no coupling between H_c and H_g. The chemical shifts and coupling constants are as follows: H_c at δ 2.15, H_e at δ 3.05, and H_g at δ 3.90 with J_{ce} = 11.2 and J_{ge} = 10 Hz.

As Scheme III illustrates, I gives two products when treated with *tert*-butyl hypochloride as described by Ke-

Scheme III
Chlorohydrin and Epoxide Derivatives of I

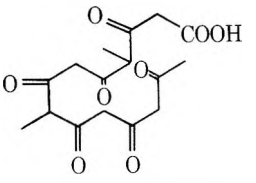


berle and Karrer.[13] The two crystalline products XII and XIII are chlorohydrins with the same molecular formula $C_{16}H_{23}O_4Cl$. The chloronium ion attacks the most electrophilic double bond and the resultant intermediate may be approached from above or below by the hydroxyl group. Since the partial positive charge of the transition state is most likely to be stabilized at the allylic position, the point of OH attachment is almost certainly the C_5 position. Compound XIII, mp 134°, has no carbonyl absorption in the ir spectrum, which indicates that one of the hydroxyl groups is in good field for hemiketal formation. Dreiding models show that the chlorhydrin which results from OH attack from below has two hydroxyl groups in good position for possible hemiketal formation. Compound XIII was isolated unchanged from refluxing acetic anhydride–pyridine solvent, conditions which normally acetylate a free secondary hydroxyl group. On this basis we conclude that the C_1 alcohol is involved in the hemiketal formation. Compound XIV, mp 172–174°, shows strong carbonyl absorption in the ir at 1695 cm^{-1}. The ^1H NMR spectra of both compounds show a split methyl signal at about δ 1.0 and a tertiary methyl signal at δ 1.32. The signal for the other tertiary methyl is at δ 1.2 in XIV but at δ 1.04 in XIII because here carbonyl deshielding is no longer operative. The spectrum of XIII has an exchangeable signal at δ 3.2 for the hemiketal OH and a very sharp exchangeable singlet at δ 5.42 for the proton of the tertiary OH at C_5. In the spectrum of XIV there are analogous exchangeable signals at δ 3.17 and 5.10. The signals between δ 1.5 and 4.2 are complex but similar in both compounds. It is in the olefinic area that the sharp diagnostic differences are observed. Both olefinic protons

of XIII are represented as a sharp singlet at δ 5.64 so they must be virtually magnetically equivalent, a circumstance which can only occur with an α hydroxyl group at C_5 as shown. In XIV these protons are shown as an AB pair as in I at δ 5.23 and 6.12 (J = 10 Hz).

Treatment of I with *m*-chloroperbenzoic acid yields a crystalline epoxide XV. The CO group in this compound is no longer chelated to the C_1 hydroxyl group since it is observed at 1708 cm^{-1} in the ir as opposed to 1680 cm^{-1} in the ir of I. Instead of the epoxide one might visualize the alternate structure XVa. This can be ruled out on the basis of mass spectral data because of the absence of a peak at *m/e* 84. The expected excision of a 3-methyl tetrahydrofuranyl fragment from XVa would give rise to *m/e* 84. In addition the proton of the tertiary OH at C_5 in both chlorohydrins is observed as a sharp singlet between δ 5.0 and 5.5 where there is every reason to expect it would also appear in the spectrum of XVa. The curve of XV shows the vinyl AB pair at δ 5.45 and 6.23 and is lacking any other signal in that area.

The biosynthetic polyketide sequence leading to the first six metabolites of *Sporormia affinis* has been mentioned briefly.[2] The structure I may be formally accommodated to the polyketide shown, which consists of five acetate and



two propionate units. Tertiary methyls such as those at C_8 and C_9 are rare in polyketide-derived material. The plant product portentol contains a tertiary methyl and is said to be formally derived from a polypropionate.[14] Although the authors do not mention it, diplodiatoxin would appear to be of polyketide origin even though it contains a tertiary methyl group.[15] Diplodiatoxin and LL-N313ζ are both fungal metabolites and Turner[16] has pointed out that no fungal product incorporates propionate within the chain but rather tertiary and secondary methyls are introduced directly from the one-carbon pool.

Experimental Section

TLC was carried out on Brinkmann plates. ^1H NMR spectra were run on Varian A-60 or A-100 instruments. Mass spectra were made on an AEI MS9 high-resolution, direct-inlet mass spectrometer. Ir and uv spectra were run on Infracord and Cary 11 spectrophotometers, respectively. A Cary 60 spectropolarimeter was used for CD (2.1 mg/ml of I in MeOH, cell width 0.1 mm) and ORD (1.27 mg/ml of I in MeOH, cell width 0.2 mm) work. Solvents and solutions were dried over anhydrous $MgSO_4$. Melting points were taken by a capillary tube method and are uncorrected.

Isolation of I. Sporormia affinis Sacc., Bomm and Rouss (Lederle culture N313) was incubated for 5 days as previously described.[1] The metabolites were recovered from the filtered beer by batch adsorption on carbon. The carbon was eluted with acidic aqueous acetone and the eluate concentrated to the aqueous phase and extracted with $CHCl_3$. The dried, concentrated $CHCl_3$ extract was chromatographed over silica gel using 1:1 $CHCl_3$–hexane to obtain crude I which could be recrystallized from EtOAc–hexane to get pure I, mp 173–173.5°. Yields varied from 1 to 3 g per 300-l. fermentation: $[\alpha]^{25}D$ −113 ± 2° (*c* 1.05, MeOH); uv max (MeOH) λ 242 nm (ε 19900); ir (KBr) 3440, 1680 cm^{-1}; ^1H NMR (see text); mass spectrum *m/e* 262 (M^+), 245, 244, 201, 172, 157, 146.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.26; H, 8.19.

The acetate of I was prepared by refluxing in acetic anhydride–pyridine solution for 1 hr. The product was recrystallized from ether–hexane: mp 114.5–115°; $[\alpha]^{25}D$ −49.8 ± 2° (*c* 1.02, MeOH); uv max (MeOH) λ 241 nm (ε 17940); ir (KBr) 1735, 1703, 1385, 1245, 1180, 1095, 945, 880cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3 H, s, 8 CH_3), 1.03 (3 H, d, J = 7 Hz, 3 CH_3), 1.25 (3 H, s, 9 CH_3), 5.03 (1 H, m, 1 CHOAc), 5.47 (1 H, d, J = 10.0 Hz, 6 CH), 5.72 (1 H, br s, 4 CH), 6.22 (1 H, d, 6 CH).

Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.70; H, 7.84.

Preparation of II. About 900 mg of I was reduced with 1.35 g of $NaBH_4$ in 20 ml of EtOH. The product was purified by silica gel chromatography and recrystallized from EtOAc to get II: mp 130–131°; $[\alpha]^{25}D$ +79 ± 2 ° (*c* 1.02, MeOH); uv max (MeOH) λ 239 nm ε 20570), sl sh 232 (17900), 247 (14700); ir (KBr) 3450, 3330, no CO peak, weak peaks 1645, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (3 H, d, J = 7.0 Hz, 3 CH_3), 1.1 (3 H, s, 9 CH_3), 1.25 (3 H, s, 8 CH_3), 5.20 (1 H, d, J = 9 Hz, 7 CH), 5.62 (1 H, s, 4 CH), 6.03 (1 H, d, J = 9.0 Hz, 6 CH).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.63; H, 9.15. Found;: C, 72.23; H, 9.11.

1,2,6-Trimethylnaphthalene (III). About 400 mg of I was mixed with 1.0 g of 5% Pd/C and heated for 2 hr to a temperature of 280°. Purification of the resultant oil over alumina yielded 80 mg of III: mp of picrate 121–122° (lit.[17] 121–122°), styphnate 148° (lit.[17] 148°); uv max (hexane) λ 327 nm (ε 1870), 320 (1090), 313 (1530), 290 sh (4670), 282 (5610), 278 (5610), curve matches that of 1,2,6-trimethylnaphthalene;[18] ^1H NMR ($CDCl_3$) δ 2.37 (3 H, aromatic CH_3), 242 (6 H, s, 2 aromatic CH_3), 7.24 (4 H, m, aromatic H), 7.5 (1 H, d, aromatic H).

Approximately 37 mg of Ill was obtained by chromatographic purification over alumina of the product from overnight refluxing of 500 mg of I in 15 ml of 2:1 dioxane–H_2O solution with 600 mg of *p*-toluenesulfonic acid added: mp of styphnate 148°, picrate 121°; uv curve identical with that mentioned above.

Conversion of II to IV. Approximately 250 mg of II was dissolved in 20 ml of dry MeOH and dry HCl gas passed into the solution until saturated. The solvent was then evaporated and the resultant oil was purified over alumina using hexane solvent to get 120 mg of pure IV: $[\alpha]^{25}D$ +183 ± 1.0° (*c* 0.82, MeOH); uv max (MeOH) λ 267 nm (ε 12000), 223 (33500); ir (KBr) 3000, 1460, 1260, 820, 785 cm^{-1}; ^1H NMR discussed in text; mass spectrum *m/e* 172 (M^+).

Anal. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.23; H, 9.40.

Oxidation of I to V. About 500 mg of I in 50 ml of ether was stirred overnight with 1.5 g of $K_2Cr_2O_7$ in 0.3 ml of concentrated H_2SO_4 and 7 ml of H_2O. The product was purified by silica gel chromatography using hexane–EtOAc. Recrystallization of V from EtOAc–hexane yielded 180 mg: mp 159–160°; $[\alpha]^{25}D$ −63.3 ± 3° (*c* 1.03, MeOH); uv max (MeOH) λ 238 nm (ε 36000); ir (KBr) 3000, 1710 (very intense), 1430, 1410, 1360, 1225, 1180, 1090, 1075, 865 (very intense), 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (3 H, s, CH_3), 1.12 (3 H, d, J = 7.0 Hz, 3 CH_3), 1.22 (3 H, s, CH_3), 5.52 (1 H, d, J = 10.0 Hz, 7 CH), 5.94 (1 H, m, 4 CH), 6.24 (1 H, d, 6 CH).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.67; H, 7.82.

Conversion of V to VI. A 200-mg sample of V was dissolved in 1.5 ml of acetone and 1 ml of 4 *N* NaOH was added. The suspension darkened rapidly and after 5 min the reaction mixture was diluted with 10 ml of H_2O and extracted with EtOAc. The solvent extract was dried and evaporated to a gum which was passed over silica gel using 20% EtOAc in hexane solvent. The major component was recrystallized from ether–hexane to yield 110 mg of VI: mp 136–137°; $[\alpha]^{25}D$ +114 ± 1° (*c* 0.85, MeOH); uv max (MeOH) λ 300 nm (ε 7100), (MeOH and NaOH) 305 (9600); ir (KBr) 3000, 2865, 1718, 1665, 1570, 1300, 1080, 830, 795 cm^{-1}; ^1H NMR discussed in text; mass spectrum *m/e* 260 (M^+), 245, 217, 204, 190, 189, 188, 173, 172, metastables 187.7*, 159,3*.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.26; H, 8.19.

Preparation of VII. About 100 mg of VI were intimately mixed with 200 mg of 10% Pd/C and placed in a sublimator equipped with a cold finger and a collector vial attachment. The apparatus was evacuated to 55 μ and then heated to 250° for 5 min using a Wood's metal bath. After cooling, the vial contained 70 mg of faintly yellow oil which was purified by passage over 7 g of Woelm alumina using 5% EtOAc in hexane solvent to obtain 31 mg of pure VII: uv max (MeOH) λ 247 nm (ε 8200), 298 (2050); ir (KBr) 3000, 1690, 1600, 1565, 1255, 1015, 810 cm^{-1}; ^1H NMR discussed in text; mass spectrum *m/e* 188 (M^+).

Upon refluxing 150 mg of V in 5 ml of MeOH with 0.2 ml of concentrated H_2SO_4 for 1 hr followed by purification of the product by alumina chromatography, a yield of 66 mg of pure VII was obtained.

Conversion of I to VIII. About 25 ml of dry MeOH was satu-

rated with dry HCl gas and then 500 mg of I was added and the resultant solution refluxed for 4 hr. During reflux the condenser was protected from moisture. The solvent was evaporated and the resultant oil taken up in $CHCl_3$ and extracted with bicarbonate solution. The extracted $CHCl_3$ solution was dried and concentrated to 480 mg of an oil which was purified by partition chromatography over diatomaceous earth using a heptane saturated with CH_3CN system. The main product consisted of 250 mg of a colorless oil labeled VIII: $[\alpha]^{25}D$ −83.5 ± 3.0° (c 1.10, MeOH); ir (KBr) 3000, 2920, 1705, 1485, 1445, 1375, 1112, 812 cm^{-1}; ^1H NMR discussed in text.

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.07; H, 8.52. Found: C, 79.22; H, 8.08.

Conversion of I to IX. A sample consisting of 500 mg of I was refluxed for 4 hr in 20 ml of dioxane with 7 ml of 4 *N* HCl added. Recovery of 180 mg of product IX was handled as described under preparation of VIII: $[\alpha]^{25}D$ −78.5 ± 2.0° (c 0.43, MeOH); uv max (MeOH) λ 264 nm (ε 6600), 222 (23000); ir (KBr) 3000, 2930, 1705, 1605, 1485, 1445, 1380, 1290, 1075, 1050, 990, 890, 815, 780, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (3 H, d, *J* = 7.5 Hz, 8 CH_3), 1.33 (3 H, s, 9 CH_3), 2.34 (3 H, s, 3 CH_3), 3.6 (2 H, m, 13 CH_2), 5.90 (1 H, dd, *J* = 9.5 and 5.5 Hz, 7 CH), 6.33 (1 H, d, *J* = 9.5 Hz, 6 CH), 6.90 (1 H, s, aromatic H), 7.06 (1 H, s, aromatic H), 7.10 (1 H, s, aromatic H).

Anal. Calcd for $C_{16}H_{19}OCl$: C, 73.16; H, 7.23; Cl, 13.14. Found: C, 73.24; H, 7.51; Cl, 12.94.

Conversion of I to X and XI. An oil suspension of NaH was washed with hexane and resuspended in dry THF to provide an approximately 1 M suspension. About 400 mg of I in 5 ml of dry THF was treated with 1.5 ml of the NaH suspension in THF and 1.5 ml of CH_3I and the reaction mixture was stirred for 2 hr at dry ice–MeOH temperature. The reaction was run under positive N_2 pressure and protected from moisture. The reaction mixture was then partitioned between EtOAc and H_2O. The EtOAc solution was dried and evaporated to a solid which was resolved by silica gel chromatography using a gradient of 5–10% EtOAc in hexane. Two products were recovered. The first product to come off the column consisted of 180 mg of material which was recrystallized from EtOAc–hexane to yield XI: mp 117–119°; $[\alpha]^{25}D$ −18.9 ± 2° (c 0.50, MeOH); uv max (MeOH) λ 240 nm (ε 26100); ir (KBr) 3650, sh at 3500, 3000, 1680, 1465, 1390, 1300, 1225, 1175, 1110, 1080, 1045, 990, 980, 885, 863, 812, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (3 H, s, 12 CH_3), 1.00 (3 H, d, *J* = 7 Hz, 3 CH_3), 1.01 (3 H, s, 12 CH_3), 1.28 (3 H, s, CH_3), 1.36 (3 H, s, CH_3), 3.56 (1 H, d, *J* = 12 Hz, 13 CH), 3.78 (1 H, d, *J* = 12 Hz, 13 CH), 3.80 (1 H, br s, 1 CH), 5.27 (1 H, d, *J* = 10 Hz, 7 CH), 5.64 (1 H, s, 4 CH), 6.05 (1 H, d, *J* = 10 Hz, 6 CH); mass spectrum *m/e* 290 (M^+), 272, 257, 243, 229, 199, 188, 173, 172, 171.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.31; H, 8.61.

The second material off the column amounted to 60 mg which upon recrystallization from EtOAc–Hexane yielded 47 mg of X: mp 144–145°; $[\alpha]^{25}D$ −111.8 ± 2.0° (c 0.50, MeOH); uv max (MeOH) λ 242 nm (ε 22100); ir (KBr) 3650, 3500, 3000, 2900, 1700, 1460, 1375, 1315, 1240, 1180, 1115, 1075, 1045, 990, 980, 875, 868, 840, 805, 790, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3 H, d, *J* = 7 Hz, 3 CH_3), 1.01 (3 H, s, CH_3), 1.04 (3 H, d, *J* = 7 Hz, 3 CH_3), 1.19 (3 H, s, CH_3), 3.46 (1 H, t, *J* = 11.5 Hz, 13 CH), 3.80 (1 H, br s, 1 CH), 3.95 (1 H, m, *J* = 10 Hz, 6 CH); mass spectrum *m/e* 276 (M^+), 258, 243, 215, 188, 173, 172, 171.

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.64; H, 8.82.

Conversion of I to XII. Approximately 400 mg of I together with 500 mg of 30% Pd/C were refluxed for 2 hr in 10 ml of *n*-dihexyl ether.[13] The product was purified by silica gel chromatography using a gradient of 0–5% EtOAc in hexane. About 120 mg of a white solid was recovered which when recrystallized from EtOAc–hexane yielded XII: mp 227–228°; $[\alpha]^{25}D$ −34.5 ± 0.3° (c 0.66, MeOH); uv max (MeOH) λ 284 nm (ε 1800), 278 (1700), 215 (5400); (MeOH + NaOH) 293 (3000); ir (KBr) 3360, 2940, 1700, 1628, 1595, 1435, 1390, 1380, 1335, 1255, 1112, 1068, 1028, 845 cm^{-1}; ^1H NMR discussed in text.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.68; H, 7.62.

Formation of Chlorohydrins XIII and XIV. A sample of 500 mg of I was dissolved in 0.5 ml of acetone and 0.5 ml of H_2O was added followed by 0.15 ml of *t*-BuOCl. The mixture was stirred at room temperature for 1 hr. The products were purified by silica gel column chromatography using a gradient of 5–10% EtOAc in hexane. The first product off the column upon recrystallization from EtOAc–hexane yielded 80 mg of XIII: mp 134°; $1\alpha]^{25}D$ +65.0 ± 0.4° (c 0.57, MeOH); ir (KBr) 3400, 2930, 1455, 1430, 1382, 1367, 1345, 1275, 1255, 1200, 843, 823, 706 cm^{-1}; ^1H NMR ($CDCl_3$) 1.01 (3 H, d, *J* = 7.5 Hz, 3 CH_3), 1.04 (3 H, s, 9 CH_3), 1.32 (3 H, s, 8 CH_3), 5.22 (1 H, d, *J* = 10 Hz, 7 CH), 5.42 (1 H, s, (exchangeable, 5 COH), 6.12 (1 H, d, *J* = 10 Hz, 6 CH); mass spectrum *m/e* 314 (M^+), 281, 263, 245, 227, 189, 171.

Anal. Calcd for $C_{16}H_{23}O_4Cl$: C, 61.04; H, 7.31; Cl, 11.28. Found: C, 61.40; H, 7.35; Cl, 11.11

The second product consisted of 70 mg of XIV: mp 172–174°; $[\alpha]^{25}D$ −110 ± 0.4° (c 0.53, MeOH); ir (KBr) 3430, 2930, 2980, 2935, 1695, 1420, 1390, 1380, 1310, 870, 843, 795, 785, 750 cm^{-1}; ^1H NMR ($CDCl_3$) 1.03 (3 H, d, *J* = 7.5 Hz, 3 CH_3), 1.20 (3 H, s, 9 CH_3), 1.32 (3 H, s, 8 CH_3), 5.10 (1 H, s, exchangeable, 5 COH), 5.64 (2 H, s, 6 CH and 7 CH).

Anal. Calcd for $C_{16}H_{23}O_4Cl$: C, 61.04; H, 7.31. Found: C, 60.84; H, 7.33.

Formation of Epoxide XV. A solution of 140 mg of I in 10 ml of CH_2Cl_2 with 100 mg of *m*-chloroperbenzoic acid was refluxed overnight. The reaction solution was then washed with dilute $NaHCO_3$ solution, dried, and evaporated to dryness to yield a white solid which was recrystallized from ether–hexane to yield a first crop of 50 mg of XV: mp 121–122°; $[\alpha]^{25}D$ −45.7 ± 2.0° (c 1.03, MeOH); ir (KBr) 3500, 3000, 1708, 1460, 1420, 1375, 1110, 925, 870, 795 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3 H, d, *J* = 7.5 Hz, 3 CH_3), 1.29 (3 H, s, CH_3), 1.31 (3 H, s, CH_3), 8.45 (1 H, d, *J* = 10 Hz, 7 CH), 6.23 (1 H, d, *J* = 10 Hz, 6 CH); mass spectrum *m/e* 278 (M^+), 263, 260, 250, 245, 236, 231.

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.80; H, 8.10.

Configuration of C_1 in I by Horeau Method. A sample of 70 mg of I was dissolved in 3 ml of pyridine, 0.3 ml of DL-α-phenylbutyric anhydride was added, and the reaction was allowed to proceed overnight. Work-up of the reaction in the standard manner yielded 200 mg of crystalline α-phenylbutyric acid (TLC, ir, and C, H analysis matched data of authentic material) which had $[\alpha]^{25}D$ −1.85 ± 0.22° (c 4.45, benzene). The excess of (−) or *R* acid indicates that C_1 is *S*.

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Registry No.—I, 53342-17-9; I acetate, 57016-66-7; II, 57016-67-8; III picrate, 57016-68-9; III styphnate, 57016-69-0; IV, 57016-70-3; V, 57016-71-4; VI, 57016-72-5; VII, 57016-73-6; VIII, 57016-74-7; IX, 57016-75-8; X, 57016-76-9; XI, 57016-77-0; XII, 57016-78-1; XII, 57016-78-1; XII, 57016-79-2; XIV, 57049-20-4; XV, 57016-80-5.

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Carbon-13 Nuclear Magnetic Resonance Spectra of Hydroxy Steroids

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^{13}C NMR spectra have been obtained and the individual resonances assigned for 31 monohydroxylated androstanes and cholestanes as well as a number of acetoxy derivatives. The chemical shifts are rationalized in terms of α, β, γ, and δ substituent effects. The variation of these effects is discussed in terms of steric interactions of the hydroxyl group. Quantitative correlations are presented relating the α and β substituent effects to the type and number of specific steric interactions of the hydroxyl group. These correlations allow the estimation of substituent shifts of α- and β-carbon atom resonances within 2.0 and 1.0 ppm, respectively. The magnitude of the γ-gauche shift is correlated with 1,3-syn-diaxial OH–CH_3 interactions; furthermore, the possible dependence of the γ-gauche shift upon the presence of a proximate hydrogen atom at the γ carbon is discussed. The downfield δ substituent effect found with OH–C(δ) skew pentane configurations is rationalized in terms of steric deformations to relieve the interaction.

Until very recently the literature data regarding ^{13}C nuclear magnetic resonance spectra of steroids have been of a somewhat fragmentary nature. Therefore we have undertaken a systematic investigation of these compounds by ^{13}C NMR in order to determine (and develop a predictive rationale to describe) the influence of substituents, position, and stereochemistry on their spectra. In the present study we describe the ^{13}C NMR spectra of a series of hydroxy steroids. A previous paper has dealt with the spectra of keto steroids[2] and a study of monounsaturated steroids will be presented in a forthcoming paper.[3] Complete assignments in these series of monofunctional steroids is an absolute prerequisite before attempting the interpretation and eventual prediction of the ^{13}C NMR spectra of polyfunctional steroids, which are frequently of great biological interest. Furthermore, because of the skeletal rigidity which precludes the possible complication of conformational interconversions, hydroxy substituted steroids (such as androstanols and cholestanols) provide an ideal material in which to study the influence of geometrical and stereochemical features upon the substituent effects of the hydroxyl group in cyclic systems. Nearly all possible geometrical environments of the hydroxyl group are represented by the 31 examples in this series, which includes 11 different epimeric pairs.

Experimental Section

The hydroxy steroids (see Table I) included in this study are all known compounds and have been prepared by the following methods: **2** by lithium aluminum hydride reduction,[4] and **4** by reduction with sodium in ethanol[5,6] of cholestan-1-one;[7] **7** by lithium aluminum hydride reduction[8] of cholestan-2-one;[7] **13** by hydroboration–oxidation[9] of Δ^4-cholestene; **15** by Jones oxidation of **13** followed by lithium aluminum hydride reduction;[10] **16** by epoxidation of Δ^4-cholestene[11] followed by lithium aluminum hydride reduction;[12] **17** by reduction with sodium in ethanol[4] of cholestan-6-one[4] and **18** by lithium aluminum hydride reduction[8] of androstan-6-one;[13] **21** by reduction with lithium in ammonia,[15] and **22** by lithium aluminum hydride reduction[8] of androstan-11-one;[14] **23** was prepared analogous to **24** (vide infra) from 12α-acetoxy-5α-spirostane; **26** by hydroboration–oxidation of Δ^{14}-cholestene;[17] **29** by lithium aluminum hydride reduction[8] of androstan-16-one.[9] The following compounds were prepared by previously described methods: **1**,[18] **3**,[18] **19**,[4] **20**,[4] **24**,[16] **27**.[19] An attempt to prepare **3** by reduction of 1-androstanone with K(*sec*-Bu)$_3$BH ("K-selectride", Aldrich)[20] gave only a very small amount (~5%) of the desired product, most of the starting material being recovered unchanged. Compounds **5, 6, 12, 14, 25, 28,** and **30** were generously provided by Dr. Paul V. Demarco.[21]

All the acetoxy steroids were prepared by reaction of the alcohol with acetic anhydride in pyridine, with the exception of 5α-acetoxycholestane, which was made according to the procedure of Plattner et al.[22]

The ^{13}C NMR spectra were recorded at 25.2 MHz using a Varian XL-100-15 system or at 22.6 MHz with a Bruker WH-90 spectrometer, both operating in the Fourier transform mode. Data were accumulated with a maximum of 1.2 Hz per data point. The chemical shifts are relative to internal Me_4Si and are estimated to be accurate to ±0.1 ppm. The probe temperature was ca. 30°.

The spectra were determined as 0.2–0.6 *M* solutions in $CDCl_3$. Variation in sample concentration was found to have a negligible influence (less than 0.1 ppm) on the chemical shift values of all carbons except the carbinyl carbon atom. With increasing sample concentration, within the employed range, this carbon atom became increasingly shielded by up to 0.3 ppm.

The shift reagent experiments were performed with commercial Eu(dpm)$_3$ or Eu(fod)$_3$, which were used without further purification. The ^{13}C spectra were first recorded in the proton noise-decoupling mode in order to measure the exact chemical shifts of all the ^{13}C nuclei present. The degree of substitution of each carbon atom was determined by obtaining a second series of spectra in the single-frequency off-center decoupling mode. Subsequently, a freshly prepared solution of shift reagent in $CDCl_3$ was added in two equal increments to each sample solution and the spectral data in the two modes redetermined. The final molar ratio of reagent to steroid was 0.3. The effects of the addition of the shift reagent on the chemical shift of the ^{13}C nuclei appeared linear in this range.

Results

Chemical shift data for the hydroxy steroids examined are given in Table I along with the values for the parent hydrocarbons, androstane and cholestane. ^{13}C NMR data for

Table I. ^{13}C Chemical Shifts in Hydroxy Steroids[a]

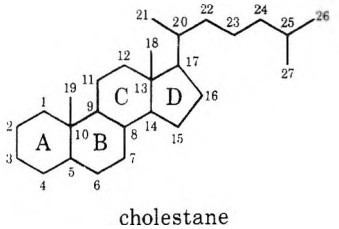
Steroid	1	2	3	4	5	6	7	8	9	10	11	12
Androstane	38.8	22.3	26.9	29.2	47.1	29.2	32.6	36.0	55.1	36.4	20.9	39.0
Cholestane	38.8	22.3	26.9	29.2	47.1	29.2	32.2	35.6	54.9	36.3	20.9	40.2
(1) 1α-Androstanol	71.5	29.0	20.3*	28.6	39.0	29.0	32.2	35.9	47.5	40.2	20.1*	38.8
(2) 1α-Cholestanol	71.5	28.9	20.2	28.5	39.0	28.9	31.8	35.5	47.2	40.1	20.2	39.8
(3) 1β-Androstanol	78.8	33.4	24.7	28.7	46.3	28.9	32.5	36.3	55.4	42.6	24.7	39.3
(4) 1β-Cholestanol	79.0	33.3	24.7	28.7	46.2	28.9	32.2	35.8	55.2	42.5	24.7	40.5
(5) 2α-Androstanol	48.2	68.0	36.3	27.7	46.4	28.2	32.4	35.3	55.0	37.6	21.1	39.0
(6) 2β-Androstanol	45.3	68.1	33.9	23.9	47.4	28.9	32.5	35.4	55.9	36.1	21.0	39.1
(7) 2β-Cholestanol	45.1	67.9	33.9	23.9	47.4	28.8	32.1	35.0	55.6	35.9	21.0	40.2
(8) 3α-Androstanol	32.4	29.1	66.6	36.0	39.2	28.7	32.5	36.0	54.7	36.3	20.9	39.0
(9) 3α-Cholestanol	32.2	29.1	66.5	35.9*	39.1	28.6	32.0	35.5	54.3	36.1	20.8	40.1
(10) 3β-Androstanol	37.1	31.6	71.2	38.3	44.9	28.8	32.5	35.9	54.5	35.6	21.3	38.9
(11) 3β-Cholestanol	37.0	31.5	71.4	38.2	44.9	28.8	32.1	35.5	54.4	35.5	21.3	40.1
(12) 4α-Androstanol	38.1*	20.5	36.4	70.5	54.3	22.8	32.1	35.6	55.1	37.7*	21.0	39.0
(13) 4α-Cholestanol	37.9*	20.4	36.2	70.3	54.0	22.7	31.6	35.1	54.6	37.5*	20.9	40.1
(14) 4β-Androstanol	38.7	17.1	33.9	72.5	50.2	26.1	32.9	36.0	55.9	36.3	20.3	39.0
(15) 4β-Cholestanol	38.6	17.0	33.8	72.4	50.0	26.0	32.4	35.6	55.6	36.2*	20.3	40.0
(16) 5α-Cholestanol	31.6	20.9	20.7	34.4*	73.1	34.6*	26.3	34.9	46.2	39.3	20.9	40.1
(17) 6α-Cholestanol	38.9	21.8	26.2	22.8	53.8	70.0	41.7	34.3	54.2	36.9	20.8	39.9
(18) 6β-Androstanol	40.5	22.2	27.1	26.1	49.8	72.5	40.0	30.7	55.0	36.4	20.7	39.0
(19) 7α-Cholestanol	38.5	22.2	26.8	28.7	39.2	36.8	68.2	39.7	46.4	36.4	20.7	39.7
(20) 7β-Cholestanol	38.7	22.1	26.6	28.7	44.1	38.7	75.2	43.6	53.1	35.7	20.9	40.1
(21) 11α-Androstanol	40.2	22.6	26.7	29.7	47.0	29.7	32.8	35.4	61.2	38.4	69.2	50.5
(22) 11β-Androstanol	38.9	22.0	26.6	28.6	47.8	28.6	32.9	31.7	59.0	36.5	68.6	47.8
(23) 12α-Androstanol	38.8	22.3	26.9	29.2	47.2	29.2	32.4	36.1	48.3	36.1	28.4	72.7
(24) 12β-Androstanol	38.7	22.2	26.8	29.0	47.1	29.0	32.2	34.9	53.9	36.3	29.9	79.7
(25) 15α-Androstanol	38.8	22.2	26.7	29.0	46.9	28.9	32.5	35.5	55.0	36.4	20.7	39.4
(26) 15α-Cholestanol	38.7	22.2	26.8	29.0	46.9	29.0	32.6	35.2	54.7	36.1	20.7	40.6
(27) 15β-Androstanol	38.8	22.3	26.9	29.1	47.4	29.1	31.9	31.9	55.7	36.6	20.8	40.6
(28) 16α-Androstanol	38.8	22.2	26.9	29.1	47.2	29.1	32.5	35.5	55.1	36.4	20.5	39.0
(29) 16β-Androstanol	38.8	22.3	26.9	29.1	47.2	29.1	32.5	35.5	55.0	36.5	20.6	39.3
(30) 17α-Androstanol	38.8	22.2	26.8	29.1	47.0	29.1	32.5	35.8	54.6	36.4	20.3	31.6
(31) 17β-Androstanol	38.8	22.2	26.8	29.1	47.2	29.1	31.8	35.8	55.0	36.4	20.5	36.9

[a] In parts per million relative to Me_4Si. Assignment of chemical shifts for close-lying peaks marked with an asterisk may

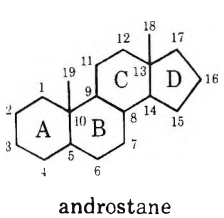
Table II. ^{13}C Chemical Shifts in Acetoxy Steroids[a]

Steroid	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2β-AcO-Cholestane	41.8	70.5	30.8	24.4	46.9	28.7	32.0	35.0	55.3	35.8	20.9	40.1	42.6	56.5
3α-AcO-Cholestane	32.9	26.1	70.0	32.9	40.1	28.3	32.0	35.5	54.3	35.8	20.8	40.1	42.6	56.5
3β-AcO-Androstane	36.9	27.6	73.5	34.1	44.7	28.7	32.4	35.9	54.5	35.6	21.3	38.9	40.8	54.6
5α-AcO-Cholestane	31.7	21.1	21.1	28.3	87.7	28.3	26.7	34.9	46.3	40.3	21.1	40.3	42.8	56.5
6α-AcO-Cholestane	38.8	21.7	26.1	22.8	50.8	73.4	37.8	34.1	54.2	36.2	20.8	40.0	42.7	56.3
6β-AcO-Androstane	40.4	22.0	25.8	26.8	48.7	74.2	36.8	31.3	54.7	36.5	20.7	38.9	40.9	54.4
7α-AcO-Cholestane	38.4	22.1	26.7	28.5	40.0	33.7	71.6	38.4	47.4	36.2	20.7	39.6	42.7	50.6
7β-AcO-Cholestane	38.6	22.1	26.6	28.6	43.7	34.7	77.0	39.5	53.2	35.6	21.0	39.8	43.5	55.4
11α-AcO-Androstane	39.4	22.6	26.5	29.6	46.7	29.6	32.8	35.4	57.0	38.1	71.7	45.5	40.9	53.4
11β-AcO-Androstane	38.9	21.8	26.6	28.6	47.8	28.6	32.8	35.2	57.6	36.2	70.3	43.7	39.8	56.1

[a] In parts per million relative to Me_4Si. [b] Acetoxy methyl group.



cholestane



androstane

a few monohydroxy steroids have been reported in the literature; these are 3β-cholestanol[24] and the epimeric pairs of 3- and 17-androstanols.[23] The chemical shifts for these compounds given in Table I have been redetermined in the present investigation and agree satisfactorily with those previously given. The recently reported ^{13}C NMR spectrum of 14β-androstanol[25] is not included in our discussion, since this compound differs from the hydroxy steroids of the present study by possessing a cis C/D ring junction.

The assignments of the individual chemical shift values to specific carbon atoms presented in Table I were based on our earlier assigned spectra of the parent hydrocarbons,[2] and on the assignment of ApSimon and co-workers for the four 3- and 17-androstanols.[23] In addition, the recently reported assignment of the spectrum of 3β-cholestanol[26] was used. This differs from the original one[24] by reversing the chemical shifts assigned to C-12 and -16 (see also ref 2), and to C-18 and -19. The resonances of carbon atoms five or more bonds removed from the hydroxyl group are in general only slightly shifted relative to the parent hydrocarbons, and the assignments can usually be carried over.

The presence of the hydroxyl group on the ^{13}C chemical shifts in spectra of cyclopentanols and cyclohexanols has been shown[27,28] to result in downfield shifts of 35–50 ppm for α carbons and 2–9 ppm for β carbons, whereas γ carbon atoms are shifted upfield by 1–8 ppm. Our assignments of the resonances of carbon atoms close to the hydroxyl substituent were based on the data quoted above, on shift reagent data, acetylation shifts, and, for those compounds available in sufficient quantity, on off-resonance decoupled spectra. By addition of $Eu(dpm)_3$ or $Eu(fod)_3$ to solutions of the hydroxy steroids (as described in the Experimental

13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
40.8	54.7	25.5	20.5	40.5	17.6	12.3								
42.6	56.7	24.2	28.3	56.4	12.2	12.2	35.9	18.7	36.3	24.0	39.6	28.0	22.5	22.8
40.8	54.5	25.6	20.5	40.5	17.5	12.9								
42.6	56.5*	24.2	28.2	56.3*	12.1	12.9	35.8	18.7	36.2	23.9	39.5	28.0	22.5	22.7
40.2	54.6	25.8	20.4	40.6	17.4	6.7								
42.0	56.5	24.5	28.0	56.5	12.0	6.7	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8
40.9	54.6	25.6	20.5	40.5	17.6	13.4								
40.9	54.7	25.5	20.5	40.5	17.7	14.8								
42.7	56.6	24.2	28.3	56.4	12.2	14.7	35.9	18.7	36.3	23.9	39.6	28.1	22.6	22.8
40.9	54.7	25.6	20.6	40.5	17.6	11.2								
42.6	56.5	24.2	28.2	56.2	12.1	11.2	35.8*	18.7	36.2	23.9	39.5	28.0	22.5	22.8
40.8	54.7	25.5	20.5	40.4	17.6	12.4								
42.6	56.5	24.3	28.3	56.3	12.1	12.3	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8
40.8	54.7	25.5	20.5	40.5	17.6	13.5								
42.4	56.5	24.2	28.3	56.3	12.1	13.5	35.8	18.7	36.2	23.9	39.5	28.0	22.5	22.7
40.9	54.8	25.6	20.5	40.5	17.6	14.7								
42.6	56.7	24.2	28.2	56.3	12.1	14.7	35.8	18.7	36.1*	23.9	39.5	28.0	22.6	22.8
42.6	56.2	24.1	28.2	56.2	12.2	16.1	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8
42.6	56.3	24.2	28.2	56.3	12.1	13.3	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8
40.9	54.4	25.5	20.5	40.5	17.6	15.8								
42.7	50.8	23.7	28.3	56.2	11.9	11.2	35.9	18.7	36.3	23.9	39.7	28.1	22.6	22.8
43.6	55.9	27.0	28.7	55.3	12.2	12.3	35.7	18.8	36.2	23.9	39.5	28.0	22.5	22.8
41.2	53.7	25.6	20.6	40.8	18.4	12.8								
39.9	56.4	25.4	20.1	40.8	20.0	15.5								
45.3	46.4	25.2	20.2	33.0	18.7	12.2								
46.3	53.3	25.2	20.7	38.2	11.8	12.2								
41.7	61.9	75.7	32.9	38.3	18.8	12.3								
44.1	64.0	74.0	40.3	53.8	13.4	12.3	35.4	18.5	36.1	23.8	39.5	28.0	22.6	22.8
40.6*	59.6	72.5	34.0	40.4*	20.0	12.3								
41.9	52.3	37.3	71.8	52.2	18.8	12.3								
40.3	54.3	37.3	71.9	51.5	19.1	12.3								
45.3	48.9	24.6	32.5	80.0	17.2	12.3								
43.1	51.3	23.4	30.6	82.1	11.2	12.3								

be reversed.

15	16	17	18	19	20	21	22	23	24	25	26	27	CH_3[b]	CO	Registry no.
24.2	28.2	56.3	12.1	14.0	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8	21.5	169.9	1107-37-5
24.2	28.3	56.4	12.1	11.3	35.8	18.7	36.2	23.9	39.5	28.0	22.5	22.8	21.4	170.2	1107-59-1
25.5	20.5	40.5	17.6	12.3									21.3	169.9	1236-13-1
24.1	28.3	56.4	12.3	15.7	35.9	18.8	36.3	23.9	39.6	28.3	22.6	22.9	22.3	169.8	41721-99-7
24.1	28.2	56.3	12.0	13.3	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8	21.3	170.2	54657-02-2
25.5	20.5	40.4	17.6	15.2									21.4	170.0	35487-68-4
23.7	28.1	56.2	11.8	11.2	35.9	18.7	36.2	24.0	39.6	28.1	22.6	22.8	21.3	170.1	54676-24-3
25.8	28.6	55.4	12.2	12.2	35.7	18.9	36.2	23.9	39.8	28.0	22.6	22.8	21.8	170.3	54712-41-3
25.5	20.7	40.1	18.1	12.3									22.0	170.4	57031-41-1
25.3	20.1	40.5	19.3	15.1									21.8	169.9	14946-61-3

Section) the peaks in the ^{13}C NMR spectra are shifted linearly downfield with the amount of added shift reagent. The shift changes for the different carbon atoms are reproduced by the pseudocontact shielding expression of McConnell and Robertson,[29] except for those carbons closest to the complexing site, in agreement with previous reports.[23,26,30] Consideration of these shifts alone frequently allows unambiguous signal assignments. Further, by acetylation of the hydroxyl group the resonances of the α and β carbon atoms shift in a predictable manner and allow identification of the corresponding peaks.[24] A secondary α carbon resonance is shifted 1–4 ppm downfield, whereas β carbons are shifted 1–5 ppm upfield; signals of tertiary carbinyl carbons experience much larger downfield α shifts (~11 ppm).[31] The chemical shift data for the acetoxy steroids examined are given in Table II; comparison of the data therein with those in Table I shows the characteristic shifts that take place upon acetylation of the hydroxyl group.

Owing to the difference in the spin-lattice relaxation time of nonmethyl hydrogen bearing carbons (0.2–0.6 sec) and quaternary carbons (4 sec)[26,32] proton noise decoupled spectra obtained under suitable experimental conditions (short pulse repetition time, large pulse width) permit direct identification of the latter as narrow peaks of very low intensity.

A number of ambiguities were resolved by comparing the spectra of corresponding cholestanols and androstanols. Thus the resonances corresponding to the carbon atoms of ring D, as well as to C-12 and C-18, were assigned by considering the shift changes following introduction of the C-17 side chain. Even carbon atoms 8 and 7 are affected by the presence of the side chain, since their resonances are shifted slightly (~0.4 ppm), but consistently, upfield in the cholestanol. The assignment for the carbon atoms of ring A and the C-19 methyl group in compounds **1–15** and **17–20** are corroborated by the hydroxyl substituent effects reported for 10-methyl-*trans*-decalols.[33]

For a few examples the above methods were either not practical or not adequate to allow unequivocal assignments. Comparison with the ^{13}C NMR spectra of further substituted steroids usually resolved the ambiguities. Thus, for the assignment of the spectra of compounds **19, 20, 22,** and

Table III
Hydroxyl Substituent Effects (in ppm)[a]

OH position	α carbon	β carbon[b]	γ carbon[b,c]
1β	40.1	11.0 (2); 6.2 (10)	−2.2 (3) t; −0.9 (5) t; 0.3 (9) g; −5.5 (19) g
1α	32.7	6.6 (2); 3.7 (10)	−6.7 (3) g; −8.1 (5) g; −7.7 (9) g; +0.7 (19) t
2α	45.7	9.4 (1); 9.4 (3)	−1.5 (4) t; 1.2 (10) t
2β	45.7	6.4 (1); 7.0 (3)	−5.3 (4) g; −0.3 (10) g
3β	44.4	9.3 (2); 9.1 (4)	−1.7 (1) t; −2.2 (5) t
3α	39.6	6.8 (2); 6.7 (4)	−6.5 (1) g; −7.9 (5) g
4α	41.2	9.4 (3); 7.1 (5)	−1.8 (2) t; −6.4 (6) g; 1.3 (10) t
4β	43.2	7.0 (3); 3.0 (5)	−5.3 (2) g; −3.1 (6) g; −0.1 (10) g
5α	26.0	5.2 (4); 5.4 (6); 3.0 (10)	−7.2 (1) g; −6.2 (3) g; −5.9 (7) g; −8.7 (9) g; 0.0 (19) t
6α	40.8	6.7 (5); 9.5 (7)	−6.4 (4) g; −1.3 (8) t; 0.6 (10) t
6β	43.3	2.7 (5); 7.4 (7)	−3.1 (4) g; −5.3 (8) g; 0.0 (10) g
7β	43.0	9.5 (6); 8.0 (8)	−3.0 (5) t; −1.8 (9) t; −0.8 (14) g
7α	36.0	7.6 (6); 4.1 (8)	−7.9 (5) g; −8.5 (9) g; −5.9 (14) g
11α	48.3	6.1 (9); 11.5 (12)	−0.6 (8) t; 2.0 (10) g; 0.4 (13) t
11β	47.7	3.9 (9); 8.8 (12)	−4.3 (8) g; 0.1 (10) g; −0.9 (13) g
12β	40.7	9.0 (11); 5.5 (13)	1.2 (9) t; −1.4 (14) t; −2.3 (17) g; −5.8 (18) g
12α	33.7	7.5 (11); 4.5 (13)	−6.8 (9) g; −8.3 (14) g; −7.5 (17) g; 1.1 (18) t
15α	50.0	7.2 (14); 12.4 (16)	−0.5 (8); 1.2 (13); −2.4 (17)
15β	47.0	4.9 (14); 13.5 (16)	−4.1 (8); −0.2 (13); −0.1 (17)
16α	51.3	11.8 (15); 11.7 (17)	1.1 (13); −2.4 (14)
16β	51.4	11.8 (15); 11.0 (17)	−0.5 (13); −0.4 (14)
17α	39.5	12.0 (16); 4.5 (13)	−7.4 (12); −5.8 (14); −0.9 (15); −0.4 (18)
17β	41.6	10.1 (16); 2.3 (13)	−2.1 (12); −3.4 (14); −2.1 (15); −6.4 (18)

[a] The numbers given are the chemical shift differences, $\delta^{ROH} - \delta^{RH}$ for corresponding carbon atoms; a negative sign signifies an upfield shift. [b] Carbon atom number given in parentheses. [c] g and t designate gauche and trans γ interactions.

23, the ^{13}C NMR spectra of the following steroids, not included in the tables, were taken into consideration: 3β-acetoxy-7α- and -7β-cholestanols, 9,12,12-trideuterioandrostane-3β,11β-diol, and 5α-pregnan-12α-ol. As a case in point, in the spectrum of 7β-cholestanol assignment of the C-9 and C-14 and the C-3 and C-15 resonances was not obvious using the above cited methods. Comparison with the spectrum of 3β-acetoxy-7β-cholestanol allows the distinction to be made, since only C-9 and C-3 are expected to shift significantly upon introduction of the C-3 acetoxy group.

Discussion

The α Substituent Effect. Several reports have appeared discussing the stereochemical dependence of the shielding of the carbinyl carbon in cyclohexanols.[34-36] Until recently there appeared to be general agreement that the chemical shift of the carbinyl carbon depends markedly on the orientation of the hydroxyl group; i.e., that an axial hydroxyl group shields the α carbon atom more than does the corresponding equatorial substituent. However, in a recent study by Grover and Stothers[33] of the ^{13}C NMR spectra of 10-methyl-*trans*-decalols, this rule was shown to be inapplicable where the hydroxyl group takes part in a syn-diaxial OH–CH_3 interaction. In the present investigation we have attempted to relate in a more general and quantitative way the hydroxyl substituent effect on the α-carbon resonance with the steric relationship between the hydroxyl group and other atoms in the molecule.

To facilitate the following discussion, the hydroxyl substituent effects in steroids are given in Table III, in which the epimeric pairs are grouped together, with the equatorially substituted compound listed first. We have found that the hydroxyl group substituent effect on chemical shift of the carbinyl carbon atom is not primarily dependent on the stereochemistry (i.e., axial or equatorial) of the hydroxyl group. Rather it can be related to the number, n, of γ-gauche carbons possessing hydrogen atoms able to interact with the hydroxyl group, and to the number of skew pentane interactions, p, of the hydroxyl group with carbon atoms. The following relationship reproduced the trend of the substituent effect, Δ_α, on the carbinyl carbon atom except where the hydroxyl group interacts strongly with atoms of ring D.

$$\Delta_\alpha(\text{ppm}) = 45.0 + 3.5p - 3.5n$$

The shifts predicted using this relationship are within 2 ppm of the experimental values, except for the 1β isomers 3 and 4, discussed below. The constant term, 45.0 ppm, is the substituent effect at a hydroxylated secondary carbon atom free of steric interactions; the corresponding constant will, of course, be different for tertiary hydroxyl groups. The α shift observed in 5α-cholestanol, the only tertiary alcohol included in the present study, suggests that for tertiary alcohols the constant term is 40.0 ppm. The experimental Δ_α for 5β-cholestanol (A/B ring junction cis) was determined to be 29.1 ppm [73.3 (ROH) − 44.2 (RH)[37]], which is within 0.4 ppm of the value calculated using 40.0 ppm as the constant term; however, neither of these two compounds, 5α- and 5β-cholestanol, exhibits a hydroxyl carbon skew pentane interaction, and it has hence not been possible to estimate whether the parameter associated with this interaction holds for tertiary alcohols.

In simpler systems (e.g., cyclohexanols), where skew pentane interactions are absent, the above relationship reduces to the usual generalization that the carbinyl carbon is less shielded in the equatorial epimer than in the axial one. This follows, since the hydroxyl group in the latter usually has a higher number of γ-gauche interactions. Dalling et al.,[38] in their parameter set for calculating the shifts of methyldecalins, found the parameter (V_g) associated with γ-gauche interactions of *neighboring* carbon atoms to be −3.5 ppm; it is noteworthy that this value is the same as the one derived here for examples in which the neighboring carbon atom is replaced by a hydroxyl group. A similar comparison of the value associated with skew pentane interactions is not possible, since this geometrical arrangement was not represented in the decalins reported by Dalling et al.[38]

In cyclohexanols the upfield α shift associated with γ-gauche interactions of the hydroxyl group with proximate hydrogens on γ carbons has been explained[36] as being due to a transmission, through the C–O bond, of this steric interaction to the carbinyl carbon. This interaction also pro-

duces the well-established steric upfield shift at the γ carbon atoms. The downfield α shift associated with a hydroxyl carbon skew pentane interaction could then be the result of geometrical deformations (torsion and valence angle deformation) induced to relieve the severe skew pentane interaction. Thus, in steroids with syn-diaxial hydroxyl–methyl interactions (e.g., 2β-cholestanol) partial relief of this interaction can be obtained by an outward bending of the hydroxyl group. Such a bending will at the same time decrease the gauche interactions of the hydroxyl group with the γ-carbon atoms, and thereby produce at least part of the downfield carbinyl carbon shift. That such deformations do take place is supported by the diminished γ-gauche hydroxyl substituent effects found in steroids with syn-diaxial interactions (see below). Furthermore, bending of the hydroxyl group will in itself influence the chemical shift at the α carbon atom by slightly changing its geometry. In certain cases [e.g., 11α-androstanol (**21**)] downfield carbinyl carbon shifts may also be the result of diminished γ-gauche interactions of the α carbon atom provided the deformations induced to relieve the skew pentane interaction(s) of the hydroxyl group with carbon atoms at the same time relieve these γ-gauche interactions. This interpretation of the observed downfield shifts is supported by noting that the carbinyl carbon resonances of the 1β steroid alcohols **3** and **4** experience a smaller downfield shift than expected. The hydroxylated carbon atom in the 1β isomers does not have a hydrogen able to interact with γ-gauche carbon atoms; undoubtedly the presence of γ-gauche interactions places restrictions on the ways in which relief can be found for the skew pentane interaction. Furthermore, the γ-gauche interaction of the hydroxyl with the C-19 methyl group is apparently not reduced by the hydroxyl C-11 skew pentane configuration, as seen by comparison with ^{13}C NMR data for 1β-10-methyl-*trans*-decalol,[33] where this interaction is absent. The relatively small Δ_α found for 1β steroid alcohols (40.1 ppm) [compared to the calculated Δ_α (45.0 ppm)] is therefore assumed to indicate that the geometrical deformations taking place around the 1β-hydroxyl group to relieve the skew pentane interaction are different from those occurring in, e.g., 11α-androstanol (**21**), due to the absence of γ-gauche interactions of the α carbon atom. In the 7β alcohol (**20**) the interactions in question are comparable to those in the 1β isomers and the experimental Δ_α (43.0 ppm) is also in this case smaller than the calculated value (48.5 ppm). Of course, this may be due partly to the five-membered nature of ring D, making the distance between C-15 and the 7β hydroxyl larger than in a usual skew pentane interaction, and consequently diminishing the requirements for relief.

In order to test the predictive value of the relationship given above the chemical shifts of the carbinyl carbon atoms in various alcohols have been calculated and compared to (experimental) literature values: *cis*- and *trans*-4-*tert*-butylcyclohexanols,[36] the epimeric 1- and 2-*trans*-decalols,[33] the epimeric 1-, 2-, 3-, and 4-10-methyl-*trans*-decalols,[33] cholic acid,[37] litho-, deoxy-, chenodeoxy-, and hyodeoxycholic acid,[37] and lanosterol.[39,40,41] All the calculated shifts are within 2 ppm of the experimental values. The agreement between predicted and experimental values could probably be improved by adding more parameters. However, the chemical shift of the carbinyl carbon atom varies with solvent and concentration, and it would be meaningless to refine the equation to yield an agreement within narrower limits than these variations allow.

The β Substituent Effect. The influence of a hydroxyl group on the chemical shift of β carbon atoms varies considerably in magnitude, covering (see Table III) a range from 13.5 to 2.3 ppm. It has previously[33,36] been found that the β carbon atom is more shielded by an axial than by an equatorial hydroxyl group; for the same orientation of this group, the more substituted β carbons show the smaller shifts.[33,42] The origin of the β-substituent effect is not yet understood, but it has been suggested[36] that the difference in β-substituent effects between axial and equatorial hydroxyl groups reflects γ-gauche interactions of the axial hydroxyl group, producing an elongation of the C^β–C^γ bond. Such an elongation should give rise to an upfield shift at the β carbon atom. The upfield β shifts previously associated with branching at the β carbon atom may very well also be a consequence of this interaction, since substitution at the β carbon atom usually leads to more γ-gauche interactions of equatorial as well as axial hydroxyl groups, except when the hydroxyl group and the substituent at the β carbon atom exist in a trans-diaxial relationship. 1α-Cholestanol (**2**) provides an example of the latter, with the hydroxyl and the substituent at the β carbon atom, the C-19 methyl group, trans to each other. The hydroxyl β shift at C-10 (3.7 ppm) is, however, close to the β shifts observed in similar compounds which lack this trans β substituent (e.g., the β shift at C-8 in 7α-cholestanol is 4.1 ppm). In general, we have found that the variation in β shifts in the six-membered rings can be related quantitatively to the number of γ-gauche interactions of the hydroxyl group, except when the latter is involved in a skew pentane arrangement (see below). The hydroxyl β substituent effects, Δ_β, for secondary hydroxyl groups are reproduced by the equation

$$\Delta_\beta(\text{ppm}) = 9.3 - 2.4q$$

where q is the number of γ-gauche interactions of the hydroxyl group with γ carbon atoms connected to the β carbon atom in question. Thus, for 7α-cholestanol, q equals 2 for C-8 and 1 for C-6. Where $q = 0$ the shifts calculated are within 0.3 ppm of the experimental values. With $q = 1$ and 2 the interval becomes larger, ±0.5 and ±0.9 ppm, respectively.

Only one of the steroids studied, 5α-cholestanol (**16**), has a tertiary hydroxyl group. The shifts of the three β carbon atoms in this compound suggest a similar equation for Δ_β in tertiary alcohols, replacing the constant term of 9.3 ppm by 7.7 ppm. This is supported by the experimental Δ_β values found for 5β-cholestanol [$\delta^{ROH} - \delta^{RH}$;[37] 5.8 ppm (C-4); 7.5 ppm (C-6); 7.7 ppm (C-10)], all of which are within 0.5 ppm of the values calculated in this way.

The relationship has in addition been used with success to calculate the expected β shifts in decalols and 10-methyl-*trans*-decalols.[33] Further support for the suggestion that the β shifts may be estimated quantitatively from the number of γ-gauche interactions of the hydroxyl group may be found in the reported[36] ^{13}C NMR data for alkylcyclohexanols. In this group of compounds the β substituent effect of a hydroxyl group is generally smaller than in the steroid series. However, the trend of the β shifts in the cyclohexanols is represented by a similar equation, as for the steroids, using 8.1 ppm as the constant and 2.6 ppm as the q parameter. The reason for the difference in the numerical values of the parameter should probably be sought in the greater flexibility of the monocyclic system and, to a certain extent, in the presence in the cyclohexanol series of interconverting conformers.

The β substituent shifts of the acetoxy group (Table II) can likewise be related quantitatively to the number (q) of γ-gauche interactions of the acetoxy group, but with considerably smaller parameter values: the constant term is found to be 5.3 ppm and the q parameter to be 1.2 ppm. These values apply for secondary acetoxy groups not involved in skew pentane interactions. In the tertiary 5α-acetoxycholestane the effect of the β acetoxy substituent is to

shield C-4 and C-6, and to deshield C-10. These observations indicate a strongly perferred conformation of the 5α-acetoxy group, with the O–CO bond symmetrically situated between C-4 and C-6 and pointing away from C-10.

As mentioned previously, the β shifts of hydroxyl (or acetoxy) groups having a skew pentane interaction with a carbon atom do not follow the relationship discussed above. In most cases one of the experimental Δ_β values agrees with the calcualted Δ_β, while the other is either too small or too large. This lack of correspondence is indeed what should be expected, if the variation in β shift is related to steric interactions of the hydroxyl group, since introduction of skew pentane interactions must cause significantly different deformations of the skeleton than do γ-gauche interactions. Thus, in 1β-androstanol (**3**), where the hydroxyl group has a skew pentane interaction with C-11, an unusually large β effect (11.0 ppm) is found at C-2. The calculated Δ_β value is 9.3 ppm (q = 0). It is conceivable that this compound can relieve the steric interaction by compression of the C^β–C^γ bond and thereby give rise to a greater downfield β shift. A quite similar geometrical arrangement is found in the 11α-hydroxy steroid (**21**), where C-12 also shows a large β hydroxyl substituent effect (11.5 ppm, calculated to be 9.3 ppm).

The β substituent shifts for hydroxyl groups located in ring D vary over a somewhat wider range (2.3–13.5 ppm) than when it is confined to one of the six-membered rings (2.9–11.5 ppm). Although the β shifts of the five-membered ring derivatives do not quantitatively follow a relationship as do the β carbon shifts in the six-membered ring alcohols, they do show similar trends. Average β substituent effects are 12–13 ppm for a hydroxyl group free from steric interactions, and in ring D this value is also reduced in proportion to the number of steric interactions of the hydroxyl group with γ carbons connected to the β carbon concerned.

The γ Substituent Effect. Inspection of Table III reveals a number of general trends for the γ substituent effect of the hydroxyl group. The expected geometrical dependence of this effect allows the separation of these shifts in the six membered rings into γ-gauche shifts, where the hydroxyl and the γ carbon atom are gauche to each other, and the analogously defined γ-trans shifts. Shifts of the latter type are often small; in the present compounds they span a range of +1.3 to −3.0 ppm. Downfield (or zero) shifts are found only at quaternary or methyl γ carbons.

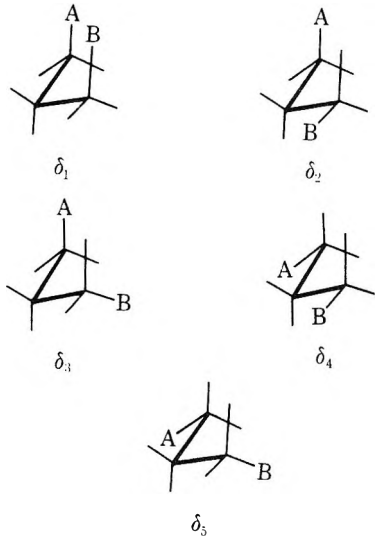
The magnitude of γ-gauche substituent effects depends upon whether the γ carbon atom is secondary or tertiary. Average values are −6.5 ppm for methylene carbons and −7.8 ppm for methine carbon atoms. The larger upfield shifts of methine carbon signals are probably a consequence of the fact that these are bridgehead carbon atoms, which will have less opportunity to escape the gauche interaction than the more flexible methylene carbons. Similar results have also been found for the decalols.[33] Exceptions to this general trend are found where the hydroxyl group is 1,3-syn-diaxial to a methyl group, as in compounds **6, 7, 14, 15, 18,** and **22** (Table I). In each of these the γ-gauche hydroxyl effect is decreased to ~−4.5 ppm for both methylene and methine γ carbon atoms. It seems reasonable to assume that this reduction of the γ-gauche effect is associated with the deformations that take place to relieve the 1,3-syn-diaxial interaction. Such deformations should cause all of the hydroxyl γ-gauche carbons to become less shielded. This is unlikely with torsional angle deformations alone, which relieve the interaction by flattening of the ring in question, because the puckering transmitted to the next ring would increase the steric interactions of γ-gauche carbons in this ring, in disaccord with the observed shifts. Thus, valence angle deformation of the interacting groups is probably significant, causing the two groups to bend away from each other. Such a bending would at the same time attenuate the γ-gauche substituent effect by diminishing the steric interactions of these γ-carbon atoms with the hydroxyl group.

A relatively large shielding γ effect is observed whenever γ carbon atoms have a gauche arrangement with a substituent.[27,28] This has been explained[43,44] in terms of steric interaction between hydrogen atoms of both the substituent and the observed γ-gauche carbon, resulting in a slight charge polarization in the C(γ)–H bond. However, this theory is not generally applicable, since similar shielding effects are also found when the substituent is without hydrogen atoms.[42,45] Lippmaa et al.[45] have discussed the origin of the γ-gauche substituent shifts and concluded that hydrogen transmitted chemical shift changes at carbon atoms can be disregarded as a possible cause of the γ effect. In the present study, however, upfield γ-gauche shifts have not been observed where the γ-gauche carbon atoms are without hydrogen atoms able to interact with the hydroxyl group. Thus, the resonances of the γ-gauche carbon atoms in 1β-androstanol (**3**), 1β-cholestanol (**4**), and in 7β-cholestanol (**20**) (C-9 and C-14, respectively) are essentially unshifted relative to their parent hydrocarbons. Likewise, C-5 in chenodeoxycholic acid is almost unshifted (+0.4 ppm) compared to C-5 in lithocholic acid.[37] Furthermore, the substituent shifts of quaternary carbon atoms that are γ-gauche to hydroxyl groups are generally within ±1 ppm. Thus, it appears that the presence of an interacting hydrogen atom on the γ-gauche carbon atom is essential for the upfield γ-gauche shift to be observed in the alcohols of the present study.

The γ effect of a hydroxyl group in ring D follows trends similar to those discussed above. It should be noted that the less puckered conformation of this ring, in which a hydroxyl group is never purely axial or equatorial, causes the steric interactions to be less severe than in rings A, B, and C, and γ-gauche shifts are consequently smaller.

The δ-Substituent Effect. In most studies dealing with substituent effects on carbon shieldings attention has been restricted to the α, β, and γ effects, and very few data relating to δ effects have been reported.[33,46] Grover et al.[33] have shown that the methyl carbon is significantly deshielded in compounds with syn-diaxial δ OH–CH_3 interactions. The more rigid systems were found to give rise to the larger shifts. This deshielding δ effect associated with the 1,3-diaxial OH–CH_3 interaction contrasts with the increased shielding caused by the γ-gauche steric effect. Accordingly we have examined about 80 examples of δ effects in the present material in order to elucidate the origin of these shifts. The five different orientations of a hydroxyl group in relation to its δ carbon atom, designated δ_1–δ_5 as in ref 33, are shown in Chart I and the δ_1 hydroxyl substituent effects are given in Table IV. A number of literature values are included for comparison. The data of the table do not support the proposed generalization[33,47] that the more rigid molecules give the larger δ_1 shifts. In fact, the opposite appears to be the case. The δ_1 effect (Table IV) of a 4β hydroxyl group in 10-methyl-*trans*-decalol (**33**) is 3.4 ppm, 1.0 ppm larger than the 2.4 ppm observed in the more rigid 4β steroidal alcohols, in which the buttressing 11β axial hydrogen prevents the angular methyl group from bending away to escape the syn-diaxial OH–CH_3 interaction; such a bending would otherwise partly relieve the steric interaction. In this connection it is remarkable that the 2β and 4β δ_1 shifts in the steroid series (**6, 7** and **14, 15**) are of the same magnitude as the 2β shift in the decalol (**32**), whereas the 4β decalol isomer (**33**), like the 6β-hydroxylated steroid (**18**), exhibits significantly higher shifts (3.4–3.5 ppm). The

Chart I
The Five Different Orientations of a Hydroxyl Group (A or B) in Relation to Its δ Carbon Atom (A or B)



latter two compounds are those without a buttressing axial hydrogen. Thus the trans fusion next to the site of substitution may well make the 4β-10-methyl-*trans*-decalol more resistant to skeletal twist than the 2β isomer, but valence angle deformation of the methyl group can also relieve the strain, and this process is partly hindered in the 2β alcohol by a buttressing hydrogen.

The 11β hydroxy steroid (**22**) is our only example of a hydroxyl group suffering from two syn-diaxial interactions, which makes comparisons with the rest of the material difficult, since the effects of valence bond deformations and conformational transmission in this crowded molecule become hard to assess. It is, however, interesting to note that the two δ_1 interactions of the 11β hydroxyl group give rise to different δ_1 shifts.

Table IV shows four examples of δ_1 interactions with methylene carbons (**3** and **4**, **20**, **21**, and **34**). A priori, this interaction would be expected to be more severe than the OH–CH_3 interaction, owing to the lesser flexibility of skeletal carbons than methyl groups. The actual δ_1 values are very different; in two situations (**3**, **4**, and **34**) quite large δ_1 shifts (3.8 and 3.2 ppm) are encountered whereas a third (**21**) exhibits the smallest δ_1 shift observed (2.0 ppm). Actually **34** is the one that most easily can reduce its syn-diaxial OH–CH_2 interaction, because the interaction in this case passes over the flexible cis fused A/B ring junction, in contrast to **21**, which has the smallest δ_1 value. Compounds **3**, **4**, and **21** are probably the most rigid cases in the table, owing to the fact that the interacting atoms are situated on each side of two connected trans fusions. Any flattening or puckering in the vicinity of C-1 and/or C-11 that would provide some relief for the interactions will cause concomitant skeletal distortions in the other rings of the steroid molecule. Upon introduction of the 1β hydroxyl group the chemical shifts even of carbon atoms 15 and 18 are affected, presumably as a result of this overall skeletal distortion. 7β-Cholestanol (**20**) represents a special case in this connection, because the five-membered nature of ring D makes the distance from the 7β hydroxyl to the C-15 δ carbon larger than the corresponding distance in, e.g., the 11α-hydroxylated compound. However, the 7β isomer shows the larger δ_1 shift.

With the exception of **3** and **4** it thus appears that when the δ_1 steric interaction can be reduced easily, either by ring flattening or puckering or by valence angle deformation, a large δ_1 value is found, as in **18**, **33**, and **34**. Conversely, the more rigid cases, such as **14**, **15**, and **21**, have smaller δ_1 shifts. This suggests that these differences in molecular flexibility have a bearing on the δ_1 values, and that these shifts reflect the geometrical distortion at the δ carbon atom caused by the relief of the steric interaction, as it is assumed for other long-range effects. That significant distortions do take place is seen from the reduced γ-gauche effects of the hydroxyl group whenever it is syn diaxial to a δ carbon atom, as discussed above. It follows that a small δ_1 shift should result when the distance between neighboring δ_1 nuclei, due to other structural features in the molecule (such as the presence of a double bond), is significantly larger than in a usual syn-diaxial arrangement, since the need for relief of the δ interaction in these cases is less. 15α-Androstanol (**25**) is an example of this, since the distance (measured on Dreiding molecular models) from the 15α hydroxyl to C-7 is considerably larger (~30%) than usual, and this compound shows almost no δ_1 shift at C-7 (0.4 ppm).

Table IV
δ_1 Hydroxyl Substituent Effects (in ppm)[a]

Compd	OH position	δ_1 shift	δ_1 carbon
		5α Steroids	
3, 4	1β	3.8	C-11
6, 7	2β	2.5	C-19
14, 15	4β	2.4	C-19
18	6β	3.5	C-19
20	7β	2.8	C-15
21	11α	2.0	C-1
22	11β	3.2	C-19
22	11β	2.4	C-18
		10-Methyl-*trans*-decalols[b]	
32	2β	2.1	C-10
33	4β	3.4	C-10
		5β Steroid[c]	
34	7α	3.2	C-4

[a] See footnote *a*, Table III. [b] Taken from ref 33. [c] The δ_1 value given is the C-4 chemical shift difference between chenodeoxycholic acid and lithocholic acid (ref 37).

The difference in δ_1 shifts for the structurally similar compounds **3**, **4**, and **21** may originate from circumstances similar to those that cause the α substituent effect in **3** and **4** (but not in **21**) to deviate from the general pattern.

Without exception the other possible orientations of δ carbons, δ_2–δ_5, give rise to shifts smaller than those found for δ_1 orientations. They span a range of +1.7 to −1.1 ppm, but of the 70 shifts examined only 8 are larger than 1 ppm. Of all the δ shifts nearly half are downfield, among which the δ_1 shifts are only a minor part. For the δ_2 shifts a trend appears, as only those compounds which have an α axial hydroxyl show small (≤0.5 ppm) shielding δ_2 shifts, whereas the remaining δ_2 shifts are deshielding. In compounds with β axial hydroxyl groups, those with a syn-diaxial interaction, the (deshielding) δ_2 effect varies from 0.2 to 1.7 ppm; compounds with equatorial hydroxyl groups all give rise to δ_2 shifts around 1 ppm. The δ_3 and δ_4 type shifts are with a few exceptions very small, while the δ_5 arrangement in general gives rise to larger (~0.8 ppm) upfield shifts.

Studies are now in progress on the ^{13}C NMR spectra of polyfunctional steroids in order to determine to what extent our generalizations of monohydroxylated steroids are usable in such more complicated cases.

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Registry No.—**1**, 2287-84-5; **2**, 15064-05-8; **3**, 15064-07-0; **4**, 2287-91-4; **5**, 20707-85-1; **6**, 1225-47-4; **7**, 604-17-1; **8**, 7657-50-3; **9**, 516-95-0; **10**, 1224-92-6; **11**, 80-97-7; **12**, 20707-77-1; **13**, 19586-33-5; **14**, 20707-78-2; **15**, 566-50-7; **16**, 910-19-0; **17**, 19043-45-9; **18**, 32215-75-1; **19**, 19037-32-2; **20**, 19037-34-4; **21**, 2872-91-5; **22**, 25814-80-6; **23**, 25814-82-8; **24**, 5672-61-7; **25**, 1090-01-3; **26**, 57031-40-0, **27**, 734-66-7; **28**, 1032-14-0; **29**, 1032-15-1; **30**, 19037-37-7; **31**, 1225-43-0; androstane, 438-22-2; cholestane, 481-21-0.

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Reactions of α-Ketols and Other 21-Hydroxy Steroids with Phosgene. IV. Formation of 20-Chloro-17,20-cyclic Carbonates from 17α-Hydroxy-20-ones[1]

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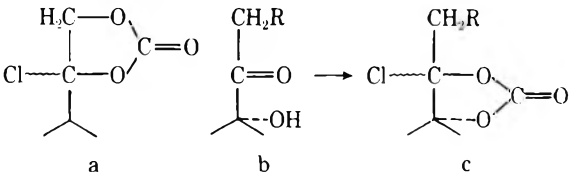
Reaction of 17-hydroxy-20-oxopregnenes and the homologous 21-norpregnenes with excess phosgene in methylene chloride–pyridine (condition C) affords chiefly 20β-chloro-17,20α-cyclic carbonates. The epimeric 20α-chloro-17,20β-cyclic carbonates are minor products. Configurational assignments at C-20 were based primarily on optical rotatory properties. Unlike 20ξ-chloro-20,21-cyclic carbonates, the new isomeric chlorocarbonates do not undergo dehydrohalogenation in hot pyridine or acetone–sodium iodide–triethylamine. However, treatment of chlorocarbonates **9a**, **2a**, and **4a** with zinc in acetic acid gave the corresponding $\Delta^{20,21}$-17,20-cyclic carbonates **21**, **22**, and **23** in modest yields. Similar reaction of the C-21-unsubstituted derivatives **7a** and **11a** furnished the corresponding 20β-acetates **26a** and **25a**. Chlorocarbonates of the latter type were converted in refluxing methanol to an epimeric mixture of 20-methoxy-17,20-cyclic carbonates (**27a,b** and **28a,b**). Acid hydrolysis of the 21-acetates **9a** and **10a** gave the respective 21-ols **29a** and **30a** in good yield together with smaller amounts of the 17-*O*-carbomethoxy-21-acetates **31** and **32**. The stability of the 17,20-cyclic carbonate ring to acidic reagents was also illustrated by the oxidation in chromic anhydride–acetic acid of the 21-ol **30a** to the 21-oic acid, obtained as the methyl ester **36a**.

In the second paper of this series[3] we reported that reaction of 17-deoxy-α-ketols in pyridine with excess phosgene at 0° (condition B) affords chiefly an epimeric mixture of 20-chloro-20,21-cyclic carbonates (partial formula a, Scheme I). Unpublished experiments at that time showed that hindered tertiary α-ketols such as cortisone acetate are not affected by these heterogeneous reaction conditions, and can be recovered in nearly quantitative yields.

Scheme I



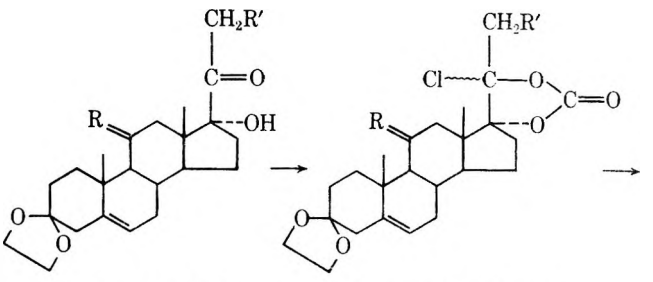
a b c

However, more recent investigations have shown that 17α-hydroxy-20-ones variously substituted at C-21 (partial formula b) react slowly with excess phosgene at room temperature under homogeneous conditions achieved by the addition of excess methylene chloride (condition C), giving 20ξ-chloro-17,20-cyclic carbonates (partial formula c). Because the Δ^4-3-keto grouping possessed by all compounds studied is also attacked under these more strenuous conditions, protection of ring A was a necessary preliminary. In this paper will be presented the preparation and properties of a number of cyclic chlorocarbonates from both pregnene and 21-norpregnene precursors.

Phosgenation of 11-deoxycortisol acetate 3-ethylene ketal (**1**, Scheme II) by condition C followed by fractional crystallization and column chromatography on silica gel in toluene–ethyl acetate furnished epimeric mobile minor and polar major cyclic chlorocarbonates (**2a,b**). Structural assignments were based primarily on positive Beilstein tests and infrared spectroscopy which showed replacement of hydroxyl and 20-ketone absorption by a very strong band in the vicinity of 1825 cm^{-1} and a medium band near 775 cm^{-1} (see Table I for constants). Application of condition C to cortisone acetate 3-ethylene ketal (**3**) provided, after chromatography, the mobile and polar epimeric chlorocarbonates **4a,b**. The corresponding C-21-unsubstituted α-ketols were also subjected to homogeneous phosgenation. The 11-deoxy analogue **5**[4] gave a major cyclic chlorocarbonate (**7a**) in good yield. The minor epimer **7b** could be obtained only as the deketalization product **11b**. Preparation of **7b** by ketalization of **11b** was unsuccessful because of significant concomitant dehydrohalogenation to the $\Delta^{20,21}$-17,20-cyclic carbonate (vide infra). The 11-keto analogue **6**[6] afforded cyclic chlorocarbonate **8a** in good yield. The minor epimer **8b** could not be recovered in pure form either as the 3-ethylene ketal or as the Δ^4-3-ketone **12b**. Deketalization of cyclic chlorocarbonates **2a, 2b, 4a, 4b, 7a,** and **8a** with *p*-TSA in acetone furnished the corresponding Δ^4-3-ketones **9a, 9b, 10a, 10b, 11a,** and **12a** in high yields.

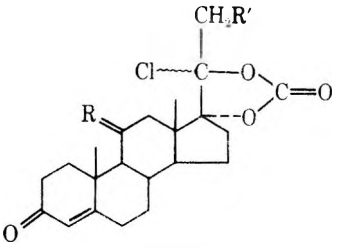
The 3-ethylene ketals of two 17β-formyl-17α-ols (**13** and **14**, Scheme III), prepared by buffered periodate oxidation of the corresponding 20β-glycerols, were also phosgenated under condition C. The 11-deoxy precursor gave mobile and polar epimeric cyclic chlorocarbonates (**15a,b**); from the 11-ketone **14** the corresponding derivatives (**16a,b**) were recovered in roughly equal yields. It is therefore evident from the examples given that the greater the size of the terminal group attached to the C-20 carbonyl the greater the stereospecificity in cyclic chlorocarbonate formation. It was later determined that where the terminal group is a proton, as in the 17β-formyl-17α-ols, phosgenation under the more mild condition B proceeds readily, obviating the need for protection of ring A. Thus such treatment of the 11-ketone **17** gave, in yields of 41 and 31%, the epimeric mobile and polar chlorocarbonates **19a** and **19b**. These compounds were identical with the deketalization products from **16a** and **16b**. Similar phosgenation of the 11-deoxy aldehyde **18** afforded an epimeric mixture (**20a,b**) which, unlike the corresponding 3-ethylene ketals, could not be separated by either fractional crystallization or column chromatography. The pure epimers **20a** and **20b** could be obtained by deketalization of **15a** and **15b**.

Scheme II

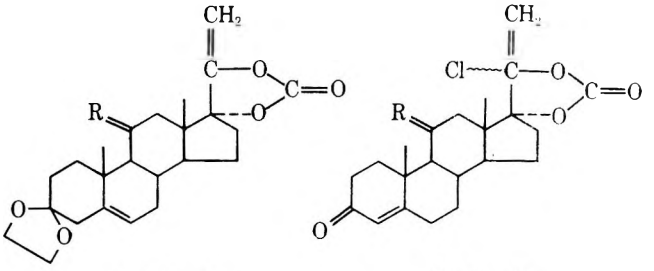


1, R = H_2; R′ = OAc
3, R = O; R′ = OAc
5, R = H_2; R′ = H
6, R = O; R′ = H

2a,b, R = H_2; R′ = OAc
4a,b, R = O; R′ = OAc
7a,b, R = H_2; R′ = H
8a,b, R = O; R′ = H

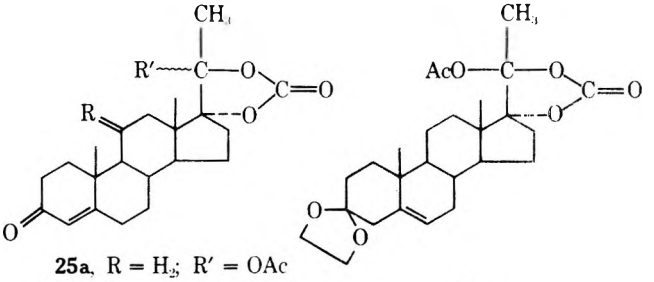


9a,b, R = H_2; R′ = OAc
10a,b, R = O; R′ = OAc
11a,b, R = H_2; R′ = H
12a,b, R = O; R′ = H
29a, R = H_2; R′ = OH
30a, R = O; R′ = OH



22, R = H_2
23, R = O

21, R = H_2
24, R = O

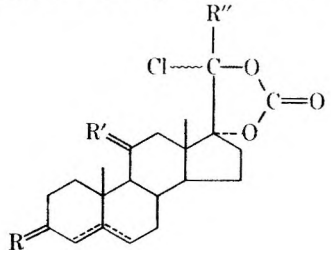


25a, R = H_2; R′ = OAc
27a,b, R = H_2; R′ = OCH_3
28a,b, R = O; R′ = OCH_3

26a

The chemical properties of the new cyclic chlorocarbonates were investigated. In the pregnene series studies were limited to the major products which on the basis of evidence given below were assigned 20β-chloro-17,20α-cyclic chlorocarbonate structures. Unlike 20ξ-chloro-20,21-cyclic chlorocarbonates, which readily undergo dehydrohalogenation during silica gel chromatography, in hot pyridine, or in acetone–sodium iodide–triethylamine,[7] the new cyclic chlorocarbonates including the 21-norpregnenes are completely unaffected by these reagents. Reaction with zinc in acetic acid was also studied since this reagent had previously been found to bring about both reductive ring opening and direct substitution of acetate for chloride at C-20 in 20ξ-

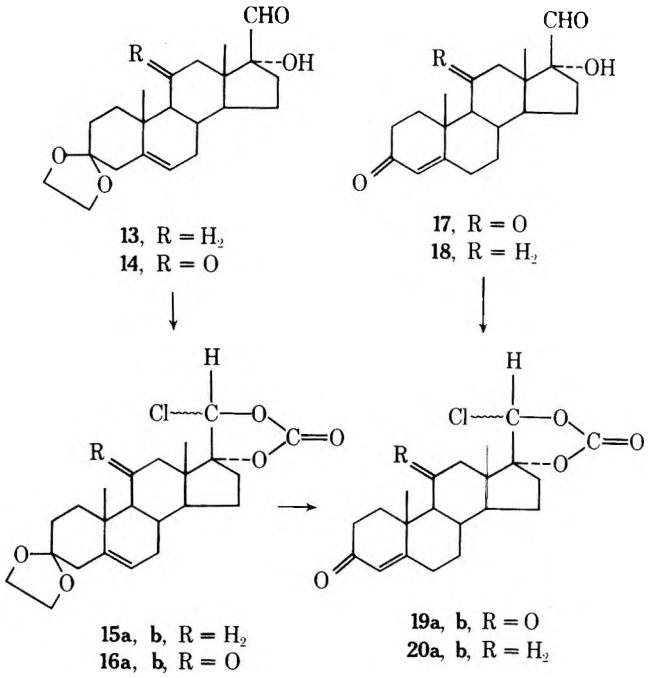
Table I
Structures and Constants of 20ξ-Chloro-17,20-cyclic Carbonates



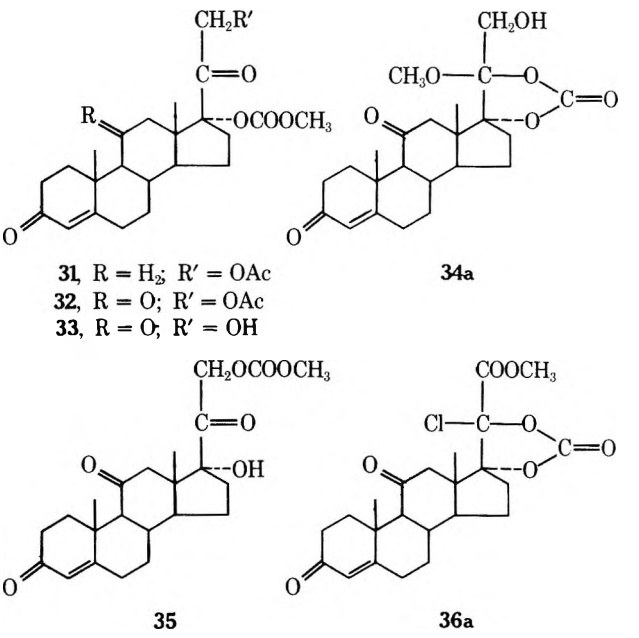
Compd	R	R′	R″	20-Cl	Mp, °C	$[\alpha]_D$, deg	λ_{max}, nm	ϵ	ν_{max}, cm^{-1}	Empirical formula	Calcd, % C	Calcd, % H	Found,[a] % C	Found,[a] % H	Yield,[b] %
2a	Δ^5-3-ketal	H_2	CH_2OAc	β	192.5–193.5	−91.0			1825, 770	$C_{26}H_{35}O_7Cl$	63.08	7.13	63.09	7.15	70
2b	Δ^5-3-ketal	H_2	CH_2OAc	α	187–188	1.19			1828, 771	$C_{26}H_{35}O_7Cl$	63.08	7.13	62.88	6.93	1.5
4a	Δ^5-3-ketal	O	CH_2OAc	β	197.5–198.5	−67.2			1830, 769	$C_{26}H_{33}O_8Cl$	61.35	6.53	61.53	6.44	73
4b	Δ^5-3-ketal	O	CH_2OAc	α	210–211	7.03			1830, 772	$C_{26}H_{33}O_8Cl$	61.35	6.53	61.54	6.53	2
7a	Δ^5-3-ketal	H_2	CH_3	β	177–179	−135			1820, 775	$C_{24}H_{33}O_5Cl$	65.96	7.61	65.90	7.50	64
8a	Δ^5-3-ketal	O	CH_3	β	177–178	−105			1834, 774	$C_{24}H_{31}O_6Cl$	63.92	6.93	63.87	6.91	78
9a	Δ^4-3-one	H_2	CH_2OAc	β	193–195	13.4	240	16700	1824, 770	$C_{24}H_{31}O_6Cl$	63.92	6.93	64.08	7.04	95
9b	Δ^4-3-one	H_2	CH_2OAc	α	195–196	127	240	16600	1830, 771	$C_{24}H_{31}O_6Cl$	63.92	6.93	64.09	6.86	88
10a	Δ^4-3-one	O	CH_2OAc	β	178–180	74.5	238	16100	1828, 770	$C_{24}H_{29}O_7Cl$	62.00	6.29	62.17	6.36	95
10b	Δ^4-3-one	O	CH_2OAc	α	209–209.5	174	238	15800	1830, 772	$C_{24}H_{29}O_7Cl$	62.00	6.29	62.21	6.35	89
11a	Δ^4-3-one	H_2	CH_3	β	167–168	−14.4	240	15400	1820, 774	$C_{22}H_{29}O_4Cl$	67.25	7.44	67.10	7.35	97
11b	Δ^4-3-one	H_2	CH_3	α	172–174	136	240	16200	1825, 775	$C_{22}H_{29}O_4Cl$	67.25	7.44	67.34	7.43	18
12a	Δ^4-3-one	O	CH_3	β	188	57.0	238	16200	1835, 772	$C_{22}H_{27}O_5Cl$	64.93	6.69	64.98	6.71	94
15a	Δ^5-3-ketal	H_2	H	β	209–212	−125			1830, 781	$C_{23}H_{31}O_5Cl$	65.31	7.38	65.21	7.41	50
15b	Δ^5-3-ketal	H_2	H	α	244–246	0.79			1830, 776	$C_{23}H_{31}O_5Cl$	65.31	7.38	65.20	7.31	20
16a	Δ^5-3-ketal	O	H	β	238–238.5	−98.5			1830, 780	$C_{23}H_{29}O_6Cl$	63.22	6.69	63.00	6.60	44
16b	Δ^5-3-ketal	O	H	α	267–269	21.8			1822, 779	$C_{23}H_{29}O_6Cl$	63.22	6.69	63.10	6.55	29
19a	Δ^4-3-one	O	H	β	267–269	73.6	238	16100	1839, 780	$C_{21}H_{25}O_5Cl$	64.20	6.41	64.33	6.43	41
19b	Δ^4-3-one	O	H	α	274–277	221	238	15700	1822, 780	$C_{21}H_{25}O_5Cl$	64.20	6.41	64.26	6.43	33
20a	Δ^4-3-one	H_2	H	β	245–247	−8.49	240	16700	1820, 780	$C_{21}H_{27}O_4Cl$	66.56	7.18	66.39	7.11	93
20b	Δ^4-3-one	H_2	H	α	254–256	138	240	16500	1822, 778	$C_{21}H_{27}O_4Cl$	66.56	7.18	66.46	7.22	95
29a	Δ^4-3-one	H_2	CH_2OH	β	182–183 dec	5.06	241	16200	1825, 771	$C_{22}H_{29}O_5Cl$	64.62	7.15	64.83	7.19	
30a	Δ^4-3-one	O	CH_2OH	β	205–207	82.8	238	15500	1828, 767	$C_{22}H_{27}O_6Cl$	62.48	6.44	62.59	6.47	
36a	Δ^4-3-one	O	$COOCH_3$	β	214–215	62.1	238	15500	1835, 785	$C_{23}H_{27}O_7Cl$	61.26	6.04	61.12	5.97	

[a] Chlorine analyses for compounds **2a**, **2b**, **4a**, **4b**, **7a**, **8a**, **11b**, **15a**, **15b**, **16a**, **16b**, **19a**, and **19b** were in close agreement with the calculated values. [b] Yields of **9a**, **9b**, **10a**, **10b**, **11a**, **12a**, and **20b** represent recovery from the corresponding Δ^5-3-ketals after treatment with acetone–*p*-TSA.

Scheme III



Scheme IV



chloro-20,21-cyclic carbonates.[3] Treatment of the 11-deoxy-21-acetate **9a** for 3.5 hr on a high-speed rotary shaker at room temperature resulted in nearly complete conversion of substrate to a single more mobile uv-positive product as well as a number of very mobile uv-negative substances. The latter products presumably arise from reduction in ring A. Fractional crystallization and column chromatography afforded in 38% yield a Beilstein-negative, five membered ring cyclic carbonate with new olefinic bands in the infrared at 3145 and 1685 cm^{-1}. Similar treatment of the 3-ethylene ketal **2a** furnished the corresponding unsaturated cyclic carbonate in 36% yield as well as 11-deoxycorticosterone acetate 3-ethylene ketal (11%). The identity of the dehydrohalogenation products as the $\Delta^{20,21}$-17,20-cyclic carbonates **21** and **22** was confirmed by NMR spectroscopy, which demonstrated an unusually large geminal coupling constant (3.8–3.9 Hz) for the terminal methylene protons. Published examples[8] lie in a range of from 0 to 3 Hz with values of 1.0–2.0 Hz being the most common. Since the coupling constant is related to the magnitude of the H–C–H bond angle, it must be concluded that this angle is considerably displaced in 17,20-cyclic carbonates.[9] Reaction of the 11-ketone **4a** with zinc in acetic acid afforded the $\Delta^{20,21}$-17,20-cyclic carbonate **23** in 39% yield. Deketalization of **23** with acetone–*p*-TSA gave the Δ^4-3-one **24** in 87% yield.

The reaction of C-21-unsubstituted cyclic chlorocarbonates with zinc in acetic acid was found to be slower and more complex. Treatment of the 17-hydroxyprogesterone derivative **11a** for 6 hr provided in low yields progesterone, 17-hydroxyprogesterone, and the $\Delta^{20,21}$-17,20-cyclic carbonate **21.** Infrared analysis of the Beilstein-negative major product (30%) showed retention of the cyclic carbonate ring and generation of new bands at 1760 and 1240 cm^{-1}. On the basis of these properties and functional group analysis, which indicated the presence of one acetyl group, the product was formulated as the 20β-acetyl-17,20α-cyclic carbonate **25a.** When the reaction was applied to the chlorocarbonate 3-ketal **7a,** the 20β-acetate **26a** was obtained only as a minor product (11%). The major product (54%) was progesterone 3-ethylene ketal. This quantitative difference between the reaction mixtures obtained from cyclic chlorocarbonates differing only in ring A substituents suggests the operation of long-range effects. Similar effects were also evident when the 11-ketone **8a** was treated with zinc in acetic acid. The major component of the reaction mixture was starting material (74%), and the only isolable product was 11-ketoprogesterone 3-ethylene ketal (13%). It was also found that despite minimal steric hindrance the corresponding 21-norpregnenes **19a** and **19b** were not affected by zinc in acetic acid.

In the course of these studies it was noted that some cyclic chlorocarbonates were adversely affected in hot methanol. In confirmation, prolonged refluxing of the C-21-unsubstituted derivatives in this solvent resulted in their complete conversion to Beilstein-negative products. A minor product (22%) in the reaction of the 11-deoxy compound **11a** is the $\Delta^{20,21}$-17,20-cyclic carbonate **21.** The major components (78%) were shown by NMR analysis to be an epimeric mixture of 20-methoxy-17,20-cyclic carbonates (**27a,b**). Repeated crystallization permitted recovery of pure **27b** in a yield of 58%. Similar reaction of the 11-keto chlorocarbonate **12a** furnished a more complex mixture from which the pure 20-methoxy-17,20-cyclic carbonates **28a** and **28b** could be isolated in modest yields. Unlike their C-21-unsubstituted counterparts, the 21-acetates **9a** and **10a** were unaffected by refluxing methanol as were the aldehyde derivatives **19a,b** and **20a,b.**

The unusual stability to acidic reagents of linear and cyclic carbonate bonds illustrated in earlier papers was exemplified in the present study by acid hydrolysis of the 21-acetates **9a** and **10a** to the corresponding 21-ols **29a** and **30a** in yields of 62 and 63%, respectively. Following acetylation of the mother liquors a significant by-product could be isolated in each case. Because both camylate (*O*-carbomethoxy) and acetate bands were present in their infrared spectra, the substances were formulated as the 17-camylates **31** and **32** (Scheme IV). Acid hydrolysis of the 11-ketone **32** afforded the 17-camylate-21-ol **33,** the structure of which was established by reacetylation to **32.** The availability of **32** and **33** made possible the testing of an hypothesis presented in an earlier publication[10] relating to the mechanism responsible for conversion in refluxing methanol of cortisone 17,21-cyclic carbonate to the 20β-methoxy-17,20α-cyclic carbonate **34a.** Cyclization to **34a** was believed to proceed via the 17-camylate **33** by a four center type mechanism. However, this assumption was not con-

Table II
MD Contributions of 20-Substituted 17,20-Cyclic Carbonates

Compd	Ring A (B)	C-11	C-20	Terminal group	MD 20α	MD 20β	$MD^{\alpha-\beta}$
15a,b	Δ⁵-3-ketal	H_2	Cl	H	−529	+3	−532
20a,b	Δ⁴-3-one	H_2	Cl	H	−32	+523	−555
16a,b	Δ⁵-3-ketal	O	Cl	H	−430	+95	−525
19a,b	Δ⁴-3-one	O	Cl	H	+290	+870	−580
7a	Δ⁵-3-ketal	H_2	Cl (β)	CH_3	−590		
11a,b	Δ⁴-3-one	H_2	Cl	CH_3	−57	+535	−592
8a	Δ⁵-3-ketal	O	Cl (β)	CH_3	−474		
12a	Δ⁴-3-one	O	Cl (β)	CH_3	−232		
2a,b	Δ⁵-3-ketal	H_2	Cl	CH_2OAc	−450	+6	−456
9a,b	Δ⁴-3-one	H_2	Cl	CH_2OAc	+61	+574	−513
29a	Δ⁴-3-one	H_2	Cl (β)	CH_2OH	+21		
4a,b	Δ⁵-3-ketal	O	Cl	CH_2OAc	−342	+36	−378
10a,b	Δ⁴-3-one	O	Cl	CH_2OAc	+346	+810	−464
30a	Δ⁴-3-one	O	Cl (β)	CH_2OH	+350		
26a	Δ⁵-3-ketal	H_2	AcO (β)	CH_3	−81		
25a	Δ⁴-3-one	H_2	AcO (β)	CH_3	+421		
27b	Δ⁴-3-one	H_2	CH_3O (α)	CH_3		+450	
28a,b	Δ⁴-3-one	O	CH_3O	CH_3	+281	+728	−447
36a	Δ⁴-3-one	O	Cl (β)	$COOCH_3$	+280		
Ref 9	Δ⁴-3-one	O	CH_3O (β)	CH_2OH	+376		
	Δ⁴-3-one	O	CH_3O (β)	CH_2OAc	+389		
	Δ⁴-3-one	O	CH_3O (β)	COOH	+441		
	Δ⁴-3-one	O	CH_3O (β)	$COOCH_3$	+509		

firmed experimentally since the 21-acetate **32** was not affected by refluxing methanol and the 21-ol **33** underwent transcamylation to the known 21-*O*-carbomethoxy derivative **35**. It therefore follows that methoxy cyclic carbonate formation must proceed by a more concerted mechanism.

Resistance of the 17,20-cyclic chlorocarbonate ring to strong oxidizing agents was demonstrated by conversion of the 21-ol **30a** with chromic anhydride in acetic acid to the 21-oic acid. Treatment of the crude acidic fraction with diazomethane followed by column chromatography gave the methyl ester **36a** in low yield.

Configurational assignments at C-20 for the new pairs of cyclic chlorocarbonates were based chiefly on their optical rotatory properties. As shown in Table II, the major, polar epimers are considerably more levorotatory than their minor, mobile counterparts. The MD differences ($\alpha-\beta$ −378 to −592 units) are of the same order of magnitude previously noted[11] for cyclic carbonates derived from 17,20-diols ($\alpha-\beta$ −283 to −430 units). The absolute values of the appropriate major, polar products are also in general agreement with those of the 20β-methoxy-17,20α-cyclic carbonates derived from cortisone 17,21-cyclic carbonate.[10] For these reasons the major, polar products and their halogen-free derivatives have been assigned a 17,20α-cyclocarbonyldioxy configuration, and the minor, mobile epimers accordingly are formulated as 17,20β-cyclic carbonates.

Additional, although limited, support for these configurational assignments was also obtained from the NMR data. Marked deshielding of 18-CH_3 signals (approximately δ 1.0) was evident for both epimeric cyclic chlorocarbonates, indicating the presence of a strongly perturbing side-chain substituent. However, a significant downfield shift of the C-12 protons from the C–H envelope was noted only in the case of 20β-chloro-17,20α-cyclic carbonates. This effect is most likely due to the greater proximity to ring C of the substituent at C-21 in 17,20α-cyclic carbonates as is readily apparent from inspection of Dreiding models.

Experimental Section

General experimental procedures are detailed in a previous paper.[10] Unless otherwise indicated column chromatography was carried out on silica gel with appropriate mixtures of isooctane and ethyl acetate. Phosgenation under condition C: to a solution of steroid (400 mg) in pyridine (5 ml) and methylene chloride (20 ml) was added a 12.5% solution of phosgene in benzene (2 ml). After 4 hr at room temperature ice and additional methylene chloride (20 ml) were added. The solution was washed successively with cold, dilute hydrochloric acid and water, filtered through anhydrous sodium sulfate, and concentrated to dryness in vacuo.

Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-5-en-3-one 3-Ethylene Ketal (2a) with Zinc in Acetic Acid. To a solution of the chlorocarbonate (600 mg) in 3:1 acetic acid–methylene chloride (24 ml) was added 1200 mg of powdered zinc. The mixture was agitated on a high-speed rotary shaker for 6 hr. The insoluble material was filtered off and washed with methylene chloride. The filtrates were combined and washed successively with cold, dilute sodium hydroxide and water. The reaction mixture was chromatographed on a silica gel column. Crystallization of the mobile product from ethyl acetate furnished 173 mg of **17,20-cyclocarbonyldioxypregna-5,20(21)-dien-3-one 3-ethylene ketal (22)** as prisms: mp 232–233°; $[\alpha]D$ 21.4°; ν_{max} 3149, 1835 (1815), 1682, and 772 ($\Delta^{20,21}$-17,20-cyclic carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.84; H, 8.06.

The polar product crystallized from ethyl acetate as prisms (57 mg, 11%): mp 205–208°. The infrared spectrum was identical with that of **11-deoxycorticosterone acetate 3-ethylene ketal.**

Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-4-en-3-one (9a) with Zinc in Acetic Acid. Treatment of the chlorocarbonate (300 mg) in 12 ml of 3:1 acetic acid–methylene chloride with 600 mg of powded zinc was carried out for 3.5 hr as in the reaction of **2a.** Direct crystallization and silica gel column chromatography provided **17,20-cyclocarbonyldioxypregna-4,20(21)-dien-3-one (21)** in a total yield of 88 mg: mp 177–178°; λ_{max} 240 nm (ε 17200); ν_{max} 3145, 1820, 1685 (sh), and 771 cm^{-1} ($\Delta^{20,21}$-cyclic carbonate); NMR δ 9.11 (s, 3, 18-CH_3), 8.80 (s, 3, 19-CH_3), 5.59, 5.04 (d, 2, J = 3.8 Hz, 21-CH_2=).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.12; H, 7.91. Found: C, 74.33; H, 7.98.

17,20-Cyclocarbonyldioxypregna-5,20(21)-diene-3,11-dione 3-Ethylene Ketal (23) from 4a. Treatment of 17,20α-cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-5-ene-3,11-dione 3-ethylene ketal (600 mg) with zinc in acetic acid was carried out as in the preparation of **22.** Silica gel chromatography and crystallization from ethyl acetate–isooctane gave 215 mg of prisms: mp 178–179°; $[\alpha]D$ 49.0°; ν_{max} 3150, 1830, 1682, and 770 ($\Delta^{20,21}$-cyclic carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.43; H, 7.39.

Treatment of **23** (50 mg) with acetone–*p*-TSA in the usual manner furnished **17,20-cyclocarbonyldioxypregna-4,20(21)-diene-3,11-dione (24)** as prisms (39 mg) from ethyl acetate: mp 232–

234°; [α]D 256°; λ_{max} 237 nm (ε 15900); ν_{max} 3149, 1820, and 760 ($\Delta^{20,21}$-cyclic carbonate), 1705 cm^{-1} (11-ketone); NMR δ 9.14 (s, 3, 18-CH_3), 8.58 (s, 3, 19-CH_3), 7.66, 7.43 (d, 2, J = 15 Hz, 12-CH_2), 5.57, 4.97 (d, 2, J = 3.9 Hz, 21-CH_2=).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.19; H, 7.19.

Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloropregn-4-en-3-one (11a) with Zinc in Acetic Acid. Treatment of the chlorocarbonate (300 mg) for 6 hr as in the reaction of **2a** followed by chromatography of the reaction mixture gave a number of identifiable products. The most mobile component (8.2 mg) crystallized from ethanol as prisms, mp 127–129°. It was identical in all respects with a reference sample of **progesterone.** The next more mobile component was obtained as needles (3.3 mg) from acetone–*n*-hexane, mp 185–187°. The infrared spectrum was identical with that of the $\Delta^{20,21}$-cyclic carbonate **21.** From the succeeding fraction was obtained 33 mg of material which was shown by infrared analysis to be a mixture of 17-hydroxyprogesterone and starting material. The last and major fraction furnished **17,20α-cyclocarbonyldioxy-20β-acetoxypregn-4-en-3-one (25a)** as prisms (94 mg) from ethyl acetate: mp 185–187°; [α]D 101°; λ_{max} 239 nm (ε 16900); ν_{max} 1820 and 780 (cyclic carbonate), 1760 and 1230 cm^{-1} (acetate); NMR δ 8.97 (s, 3, 18-CH_3), 8.82 (s, 3, 19-CH_3), 8.01 (s, 3, CH_3CO), 7.92 (s, 3, 21-CH_3).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75; CH_3CO, 10.33. Found: C, 69.16; H, 7.68; CH_3CO, 10.01.

Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloropregn-5-en-3-one 3-Ethylene Ketal (7a) with Zinc in Acetic Acid. Treatment of the chlorocarbonate ketal (500 mg) for 5 hr as in the reaction of **2a** was followed by chromatography. The mobile product, **pregn-5-ene-3,20-dione 3-ethylene ketal,** crystallized from ethyl acetate–*n*-hexane as long needles (160 mg, mp 171.5–173.5°; 60 mg, mp 170.5–172°) in a yield of 54%. Deketalization of a sample in acetone–*p*-TSA afforded prisms (acetone–*n*-hexane), mp 128–130°, which were identical in all respects with a reference sample of **progesterone.**

Crystallization of the polar fraction from ethyl acetate gave **17,20α-cyclocarbonyldioxy-20β-acetoxypregn-5-en-3-one 3-ethylene ketal (26a)** as rosettes (60 mg, mp 166–169°): [α]D −17.6°; ν_{max} 1822 and 779 (cyclic carbonate), 1765 and 1230 (acetate), 1103 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.58; H, 8.00.

Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloropregn-4-en-3-one (11a) with Refluxing Methanol. A solution of the chlorocarbonate (300 mg) in methanol (30 ml) containing 0.8 ml of pyridine was refluxed for 4 hr. The residue was chromatographed on a silica gel column. From the mobile fraction was obtained 59 mg (22%) of the $\Delta^{20,21}$-cyclic carbonate **21,** mp 191–193°. The crude polar fraction (230 mg, 78%) was shown by NMR to be an epimeric mixture of 20-methoxy-17,20-cyclic carbonates **(27a,b).** Several crystallizations from methanol furnished pure **27b** (173 mg) as plates: mp 232–235°; [α]D 116°; λ_{max} 240 nm (ε 16900); ν_{max} 1805 and 780 (cyclic carbonate), 1290 cm^{-1} (methoxyl); NMR δ 9.08 (s, 3, 18-CH_3), 8.82 (s, 3, 19-CH_3), 8.34 (s, 3, 21-CH_3), 6.56 (s, 3, 20α-CH_3O).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; CH_3O, 7.99. Found: C, 71.23; H, 8.38; CH_3O, 8.08.

NMR for **27a** component: δ 9.10 (s, 3, 18-CH_3), 8.82 (s, 3, 19-CH_3), 8.38 (s, 3, 21-CH_3), 6.61 (s, 3, 20β-CH_3O).

Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloropregn-4-ene-3,11-dione (12a) with Refluxing Methanol. The chlorocarbonate (300 mg) was treated for 22 hr as in the reaction of **11a.** The residue was chromatographed on a silica gel column. Crystallization of the mobile fraction (250 mg) from ethyl acetate–isooctane gave 105 mg of **17,20β-cyclocarbonyldioxy-20α-methoxypregn-4-ene-3,11-dione (28b)** as needles: mp 188–191°; [α]D 181°; λ_{max} 238 nm (ε 15800); ν_{max} 1800 and 780 (cyclic carbonate), 1290 (methoxyl), 1702 cm^{-1} (11-ketone); NMR δ 9.12 (s, 3, 18-CH_3), 8.59 (s, 3, 19-CH_3), 8.36 (s, 3, 21-CH_3), 6.54 (s, 3, 20α-CH_3O).

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; CH_3O, 7.71. Found: C, 68.80; H, 7.65; CH_3O, 7.51.

From the polar fraction (50 mg) was obtained 21 mg of **17,20α-cyclocarbonyldioxy-20β-methoxypregn-4-ene-3,11-dione (28a)** as platelets from methanol: mp 250–253°; [α]D 70.0°; λ_{max} 238 nm (ε 15900); ν_{max} 1802 and 780 (cyclic carbonate), 1290 (methoxyl), 1705 cm^{-1} (11-ketone); NMR δ 9.13 (s, 3, 18-CH_3), 8.60 (s, 3, 19-CH_3), 8.38 (s, 3, 21-CH_3), 6.60 (s, 3, 20β-CH_3O).

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; CH_3O, 7.71. Found: C, 68.84; H, 7.45; CH_3O, 7.42.

Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-4-en-3-one (9a) with Methanolic Hydrochloric Acid. To a solution of the chlorocarbonate (1 g) in methylene chloride (50 ml) and methanol (850 ml) was added (without external cooling) water (100 ml) and concentrated hydrochloric acid (200 ml). After 2.5 hr at room temperature methylene chloride (750 ml) was added, and the organic layer was washed successively with cold, dilute sodium hydroxide and water, then concentrated to dryness. Several crystallizations from ethyl acetate provided 560 mg of **17,20α-cyclocarbonyldioxy-20β-chloro-21-hydroxypregn-4-en-3-one (29a)** as rosettes: mp 182–183° dec; [α]D 5.06°; λ_{max} 241 nm (ε 16200); ν_{max} 3440 (hydroxyl), 1825 and 771 cm^{-1} (cyclic chlorocarbonate).

Anal. Calcd for $C_{22}H_{29}O_5Cl$: C, 64.62; H, 7.15. Found: C, 64.83; H, 7.19.

The mother liquor residue was treated with excess acetic anhydride–pyridine for 18 hr. Silica gel chromatography of the reaction mixture resulted in partial separation of two components. From the earlier fractions was obtained 10 mg of **17-*O*-carbomethoxy-21-acetoxypregn-4-ene-3,20-dione (31)** as platelets from methanol: mp 220–222°; [α]D 90.6°; λ_{max} 241 nm (ε 15800); ν_{max} 1750, 1292, and 792 (camylate), 1745 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.18; H, 7.59.

Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-4-ene-3,11-dione (10a) with Methanolic Hydrochloric Acid. Treatment of the chlorocarbonate (1.5 g) in methylene chloride (75 ml) and methanol (1500 ml) with water (150 ml) and concentrated hydrochloric acid (300 ml) for 2.5 hr was carried out as in the reaction of **9a.** Successive crystallizations from ethyl acetate and methanol gave 1710 mg of **17,20α-cyclocarbonyldioxy-20β-chloro-21-hydroxypregn-4-ene-3,11-dione (30a)** as rosettes: mp 205–207°; [α]D 82.8°; λ_{max} 238 nm (ε 15500); ν_{max} 3440 (hydroxyl), 1828 and 767 (cyclic chlorocarbonate), 1705 cm^{-1} (11-ketone).

Anal. Calcd for $C_{22}H_{27}O_6Cl$: C, 62.48; H, 6.44. Found: C, 62.59; H, 6.47.

Treatment of **30a** with acetic anhydride–pyridine afforded a product identical in all respects with starting material **(10a).**

Acetylation of the mother liquor residue from **30a** and two crystallizations of the product from methanol furnished 500 mg (24%) of **17-*O*-carbomethoxy-21-acetoxypregn-4-ene-3,11,20-trione (32)** as needles: mp 234–236°; [α]D 148°; λ_{max} 238 nm (ε 15500); ν_{max} 1745, 1290, and 790 (camylate), 1745 and 1232 (acetate), 1710 (sh), and 1705 cm^{-1} (11- and 20-ketone).

Anal. Calcd for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01; CH_3O, 6.74. Found: C, 65.44; H, 7.11; CH_3O, 6.59.

Treatment of the 21-acetate **32** (200 mg) in methylene chloride (5 ml) and methanol (85 ml) with water (10 ml) and concentrated hydrochloric acid (20 ml) for 4 hr was followed by the usual workup. The reaction mixture was chromatographed on a Celite column (30% impregnation) in chloroform–isooctane–formamide (500:500:30). From the mobile fraction was obtained 135 mg (74%) of **17-*O*-carbomethoxy-21-hydroxypregn-4-ene-3,11,20-trione (33)** as an amorphous foam: [α]D 123°; ν_{max} 3450 (hydroxyl), 1745, 1295, and 793 (camylate), 1708 cm^{-1} (11- and 20-ketone). From the polar fraction was recovered 30 mg (16%) of **21-*O*-carbomethoxy-17-hydroxypregn-4-ene-3,11,20-trione (35)** as needles from methanol, mp 222–224°. A mixture melting point with a reference sample[10] showed no depression and their ir spectra were identical.

35 from 33. A sample (10 mg) of the 17-*O*-camylate was refluxed in methanol for 18 hr. Concentration of the solution gave 8 mg of prismatic needles, mp 224–225°, identical in all respects with the 21-*O*-camylate **35.**

Methyl 17,20α-Cyclocarbonyldioxy-20β-chloro-3,11-dioxopregn-4-en-21-oate (36a) from 30a. To a solution of 17,20α-cyclocarbonyldioxy-20β-chloro-21-hydroxypregn-4-ene-3,11-dione (106 mg, 0.25 mmol) in acetic acid (4.75 ml) was added 100 mg (1 mmol) of chromic anhydride in water (0.25 ml). After 4 days at room temperature the solvent was evaporated and the residue was partitioned between ethyl acetate and dilute sodium bicarbonate solution. Acidification of the aqueous layer with hydrochloric acid and extraction with ethyl acetate furnished the crude acidic fraction (68 mg). Successive treatment with excess diazomethane and silica gel column chromatography gave the methyl ester **36a** (19 mg) as leaflets from methanol: mp 214–215°; [α]D 62.1°; λ 238 nm (ε 15500); ν_{max} 1835 and 785 (cyclic chlorocarbonate), 1765 and 1285 (carbomethoxy), 1710 cm^{-1} (11-ketone); NMR δ 8.91 (s, 3, 18-CH_3), 8.58 (s, 3, 19-CH_3), 7.16, 6.99 (d, 2, J = 14 Hz, 12-CH_2), 6.05 (s, 3, CH_3O).

Anal. Calcd for $C_{23}H_{27}O_7Cl$: C, 61.26; H, 6.04. Found: C, 61.12; H, 5.97.

Registry No.—**2a**, 57015-41-5; **2b**, 57015-42-6; **4a**, 57015-43-7; **4b**, 57015-44-8; **7a**, 57015-45-9; **8a**, 57015-46-0; **9a**, 57015-47-1; **9b**, 57015-48-2; **10a**, 57015-49-3; **10b**, 57015-50-6; **11a**, 57015-51-7; **11b**, 57015-52-8; **12a**, 57015-53-9; **15a**, 57015-54-0; **15b**, 57015-55-1; **16a**, 57015-56-2; **16b**, 57015-57-3; **19a**, 57015-58-4; **19b**, 57015-59-5; **20a**, 57015-60-8; **20b**, 57015-61-9; **21**, 57015-62-0; **22**, 57015-63-1; **23**, 57015-64-2; **24**, 57015-65-3; **25a**, 57015-66-4; **26a**, 57031-28-4; **27a**, 57015-67-5; **27b**, 57015-68-6; **28a**, 57015-69-7; **28b**, 57015-70-0; **29a**, 57015-71-1; **30a**, 57015-72-2; **31**, 57015-73-3; **32**, 57015-74-4; **33**, 57015-75-5; **35**, 36623-21-9; **36a**, 57015-76-6; phosgene, 75-44-5.

References and Notes

(1) This research was supported wholly by a grant, AM 01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U.S. Public Health Service. We are grateful to this Institute for its continued and generous support of our work.

(2) Address correspondence to Department of Medicine, Crozer-Chester Medical Center, Chester, Pa. 19013.

(3) M. L. Lewbart, *J. Org. Chem.*, **38**, 2328 (1973).

(4) The preparation of this previously undescribed monoketal was made possible by our observation that the presence of a 17α-acetoxy group prevents ketalization at C-20. Thus treatment of 17α-acetoxypregn-4-ene-3,20-dione (5.0 g) in benzene (250 ml) and ethylene glycol (40 ml) with *p*-TSA (150 mg) for 8 hr by the Bernstein procedure gave 5.2 g (93%) of leaflets from ethyl acetate: mp 230–233°; $[\alpha]D$ −17.4°. Reported[5] for **17-acetoxypregn-5-ene-3,20-dione 3-ethylene ketal:** mp 241–243°; $[\alpha]D$ −62° (chloroform). Saponification of the acetoxy ketal (4.16 g) in a mixture of methylene chloride (100 ml) and methanol (250 ml) with aqueous 1 *N* sodium hydroxide (50 ml) was carried out for 2 hr on a steam bath. The product crystallized spontaneously from the concentrated solution. Recrystallization of the crude material from ethyl acetate afforded **17-hydroxypregn-5-ene-3,20-dione 3-ethylene ketal** as leaflets in a total yield of 2.54 g (68%): mp 244–246°; $[\alpha]D$ −58.9°; ν_{max} 3490 (hydroxyl), 1705 (sh), 1695 (20-ketone), 1100 cm^{-1} (ketal). Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.91; H, 9.26. Deketalization of the saponification product in acetone–*p*-TSA gave a product identical in all respects with **17-hydroxyprogesterone.**

(5) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson, and J. A. Campbell, *Chem. Ind. (London)*, 1002 (1958).

(6) As far as we are aware the monoketal **6** has not been described previously. The reaction sequence, as in the preparation of the 11-deoxy analogue **5**, follows. Forced acetylation of 21-deoxycortisone (3.0 g) in acetic acid (120 ml) and acetic anhydride (24 ml) in the presence of *p*-TSA (2.4 g) was carried out for 1.25 hr at room temperature. The crude product, recovered in the usual manner, was chromatographed on a silica gel column. Crystallization of the mobile component from methanol gave 800 mg (21%) of **3,17-diacetoxypregna-3,5-diene-11,20-dione** as prisms: mp 163–165°; $[\alpha]D$ −79.5°; λ_{max} 234 nm (ϵ 19500); ν_{max} 1735, 1250, and 1220 (acetate), 1706 (11- and 20-ketone), 1671 and 1638 cm^{-1} ($\Delta^{3,5}$). Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53; CH_3CO, 20.09. Found: C, 69.90; H, 7.64; CH_3CO, 19.45. Crystallization of the major, polar fraction from methanol furnished 2.0 g (59%) of **17-acetoxypregn-4-ene-3,11,20-trione** as platelets: mp 205–207°; $[\alpha]D$ 143°; λ_{max} 238 nm (ϵ 16100); ν_{max} 1733 and 1255 (acetate), 1710 cm^{-1} (11- and 20-ketone). Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; CH_3CO, 11.14. Found: C, 71.38; H, 7.86; CH_3CO, 10.70. Ketalization of the 17-acetate by the Bernstein procedure afforded **17-acetoxypregn-5-ene-3,11,20-trione 3-ethylene ketal** (75% yield) in the form of prisms from ethyl acetate: mp 207–211°; $[\alpha]D$ 0.85°; ν_{max} 1733 and 1255 (acetate), 1705 (11- and 20-ketone), 1100 cm^{-1} (ketal). Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.64; H, 7.96. Saponification of the acetoxy ketal as in the preparation of the 11-deoxy analogue afforded in 41% yield **17-hydroxypregn-5-ene-3,11,20-trione 3-ethylene ketal (6)** as prisms from ethyl acetate: mp 208–212°; $[\alpha]D$ −41.4°; ν_{max} 3460 (hydroxyl), 1705 (11- and 20-ketone), 1098 cm^{-1} (ketal). Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.88; H, 8.34.

(7) M. L. Lewbart, *J. Org. Chem.*, **38**, 2335 (1973).

(8) N. S. Bhacca and D. H. Williams, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 57.

(9) The author is deeply indebted to Dr. Byron Arison of the Merck Institute for the determination and interpretation of all NMR spectra included in this paper.

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Nucleosides. XCIV. Synthesis of Some C Nucleosides by 1,3-Dipolar Cycloadditions to 3-(Ribofuranosyl) Propiolates[1]

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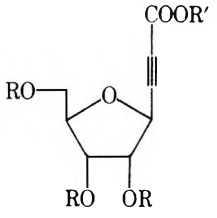
Condensation of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl chloride (**3**) with the silver acetylide of methyl (or ethyl) propiolate **4a** (or **4b**) gives fair yields of the β-D-ribofuranosyl propiolate **5a** (or **5b**). 1,3-Dipolar cycloaddition of **5a** with trimethylsilyl azide gives directly the deblocked 1,2,3-triazole ester **7** which on treatment with methanolic ammonia affords amide **8**. 1,3-Dipolar cycloaddition of **5a** (or **5b**) with diazomethane gives the fully blocked 4-ribosylated pyrazole ester **9a** (or **9b**) in good yields along with the *N*-methyl derivative **10a** (or **10b**). Compound **9a** (or **9b**) can be readily deblocked to the corresponding 4-ribosylpyrazole ester **13a** (or **13b**) or treated with ammonia to give the blocked pyrazole amide **11**. A similar cycloaddition reaction of **5a** with ethyl diazoacetate (**15**) affords the 4-ribofuranosylpyrazole-3,5-dicarboxylate **16** as the major product and some 3-ribofuranosylpyrazole-4,5-dicarboxylate **17**. These two products have been unequivocally identified by comparing them with the products (**16** and **19**) obtained from the cycloaddition reaction of **5b** with methyl diazoacetate (**18**).

A relatively new group of naturally occurring nucleosides[2] exhibiting important biological activities has been isolated recently. They are the C-nucleoside antibiotics formycin, formycin B, showdomycin, and pyrazomycin. Also belonging to this class of compounds is the most recently isolated oxazinomycin,[3] a close analogue of pseudouridine.[4] All, except pseudouridine, possess antibiotic properties and many exhibit anticancer and antiviral activities. These biological properties, together with their unique structural feature (a C–C linkage between the heterocycle and the sugar), have elicited many efforts directed toward the synthesis of such compounds or analogues thereof.

The methods described for the synthesis of C nucleosides can be classified into three general types. The first involves the conversion of some available C nucleosides to prepare new ones. 6-Azapseudouridine, for example, has been synthesized[5] from pseudouridine. Oxazinomycin has been converted to pseudouridine[3c] and formycin has been obtained from formycin B.[6] The second approach, direct condensation of suitably blocked sugar derivatives with appropriate heterocyclic bases (usually as metalated derivatives), has been utilized for the preparation of pseudouridine[7] or some of its sugar analogues,[8] 5-ribosylcytosine[9] and 1-deazauridine.[10] The third and most fruitful approach to date has been the multistep elaboration of the desired heterocycle

from a C-glycosyl derivative functionalized at the $C_{1'}$ substituent. By this general method showdomycin,[11] formycin B,[12] oxoformycin,[13] and pyrazomycin[14] were prepared. One type of *C*-glycosyl derivative which has received much attention recently is represented by the *C*-glycosyl acetylenes,[15-20] some of which have been utilized to prepare simple triazole,[15a,18] pyrazole,[20] and isoxazole[19] C nucleosides via 1,3-dipolar cycloaddition reactions to the triple bond.[21]

Synthesis of Ribofuranosyl Acetylenic Esters. We have investigated the synthesis of ribosyl acetylenic derivatives such as 1 because (1) acetylenic esters are more reac-



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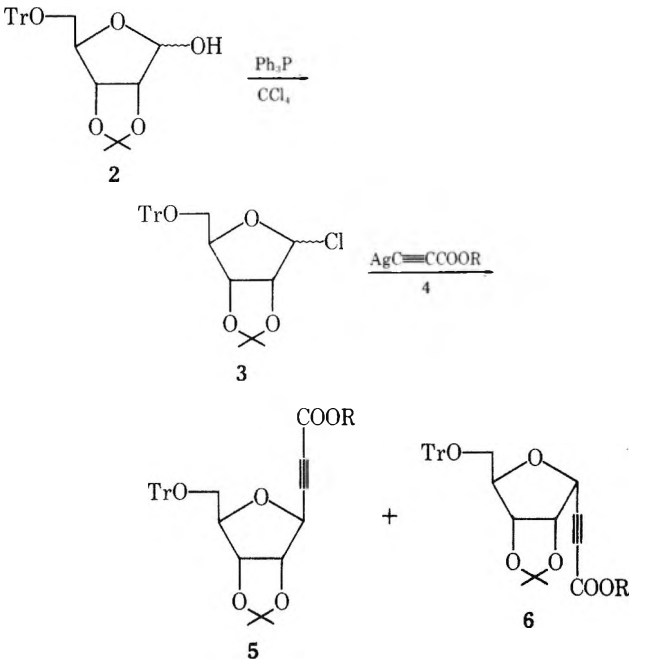
tive to 1,3-dipolar cycloaddition reactions than ordinary alkynes[21] and (2) they can also be used as intermediates for the elaboration of six-membered heterocycles via reaction of the two electrophilic sites (acyl function and β carbon) with reagents containing the amidino or ureido function,[22] or for the synthesis of five-membered heterocycles with reagents such as hydrazine[23] or hydroxylamine.[24]

Most methods described to prepare glycosyl acetylenes have used the reaction of a suitably blocked sugar[15,17] or a glycosyl halide[16,20] with an acetylene Grignard reagent[25] and therefore such methods were not immediately applicable to the synthesis of the ester 1. As an alternate approach, the reaction of a suitably protected halogenose with the silver acetylide of an alkyl propiolate[26] was considered. The potential utility of readily available halogenoses such as the tri-*O*-acyl D-ribofuranosyl halides seemed doubtful in view of the known propensity of sugar halides bearing participating acyl groups at C-2 to give 1,2-ketal derivatives upon reaction with organometallic compounds.[10,27,28] This view was recently confirmed by a report from Albrecht, Repke, and Moffatt,[29] who have obtained 3,5-di-*O*-benzoyl-1,2-*O*-[α-(2-carbomethoxyethynyl)benzylidene]-α-D-ribofuranose as a major product of the reaction of tri-*O*-benzoyl-D-ribofuranosyl bromide with the silver derivative of methyl propiolate. The recently synthesized 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (**3**),[30] on the other hand, appeared to be a promising candidate for this type of reaction.

Condensation of the silver acetylide of ethyl propiolate (**4b**, Chart I) with the crystalline 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (β anomer of **3**) afforded an "anomeric"[31a] mixture of ethyl 3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)propiolates (**5b** and **6b**).[31b,32] After ready separation by dry column chromatography, the faster moving β anomer **5b** was isolated as a syrup while the slower moving α anomer was obtained in crystalline form (**5b**/**6b** ~ 3, by weight). The assignment of anomeric configurations was based on the following ^{1}H NMR data: (a) The chemical shift of H-1′ for **5b** is smaller (δ 4.76) than that for **6b** (δ 5.18). This consistent relationship between the chemical shift of H-1′ of a pair of anomers has been utilized previously to assign the configuration at C-1′ to nucleosides[33] and C glycosides.[34] (b) The $J_{1',2'}$ value in **5b** is smaller (2.8 Hz) than that in **6b** (4.7 Hz). Although not conclusive, the difference in coupling constants for these two fairly rigid 2,3-*O*-isopropylidenated ribofuranosyl systems supports the assignments made. (c) The ^{1}H NMR spectra of *all* C nucleosides (**9b**, **10b**, **11**, **16**, and **19**)

Chart I



For compounds 4, 5, and 6: a, R = Me; b, R = Et

derived from **5b** (vide infra) exhibit differences between the chemical shifts of the isopropylidene methyl signals ($\Delta\delta$ 0.23–0.30) in excellent agreement with the values characteristic of β nucleosides.[35]

This condensation reaction (**3** → **5** + **6**) is affected by several factors. (a) For optimum yields, the silver acetylide must be dried in vacuo (pump) at room temperature[36] for at least 2 days. (b) Condensation rates are dependent on the solvent used. Under comparable reagent concentrations, a reaction would be completed, for example, in 3 hr in dichloromethane whereas in benzene, 2 weeks are required. In both cases, however, the ratio of β (**5b**) to α (**6b**) anomers was fairly constant (~3:1) with a total yield of 55–60%. (c) It was found that if conditions were not kept scrupulously free of protic impurities, the amount of various side products, that are always formed to some extent, increased appreciably. Some of the side products which have been isolated by chromatography were identified by ^{1}H NMR spectroscopy as 1,5-anhydro-2,3-*O*-isopropylidene-β-D-ribofuranose, ethyl 3-trityl propiolate, and compound **2**.

In order to avoid the fairly elaborate work-up which accompanies the isolation of crystalline ribofuranosyl chloride **3**[30b] and the unavoidable partial loss of material, conditions were sought which would permit preparation of **3** and its condensation in situ with **4b** to give **5b** (Chart I) in a "one pot" reaction. Of particular importance was the desirability of a solvent suitable for both reactions (**2** → **3** → **5** + **6**) since DMF, the solvent originally used in the preparation of the ribosyl chloride **3**,[30] was found to be totally inadequate for the condensation step, giving mostly products resulting from undesirable reactions. The reasons for this are not yet clear. It was found that acetonitrile is a suitable solvent for the preparation of **3** and its condensation in situ with **4b**. This method has afforded reproducible yields (45% from **2**) of a mixture of the β (**5b**) and α (**6b**) anomers in a ratio of ~5:1. Slightly lower yields have been obtained when dichloromethane was used as the solvent.

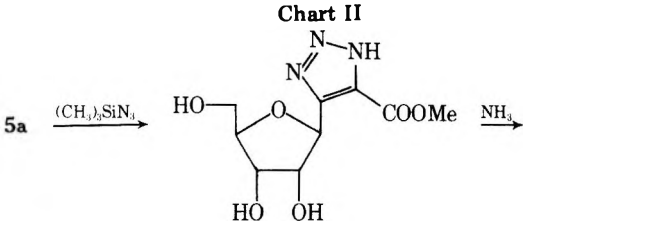
A similar procedure for the in situ condensation of **3** with the silver acetylide of methyl propiolate **4a** in acetonitrile or dichloromethane has yielded results comparable to those described above for the ethyl derivatives.

It has been shown also that reaction of **2** with triphenylphosphine and carbon tetrachloride gives the β anomer of the chloro sugar **3** via an intermediate. Thus TLC monitoring of the reaction of **2** with triphenylphosphine and carbon tetrachloride in acetonitrile or dichloromethane revealed the initial formation of an intermediate compound (R_f ~0.45 in petroleum ether–ethyl acetate, 10:1) which is slowly but completely converted to the known 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (the β anomer of **3**) (R_f ~0.6 in petroleum ether–ethyl acetate, 10:1). Since the starting material **2** is a mixture of anomers with the β anomer predominating[30] and since this type of reaction generally proceeds by inversion of configuration,[37] it is reasonable to assume that the initially formed product is the α-ribosyl chloride which in the presence of chloride ion epimerizes to the more stable β-chloro anomer. This hypothesis is supported by monitoring the reaction of **2** with triphenylphosphine and carbon tetrachloride in $CDCl_3$ simultaneously by ^1H NMR[38] and TLC. As the signals for the β anomer of **2** (H-1, δ 5.30, $J_{1,2}$ = 0 Hz) decrease in intensity, a new set of signals, attributable to the intermediate described above, appears which includes a doublet at low field (δ 6.30 $J_{1,2}$ = 6.2 Hz). As the reaction proceeds, the signals of **2** slowly disappear while signals corresponding to the known β-chloro anomer of **3** (H-1, δ 6.09, $J_{1,2}$ = 0 Hz) increase in intensity. The relative values of the chemical shifts and coupling constants of the low-field doublet (δ 6.30) and of the H-1 signal of the β anomer of **3** are consistent with the expected parameters of the anomeric pair of **3**. Analogous results have been obtained by following the course of the reaction in CD_3CN by ^1H NMR spectroscopy.

1,3-Dipolar Cycloaddition Reactions of 5a and 5b. Among the various 1,3-dipolar cycloaddition reactions that alkynes undergo readily, the reaction with azides has been found of synthetic value for the preparation of 1,2,3-triazoles.[39] The use of trimethylsilyl azide is of particular interest since this reagent is stable and can be used in place of the explosive hydrazoic acid for the synthesis of N-unsubstituted triazoles (the Si–N bond being easily cleaved by protic solvents).[40]

Treatment of the methyl ester **5a** (Chart II) with 5–6 equiv of trimethylsilyl azide at 105°C for 20 hr in a sealed

Chart II



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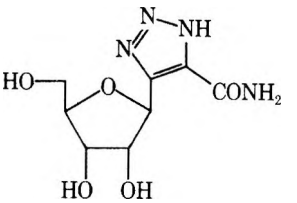


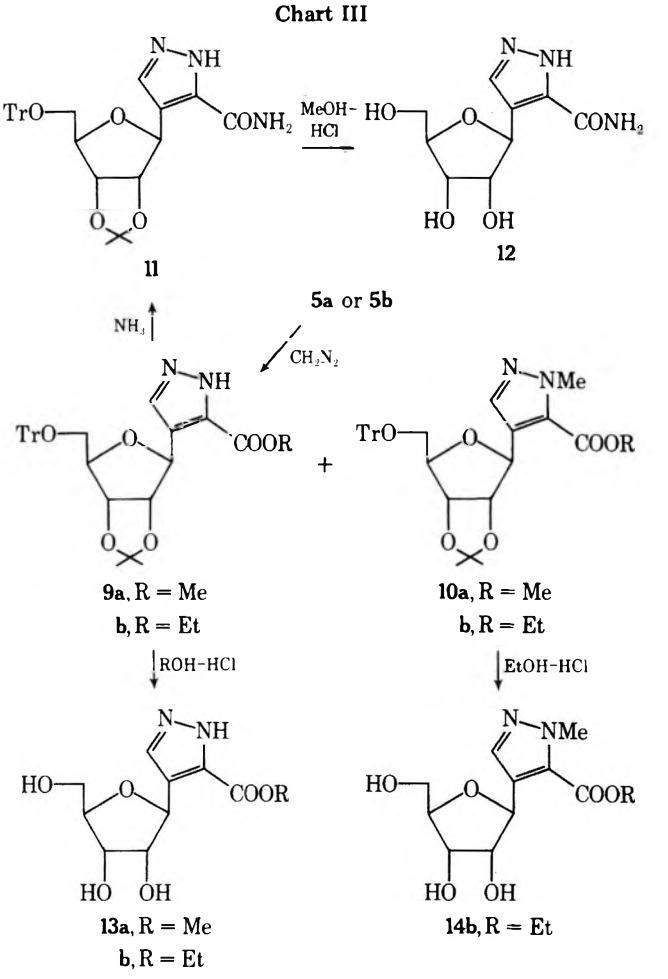
8

vessel was sufficient for complete conversion of the acetylenic function to the triazole. This major reaction, however, was accompanied by partial removal of the trityl and isopropylidene functions, leading to a mixture of partially blocked derivatives of 5(4)-carbomethoxy-4(5)-(β-D-ribofuranosyl)-1,2,3-triazole (**7**). These side reactions may have been catalyzed by the formation of some hydrazoic acid during the reaction. Extending the reaction time had no adverse effect, however, on the stability of the already formed triazole ring while allowing complete removal of all blocking groups from the ribose moiety. This procedure has afforded directly the desired crystalline triazole **7** from **5a** in good yield. Conversion of the ester **7** to the amide **8** was accomplished in good yield on treatment of **7** with 50% NH_3 in methanol for 3 days at 60°C in a sealed vessel.

Another type of 1,3-dipolar cycloaddition to acetylenes is their reaction with diazoalkanes to afford pyrazoles.[23] In view of the biological importance of the formycins and pyrazomycins which contain a pyrazole ring ribosylated at position 3(5), it was of interest to determine the utility of esters **5a** and **5b** as intermediates for the synthesis of pyrazole C nucleosides by reaction with diazoalkanes.

Reaction of **5a** with a slight excess of diazomethane (Chart III) in ether at 0°C was completed within 30–45

Chart III



min. Two products detected by TLC were isolated by column chromatography. The major component, obtained in 72% yield, was identified as the pyrazole ester **9a**. The minor component, obtained in 3.5% yield, was found to be a *N*-methyl derivative formed by the secondary reaction of **9a** with an excess of diazomethane. Similarly, reaction of **5b** with diazomethane gave **9b** (72%) and **10b** (10%).

The minor products were tentatively assigned structure **10** by analogy with many studies on alkylation in the pyrazole series.[41] These have led to the generalization that pyrazoles substituted by an electron-withdrawing group (such as acyl) at the 3 or 5 positions usually undergo alkylation mainly, if not exclusively, at the adjacent nitrogen atom. Although these results may vary depending on the condi-

tions of alkylation, the rule seems to have no exception when diazomethane is employed as the alkylating agent.

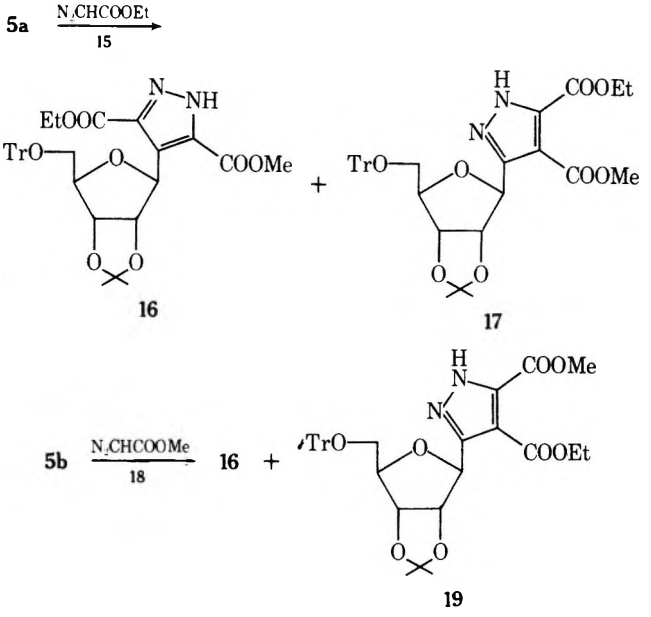
Treatment of **9a** or **9b** with ammonia–methanol (50%) at 50–75° for 3–4 days afforded good yields of the crystalline amide **11**. Removal of the protecting groups with methanolic HCl afforded a good yield of the known crystalline amide **12**.[29,42] Similar deblocking reactions of **9b** and **9a** with methanolic HCl afforded **13b** and the known **13a**,[29] both as crystalline materials. Treatment of the minor product **10b** with MeOH–HCl gave the unblocked N-methylated derivative **14b** in crystalline form.

The foregoing reactions of the acetylenic esters **5a** and **5b** with diazomethane afforded as expected the pyrazole esters ribosylated at position 4 as the only detectable product. These results are consistent with previous studies[21,23,43] on the mechanism and mode of addition of diazoalkanes to activated dipolarophiles. According to these studies the terminal nitrogen of the diazo compound attaches to the carbon α to the activating electron-withdrawing group (COOR). Our results also parallel recent observations by Albrecht, Repke, and Moffatt,[29] who found no positive evidence for the inverse mode of cycloaddition of diazomethane or diazo esters to a blocked derivative of the acrylate analogue of **5a**. The products of such inverse addition are desirable since they possess the common structural feature present in pyrazomycin and formycin, namely a 3(5)-ribosyl pyrazole.

Since there are numerous reports showing that inverse 1,3-dipolar addition of diazoalkanes occur more readily to substituted acetylenic dipolarophiles than to the corresponding analogously substituted ethylenic derivatives,[21b,43c,d,44,45] further investigation of the cycloaddition reactions of **5a** and **5b** with other diazoalkanes was undertaken. Diazo esters are particularly suitable for such a study for the following reasons. It has been reported, for example, that while diazomethane adds to $C_6H_5C{\equiv}C$–COOEt to give equal amounts of the products formed by "normal" and "inverse" mode of addition, the reaction with methyl diazoacetate gives chiefly the product derived from "inverse" addition.[44] Furthermore, should inverse addition occur with **5a** or **5b** the products obtained (such as **17** and **19**) would be directly suitable for the synthesis of formycins or formycin analogues.[12,13]

Reaction of the methyl propiolate derivative **5a** with an excess of ethyl diazoacetate (**15**, Chart IV) afforded two products of different chromatographic mobilities on silica thin layer. The major product (slower moving) was obtained in 63% yield after crystallization from the reaction mixture and subsequent chromatography of the mother liquors, while the minor component could be isolated in 10% yield by chromatography. Uv and ^{1}H NMR spectroscopic data indicated that the two components were indeed the expected pyrazole derivatives **16** and **17**, each formed by one of the two possible modes of cycloaddition. It was not possible, however, to assign these products a definite structure (such as **16** or **17**) since their physical properties (uv, ir, ^{1}H NMR) could fit either one. Chemical proof of their structures was obtained as follows. After treatment of the ethyl propiolate derivative **5b** with methyl diazoacetate (**18**) at room temperature for 9 days, two products of different mobility could be detected by TLC. The major slower moving component obtained in 56% yield by crystallization directly from the reaction mixture and subsequent column chromatography of the mother liquor was found to be identical in all respects with the major product **16** obtained from the previous reaction. This common product only could arise from the "normal" mode of addition and has, therefore, structure **16**. The minor product (8% after chromatography), as expected, was found to be different from all other products, as deduced from its melting point, ir, and ^{1}H NMR spectra, and its behavior on TLC. It was therefore assigned structure **19**. It also follows that the minor component obtained from the previous reaction of **5a** with **15** has structure **17**. In view of the synthetic significance of compounds **17** and **19** as potential intermediates for the synthesis of formycin analogues, the 1,3-dipolar cycloaddition reactions of **5a** and **5b** with the diazo esters described above were repeated at higher temperature, since a decrease in the stereoselectivity of the reaction should result in a corresponding increase in the relative yield of the desired minor products. Such modifications in the original conditions resulted in appreciable increases in the yields of **17** and **19**. Thus, reaction of **5a** with **15** at 50°C for 20 hr afforded 61% of **16** and 15% of **17** and reaction of **5b** with **18** at 50°C for 2 days afforded 54% of **16** and 13% of **19**.

Chart IV



The present method which readily provides pyrazole dicarboxylic acid derivatives such as **17** and **19** in essentially two steps from the readily available blocked ribose **2** offers, to our view, an attractively short alternate route for the synthesis of formycin analogues.

Experimental Section

General Procedure. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were obtained on a Varian A-60 or Jeol PS-100 spectrometer with Me_4Si as internal standard. Chemical shifts are reported in parts per million (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Values given for coupling constants are first order. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography (TLC) was performed on microscope slides coated with Merck silica gel GF_{254} and substances were visualized either by uv absorption or by spraying with 20% ethanolic sulfuric acid and charring. Column chromatography was performed by the dry column technique[46] in nylon tubes filled with Woelm silica gel (70–230 mesh) using a 60:1 ratio of absorbent to substance unless otherwise specified.

Silver Acetylides of Methyl and Ethyl Propiolate (4a and 4b). The silver acetylide **4a** (or **4b**) was prepared from the reaction of an ethanolic solution of methyl (or ethyl) propiolate with ammoniacal $AgNO_3$ in the manner described in ref 26a. The precipitated silver acetylide **4a** (or **4b**) was repeatedly washed with H_2O, EtOH, and ether and dried at room temperature[36] over P_2O_5 under vacuum for at least 2 days before use.

Methyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β- and -α-D-ribofuranosyl)propiolate (5a and 6a). To a solution of 13.0 g (0.03

mol) of **2** in 70 ml of anhydrous CH_3CN (dried over molecular sieves 3 Å) were added 9.2 g (0.06 mol) of CCl_4 and 11.8 g (0.045 mol) of $(Ph)_3P$. The mixture was stirred at room temperature until TLC indicated the disappearance of the starting material **2** ($R_f \sim 0.18$ in petroleum ether–EtOAc, 10:1) (usually within 20 min). At this point, 5 g of 3 Å molecular sieves and 13.3 g (0.07 mol) of silver acetylide of methyl propiolate **4a**[26a] were added and the mixture was stirred at room temperature, in the dark, until TLC indicated the disappearance of all the chloro sugar **3** [$R_f \sim 0.45$ for the α anomer and $R_f \sim 0.6$ for the β anomer in petroleum ether (30–60°)–EtOAc,(10:1)]. The reaction took ~10 days. The mixture was then diluted with 200 ml of CH_2Cl_2 and filtered. The filtrate, on evaporation, afforded a thick syrup which partially dissolved on warming with diethyl ether (300 ml) leaving an oil which was removed by filtration through 50 g of silica gel. The filtrate, which contained mainly the β-acetylenic ester **5a** ($R_f \sim 0.36$ in petroleum ether–EtOAc, 10:1) was evaporated to dryness and the residue chromatographed on a dry silica gel column (600 g) using a mixture of petroleum ether–EtOAc (10:1) as eluent.

Compound **5a** was isolated as a syrup (5.14 g, 34%) and was obtained analytically pure by a second chromatography using the same system: λ_{max} (EtOH) 253 nm (ϵ 750), 260 (790), 263 (710) sh, 266 (610) sh, 269 (440) sh; ν_{max} ($CHCl_3$) 2260 (C≡C), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.30 and 1.50, (2 s, 6, CMe_2), 3.28 (m, 2, H-5′), 3.66 (s, 3, COOMe), 4.33 (m, 1, H-4′), 4.62 (dd, 1, H-3′, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 1.5 Hz), 4.75 (d, 1, H-1′, $J_{1',2'}$ = 2.9 Hz), 4.83 (dd, 1, H-2′), 7.19–7.52 (m, 15, trityl).

Anal. Calcd for $C_{31}H_{30}O_6$ (498.6): C, 74.68; H, 6.07. Found: C, 74.67; H, 6.02.

Elution of a slower moving band afforded 1.15 g (7.6%) of **6a** as a syrup which crystallized on standing. Recrystallization from EtOAc–petroleum ether gave the analytical sample: mp 157–158°; λ_{max} (EtOH) 253 nm (ϵ 570), 259 (670), 262 (560), 266 (480), 269 (310); ν_{max} (KBr) 2265 (C≡C), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.35 and 1.56 (2 s, 6, CMe_2), 3.11 (dd, 1, H-5′ a, $J_{4',5'a}$ = 3.11, $J_{5'a,5'b}$ = 10.2 Hz), 3.43 (dd, 1, H-5′b, $J_{4',5'b}$ = 3.1 Hz), 3.77 (s, 3, COOMe), 4.26 (t, 1, H-4′), 4.70 (d, 1, H-3′, $J_{2',3'}$ = 6.1 Hz), 4.95 (dd, 1, H-2′), 5.18 (d, 1, H-1′, $J_{1',2'}$ = 4.6 Hz), 7.23–7.39 (m, 15, trityl).

Anal. Calcd for $C_{31}H_{30}O_6$ (498.6); C, 74.68; H, 6.07. Found: C, 74.55; H, 6.13.

Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β- and -α-D-ribofuranosyl)propiolate (5b and 6b). Method A. From Compound 2. To a solution of 43.2 g (0.1 mol) of **2** in 250 ml of dried CH_3CN were added 39.4 g (0.15 mol) of $(Ph)_3P$ and 30.8 g (0.2 mol) of CCl_4 and the clear solution was stirred at room temperature until TLC indicated the disappearance of **2** (usually 20 min). A suspension of 43 g (0.21 mol) of the silver derivative of ethyl propiolate **4b**[26a] in dry CH_3CN (160 ml) which had been prestirred with 3 Å molecular sieves (80 g) for 2 hr was then added to the solution of chloro sugar **3** prepared above. This mixture was stirred in the dark until TLC indicated the disappearance of the chloro sugar **3**. This usually takes 5 days. The procedure described above for the isolation of the methyl derivatives **5a** was used to obtain 18.4 g (36%) of **5b** as a syrup. This compound was obtained analytically pure after another chromatography using the same system: λ_{max} (EtOH) 254 nm (ϵ 840), 259 (910), 263 (770), 266 (670), 269 (480); ν_{max} ($CHCl_3$) 2260 (C≡C), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.19 (t, 3, CH_2CH_3), 1.30 and 1.50 (2 s, 6, CMe_2), 3.29 (m, 2, H-5′), 4.13 (q, 2, $COOCH_2$), 4.33 (m, 1, H-4′), 4.62 (dd, 1, H-3′, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 1.8 Hz), 4.76 (d, 1, H-1′, $J_{1',2'}$ = 2.8 Hz), 4.84 (dd, 1, H-2′), 7.20–7.53 (m, 15, trityl).

Anal. Calcd for $C_{32}H_{32}O_6$ (512.6); C, 74.98; H, 6.29. Found: C, 74.97; H, 6.35.

By the same procedure also was isolated 4.3 g (8.4%) of **6b:** mp 133–134° (from EtOAc–petroleum ether); λ_{max} (EtOH) 253 nm (ϵ 680), 259 (750), 263 (630), 266 (530), 269 (370); ν_{max} (KBr) 2265 (C≡C), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3, CH_2CH_3), 1.35 and 1.56 (2 s, 6, CMe_2), 3.10 (dd, 1, H-5′a, $J_{4',5'a}$ = 3.1, $J_{5'a,5'b}$ = 10.2 Hz), 3.43 (dd, 1, H-5′b, $J_{4',5'b}$ = 3.0 Hz), 4.24 (m, 3, $COOCH_2$, H-4′), 4.70 (d, 1, H-3′, $J_{2',3'}$ = 6.0 Hz), 4.96 (dd, 1, H-2′), 5.18 (d, 1, H-1′, $J_{1',2'}$ = 4.7 Hz), 7.27–7.38 (m, 15, trityl).

Anal. Calcd for $C_{32}H_{32}O_6$ (512.6): C, 74.98; H, 6.29. Found: C, 75.05; H, 6.31.

Method B. From Compound 3. A suspension of **4b** (4.1 g, 0.2 mol) and of 3 Å molecular sieves (10 g) in a mixture of benzene (40 ml) and CH_2Cl_2 (10 ml) previously dried over molecular sieves was stirred for 20 min at room temperature in the absence of light. The crystalline β anomer of **3**[30] (4.51 g, 0.01 mol) was then added and the reaction mixture was stirred for 40 hr. The products were obtained as described in method A. The isolated compounds **5b** and **6b** weighed 2.27 g (44.5% from **3**) and 0.80 g (15.5%).

5(4)-Carbomethoxy-4(5)-(β-D-ribofuranosyl)-1,2,3-triazole (7). The propiolate derivative **5a** (2.50 g, 5 mmol) was dissolved in 3.0 g (26 mmol) of trimethylsilyl azide and heated in a sealed vessel at 105° for 48 hr. After cooling to room temperature the solution was diluted with 10 ml of MeOH and evaporated to dryness. The residue was triturated with EtOAc and filtered to give **7** (0.823 g, 63%) as a solid which crystallized from CH_3CN: mp 146–147°; λ_{max} (EtOH) 218 nm (ϵ 7660); λ_{max} (pH 13) 235 nm (ϵ 6880); ^1H NMR (Me_2SO-d_6) δ 3.56 (m, 3, H-5′, OH), 3.84 (s, 3, $COOCH_3$), 3.7–4.1 (m, 3, H-2′, H-3′, H-4′), 4.99 (d, 1, OH, $J_{OH,H}$ = 4.9 Hz), 5.15 (d, 1, OH, $J_{OH,H}$ = 5.5 Hz), 5.23 (d, 1, H-1′, $J_{1',2'}$ = 5.2 Hz).

Anal. Calcd for $C_9H_{13}N_3O_6$ (259.2): C, 41.70; H, 5.06; N, 16.21. Found: C, 41.72; H, 5.12; N, 16.22.

5(4)-Carboxamido-4(5)-(β-D-ribofuranosyl)-1,2,3-triazole (8). A solution of 1.30 g (5 mmol) of **7** in 20 ml of MeOH and 20 ml of liquid ammonia was heated at 60° in a sealed vessel for 3 days. The solution was cooled to room temperature and evaporated to dryness to afford, after chromatography (MeOH–EtOAc–$CHCl_3$, 2:1:1) **8** as a syrup (0.98 g, 80%): λ_{max} (EtOH) 210 nm (ϵ 9970); ^1H NMR (Me_2SO-d_6) δ 3.1–4.0 (m, 6, H-2′, H-3′, H-4′, H-5′, OH), 4.91 and 5.12 (2 broad s, 2, OH), 5.27 (d, 1, H-1′, $J_{1',2'}$ = 4.6 Hz), 7.40 and 7.71 (2 s, 2, $CONH_2$).

This compound could not be obtained analytically pure and was further characterized as its tri-*O*-acetyl derivative by treating **8** (0.300 g, 1.2 mmol) in pyridine with acetic anhydride. Subsequent column chromatography (EtOAc–petroleum ether, 3:1) afforded 0.41 g (88%) of 5(4)-carboxamido-4(5)-2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl-1,2,3-triazole. An analytical sample was obtained by a second chromatography using the same solvent system: λ_{max} (EtOH) 209 nm (ϵ 8650); λ_{max} (pH 13) 238 nm (ϵ 7380); ^1H NMR ($CDCl_3$) δ 2.07, 2.09, and 2.09 (3 s, 9, OAc), 4.36 (broad s, 3, H-4′, H-5′), 5.42 (dd, 1, H-3′, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 5.2 Hz), 5.69 (dd, 1, H-2′), 5.76 (d, 1, H-1′, $J_{1',2'}$ = 4.5 Hz), 6.75 and 7.39 (2 s, 2, $CONH_2$).

Anal. Calcd for $C_{14}H_{18}N_4O_8$ (370.3): C, 45.51; H, 4.90; N, 15.13. Found: C, 45.25; H, 4.90; N, 14.96.

Reaction of Methyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (5a) with Diazomethane. To 4.0 g (8 mmol) of **5a** in 30 ml of ether at 0°C (ice–water bath) was added 100 ml of a cold, dried ethereal solution of CH_2N_2 (~12–15 mmol). The mixture was kept at 0° for 30 min. It was then treated dropwise with a diluted solution of AcOH in ether until the evolution of nitrogen stopped. Evaporation to dryness and column chromatography of the residue (petroleum ether–EtOAc, 2:1) afforded two products. The major and more polar component was obtained as a white foam (3.15 g, 72%) and identified as 3(5)-carbomethoxy-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**9a**). It crystallized from MeOH with one molecule of crystallization (as shown by NMR), mp 120–125°. Product **9a** also could be obtained in crystalline form (54%) by direct crystallization of the residue from MeOH without chromatography: λ_{max} (pH 13) 232 nm (ϵ 12650), 250 (7830) sh; ^1H NMR ($CDCl_3$) δ 1.34 and 1.60 (2 s, 6, CMe_2), 3.33 (m, 2, H-5′), 3.46 (s, 3, CH_3OH from crystallization), 3.68 (s, 3, $COOCH_3$), 4.26 (m, 1, H-4′), 4.67 (m, 2, H-2′, H-3′), 5.47 (d, 1, H-1′, $J_{1',2'}$ = 2.7 Hz), 7.17–7.54 (m, 15, trityl), 7.83 (s, 1, H-3).

Anal. Calcd for $C_{32}H_{32}N_2O_6 \cdot CH_3OH$ (572.7): C, 69.21; H, 6.34; N, 4.89. Found: C, 69.13; H, 6.31; N, 4.89.

From the column was also isolated 0.14 g of a minor and less polar product (syrup). From the similarity of its NMR spectrum to that of **10b** (vide infra) it was identified as 5-carbomethoxy-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-1-methylpyrazole (**10a**) resulting from further reaction of the pyrazole initially formed with CH_2N_2: ^1H NMR ($CDCl_3$) δ 1.31 and 1.59 (2 s, 6, CMe_2), 3.26 (d, 2, H-5′, $J_{4',5'}$ = 4.9 Hz), 3.87 (s, 3, NCH_3), 4.13 (s, 3, $COOCH_3$), 4.22 (m, 1, H-4′), 4.59 (m, 2, H-2′, H-3′), 5.39 (d, 1, H-1′, $J_{1',2'}$ = 3.4 Hz), 7.22–7.57 (m, 16, trityl, H-3).

Reaction of Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (5b) with Diazomethane. To 0.57 g (1.1 mmol) of **5b** in 5 ml of ether at 0° was added 15 ml of a cold ethereal solution of CH_2N_2 (~1.5 mmol). The mixture was left at 0° for 45 min and treated dropwise with a solution of AcOH in ether. The colorless solution was then evaporated to a syrup which was chromatographed on a dry column of silica gel using petroleum ether–EtOAc (2:1) as eluent. Two products were isolated. Elution of the major component (slower moving) gave 0.451 g (73%) of 3(5)-carbethoxy-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**9b**) as a white foam which crystallized from MeOH with one solvent molecule of crystallization, mp 95–105° (only partial removal of the solvent of crystallization could be achieved by

drying **9b** for 6 days at 80°C): λ_{max} (pH 13) 233 nm (ϵ 11840), 251 (7850) sh; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3, CH_2CH_3), 1.33 and 1.60 (2 s, 6, CMe_2), 3.33 (m, 2, H-5′), 3.48 (s, 3, CH_3OH crystallization), 4.28 (m, 3, $COOCH_2$, H-4′), 4.65 (m, 2, H-2′, H-3′), 5.84 (d, 1, H-1′, $J_{1',2'}$ = 2.4 Hz), 7.24–7.53 (m, 15, trityl), 7.77 (s, 1, H-3).

Anal. Calcd for $C_{33}H_{34}N_2O_6 \cdot CH_3OH$ (586.7): C, 69.61; H, 6.53; N, 4.77. Found: C, 69.65; H, 6.44; N, 4.78.

Elution of the minor (and less polar) product afforded 0.065 g (10%) of 5-carbethoxy(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-1-methylpyrazole (**10b**) as a syrup. Purification of this compound by a second chromatography (petroleum ether–EtOAc, 6:1) afforded the analytical sample: λ_{max} (EtOH) 248 nm (ϵ 7129) sh; ^{1}H NMR ($CDCl_3$) δ 1.31 and 1.58 (2 s, 6, CMe_2), 1.40 (t, 3, CH_2CH_3), 3.22 (d, 2, H-5′, $J_{4',5'}$ = 4.6 Hz), 4.16 (s, 3, NCH_3), 4.16 (t, 1, H-4′), 4.38 (q, 2, $COOCH_2$), 4.57 (m, 2, H-2′, H-3′), 5.43 (d, 1, H-1′, $J_{1',2'}$ = 2.8 Hz), 7.23–7.50 (m, 15, trityl), 7.55 (s, 1, H-3).

Anal. Calcd for $C_{34}H_{36}N_2O_6$ (568.7): C, 71.81; H, 6.38; N, 4.93. Found: C, 71.90; H, 6.31; N, 4.87.

3(5)-Carboxamido-4-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (11). A. From 9a. A methanolic solution (5 ml) of **9a** (1.36 g, 2.5 mmol) was added to a mixture of 10 ml of MeOH and 15 ml of liquid ammonia. The mixture was heated in a sealed tube for 3 days at 54°, cooled at room temperature, evaporated to dryness, and dissolved in hot benzene. On cooling 0.808 g (61%) of **11** was obtained as colorless crystals: mp 214–215°; λ_{max} (pH 13) 232 nm (ϵ 13580), 248 (8990) sh; ^{1}H NMR ($CDCl_3$) 1.36 and 1.59 (2 s, 6, CMe_2), 3.16–3.46 (m, 2, H-5′), 4.27 (m, 1, H-4′), 4.75 (m, 2, H-2′, H-3′), 5.18 (d, 1, H-1′, $J_{1',2'}$ = 4.2 Hz), 5.59 and 7.88 (2 broad s, 2, $CONH_2$) 7.21–7.45 (m, 15, trityl), 7.63 (s, 1, H-3).

Anal. Calcd for $C_{31}H_{31}N_3O_5$ (525.6): C, 70.84; H, 5.94; N, 7.99. Found: C, 70.75; H, 5.85; N, 7.94.

B. From 9b. Similar treatment of **9b** (0.300 g, 0.54 mmol) for 4 days at 72° afforded 0.233 g (82%) of **11** identical in all respects with that obtained by method A.

3(5)-Carboxamido-4-(β-D-ribofuranosyl)pyrazole (12). To a solution of 0.525 g (1 mmol) of **11** in 10 ml in MeOH was added 5 ml of a saturated solution of HCl in MeOH. After standing for 90 min, the reaction mixture was evaporated to dryness and the residue was partitioned between water and $CHCl_3$. The aqueous phase was washed twice with $CHCl_3$ and evaporated to dryness. The residue was redissolved in water and evaporated again, leaving 0.238 g of **12** as a white foam (homogeneous material on TLC). Recrystallization from MeOH afforded a pure sample (0.188 g, 75%) of the known **12**,[29,42] mp 199–201°C (reported 200–202°C,[29] 208–210°C[42]), with physical properties identical with those previously reported for that compound.

3(5)-Carbomethoxy-4-(β-D-ribofuranosyl)pyrazole (13a). A solution of 0.270 g (0.5 mmol) of **9a** in 5 ml of MeOH was treated with 25 ml of a saturated solution of HCl. After standing for 90 min, the product was isolated as described above for the preparation of **12**. The procedure afforded 0.125 g of a crystalline residue. This material was recrystallized from EtOH–ether to give the known **13a**[29] in pure form (0.092 g, 72%), mp 181–182.5°C (reported 186–188°C[29]).

3(5)-Carbethoxy-4-(β-D-ribofuranosyl)pyrazole (13b). Into 13 ml of EtOH containing 0.550 g (1 mmol) of **9b** was dissolved 0.9 g of anhydrous HCl. After 2 hr at room temperature the mixture was processed as described above for the preparation of **12**. Thus 0.270 g of **13b** was obtained as a white foam which crystallized from MeOH–ether to give 0.191 g (70%) of **13b** analytically pure: mp 155–156°; λ_{max} (EtOH) 222 nm (ϵ 11510), λ_{max} (pH 13) 241 nm (ϵ10390); ^{1}H NMR (Me_2SO-d_6) δ 1.30 (t, 3, CH_2CH_3), 3.32–3.86 (m, 5, H-2′, H-3′, H-4′, H-5′), 4.27 (q, 2, $COOCH_2$), 4.75 (broad s, 3, OH's), 5.09 (d, 1, H-1′, $J_{1',2'}$ = 3.7 Hz), 7.90 (s, 1, H-3).

Anal. Calcd for $C_{11}H_{16}N_2O_6$ (272.3): C, 48.53; H, 5.92; N, 10.29. Found: C, 48.59; H, 6.07; N, 10.16.

5-Carbethoxy-1-methyl-4-(β-D-ribofuranosyl)pyrazole (14b). To 50 ml of an ethanolic solution of **10b** (0.57 g, 1 mmol) was added 5 ml of a saturated solution of HCl in EtOH. After 2 hr at room temperature the mixture was treated as described previously to afford 0.19 g (66%) of a syrup which crystallized from MeOH–ether to give analytically pure **14b**: mp 144–146°; λ_{max} (EtOH) 233 nm (ϵ 8680), 246 (ϵ 6800) sh; λ_{max} (pH 13) 236 nm (ϵ5130); ^{1}H NMR (Me_2SO-d_6) δ 1.33 (t, 3, CH_2CH_3), 3.56 (m, 2, H-5′), 3.72–4.41 (m, 8, H-2′, H-3′, H-4′, 3 OH's, $COOCH_2$), 4.03 (s, 3, NCH_3), 5.06 (d, 1, H-1′, $J_{1',2'}$ = 4.6 Hz), 7.67 (s, 1, H-3).

Anal. Calcd for $C_{12}H_{18}N_2O_6$ (286.3): C, 50.35; H, 6.34; N, 9.79. Found: C, 50.28; H, 6.32; N, 9.80.

Reaction of Methyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (5a) with Ethyl Diazoacetate (15). A mixture of 1.05 g (2.1 mmol) of **5a** and 0.93 g (8 mmol) of **15** was heated at 50° for 20 hr. The mixture was then cooled at room temperature for 2 hr and the crystalline product which had precipitated was filtered and washed twice with ether (2 × 2 ml) to give 0.606 g (46%) of 3(5)-carbethoxy-5(3)-carbomethoxy-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**16**). Recrystallization from EtOAc–petroleum ether afforded the analytical sample: mp 202–204°; λ_{max} (pH 13) 254 nm (ϵ 9660); ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.61 (2 s, 6, CMe_2), 1.34 (t, 3, CH_2CH_3), 3.20 (dd, 1, H-5′a, $J_{4',5'a}$ = 4.1 Hz, $J_{5'a,5'b}$ = 9.7 Hz), 3.42 (dd, 1, H-5′b, $J_{4',5'b}$ = 7.3 Hz), 3.74 (s, 3, $COOCH_3$), 4.01–4.38 (m, 3, H-4′, $COOCH_2$), 4.25 (dd, 1, H-3′, $J_{2',3'}$ = 7.3, $J_{3',4'}$ = 5.5 Hz), 4.75 (dd, 1, H-2′), 5.81 (d, 1, H-1′, $J_{1',2'}$ = 5.0 Hz), 7.19–7.52 (m, 15, trityl).

Anal. Calcd for $C_{35}H_{36}N_2O_8$ (612.7): C, 68.61; H, 5.92; N, 4.57. Found: C, 68.66; H, 5.91; N, 4.52.

The filtrate and washings were combined and chromatographed on dry column (petroleum ether–EtOAc, 2:1) to afford 0.186 g of a slower moving product identical with **16** (total yield 61%) and 0.195 g (15%) of a faster moving product which after crystallization from EtOAc–petroleum ether (mp 183–184°) was identified as 3(5)-carbethoxy-4-carbomethoxy-5(3)-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**17**): λ_{max} (pH 13) 230 nm (ϵ 11460) sh, 253 (9200); ^{1}H NMR ($CDCl_3$) δ 1.34 and 1.60 (2 s, 6, CMe_2), 1.39 (t, 3, CH_2CH_3), 3.06 (dd, 1, H-5′a, $J_{4',5'a}$ = 6.6, $J_{5'a,5'b}$ = 10.8 Hz), 3.44 (dd, 1, H-5′b, $J_{4',5'b}$ = 3.5 Hz), 3.83 (s, 3, $COOCH_3$), 4.41 (m, 3, H-4′, $COOCH_2$), 4.59 (dd, 1, H-3′, $J_{2',3'}$ = 5.5, $J_{3',4'}$ = 3.3 Hz), 4.83 (dd, 1, H-2′), 5.52 (d, 1, H-1′, $J_{1',2'}$ = 2.8 Hz), 7.25–7.50 (m, 15, trityl).

Anal. Calcd for $C_{35}H_{36}N_2O_8$ (612.7): C, 68.61; H, 5.92; N, 4.57. Found: C, 68.82; H, 5.81; N, 4.71.

When this reaction was carried out at room temperature for 3 days, the same procedure of isolation and purification afforded **16** and **17** in 63 and 10.3% yield, respectively.

Reaction of Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (5b) with Methyl Diazoacetate (18). A mixture of 0.700 g (1.37 mmol) of **5b** and 0.460 g (4.6 mmol) of **18** was heated at 50° for 2 days. The mixture was then cooled at room temperature for 2 hr and the crystalline product which had precipitated was filtered and washed twice with ether (2 × 2 ml) to give 0.369 g (44%) of **16**. The filtrate and washings were combined and chromatographed on a dry column (petroleum ether–EtOAc, 2:1) to give 0.086 g of **16** (total yield 54.4%) and 0.112 g (13.3%) of a faster moving product which after crystallization from EtOAc–petroleum ether (mp 159–161°) was identified as 4-carbethoxy-3(5)-carbomethoxy-5(3)-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**19**): λ_{max} (pH 13) 230 nm (ϵ 11890) sh, 252 (9800); ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.59 (2 s, 6, CMe_2), 1.33 (t, 3, CH_2CH_3), 3.07 (dd, 1, H-5′a, $J_{4',5'a}$ = 6.8, $J_{5'a,5'b}$ = 10.8 Hz), 3.47 (dd, 1, H-5′b, $J_{4'5'b}$ = 3.4 Hz), 3.93 (s, 3, $COOCH_3$), 4.32 (q, 2, $COOCH_2$), 4.42 (m, 1, H-4′), 4.60 (dd, 1, H-3′, $J_{2',3'}$ = 6.1, $J_{3',4'}$ = 3.7 Hz), 4.84 (dd, 1, H-2′), 5.55 (d, 1, H-1′, $J_{1',2'}$ = 2.4 Hz), 7.26–7.51 (m, 15, trityl).

Anal. Calcd for $C_{35}H_{36}N_2O_8$ (612.7): C, 68.61; H, 5.92; N, 4.57. Found: C, 68.68; H, 5.89; N, 4.53.

When this reaction was carried out at room temperature for 9 days and the same subsequent procedure was followed, **16** and **19** were obtained in 56 and 8.3% yield, respectively.

Registry No. —**2**, 55726-19-7; **4a**, 57031-37-5; **4b**, 57016-89-4; **5a**, 57016-90-7; **5b**, 57016-91-8; **6a**, 57016-92-9; **6b**, 57016-93-0; **7**, 57049-19-1; **8**, 57016-94-1; **8** triacetate, 57016-95-2; **9a**, 57016-96-3; **9b**, 57016-97-4; **10a**, 57016-98-5; **10b**, 57016-99-6; **11**, 57017-00-2; **12**, 50720-82-6; **13a**, 50866-58-5; **13b**, 57017-01-3; **14b**, 57017-02-4; **15**, 623-73-4; **16**, 57017-03-5; **17**, 57017-04-6; **18**, 6832-16-2; **19**, 57017-05-7; trimethylsilyl azide, 4648-54-8; diazomethane, 334-88-3.

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Nitrite Esters of Polyhydroxy Polymers[1]

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Nitrite esters of polysaccharides and synthetic polyhydroxy polymers are obtained by reaction of polyhydroxy polymer with dinitrogen tetroxide or nitrosyl chloride in a medium containing a suitable proton acceptor. The polymeric nitrite esters are relatively unstable compounds and can be isolated only at low temperatures as wet, fibrous materials from a neutral or alkaline medium. In the presence of a protic solvent, such as water or alcohol, and catalytic amounts of mineral acid, they decompose immediately with formation of nitrous acid or alkyl nitrite and regeneration of the corresponding polyhydroxy polymer. Results suggest that nitrosation of alcoholic hydroxyl groups, irrespective of their origin, follows the same mechanism and is subject to an equilibrium $ROH + N_2O_4 \rightleftharpoons RONO + HNO_3$, whose equilibrium constant depends greatly on the stability of the nitrite ester.

It has been found previously that cellulose can be solubilized with nitrogen dioxide or nitrosyl chloride in *N,N*-dialkylacylamide, with formation of clear and viscous solutions.[2] More recent results indicate that the reason for this solvation lies in the formation of cellulose trinitrite ester, a compound that decomposes immediately in the presence of a protic solvent and mineral acid as a catalyst with regeneration of the cellulose.[3] A reaction mechanism has been proposed[3] in which the nitrosyl nitrate form,[4] not the symmetric nitrogen dioxide dimer, is the reactive agent that quantitatively esterifies the cellulose molecule. Nitrosyl chloride reacts in a similar fashion producing nitrite ester and, instead of nitrate ion, chloride ion. However, a 2.5- to 3-fold excess of nitrosyl chloride is required for completion of the reaction probably as a result of a higher stability, i.e., lower reactivity, of nitrosyl chloride.

It is postulated that the *N,N*-dialkylacylamide functions as a proton acceptor, so the equilibrium as shown in Scheme I would shift to the right to provide for an essentially quantitative nitrite ester formation. Consistent with this mechanism, the rate of esterification increases and the conversion with nitrosyl chloride can be completed with

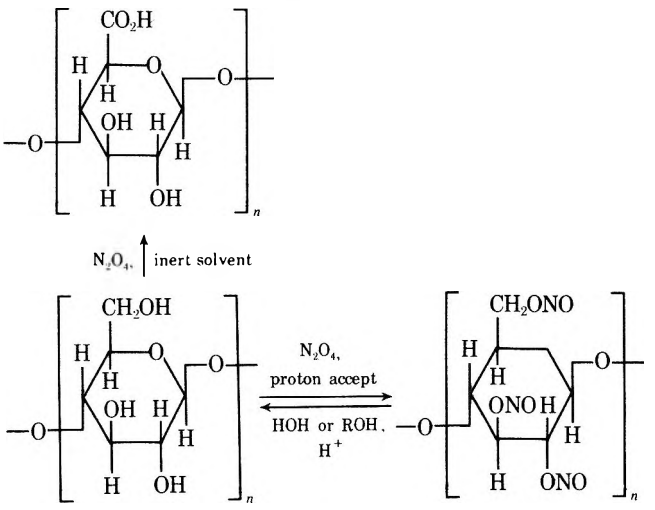
Scheme I

$$ROH + ONONO_2 \rightleftharpoons RONO + HNO_3$$
$$ROH + ONCl \rightleftharpoons RONO + HCl$$

stoichiometric amounts of reagent if the more strongly basic tertiary amines, such as pyridine or quinoline, are used as solvent. The reaction proceeds also in inert solvents, such as benzene, chloroform, acetone, or ethyl acetate, provided that at least 1 mol of amine per mole of nitrosating agent is present. However, if a strongly basic tertiary amine, such as trialkylamine, is used, no nitrite ester formation occurs but, instead, a highly exothermic reaction of the nitrosating reagent with the amine is observed making nitrosyl nitrate or chloride unavailable for nitrosation of the cellulose.

Previously it was believed that the only principal reaction of cellulose (and other hexosans) with nitrogen dioxide was oxidation of *primary* hydroxyl groups at C-6 to form carboxyl groups with minor side reactions being oxidation of *secondary* hydroxyl groups and nitration.[5] The present results establish that, in a medium containing cellulose and nitrogen dioxide, an equilibrium as shown in Scheme I exists and, depending on the medium, the reaction may proceed either toward oxidation or nitrite ester formation as shown in Scheme II. In relatively inert solvents, the equi-

Scheme II



librium is very much in favor of the left side, i.e., cellulose and free dinitrogen tetroxide, and practically no nitrite ester is detectable. Then, oxidation of *primary* hydroxyl groups, a relatively slow reaction, will take place. No such oxidation, however, is possible in the presence of a suitable proton acceptor even with an excess of nitrogen dioxide since the rate of nitrite ester formation is much higher than that of oxidation and, once the nitrite ester is formed, the hydroxyl groups are protected from oxidative attack.

Nitrite ester formation as shown above is not limited to cellulose but is a reaction common to all polysaccharides and synthetic polyhydroxy polymers. Thus, other polysaccharides, such as starch, guar gum, locust bean gum, alginic acid, and hemicellulose, and polyvinyl alcohol form clear and viscous solutions in *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), pyridine, or quinoline when a sufficient amount of nitrogen dioxide or nitrosyl chloride is introduced. The amounts of dinitrogen tetroxide necessary to solubilize the various polyhydroxy polymers are shown in Table I. During introduction of the nitrogen dioxide, the mixtures remain colorless to very lightly colored until the ratios in Table I are closely approached.

Table I
Reactions of Dinitrogen Tetroxide with Polyhydroxy Polymers in DMF

Polyhydroxy polymer	Molar equiv of N_2O_4 reacted	Number of free OH groups in polymer units
Cellulose	2.7–2.8	3
Starch	2.7–2.8	3
Guar gum	3.0–3.2	3
Locust bean gum	3.0–3.2	3
Alginic acid	1.8–1.9	2
Hemicellulose	2.0–2.1	2
Polyvinyl alcohol	0.9–0.95	1

Then, an intensive color change toward bluish green occurs indicative of free nitrogen dioxide. The molar ratio, polyhydroxy polymer:nitrosyl chloride, is essentially the same if pyridine or quinoline is used as the proton acceptor. With DMF or DMA, a 2.5- to 3-fold excess of nitrosyl chloride is required for completion of the reaction. In all cases, the ratio coincides remarkably well with the number of free hydroxyl groups per polymer unit, i.e., three for hexosans, two for polyuronic acid and pentosans, and one for polyvinyl alcohol. Slight deviations from the theory toward higher values may be due to the presence of impurities, such as protein, and, in the case of hemicellulose, to a small percentage of anhydrohexose as a molecular building unit. The yellow color of regenerated guar and locust bean gums may be an indication of protein impurities that have reacted with nitrogen dioxide.

The nitrite esters of polyhydroxy polymers can be isolated by addition of their solution, neutralized with a tertiary amine, to water. All nitrite esters prepared exhibit similar solution properties and an instability similar to that of the cellulose nitrite ester described previously.[3] Thus, they can be isolated only at a low temperature, they cannot be dried without decomposition unless the temperature is extremely low, and they decompose immediately in the presence of a protic solvent and mineral acid as a catalyst. The consumptions given in Table I indicate that all polymers form fully substituted nitrite esters. This has been established by direct analysis of the nitrite ester through decomposition with acid, determination of the regenerated polymer by weight, and titration of the nitrous acid with permanganate followed by isolation of the nitric acid formed as nitron nitrate. Degrees of substitution calculated from the weight of the polymer and the amount of nitrous acid titrated were found to be 2.8–3.0 for the hexosans (including cellulose), 1.9–2.0 for polyuronic acid and pentosans, and 0.9–1.0 for polyvinyl alcohol.

Regeneration of the polyhydroxy polymer is accomplished by addition of a protic solvent, such as water or alcohol, to the nitrite ester solution containing mineral acid. With water, this is a simple hydrolysis while, with alcohol, it is a transesterification producing alkyl nitrite as the most stable nitrite ester in this system. Stoichiometric amounts of protic solvent are sufficient to remove the nitrite groups quantitatively from the polymer molecule as this has been demonstrated previously for cellulose.[3] Nitrogen determinations of the regenerated materials are negative or do not show an increase of the nitrogen content originally present, and ir spectra are identical with those of the corresponding starting materials indicating that the regenerated polyhydroxy polymers are chemically unmodified.

Comparison of the viscosities of the regenerated polysaccharides with those of the corresponding starting materials is made in Table II. It indicates that degradation is negligible with the exception of galactomannans, which appear to

Table II
Viscosity of Original and Regenerated Polysaccharide

Material	Concn, %	pH	Viscosity	
			Original	Regenerated
Cellulose[a]	0.5		28.8	28.8
Starch	1.0	6.0	30.4	29.3
Guar gum	0.25	6.3	287	70.7
Locust bean gum	0.25	6.6	255	117.2
Alginic acid[b]	0.25	6.5	114	104.6
Hemicellulose	2.0	6.7	146.2	138.5
Water			12	

[a] The viscosity of cellulose was determined in cuprammonium hydroxide solution as described previously.[3] [b] EDTA (0.1%) was added to exclude any influence on viscosity by traces of calcium ions.

depolymerize to a significant extent as shown by the reduction of their solution viscosity.

Apparently, all polyhydroxy polymers irrespective of their structure or composition are subject to the equilibrium in Scheme I, producing polymeric nitrite ester if a suitable proton acceptor is present. Aliphatic alcohols undergo the same reaction with dinitrogen tetroxide,[3] but the presence of a proton acceptor is not necessary for alkyl nitrite formation, and the reaction proceeds with or without the addition of an inert solvent.[4,6] Assuming that the formations of alkyl nitrite and polymeric nitrite proceed along the same reaction path so both are subject to the equilibrium in Scheme I and ignoring the fact that there are one- and two-phase reactions, the principal remaining difference is in the stability of the nitrite esters. Such difference is expressed in the value of the equilibrium constant, $C = [ROH][N_2O_4]/[RONO][HNO_3]$, which is reversely proportional to nitrite ester stability. Relatively large constants favoring unsubstituted hydroxyl groups and free dinitrogen tetroxide would thus be expected for the relatively unstable polymeric nitrite esters while relatively small constants would be typical of the more stable alkyl nitrites.

Experimental Section

Cellulose Trinitrite Ester. Cellulose trinitrite ester was prepared by treating cellulose (10 g) with N_2O_4 or NOCl as described previously,[3] but instead of DMF, 100 ml of (a) pyridine, (b) quinoline, (c) benzene–pyridine, 1:1 and 4:1, (d) acetone–pyridine, 4:1, and (e) ethyl acetate–pyridine, 4:1, was used. All mixtures formed viscous solutions with about 1 mol of N_2O_4 or NOCl per mole of hydroxyl radical. Experiments c–e formed some white precipitate consisting probably of pyridinium nitrate.

Similar results were obtained when a benzene–pyridine mixture was used in which the amount of pyridine was about 1 mol per mole of N_2O_4 or NOCl.

If triethyl- or tripropylamine was substituted for the pyridine, a strongly exothermic reaction occured on addition of N_2O_4 or NOCl without esterification of the cellulose. The same exothermic reaction was observed when N_2O_4 or NOCl was added to trialkylamine without cellulose being present.

Nitrite Esters of Polymers Other Than Cellulose. Pregelatinized corn starch (4 g) was dried at 60° in vacuo for 3 hr and suspended in 100 ml of DMF or DMA, and N_2O_4 was introduced at room temperature with mechanical stirring and under exclusion of moisture. After introduction of 5 g of N_2O_4, the mixture had thickened but still contained a considerable amount of suspended particles. The color of the mixture was slightly bluish green. Complete solubilization and deepening of the color occurred with about 6.1 g, and further addition of N_2O_4 did not increase the viscosity but only intensified the deep green color of the solution. Without pregelatinization of the starch, no solubilization was achieved under these reaction conditions.

Four-gram portions of guar gum, locust bean gum, alginic acid, hemicellulose, and polyvinyl alcohol were treated under identical conditions in 400, 400, 150, 150, and 40 ml of DMF or DMA, respectively. Prior to the reaction with N_2O_4, guar and locust bean gums were dissolved in water, precipitated and dehydrated with methanol, and dried in vacuo at 60° for 2 hr. Alginic acid was obtained from Kelco Gel HV[7] by dissolution in water, precipitation with $CaCl_2$, washing of the precipitate with 0.1 *N* HCl followed by water, dehydration with alcohol, and drying in vacuo at 50° for 2 hr. Hemicellulose was prepared by alkaline extraction of corn hulls[8] and purified by redissolving in water, precipitation with methanol, and drying at 110° for 2 hr. Polyvinyl alcohol (fully hydrolyzed) was used as supplied without further treatment.

Table III

Polyhydroxy polymer	Amount of N_2O_4 introduced, g	Observation
Guar	4.3	Thickening, light color
	6.2	Gelatinous, clear, deeper color
	7.2	Gelatinous, clear, deep green
Locust bean	5.6	Thickening, light color
	6.4	Gelatinous, clear, deeper color
	7.4	Gelatinous, clear, deep green
Alginic acid	3.5	Thick solution, light color
	3.8	Clear viscous solution, bluish green
Hemicellulose	5.5	Thick solution, undissolved particles
	5.8	Clear solution, bluish green
Polyvinyl alcohol	4.0	Thickening, colorless
	8.0	Clear solution after prolonged stirring, bluish green

The observations in Table III were made after introduction of various amounts of N_2O_4. With NOCl and DMF or DMA, the molar amount of reagent had to be increased substantially to obtain similar results. In the presence of pyridine, however, stoichiometric quantities of NOCl were sufficient. Similar results were also obtained when solvent mixtures as described above for cellulose were used.

Regeneration of Polyhydroxy Polymer. The nitrite ester solution in DMF was poured in a thin stream and with vigorous agitation into about 3 volumes of methanol, and the precipitate was filtered off and pressed out on a Büchner funnel, resuspended in fresh methanol, filtered off again, and dried in vacuo at 60°. All regenerated polymers were practically colorless, with the exception of guar and locust bean gums being light yellow. Films were obtained by spreading the solution on a glass plate and contacting it with aqueous methanol. The film was removed, washed with methanol, and dried in vacuo at 60°.

Analytical Procedures. Ir spectra were obtained with a Perkin-Elmer spectrophotometer, Model 257. All samples were used in the form of films prepared as described above.

Nitrogen was determined by the Kjeldahl method, and each polymer was analyzed before solvation and after regeneration.

For viscosity measurements, the polysaccharides were kept in DMF–N_2O_4 for 24 hr at 5°, regenerated, and the viscosities of their aqueous solutions determined at a pH of 6–7 with a Cannon Fenske Viscometer at 25°. pH values, if too low, were adjusted by the addition of dilute sodium hydroxide. Alginic acid prepared as described above was transformed into the ammonium salt before the viscosity measurement. Viscosities of aqueous solutions of the corresponding starting materials were measured under the same conditions, and results are given in Table II. Evidence of alkyl nitrite formation during regeneration of polysaccharide or polyvinyl alcohol by the addition of stoichiometric amounts of alcohol was obtained by isolation of the alkyl nitrite formed as described previously for cellulose.[3]

Isolation and Analysis of Polymeric Nitrite Ester. The nitrite ester solution in pyridine (or in DMF to which an excess of trialkylamine had been added) was poured slowly and with stirring into ice-cold water. The fibrous precipitate was removed, washed with ice-cold water, and pressed out on a Büchner funnel. Care had to be taken to maintain the temperature at below about 5° to avoid decomposition of the nitrite ester.

The moist nitrite esters thus obtained decomposed on drying.

They were soluble in DMF, pyridine, ethyl acetate, benzene, toluene, chloroform, acetone, and other common solvents for polymeric esters even in the presence of a protic solvent, such as alcohol. Solutions gelled on standing over an extended period of time finally resulting in separation of the corresponding polysaccharides or polyvinyl alcohol. On addition of mineral acid, the regenerated polymer separated immediately. The nitrite esters were analyzed by suspending the moist fibrous material in water, acidifying with sulfuric acid, and keeping the mixture in a closed Erlenmeyer flask with occasional shaking. After about 1 hr, a portion of the sample was neutralized with sodium hydroxide and the nitrite titrated with permanganate solution. The nitrate formed during titration was precipitated and identified as nitron nitrate.[9] The other portion was poured slowly and with agitation into 3–4 volumes of isopropyl alcohol to precipitate the polysaccharide and the precipitate was removed, dried in vacuo over P_2O_5 at 60°, and weighed.

Registry No.—Cellulose nitrite, 57255-90-0; starch nitrite, 57255-91-1; quar gum nitrite, 57108-91-5; locust bean gum nitrite, 57108-95-9; alginic acid nitrite, 57108-92-6; hemicellulose nitrite, 57108-93-7; polyvinyl alcohol nitrite, 57108-94-8; dinitrogen tetroxide, 10544-72-6; nitrosyl chloride, 2696-92-6.

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Selective Chlorinations in Sulfuric Acid. Synthesis of Some 2-Amino-5-chloro-, 2-Amino-3-chloro-, and 2-Amino-3,5-dichloropyridines

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A convenient and general process is described for the selective monochlorination of 2-aminopyridine and a number of methyl-substituted 2-aminopyridines. The chlorination of 2-aminopyridine at various sulfuric acid concentrations and the distribution of chlorinated products has been studied in detail. The results show that with increasing acidity dichlorination decreases, and in 72% sulfuric acid only traces of dichlorination occur. The selectivity of the chlorination reaction is ascribed to differences in the rate of chlorination of protonated vs. nonprotonated substrates.

We wish to report a convenient and general process for the selective monochlorination of 2-aminopyridine and a number of methyl-substituted 2-aminopyridines.

Several procedures for the chlorination of 2-aminopyridine have appeared in the literature. Chichibabin[1] reported the chlorination of 2-aminopyridine in ethanol. Later workers,[2,3] unable to duplicate the literature results, utilized 20% aqueous sulfuric acid at 25° as the solvent. However, in each of these procedures the desired monochlorinated product was found to be contaminated with significant amounts of 2-amino-3,5-dichloropyridine. A 70% yield of 2-amino-5-chloropyridine, with only slight formation of dichlorinated product, was obtained by treating 2-aminopyridine in concentrated hydrochloric acid with hydrogen peroxide.[4] These results on the chlorination of 2-aminopyridine in highly acidic media, and the varied selectivity reported in the halogenation of other aminopyridines,[5,6] led us to undertake a systematic investigation of this reaction.

Results

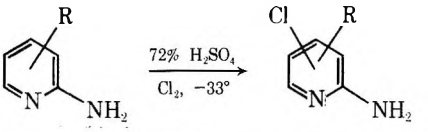
Chlorination of 2-Aminopyridine. Reaction of 2-aminopyridine (1) with a 2 molar excess of chlorine gas at various sulfuric acid concentrations gave the products listed in Table I. The distribution clearly shows that with increasing acidity dichlorination decreases, and in 72% sulfuric acid only traces of 2-amino-3,5-dichloropyridine (1c) are formed. Under optimum conditions (see Table II) the crude product 2-amino-5-chloropyridine (1b) had 99% purity and was obtained in 82–85% yield (98% based on recovered 1).

Table I
Chlorination of 2-Aminopyridine in Sulfuric Acid

Sulfuric acid concn		% product distribution	
Wt %	H_0	5-Chloro-	3,5-Dichloro-
17	−0.8	50	50
30	−1.5	52	48
45	−2.7	77	23
55	−3.7	92	8
72	−5.8	98	2

Chlorination of Substituted 2-Aminopyridines. The generality of the chlorination process and the specificity toward monochlorination were demonstrated by chlorination of the compounds listed in Table II. As one might anticipate, the methyl groups facilitate 3 substitution. The combined effect of the methyl group on product distribution in the case of the 2-amino-4-methyl- and 2-amino-6-methylpyridines (3 and 5) when compared with 2-amino-4,6-dimethylpyridine (6) was very close to an average. The structure of each chlorinated product was easily determined by ^1H NMR spectroscopy except in the case of 2-amino-6-methylpyridine (5). Each monochloro derivative of 5 displayed an AB system for the aromatic protons, and the spectra were almost identical. A literature search revealed that Parker and Shive had prepared the nitro derivative (9) of 2-amino-3-chloro-6-methylpyridine by an alternate route.[7] Using their procedure we nitrated 5 and separated the mononitro products (7 and 8), and subsequent

Table II
Selective Chlorination in Sulfuric Acid

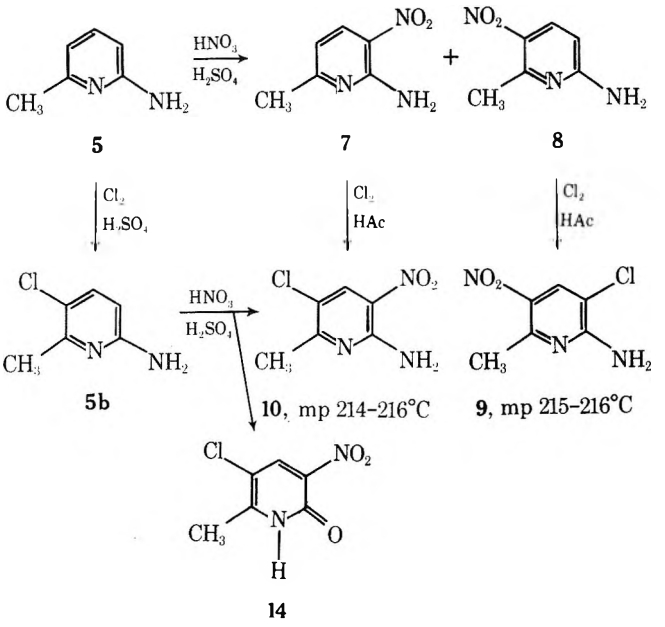


(1)

No.	Starting material	pK_a[a]	% product distribution[b] a, 3-Chloro	b, 5-Chloro	c, 3,5-Dichloro	% yield[c]
1	2-Aminopyridine	6.14	0	98	Tr	85 (98)
2	2-Amino-3-methylpyridine	6.52	0	99	0	92 (98)
3	2-Amino-4-methylpyridine	6.76	58	41	Tr	90 (99)
4	2-Amino-5-methylpyridine	6.50	87	0	0	14 (16)
5	2-Amino-6-methylpyridine	6.69	12	88	Tr	85 (99)
6	2-Amino-4,6-dimethylpyridine	7.12	39	59	2	67 (82)
1b	2-Amino-5-chloropyridine	4.71	0	97	3	3 (99)

[a] The pK_a data were taken from W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, 31, 1295 (1966), except for 1b which was from P. J. Brignell, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc. B*, 117 (1970). [b] Product distribution was determined by GLC on the entire product mixture. [c] Yields in parentheses are based on recovered starting material.

Scheme I



chlorination of the individual isomers afforded respectively the known 2-amino-3-chloro-5-nitro-6-methylpyridine (**9**) and the new chloro derivative **10** (Scheme I). The major monochlorinated isomer from **5**, which consisted of 88% of the product, was nitrated and gave two products, one of which was a mononitro derivative identical in all respects with **10**. A mixture melting point with **10** was not depressed, although one with **9** was depressed. Thus the structure of the major monochlorinated product from **5** was **5b**. The other product from nitration of **5b** was identified as 3-nitro-5-chloro-6-methyl-2-pyridone (**14**), formed by hydrolysis of the 2-amino moiety.

To determine the specificity and relative reactivity of the aminopyridine nucleus for monochlorination, the compounds listed in Table III were treated with 2 mol of chlorine in 72% sulfuric acid. 2-Amino-5-chloropyridine (**1b**) completely resisted further chlorination and the results were identical with the reaction with 1 mol of chlorine. Selective monochlorination was lost with **3**, **5**, and **6** owing to the enhanced activity caused by the methyl group(s). It is interesting to note that while both the 4-methyl- (**3**) and 6-methyl- (**5**) pyridines form 3-chloro derivatives with 1 mol of chlorine, treatment with a second mole of chlorine converts these isomers completely to the 3,5-dichloro derivatives, while the 5-monochloro isomers survive.

Table III
Chlorination with 2 Mol of Chlorine in 72% Sulfuric Acid

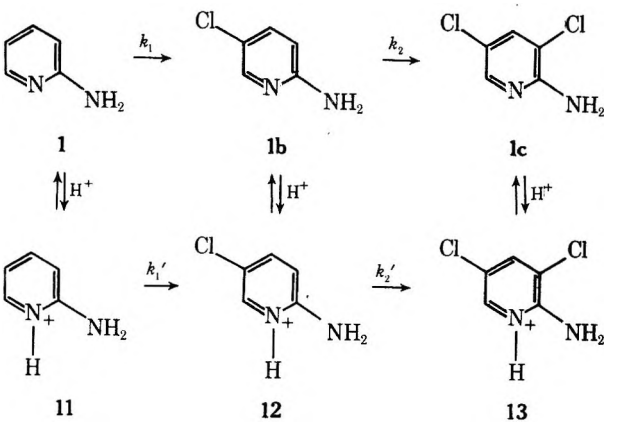
No.	Starting material	% product distribution[a] a, 3-Cl	b, 5-Cl	c, 3,5-DiCl	% yield[b]
1	2-Aminopyridine	0	98	Tr	85 (98)
3	2-Amino-4-methylpyridine	36	31	33	95 (99)
5	2-Amino-6-methylpyridine	Tr	52	48	95 (98)
6	2-Amino-4,6-dimethylpyridine	Tr	8	92	83 (92)

[a] Product distribution was determined by VPC. [b] Yields in parentheses are based on recovered starting material.

Discussion

We have interpreted our results on these chlorination reactions with respect to the equilibria shown for 2-aminopyridine in Scheme II. Katritzky and co-workers[8] determined

Scheme II



the rate of bromination of **1b** in dilute sulfuric acid at 20° and showed that it decreased rapidly with increasing acidity. Therefore, at very high acidities (≥72% sulfuric acid) both **1** and **1b** are predominantly protonated and reaction with chlorine would be largely limited to **11** and **12**. One plausible explanation of our results with these 2-aminopyridines is (cf. Tables II and III) that k_1' is much greater

Table IV
Properties of Some Chloro-2-aminopyridines

No.	Compd	Mp, °C	Proton chemical shifts, τ[a] 3	4	5	6	Anal.[b]
1b	2-Amino-5-chloropyridine	136–137	H 3.54 (d)	H 2.65 (dd)		H 2.13 (d)	
1c	2-Amino-3,5-dichloropyridine[c]	85–86		H 2.34 (d)		H 2.04 (d)	
2b	2-Amino-3-methyl-5-chloropyridine	67–68	CH_3 7.91	H 2.77 (d)		H 2.14 (d)	C, H, N, Cl
3a	2-Amino-3-chloro-4-methylpyridine[c]	96–98		CH_3 7.70	H 3.49 (d)	H 2.18 (d)	C, H, N
3b	2-Amino-4-methyl-5-chloropyridine[c]	149–151	H 3.65 (s)	CH_3 7.75		H 2.07 (s)	C, H, N, Cl
3c	2-Amino-3,5-dichloro-4-methylpyridine[c]	124–126				H 2.03 (s)	C, H, N, Cl
4a	2-Amino-3-chloro-5-methylpyridine	61–62		H 2.70 (d)	CH_3 7.83	H 2.20 (br)	C, H, N, Cl
5a	2-Amino-3-chloro-6-methylpyridine[c]	63–66		H 2.68 (d)	H 3.79 (d)	CH_3 7.94	C, H, N, Cl
5b	2-Amino-5-chloro-6-methylpyridine	73–74	H 3.73 (d)	H 2.68 (d)		CH_3 7.94	C, H, N, Cl
5c	2-Amino-3,5-dichloro-6-methylpyridine	133–135		H 2.59 (s)		CH_3 7.90	C, H, N, Cl
6a	2-Amino-3-chloro-4,6-dimethylpyridine[c]	110–113		CH_3 7.77	H 3.60 (s)	CH_3 7.77	C, H, N
6b	2-Amino-5-chloro-4,6-dimethylpyridine	123–124	H 3.77 (s)	CH_3 7.71		CH_3 7.57	C, H, N, Cl
6c	2-Amino-3,5-dichloro-4,6-dimethylpyridine	151–152		CH_3 7.60		CH_3 7.57	C, H, N, Cl

[a] Compounds **1b** and **1c** were run in Me_2SO, and all others were done in $CDCl_3$. The coupling constants, where applicable, were $J_{3,4}$ and $J_{4,5} \simeq 8$, $J_{4,6} \simeq 2$, and $J_{5,6} \simeq 5$ Hz. [b] The analytical data were acceptable within 0.3% for all elements. [c] These substances were separated by preparative silica gel chromatography (3:2 chloroform–dioxane), and purified by sublimation.

than k_2', and this difference is what allows selective chlorination to proceed.

Experimental Section

^{1}H NMR spectra were determined on a Varian T-60 spectrometer. The high-resolution mass spectra were determined on a Model 21-110 Consolidated Electrodyne Corp. spectrometer. Other mass spectra were determined on a Hitachi RMU-6E spectrometer. Melting points were run on a Thomas-Hoover apparatus and were corrected. The gas chromatographic analyses were done by Mr. M. Yager and Mr. C. Hartlage on a 6-ft column packed with 2% Carbowax 20M on Chromosorb G (80–100 mesh) with a He flow rate of 25 ml/min at 140°C. Elemental analyses were performed by Mr. G. Maciak and associates of Eli Lilly and Co.

General Chlorination Procedure [e.g., Synthesis of 2-Amino-5-chloropyridine (1b)]. To a 1-l. flask equipped with a stirrer, thermometer, gas addition tube, and dry ice condenser was added 470 ml of 72% aqueous sulfuric acid. With external cooling, 94.1 g (1.0 mol) of 2-aminopyridine (1) was added in portions to maintain an internal temperature of 25° or below. The ice bath was removed and precondensed chlorine gas (71 g, 45.5 ml, 1.0 mol) was allowed to evaporate over a 2-hr period through the gas inlet tube beneath the surface of the reaction mixture. The temperature dropped slowly to −30°, and after completion of the chlorine addition, the mixture was stirred for an additional 90 min with a chlorine reflux. The dry ice condenser was removed, and the solution was allowed to come to room temperature. The solution was poured into 1 kg of ice and the pH adjusted to 10 with 50% aqueous sodium hydroxide. The resulting chilled slurry was filtered and the solid was washed with cold water and afforded after drying (2 hr, 50°, in vacuo) 105.3 g (82%) of **1b**, mp 135–137° (lit. 135–137°), GLC analysis showed 0.2% **1**, and 1.1% **1c**. The filtrate and washes were extracted with chloroform (3 × 100 ml), and the combined extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness in vacuo, affording 18.0 g of tan, crystalline solid; GLC analysis showed 64.5% (11.6 g) **1**, 7.3% (1.3 g) **1c**, and 28.2% (5.1 g) **1b**.

The chloro-2-aminopyridines described in Tables II and III were prepared by the general chlorination procedure and in most cases the scale was 0.2–0.25 mol per run. Unless indicated otherwise in Table IV, when a mixture was obtained, the individual isomers were separated and purified by chormatography on silica gel and eluted with ethyl acetate. Some properties of the chloro-2-aminopyridines are listed in Table IV.

2-Amino-3-chloro-5-nitro-6-methylpyridine (9). To compound 8 (1.53 g, 10 mmol, mp 188–190° [7]) in 40 ml of glacial acetic acid at 25° was added chlorine gas beneath the surface from 0.45 ml (10 mmol) of liquid chlorine. The mixture was stirred for 12 hr and poured into 40 ml of water, and the resulting solid was washed with water and dried, affording 0.5 g of a yellow-orange powder, mp 195–200°. Two crystallizations from ethanol gave needles, mp 211–214° (lit.[7] mp 215–216°). A mixture melting point of **9** with **10** made from **5b** was depressed (mp 180–190°). TLC, methylene chloride–silica gel, showed R_f **9** 0.40 and R_f **10** 0.54.

2-Amino-3-nitro-5-chloro-6-methylpyridine (10). A. Preparation from 7. To compound **7** (1.53 g, 10 mmol, mp 154–155° [7]) in 40 ml of glacial acetic acid at 25° was added chlorine gas beneath the surface from 0.45 ml (10 mmol) of liquid chlorine. The mixture was stirred for 2 hr and poured into 40 ml of water, and the yellow solid was washed with water and dried, affording 1.3 g (70%). Crystallization from ethanol gave **10**, 1.2 g of yellow needles, mp 214–216°. A mixture melting point of this sample with **10** made from **5b** was not depressed (mmp 213–216°). The two samples were identical by TLC and VPC.

B. Preparation from 5b. To 3 ml of concentrated sulfuric acid (*d* 1.84) at 5° was added 1.42 g (10 mmol) of **5b**, followed by 2 ml of a 1:1 mixture of nitric acid (*d* 1.42) and sulfuric acid (*d* 1.84). The mixture was slowly heated to 50° when an exotherm occurred to 70° and rapidly subsided. Heating at 50–60° was continued for 2 hr, and the solution was cooled to 25° and poured on 10 g of ice, affording a yellow solid which was filtered, washed with water, and dried. The crude yellow powder (1.0 g) was a 1:1 mixture of TLC. Two crystallizations from ethanol and one from acetone gave yellow plates (0.4 g), mp 210–214°, identical with **10** from **7** by TLC, VPC, and mixture melting point. A mixture melting point of **10** with **9** was depressed.

Isolation of 3-Nitro-5-chloro-6-methyl-2-pyridone (14). The combined ethanol filtrates from the crystallization of **10** were shown by TLC to contain the other spot found in the crude prod-

uct. Crystallization from benzene gave gold needles, mp 216–218°. The high-resolution mass spectrum gave the empirical formula $C_6H_5N_2O_3Cl$, and revealed the replacement of NH_2 by O, the presence of Cl, and NO_2: ir ($CHCl_3$) 1690 cm^{-1} (C=O).

Supplementary Material Available. GC–mass spectral data for product mixtures from chlorination of **3, 5,** and **6** (6 pp) will appear following these pages in the microfilm edition of this volume of the journal.

Registry No.—**1,** 504-29-0; **1b,** 1072-98-6; **1c,** 4214-74-8; **2b,** 20712-16-7; **3a,** 56960-76-0; **3b,** 36936-27-3; **3c,** 31430-47-4; **4a,** 31430-41-8; **5a,** 56960-77-1; **5b,** 36936-23-9; **5c,** 22137-52-6; **6a,** 56960-78-2; **6b,** 56960-79-3; **6c,** 56960-80-6; **7,** 21901-29-1; **8,** 22280-62-2; **9,** 56960-81-7; **10,** 56960-82-8; **14,** 56960-83-9.

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Pivaloylnitrene. Reactions with Olefins and Dichloromethane Solvent Effect

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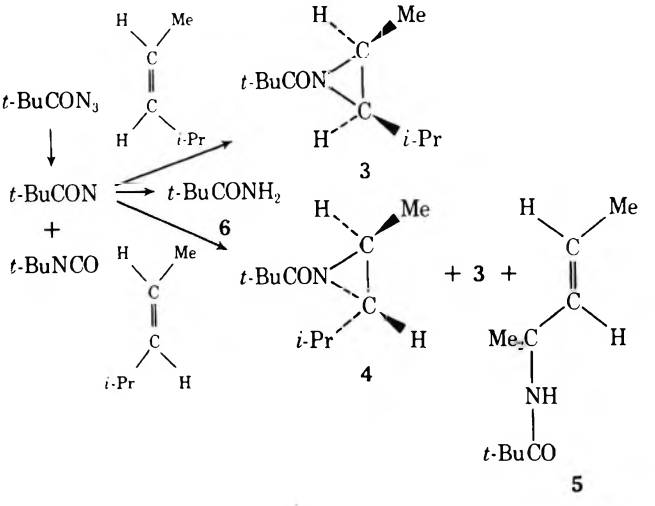
Pivaloylnitrene, generated photolytically from pivaloyl azide, adds to olefins stereospecifically in its singlet state and stereoselectively in its triplet state. Dichloromethane solvates and stabilizes the singlet nitrene without markedly decreasing its reactivity. Hydrocarbon solvents did not show such a stabilizing effect.

The photolysis of pivaloyl azide, *t*-BuCON$_3$ (**1**), generates pivaloylnitrene, *t*-BuCON (**2**), in about 50% yield, together with about the same yield of *tert*-butyl isocyanate. The latter is formed by an independent, parallel, concerted path[2,3]—the nitrene does not rearrange to *t*-BuNCO at an appreciable rate.[4–6] Of the pivaloylnitrene formed, most can be intercepted by cyclohexene; we obtained a 45% yield of 7-pivaloyl-7-azabicyclo[4.1.0]heptane plus minor yields of other nitrene products by trapping *t*-BuCON with cyclohexene.[2] Including the 41% yield of *t*-BuNCO, the material balance is in the order of 90%. Thus, pivaloylnitrene seemed to be a suitable as well as a representative[2,3] carbonylnitrene for the study of solvent effects and stereochemistry in reactions of singlet and triplet carbonylnitrenes with olefins. Such a study is reported here. A part of our results forms part of a communication,[7] and a small part overlaps with Swern's[6] work on the photolysis (with 254-nm light) of pivaloyl azide in neat *cis*- and *trans*-4-methyl-2-pentene. The results of the few duplicated experiments agree with those of Swern.

Scheme I



Results and Discussion

Photolysis of pivaloyl azide by 254-nm light in the presence of *cis*-4-methyl-2-pentene gave the cis aziridine **3** and traces of pivalamide (**6**). Under the same conditions, *trans*-4-methyl-2-pentene gave both aziridine stereoisomers, **3** and **4**, some **6**, and also the apparent allylic C–H insertion product **5**. The structures of the products **3, 4, 5,** and **6** were confirmed by their comparison with authentic samples. Table I shows the yields of the products. The apparent tertiary allylic C–H insertion product **5** was formed only from the trans olefin, and no analogous cis product was found in photolyses in cis olefin or its solutions. This might be due to the greater reactivity of the cis double bond (see below), which intercepts all the nitrene. It could also be due to steric hindrance of the approaching nitrene by the methyl group in the cis olefin, or both factors could combine to render the C–H insertion on C-4 unobservable in the case of the *cis*-4-methyl-2-pentene. Reactions analogous to the formation of the aziridines and of **5** have been observed earlier with cyclohexene as the substrate.[2]

Table I shows some regularities. The cis olefin gives only cis aziridine, while the trans olefin gives trans and cis aziridines and **5**. Furthermore, the yield of the trans aziridine increases with decreasing olefin concentration, while the yields of **5** and of cis aziridine are nearly constant in the photolyses of trans olefin in various concentrations in dichloromethane solutions. However, caution is in order owing to the photolability of *N*-pivaloylaziridines when using 254-nm light.[2] The aziridines **3** and **4** absorb significantly at 254 nm: **4** has ϵ 414 at 254 nm (λ_{max} 244 nm, ϵ 483) and **3** has ϵ 473 at 254 nm (λ_{max} 247 nm, ϵ 514). With the absorption coefficient of the azide **1** being only about 100 at 254 nm, the danger of photodecomposition of products exists, even when the photolyses are not carried to the point of quantitative nitrogen evolution. Therefore, all subsequent photolyses were carried out using fluorescent uv lamps which emit 83% of their light between 280 and 450

Table I
Photolyses of Pivaloyl Azide with 254-nm Light in the Presence of *cis*- and *trans*-4-Methyl-2-pentene

Olefin	Mol % olefin in CH_2Cl_2	% completion[a]	Aziridine yields,[b] %			Yield of 5, %	Yield of 6, %
			Total	Cis	Trans		
Cis	100	74	25.2	25.2	0	0	Trace
Trans	100	89	8.3	3.9	4.4	11.8	Trace
Cis	50	88	37.8	37.8	0	0	Trace
Trans	10	84	19.4	5.4	14.0	12.0	3.6
Cis	5	82	34.0	34.0	0	0	Trace
Trans	5	86	16.4	3.9	12.5	12.8	3.1

[a] Reaction stopped at this yield of nitrogen evolved. [b] Based on nitrogen evolved (= azide decomposed).

Table II
Photolyses of Pivaloyl Azide with 300-nm light in the Presence of *cis*-4-Methyl-2-pentene and Dichloromethane[a]

Mol % olefin in CH_2Cl_2	% completion	Aziridine yields, %		Yield of 5	Yield of 6
		Cis	Trans		
100	75	40	0	0	0
47	78	38	0	0	0
36	74	48	0	0	0
18	69	45	0	0	0
4.4	99	33	0	0	0
1.3	68	2.1	0	0	0

[a] All yields based on azide decomposed.

nm, with a peak output near 300 nm. These lamps improved the aziridine yields over those reported in Table I and by Swern.[6]

Table II shows the results of photolyzing pivaloyl azide in *cis*-4-methyl-2-pentene and its dichloromethane solutions. The yield of the cis aziridine peaks at 36 mol % olefin concentration and drops off sharply below 4 mol %, without the formation of a detectable yield of pivalamide (**6**), or of the trans aziridine **4**. As discussed in more detail below, this is consistent with all of the singlet and triplet nitrene reacting with the olefin to form the cis aziridine, or dissociating to HNCO and isobutene (or to corresponding ion or radical pairs), which then form the observed polymer.[2]

The results obtained with *trans*-4-methyl-2-pentene under the same conditions are shown in Table III. Besides *t*-BuNCO, three main products are formed. The yield of the trans aziridine **4** is seen to increase with decreasing olefin concentration in the range from 78 to 3 mol %. The cis aziridine **3** is formed in 5.56 ± 0.45% yield, constant over the same concentration range. The tertiary allylic insertion product **5** also is formed in constant yield: 9.11 ± 0.78% if computed over the olefin concentration range from 78 to 12 mol %, or 9.42 ± 0.82% if computed over the range from 78 to 9 mol %. At 1.3 mol % olefin concentration the yields of both aziridine isomers are down, while that of **5** is up. The drastic differences between the two olefin isomers prompted an attempt to measure their relative reactivities toward *t*-BuCON. Photolysis of *t*-BuCON$_3$ in a 1:1 mixture of *cis*- and *trans*-4-methyl-2-pentene gave a 40% yield of the cis aziridine **3** only. A 9:1 trans:cis olefin mixture gave a 23% yield of **3**, no trans aziridine **4**, and a 0.8% yield of **5**. Given the detectability of a 1% yield of **4**, the rate constant for the formation of cis aziridine (**3**) from the cis olefin must be at least 230 times as large as the rate constant for the formation of the trans aziridine (**4**) from the trans olefin. In contrast to this factor of ≥230, ethoxycarbonylnitrene forms aziridine (stereospecifically) only 1.4 times faster with *cis*- than with *trans*-4-methyl-2-pentene.[8] Since the two nitrenes are quite similar in their general chemical behavior,[2] the difference here must be due to steric reasons. As seen on molecular models, the *t*-BuCO on the nitrogen can avoid

Table III
Photolyses of Pivaloyl Azide with 300-nm Light in Dichloromethane Solutions of *trans*-4-Methyl-2-pentene[a]

Mol % olefin	% completion	Aziridine yields, %		Yield of 5, %	Ratio of 3:5	Mol % CH_2Cl_2
		Trans	Cis			
78	79	7.4	5.8	9.7	0.60	22
68	83	7.7	5.8	10.5	0.55	32
57	59	11.0	6.2	9.9	0.63	43
47	29	12.9	5.8	9.0	0.64	53
47	65	13.0	5.0	7.6	0.66	53
47	51	13.0	5.6	9.6	0.58	53
47	75	13.0	5.8	9.4	0.62	53
23	65	16.2	5.1	9.3	0.55	77
23	65	16.2	4.6	8.7	0.53	77
23	65	15.6	5.2	8.7	0.60	77
18	49	15.8	5.9	8.5	0.69	82
12	49	15.1	5.9	8.4	0.70	88
9	56	18.5	6.1	10.3	0.59	91
3	66	20.5	5.4	12.3	0.44	97
1.3	65	16.3	4.1	13.5	0.30	98.7

[a] Yields are based on azide decomposed and would have to be approximately doubled to base them on nitrene produced.

all interaction with the alkyl groups on C_2 and C_3 in the cis aziridine **3** only, by assuming the anti configuration on the ring. Such an orientation should be maintained already during the approach of the nitrene to the olefin, and in the transition state. In the trans aziridine **4** (and during its formation), no such orientation is possible; both N invertomers of **4** have pivaloyl–alkyl interactions. Of the olefins, the cis isomer has the higher thermochemical energy, and together with the steric hinderance developed in the two transitions states, the one forming the trans aziridine ends up with a free energy of activation sufficiently larger than that of its cis counterpart to explain the difference in reactivity of the two olefins. Similarly, the diradical *t*-BuCON-ĊHMeĊH-*i*-Pr, formed from triplet *t*-BuCON and either cis or trans olefin, should prefer ring closure to the cis aziridine **3**. Thus, we expect the triplet nitrene addition to be stereoselective (if nonstereospecific) and form cis aziridine from either olefin. The hypothesis explains both the high relative reactivity of the cis olefin and the absence of trans aziridine **4** in all reaction mixtures arising from cis olefin, regardless of the experimental conditions.

The 0.8% yield of **5** from a 9:1 trans:cis olefin mixture attests to the presence of triplet pivaloylnitrene, but no trans aziridine was formed. How much of the cis isomer **3** formed in this reaction is due to the reaction of triplet nitrene with cis olefin we do not know. The formation of **3** from the trans olefin is attributed to the triplet nitrene because an open-chain intermediate must intervene to change the configuration at one C atom. This intermediate, by analogy with other nitrene reactions,[8,9] is assumed to be the triplet diradical *t*-BuCONĊHMeĊH-*i*-Pr. We also attribute to

the triplet nitrene the formation of 5, because its yield is unaffected by the concentration of CH_2Cl_2 in the reaction mixtures. Singlet C–H insertion yields of similar alkanoylnitrenes have been found to increase drastically with increasing dichloromethane concentration.[7] The formation of 5 seems to involve the abstraction of the tertiary allylic hydrogen of the trans olefin, followed by the combination of the radical pair *t*-BuCONH $\dot{C}Me_2CH$=CHMe. The constant yields of 3 and 5 (Table III) over a wide olefin concentration range suggest that the triplet nitrene forming them is present in constant concentration—it cannot be formed by intersystem crossing (favored where the trapping agent concentration is low). The triplet nitrene must thus be formed directly in the photolysis of the parent azide. Such direct triplet species formation is already known for ethoxycarbonylnitrene[9] and certain carbenes.[10]

The almost threefold yield increase of the thermodynamically disfavored trans aziridine 4 with decreasing concentration of the trans olefin would not be expected in a truly inert medium. Rather, the delay incurred before reactive collision with an olefin molecule would favor competing reactions, such as decomposition or intersystem crossing of the nitrene. This would lower the trans aziridine yield. Intersystem crossing would produce triplet nitrene and increase the yields of 3 and 5, which is not observed. Indeed, the total yield of (singlet and triplet) nitrene products increased with decreasing olefin concentration (increasing dichloromethane concentration) to over 38% at 97 mol % dichloromethane (3% olefin) concentration from 23% at 30 mol % CH_2Cl_2 (70% olefin). (The yields are based on azide decomposed; based on nitrene presumably formed they are about 76 and 46%, respectively.) Thus, it appears that dichloromethane has a singlet nitrene stabilizing effect of the kind predicted by Hoffmann.[11] To test this, we ran photolyses in neopentane instead of dichloromethane solutions. Neopentane is very unreactive toward carbonylnitrenes, possessing only primary C–H bonds. The yield of *N*-neopentylpivalamide from the photolysis of pivaloyl azide in neat neopentane is only 0.2%.[3] Photolyses of *cis*-4-methyl-2-pentene in neopentane solution gave cis aziridine yields of 40.2% at 70 mol % olefin concentration, 21.3% at 25% olefin concentration, and only a trace of cis aziridine at 10% olefin concentration. This is in sharp contrast to the 33% yield of 3 obtained in a 4.4% cis olefin solution in dichloromethane (Table II). As expected from the stereoselectivity argument (above), no trans aziridine 4 was formed.

Using *trans*-4-methyl-2-pentene in neopentane solutions gave complex mixtures, and no quantitative method was found for separating the volatile products from a gummy material very similar to that resulting from photolyzing pivaloyl azide in inert solvents.[3] The yield of volatile products decreased with decreasing olefin concentration, while the ratio of 3:4 remained approximately constant. The mixture was much more complex than that formed in dichloromethane solution, and the yield of singlet products was low.

In Hoffmann's model[11] singlet nitrenes are stabilized by the symmetrical approach of solvent unshared electron pairs to the nitrene. This certainly agrees with our results, as well as with those of Breslow[12] (published simultaneously with our communication[11]), who used hexafluorobenzene. More recently, dichloromethane has been found to stabilize the singlet state of ethoxycarbonylnitrene as well.[13,14]

The use of the cis and trans butenes, rather than the 4-methyl-2-pentenes, promised greater reactivity (less hindrance) of the trans olefin and less reactivity of the allylic, but now primary, C–H bonds. Photolyses of *cis*-2-butene (7)–dichloromethane–pivaloyl azide solutions gave, besides

Table IV
Photolyses of Pivaloyl Azide in Dichloromethane Solutions of *cis*-2-Butene

Mol % olefin	% completion	Yields, % Cis oxazoline 9	Cis aziridine 8	Sum 8 + 9
20	69	1.1	48.9	50.0
15	63	1.2	58.0	59.2
10	72	1.0	53.4	54.4
5	60	1.7	57.9	59.6
3.3	51	6.1	10.8	16.9

t-BuNCO, the cis aziridine 8. VPC analysis of the mixture converted part of the 8 into its ring expansion product 9, *cis-tert*-butyl-4,5-dimethyl-2-oxazoline. This rearrangement occurs, upon VPC, with pure 8 as well, and our ir and NMR spectra of the crude reaction mixture showed 9 to be absent. We therefore regard the sum of the yields of 8 and 9 as the minimum yield of 8 originally formed. The stereospecific rearrangement of *N*-acylaziridines to oxazolines of the same configuration is well known,[15] as is the ring opening of *N*-acyl-2-alkylaziridines to allylamides.[16] In our cases, such a ring opening did not occur during our analytical VPC routine, but 8 was converted to 10 under more drastic VPC conditions.

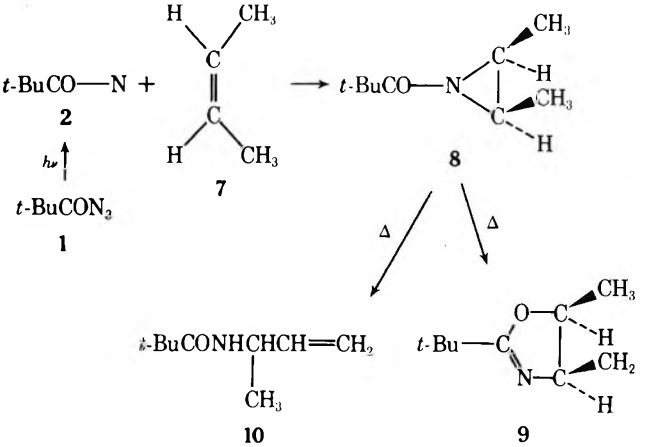


Table IV shows no distinct yield maximum for 8 + 9 in photolyses of 1 in the presence of 5–20% of 7. No trans aziridine 12 or the corresponding oxazoline 13 were found. It seems that the nitrene 2 adds rapidly and almost quantitatively to the olefin, since the yield average obtained (55.8 ± 4.5%) is based on the azide decomposed and represents almost all the nitrene formed. The sudden drop in yields from 5 to 3.3 mol % olefin concentration might not be real but rather the result of some systematic error, such as a solvent impurity. The disproportionate yield of 9 supports this suspicion.

Photolyses using *trans*-2-butene (11) gave rather constant yields of the trans aziridine 12 (and its ring expansion product 13), 31.6 ± 1.4% over an olefin concentration range from 50 to 2 mol % (Table V). Nonstereospecific addition gave 8 in 1.1% yield. Thus, the pivaloylnitrene–dichloromethane adduct or solvate adds stereospecifically to the olefins. The products of nonstereospecific addition are attributed to triplet pivaloylnitrene. Just how large their fraction is, is hard to say. The ratio of aziridine of retained configuration (trans) to that of its cis isomer is much higher than the corresponding ratio 4/(3 + 5) in the experiments using *trans*-4-methyl-2-pentene as the olefin (Table III). Possibly, less triplet is formed in the presence of 2-butene, or less of the triplet nitrene is captured by the *trans*-2-butene, or less of the capture product is converted to recognizable final products.

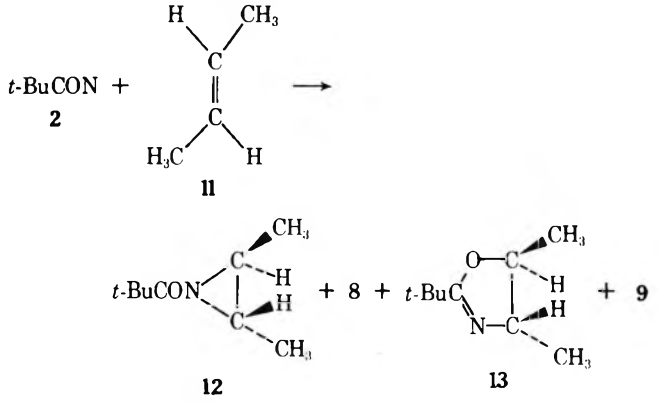
Table V
Photolyses of Pivaloyl Azide in Dichloromethane Solutions of *trans*-2-Butene

Mol % olefin	% completion	Aziridine yields, %		Oxazoline yields, %		Total yields, %	
		Trans	Cis	Trans	Cis	Trans	Cis
50	63	25.0	1.2	5.8	Trace	30.8	1.2
20	56	28.8	0.9	3.2	Trace	32.0	0.9
10	81	25.8	0.9	5.3	0	31.1	0.9
5	88	25.8	1.2	8.0	0	33.8	1.2
2	82	20.8	1.5	9.3	Trace	30.1	1.5

Table VI
Photolyses of Pivaloyl Azide in Cyclopentane Solutions of *cis*-2-Butene

Mol % olefin	% completion	Yields, %		
		Cis oxazoline 9	Cis aziridine 8	Sum 8 + 9
20	67	0.8	54.1	54.9
15	71	1.1	54.6	55.7
15	75	0	58.8	58.8
5	65	1.9	59.6	61.5

To single out a dichloromethane solvent effect, the 2-butene–pivaloyl azide photolyses were also run in a hydrocarbon solvent. Since, in principle, it could be true that neopentane, rather than dichloromethane, is the "special" solvent, we used the structurally rather different cyclopentane. While it reacts more readily with pivaloylnitrene than does neopentane, the olefins could still be expected to compete well with the C–H insertion into the solvent. Photolysis of pivaloyl azide in pure cyclopentane gave a maximum yield of 13% of *N*-cyclopentylpivalamide,[3] less when the cyclopentane concentration was lowered. Photolyses of **1** in cyclopentane solutions of *cis*-2-butene (**7**) gave results very similar to those obtained in dichloromethane, an average 58% yield of **8** + **9**. That indicates a practically quantitative



interception of the nitrene, at a rate much faster than that of any competing process (Table VI). Photolyses of **1** in cyclopentane solutions of the trans olefin **11** again produced a strong contrast of results, both in comparison with the cis olefin–cyclopentane runs, and with the trans olefin–dichloromethane runs. As shown in Table VII, photolyses in cyclopentane solutions of **11** gave about the same yields of the cis aziridine as found in dichloromethane solutions. The trans aziridine **12**, however, is formed in much lower yields and its formation could no longer be observed at 5 and 2 mol % concentrations of **11**, concentrations at which 34 and 30% yields were formed in dichloromethane. At 5 and 2 mol % **11** in cyclopentane, the reactions mixtures became intractable for quantitative analysis. The diminished aziridine yields in cyclopentane solutions cannot be explained by a removal of singlet nitrene due to C–H insertion into cyclopentane. *N*-Cyclopentylpivalamide is formed in a maximum yield of 12–13% in pure cyclopentane,[3] which thus is not reactive enough to compete effectively with the olefin. This is confirmed by the data in Table VI and VII, which show no such competitive effect. Our VPC analysis procedure was not suitable for measuring the yield of *N*-cyclopentylpivalamide, but a modest yield of it was isolated and identified spectrally. Interestingly, the yield of nonstereospecific addition products (Table VII) remains reasonably constant between 70 and 10 mol % *trans*-2-butene concentration (av 1.03 ± 0.2), the same value as in dichloromethane solution (av 1.1 ± 0.2).

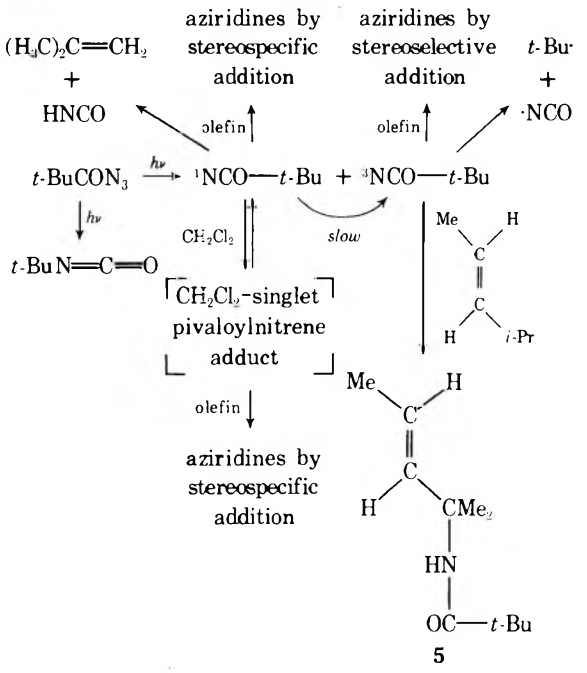
Conclusions

The experimental results agree with Scheme II. Photolysis of pivaloyl azide (**1**) produced pivaloylnitrene (**2**), a part of which is formed directly in the triplet state. This triplet nitrene adds nonstereospecifically to olefins and attacks the tertiary allylic C–H of *trans*-4-methyl-2-pentene to give **5**. Given sufficient steric hindrance, such as in the 4-methyl-2-pentenes, the addition of the triplet nitrene to the C=C double bond is highly stereoselective, producing the cis aziridine from both cis and trans olefins. Thus, the triplet products are not directly apparent in reactions with the cis olefin. In reactions with *trans*-4-methyl-2-pentene the triplet products are the cis aziridine **3** and the formal allylic insertion product **5**, produced in about 18% total yield. In reactions with *trans*-2-butene, only about 1% triplet products are actually detected. This might be due to a loss of triplet nitrene (^{3}NCO-*t*-Bu → HNCO + $Me_2C{=}CH_2$) because of a less reactive substrate, or it could be due to lesser direct formation of triplet nitrene in the photolysis process, as compared to solutions containing the 4-methyl-2-pentene. Intersystem crossing seems to become important only at very low olefin concentrations. The main paths for disappearance of singlet pivaloylnitrene are bimolecular reactions with olefins and dissociation to HNCO and isobutene.[2,3] A powerful "singlet stabilizing" effect is

Table VII
Photolyses of Pivaloyl Azide in Cyclopentane Solutions of *trans*-2-Butene

Mol % olefin	% completion	Aziridine yields, %		Oxazoline yields, %		Total yields, %	
		Trans	Cis	Trans	Cis	Trans	Cis
70	65	10.1	0.9	3.0	Trace	13.1	0.9
50	62	16.1	1.2	4.4	Trace	20.5	1.2
20	57	15.2	0.8	3.2	Trace	18.4	0.8
20	64	15.0	1.4	3.9	Trace	18.9	1.4
15	67	13.2	1.1	3.2		16.4	1.1
10	70	5.8	0.8	3.7		9.5	0.8

Scheme II



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exerted by dichloromethane, but not by neopentane or cyclopentane. The effect is most clearly seen in reactions of trans olefins, rather than in those of the more reactive cis olefins, which intercept efficiently even the unstabilized singlet pivaloylnitrene. We assume the existence of a singlet nitrene–dichloromethane solvate or complex, in equilibrium with the "free" nitrene. This complex is much longer lived than the "free" nitrene but is still capable of reacting with C=C double bonds, much in the manner of the "free" nitrene. Our earlier work[7] shows that the complex is also capable of reacting with C–H bonds. The nature of the complex and the requirements for a solvent to form "singlet stabilized" solvates or complexes remain to be investigated.

Experimental Section

Hydrocarbons used were Phillips pure grade (99% minimum purity). The dichloromethane was MCB spectroquality grade. *cis*- and *trans*-4-methyl-2-pentene were distilled before use and stored under nitrogen.

Pivaloyl azide (1) was prepared from *t*-BuCOCl and NaN_3.[2] It starts to decompose above 0°, might explode without warning, and its vapor is toxic.

2-Isopropyl-3-methyl-*N*-*tert*-butylcarbonylaziridines (cis, 3, and trans, 4) were prepared by Hassner's method.[17] The diastereomeric **2-*N*-ethoxycarbonylamino-3-iodo-4-methylpentanes** were obtained by adding 0.1 mol of the olefin at −10° over 30 min to a slurry of 0.1 mol of iodine and 0.13 mol of freshly prepared silver cyanate in 200 ml of ether. After addition and stirring at room temperature for 5 hr, the solutions were filtered, then concentrated to half their volumes. Absolute ethanol (200 ml) was added and the mixtures heated to reflux for 4 hr, then concentrated to 75 ml and poured onto ice. Thorough extraction into ether, drying, and removal of solvent gave oils. The yield from the cis olefin was 68%, from the trans olefin 60%. To obtain the aziridines, 0.07 mol of the appropriate 2-*N*-ethoxycarbonylamino-3-iodo-4-methylpentane in 600 ml of ethanol was heated to reflux with 30 g of KOH for 3 hr. Water (100 ml) was added to the cooled solution and the mixture was extracted exhaustively with ether. The dried ether solution was concentrated to 500 ml, and 0.09 mol of triethylamine and then dropwise 0.07 mol of pivaloyl chloride were added. The concentrated (125 ml) solution was washed with water, dried, and distilled. The cis aziridine 3, bp 47–48° (0.3 mm), was obtained in 41% yield: ir spectrum C=O at 1680 cm^{-1} (neat); NMR *i*-Pr as two doublets, 6 H, at δ 0.94 and 1.06, split by the methine H, J = 6 Hz, and due to the chirality of the adjacent ring carbon;[18,19] ring CH_2 d, δ 1.30, integrated together with *t*-Bu, s, δ 1.22, 12 H; isopropyl CH m, δ 2.0–2.2, 1 H, ring hydrogens m, δ 2.2–2.7, 2 H; mass spectrum P *m/e* 183 (6%), 98 (86%) (P − *t*-BuCO), 70 (89%), 57 (100%) (*t*-Bu). Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.52; N, 7.64. Found for **3**: C, 71.95; H, 11.72; N, 7.57. Found for **4**: C, 71.99; H, 11.76; N, 7.82.

The trans aziridine 4 was obtained in 23% yield: ir C=O at 1670 cm^{-1} (neat); NMR isopropyl CH_3's δ 0.90 and 1.02, two doublets, 6 H; *t*-Bu, s, δ 1.21, integrated with ring CH_3 at δ 1.28, 12 H; *i*-Pr CH m, δ 2.0–2.2, 1 H; ring H's δ 2.3–2.7, m, 2 H. The mass spectrum is similar to that of **3**, P *m/e* 183 (15%), 70 (100%).

***trans*-2,2-Dimethyl-3-pentenoic acid**[20] was prepared and its trans stereochemistry[21] further confirmed by the strong ir absorptions at 972 cm^{-1} (both in the acid and its ethyl ester). The acid was converted to its amide by standard procedures.[22,23] The amide showed ir absorptions at 3385, 3200, 3020, 2962, 1650, 1622, and 969 cm^{-1}. It was subjected to standard Hofmann rearrangement conditions to give a 30% yield of ***trans* 2-methyl-3-penten-2-amine,** which showed ir absorptions at 3350, 3020, 1675, and 971 cm^{-1}. The amine was immediately acylated by treating a solution of 0.30 g (3 mmol) in 50 ml of anhydrous ether with 3 mmol of triethylamine and 3 mmol of pivaloyl chloride. A 96% yield (0.53 g) of ***trans*-*N*-2′-(2′-methyl-3-pentenyl)-2,2-dimethylpropanamide (5)** was obtained: mp 67.5–68.5°; ir absorptions at 3335, 3030, 1635, and 958 cm^{-1} (KBr); NMR spectrum *t*-Bu at δ 1.17 s, 9 H; 2-methyls δ 1.42 s, 6 H; allylic methyl δ 1.68, d, 3 H; olefinic and NH, m, δ 5.45–5.85, 3 H; mass spectrum P *m/e* 183 (100%), 168 (69%) (P − CH_3), 126 (14%) (P − MeC), 83 (40%) (P − *t*-BuNHCO), 57 (35%) (*t*-Bu).

Anal. Calcd: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.69; H, 11.61; N, 7.08.

Photolyses of Pivaloyl Azide in Dichloromethane Solutions of *cis*- and *trans*-4-Methyl-2-pentene. A silica photolyses tube was charged with 14.6 ml (116 mmol) of the olefin, 1.0 ml (7.72 mmol) of pivaloyl azide, and sufficient dichloromethane to obtain the desired concentrations. Coolant of −10° was pumped through a cooling finger in the center of the tube, which was suspended along the axis of a Rayonet photochemical reactor equipped with RPR 254- or 300-nm lamps. The progress of the photolyses was followed by monitoring the nitrogen evolution. After the photolyses, solvent, excess olefin, and *tert*-butyl isocyanate were removed in vacuo at 0°. The residue was diluted to 5 ml with chloroform, and aliquots were analyzed. VPC on a 6 ft × 0.25 in. phenylsilicone OV-17 column at 110° separated **5** from **3** + **4**. Quantitative results were obtained by planimetry of the trace and calibrating the instrument with pure authentic samples. The aziridine mixture (**3** + **4**) was pure by NMR and elemental analysis. The ratio **3**:**4** was determined by NMR, using the isopropyl CH_3 signals. This method was checked with artificial mixtures of known composition, the agreement being ±3% of the real value. The aziridines **3** and **4** were separated by peak center cutting using VPC on a preparative scale, for comparison with the authentic samples. The yield of *t*-BuNCO was determined by converting it to *N*-*n*-butyl-*N*′-*tert*-butylurea and determining this by VPC under the same conditions as described above. The *t*-BuNCO yield varied between 40 and 42%, based on azide decomposed. The ratio **3**:**4** was monitored in a run (50 mol % trans olefin) by withdrawing samples at 20, 35, 50, and 65% completion. The fraction of **4** in **3** + **4** was 0.705 ± 0.03.

Photolyses of pivaloyl azide in neopentane solutions of *cis*- and *trans*-4-methyl-2-pentene were done like those in dichloromethane, except that, after sweeping with nitrogen, the appropriate quantity of neopentane was condensed in the dry ice cooled reaction vessel. Analyses were done as above, except that in the runs using trans olefin an aliquot of the residue was injected directly onto a 4 ft × 0.25 in. column of 15% Ucon Polar 50HB2000 on 50/60 mesh Anakrom ABS at 112°.

***trans*-2,3-Dimethyl-1-(2′,2′,-dimethylpropanoyl)aziridine (12).** *trans*-2,3-dimethylaziridine[24] was acylated with pivaloyl chloride and triethylamine in ether in 93% yield. The ir spectrum showed bands at 2960 (s), 2923 (s), and 1665 cm^{-1}; NMR, a singlet at δ 1.28 and a doublet at δ 1.25 integrated as 15 H, a multiplet δ 2.1–2.5 as 2 H; mass spectrum P *m/e* 155 (5%), 140 (5%) (P − CH_3), 98 (24%) (P − *t*-Bu), 70 (P − *t*-BuCO), 57 (100%) (*t*-Bu^+).

Anal. Calcd for $C_9H_{17}NO$: C, 69.64; H, 11.04; N, 9.02. Found: C, 69.81; H, 11.31; N, 9.18.

***cis*-2,3-Dimethyl-1-(2′,2′-dimethylpropanoyl)aziridine (8)** was prepared in 96% yield like the trans isomer from the aziridine.[24] The NMR spectrum had 15 H at δ 1.20 (d) and 1.23 (s) and a multiplet of 2 H at δ 2.2–2.6; mass spectrum P *m/e* 155 (3%), 140 (3%), 98 (17%), 57 (100%).

Anal. Calcd for $C_9H_{17}NO$: C, 69.64; H, 11.04; N, 9.02. Found: C, 69.81; H, 11.31; N, 9.18.

Preparation of 2-*tert*-Butyl-4,5-dimethyl-4,5-dihydrooxazoles, Cis (9) and Trans (13). Iodine-catalyzed rearrangement of the cis aziridine 8, using Heine's method,[25] gave a 5:1 mixture of **9** and **13**. Thermal rearrangement of 8 and 12 was completely stereospecific with retention of geometry. The ir spectra of both showed a strong band at 1660 cm^{-1}. The NMR spectrum of **9** (cis) has methyl signals at δ 1.21 (s), 1.18 (s), and 1.12 (s), together 15 H. The ring methine protons form multiplets at δ 3.8–4.35 (1 H, C-4) and 4.35–5.0 (1 H, C-5), with splitting between the methine protons. The trans compound **13** shows much cleaner ring methine proton signals, multiplets at δ 3.4–3.85 (C-4) and 3.85–4.3 (C-5) with no discernible splitting between them. Splitting as well as relative chemical shifts agree with previous work.[26] The trans isomer **13** has methyl signals at δ 1.21 (s), 1.17 (s), and 1.27, together 15 H; mass spectrum (**9**) P *m/e* 155 (89%), 140 (100%) (P − CH_3), 111 (40%) (P − CH_3CHO), 57 (63%) (t-Bu^+). The trans isomer **13** has a very similar mass spectrum, with the base peak at *m/e* 111.

Anal. Calcd for $C_9H_{17}NO$: C, 69.64; H, 11.04; N, 9.02. Found for **9**: C, 69.84; H, 11.33; N, 9.09. Found for **13**: C, 69.43; H, 11.16; N, 8.99.

***trans*-*N*-1′-(2′-Butenyl)-2,2-dimethylpropanamide** (*trans*-1-pivaloylamino-2-butene, **14**) was prepared by acylation (as above) of *trans*-2-buten-1-amine.[27] No **14** was found in our photolysis reaction mixtures: ir (neat) 3330, 2955, 1645, 1531, 968 cm^{-1}; NMR δ 1.20, s, 9 H (t-Bu); 1.70, d, 3 H; 3.80, t, 2 H; 5.4–5.7, m, 3 H; mass spectrum P *m/e* 155 (36), P − H at 154 (85%), 138 (24%), 124 (71%), 57 (100%).

Anal. Calcd for $C_9H_{17}NO$: C, 69.64; H, 11.04; N, 9.02. Found: C, 69.79; H, 11.23; N, 9.04.

***N*-3′-(1-Butenyl)-2,2-dimethylpropanamide** (*N*-pivaloyl-3-amino-1-butene, **15**) was prepared by acylation of 3-amino-1-butene.[27] No **15** was found in our photolysis reaction mixtures: ir (KBr) 3300, 2950, 1620, 1516, 1204, 908 cm^{-1}; NMR δ 1.23 (s) and 1.26 (d), together 12 H, a series of multiplets δ 4.0–6.2, 5 H; mass spectrum P *m/e* 155 (21%), 140 (13%), 72 (12%), 58 (100%).

2,2-Dimethyl-1-(2′,2′-dimethylpropanoyl)aziridine (16) was prepared by standard acylation of 2,2-dimethylaziridine.[28] No **16** was found in our photolysis reaction mixtures: ir (neat) 2960 and 1675 cm^{-1}; NMR δ 1.24, s, 9 H; 1.33, s, 6 H; 2.17, s, 2 H.

Anal. Calcd for $C_9H_{17}NO$: C, 69.64; H, 11,04; N, 9.02. Found: C, 69.48; H, 11.33; N, 9.19.

Photolyses of Pivaloyl Azide in Solutions of *cis*- and *trans*-2-Butene. In a nitrogen-flushed photolysis tube, 6.5 g (0.12 mol) of the butene was condensed using dry ice as coolant. Then 1.00 ml (7.72 mmol) of pivaloyl azide and the desired quantity of dichloromethane or cyclopentane were added. Coolant of −15° was circulated through the cooling finger in the center of the tube, which was suspended coaxially in a Rayonet photochemical reactor. The photolyses were conducted and worked up as described above, but a 10 ft × 0.25 in. aluminum column containing 15% cyanosilicone QF-1 on 50/60 mesh Anakrom ABS was used at 112°. The detector was calibrated with authentic samples. The amount of rearrangement of the aziridines 8 and 12 depended on the history of the column.

Acknowledgment. We are greatly indebted to the National Science Foundation for support of this work.

Registry No.—**1**, 4981-48-0; **2**, 18677-63-9; **3**, 56930-40-6; **4**, 56930-41-7; **5**, 56930-42-8; **6**, 754-10-9; **7**, 590-18-1; **8**, 56930-43-9; **9**, 56930-44-0; **11**, 624-64-6; **12**, 56930-45-1; **13**, 56930-46-2; **14**, 56930-47-3; **15**, 56930-48-4; **16**, 56930-49-5; 2-*N*-ethoxycarbonylamino-3-iodo-4-methylpentane isomer 1, 56930-50-8; 2-*N*-ethoxycarbonylamino-3-iodo-4-methylpentane isomer 2, 56930-51-9; *trans*-2,2-dimethyl-3-pentenoic acid, 56930-52-0; *trans*-2,2-dimethyl-3-pentenamide, 56930-53-1; *trans*-2-methyl-3-penten-2-amine, 31978-79-7; pivaloyl chloride, 3282-30-2; *cis*-4-methyl-2-pentene, 691-38-3; *trans*-4-methyl-2-pentene, 674-76-0; *trans*-2,3-dimethylaziridine, 930-20-1; *cis*-2,3-dimethylaziridine, 930-19-8; *trans*-2-buten-1-amine, 56930-04-2; 3-amino-1-butene, 34375-90-1; 2,2-dimethylaziridine, 2658-24-4.

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Some Reactions of 1-Carboethoxytetrahydrocarbazole Chloroindolenine

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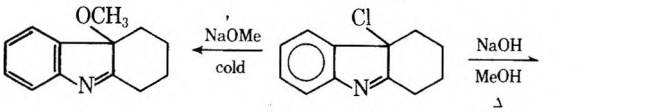
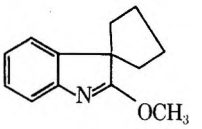
The chloroindolenine of 1-carboethoxytetrahydrocarbazole, when treated with excess methanolic base and worked up with mild acid, gave the 1-methoxy derivative **5**, while work-up with strong acid gave the 1-hydroxy product **6**. Treatment of **5** with dilute acid yielded **6**, which gave back **5** when treated with absolute methanol–acetic acid. Reaction of 1-carboethoxytetrahydrocarbazole with NBS–pyridine gave 1-carboethoxycarbazole.

Recently we reported that the chloroindolenine of tetrahydrocarbazole (**1**), when treated with cold NaOMe, gave 4a-methoxytetrahydrocarbazole (**2**), while 2-methoxy-3-(1′-spirocyclopentane)(3*H*)-indole (**3**) was formed in the presence of refluxing MeOH–NaOH.[1] Treatment of **1** with HCl–MeOH gave the bis-1,9-tetrahydrocarbazole dimer.



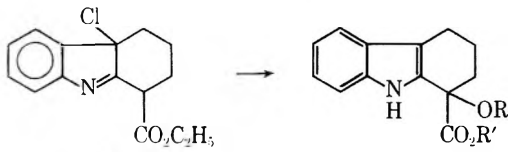
2 **1**



3

Though the expected 1-methoxytetrahydrocarbazole was not found in any of these reactions, it was readily prepared by the reaction of NaOMe with the 1-pyridinium bromide salt of tetrahydrocarbazole. This behavior of the chloroindolenine was unexpected in light of the work of Gassman et al.,[2] where, under appropriate conditions, the chloroindolenine of 2,3-dimethylindole thermally rearranged and gave 2-methoxymethyl-3-methylindole on treatment with NaOMe. While investigating the chemistry of the closely related 1-carboethoxytetrahydrocarbazole chloroindolenine (**4**), we discovered that it behaved anomalously when compared to **1**.

Reaction of 1-carboethoxytetrahydrocarbazole[3] with *tert*-butyl hypochlorite and triethylamine in methylene chloride gave a solution whose uv and NMR were compatible with **4**. Reaction of **4** with NaOMe at room temperature, followed by work-up with acetic acid and treatment with diazomethane, gave **5** in 83% yield.



4

5, R = R = CH_3

6, R = H; R′ = CH_3

7, R = CH_3; R′ = C_2H_5

In contrast, reaction of **4** with refluxing NaOH–MeOH, followed by addition of HCl, and reesterification gave a different product. The mass spectrum of this material gave a molecular ion at *m/e* 245, and peaks at M − 18 (minus OH) and M − 59 (minus CO_2CH_3). The uv spectrum was that of an indole, and the ir spectrum had a new band, compatible with an alcohol group, in addition to those found for **5**. The NMR differed from that of **5** only in the disappearance of a methoxyl signal, suggesting structure **6** for this product.

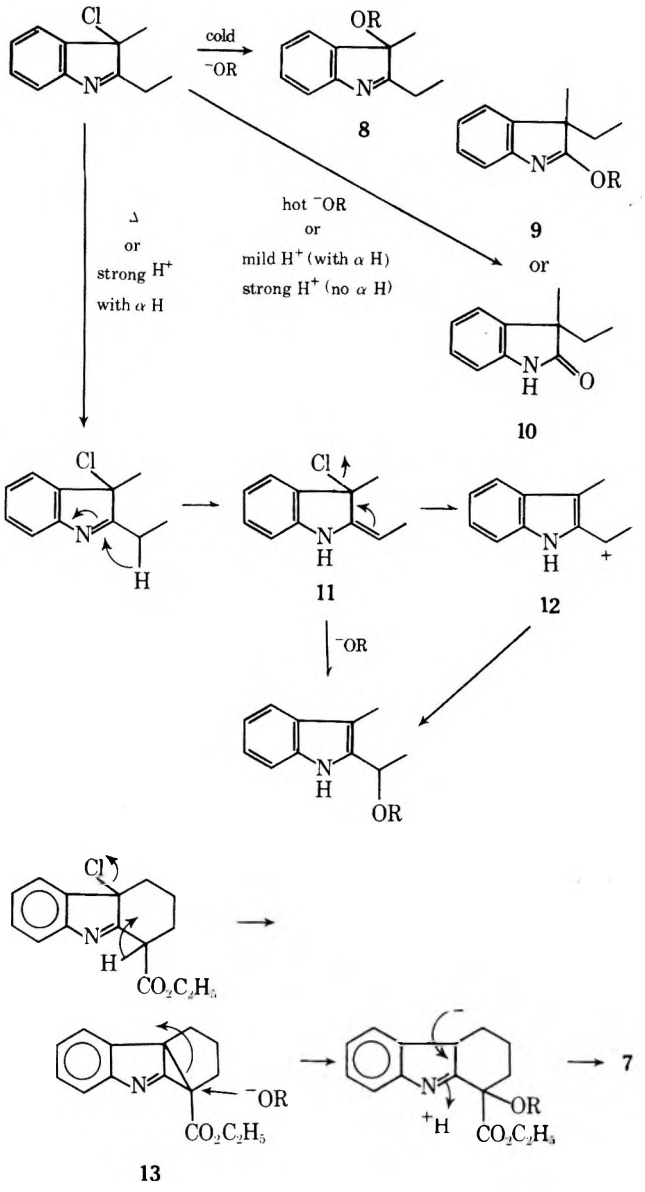
Further experiments showed that regardless of whether NaOMe at 0° or NaOH at reflux was employed, product **5** predominated when the reaction mixture was brought to pH 4 prior to extraction and diazomethane treatment, while **6** predominated when the pH was <1 (NMR). When a large volume of CH_2Cl_2 was used and treatment with either refluxing NaOH or cold NaOMe was performed with minimal MeOH present, the sole product was the ethyl ester **7**.

When **5** was treated with dilute HCl in THF at room temperature, it was readily hydrolyzed to **6** (NMR data). When 1-methoxytetrahydrocarbazole was treated with dilute aqueous HCl, or hot dilute aqueous HOAc, the only identifiable product was the bis-1,9-tetrahydrocarbazole dimer, not unexpected from prior reports[4,5] if the 1-hydroxy compound is initially formed. On the other hand, when 1-hydroxytetrahydrocarbazole was treated with 5% HOAc in absolute MeOH, 1-methoxytetrahydrocarbazole was readily formed at room temperature, in a manner similar to the methylation of the hydroxylactam of dihydrocorynantheine.[6] When **6** was treated in this latter manner, the major product was **5**, as well as a small amount of 1-carbomethoxycarbazole.

When 1-carboethoxytetrahydrocarbazole was treated with NBS and pyridine, in an attempt to prepare **5** via the expected 1-pyridinium bromide salt, the product was instead 1-carboethoxycarbazole, in contrast to the behavior of tetrahydrocarbazole in the same reaction sequence.[7]

We reviewed our past experience and that of others with chloroindolenines regarding the structural features and reaction conditions leading to each of the varied products obtained. When simple unsubstituted chloroindolenines are treated with cold base, the product is the 3-alkoxy indolenine **8**.[1,2] With base at elevated temperature,[1,8,9] mild acid,[10,11] or with strong acid where there is no α-methylene proton,[11] the product is the 2-alkoxyindolenine **9**, or its corresponding oxindole **10**, a result of the well-known Wagner–Meerwein rearrangement. When an α proton is present, either thermal rearrangement of the chloroindolenine[2] or the action of strong acid[1,10b,11,12] promotes formation of the tautomeric intermediate **11**. This intermediate may then readily either yield the carbonium ion **12** (or one of its many resonance forms), or react directly with base to give the α-substituted products observed.

In the present set of reactions of the chloroindolenine of 1-carboethoxytetrahydrocarbazole, we have prepared the 1-alkoxy derivatives directly for the first time under cold basic conditions. We rationalized this on the basis that the electron-withdrawing 1-carboxyl group makes the α proton more acidic than normal, and promotes a facile tautomerization to structure **11**. This tautomeric enamine intermediate then reacts with RO^-, or eliminates Cl^-, to yield the 1-substituted products. An alternate route might involve the formation of a Favorskii-type intermediate, such as **13**, but we consider this very unlikely, as it would involve consider-



able strain in forming the three-membered ring, grossly distorting the planarity of the five-membered nitrogen-containing ring. For this reason, we consider **11** the most probable route of reaction.

Experimental Section[13]

1-Methoxy-1-carbomethoxytetrahydrocarbazole (5). A solution of 0.90 g (8.3 mmol) of *tert*-butyl hypochlorite in 5 ml of CH_2Cl_2 was run, over 15 min, into a mixture of 1.00 g (4.1 mmol) of 1-carboethoxytetrahydrocarbazole and 0.84 g (8.3 mmol) of triethylamine in 25 ml of CH_2Cl_2 precooled to 0°, and the reaction mixture was stirred for 30 min. The uv spectrum of this solution had maxima at 235 nm (ε 11080) and 275 (3330), and the NMR (of the reaction run in $CDCl_3$ followed by several washes with water) had signals at δ 1.0–2.3 (multiplet, 7 H), 2.4–3.1 (3 H), 3.8–4.5 (quartet, 2 H), and 7.0–7.7 (4 H). The above mixture was then run into a solution of 2.5 g of sodium in 50 ml of methanol at room temperature, and stirred for 2 hr. After evaporation of the solution, addition of water, and extraction with CH_2Cl_2, the aqueous solution was acidified and extracted with ether and the extract was treated with CH_2N_2 to give 0.89 g of **5** (83% yield). Crystallization twice from Et_2O gave colorless prisms melting at 111–112°: ir 3400, 1735 cm^{-1}; uv 227 nm (ε 16800), 278 (sh, 6370), 284 (6615), 292 (5365); NMR δ 1.75–2.50 (4 H), 2.59–2.92 (2 H), 3.28 (singlet, 3 H), 3.67 (singlet, 3 H), 7.01–7.67 (4 H), 8.55 (singlet, 1 H); mass spectrum *m/e* 259, 228, 200, 185, 167–168. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.52; H, 6.56, N, 5.40. Found: C, 70.12; H, 6.02; N, 5.34.

1-Hydroxy-1-carbomethoxytetrahydrocarbazole (6). A solution of the chloroindolenine **4** was prepared from 1.0 g of 1-carboethoxytetrahydrocarbazole, as in the case of **5** above, then run rapidly into a refluxing solution of 2.5 g of NaOH in 50 ml of methanol, and the reflux was continued for 30 min. Work-up identical with that for 5 above gave 0.68 g of **6** (67% yield). Crystallization and recrystallization from benzene gave a product melting at 138–139°; ir 3540, 3330, 1720 cm^{-1}; uv 230 nm (ε 16800), 276 (sh, 7600), 283 (8000), 292 (6500); NMR δ 1.78–2.50 (4 H), 2.60–2.90 (2 H), 3.71 (singlet, 3 H), 4.08 (singlet, 1 H), 6.94–7.65 (4 H), and 8.50 (singlet 2 H); mass spectrum *m/e* 245, 228, 186, 167–168. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.79; H, 6.22; N, 5.71.

1-Methoxy-1-carboethoxytetrahydrocarbazole (7). A solution of 4.0 g of 1-carboethoxytetrahydrocarbazole and 3.6 ml of triethylamine in 170 ml of CH_2Cl_2 was stirred under nitrogen in an ice bath. To this was added 3.6 ml of *tert*-butyl hypochlorite in 10 ml of CH_2Cl_2. The mixture was stirred for an additional 30 min, then one-half was run into 0.50 g of NaOH in 10 ml of MeOH and refluxed for 30 min, while the other one-half was run into 0.25 g of Na dissolved in 10 ml of MeOH at 0° and stirred for 30 min. Each reaction mixture was poured over NH_4OH–ice and extracted into CH_2Cl_2, which after drying over Na_2SO_4 was evaporated to give a quantitative yield of 1-methoxy-1-carboethoxytetrahydrocarbazole in both cases, as an oily, crystalline mass. Recrystallization from EtOH–H_2O gave white needles, melting at 98–100°: ir 3340 and 1730 cm^{-1}; uv 227, 285, and 294 nm; NMR δ 1.22 (triplet, 3 H), 1.90–2.50 (4 H), 2.73 (triplet, 2 H), 3.25 (singlet, 3 H), 4.23 (quartet, 2 H), 7.00–7.72 (4 H), 8.61 (singlet, 1 H); mass spectrum *m/e* 273, 259, 242, 200, 168–167.

1-Carboethoxycarbazole. To a solution of 3.00 g of 1-carboethoxytetrahydrocarbazole and 3.60 ml of pyridine in 60 ml of benzene was added at once 3.40 g of *N*-bromosuccinimide, and following an exothermal reaction, the mixture was stirred at room temperature for 2 hr. The benzene phase was separated from a crystalline mass, washed four times with water, and dried over Na_2SO_4, and after evaporation of the solvent in vacuo, the residue was crystallized from ethanol to yield 2.45 g (83%) of 1-carboethoxycarbazole, which after recrystallization from ethanol melted at 104–106° (lit. 106–107°[14]): uv 358, 305, 279, 249, 240, 227 nm; NMR δ 1.46 (triplet, 3 H), 4.52 (quartet, 2 H), 7.15–7.62 (4 H), 8.05–8.42 (3 H), 10.05 (singlet, 1 H). Treatment of 1-carboethoxycarbazole with NaOMe, followed by acid (HCl) and ether extraction, gave the free acid, mp 260–264° (lit. 268–269°[15]), while treatment of the acid with diazomethane in ether gave 1-carbomethoxycarbazole, which when recrystallized from 2-propanol gave fine tan needles melting at 140–141.5°: ir 3440, 1675, 1600 cm^{-1}; uv 359 nm (ε 6000), 303 (6700), 279 (15700), 250 (11800), 243 (11600), 225 (23000); NMR δ 3.92 (singlet, 3 H), 6.98–7.50 (4 H), 7.88–8.27 (3 H), 9.91 (singlet, 1 H); mass spectrum *m/e* 225, 193, 165, 139.

1-Hydroxytetrahydrocarbazole. To a solution of 440 mg of 1-ketotetrahydrocarbazole[16] in 15 ml of absolute methanol was added 180 mg of $NaBH_4$, and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated, water was added, and the mixture was extracted into $CHCl_3$; the $CHCl_3$ was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 318 mg (72%) of crystalline product, melting at 115.5–117.5° (lit. 115–116°[4,17]); ir (Nujol) 3430, 3270 cm^{-1}; uv 293 nm (ε 4200), 284 (5000), 229 (16500); NMR δ 1.55–2.20 (4 H), 2.48–3.10 (2 H), 4.64–4.94 (1 H), 7.00–7.63 (4 H), 8.22–8.49 (1 H).

1-Methoxytetrahydrocarbazole (from 1-Hydroxytetrahydrocarbazole). A solution of 100 mg of 1-hydroxytetrahydrocarbazole in 10 ml of 5% HOAc in absolute MeOH was stirred overnight at room temperature, then evaporated to dryness. The ir, uv, and NMR of the resulting oil were identical with those of 1-methoxytetrahydrocarbazole, and crystallization from hexane gave 60 mg of material melting at 75–76°[1]; a mixture melting point with authentic 1-methoxytetrahydrocarbazole was undepressed.

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Registry No.—**4**, 56995-01-8; **5**, 56995-02-9; **6**, 56995-03-0; **7**, 56995-04-1; *tert*-butyl hypochlorite, 507-40-4; 1-carboethoxytetrahydrocarbazole, 50845-41-5; 1-carboethoxycarbazole, 56995-05-2; *N*-bromosuccinimide, 128-08-5; NaOMe, 124-41-4; 1-carbomethoxycarbazole, 51035-15-5; 1-hydroxytetrahydrocarbazole, 1592-62-7; 1-ketotetrahydrocarbazole, 3456-99-3; 1-methoxytetrahydrocarbazole, 42540-57-8.

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Intramolecular Diels–Alder Reactions. Synthesis of 3a-Phenylisoindolines as Analgetic Templates

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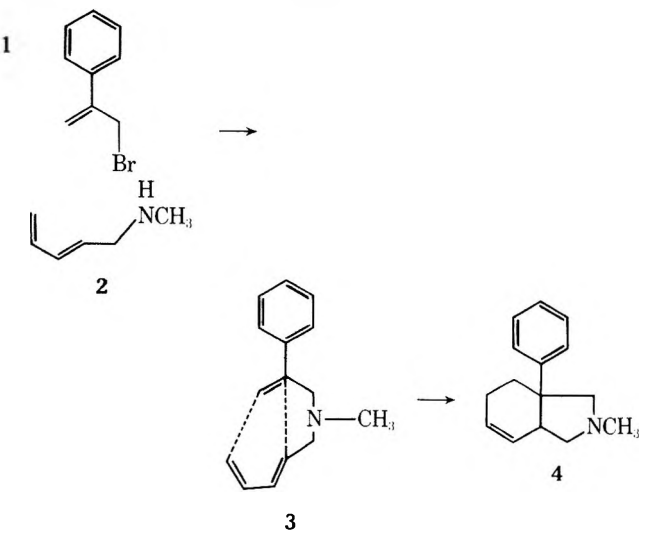
A preparatively efficient method for the synthesis of the substrate **10** is described. This undergoes an intramolecular [4 + 2] cycloaddition to give the lactam **11**. Reduction of the amide carbonyl gives **6**, the product of an extremely facile [4 + 2] cycloreversion, and no trace of the Diels–Alder adduct **7** was found. A number of transformations of **11**, including a skeletal rearrangement of **14** to **16**, are described, and the structure and relative stereochemistry of the products is elaborated largely on the basis of their NMR data. The cis stereochemistry of **20**, a product obtained from the cycloadduct **11** via hydrogenation, eliminative ether cleavage, and hydrogenation, is established by correlation with a relay compound **27**, independently synthesized via a bimolecular Diels–Alder reaction.

The application of intramolecular Diels–Alder reactions in the elaboration of substituted perhydroisoindolines, as well as kinetic aspects of these reactions, was the subject of earlier reports.[1-3] In this study we describe the use of these intramolecular cycloadditions in the synthesis of 3a-phenylisoindolines. Such compounds appeared particularly attractive to us, as this structural type incorporates some of the essential molecular features of such potent analgetics as Profadol[4] and related molecules.[5]

Our initial goal, in essence, was the preparation of a substrate **3** from α-bromomethylstyrene (**1**) and a pentadienyl amine **2**, followed by an intramolecular [4 + 2] cycloaddition to give the desired **4** (Scheme I). Our attempts to attain practical access to the amine **2** (or the corresponding halide) failed because of its inherent instability. We therefore turned our attention to alternate sources of suitable diene–methylamines, such as *N*-methylfurfurylamine (**5**). In fact we were rather encouraged by earlier reports[6,7] on the successful internal cycloaddition of the *N*-allyl derivative of **5**. The choice of **5** as the diene part added a considerable amount of flexibility, as the oxygenated character of the resulting cycloadduct provides numerous possibilities for further modifications.[8]

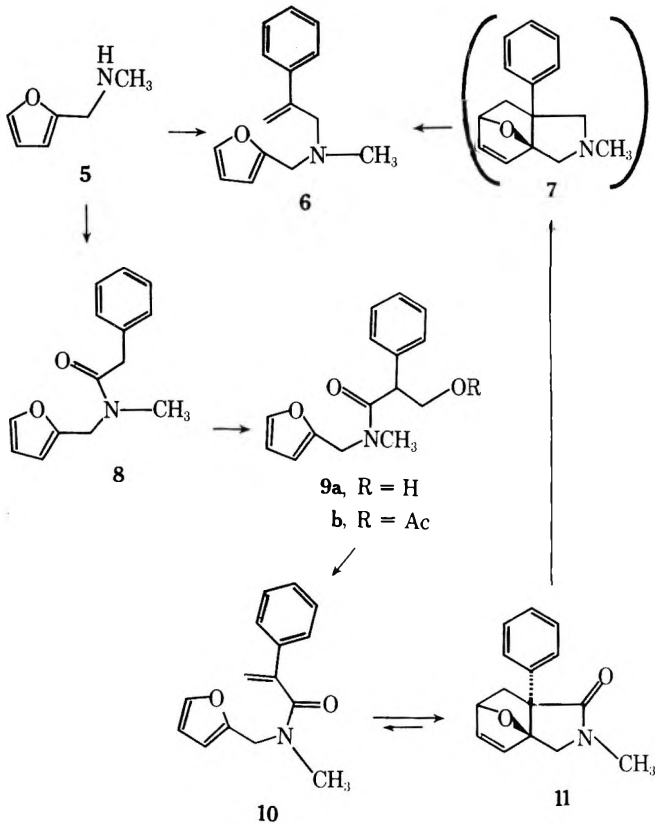
The desired substrate **6** was prepared readily and in high yield from **1** and **5**. Surprisingly, however, **6** resisted any attempt to effect the desired cycloaddition to produce **7**; in fact, compound **6**, when heated in a sealed NMR tube (C_6D_6), remained unchanged up to temperatures of 230°. Suspicions about an extremely facile retro-Diels–Alder reaction led us to lower the temperatures, but even at −60° the NMR spectrum of **6** did not reveal a trace of the elusive cycloadduct **7**. In view of the results reported with the de-

Scheme I



phenyl derivative of **6**,[6] we concluded that the phenyl substituent in **7** would sufficiently destabilize the σ bond to be formed to make **7** essentially nonexistent between −60 and 230°. That this was indeed the case will be corroborated below. Faced with these results we planned to neutralize the destabilizing effects of the phenyl group in **7** with the introduction of a carbonyl group as in **10**, i.e., to synthesize a molecule which would incorporate the "normal" electron-rich diene and an electron-deficient dienophile.[9] The synthesis outlined in Scheme II proved to be more efficient over some more obvious routes involving the highly unsta-

Scheme II

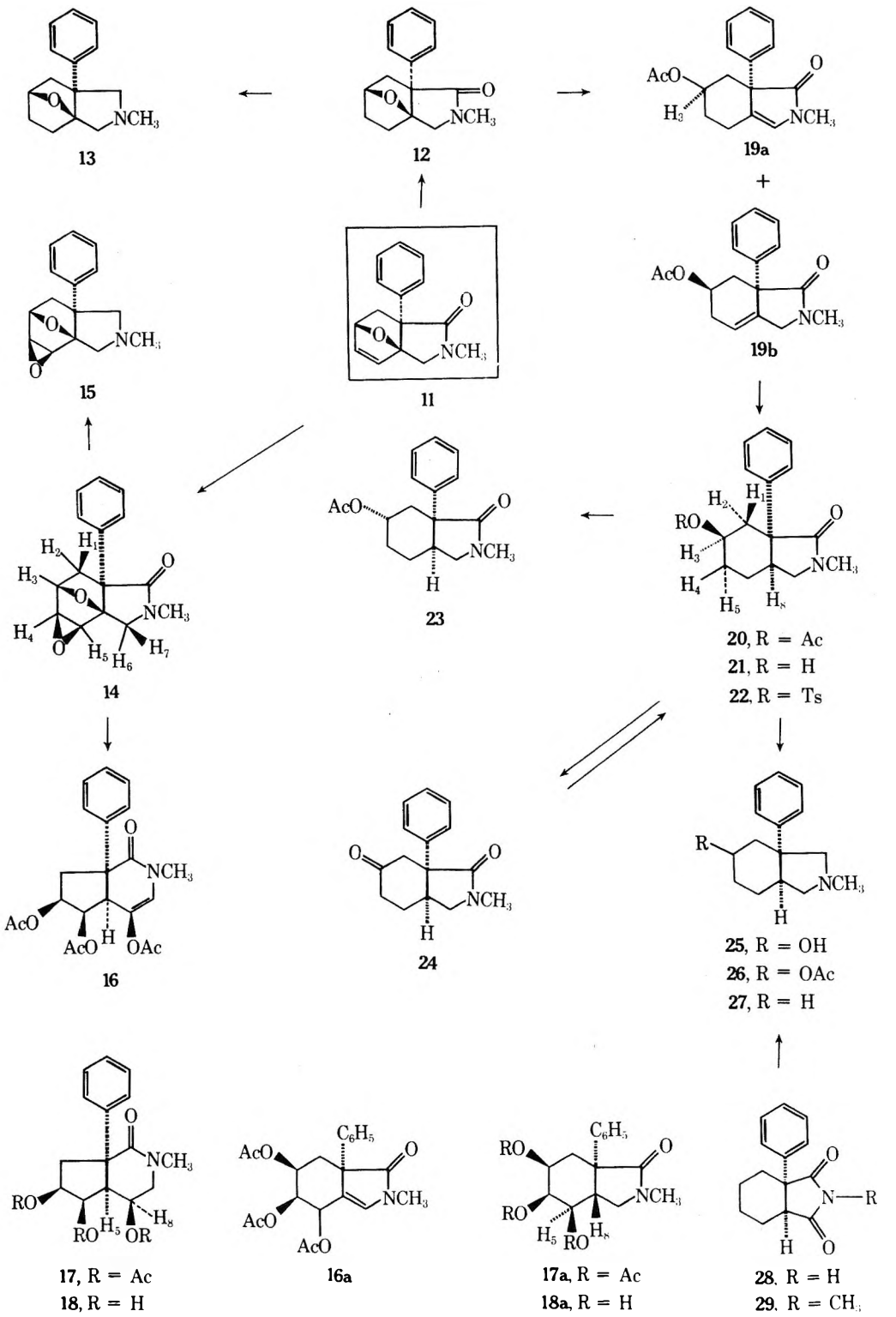


ble furfuryl chloride or atropic acid chloride. The anion of the easily accessible phenylacetamide **8**, generated with lithium diisopropylamide,[10] was quenched with paraformaldehyde and the resulting alcohol **9a** was acylated with AcCl. Elimination of HOAc from **9b** with NaOEt in refluxing EtOH produced, via the substrate **10**, the crystalline cycloadduct **11**, which was isolated in a 55% overall yield based upon **8**. The structure of **11**, in particular the relative configurational relationship (trans) between the ether bridge and the angular phenyl substituent, is based largely on considerations of both secondary orbital overlap during the transition state of the cycloaddition and steric strain factors. A trans-fused cycloadduct would appear to be highly strained and thus its formation rather unlikely. The extraordinarily transparent NMR spectrum supports this assignment. The propensity of **11** to undergo a $[_{\pi}4_s + {}_{\pi}2_s]$ cycloreversion was, although far less pronounced than in **7**, still evident; and the following solvent and temperature dependent equilibrium mixtures of **10** and **11** could be observed. By heating a C_6D_6 solution of pure **11** (or pure **10**) in a sealed tube at 120° for 15 hr, an equilibrium of 52% **10** and 48% **11** was attained; in a more polar solvent, such as ethanol (reflux, 15 hr), the equilibrium favored the cycloadduct **11** over the open form **10** by a ratio of 61:39. This ratio was determined by actual isolation (preparative TLC chromatography) of **10** and **11**. With the lactam **11** in hand we then set out to test the suspected instability of the elusive cycloadduct **7**. $LiAlH_4$ reduction of the lactam **11** produced an essentially quantitative yield of the styryl amine **6**, thus firmly establishing the inherent instability of the intermediate **7**.

Subsequently a number of transformations were performed in order to prepare oxygenated 3a-phenylisoindolines as originally planned (Scheme I). Catalytic hydrogenation of the dihydrofuran double bond produced the bridged ether **12** (Scheme III), which in turn was reduced to the amine **13**. Epoxidation of the double bond in **11** with *m*-chloroperbenzoic acid gave an 80% yield of an isomerically pure epoxide (**14**). The electrophilic attack of the peracid appeared to take place with high selectivity on the side opposite to the phenyl group, i.e., on the same face of the molecule already occupied by the ether bridge. The stereochemical course of this epoxidation parallels the cis stereoselectivity observed with allylic or homoallylic alcohols[11a] or the exo epoxidation of double bonds in [2.2.1] systems.[11b] This cis relationship of the oxygen functions in **14** was apparent by analyzing the NMR (100 MHz) data. With H_2 and H_3 as well as H_3 and H_4 forming practically 90° angles, the only vicinal coupling left is between H_1 and H_3. The 5-Hz coupling of H_1 collapses to the normal AB part (H_1/H_2) upon irradiation of the frequency of H_3. The assignment of H_1 and H_2 is based on the differential shift upon complexation with $Eu(fod)_3$. As H_1 is affected by the complexation at the ether oxygen, it experiences a greater paramagnetic shift than does H_2. In addition it is observed that only two out of the five aromatic protons (in positions 2 and 6, each with ortho and meta coupling) are shifted to lower field. It can thus be assumed that, with the epoxide ring on the same side as the phenyl substituent, more than just two aromatic protons would experience a downfield shift. Reduction of the lactam carbonyl in **14** with $LiAlH_4$ could be selectively achieved without hydrogenolysis of the epoxide, and the amine **15** was isolated as a crystalline malonate salt.

Treatment of the epoxide **14** with $BF_3{\cdot}Ac_2O$ led to a number of products, the major and most interesting of which was the triacetate **16**, isolated in 29% yield. By analogy with the reaction **12** → **19**, described below, it was originally assumed that the five-membered ether bridge had been cleaved with the formation of the Δ^2-pyrrolenin-5-one moiety, thus leading to a compound represented by formula **16a**. However a careful analysis of the spectral data of **16** and its dihydro derivative **17** led to the conclusion that **16a** was a rather unlikely structure. After considering various alternative possibilities and mechanisms for the formation of the triacetate, the skeletal rearrangement as outlined in Scheme IV appeared particularly attractive not only from a mechanistic point of view, but, more importantly, because the resulting structure **16** could be reconciled with all the available analytical data. While the infrared spectrum in solution was not particularly conclusive, a spectrum in Nujol revealed absorptions at 1760, 1748, and 1674 cm^{-1} attributable respectively to an enol acetate, the two saturated acetates, and a lactam. Above all it was the presence of the enol acetate absorption and the frequency of the unsaturated δ-lactam (1674 vs. 1695 cm^{-1} for **19a**) which led us to favor structure **16** over **16a**. The NMR spectrum of **16** features the vinylic proton H_6 at 6.28 ppm as a singlet and only two hydrogens attached to acetoxy carbon (H_3 at 5.2 and H_4 at 5.52 ppm). The chemical shift of H_5 (d, $J_{5,4}$ = 4 Hz, 3.38 ppm) appears reasonable for structure **16** but would have to be explained by an unusually pronounced shielding influence of the axial phenyl group in **16a**. Upon catalytic hydrogenation of **16** a third downfield proton (H_8) appeared in the 5.30-ppm region, a fact which could easily be reconciled with structure **17**. Alternatively for structure **17a**, which is a trans-fused and hence conformationally immobile cyclohexane system, the unusual low field chemical shift of H_8 would have to be accounted for by a marked deshielding effect of a cis-diaxial acetyl group. In order to pursue such a possibility, **17** (or **17a**) was hydrolyzed to the triol **18** (or **18a**), on the assumption that H_8 would then appear in a more normal position (ca. 3 ppm). However, **18** (or **18a**) continued to exhibit three hydrogens in the carbinol area (ca. 4.2 ppm), thus again favoring the structure as **18**. Finally, in structure **17a** or **18a**, H_5 with its unusual high field signal would be required to exhibit a large axial–axial

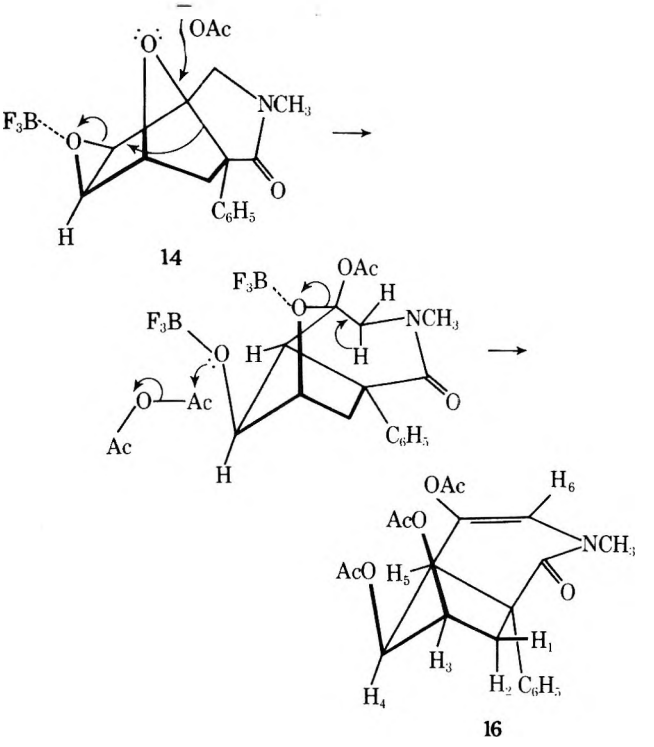
Scheme III



coupling (J = 8.6–11.5 Hz)[12] because of the conformational rigidity of the trans-fused ring system. In the NMR spectrum (in C_6D_6) of **18**, however, H_5 could be observed as a clearly separated triplet resonance with a coupling constant of 5 Hz at 2.74 ppm. The failure to exhibit a larger coupling clearly rules out the structure **18a** and thus **17a** and **16a**. On the basis of the small coupling constant it was also possible to establish the cis configurational relationship between H_5 and H_8 in **17** (and **18**). Thus, the addition of hydrogen took place on the convex side of the cis-fused molecule **16**, leading to an all-cis arrangement of the oxygen function. Additional evidence in support of the rearranged structures **16–18** could be drawn from a comparison of the ir frequencies of the lactam carbonyl in **17** (1633 cm^{-1}) and **20** (1690 cm^{-1}, see below): the rather low frequency of 1633 cm^{-1} is more adequately explained by an acetoxy-δ-lactam (**17**) than by a γ-lactam **17a**, which, after a comparison with **20**, can essentially be eliminated as a possibility. Although a number of attempts were made, we were unable to selectively hydrolyze the enol acetate functionality in **16**, which would have further corroborated its structure.

By subjecting the ether **12** to the same cleavage conditions (BF_3–Ac_2O) a mixture of **19a,b**, differing in the position of the double bond, was obtained. While this elimina-

Scheme IV



tive ether cleavage proceeded rather efficiently when judged by the 60–70% overall yield of **20**, realized by directly hydrogenating the crude mixture of **19a,b**, the pure isomers **19a,b** could only be isolated after extensive chromatography. The major product **19a** was accessible in 25% yield after such a separation. The trans relationship of phenyl and acetoxy group, which could be anticipated based on the relative configuration of the starting material **12**, is firmly corroborated by the NMR data. With the assumption of a chair conformation, the acetoxy group occupies an equatorial and the phenyl ring an axial position. H_3, which could easily be identified with double resonance experiments, exhibits two large couplings indicative of its axial nature. The isomeric lactam **19b** is clearly characterized by the presence of an ABX system assigned to the two protons between double bond and N atom. Upon hydrogenation of either **19a** or **19b** one and the same dihydro product **20** was obtained. Against normal expectations hydrogen was added to the double bond on the same face of **19a,b** already occupied by the large phenyl group, leading to the cis-fused ring system (**20**). This unusual result was initially apparent from NMR spectroscopic data and was later corroborated by an unambiguous chemical synthesis. Analysis of the NMR spectrum of **20** clearly leads to the conclusion that H_3 with no large axial–axial couplings now resides in an equatorial position. Decoupling H_4 and H_5 from H_3 supports this finding. With a trans-fused ring system, an axial position of H_3 would appear highly unlikely. Chemical proof for the cis-fused ring system was obtained by converting the acetate **20** via the alcohol **21** to the tosylate **22**. This was reduced with $LiAlH_4$ to the amine **27**, isolated and characterized as its citrate salt. An independent synthesis began with the Diels–Alder adduct of 3-phenylmaleimide with butadiene which was reported by Huebner.[13] This cis-fused tricyclic imide was then hydrogenated (**28**), N-methylated (**29**), and reduced with $LiAlH_4$ to give the bicyclic amine **27** identical by NMR spectrum, melting point, and mixture melting point of its citrate salt with **27**, obtained from **20**.

An SN2 transformation of the acetoxy group in **20** was achieved by nucleophilic displacement of the tosylate **22** with NaOAc in Me_2SO to produce the desired acetate **23**, isolated by preparative thin layer chromatography, together with an appreciable amount of elimination products and the ketone **24**.[14] Spin–spin decoupling experiments, ideally carried out in C_6D_6 solutions of **23**, clearly indicate that H_3 now occupies an axial position. In an attempt to realize a more efficient access to **23**, the alcohol **21** was oxidized to the ketone with CrO_3–pyridine[15] in 65% yield. $NaBH_4$ reduction of **24**, however, proceeded highly stereoselectively to give almost exclusively the axial alcohol **21** in better than 85% yield. Attempts to reduce **24** to **23** by the use of hydrogen–Pd/C[8] or Li(O-*t*-Bu)$_3$AlH failed.

Final transformations consisted of the reduction of the lactam **20** to the amino alcohol **25** with $LiAlH_4$ and the acylation of the latter to **26**. All the amines described were evaluated for their potential analgetic activity. In an analogous manner our intramolecular Diels–Alder reaction, as well as the subsequently described transformations, was carried out on a substrate bearing a *m*-CH_3O-phenyl substituent.

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); ir spectra on a Perkin-Elmer 521; uv curves on a Cary Model 14; mass spectra on a AEI MS 902 by direct insertion; NMR spectra on either a Varian A-60 or a XL-100 using tetramethylsilane as internal standard. The following abbreviations are used: (br) broad, (w) weak, (sh) shoulder, (ex) exchangeable with D_2O, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet.

2-[(2-Furyl)methyl]-*N*-methylbenzeneacetamide (8). To an ice-cooled solution of 33.3 g (300 mmol) of **5** and 42.6 g (300 mmol) of diisopropylethylamine in 300 ml of CH_2Cl_2 was added with stirring 46.2 g (300 mmol) of phenylacetyl chloride in 300 ml of CH_2Cl_2. After the addition was complete, the reaction mixture was stirred at room temperature for 3 hr. Then the organic layer was washed with 1 *N* HCl, then with 10% Na_2CO_3 solution, water, and finally with brine. After drying the organic layer over Na_2SO_4 and removal of the solvent, the residue of 74 g was distilled (140°, 0.2 mmHg) to give 65.0 g of a yellow oil. The oil was crystallized from AcOEt–hexane to give 57.2 g (84%) of amide **8**: mp 69–71°; ir (Nujol) 1635 (br), 1609 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.32; H, 6.73; N, 6.12.

***N*-[(2-Furyl)methyl]-α-hydroxymethyl-*N*-methylbenzeneacetamide (9a).** To an ice-cooled solution of 24.3 g of diisopropylamine in 300 ml of dry THF was added 140 ml of a 1.6 *m* solution of *n*-BuLi in hexane. The solution was then cooled under an atmosphere of N_2 to −45°, at which temperature a solution of 50 g of the amide **8** in 250 ml of dry THF was added dropwise while stirring magnetically. After the addition, during which the reaction mixture turned purplish, the temperature was allowed to rise to −20° over a 1-hr period. Subsequently, the temperature was lowered again to −45° and 9.8 g of dry paraformaldehyde was added. The mixture was then stirred at room temperature for 16 hr, cooled again in a dry ice–acetone bath, and quenched with 230 ml of 2 *N* HCl to adjust the pH to 5. The mixture was diluted with ether, the two layers separated, the aqueous phase reextracted with ether, and the organic layers washed with water and brine. After drying (Na_2SO_4) and removal of the solvent, 53.6 g of an oily residue was obtained (**9a**), ir (liquid) 3500, 1630 cm^{-1}.

Intramolecular Cycloaddition. 2,3,6,7-Tetrahydro-2-methyl-7a-phenyl-3a,6-epoxyisoindol-1-one (11). A solution of 198 g of crude hydroxy amide **9a** in 540 ml of acetyl chloride was refluxed for 1 hr. After removal of the reagent, the residue was dried under vacuum to give 220 g of a dark oil (**9b**): NMR ($CDCl_3$) δ 1.5 (s, 3 H), 2.9 (2 s, 3 H), 3.85–5.9 (m, 5 H), 6.0–6.4 (m, 2 H), 7.35 (s, 5 H).

A solution of 53 g (2.3 mol) of Na in 1.64 l. of ethanol was refluxed with 164 g (0.57 mol) of the crude acetoxy amide **9b** under N_2 for 16 hr. The solvent was then evaporated to dryness and the residue taken up in CH_2Cl_2 and washed twice with water, then with brine. After drying and removal of the solvent a residue of 134.7 g was obtained. This was dissolved in 350 ml of ether, whereupon the cycloadduct crystallized out. A first crop of 50.1 g of **11** (mp 155–156°) (36%) was collected. The mother liquor was evapo-

rated and refluxed for 1 week in 730 ml of benzene. An additional 18.2 g of **11** could be collected. Repetition of this procedure gave another 8 g of product (mp 155°), thus bringing the total yield to 76.3 g (55% overall based on crystalline phenylacetamide **8**): ir (Nujol) 1685, 750, 740, 720, 710, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.85 (d, J = 12 Hz, 1 H), 2.82 (dd, J = 12 and 4.5 Hz, 1 H), 3.0 (s, 3 H), 3.83 (AB, J = 12 Hz, 2 H), 5.09 (dd, J = 4.5 and 1.9 Hz, 1 H), 6.26 (d, J = 6.1 Hz, 1 H), 6.53 (dd, J = 6.1 and 1.9 Hz, 1 H), 7.21 (m, 5 H).

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.76; H, 6.11; N, 5.93.

Reduction and Retro-Diels–Alder. 11 → 6 (*N*-Methyl-*N*-(2-methylene-2-phenylethyl)-2-furanmethanamine. To a solution of 2.41 g (10 mmol) of isoindolone **11** in 300 ml of dry ether was added 1.68 g (30 mmol) of $LiAlH_4$. The mixture was refluxed for 24 hr. After cooling in an ice bath, excess reagent was destroyed with 1.68 ml of H_2O, 1.68 ml of 15% NaOH, and 5.04 ml of H_2O. The granular precipitate was then removed by filtration and the solvent evaporated in vacuo to give 2.1 g (93%) of an oil (**6**): ir (liquid) no >CO absorption; NMR ($CDCl_3$) identical with the one described for the independently synthesized compound (**5** + **1** → **6**).

***N*-Methyl-*N*-(2-methylene-2-phenylethyl)-2-furanmethanamine (6).** To a solution of 1.11 g (10 mmol) of **5** in 20 ml of dry ether, cooled to −70°, was added 6.3 ml (10 mmol) of 1.6 *m* *n*-BuLi–hexane. Then 2 g (10 mmol) of α-bromomethylstyrene (**1**) in 10 ml of dry ether was added and the temperature of the reaction mixture was allowed to rise to 25°. After 3 hr of stirring at room temperature the reaction mixture became homogeneous and was quenched with H_2O. The product was extracted into 1 *N* HCl, the aqueous acidic layer basified with 20% NaOH, and the product extracted into ether. After drying and removal of the solvent 1.82 g (80%) of a yellow oil (**6**) was obtained: NMR ($CDCl_3$) δ 2.2 (s, 3 H), 3.36 (s, 2 H), 3.55 (s, 2 H), 5.26 (d, J = 1.1 Hz, 1 H), 5.43 (d, J = 1.1 Hz, 1 H), 6.07–6.35 (m, 2 H), 7.16–7.55 (m, 6 H).

Heating of a 10% solution of this amine **6** in C_6D_6 (sealed NMR tube) for extended periods of time at 85, 106, 130, 160, 180, and 230° did not result in a change of the NMR spectrum. Also at −60°, the NMR spectrum remained unchanged.

2,3,4,5,6,7-Hexahydro-2-methyl-7a-phenyl-3a,6-epoxyisoindol-1-one (12). A solution of 30 g (124 mmol) of isoindolone **11** in 750 ml of EtOH was hydrogenated over 3 g of PtO_2 and 45 lb of H_2 pressure until the theoretical amount of H_2 had been taken up. The solvent was freed from catalyst by filtration through Filtercell. After evaporation of the filtrate, the residue (28.8 g) was crystallized from benzene–hexane to give 25.4 g (85%) of **12**: mp 98–99°; ir (Nujol) 1690, 770, 740, 720, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.8 (m, 6 H), 3.0 (s, 3 H), 3.64 (AB, J = 11 Hz, 2 H), 4.62 (t, br, J = 4.5 Hz, 1 H), 7.26 (s, 5 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.29; H, 7.33; N, 5.53.

1,3,4,5,6,7-Hexahydro-2-methyl-7a-phenyl-3a,6-epoxyisoindole (13). To a solution of 650 mg (17 mmol) of $LiAlH_4$ in 250 ml of ether was added 2.7 g (11 mmol) of solid lactam **12** and the mixture refluxed for 16 hr. After cooling the reaction mixture, excess reagent was destroyed with a saturated solution of Na_2SO_4. After removing the inorganic solid by filtration and evaporation of the solvent, 2.4 g of an oily residue was obtained. The oil was dissolved in 50 ml of acetone and neutralized with 1.98 g of cyclohexylsulfamic acid to give 3.73 g of salt **13**, mp 152–153°.

Anal. Calcd for $C_{15}H_{19}NO{\cdot}C_6H_{13}NO_3S$: C, 61.73; H, 7.90; H, 6.86. Found: C, 61.73; H, 8.15; N, 6.83.

5-Methyl-3-phenyl-9,11-dioxa-5-azatetraeyclo[5.3.1.$0^{3,7}$.-$0^{8,10}$]undecan-4-one (14). To a solution of 10 g (41.5 mmol) of **11** in 200 ml of CH_2Cl_2 was added 17.6 g of solid K_2CO_3. After cooling to 0° a solution of 8.5 g of *m*-chloroperbenzoic acid in 200 ml of CH_2Cl_2 was added with vigorous stirring. The mixture was allowed to warm up to room temperature and stirred for 16 hr. The K_2CO_3 was filtered off and the organic layer washed with 10% aqueous Na_2CO_3, water, and brine and dried over Na_2SO_4. After removal of the solvent, the solid residue (11.0 g) was recrystallized from AcOEt to give a first crop of 7.6 g (mp 184–187°) and a second crop of 1.3 g (80%): ir (Nujol) 1690 cm^{-1}; NMR ($CDCl_3$) δ 2.15 (d, J = 13.5 Hz, 1 H), 2.72 (dd, J = 13.5 and 5 Hz, 1 H), 3.95 (s, 3 H), 3.27 (d, J = 3.5 Hz, 1 H), 3.47 (d, J = 3.5 Hz, 1 H), 3.8 (AB, J = 11.5 Hz, 2 H), 4.57 (d, J = 5 Hz, 1 H), 7.5 (s, 5 H).

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.34; H, 5.97; N, 5.61.

5-Methyl-3-phenyl-9,11-dioxa-5-azatetracyclo[5.3.1.$0^{3,7}$.-$0^{8,10}$]undecane (15). A solution of 12 g (46.5 mmol) of **14** in 200 ml of dry THF was added to a suspension of 7.08 g (185 mmol) of $LiAlH_4$ in 300 ml of THF. The reaction mixture was then refluxed for 16 hr and cooled in an ice bath and excess reagent was destroyed by adding 7 ml of H_2O, 7 ml of 15% NaOH, and 21 ml of H_2O. Filtration and evaporation of the filtrate gave an oily residue which was taken up in AcOEt and which was extracted with 2 *N* HCl. The acidic layer was made basic with 20% NaOH and extracted into AcOEt. After drying and evaporating the organic layer 9.8 g of an oil was obtained. Filtration through a silica gel column using benzene–ether (1:1) gave 7.8 g of an oil: NMR ($CDCl_3$) δ 1.97 (d, J = 13 Hz, 1 H), 2.3 (dd, J = 13 and 4.5 Hz, 1 H), 2.4 (s, 3 H), 2.8 (AB, J = 8.5 Hz, 2 H), 3.25 (AB, J = 12 Hz, 2 H), 3.27 (s, 2 H), 4.53 (d, J = 4.5 Hz, 1 H), 7.25 (s, 5 H). A 6.45-g portion of this oil was converted into the malonate salt which crystallized from acetone to give 6.7 g: mp 152–153°; ir (Nujol) 1730–1700, 1600 cm^{-1} (br).

Anal. Calcd for $C_{15}H_{17}NO_2{\cdot}C_3H_4O_4$: C, 62.24; H, 6.10; N, 4.03. Found: C, 62.50; H, 6.13; N, 3.99.

4,5,6-Triacetoxy-4a,5,6,7-tetrahydro-2-methyl-7a-phenyl-2-pyrindin-1-one (16). To a suspension of 12 g (47.5 mmol) of the epoxide **14** in 94 ml of Ac_2O was added dropwise a solution of 12.6 ml (110 mmol) of boron trifluoride etherate in 150 ml of benzene. After the mixture was refluxed for 2 hr it turned dark. The reaction mixture was cooled, diluted with AcOEt, and washed with 10% aqueous Na_2CO_3, then with H_2O and brine. After drying and removal of the solvent, a black solid (19.6 g) was obtained which was passed through a column of 400 g of alumina (activity III) using benzene–ether (1:1). The first fraction eluted 11.6 g of an oil which was crystallized from ethyl acetate to give a total of 5.4 g (29%) of **16**: mp 141–142°; ir (Nujol) 1760, 1748, 1674 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 2.0, 2.05, 2.15 (3 s, 9 H), 2.52–3.26 (ABX, J = 8 and 14 Hz, 2 H), 3.03 (s, 3 H), 3.38 (d, J = 4 Hz, 1 H), 5.2 (six lines, J = 4 and 8 Hz, 1 H), 5.52 (t, J = 4 Hz, 1 H), 6.28 (s, 1 H), 7.2–7.6 (m 5 H).

Anal. Calcd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.79; H, 6.03; N, 3.79.

4,5,6-Triacetoxy-3,4,4a,5,6,7-hexahydro-2-methyl-7a-phenyl-2-pyrindin-1-one (17). A solution of 200 mg (0.5 mmol) of triacetate **16** in 100 ml of EtOH was hydrogenated over 200 mg of 10% Pd/C at 45 lb of H_2 pressure for 3 hr. After filtration through Filter-Cell and removal of the solvent, the residual solid was recrystallized from AcOEt to give 150 mg of dihydro compound **17**: mp 147–148°; ir (Nujol) 1745 (s), 1738, 1633 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.09 (s, 6 H), 2.5–3.2 (m, 3 H), 3.05 (s, 3 H), 3.51 (ABX, J = 5 and 12 Hz, 2 H), 5.3 (m, 2 H), 6.59 (t, J = 4 Hz, 1 H), 7.31 (m, 5 H).

Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.76; H, 6.21; N, 3.38.

4,5,6-Trihydroxy-3,4,4a,5,6,7-hexahydro-2-methyl-7a-phenyl-2-pyrindin-1-one (18). A solution of 500 mg of **17** in 50 ml of saturated methanolic ammonia was refluxed for 3 days. All solvent was then removed in vacuo and the solid residue recrystallized from CH_3OH–AcOEt to give 260 mg, mp 113–116° (**18**): ir (Nujol) 1609 cm^{-1}; mass spectrum m/e 277 (M^+), 259, 230, 204, 192, 186, 172, 150; NMR (100 MHz, C_6D_6) (after H → D exchange) δ 2.5 (dd, J = 7 and 14 Hz, 1 H), 2.74 (t, J = 5 Hz, 1 H), 2.90 (s, 3 H), 3.20 (dd, J = 5 Hz, 1 H), 3.22 (dd, J = 7 and 12 Hz, 1 H), 3.49 (dd, J = 7 Hz, 1 H), 4.24 (m, 3 H), 7.22 (m, 5 H).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.58; H, 7.21; N, 5.00.

6-Acetoxy-3(or 4),5,6,7-tetrahydro-2-methyl-7a-phenylisoindol-1-one (19a,b). After dissolving 25.8 g (53 mmol) of **12** in 26 ml of Ac_2O, a solution of 14.6 ml of boron trifluoride etherate in 260 ml of benzene was added and the mixture was refluxed for 2 hr. The reaction mixture was diluted with AcOEt, and the organic layer was washed to neutral with aqueous $NaHCO_3$ and water and finally dried over Na_2SO_4. After removal of the solvent 32 g of a dark oily residue was obtained which was passed through a column of neutral alumina (activity III) using benzene–ether (1:1). The eluated material was dissolved in 50 ml of ether and the crystals thus formed collected to give 6 g of **19a**, mp 112–120°. Recrystallization from AcOEt gave analytically pure material: mp 120–123°; ir (Nujol) 1730, 1695 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.16–1.8 (m, 2 H), 2.0 (s, 3 H), 2.0–2.7 (m, 3 H), 2.99 (s + m, 3 + 1 H), 4.71 (tt, J = 12 and 4 Hz, 1 H), 6.27 (m, 1 H), 7.3 (m, 5 H).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.69; H, 6.90; N, 5.10.

Careful rechromatography of 1.3 g of oily mother liquor on 39 g of alumina (III, neutral) and elution with benzene gave 260 mg of reasonably pure isomeric acetate **19b**: NMR ($CDCl_3$) δ 1.2–3.1 (m, H), 1.92 (s, 3 H), 2.74 (s, 3 H), 3.85 (ABX, 2 H), 4.7 (m, 1 H), 5.83 (m, 1 H), 7.3 (m, 5 H).

6-Acetoxy-3,3a,4,5,6,7-hexahydro-2-methyl-7a-phenylisoindol-1-one (20). A solution of 200 mg of acetate **19a** in 100 ml of ethanol was hydrogenated over 200 mg of 10% Pd/C at 45 lb H_2 pressure for 1.5 hr. After filtration through Filter-Cell, removal of the solvent, and recrystallization of the solid residue from AcOEt, 150 mg of **20** was obtained: mp 108–109°; ir (Nujol) 1728, 1690 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.75 (m, 4 H), 2.01 (s, 3 H), 2.14 (d, J = 5 Hz, 2 H), 2.75 (m, 1 H), 2.88 (s, 3 H), 3.04 and 3.28 [2 dd (AMX)], 4.88 (m, 1 H), 7.3 (m, 5 H).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.95; H, 7.46; N, 5.02.

Analogous treatment of isomer **19b** (200 mg of oily material) gave a similar yield of the same product, identical by melting point, mixture melting point, ir, and NMR spectrum.

For the preparation of larger quantities of **20**, it was more convenient to subject the crude material of the BF_3–Ac_2O treatment directly to the same hydrogenation conditions. A 60–70% overall yield (from **12**) of **20** could thus be achieved.

Octahydro-2-methyl-7a-phenylisoindol-6-ol (25). A solution of 16 g (55.6 mmol) of acetoxy lactam **20** and 8.5 g (223 mmol) of $LiAlH_4$ in 600 ml of ether was refluxed for 16 hr. Excess reagent was then destroyed with 8.5 ml of H_2O, 8.5 ml of 15% NaOH, and 25.5 ml of water. Removal of the granular precipitate by filtration and evaporation gave 13.2 g of an oily residue (**25**): NMR ($CDCl_3$) δ 1.85–2.4 (m, 6 H), 2.6 (s, 3 H), 2.77–3.35 (m, 5 H), 3.45–3.85 (m, 1 H), 4.75 (s, 1 H), 7.45 (s, 5 H).

This oil (6 g) was dissolved in 200 ml of 2-butanone and converted to the citrate salt with 5.5 g of citric acid in 100 ml of 2-butanone. The precipitate was filtered and recrystallized from EtOH to give 8.8 g (80%): mp 193–194°; ir (Nujol) 3525, 1740 cm^{-1}.

Anal. Calcd for $C_{15}H_{21}NO{\cdot}C_6H_8O_7$: C, 59.56; H, 6.90; N, 3.31. Found: C, 59.17; H, 7.19; N, 3.30.

Octahydro-2-methyl-7a-phenylisoindol-6-ol Acetate (26). A solution of 7 g (30.2 mmol) of the above crude amino alcohol **25** in 200 ml of AcCl was refluxed for 1 hr. Excess reagent was then removed in vacuo, and the solid residue recrystallized from 200 ml of acetone to give 6.9 g of HCl salt (**26**), mp 228–230°, ir (Nujol) 1720 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_2{\cdot}HCl$: C, 65.90; H, 7.80; N, 4.51. Found: C, 66.18; H, 8.07; N, 4.38.

6-Hydroxy-3,3a,4,5,6,7-hexahydro-2-methyl-7a-phenylisoindol-1-one (21). A solution of 861 mg (3 mmol) of **20** and 15 mmol of $NaOCH_3$ in 10 ml of CH_3OH was refluxed for 1 hr. The solvent was evaporated to dryness, and the residue was taken up in CH_2Cl_2 and washed with dilute HCl, water, and brine. After drying and removal of the solvent, the oily residue (640 mg) was crystallized from AcOEt–hexane to give 350 mg of **21**: mp 114–116°; ir ($CHCl_3$) 3500, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.58–2.15 (m, 6 H), 2.5–3.45 (m, 4 H), 2.85 (s, 3 H), 3.85 (t, br, J = 4 Hz, 1 H), 7.29 (s, br, 5 H).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.67; H, 7.76; N, 5.69.

3,3a,4,5,6,7-Hexahydro-2-methyl-7a-phenyl-6-(4-methylphenyl)sulfonyloxyisoindol-1-one (22). A solution of 6 g (24.5 mmol) of alcohol **21** in 72 ml of dry pyridine was cooled in an ice bath and treated with 9.3 g (49 mmol) of p-toluenesulfonyl chloride. The mixture was left in a stoppered flask at 0° for 18 hr. Then it was poured into ice water and the precipitate collected and washed with water. Recrystallization from benzene–hexane produced 7.8 g (80%) of tosylate **22**: mp 181–182°; ir ($CHCl_3$) 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.7–2.2 (m, 6 H), 2.46 (s, 3 H), 2.88 (s, 3 H), 3.1–3.4 (m, 2 H), 4.16–4.6 (m, 1 H), 7.16–7.8 (m, 9 H).

Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.30; N, 3.50. Found: C, 66.10; H, 6.56; N, 3.82.

Octahydro-2-methyl-7a-phenylisoindole (27). A solution of 3.99 g (10 mmol) of tosylate **22** in 200 ml of ether was refluxed with 1.52 g of $LiAlH_4$ for 16 hr. Excess hydride was then destroyed by adding 1.5 ml of H_2O, 1.5 ml of 15% NaOH, and 4.5 ml of H_2O. After filtering off the granular inorganic precipitate and evaporation of the solvent, 2.05 g of an oily residue were obtained, NMR ($CDCl_3$) δ 1.2–3.1 (m, 13 H), 2.4 (s, 3 H), 7.25 (s, 5 H).

The crude product was dissolved in 2-butanone and neutralized with citric acid. Recrystallization of the salt thus formed from CH_3OH gave 2.5 g (81%), 189–190°.

Anal. Calcd for $C_{15}H_{21}N{\cdot}C_6H_8O_7$: C, 61.90; H, 7.17; N, 3.44. Found: C, 61.82; H, 7.27; N, 3.51.

3,3a,4,5-Tetrahydro-2-methyl-7a-phenylisoindol-1,6(7*H*)-dione (24). To a magnetically stirred solution of 9.49 g (120 mmol) of dry pyridine in 150 ml of CH_2Cl_2 was added 6 g (60 mmol) of CrO_3. The mixture was allowed to stir at room temperature for 15 min. To this solution was then added a solution of 2.45 g (10 mmol) of alcohol **21** in 10 ml of CH_2Cl_2. The reaction mixture turned dark, and after an additional 15 min of stirring at room temperature the solvent was decanted, washed with 5% aqueous NaOH, then with 5% HCl, with saturated $NaHCO_2$, and finally with brine. After drying over Na_2SO_4, the solvent was evaporated to give 2.1 g of an oily residue. Crystallization from AcOEt–ether gave 1.6 g of ketone **24** (65%): mp 64–66°; ir ($CHCl_3$) 1720, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.75–3.31 (m, 8 H), 2.92 (s, 3 H), 3.62 (dd, J = 10 and 7 Hz, 1 H), 7.2 (s, 5 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.37; H, 7.14; N, 5.73.

6-Hydroxy-3,3a,4,5,6,7-hexahydro-2-methyl-7a-phenylisoindol-1-one (21 ← 24). A solution of 486 mg (2 mmol) of ketone **24** in 10 ml of EtOH was stirred for 2 hr with 148 mg of $NaBH_4$ at 5°. The mixture was then concentrated to dryness, excess hydride destroyed with 2 N HCl, and the product extracted into CH_2Cl_2. After washing the organic layer with brine, drying it over Na_2SO_4, and removal of the solvent, 430 mg of solid alcohol **21** was obtained, mp 107–109°; ir and NMR spectra, as well as TLC (silica, ether–benzene, 1:1) were identical with those of the alcohol described earlier (**20** → **21**).

SN2 on Tosylate 22 → 23 + 24. A solution of 798 mg of tosylate **22** and 650 mg of anhydrous NaOAc in 10 ml of Me_2SO were stirred in an oil bath of 120° for 5 hr. The mixture was then cooled, diluted with CH_2Cl_2, and washed with brine. After drying the organic layer over Na_2SO_4 and removal of all solvents, 450 mg of a yellow oil was obtained. Preparative TLC (silica, $CHCl_3$–AcOEt, 4:1) gave **24** (59 mg, R_f 0.20), **23** (143 mg, R_f 0.4), and 210 mg (R_f 0.55) of elimination products. **23**: NMR (100 MHz, $CDCl_3$) δ 1.2–1.6 (m, 2 H), 1.68 (dd, J = 11 and 13 Hz, 1 H), 1.92 (s, 3 H), 2.02 (m, 2 H), 2.59 (m, 2 H), 2.72 (d, J = 9 Hz, 1 H), 2.86 (s, 3 H), 3.22 (dd, J = 5 and 9 Hz, 1 H), 4.68 (m, 1 H), 7.3 (m, 5 H). **24**: NMR identical with that of oxidation product from **21** → **24**.

Independent Synthesis of Octahydro-2-methyl-7a-phenylisoindole (27 ← 28). To a solution of 460 mg (2 mmol) of imide **28** in 5 ml of DMF was added 100 mg of NaH (55%, washed twice with ether). After 10 min 300 mg of CH_3I was added and the mixture stirred at ambient temperature for 1.25 hr. The mixture was then poured onto ice–water and the product extracted into ether. After drying (Na_2SO_4) and evaporating the organic layer, the residue of 500 mg was crystallized from ether to give 340 mg of **29**, mp 95°. This imide (220 mg) was dissolved in 25 ml of ether and reduced with 100 mg of $LiAlH_4$. After 2 hr at 25°, excess reagent was destroyed, the inorganic material filtered, and the ether evaporated to give an oil (200 mg) whose NMR spectrum was superimposable on the one of **27**. The melting point of its citrate salt was 189° and a mixture melting point with **27** (obtained from **22**) gave no depression.

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2-(3-Aryl-5-pyrazolyl)benzoic Acid Chemistry

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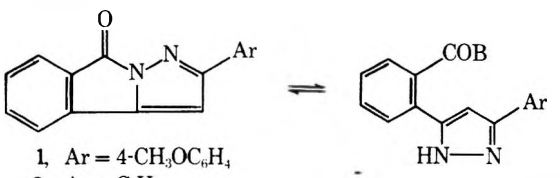
The nucleophilic ring-cleavage reactions of 2-(4-methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (**1**) and its analogues with aqueous base, alcohols, and primary and secondary amines are convenient syntheses of 2-[3-(4-methoxyphenyl)-5-pyrazolyl]benzoic acid (**4**), its esters (**5**), and amides (**6**), and their analogues. These reactions may be reversed by heat and by dehydrating agents such as $SOCl_2$, $POCl_3$, and Ac_2O. The derivative chemistry of **4** is discussed.

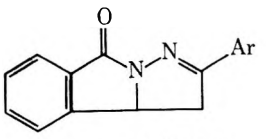
We have described[1] the synthesis of 2-(4-methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (**1**) from its 3,3a-dihydro derivative (**9**), which was prepared from phthalaldehydic acid, 4-methoxyacetophenone, and hydrazine. We now wish to report the further chemistry of these interesting plant growth regulants,[2–9] which concerns their conversion to 2-[3-(4-methoxyphenyl)-5-pyrazolyl]benzoic acid (**4**), its esters (**5**), and amides (**6**) by reaction with aqueous base, alcohols, and amines. These new compounds are also plant growth regulants.[10,11] In solution at 25°, the pyrazoloisoindolone **1** and its analogues are very susceptible to nucleophilic attack at the γ-lactam function to form **4–6** and their analogues. The progress of these reactions is readily followed by the rapid disappearance of the bright yellow color of **1**, an observation which appears to have escaped Leclerc,[12] who reported the uv spectrum of the phenyl analogue **2** in ethanol as λ_{max} 248 nm (ε 36000) and 335 (1480). The true spectrum of **2**, obtained in an unreactive solvent such as THF, has λ_{max} 337 nm (ε 10960), 323 (10880), 290 (13890), and 254 (35950), showing clearly that Leclerc's sample had partly decayed in solution to ester **7** after preparation. The ring-opened ester **7** has λ_{max} (EtOH) 252 nm (ε 25140), a value which is typical of this class of compounds.



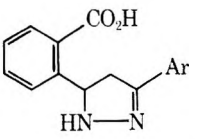
1, Ar = 4-$CH_3OC_6H_4$
2, Ar = C_6H_5
3, Ar = 4-HOC_6H_4

4, Ar = 4-$CH_3OC_6H_4$; B = OH
5, Ar = 4-$CH_3OC_6H_4$; B = OR
6, Ar = 4-$CH_3OC_6H_4$; B = NR_1R_2
7, Ar = C_6H_5; B = OC_2H_5
8, Ar = 4-HOC_6H_4; B = OH

The 3,3a-dihydro derivative **9** behaves similarly to **1** toward nucleophiles, but the resulting 2,3-dihydropyrazole derivatives (e.g., **11**) are oxidatively unstable, and the usual product after atmospheric isolation is a mixture of **11** and **4**. An exception is the phenol **12**, which can be isolated pure in good yield by treating the phenol **10** with aqueous base.



9, Ar = 4-$CH_3OC_6H_4$
10, Ar = 4-HOC_6H_4



11, Ar = 4-$CH_3OC_6H_4$
12, Ar = 4-HOC_6H_4

Although dihydropyrazole **10** may be prepared most conveniently by the demethylation of **9** with 48% HI, the corresponding pyrazole **1** is converted to the ring-opened phenol **8** by this treatment.[13] Table I lists the compounds prepared by these methods, using the general procedures described in the Experimental Section.

Spectra. The fused γ-lactam structure of **1** and **2** gives their spectra characteristic ir bands at 1780 and 1760 (**1**), 1790 and 1760 cm^{-1} (**2**), and a pair of intense uv bands at 346 and 331 (**1**) and 337 and 323 nm (**2**). The compounds in Table I have entirely different spectra, with the ir carbonyl frequencies expected for aromatic acids (1670–1690 cm^{-1}), their esters (1705–1720 cm^{-1}), and amides (1610–1670 cm^{-1}), and uv absorptions near 260 nm with slight variations in extinction coefficient for the acids (30000–36000), esters (26000–29000), and amides (31000–33000). The position of the singlet pyrazole proton signal (δ 6.60–7.00 ppm) in the proton NMR spectra of the ring-opened compounds does not distinguish them from the cyclic forms where the signal is at 6.63 ppm in **1** and 6.68 ppm in **2**. The spectral differences between the cyclic dihydro form **9** [1690 cm^{-1}, 323 nm (ε 18070), 277 (9080), and 268 (9150)] and its cleavage product **12** [1700 cm^{-1}, 282 nm (ε 17400)] are less pronounced, but do reflect the differences between these structures.

Table I
2-(3-Aryl-5-pyrazolyl)benzoic Acids and Their Derivatives[a]

Entry	Structure	Yield, %	Recrystn solvent	Mp, °C	Ir ν_{max} (KBr), cm^{-1}	Uv λ_{max} (EtOH) (ϵ_{max})	NMR, δ ppm[b] ($CDCl_3$–Me_4Si)	Formula
				2-(3-Aryl-5-pyrazolyl)benzoic Acids				
1	4	85	60% EtOH	223–225 dec	1690	266 (35700)[c]	6.80[d]	$C_{17}H_{14}N_2O_3$
2	8	76	3:1:1 EtOH–Me_2SO–H_2O	260–264 dec	1690	261 (30000)	6.75[d]	$C_{16}H_{12}N_2O_3$
				2-(3-Aryl-5-pyrazolyl)benzoic Acid Esters				
3	5, R = CH_3	59	Hexane–EtOAc	92–93	1720[e]	261 (28200)	6.65	$C_{18}H_{16}N_2O_3$
4	5, R = CH_3, HCl salt	55	Me_2CO	181–191 dec	1710	261 (28100)	6.85[d]	$C_{18}H_{17}N_2O_3Cl$
5	5, R = C_2H_5	23	Hexane–EtOAc	99.5–101	1710[e]	260 (28400)	*f*	$C_{19}H_{18}N_2O_3$
6	5, R = C_2H_5, HCl salt	66	Me_2CO	164–167.5	1720	262 (28000)	6.95[d]	$C_{19}H_{19}N_2O_3Cl$
7	7	50	Hexane–EtOAc	66–70	1710[e]	252 (25140)	6.68	$C_{18}H_{16}N_2O_2$
8	5, R = *n*-C_3H_7	58	Hexane–EtOAc	107–109	1710[e]	261 (28800)	7.00	$C_{20}H_{20}N_2O_3$
9	5, R = *n*-C_4H_9	47	Hexane–EtOAc	92–94	1710[e]	260 (29000)	*f*	$C_{21}H_{22}N_2O_3$
10	5, R = *n*-C_5H_{11}	23	Hexane–EtOAc	82–83.5	1705[e]	261 (28200)	6.63	$C_{22}H_{24}N_2O_3$
11	5, R = *n*-C_6H_{13}	73	*g*	*g*	1710[e]	262 (26600)	6.60	$C_{23}H_{26}N_2O_3$
12	5, R = $HOCH_2CH_2$	79	50% EtOH	148–150	1710	261 (28400)	6.62	$C_{19}H_{18}N_2O_4$
				2-(3-Aryl-5-pyrazolyl)benzoic Acid Amides				
13	6, $R_1 = R_2 = H$	89–96	1:1 EtOH–Me_2SO	205–207 dec	1660, 1610	261 (31600)	6.86[d]	$C_{17}H_{15}N_3O_2$
14	6, $R_1R_2 = (CH_2)_4$	81	EtOAc–$CHCl_3$	199–201 dec	1660, 1630, 1610	261 (32300)	6.77[d]	$C_{21}H_{21}N_3O_2$
15	6, $R_1R_2 = CH_2CH_2OCH_2CH_2$	84	EtOAc–MeOH	221–223 dec	1610, 1500	262 (32600)	6.73[h]	$C_{21}H_{21}N_3O_3$
16	6, $R_1 = C_6H_5CH_2O$, $R_2 = H$	61	3:1:1 EtOH–Me_2SO–H_2O	180–181.5	1650	261 (31800)	6.93[d]	$C_{24}H_{21}N_3O_3$
				2-[3-Aryl-(2-acetyl-5-pyrazolyl)]benzoic Acid Esters				
17	13	92	1:1 petroleum ether–EtOAc	119–121	1730, 1610	300 (14500) 282 (21100) 233 (21200)	6.57	$C_{20}H_{18}N_2O_4$
18	14	37	1:1 petroleum ether–EtOAc	71–73.5	1730, 1610	305 (12600) 288 (21500) 235 (22900)	6.60	$C_{22}H_{22}N_2O_4$
19	15	77	1:1 petroleum ether–EtOAc	65–69	1730, 1610	305 (12300) 288 (20800) 235 (21300)	6.50	$C_{23}H_{24}N_2O_4$

[a] Analytical data (C, H, N) agree with theoretical values (±0.3%). [b] Chemical shift of singlet pyrazole proton signal. [c] Measured in DMF. [d] Measured in Me_2SO-d_6. [e] Measured in $CHCl_3$. [f] Signal obscured by other aromatic protons. [g] Not obtained crystalline. [h] Measured in CF_3CO_2H.

Cyclization of Pyrazolylbenzoic Acids to Pyrazoloisoindolones. The reverse process, the cyclization of 4 to 1, requires a chemically active dehydrating agent such as $SOCl_2$, $POCl_3$, or Ac_2O. Strong acids such as H_2SO_4, *p*-TsOH, or CF_3CO_2H are ineffective cyclization reagents for this reaction. The cyclization is rapid, proceeds in good yield, and is signaled by the return of the yellow color of 1. Thermal cyclization of structures 4–6 to 1 occurs at 200°, but the yields are low, and the isolation procedures are less satisfactory than for the chemical methods. Visually, this thermal reversion is seen in a melting point capillary with those compounds in the series which melt above 200° with decomposition. Thermal cyclization is the only known method with the esters 5 and amides 6. The phenol 3 must be prepared by the circuitous route 9 → 1 → 8 → 3, using $SOCl_2$ as the cyclization reagent, because 10 cannot be dehydrogenated to 3 with DDQ.[13]

Kinetics of Ester Formation and Hydrolysis. Qualitatively, the disappearance of the yellow color of 1 is a useful indication of the progress of its conversion to 4–6. In alcoholic solvents, the reaction becomes visually slower as the chain length or bulk of the nucleophile increases, there being essentially no reaction with *t*-BuOH. These reactions are accelerated by a trace of base, and in MeOH or EtOH containing a chip of sodium, the conversion to 5 (B = OCH_3 or OC_2H_5) is complete within a few minutes. The solubility of 1 in the solvent containing the nucleophile is important; structure 1 is insoluble in, and is not attacked by, dilute aqueous alkali, but the addition of MeOH or EtOH to such mixtures causes rapid conversion to the anion of 4.

The rate of alcoholysis of 1 in neutral solution can be easily followed by the disappearance of its 346- and 331-nm bands in a uv spectrophotometer. Table II lists the first-order pseudounimolecular rate constants determined this way at 25°, methanolysis being approximately 100 times faster than ethanolysis. The arylpyrazolyl substituent was found to enhance the rate of base-catalyzed hydrolysis of benzoate esters approximately sixfold when the methyl and *n*-butyl esters 5 (B = OCH_3, B = O-*n*-C_4H_9) were compared with methyl and *n*-butyl benzoates in aqueous EtOH. Table II lists the second-order bimolecular rate constants for these compounds.

***N*-Alkyl and *N*-Acyl Derivatives.** Because 4 is rapidly

Table II
Kinetics of Ester Formation and Hydrolysis

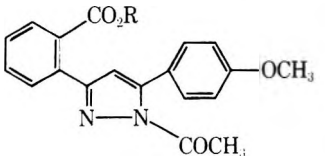
A. Alcoholysis of 1 at 25 ± 1°

Solvent	k_1, sec^{-1}	Relative rate
CH_3OH	$(4.94 \pm 0.19) \times 10^{-4}$	99.5
C_2H_5OH	$(4.96 \pm 0.20) \times 10^{-6}$	1.0

B. Hydrolysis of Esters at 26 ± 0.1°

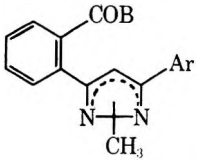
Compd	k_2, $l.^{-1}$ mol^{-1} sec^{-1}	Relative rate
5, B = OCH_3	$(3.26 \pm 0.15) \times 10^{-3}$	6.65
5, B = O*n*-C_4H_9	$(3.04 \pm 0.27) \times 10^{-3}$	6.45
$C_6H_5CO_2CH_3$	$(6.54 \pm 0.47) \times 10^{-4}$	1.33
$C_6H_5CO_2$*n*-C_4H_9	$(4.79 \pm 0.16) \times 10^{-4}$	1.00

cyclized to **1** in the presence of acid anhydrides, *N*-acyl derivatives of the ring-opened forms must be prepared from the esters **5**. Treatment of **5** (B = OCH_3, O-*n*-C_3H_7, or O-*n*-C_4H_9) with Ac_2O in pyridine gave only one of the two possible *N*-acetyl derivatives as determined by spectra of the crude and purified materials.[14] Mass spectral fragmentation data favor the 2-acetyl derivatives (**13–15**) rather



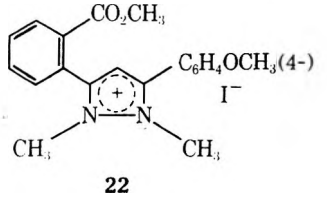
13. R = CH_3
14. R = *n*-C_3H_7
15. R = *n*-C_4H_9

than the isomeric 1-acetyl derivatives with *m/e* 350 $(M)^+$, 308 $(M - CH_2CO)^+$ base peak, and 176 $(C_{10}H_{10}NO_2)^+$ corresponding to the fragment $[4\text{-}CH_3OC_6H_4CNCOCH_3]^+$ in **13**. The alkylation of **4** with CH_3I in DMF in the presence of Na_2CO_3 gives a mixture of the isomeric *N*-methyl esters **16** and **17** and the quaternary iodide **22**. After separation,



16, 1-CH_3; B = OCH_3; Ar = 4-$CH_3OC_6H_4$
17, 2-CH_3; B = OCH_3; Ar = 4-$CH_3OC_6H_4$
18, 1-CH_3; B = OH; Ar = C_6H_5
19, 2-CH_3; B = OH; Ar = C_6H_5
20, B = Cl; Ar = C_6H_5
21, B = OC_2H_5; Ar = C_6H_5; HCl salt

the mixture of **16** and **17** is readily quaternized to **22**, and **22** is readily demethylated to the mixture of **16** and **17**. The *N*-methyl derivatives of the parent acid (**18**, **19**) may be prepared by treating the disodium salt (**23**)[15] with meth-



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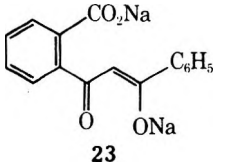

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ylhydrazine hydrochloride. The product of this reaction is a 5:1 isomer mixture from which the major isomer may be separated by recrystallization. Mass spectra did not distinguish between the isomers. The major isomer was converted to its acid chloride (**20**) and its ethyl ester hydrochloride (**21**) by the usual procedures. These experiments demonstrate that blocking (a) the pyrazole nitrogen by alkyl substitution prevents cyclization to the pyrazoloisoindolone structure, and (b) the carboxyl group by esterification increases the difficulty of cyclization.

Experimental Section[16]

2-[3-(4-Methoxyphenyl)-5-pyrazolyl]benzoic Acid (4). A mixture of **1** (46.7 g, 0.169 mol), H_2O (750 ml), MeOH (750 ml), and NaOH (8.0 g, 0.20 mol) was stirred mechanically at 25° for 6 hr, then acidified with 25 ml of concentrated HCl, and cooled to 0°. The colorless precipitate of **4** was filtered and recrystallized from a mixture of EtOH (1400 ml) and H_2O (1000 ml), yield 42.1 g (0.143 mol, 85%) of colorless, crystalline solid, mp 223–225° dec.

2-[3-(4-Hydroxyphenyl)-5-pyrazolyl]benzoic Acid (8). A mixture of **1** (5.0 g, 18.1 mmol) and constant boiling point HI (50 ml) was stirred at reflux for 6 hr, then poured into 250 ml of H_2O, cooled, and filtered. The crude phenol **8** was rinsed with aqueous $Na_2S_2O_3$ and H_2O, and recrystallized from a mixture of EtOH (30 ml), Me_2SO (10 ml), and H_2O (10 ml), yield 3.85 g (13.7 mmol, 76%) of colorless, crystalline solid, mp 260–264° dec.

Preparation of Esters of 2-[3-(4-Methoxyphenyl)-5-pyrazolyl]benzoic Acid (5). A. A mixture of **1** (5.0 g, 18.0 mmol) and the appropriate alcohol (100 ml) containing 0.1 g (4 mg-atom) of Na was stirred at 25° until the yellow color had disappeared (1–2 hr). The alcohol was evaporated or removed by steam distillation (*n*-$C_5H_{11}OH$, *n*-$C_6H_{13}OH$), and the residue was dissolved in C_6H_6 (100 ml) and stirred overnight with a few grams of Florisil. Filtration and evaporation left a colorless, gummy residue of crude ester which was recrystallized from EtOAc–hexane mixtures. The ethylene glycol monoester (Table I, entry 12) was directly filtered from the reaction mixture and recrystallized from 50% EtOH.

B. Ester **7** was similarly prepared from **2**[1] and EtOH.

C. The hydrochlorides of the methyl and ethyl esters **5** (B = OCH_3, OC_2H_5) were prepared by dissolving the crude esters in Et_2O and treating this solution at 0° with HCl gas. The crude hydrochlorides were recrystallized from Me_2CO containing a drop of HCl.

D. Acid **4** (5.0 g) was directly converted to ester **5** (B = OCH_3) in 26% yield by 4 hr reflux in a mixture of MeOH (50 ml) and H_2SO_4 (1.0 ml).

Preparation of Amides of 2-[3-(4-Methoxyphenyl)-5-pyrazolyl]benzoic Acid (6). A mixture of **1** (5.0 g, 18.0 mmol) and excess amine was stirred for several hours until the yellow color had disappeared. With liquid NH_3, the reaction temperature was −33°, and with other amines it was 25°. Low-boiling amines were evaporated to leave the crude amide as a solid. The reaction product with morpholine was isolated by pouring the reaction mixture into H_2O. The reaction with benzyloxyamine was done in C_6H_6 solution from which the crude product precipitated. The crude amides were recrystallized from suitable solvents (Table I).

2-[3-(4-Hydroxyphenyl)-4,5-dihydro-5-pyrazolyl]benzoic Acid (12). A. A mixture of **9** (5.0 g, 18.0 mmol) and constant boiling point HI (50 ml) was heated at reflux for 5 hr, poured into 250 ml of H_2O, and filtered. The crude phenol **10** was recrystallized from a mixture of MeOH (200 ml) and DMF (50 ml), yield 3.34 g (12.65 mmol, 70%) of colorless, crystalline solid: mp 283–285° dec; ν_{max} (Nujol) 3295 and 1670 cm^{-1}; λ_{max} (DMF) 324 nm (ϵ 17800); ^1H NMR (Me_2SO-d_6) δ 7.70–6.81 (m) 8 H (aromatic), 5.55 (X part) 1 H and 3.60–3.07 ppm (AB part) 2 H ($CHCH_2$). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.61; H, 4.56; N, 10.52.

B. A mixture of **10** (5.0 g, 18.9 mmol) and 10% NaOH (50 ml) was stirred at 25° for 2 hr; then it was acidified with concentrated HCl, cooled, and filtered to give crude **12** (4.93 g, 17.5 mmol, 92%) which could be purified either by reprecipitation from NaOH solution with HCl, or by recrystallization from 30% DMF. Pure **12** formed colorless crystals: mp 248–250° dec; ν_{max} (KBr) 3440, 1610, and 1570 cm^{-1}; λ_{max} (DMF) 282 nm (ϵ 17400); ^1H NMR (D_2O + KOH) δ 7.61–6.81 (A_2B_2 + m) 8 H (aromatic), 5.30 (X part) 1 H, and 3.73–2.82 ppm (AB part) 2 H (CH_2CH). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.89; H, 4.90; N, 9.98.

2-(4-Hydroxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (3). A mixture of **8**[1] (1.0 g, 3.6 mmol) and $SOCl_2$ (10 ml) was allowed to

evaporate at 25°. The yellow residue was recrystallized from 25% Me_2CO: yield 0.69 g (71%) of yellow needles of **3**; mp 220–223° dec; ν_{max} (KBr) 3400, 1780, and 1740 cm^{-1}; λ_{max} (THF) 390 nm (ϵ 2040), 347 (11000), 332 (11100), 297 (15500), 286 (20000), 265 (28700), 240 (25100), and 235 (24200); ^1H NMR (Me_2SO-d_6) δ 7.78–6.91 (A_2B_2 + m) 8 H (aromatic) and 7.03 ppm (s) 1 H (pyrazole proton). Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.25; H, 4.18; N, 10.30.

2-(4-Methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (1) from 4–6. A. $SOCl_2$. Treatment of **4** with $SOCl_2$ as described above for **8** gave a 90% yield of **1**, identified by mixture melting point and spectra.

B. Ac_2O–C_5H_5N. Treatment of **4** (5.0 g, 17.0 mmol) with a mixture of Ac_2O (30 ml) and pyridine (20 ml) at 25° produced a copious yellow precipitate of **1** after 1 hr. The product was isolated by pouring the reaction mixture into 400 ml of H_2O and filtration, and was identified as in A.

C. $POCl_3$–C_5H_5N. Treatment of **4** (1.0 g, 3.4 mmol) with a mixture of $POCl_3$ (0.54 g, 3.4 mmol) and pyridine (25 ml) at 25° for 3 hr, followed by isolation as in B, gave an 88% yield of **1**.

D. Heat. One-gram samples of **4**, **5** (B = OCH_3), and **6** (B = NH_2) were each held at 200–220° (0.1 mm) in a sublimer for 2–4 hr. The yellow sublimate from **4** was rinsed with 5% $NaHCO_3$ to remove unreacted **4**, and the insoluble residue was recrystallized from Me_2CO to give 0.37 g (1.34 mmol, 39%) of **1**. NMR and ir examination of the yellow sublimate from **5** (B = OCH_3) showed that it was an 85:15 mixture of **5**:**1**. The yellow sublimate from **6** (B = NH_2) was rinsed with $CHCl_3$ to remove **1** (0.77 g, 2.78 mmol, 82%) and leave unreacted **6** on the filter.

Kinetics of Alcoholysis of 1. The glassware was rinsed with dilute acid and distilled water before use to remove basic impurities. Approximately 10^{-4} *M* solutions of **1** were prepared at time zero by diluting more concentrated THF solutions of **1** with MeOH and EtOH; the reaction solutions were 95:5 alcohol–THF by volume. The disappearance of the 346- and 331-nm bands of **1** in the uv was followed by recording the optical densities at regular intervals (3 min for MeOH, 3 hr for EtOH), the spectrum in pure THF being used for the zero-time and blank readings. The rate constants were calculated in the usual way from $k_1 = 2.303/t\ [\log a/(a - x)]$.

Kinetics of Ester Hydrolysis. The hydrolysis medium[17] was 0.03 *N* base prepared by the addition of Na(0.7 g $l.^{-1}$) to degassed 87.8% w/w EtOH–H_2O, and standardized by adding a 10-ml aliquot to 20 ml of standard H_2SO_4, followed by back-titration with standard NaOH to phenolphthalein end point. Three volumetric flasks were partly filled with the hydrolysis medium and allowed to equilibrate at 26 ± 0.1° before the hydrolysis was started by adding the ester under study to two of the flasks, and using the contents of the third flask to bring the solution up to the mark and serve as a blank control. At selected times (0.5–1.0-hr intervals) 10-ml aliquots of the hydrolysis medium were titrated as described above. The second-order rate constants were calculated in the usual way from $k_2 = 2.303/t(a - b)\ [\log b(a - x)/a(b - x)]$.

2-[2-Acetyl-3-(4-methoxyphenyl)-5-pyrazolyl]benzoate Esters (13–15). A mixture of ester **5** (B = OCH_3, O-*n*-C_3H_7, or O-*n*-C_4H_9) (1–3 g), pyridine (10–25 ml), and Ac_2O (5–12 ml) was left overnight at 25°, then poured into H_2O and extracted with C_6H_6. The crude products were recrystallized from 1:1 petroleum ether–EtOAc; the details are given in Table I. The NMR spectra showed the presence of only one isomer (singlet peaks for pyrazole and *N*-acetyl signals).

Reaction of 4 with CH_3I. A. A mixture of DMF (100 ml), **4** (13.0 g, 44.1 mmol), Na_2CO_3 (9.36 g, 88.2 mmol), and CH_3I (25 ml) was stirred at reflux for 6 hr, poured into 100 ml of H_2O, acidified to pH 3, and extracted with $CHCl_3$. The yellow syrup obtained from the extracts was chromatographed on 100 g of SilicAR CC-4, taking 200-ml fractions. Fractions 1–6 (2:1 cyclohexane–EtOAc) gave 6.04 g (19.6 mmol, 44%) of a mixture of **16** and **17** in approximately equal proportions, and fractions 7 and 8 (MeOH) gave 8.47 g (18.3 mmol, 41%) of **22**. The ester mixture (**16**, **17**) has ν_{max} ($CHCl_3$) 1720 cm^{-1}; ^1H NMR ($CDCl_3$–Me_4Si) δ 8.12–6.85 (A_2B_2 + m) 8 H (aromatic), 6.44 (s) 1 H (pyrazole proton), 3.76 (s) and 3.68 (s) 3 H (OCH_3 isomers), and 3.64 ppm (s) 3 H (NCH_3); *m/e* 322 (M^+), 291 ($M - OCH_3$)$^+$, 176 ($C_{10}H_{10}NO_2$)$^+$, and 133 (C_8H_7NO)$^+$ from **16**, 161 ($C_9H_7NO_2$)$^+$ and 148 ($C_9H_{10}NO$)$^+$ from **17**. The quaternary iodide **22** was recrystallized twice from EtOH (35 ml) as a colorless, crystalline solid: mp 153–155°; ν_{max} ($CHCl_3$) 1720 cm^{-1}; λ_{max} (EtOH) 277 nm (ϵ 19500) and 218 (37400); ^1H NMR ($CDCl_3$–Me_4Si) δ 8.20–7.00 (m) 8 H (aromatic), 6.56 (s) 1 H (pyrazole), 4.35 (s) 3 H and 4.21 (s) 3 H (NCH_3), and 3.88 ppm (s) 3 H (OCH_3). Anal. Calcd for $C_{20}H_{21}N_2O_3I$: C, 51.73; H, 4.56; N, 6.03. Found: C, 51.57; H, 4.65; N, 5.95.

B. The same experiment done in refluxing Me_2CO with K_2CO_3 as the base gave a 98% yield of the ester mixture (**16**, **17**).

C. The ester mixture from A or B was converted to methiodide **22** in 20–60% yield by stirring at reflux in a mixture of DMF and CH_3I.

D. Treatment of methiodide **22** (1.0 g, 2.16 mmol) with a mixture of Ag_2O (from 2.0 g of $AgNO_3$), MeOH (25 ml), H_2O (25 ml), and NaOH (1.0g) at 25° for 1 hr gave, after filtration and evaporation, a residue which reverted to the ester mixture (**16**, **17**) (0.21 g, 30%) on heating at 180° (0.1 mm).

2-[3-Phenyl-5-(*N*-methylpyrazolyl]benzoic Acids (18, 19). A. A mixture of **23**[15] (12.0 g, 40 mmol), EtOH (80 ml), 1 *N* HCl (40 ml, 40 mmol), and methylhydrazine (8.0 g, 0.17 mol) was stirred at reflux for 1 hr, cooled, acidified to pH 3 with HCl, and filtered. The crude solid precipitate (6.46 g, 23 mmol, 58%) was a 5:1 isomer mixture by NMR [*N*-methyl signals at δ 3.88 (major) and δ 3.63 ppm (minor)]. Recrystallization of 2.90 g of this material from 85% EtOH (17 ml) gave 0.59 g of the pure major isomer as a colorless, crystalline solid: mp 163–165°; ν_{max} (KBr) 1680 cm^{-1}; λ_{max} (EtOH) 248 nm (ϵ 23200); ^1H NMR ($CDCl_3$–Me_4Si) δ 9.03 (s) 1 H (CO_2H), 8.29–7.25 (m) 8 H (aromatic), 6.57 (s) 1 H (pyrazole), and 3.88 ppm (s) 3 H (OCH_3). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07; *m/e* 278.1055. Found: C, 73.35; H, 5.27; N, 10.06; *m/e* 278.1029.

B. The pure major isomer (0.10 g) was converted to its acid chloride **20** with $SOCl_2$ (2 ml). Evaporation gave crude **20**, ν_{max} ($CHCl_3$) 1790 and 1750 cm^{-1}, which was treated with warm EtOH (2 ml). Evaporation of this mixture left the colorless ethyl ester hydrochloride **21** as a solid: mp 139–148° dec; ν_{max} (KBr) 3420, 1710 cm^{-1}; λ_{max} (EtOH) 244 nm (ϵ 22200); ^1H NMR (Me_2SO-d_6) δ 12.83 (s) 1 H (NH), 8.10–7.33 (m) 8 H (aromatic), 6.63 (s) 1 H (pyrazole proton), 4.35 (q, J = 7 Hz) 2 H (OCH_2), 4.26 (s) 3 H (NCH_3), and 1.32 ppm (t, J = 7 Hz) 3 H (CH_3). Anal. Calcd for $C_{19}H_{19}N_2O_2Cl$: C, 66.56; H, 5.59; N, 8.17. Found: C, 66.21; H, 5.57; N, 8.07.

Registry No.—**1**, 37564-17-3; **3**, 54665-99-5; **4**, 56978-19-9; **5** (R = Me), 56978-20-2; **5** (R = Me) HCl, 56978-21-3; **5** (R = Et), 56978-22-4; **5** (R = Et) HCl, 56978-23-5; **5** (R = Pr), 56978-24-6; **5** (R = Bu), 56978-25-7; **5** (R = C_5H_{11}), 56978-26-8; **5** (R = C_6H_{13}), 56978-27-9; **5** (R = CH_2CH_2OH), 56978-28-0; **6** (R_1 = R_2 = H), 56978-29-1; **6** (R_1R_2 = $(CH_2)_4$), 56978-30-4; **6** (R_1R_2 = $CH_2CH_2OCH_2CH_2$), 56978-31-5; **6** (R_1 = $C_6H_5CH_2O$; R_2 = H), 56978-32-6; **7**, 56978-33-7; **8**, 56978-34-8; **9**, 21138-13-6; **10**, 56978-35-9; **12**, 56978-36-0; **13**, 39785-21-2; **14**, 56978-37-1; **15**, 56978-38-2; **16**, 39785-18-7; **17**, 39785-19-8; **18**, 39785-20-1; **19**, 56978-39-3; **21** isomer A, 56978-40-6; **21** isomer B, 56978-41-7; **22**, 57014-90-1; **23**, 56978-42-8; methanol, 67-56-1; ethanol, 2348-46-1; propanol, 71-23-8; butanol, 71-36-3; pentanol, 71-41-0; hexanol, 111-27-3; 1,2-ethanediol, 107-21-1; iodomethane, 74-88-4.

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(13) A referee has commented that 48% HI converts **1** to **8** and **9** to **10** (rather than **12**). Some possible reasons for this difference are (a) the dihydro system **9** is less strained than the pyrazole **1**, as indicated by ir and uv, (b) more importantly, **1** is an *N*-acylpyrazole, whereas **9** is more like a tertiary amide or hydrazide. The former readily undergo cleavage (ref 14, p 96) whereas the latter should be more stable to hydrolysis.
(14) T. L. Jacobs in "Heterocyclic Compounds", Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, p 95, states that generally, in the acylation of pyrazoles, only the more stable isomer is obtained, and the less stable isomer (obtained by another method) rearranges readily to the more stable isomer.

(15) Kindly supplied by Dr. R. M. Forbis, Biochemicals Department, E. I. du Pont de Nemours and Co., Experimental Station, Wilmington, Del.
(16) All melting points are uncorrected; ir spectra were determined on Perkin-Elmer 21, 221, and 621 instruments, uv spectra on a Carey 14 instrument, NMR spectra on a Varian Associates A-60 instrument, and mass spectra on Consolidated 103 and 110B (high-resolution) instruments.
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Conjugate Addition Reactions of Alkali Diphenylmethides to Acrylic Esters

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In contrast to previous failure to obtain conjugate addition products from the reaction of alkali diphenylmethides to acrylic esters, reaction conditions can be selected to afford adducts even from methyl acrylate. Yields of addition products are increased as alkyl substituents are introduced into the acrylate. Certain highly substituted cinnamates do not undergo conjugate addition but instead undergo carbonyl addition to give low yields of ketones.

The addition of anions to conjugated carbonyl compounds has been the object of much study and ranks among the most useful of organic synthetic reactions. The mechanism for the reversible addition of weaker bases (conjugate bases of carbon acids strong enough to be deprotonated by Grignard reagents[1]) to conjugated systems is generally accepted as involving direct addition to the β carbon to produce an enolate (eq 1).[2] Recently the importance of a second mechanism, an electron transfer from the nucleophile to the enone, has been demonstrated (eq 2).[3]

$$\mathrm{N{:}^-} + \mathrm{C{=}C{-}C{=}O} \longrightarrow \mathrm{N{-}C{-}C{=}C{-}O{:}^-} \qquad (1)$$

$$\mathrm{N{:}^-} + \mathrm{C{=}C{-}C{=}O} \longrightarrow \mathrm{N\cdot} + \overset{5e}{\overline{\mathrm{C{\cdots}C{\cdots}C{\cdots}O^-}}} \longrightarrow \mathrm{N{-}C{-}C{=}C{-}O^-} \qquad (2)$$

Strongly basic nucleophiles, for example, diphenylmethide ion, are less commonly encountered as Michael donors. The reaction with ethyl cinnamate to give ethyl 3,4,4-triphenylbutyrate[4] and with ethyl α-phenylacrylate to give ethyl 2,4,4-triphenylbutyrate[5] and addition to several 1,1-diarylethylenes[6] have been reported, but an attempt to synthesize ethyl 4,4-diphenylbutyrate from potassium diphenylmethide and ethyl acrylate gave no adduct, although the color of the anion was discharged. Instead, polymerization of the ethyl acrylate apparently took place, and diphenylmethane was recovered.

We now find that sodium or potassium diphenylmethide will react with acrylates and substituted acrylates, and that the ease of reaction is remarkably affected by the structure of the acrylate, in a manner not predicted by a consideration of the usual addition mechanism of eq 1.

When sodium diphenylmethide in liquid ammonia was treated with 1 molar equiv of methyl acrylate, 80% of the diphenylmethane was recovered, 8% of a high-boiling ester was obtained along with a large amount of nonvolatile residue, and none of the Michael adduct, methyl 4,4-diphenylbutyrate, was detected. The reaction was interpreted as a polymerization of the methyl acrylate initiated by diphenylmethide ion, and neutralization of the unreacted diphenylmethide ion by the relatively acidic α hydrogens of the polyester (Scheme I). The small amount of distillable ester

Scheme I

$$(C_6H_5)_2CH^- + CH_2{=}CHCO_2CH_3 \longrightarrow (C_6H_5)_2CHCH_2\bar{C}HCO_2CH_3$$

$$\xrightarrow{n\,CH_2{=}CHCO_2CH_3} (C_6H_5)_2CH(CH_2\underset{|\atop CO_2CH_3}{CH})_nCH_2\bar{C}HCO_2CH_3 \xrightarrow{n(C_6H_5)_2CH^-}$$

$$n(C_6H_5)_2CH_2 + (C_6H_5)_2CH(CH_2\underset{|\atop CO_2CH_3}{\bar{C}})_nCH_2\bar{C}HCO_2CH_3$$

presumably corresponded to short chains of self-addition. Since the anionic polymerization of methyl acrylate is itself a series of conjugate additions reactions, it seemed possible to manipulate conditions so that mono adduct 1 could be

$$\underset{\mathbf{1}}{(C_6H_5)_2CHCH_2CH_2CO_2CH_3} \qquad \underset{\mathbf{2}}{(C_6H_5)_2CHCH_2\underset{|\atop CH_2CH_2CO_2CH_3}{CH}CO_2CH_3}$$

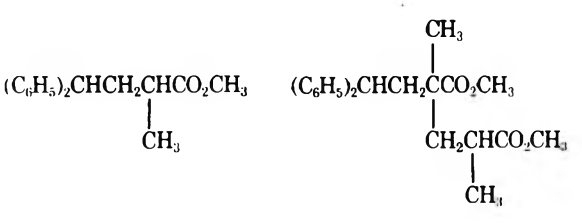
obtained. Accordingly, a very dilute ethereal solution of methyl acrylate was added very slowly (2 hr) to sodium diphenylmethide. Work-up of this reaction afforded the mono adduct 1 in 10% yield, 60% of the diphenylmethane, and much nonvolatile material. Polymerization was further minimized by an increase in the mole ratio of sodium diphenylmethide to methyl acrylate to four. From this reaction the mono adduct 1 was obtained in 40% yield, the diadduct dimethyl 2-(2′,2′-diphenylethyl)glutarate 2 was isolated in 10% yield, and 83% (3.3 molar equiv) of the diphenylmethane was recovered. These results can be interpreted as indicating that the affinity of methyl acrylate for

Table I
Reactions of Sodium Diphenylmethide with Acrylates

Registry no.	Acrylate	Product	Yield, %	Bp (mp), °C (mm)	Registry no.
96-33-3	$CH_2=CHCO_2CH_3$	1	40[a]	150–155 (0.8)[b]	10347-50-9
80-62-6	$CH_2=C(CH_3)CO_2CH_3$	3	40[c]	155–160 (0.8)[d]	57090-69-4
18707-60-3	$CH_3CH=CHCO_2CH_3$	$(C_6H_5)_2CHCH(CH_3)CH_2CO_2CH_3$	87[f]	155 (0.5)[g]	57090-72-9
41725-90-0	$CH_3CH=C(CH_3)CO_2CH_3$	$(C_6H_5)_2CHCH(CH_3)CH(CH_3)CO_2CH_3$	85	165 (0.5)[e]	57090-73-0
924-50-5	$(CH_3)_2C=CHCO_2CH_3$	$(C_6H_5)_2CHC(CH_3)_2CH_2CO_2CH_3$	90	160 (0.5)[h]	57090-74-1
49714-66-1	$(CH_3)_2C=(CH_3)CO_2CH_3$	$(C_6H_5)_2CHC(CH_3)_2CH(CH_3)CO_2CH_3$	80	170 (0.8)[e,i,j]	57090-75-2
25692-59-5	$C_6H_5CH=C(CH_3)CO_2CH_3$	$(C_6H_5)_2CHCH(C_6H_5)CH(CH_3)CO_2CH_3$	75	(116)[e]	57090-76-3
945-93-7	$C_6H_5C(CH_3)=CHCO_2C_2H_5$	$(C_6H_5)_2CHC(CH_3)CH_2CO_2C_2H_5$ (C6H5)	76	210 (0.8)[e]	57090-77-4
57090-70-7	$(CH_3)_2C=C(CH_2CO_2H)CO_2C_2H_5$	$(C_6H_5)_2CHC(CH_3)_2C(CH_2CO_2H)CO_2C_2H_5$	55	(161)[e,k]	57090-78-5
3461-34-5	$(C_6H_5)_2C=CHCO_2CH_3$	$(C_6H_5)_2C=CHCOCH(C_6H_5)_2$	25	(98)[e]	57090-79-6
57090-71-8	$C_6H_5C(CH_3)=C(CH_3)CO_2CH_3$	$C_6H_5C(CH_3)=C(CH_3)COCH(C_6H_5)_2$	16	185–190 (0.5)[e]	57090-80-9
22035-53-6	$(CH_3)_2C=C(CO_2CH_3)_2$	$(C_6H_5)_2CHC(CH_3)_2CH(CO_2CH_3)_2$	75	(109)[e]	57090-81-0

[a] 4:1 ratio of sodium diphenylmethide, slow addition of dilute ethereal solution of methyl acrylate. [b] Hydrolyzed to 4,4-diphenylbutyric acid, mp and mmp 105°. [c] 2:1 ratio of sodium diphenylmethide, slow addition of dilute ester. [d] Hydrolyzed to 2-methyl-4,4-diphenylbutyric acid,[e] mp 95°. [e] Satisfactory CH analysis was obtained for this compound and was submitted for review. [f] When potassium diphenylmethide was used the yield was 60%. [g] Hydrolyzed to 3-methyl-4,4-diphenylbutyric acid,[e] mp 113° (reported[7] 113°). [h] Hydrolyzed to 3,3-dimethyl-4,4-diphenylbutanoic acid, [e] mp 129°. [i] The ester was not hydrolyzed with base or aqueous acid. The ester was cyclized with concentrated sulfuric acid to 2,3,3-trimethyl-4-phenyl-1-tetralone,[e] mp 137°. [j] The starting material was prepared by the condensation of acetone with diethyl 1-carbethoxyethanephosphonate.[8] [k] Because of the carboxyl proton a 2:1 ratio of sodium diphenylmethide was used.

an ester α anion is greater than for the diphenylmethide ion, but that dilution of the ester or an increase in the relative amount of diphenylmethide ion favored formation of the mono Michael adduct. To test the postulate of proton transfer from polyester to anion, an experiment was carried out with potassium diphenylmethide and methyl methacrylate. Here the polymeric ester has no α hydrogen, and as expected the color of the diphenylmethide ion was not discharged by 1 mol of ester. Work-up of this mixture gave 80% of the diphenylmethane, 12% of high-boiling ester, and a larger quantity of nonvolatile residue. Repetition of the experiment with sodium diphenylmethide gave 70% recovery of the diphenylmethane and 20% of high-boiling ester. Finally, slow addition of a dilute ethereal solution of methyl methacrylate to 1 mol of sodium diphenylmethide gave 60% recovery of diphenylmethane, 15% of the 1:1 adduct, methyl 2-methyl-4,4-diphenylbutyrate (3), and 5% of the 1:2 adduct, dimethyl 2,4-dimethyl-2-(2′,2′-diphenylethyl)-glutarate (4). The yield of 3 reached a maximum at 40% when the ratio of diphenylmethide to methyl methacrylate was increased to 2:1.



3 4

It was surprising that the presence of an α methyl group seemed to facilitate the conjugate addition, since the adduct is a tertiary anion. Further investigation with other substituted acrylates revealed that the normal (1:1) adduct can be obtained in good yield with methyl crotonate, methyl tiglate [methyl (*E*)-2-methyl-2-butenoate], ethyl trimethylacrylate, methyl isopropylidenemalonate, methyl α-methylcinnamate, and methyl β-methylcinnamate. No carbonyl addition was observed with these compounds; however, with ethyl 3,3-diphenylpropenoate and ethyl dimethylcinnamate the Michael adduct was not obtained and only carbonyl addition products were obtained. These results are summarized in Table I.

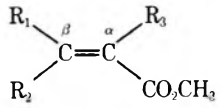
Possibly substituents on the acrylate moiety offer steric hindrance to addition, and this hindrance is overcome only by a very strong nucleophile (diphenylmethide), and not the less nucleophilic ester anion. This seems to be an unsatisfactory explanation, since it would be unlikely that the course of the reaction can be completely changed from polymerization of methyl acrylate (with a 1:1 mole ratio of reactants) to simple addition of methyl crotonate.[9]

An alternative explanation is that with very strong nucleophiles such as diphenylmethide ion, electron density at the β carbon in the transition state for addition is important. Calculation of the electron distribution in acrylates lends support to this idea, since increasing substitution on the double bond *decreases* the electron density at the β carbon, thus facilitating attack by the nucleophile; presumably electron distribution in the transition state is even more important than in the ground state. There may still be some steric effect, since diphenylmethide does not undergo conjugate addition to dimethylcinnamate and diphenylacrylate, only a small amount of carbonyl adduct being produced.

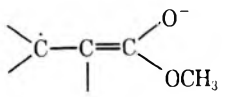
The electron density calculations are listed in Table II.

The stabilization introduced by substitution at the β carbon could also suggest the electron transfer mechanism, since the radical anion product of electron transfer (5) would also be stabilized by substitution. However, in view of the oxidation potential of diphenylmethide ion (−1.1 V[10]) and the reduction potential of acrylic esters (−1.78

Table II
Calculated Electron Densities in Acrylate Esters



R_1, R_2	R_3	α	β
H, H	H	4.0448	3.9498
H, H	CH_3	4.0408	3.9643
CH_3, H	H	4.0738	3.9163
CH_3, H	CH_3	4.0638	3.9319
CH_3, CH_3	H	4.1101	3.8973
CH_3, CH_3	CH_3	4.0910	3.9180



5

V^{11}), electron transfer in this system appears to be highly unlikely.[10]

Experimental Section

The procedures for the reactions of acrylates with alkali diphenylmethides are so similar that only one is given in detail. Variations are indicated in the Discussion or in Table I, as are physical constants.[12]

Reactions of Acrylic Esters with Alkali Diphenylmethides. Methyl 2,3,3-Trimethyl-4,4-diphenylbutanoate. Sodium diphenylmethide was prepared by addition of 16.8 g (0.1 mol) of diphenylmethane in 50 ml of ether to 0.1 mol of sodium amide in liquid ammonia, prepared from 2.3 g (0.1 g-atom) of sodium and a small amount of anhydrous ferric chloride in 250 ml of liquid ammonia. The resulting deep orange solution was stirred for 10 min and 12.8 g (0.1 mol) of methyl trimethylacrylate in 25 ml of ether was added during 10 min. To the resulting green solution was added 6 g of ammonium chloride. The ammonia was replaced by ether and the mixture was stirred with 250 ml of 0.1 *N* hydrochloric acid. The aqueous layer was separated and extracted with 100 ml of ether, and the combined ether solutions were dried over sodium sulfate and concentrated to give 28 g of a pale yellow liquid. Distillation afforded 6 g of starting materials [bp 70–200°/(1 mm)] and 22 g of methyl 2,3,3-trimethyl-4,4-diphenylbutanoate, bp 170° (0.8 mm). A solution of 4 g of the ester was dissolved in 20 ml of cold concentrated sulfuric acid, and the orange solution was stirred for 5 min and poured onto ice. Recrystallization from petroleum ether afforded 1.5 g (40%) of 4-phenyl-2,3,3-trimethyl-1-tetralone, mp 137°.

Acknowledgement. The authors wish to thank Dr. H. A. Kuska, who provided the CNDO/2 programs from QCEP and assisted in their use.

Registry No.—Sodium diphenylmethide, 5152-68-1; 2-methyl-4,4-diphenylbutyric acid, 57090-82-1; 3,3-dimethyl-4,4-diphenylbutanoic acid, 57090-83-2; 2,3,3-trimethyl-4-phenyl-1-tetralone, 57090-84-3; diphenylmethane, 101-81-5; sodium amide, 7782-92-5.

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Oxidative Addition of Sodium and Zinc Arenesulfinates to Derivatives of Diazenedicarboxylic Acid[1,2]

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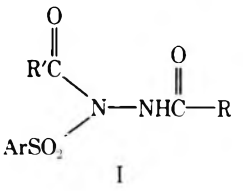
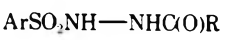
1,2-Diazenedicarboxamide (DDA), a number of substituted diazenedicarboxamides, and diethyl diazenedicarboxylate react with the sodium and zinc salts of *p*-toluene- and benzenesulfinic acids in Me_2SO or DMF to give addition products (I) and/or addition–elimination products (II). With DDA and the N,N-disubstituted derivatives, the trisubstituted diazane (I) is unstable under alkaline conditions generated and undergoes elimination. The resulting products, sulfonyldiazanecarboxamides (II), are formed in high yield. DDA also undergoes oxidative addition with sodium arenesulfinates in aqueous media and subsequent elimination to give II in nearly quantitative yield. Symmetrically substituted diazenedicarboxamides, exemplified by *N,N'*-diethyl-1,2-diazenedicarboxamide and *N,N'*-diphenyl-1,2-diazenedicarboxamide, react with arenesulfinate salts in Me_2SO to yield a mixture of I and II. The latter may result from elimination of an isocyanate from I under alkaline conditions. Tetrasubstituted diazenedicarboxamides, such as *N,N,N',N'*-tetramethyl-1,2-diazenedicarboxamide (TMDDA), and diazenedicarboxylates, such as diethyl diazenedicarboxylate (DEDD), afford only the trisubstituted product (I), the latter or its anion being stable under basic conditions.

α-Carbonyl diazenes may be characterized as oxidants by virtue of their tendency to act as strong electron acceptors. Oxidation may result in the formation of addition products involving a diazene and substrate.[3] The currently described reaction of α-carbonyl diazenes with salts of arenesulfinic acids to give products possessing the general structures I and II may be placed in this category. The oxidation of arenesulfinic acids by diphenyldiazene (azobenzene) and certain substituted analogues has been reported,[4,5] the reaction proceeding by addition of the acid across the diazene



I



II

linkage to give sulfonyldiazanes. The reaction of sulfinic acids or their salts with α-carbonyl diazenes is relatively unexplored.

Messinger[6] recently reported the preparation of several trisubstituted diazanes (I) by the addition of benzene- or *p*-toluenesulfinic acid to either ethoxy or morpholino derivatives of diazenedicarboxylic acid. We have examined the reaction of several zinc and sodium arenesulfinates with a number of diazenedicarboxylic acid derivatives in some detail and we are presenting here these results and some information bearing on the mechanisms of the reaction.

Results

Reaction of 1,2-Diazenedicarboxamide (DDA) with Salts of Arenesulfinic Acids. When DDA and either the zinc or sodium salt of arenesulfinic acids are combined in equivalent amounts in Me_2SO solution[7] at room temperature, a rapid reaction occurs, to yield the corresponding sulfonyldiazanecarboxamides (II, R = NH_2) in high yield. NMR analysis of freshly combined Me_2SO-d_6 solutions of DDA and zinc bis(*p*-toluenesulfinate) (1) (2:1 mole ratio) confirmed the rapidity of the reaction; signals due to DDA and sulfinate were absent after several minutes. Following the mixing of reactants, NMR signals appear, some of which are coincident with those of the sulfonyldiazanecarboxamide (2) ultimately isolated, while others are presumably associated with some labile intermediate or adduct. In time, these latter absorptions disappear,[8] and those characteristic of the major reaction product, *p*-toluenesulfonyldiazanecarboxamide (2), predominate.

In one case, the free sulfinic acid, *p*-acetamidobenzenesulfinic acid, was used in place of the corresponding salt. In Me_2SO, no apparent reaction occurred; however, adding the reaction mixture to water several hours after mixing resulted in the precipitation of a white, gelatinous solid. The product (87.5% yield) was formulated as 1-*p*-acetamidobenzenesulfonyl-1,2-diazanedicarboxamide (4) on the basis of its elemental analysis, molecular weight, and NMR spectrum (Table III) (see Experimental Section). 4 is converted to *p*-acetamidobenzenesulfonyldiazanecarboxamide (5) (77% conversion) by consecutive treatments with aqueous base and acid.

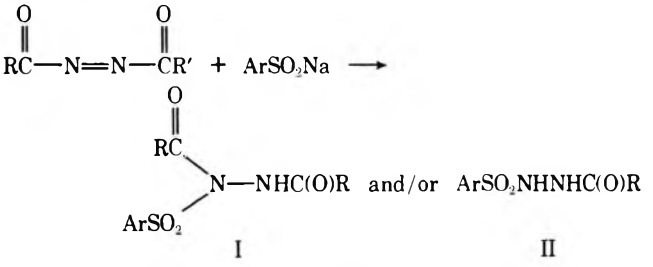
Monitoring the reaction of DDA with *p*-acetamidobenzenesulfinic acid in Me_2SO-d_6 by NMR confirmed the qualitative observation that essentially no immediate reaction occurs. The NMR spectrum simply consists of a composite of absorptions due to the reactants. After ca. 20 hr, however, the spectrum was again recorded and exhibited absorptions that were comparable to those of the isolated product 4. After ca. 6 days, the reaction mixture remained unchanged, as determined by NMR.

To broaden the scope of reaction conditions, a suspension of DDA in water and the water-soluble sodium benzene- or *p*-toluenesulfinates was allowed to react. The corresponding sulfonyldiazanecarboxamides 2 and 3 were obtained in near quantitative yields.

Reaction of Substituted Diazenedicarboxamides with Salts of Sulfinic Acids. A number of substituted diazenedicarboxamides were allowed to react with sodium *p*-toluenesulfinate in Me_2SO. In the case of *N,N'*-diethyl-1,2-diazenedicarboxamide (DEDDA), an immediate reaction occurred upon combining solutions of DEDDA and sulfinate. A 39% yield of 1-*p*-toluenesulfonyl-*N*-ethyl-2-diazanecarboxamide (6) was obtained (Table I).

The facility with which the reaction of DEDDA and sodium *p*-toluenesulfinate proceeds was substantiated by NMR. NMR spectra obtained directly after combining DEDDA with zinc bis(p-toluenesulfinate) (1) in Me_2SO-d_6 may be interpreted as showing the presence of an adduct, namely, 1-*p*-toluenesulfonyl-*N,N'*-diethyl-1,2-diazanedicarboxamide (7) (Table III). After ca. 24 hr, the NMR spectrum of the reaction mixture showed a diminution in the intensity of absorptions attributed to 7, and the emergence of absorptions coincident with those of *p*-toluenesulfonyl-*N*-ethyl-2-diazanecarboxamide (6), the isolated product (Tables I and II). In addition to 6 and the postulated adduct 7, an absorption at δ 5.78 (ill-defined triplet attributed to NH adjacent to ethyl group) and the complexity of absorptions in the regions ca. δ 1.0 and 3.0 attributed to the methylene and methyl protons of the ethyl groups suggested the presence of a third component. The composition of the reaction mixture continued to change with time; after

Table I
Reaction Products from Substituted DDA's and Sodium *p*-Toluenesulfinate[a]



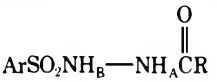
I II

Ar = *p*-$CH_3C_6H_4$

R'	R	Product type	% yield	Mp, °C
EtNH	EtNH	II (6)	39	199–200 dec[b]
Me_2N	Me_2N	I (8)	77	197–198 dec[c]
H_2N	Ph_2N	II (9)	98	186–188 dec[d]
PhNH	PhNH	I (11)	33	180–182.5 dec
		II (10)	27	210–211 dec

[a] Satisfactory elemental analyses and molecular weight determinations were recorded for all compounds. [b] Recrystallized from chloroform. [c] Recrystallization from carbon tetrachloride–chloroform (4:1). [d] Recrystallized from absolute alcohol.

Table II
NMR Data and Assignments for Sulfonyldiazanecarboxamides (II)[a]



II

Compd	Chemical shifts, ppm, δ		
	H_A	H_B	R
3	7.91 (s)	9.50 (s)	NH_2, 5.92 (s)
2	7.91 (s)	9.42 (s)	NH_2, 5.95 (s)
6	7.85 (s)	9.36 (s)	NH_FEt: H_F, 6.28 (t, J = 5.0 Hz); CH_2, 2.95 (q, J = 7.0 Hz); CH_3, 0.90 (t, J = 7.0 Hz)
9	8.55 (s)	9.40 (s)	NPh_2, 7.2 (m)
5	8.00 (s)	9.37 (s)	NH_2, 6.0 (s)
10	8.53	9.60	NH_FPh: H 8.34 (s), Ph, ca. 7.2 (m)

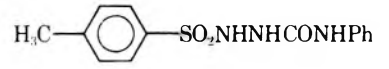
[a] Solvent: Me_2SO-d_6.

ca. 6 days, both 6 and the unknown third component were present in greater amounts.

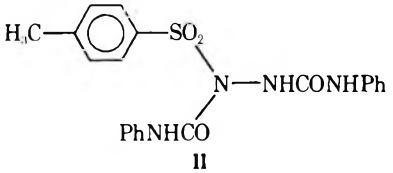
When *N,N,N′,N′*-tetramethyl-1,2-diazenedicarboxamide (TMDDA) was allowed to react with sodium *p*-toluenesulfinate, the characteristic color was not dissipated. Work-up of the reaction mixture in a manner similar to that utilized for the reaction product from DEDDA gave 1-*p*-toluenesulfonyl-*N,N,N′,N′*-tetramethyl-1,2-diazanedicarboxamide (8) in 77% yield (Table I). When the reaction was repeated with zinc bis(*p*-toluenesulfinate) (1) in Me_2SO-d_6 using a 2:1 mole ratio of the α-carbonyl diazene compound to sulfinate, NMR absorptions indicated the relatively rapid formation of a single component. The NMR absorptions[9] attributed to this reaction product were comparable to those exhibited by the trisubstituted diazane derivative (8) (Tables I and III) previously identified.

Variable results were obtained when a series of *N*-phenyl substituted diazenedicarboxamides were allowed to react with sodium *p*-toluenesulfinate in Me_2SO at room temperature. With unsymmetrical *N,N*-diphenyl-2-diazenedicarboxamide, an immediate reaction occurred; work-up of the reaction mixture gave a nearly quantitative yield of 1-*p*-toluenesulfonyl-*N,N*-diphenyl-2-diazanecarboxamide (9) (Table I). The relative rapidity of the reaction and the formation of the sulfonyldiazanecarboxamide (9) as the major reaction product was confirmed by following the reaction by NMR.

Reaction of *N,N′*-diphenyl-1,2-diazenedicarboxamide with the sulfinate gave a mixture of two products. Identification of the products as 1-*p*-toluenesulfonyl-*N*-phenyl-2-diazanecarboxamide (10) and 1-*p*-toluenesulfonyl-*N,N′*-diphenyl-1,2-diazanedicarboxamide (11) was made on the basis of elemental analysis and NMR spectral data.



10



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N,N,N′,N′-Tetraphenyl-1,2-diazenedicarboxamide, which is sparingly soluble in Me_2SO at room temperature, failed to undergo significant reaction with the sulfinate under typical reaction conditions; 88% was recovered.

Miscellaneous Reactions of Some Diazenes with Sulfinic Acids and Their Salts. Diethyl diazenedicarboxylate (DEDD) reacted readily with zinc bis(benzenesulfinate) (12) in Me_2SO to give 1-benzenesulfonyl diethyl-1,2-diazanedicarboxylate (13) in high yield.

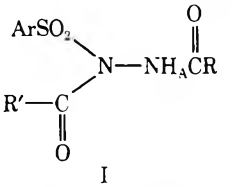
Diphenyldiazene and bis(2-cyano-2-propyl)diazene (BMPD) were also allowed to react with sodium *p*-toluenesulfinate under typical reaction conditions. In neither case was there any evidence for oxidative addition; 96% of the diphenyldiazene and 89% of the BMPD were recovered.

Sodium formaldehyde sulfoxylate reacts immediately with DDA in Me_2SO at room temperature to give a precipitate of 1,2-diazanedicarboxamide in 78% yield. Reaction of aminoiminomethanesulfinic acid with DDA in Me_2SO also failed to give an isolable addition product. Instead, 47% of the starting DDA was reduced to 1,2-diazanedicarboxamide and of the remaining starting material, 90% was recovered.

Kinetic Results. The rate of disappearance of DDA in the presence of an equivalent amount of sodium benzenesulfinate in dry DMF was determined at low temperatures (see Experimental Section). Plots of 1/(DDA) vs. time were linear over 3–4 half-lives, consistent with straightforward second-order kinetics. Pertinent rate data are included in Table IV. These data yielded a straight-line Arrhenius plot giving an activation energy of 5.1 ± 0.3 kcal/mol. Added water has virtually no effect on the reaction rate (Table IV).

The addition of zinc acetate dihydrate accelerates the

Table III
NMR Data and Assignments for Trisubstituted Diazanes (I)[a]



I

Compd	Chemical shifts, ppm, δ		
	H_A	R′	R
8	9.0 (s)	NME_2, 2.92 (s)	NMe_2, 2.78 (s)
13	10.46 (s)	OEt: OCH_2, 4.1 (m);[b] CH_3, 1.15 (m)	OEt: see R′
4	8.94 (s)	NH_2, 6.88 (s)	NH_2, 6.22 (s)
7	8.87 (s)	NH_EEt: H_E, ca. 7.4;[c] CH_2, ca. 3.19 (q), J = 6.5 Hz; CH_3, 1.07 (t), J = 6.5 Hz	NH_FEt: H_F, 6.5 (t) J = 5.0 Hz; CH_2, ca. 3.02 (q), J = 6.5 Hz; CH_3, 0.94 (t), J = 6.5 Hz
11	8.68	$PhNH_E$: H_E, 10.04 (s); Ph, ca. 7.4 (m)	$PhNH_F$: H_F, 10.6 (s); Ph, ca. 7.2 (m)

[a] Solvent: Me_2SO-d_6. [b] Methylene and methyl protons appear as multiplets due to overlap of signals. [c] Signal appeared as a broad, poorly defined triplet.

Table IV
Rate Data for the Disappearance of 0.015 *M* DDA in the Presence of Selected Benzenesulfinates[a]

Benzenesulfinate[d]	Temp, °C	2nd order rate const, l. mol^{-1} min^{-1}	Half-life, min
Sodium [c]	−25.0	19.5	3.4
Sodium [c]	−19.5	26.8	2.5
Sodium [c]	−15.5	30.3	2.2
Sodium [c]	−5.0	47.8	1.4
Sodium + water (0.06 *M*)	−14.5	30.1	2.2
Sodium + water (0.06 *M*)	−9.5	39.6	1.7
Sodium + $Zn(OAc)_2 \cdot 2H_2O$ (0.00375 *M*)	−32.0	*b*	5.9
Sodium + $Zn(OAc)_2 \cdot 2H_2O$ (0.015 *M*)	−25.0	*b*	2.7
Sodium + $Zn(OAc)_2 \cdot 2H_2O$ (0.06 *M*)	−25.5	*b*	0.7
Sodium + $Zn(OAc)_2 \cdot 2H_2O$ (0.125 *M*)	−22.5	*b*	0.6
Zinc (0.0075 *M*)	−30.0	*b*	~0.2
Zinc (0.0075 *M*)	−22.5	*b*	<0.2
Zinc (0.0075 *M*) + NaOCN (0.015 *M*)	−20.0	21.9	2.8

[a] Unless noted otherwise, all experiments were conducted in dry DMF. [b] These experiments did not yield straight-line plots. Half-lives were taken directly from concentration–time data. [c] An Arrhenius plot for this reaction yielded an activation energy of 5.1 ± 0.3 kcal/mol. [d] Sodium salt (0.015 *M*) in all cases.

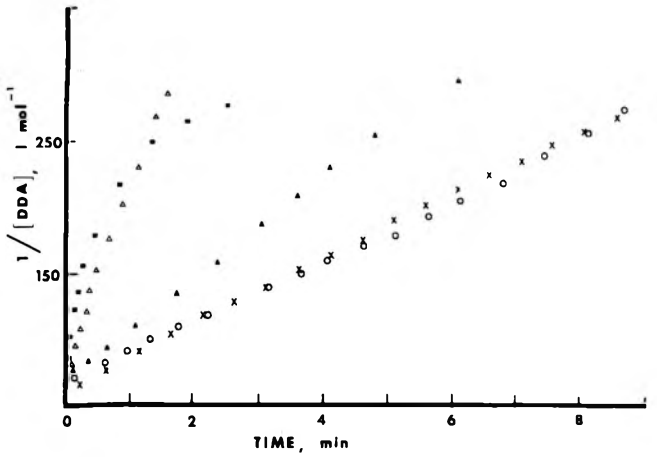


Figure 1. Comparative second-order kinetic plots for the disappearance of 0.015 *M* DDA: ×, 0.015 *M* $PhSO_2Na$, −22.0°; ○, 0.0075 *M* $Zn(PhSO_2)_2$ + 0.015 *M* NaOCN, −20.0°; ▲, 0.015 *M* $PhSO_2Na$ + 0.015 *M* $Zn(OAc)_2{\cdot}2H_2O$, −20.5°; △, 0.015 *M* $PhSO_2Na$ + 0.125 *M* $Zn(OAc)_2{\cdot}2H_2O$, −20.5°; ■, 0.0075 *M* $Zn(PhSO_2)_2$, 22.5°.

rate of disappearance of DDA in the presence of sodium benzenesulfinate. As the initial concentration of zinc is increased, the rate of DDA disappearance increases. However, the resulting second-order kinetic plots are not linear. Rate constants were not calculated for these, but half-lives were determined and these are shown in Table IV. Representative second-order plots are shown in Figure 1. Very rapid reactions occur between DDA and zinc bis(benzenesulfinate) in DMF. These did not yield straight-line second-order kinetic plots (See Figure 1). At all temperatures above −30°, the half-life was too short to determine precisely. It was less than 0.2 min at −22.5° (Table IV).

The addition of 1 equiv (with respect to benzenesulfinate) of sodium or potassium cyanate to zinc bis(benzenesulfinate) effectively eliminates the accelerating action of the zinc salt and yields a kinetic plot for the disappearance of DDA that is nearly identical with that obtained with sodium benzenesulfinate alone. This is shown in Table IV and Figure 1.

Discussion

The reaction of arenesulfinate salts with DDA in Me_2SO may be interpreted as involving addition of a nucleophile, the arenesulfinate anion, to the electrophilic diazene linkage to form the substituted diazane anion (III) (Scheme I). The reaction is facilitated by solvation of the particular metal cation of the sulfinate salt by Me_2SO. If traces of moisture[10] are present, III may be converted to the 1-arenesulfinate-1,2-diazanedicarboxamide (I, R = R′ = NH_2), thereby enhancing the basicity of the reaction medium (Scheme I). Under conditions of relative high basicity I may be expected to eliminate cyanate to give the sulfonyldiazanecarboxamide (II, R = NH_2) and the cyanate of the metal cation present. Diazanetriscarboxamide is known to undergo rapid elimination of isocyanic acid in basic media to give 1,2-diazanedicarboxamide and a cyanate.[11]

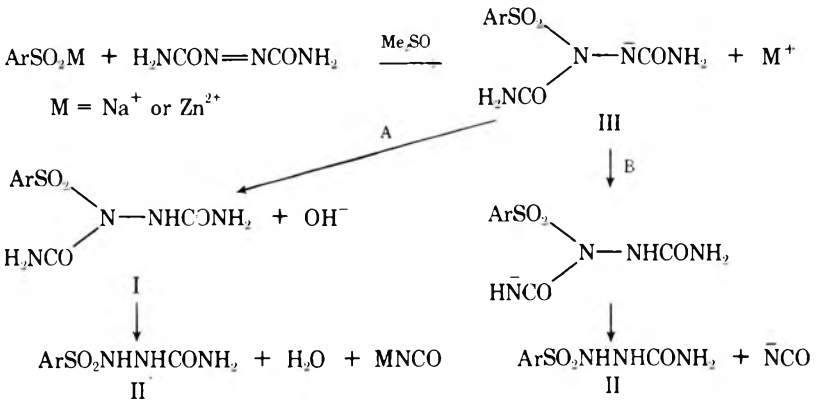
Alternatively, one may assume that moisture is not involved in the initial stages of the reaction and that the substituted diazane anion (III) simply undergoes a series of rearrangements resulting in the loss of cyanate and formation of the sulfonyldiazanecarboxamide (I) (Scheme I, path B). In the case of DDA and its reaction with sodium benzenesulfinate in DMF, water was found to have no effect on the rate of DDA disappearance (Table IV).

The relative ease with which the reaction proceeds in an aqueous medium, even though the system is heterogeneous (DDA is insoluble in water), may be taken as support for the participation of small amounts of water under homogeneous reaction conditions in Me_2SO.

Further evidence that small amounts of water may be involved in the reaction scheme arises from NMR studies of the reaction of TMDDA with anhydrous zinc bis(*p*-toluenesulfinate) (1). The NMR spectrum indicated the formation of the trisubstituted diazane derivative (8) directly. Since TMDDA does not possess any labile hydrogens, one can reasonably assume that the required NH proton in 8 was furnished by water. In the case of TMDDA a stoichiometric amount of water would be necessary to bring about complete formation of 8, contrary to the proposed reaction course involving DDA (Scheme I, path A). The formation of a trisubstituted diazane (I) as a reaction intermediate probably occurs in all cases involving reactions of diazenedicarboxamides with arenesulfinates. In those instances where the diazene compound bears a formamoyl group, the trisubstituted diazane derivative (I, R′ = NH_2; R = NH_2 or NR_2) is relatively unstable and eliminates cyanate to give the sulfonyldiazanecarboxamide (II, R = NR_2 or NH_2). The relatively high basicity of the medium, enhanced as described above, probably contributes to the instability of I. In the one case where the free arenesulfinic acid (reaction involving *p*-acetamidobenzenesulfinic acid) was used, I was isolable. The latter readily lost the elements of isocyanic acid upon attempted purification by dissolution in aqueous base followed by acidification.

The kinetic studies provide additional support for the primary steps in Scheme I. The uncomplicated second-order kinetics observed for the reaction of sodium benzenesulfinate with DDA is consistent with a simple addition step. The reaction is rapid and its activation energy is exceptionally low.[12]

Scheme I

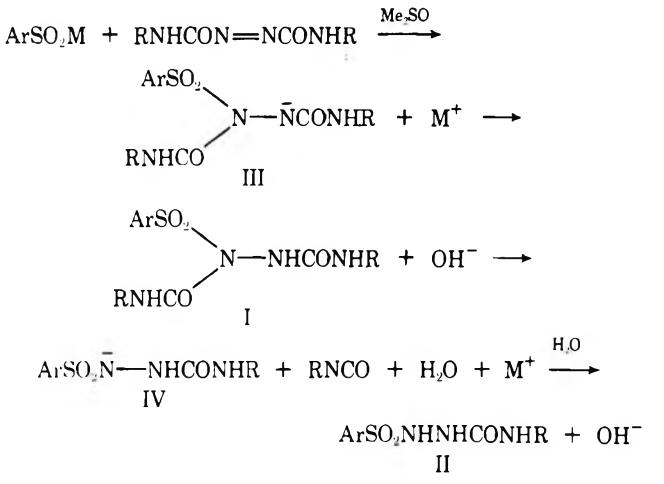


Zinc bis(benzenesulfinate) reacts with DDA at a considerably greater rate than that of the sodium salt. The rate of disappearance of DDA in the presence of sodium benzenesulfinate is accelerated by the addition of zinc acetate. These results are consistent with a catalytic effect by zinc. However, the apparent catalytic effect is not typical in that equivalent rather than trace amounts are required. If zinc ion is a catalyst for the addition of benzenesulfinate to DDA, it was reasoned that during the course of the reaction, zinc must be rendered inactive. Cyanate is a by-product of the addition reaction. If cyanate reacts with zinc to form an unreactive species, then this would explain the observed behavior.

Sodium (or potassium) cyanate, when added to zinc bis(benzenesulfinate) before mixing with DDA, completely eliminates the accelerating action of the zinc and yields kinetic curves virtually identical with those obtained with sodium benzenesulfinate.

When both formamoyl groups of DDA are replaced by N-monosubstituted carbamoyl groups, a mixture of the trisubstituted diazanes (I, R = R′ = NHR) and the sulfonyldiazanecarboxamide (II, R = NHR) may result (Scheme II). This reflects on the stability of the initially formed tri-

Scheme II



substituted diazane derivative (I, R = R′ = NHR) under basic conditions. In the case of 1,2-diazenedicarboxamide bearing N-monosubstituted carbamoyl groups, the sulfonyldiazanecarboxamide may well exist as the anion (IV, R′ = NHR), since the fragment leaving I is a neutral organic isocyanate rather than a cyanate ion as in Scheme I (path B). The isocyanate may react with water and ultimately give the corresponding urea. In view of this it can be seen that the requirements of these systems for water may be intermediate between those involving diazenes bearing formamoyl groups and those possessing complete N,N disubstitution.

The course of reaction for fully substituted diazenedicarboxamides, such as TMDDA, has been discussed to some extent. The initially formed anion may react with any water present to give the trisubstituted diazanes (I, R = R′ = NR_2) when zinc is the counterion, as NMR evidence suggests. Conversely, when sodium is the counterion, as in the preparative procedure leading to 7, the oxidative coupling product exists as the anion and 7 is formed after addition of the reaction mixture to water followed by acidification.

In the case of the diazenedicarboxylates, specifically DEDD, and its reaction with zinc bis(benzenesulfinate) (12) the initially formed addition product may remain as the salt after addition to water. Only upon acidification is I (R = OEt) obtained. The apparent stability of the trisubstituted diazane anion (III, R = R′ = OEt) is evidenced by the isolation of I in high yield. Neither bis(2-cyano-2-propyl)diazene nor diphenyldiazene undergoes reaction with sodium *p*-toluenesulfinate. Obviously neither of these diazenes possesses electrophilicity comparable to the α-carbonyl diazenes discussed above.

The aliphatic derivatives, sodium formaldehyde sulfoxylate and aminoiminomethanesulfinic acid, failed to give any isolable products analogous to either I or II upon reaction with DDA. The reactions were only briefly studied. However, if the initial step is addition to form a trisubstituted diazane anion or neutral species as with the arenesulfinates it can only be concluded that the sulfinate moiety is eliminated rather than isocyanic acid to give 1,2-diazanedicarboxamide as a major product.

In the case of α-carbonyl diazenes and arenesulfonates, the mild conditions required, the rapidity of the reactions, and the generally high yields suggest that the process described offers an attractive alternate synthetic route to trisubstituted diazanes and sulfonyldiazanecarboxamides.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer 451 infrared spectrophotometer. NMR spectra were recorded on a Jeolco Model JNM-4H-100, 100 MHz (using Me_4Si as an internal standard). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected.

Materials. Diazenes. 1,2-Diazenedicarboxamide (DDA) was used as received from Aldrich Chemical Co. Diphenyldiazene and bis(2-cyano-2-propyl)diazene (BMPD) from Eastman Organic Chemicals were also used as received. *N,N′*-Diethyl-1,2-diazenedicarboxamide (DEDDA) and *N,N,N′,N′*-tetramethyl-1,2-diazenedicarboxamide (TMDDA) were prepared as reported previously;[13] material melting at 135–137° dec and 111–113°, respectively, was used in this work. Diethyl diazenedicarboxylate (DEDD), bp 69–71° (0.8 mm), was prepared according to a reported procedure.[14]

N,N-Diphenyl-1,2-diazenedicarboxamide (mp 155–157° dec, recrystallized from chloroform–hexane) was obtained in 70% yield by the lead tetraacetate (LTA) oxidation of the corresponding 1,2-diazane:[15] ir (KBr) 3370 (s), 3275 (m), 1745 (sh, s), 1725 (s), 1690 (s), 1585 (m), 1485 (s), and 1355 cm^{-1} (s); NMR (Me_2SO-d_6) δ 8.10 (s, 2 H, NH_2) and 7.44 ppm (s, 10 H, Ph).

Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.83; H, 4.46; N, 20.78.

N,N,N′,N′-Tetraphenyl-1,2-diazenedicarboxamide was also prepared (67% yield) by the LTA oxidation of its 1,2-diazane analogue.[16] One recrystallization from DMF gave analytically pure product: mp 217–218°; ir (KBr) 1720 (s), 1575 (w), 1485 (s), 1445 (w), 1340 (s), 1325 (s), and 1315 cm^{-1} (s).

Anal. Calcd for $C_{26}H_{20}N_4O_2$: C, 74.27; H, 4.80; N, 13.33. Found: C, 74.37; H, 4.80; N, 13.46.

N,N′-Diphenyl-1,2-diazenedicarboxamide, from the nitric acid oxidation of *N,N′*-diphenyl-1,2-diazanedicarboxamide,[17] mp 174–174.5° (lit. 182–183°),[18] was used in this study: ir (KBr) 3295 (m), 1725 (s), 1710 (s), 1590 (m), 1525 (s), 1515 (s), and 1440 cm^{-1} (s); NMR (Me_2SO-d_6) δ 11.51 (s, 2 H, NH) and 7.1–7.8 ppm (complex m, 10 H, Ph).

Sulfinic Acids and Their Salts. Sodium benzenesulfinate, sodium *p*-toluenesulfinate, and *p*-acetamidobenzenesulfinic acid were used as received from Aldrich Chemical Co. Similarly, aminoiminomethanesulfinic acid (Eastman Organic Chemicals) and sodium formaldehyde sulfoxylate (Nopco Chemical Co.) were used as received. Zinc bis(benzenesulfinate) (12) and zinc bis(*p*-toluenesulfinate) (1) were prepared as their dihydrates in >80% yield by the addition of aqueous solutions of zinc acetate to the corresponding sodium sulfinates. The hydrated zinc bis(*p*-toluenesulfinate) (**1a**) and zinc bis(benzenesulfinate) (**12a**) were dried in vacuo at <40° in presence of P_2O_5 and gave analytically pure **1a** and **12a**, melting at 264–266 and 223–225°, respectively.

Anal. Calcd for $C_{14}H_{14}O_4S_2Zn$-$2H_2O$ (**1a**): C, 40.83; H, 4.41; S, 15.57; Zn, 15.88. Found: C, 41.10; H, 4.20; S, 15.75; Zn, 15.83.

Anal. Calcd for $C_{12}H_{10}O_4S_2Zn\cdot 2H_2O$ (**12a**): C, 37.56; H, 3.68; S, 16.71; Zn, 17.04. Found: C, 37.66; H, 3.69; S, 16.94; Zn, 17.02.

Upon drying the hydrated zinc bis(arenesulfinates) **1a** and **12a** at 110° (<0.1 mm) the corresponding analytically pure anhydrous salts were obtained, melting points were essentially unchanged: NMR (Me_2SO-d_6) (**1**) δ 7.46 (d, 4 H, adjacent to $-SO_2-$, J = 8.0 Hz), 7.16 (d, 4 H, adjacent to methyl, J = 8.0 Hz), and 2.31 (s, 6 H, $-CH_3$'s); NMR (Me_2SO-d_6) (**12**) 7.56 (m, 4 H, phenyl rings adjacent to $-SO_2-$) and 7.36 ppm (m, 6 H of Ph's).

Anal. Calcd for $C_{14}H_{14}O_4S_2Zn$ (**1**): C, 44.75; H, 3.76; S, 17.07; Zn, 17.40. Found: C, 44.77; H, 3.75; S, 17.19; Zn, 17.35.

Anal. Calcd for $C_{12}H_{10}O_4S_2Zn$ (**12**): C, 41.45; H, 2.90; S, 18.44; Zn, 18.80. Found: C, 41.45; H, 2.68; S, 18.35; Zn, 18.71.

General Procedure for Reaction of 1,2-Diazenedicarboxamide (DDA) with Metal Arenesulfinates in Me_2SO. 1,2-Diazenedicarboxamide (0.01 mol) and the metal arenesulfinate (0.005 or 0.01 mol depending on metal cation) were dissolved in a suitable amount of Me_2SO (typically 25 ml per 0.01 mol for both DDA and the sulfinate).[19] When the two solutions were mixed, the yellow to orange color of DDA faded almost immediately. The color was usually completely discharged after several minutes. Typically, the reaction mixtures were left at room temperature overnight prior to work-up.[20]

The relatively clear, colorless reaction mixtures were added to excess water (ca. 300 ml per 50 ml of reaction mixture) and cooled to ice-bath temperatures. The white solid precipitate was filtered, washed with fresh cold water, and dried in vacuo (in presence of P_2O_5).

Using either zinc or sodium salts of benzene- or *p*-toluenesulfinic acid (anhydrous or hydrated) as coreactants with DDA typically gave yields of the corresponding sulfonyl diazanecarboxamides (**2** or **3**) in the range of 80–90%. The benzenesulfonyl diazanecarboxamide (**3**) melts at 224–225° dec (lit.[21] mp 218° dec) and the *p*-toluene analogue (**2**) at 232–234° dec (lit.[21] mp 236° dec).

In one case, using zinc bis(*p*-toluenesulfinate) (**1**) as a reactant with DDA, a solution of silver nitrate (6% excess based on zinc salt) was added to the aqueous Me_2SO filtrate. A white solid precipitated immediately, the filtered and dried solid (100% yield when calculated as silver cyanate) gave ir absorptions (KBr) at 2150 (s), 1300 (m), 1210 (m), 637 (m), and 628 cm^{-1} (m).

The procedure followed when DMF was used as the solvent was identical with that described above.

Kinetic Studies. Solutions of DDA and sodium benzenesulfinate were prepared in dry DMF just before use. The initial concentration of each was 0.030 *M*. The 1:1 stoichiometry was verified by a photometric titration of a stock 0.03 *M* DDA solution in DMF with a similar solution of sodium benzenesulfinate. To aliquots of the DDA solution were added from a buret varying quantities of the sulfinate but maintaining an excess of DDA. After standing for 1 hr, the remaining DDA was determined spectrophotometrically.

In a typical kinetic experiment, 3 ml of 0.030 *M* DDA in DMF was pipetted into a modified 1-cm spectrophotometer cell which was fitted with a rubber serum cap. The cell was evacuated and placed in a Dewar flask containing methanol at the required temperature. The Dewar flask was strip silvered to provide an optical path for an analyzing light beam. A tungsten source and monochromator provided a beam of 419 nm (DDA maximum) light which passes through the cell and into a photomultiplier tube whose output was displayed on a strip-chart recorder. A syringe containing an equivalent quantity of sodium benzenesulfinate (3.0 ml, 0.03 *M*) solution was placed in the Dewar to equilibrate to the reaction temperature. The experiment was then started by injecting the sodium benzenesulfinate solution through the serum cap into the evacuated spectrophotometer cell. Mixing occurred rapidly and the decreasing DDA absorption was displayed on the recorder. The optical system was calibrated with known concentrations of DDA. Beer's law was followed over the concentration range employed. A plot of 1/[DDA] vs. time was linear over the duration of the measurements, typically 3–4 half lives.

In some later experiments, the procedure was modified to permit direct mixing of the reactants in a mixing head before entering the spectrophotometer cell. Each reactant was placed in a separate syringe and a syringe pump used to meter the solutions through heat-exchange coils and thence into a mixing chamber and finally directly into the cell. The total mixing time was approximately 5 sec. This modification assured more uniform temperature control, particularly at the lower limits (−30 to −20°).

General Procedure for Reaction of 1,2-Diazenedicarboxamide (DDA) with Metal Arenesulfinates in Water. A solution of sodium arenesulfinate (0.05 mol) in 50 ml of water was added rapidly to a stirred suspension of DDA (0.05 mol) in 100 ml of water (containing 2 drops of Tween 85, a commercially available wetting agent). No apparent reaction occurred and the reaction mixture was quickly heated to 45–50°. The reaction mixture was maintained at 45–50° for a varied period of time (0.75–1.5 hr) until the suspended solid phase became white. After cooling to room temperature, the alkaline reaction mixture was neutralized and filtered and the filter cake was washed thoroughly with water and dried in vacuo (in presence of P_2O_5). The reaction products were identified as sulfonyldiazanecarboxamides by elemental analysis, molecular weight, melting point, ir, and NMR spectra.

Benzenesulfonyldiazanecarboxamide (**3**), mp 220–221° dec (92% yield), was obtained from DDA and sodium benzenesulfinate. The reaction product (**2**), mp 233–234.5° dec, 98% yield from sodium *p*-toluenesulfinate, was analyzed directly after drying in vacuo for 1.5 hr at 78°. Anal. Calcd for $C_8H_{11}N_3O_3S$ (**2**): C, 41.91; H, 4.84; N, 18.33; S, 13.99; mol wt, 229.3. Found: C, 42.06; H, 4.84; N, 18.28; S, 14.09; mol wt, 230 (determined in DMF by vapor phase osmometry).

In the case involving sodium *p*-toluenesulfinate, the basic aqueous filtrate obtained directly from the reaction product, *p*-toluenesulfonyldiazanecarboxamide (**2**), was evaporated to dryness. The solid residue was mainly sodium cyanate as identified by ir (KBr): 2220 (s), 1300 (m), 1218 (m), and 623 cm^{-1} (m).

General Procedure for the Reaction of Substituted Diazenedicarboxamides with Sodium *p*-Toluenesulfinate. The substituted diazenedicarboxamides (0.01 mol), dissolved in 25 ml of Me_2SO, were combined with solutions of sodium *p*-toluenesulfinate (0.01 mol) in 25 ml of Me_2SO and the reaction mixtures were worked up in a manner similar to that described for DDA. Addition of the reaction mixtures to water gave weakly basic solutions. In the case of the *N,N'*-diethyl- and *N,N,N',N'*-tetramethyldiazenedicarboxamides the basic solutions remained clear, but solid reaction products precipitated upon acidification (see Table I). When added to water, reaction mixtures containing the substituted *N*-phenyl derivatives gave milky basic reaction mixtures; acidification gave the products shown in Table I.

In the case of *N,N'*-diphenyl-1,2-diazenedicarboxamide the crude reaction product consisting of **10** and **11** was resolved into its components by treatment with cold aqueous 5% sodium hydroxide. 1-*p*-Toluenesulfonyl-*N,N*-diphenyl-1,2-diazanedicarboxamide (**11**) is insoluble in the cold alkali and can be purified by repeated recrystallization from benzene. The aqueous alkali solubles were acidified to precipitate **10**; repeated recrystallization from acetic acid afforded analytically pure product (**10**).

Reaction of 1,2-Diazenedicarboxamide (DDA) with *p*-Acetamidobenzenesulfinic Acid. Solutions of DDA (2.32 g, 0.02 mol) in 50 ml of Me_2SO and *p*-acetamidobenzyenesulfinic acid (3.98 g, 0.02 mol) in 25 ml of Me_2SO were combined. After several hours at room temperature, the clear, pale orange reaction mixture was added to 300 ml of water. The resulting clear, pale yellow solution was cooled to ice-bath temperatures and after ca. 0.5 hr, the mixture turned to a solid gelatinous mass.

The reaction mixture was filtered and the solid filter cake was washed consecutively with water, alcohol, and ether to give 5.5 g (87.5%) of crude **4**, a white solid, mp 206–208° dec. A portion of the product (**4**) was recrystallized from glacial acetic acid to give analytically pure **4**, mp 203–204.5° dec. Anal. Calcd for $C_{10}H_{13}N_5O_5S$ (**4**): C, 38.09; H, 4.15; N, 22.21; S, 10.17. Found: C, 38.16; H, 4.14; N, 22.17; S, 10.08. Still another portion (1.5 g) of the dried, crude reaction product (**4**) was dissolved in aqueous 10% sodium hydroxide. Acidification (3 *N* HCl) of the filtered, clear alkaline solution gave a crystalline white solid (1.0 g, 78%), mp 218–219° dec, that analyzed for *p*-acetamidobenzenesulfonyldiazanecarboxamide (**5**). Anal. Calcd for $C_9H_{12}N_4O_4S$ (**5**): C, 39.70; H, 4.44; N, 20.58; S, 11.76; mol wt, 272.3. Found: C, 39.36; H, 4.93; N, 20.18; S, 11.85; mol wt, 281 (determined in DMF by vapor phase osmometry).

Reaction of Diethyl Diazenedicarboxylate with Zinc Bis(benzenesulfinate) (12). A solution of diethyl diazenedicarboxylate (DEDD, 3.48 g, 0.02 mol) in 25 ml of Me_2SO was combined with a solution of zinc bis(benzenesulfinate) (**12**, 3.47 g, 0.01 mol) in 50 ml of Me_2SO. The amber color of the diazene was immediately discharged and after several hours, the clear, colorless reaction mixture was added to 500 ml of water. A weakly alkaline mixture containing a finely divided white solid was obtained. The mixture was acidified and the water insoluble white solid was filtered. The washed and dried filter cake, 1-benzenesulfonyl diethyl-1,2-diazanedicarboxylate (**13**, 5.9 g, 93.5% yield) melted at 103–105°. One recrystallization from carbon tetrachloride gave analytically pure **13**, mp 104–106°. Anal. Calcd for $C_{12}H_{16}N_2O_6S$ (**13**): C, 45.56; N,

5.10; N, 8.86; S, 10.14; mol wt, 316.3. Found: C, 45.55; H, 5.13; N, 8.78; S, 10.21; mol wt, 323 (determined in DMF by vapor phase osmometry).

Acknowledgment. We are grateful to Professor D. Swern, Temple University, for helpful suggestions in preparing this manuscript and to Messrs. W. Y. Whitmore and A. G. Geigley for recording the NMR spectra.

Registry No.—**1**, 24345-02-6; **2**, 10396-10-8; **3**, 10195-68-3; **4**, 57049-47-5; **5**, 10396-14-2; **6**, 57049-48-6; **7**, 57049-49-7; **8**, 57049-50-0; **9**, 57049-51-1; **10**, 28744-07-2; **11**, 57049-52-2; **12**, 24308-84-7; **13**, 57049-53-3; DDA, 123-77-3; sodium benzenesulfinate, 873-55-2; sodium *p*-toluenesulfinate, 824-79-3; sodium cyanate, 143-33-9; *N,N'*-diethyldiazenedicarboxamide, 18880-19-8; *N,N,N',N'*-tetramethyldiazenedicarboxamide, 10465-78-8; *N,N'*-diphenyl-1,2-diazenedicarboxamide, 17693-77-5; *N,N*-diphenyl-1,2-diazenedicarboxamide, 57049-54-4; *p*-acetamidobenzenesulfinic acid, 710-24-7; diethyl diazenedicarboxylate, 1972-28-7.

References and Notes

(1) Presented in part at the International Symposium on Nucleophilic Substitution, Pocono Manor, Pa., April 13–18, 1975.
(2) The diazene derived nomenclature suggested for azo, hydrazo, etc., compounds by J. H. Fletcher, O. C. Dermer, and R. B. Fox, *Adv. Chem. Ser.*, **No. 126**, 246 (1974), is utilized in this paper. In accordance with the recommended nomenclature 1,1'-azobisformamide is referred to as 1,2-diazenedicarboxamide. The naming of other derivatives follows.
(3) E. Fahr and H. Lind, *Angew. Chem., Int. Ed. Engl.*, **5**, 372 (1966).
(4) A. Hantzsch and R. Glogauer, *Ber.*, **30**, 2555 (1897).
(5) W. Bradley and J. D. Hannon, *J. Chem. Soc.*, 2713 (1962).
(6) P. Messinger, *Arch. Pharm. (Weinheim Ger.)*, **307**, 348–355 (1974).
(7) Although Me_2SO is the solvent of choice, DMF may also be used with similar results. In DMF as reaction solvent the rate of reaction may be reduced by cooling the reactants to ca. 5° prior to combining.
(8) After 16 hr absorptions attributed to reaction intermediates had disappeared.
(9) Absorptions attributed to the aromatic protons (A_2B_2 quartet) and the single NH proton were displaced ca. 0.7–0.8 ppm downfield from those in the isolated product **8**. Similarly, absorptions assigned to the *N*-methyl and methyl arene protons were ca. 0.3–0.4 ppm downfield from their counterparts in **8**.
(10) Water was not added purposely nor were any attempts made to exclude it. Me_2SO was usually stored over molecular sieves prior to use.
(11) J. E. Herweh and R. M. Fantazier, *J. Org. Chem.*, **38**, 2650 (1973).
(12) Alternately, the initial step in the reaction might be regarded as an electron-transfer (redox) process, $ArSO_2^- + DDA \rightleftarrows [ArSO_2\cdot + DDA\cdot^-]$. This interpretation does not alter the significant steps in Scheme I, and may be a better explanation for the observed rates.
(13) R. M. Fantazier and J. E. Herweh, *J. Am. Chem. Soc.*, **96**, 1187 (1974).
(14) J. C. Kauer, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 411.
(15) *N,N*-Diphenyl-1,2-diazanecarboxamide was obtained from the reaction of *N,N*-diphenyldiazanecarboxamide and isocyanic acid (from potassium cyanate and aqueous hydrochloric acid); material of mp 166–168° was used in this work.
(16) *N,N,N',N'*-Tetraphenyl-1,2-diazanedicarboxamide was obtained (75.2% yield) from the reaction of diphenylcarbamoyl chloride with diazane (triethylamine present as acid acceptor). Material of mp 213.5–217° (slow dec) was used in the current study.
(17) The diazane derivative (mp 246–247.5°, lit.[18] mp 245°) was prepared 86% yield) by treating phenyl isocyanate with diazane.
(18) T. Curtius and W. Burkhardt, *J. Prakt. Chem.*, **58**, 227 (1898).
(19) Warming to 40–45° may be necessary to obtain solution of each reactant.
(20) When the reaction was followed by NMR, indications were that the reaction was complete in ca. 1 hr and consequently work-up may be initiated sooner.
(21) (a) British Patent 896,497; *Chem. Abstr.*, **57**, 11109 (1962); (b) U.S. Patent 3,152,176.

Thermal Decomposition of the Potassium Salts of Dinitroalkanes

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The potassium salts of phenyldinitromethane, 1,1-dinitroethane, and 1,1-dinitropropane decompose at 80° in DMF and other polar solvents in the presence of alkenes to yield Δ^2-isoxazolines and potassium nitrate. When the alkene bears carboalkoxy groups, cis and trans isomeric alkenes yield only trans Δ^2-isoxazolines. The cis isomer, 3-phenyl-4,5-dicarbethoxy-Δ^2-isoxazoline, was found to isomerize to the more stable trans isomer under the conditions of the original thermal decomposition.

Torssell and Ryhage[1] have reported the thermal decomposition products of the potassium salts of polynitroalkanes to be mainly potassium nitrate and varying ratios of nitrous oxide and carbon dioxide with traces of other gases and potassium nitrite. They also reported ketene and a ketene dimer from the decomposition of potassium nitroethylnitronate in the mass spectrometer.

We report that in the presence of polar solvents such as dimethylformamide (DMF), dimethyl sulfoxide (Me_2SO), and dimethoxyethane the potassium salts of dinitroalkanes, 1, decompose at 80°C to yield carboxylic acids (more than 75%) and potassium nitrite (at least 95%). When an alkene intervenes under the same conditions, an isoxazoline and potassium nitrate are formed. We propose the nitrile oxide 4 as the immediate precursor of the isoxazoline 5. Intermediate 2 (or an electronically equivalent "nitrocar-

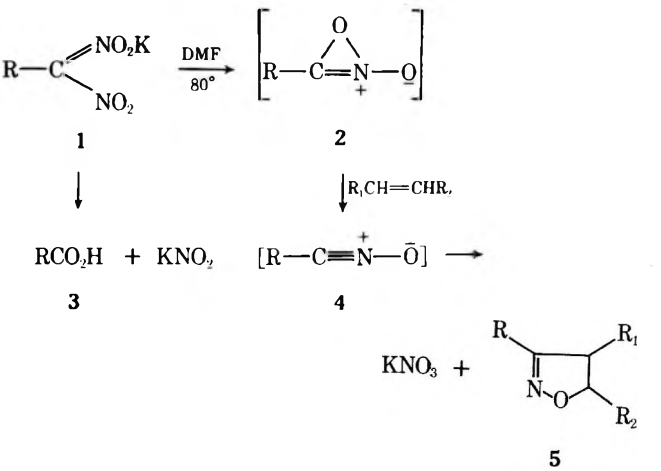
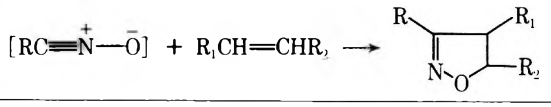


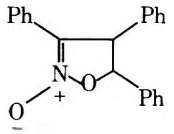
Table I
Formation of Δ^2-Isoxazolines by Thermal Decomposition of Potassium Salts of Dinitroalkanes with Various Dipolarophiles



Compd 5	R	R_1	R_2	Yield, %	Mp or bp, °C (mm)	J, Hz	δ, ppm C4H	δ, ppm C5H
a	Ph	CO_2Et	CO_2Et	52[a]	158–160 (0.2)	5.0	4.68	5.28
b	Ph	CO_2Me	CO_2Me	53[a,b]	50–51	5.0	4.75	5.35
c	Ph	H	OAc	70[b]	98–100	6.0[c], 2.0[d]	3.45	6.76
d	Ph	H	CO_2Et	39	150 (5)	8.5[c], 1.0[d]	3.5	5.01
e	Ph	H	OC_4H_9(n)	66	125–127 (1)		3.3	5.5
f	Ph	CO_2Et	Ph	40[a,e]	170–172 (0.8)	6.62	4.41	5.95
g	Ph	H	CH_2OEt	47	38–40		3.4	4.7
h	Et	H	OC_4H_9(n)	50[f]	75 (1)	6.0[c], 2.0[d]	2.78 2.51	5.12
i	Et	CO_2Et	CO_2Et	22[a]	75–77 (0.2)	6.0	4.4	5.18
j	Et	H	Ph	40[f]	135–137 (5)	6.2	3.2	5.3
k	Et	H	CO_2Et	55	125–127 (1)	8.5	3.79	5.46
l	Et	H	OAc	52[f]	36–38	6.0[c], 2.0[d]	2.9	5.75
m	Me	H	OC_4H_9(n)	60[f]	80–82 (3)	6.0[c], 3.0[d]	3.82	5.2
n	Me	CO_2Et	CO_2Et	26[f]	141–143 (3)	6.9	4.28	5.27
o	Me	H	CH_2OAc	50[f]	116–118 (3.5)		3.2	4.6
p	Me	H	OAc	55[f]	76–78	6.0[c], 2.5[d]	2.9	6.4
q	Me	H	Ph	51[f]	123–125 (3)	5.5	3.1	5.2
r	3-Methyl-4,5-diphenyl-Δ^2-oxadiazoline			10[f]	74–76			

[a] Trans isomer. [b] Reference 17. [c] Trans C4H. [d] Cis C4H. [e] F. Monforte and G. LoVecchio, *Gazz. Chim. Ital.*, 82, 130 (1952); P. Grünanger, C. Gandini, and A. Quilico, *Rend. Ist. Lomb. Sci. Lett., Cl. Sci. Mat. Nat.*, 93A, 467 (1959). [f] Reference 6. [g] Satisfactory analytical values (±0.3% for C, H, N) were reported for new compounds 5a–d,g–h. Ed.

bene") should add an alkene to give an isoxazoline *N*-oxide but the known compound 3,4,5-triphenylisoxazoline *N*-oxide[2] (6) did not lose oxygen to potassium nitrite in DMF



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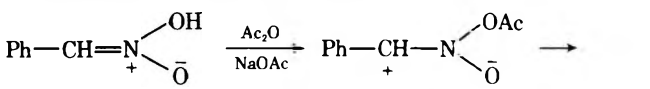
at 80° after 12 hr. Other reducing reagents, phosphorus trichloride,[3] sodium dithionite,[4] and zinc in acetic acid,[5] are known to remove such oxygens. We, therefore, exclude an isooxazoline *N*-oxide as the immediate precursor of **5**.

Benzhydroxamoyl chloride forms benzonitrile oxide in the presence of base at room temperature which dimerizes to diphenylfuroxane.[6] However, in DMF at 80° we obtained only benzoic acid from benzhydroxamoyl chloride. Diphenylfuroxane cannot have been the precursor of benzoic acid in this case because diphenylfuroxane is stable in DMF at 80°. No furoxanes were detected in the reactions in polar solvents at 80°. We conclude that **4** is the intermediate but 1,3-dipolar addition of the nitrile oxide to the alkene occurs faster than dimerization at the elevated temperature.

In related work, McKillop and Kobylecki[7] proposed the 1,3-dipolar intermediate, **7**, in the reaction of phenylnitromethane with acetic anhydride and sodium acetate.[8] Their



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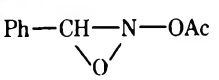

dipolar intermediate was highly selective, added only acetylenedicarboxylate to give an isoxazole, and did not lose acetic acid to give a nitrile oxide. Our proposed intermediate, **4**, was much less selective, as is known, and gave addition products with a number of less reactive dipolarophiles (Table I).

Since the results of the work of McKillop and Kobylecki differ from the present work, along with the stereochemical results (below), mutually exclusive intermediates, **4** and **7**, are warranted, as is suggested.

When the decomposition of the potassium salt of phenyldinitromethane was carried out at 80° in dimethylformamide in the presence of diethyl fumarate, a 52% yield of the Δ^2-isoxazoline **5a** was obtained. The NMR spectrum of the isoxazoline had peaks for protons at C4 (δ 4.68) and C5 (δ 5.28) corresponding to those reported[9] at C4 (δ 4.88) and C5 (δ 5.51) for the methyl ester **5b**.[10] The coupling constant for the trans protons (J = 5.0 Hz) was exactly that reported.[9]

When diethyl maleate was used as the trapping agent under the same conditions the more stable trans form **5a** was again obtained. To substantiate the isomerization, the cis 3-phenyl-Δ^2-isoxazoline was prepared by releasing benzonitrile oxide from benzhydroxamoyl chloride (Quilico's method[11]) at room temperature. Upon heating to 80° or within a few minutes upon standing at room temperature with a few drops of triethylamine the cis isoxazoline isomerized to the more stable trans form, **5a**.

By a similar procedure 3-phenyl-5-acetoxy-Δ^2-isoxazoline (**5c**) was obtained in 70% yield, mp 98–100° (lit.[10,12] 88–89°). The NMR spectrum for protons at C4 (δ 3.35, J = 2.0 Hz, and 3.45, J = 6.0 Hz) and at C5 (δ 6.75, doublet of doublets, J = 2.0 and 6.0 Hz) corresponded well with those calculated (δ 3.35, 3.38, and 6.81, respectively) for 3-phenylisoxazolines by Huisgen.[13] We obtained the lower melting point (as reported[10]) by Quilico's synthesis but recrystallization from carbon tetrachloride gave a higher

melting point. The melting point phenomenon appears to be a case of isomorphic crystals, since a third author has reported[14] the melting point 90–91°, remelting at 107–108°. Acetic acid was lost from **5c** at 160° to give 3-phenylisoxazole.[14]

Thermal decomposition of potassium 1-nitropropylnitronate in diethyl maleate in the presence of Me_2SO resulted in the isolation of *trans*-3-ethyl-4,5-dicarbethoxy-Δ^2-isoxazoline (**5i**). An identical product was obtained when propionitrile oxide, generated by Mukaiyama's method,[6] was added to diethyl maleate. The trans stereochemistry was assigned from the following argument on coupling constants. The coupling constants of C4 and C5 protons of a number of 3-phenyl-Δ^2-isoxazolines were reported[6] and it was shown that trans protons had J values in the range 4.4–6.6 Hz, whereas the cis protons had J values in the range 9.5–11.37 Hz. The coupling constant of C4 and C5 protons shown in the NMR spectrum of **5i** was 6.0 Hz, suggesting trans stereochemistry.

With vinyl acetate as the dipolarophile 3-ethyl-5-acetoxy-Δ^2-isoxazoline was prepared. On heating to 160° it also lost a molecule of acetic acid and was converted to 3-ethylisoxazole, a known compound.[6]

The 3-methyl-Δ^2-isoxazolines **5m–q** and the 1,2,4-oxadiazoline **5r** (Table I) were also obtained by the thermal decomposition of potassium nitroethylnitronate in vinyl *n*-butyl ether, diethyl maleate, allyl acetate, vinyl acetate, styrene, and benzalaniline, respectively, in the presence of DMF. The characterization of these compounds was made by their NMR and ir spectra and by synthesis of each from nitroethane. The compound 3-methyl-5-acetoxy-Δ^2-isoxazoline (**5p**) was also converted on heating (in 80% yield) to 3-methylisoxazole, a known compound.[14]

Thermal decomposition of potassium phenylnitromethylnitronate in DMF alone gave benzoic acid, polymeric material, and potassium nitrite, the latter identified through quantitative liberation of nitrogen gas from sulfamic acid.[15] The potassium salts of 1,1-dinitropropane and 1,1-dinitroethane gave propionic and acetic acids, respectively, under the same conditions. Whether the hydrogen came from the solvent, DMF, was not determined. Liu and Toriyama[16] reported that thermal decomposition of 3-chloro-3-phenylazirine in Me_2SO or dimethoxyethane gave benzoic acid.

Experimental Section

Melting points are corrected; boiling points are not corrected. *N,N*-Dimethylformamide (DMF) and dimethyl sulfoxide (Me_2SO) were dried over a molecular sieve, Linde type 3A (1/16 in.), before use. Instruments used were a Perkin-Elmer Model 257 infrared spectrophotometer and a Varian A-60A proton magnetic resonance spectrometer.

***trans*-3-Phenyl-4,5-dicarbethoxy-Δ^2-isoxazoline (5a). A. From Diethyl Fumarate.** Potassium phenylnitromethylnitronate (4.4 g, 0.02 mol) and 40 ml of diethyl fumarate was stirred with a magnetic stirrer in a 250-ml round-bottomed flask connected with a water condenser, protected from moisture with a calcium chloride guard tube and heated to 80°. *N,N*-Dimethylformamide was then added slowly until a clear solution was obtained (about 40 ml). After 2 hr a white precipitate of potassium nitrate started settling out but the stirring was continued for another 20 hr. The solution was filtered under suction and the precipitate of potassium nitrate (1.9 g, 94%) was washed with 10 ml of ether. The potassium nitrate gave the old brown ring test and failed to liberate nitrogen gas from sulfamic acid.[15] Washings and the filtrate were transferred to a separatory funnel and treated with 60 ml more of ether. The DMF was removed by washing three times with 30-ml portions of water. The ethereal layer was dried over anhydrous sodium sulfate and the ether evaporated on a rotary evaporator. The yellow solution was distilled under reduced pressure to remove diethyl fumarate and traces of DMF. *trans*-3-Phenyl-4,5-dicarbethoxy-Δ^2-isoxazoline was then collected at 158–160° (0.2 mm), yield 3.0 g (52%).

B. From Diethyl Maleate. A mixture of 2.2 g (0.01 mol) of potassium phenylnitromethylnitronate, 20 ml of diethyl maleate, and 20 ml of *N,N*-dimethylformamide was stirred at 80° in a 250-ml round-bottomed flask for 24 hr. A precipitate of potassium nitrate was obtained which was filtered. The solution was transferred to a separatory funnel and treated with 30 ml of ether, washed three times with 20-ml portions of water. The ethereal layer was dried over anhydrous sodium sulfate. Ether and diethyl maleate were removed by distillation under reduced pressure and the *trans*-3-phenyl-4,5-dicarbethoxy-Δ^2-isoxazoline was collected at 158–160° (0.2 mm). The NMR and ir spectra of the compound obtained using diethyl fumarate and diethyl maleate were identical, yield 1.48 g (50%).

C. By Isomerization of *cis*-3-Phenyl-4,5-dicarbethoxy-Δ^2-isoxazoline. Benzonitrile oxide was generated by Quilico's method[11] in the presence of diethyl maleate to give *cis*-3-phenyl-4,5-dicarbethoxy-Δ^2-isoxazoline. A sample of the reaction mixture was removed and its NMR spectrum verified the cis configuration for this method of synthesis: NMR ($CDCl_3$) C4 H δ 4.5, d, 1, J = 11.0 Hz; C5 H, 5.2, d, 1, J = 11.0 Hz.

The isolated cis isoxazoline was warmed on a hot plate until it changed color from light yellow to orange-yellow (15 min). The cis form was totally isomerized to the trans compound as determined by an NMR spectrum (Table I). The same result was obtained by treating the cis isoxazoline with a few drops of triethylamine at room temperature.[17]

3-Phenyl 5-Substituted Δ^2-Isoxazolines. Potassium phenylnitromethylnitronate (0.015 mol) was mixed with 40 ml of the monosubstituted volatile olefin (for **5c–e**) and stirred magnetically in a 150-ml round-bottomed flask at 70°. After 0.5 hr, 30 ml of DMF was slowly added through the condenser, and the stirring was continued for 24 hr. A white precipitate of potassium nitrate settled out during this time. A condenser set downward for distillation was connected and the olefin was stripped from the solution at reduced pressure. The residue was transferred to a separatory funnel, 50 ml of ether was added, and the solution was washed with three 30-ml portions of water. The ethereal layer was dried over anhydrous sodium sulfate. The yellow oil remaining after removal of the ether was distilled at reduced pressure.

The solid isoxazolines, **5b** and **5f**, were prepared in the same way and recrystallized from absolute methanol.

The 3-methyl-Δ^2-isoxazolines **5m–r** were prepared in an analogous manner. However, the reactions to prepare 3-ethyl-Δ^2-isoxazolines **5h–l** were carried out in Me_2SO because of the better solubility of potassium nitroethylnitronate in this solvent.

Attempted Deoxygenation of 3,4,5-Triphenyl-Δ^2-isoxazoline *N*-Oxide. One gram of 3,4,5-triphenyl-Δ^2-isoxazoline *N*-oxide[2] in 15 ml of dry DMF was allowed to react with 1 g of potassium nitrite at 80° with constant stirring for 12 hr. The potassium nitrite and DMF were washed out with water and the unreacted *N*-oxide was recovered quantitatively.[18]

Warning: It is unwise to use more than 0.02 mol of the potassium salts of dinitroalkanes in any new experiment as they are explosive. However, 1,1-dinitroethane and 1,1-dinitropropane were distilled as colorless liquids that have remained colorless in our laboratory for 22 years. Potassium 1-nitropropylnitronate was also stable in the bottle over the same period but potassium 1-nitroethylnitronate should only be prepared before use. The salts were prepared by the ter Meer reaction.[19]

Registry No.—**1** (R = Ph), 28198-51-8; **1** (R = Et), 33552-85-1; **1** (R = Me), 2517-91-1; *trans*-**5a**, 57065-93-7; *cis*-**5a**, 57065-94-8; **5b**, 17669-31-7; **5c**, 7064-07-5; **5d**, 50899-14-4; **5e**, 50899-19-9; **5f**, 17669-34-0; **5g**, 57065-95-9; **5h**, 57065-96-0; **5i**, 57065-97-1; **5j**, 55134-83-3; **5k**, 57065-98-2; **5l**, 57065-99-3; **5m**, 57066-00-9; **5n**, 57066-01-0; **5o**, 57066-02-1; **5p**, 7063-89-0; **5q**, 7064-06-4; **5r**, 18885-88-6; diethyl fumarate, 623-91-6; diethyl maleate, 141-05-9; vinyl *n*-butyl ether, 111-34-2; allyl acetate, 591-87-7; vinyl acetate, 108-05-4; styrene, 100-42-5; benzalaniline, 538-51-2; dimethyl fumarate, 624-49-7; ethyl acrylate, 140-88-5; ethyl cinnamate, 103-36-6; allyl ethyl ether, 557-31-3.

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Iodonium Ylides. Reactions of Phenyldimedonyliodone with Several Thiocarbonyl Compounds. Evidence for Sulfur Ylide Intermediates

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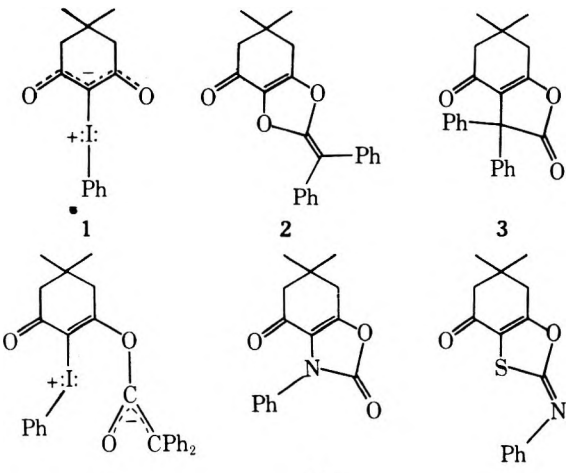
When phenyldimedonyliodone (1) was allowed to react with phenyl isothiocyanate, the products were iodobenzene, 7 (8%), 8 (36%), and 9 (14%). Similar reaction of 1 with methyl isothiocyanate gave 7 (35%) and 9 (26%). The intermediacy of sulfur ylide 11, an analogous sulfur ylide from 1 and methyl isothiocyanate, and thiotrione 12 in those reactions seems to be indicated. An attempt to synthesize authentic 12 by treatment of 1 with hydrogen sulfide failed. However, compound 9 was isolated in 40% yield. Finally, when 1 was allowed to react with thiourea, the delocalized sulfur ylide 13 was obtained (67%).

The formation of halonium ylides as reactive intermediates when certain carbenes are generated in the presence of organic halides is now a matter of record.[1-7] However, because of their instability, the halonium ylides have largely eluded isolation and study. Partially for that reason, we began an investigation of the chemical properties of phenyldimedonyliodone (1), a stable iodonium ylide which can be prepared by the condensation of dimedone with iodosobenzene diacetate.[8] Our first objective was to characterize the reactivity of 1 toward several electrophilic heterocumulenes, and we have already reported that 1 reacts with diphenylketene to afford ketene acetal 2 and lactone 3, presumably through the betaine 4, while phenyl isocyanate reacts with 1 to afford azalactone 5.[9] We now wish to report that the reaction of 1 with phenyl isothiocyanate takes a markedly different course, and, while we fully expected to obtain adduct 6, that compound was not isolated. In connection with this, the reactions of 1 with methyl isothiocyanate, hydrogen sulfide, and thiourea were also studied.

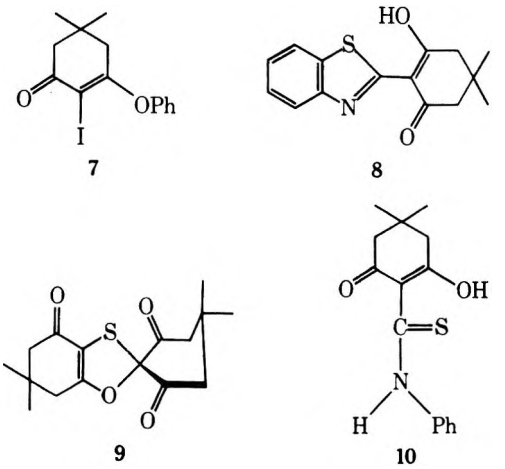


1 2 3

4 5 6

Results and Discussion

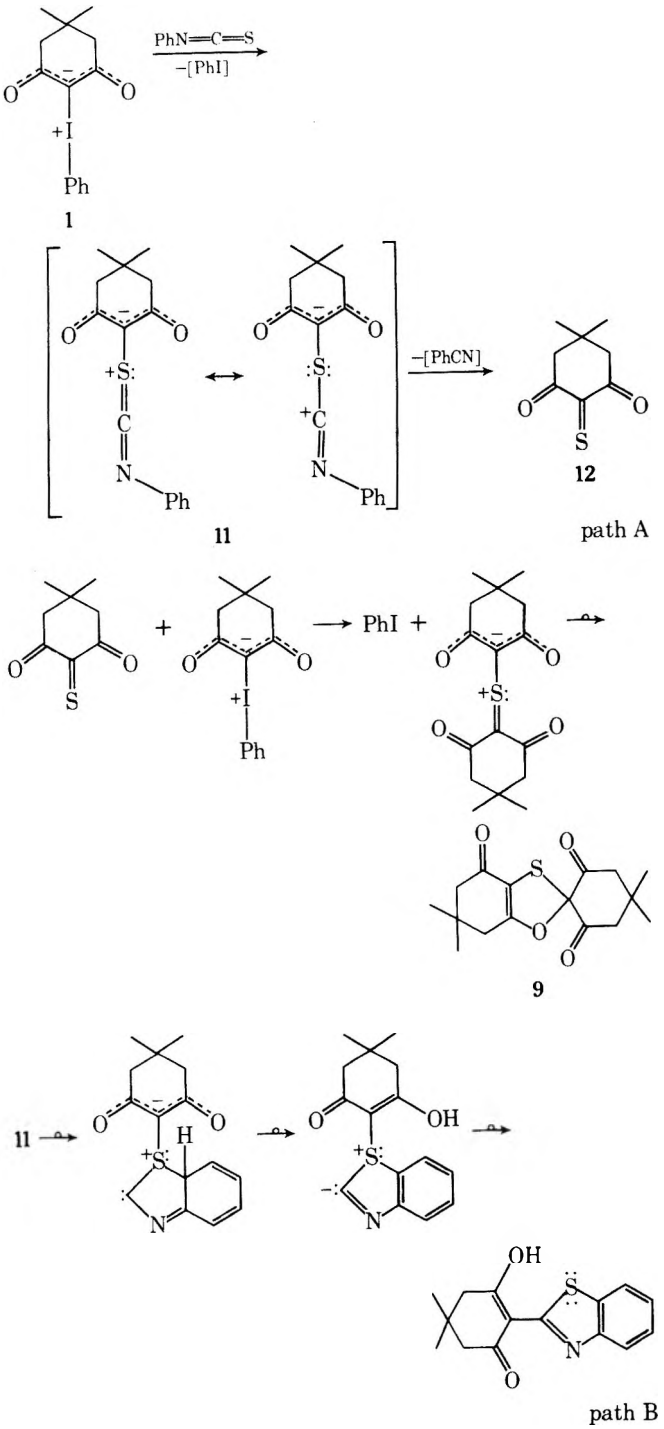
When phenyldimedonyliodone (1) and phenyl isothiocyanate were allowed to react in dichloromethane at room temperature, three products were obtained. One of these, isolated in 8% yield, was identified as phenyl 2-iododimedonyl ether (7), a known rearrangement product.[10] A second compound, isolated in 36% yield, was 2-(2-benzthiazolyl)dimedone (8), the structure of which was confirmed by its comparison with authentic material prepared by the action of bromine on dimedone-2-thiocarboxanilide (10).[11]



7 8

9 10

Chart I



The third product, a yellow solid isolated in 14% yield, was identified as **9** by elemental and spectral analysis. In particular, the 300-MHz ^{1}H NMR spectrum of **9** clearly reveals two "types" of dimedone rings, one with enol symmetry and one with keto symmetry. The former exhibits a six-proton singlet at δ 1.16 and a pair of two-proton singlets at δ 2.31 and 2.60 while the latter shows a pair of three-proton singlets at δ 0.89 and 1.23 and a pair of two-proton doublets at δ 2.51 and 3.01 ($J_{gem} \cong 13.5$ Hz). Iodobenzene is also formed in this reaction, and, in a separate study, the yield of iodobenzene was determined by GLC analysis to be 86%.

Several plausible reaction pathways for the formation of iodobenzene, **8**, and **9** from **1** and phenyl isothiocyanate are illustrated in Chart I.

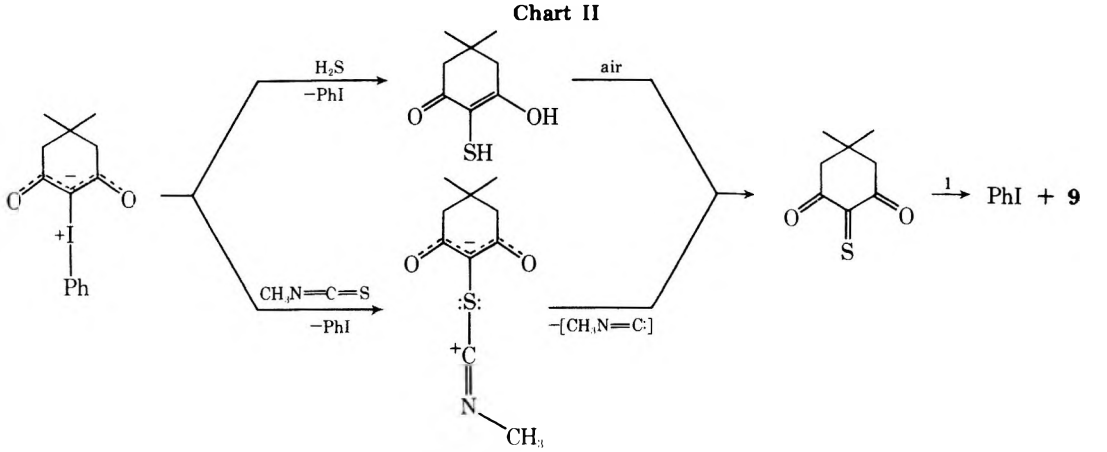
In this scheme, reaction is presumed to be initiated by displacement of iodobenzene from **1** by phenyl isothiocyanate with formation of sulfur ylide **11** which could then react in one of two ways. It could undergo an intramolecular rearrangement which eventuates in thiazole **8** (path B) or it could fragment to phenyl isocyanide and thiotrione **12** (path A). Subsequent attack of **12** on **1** would yield **9**. The proposed sulfur ylide **11** possesses several features which should drive the indicated rearrangement; it has a nucleophilic sulfur atom, positive charge which is most certainly delocalized into the benzene ring, and a basic oxygen atom situated favorably for deprotonation of the benzene ring at the right moment. Evidence bearing on this sequence of events was provided by the following experiments.

Phenyl isocyanide has not been isolated from the reaction of **1** with phenyl isothiocyanate. However, an insoluble, high melting (~290°) white solid was isolated. The solid exhibits no distinctive spectral features, but it does contain 5.1% nitrogen and only trace amounts of sulfur.

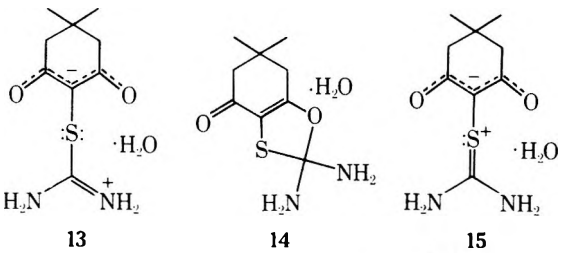
An attempt to synthesize **12** by treatment of **1** with hydrogen sulfide was unsuccessful. However, compound **9** was isolated in 40% yield. Also, when **1** was allowed to react with methyl isothiocyanate, the products were **7** (36%) and **9** (26%). It seems likely that both reactions proceed through a common intermediate, and one which is independent of the structural diversity of hydrogen sulfide and methyl isothiocyanate, and it seems plausible that **12** is that intermediate (Chart II).

Finally, we sought corroborative evidence that compounds containing the >C=S: moiety can indeed displace iodobenzene from **1**. To this end, phenyldimedonyliodone was allowed to react with thiourea at room temperature, and compound **13** was isolated in 67% yield as a white, crystalline solid. The cyclic structure **14** for the white solid is clearly inconsistent with its NMR spectrum. Specifically, the methylene groups give rise to a four-proton singlet rather than a pair of two-proton singlets as expected for

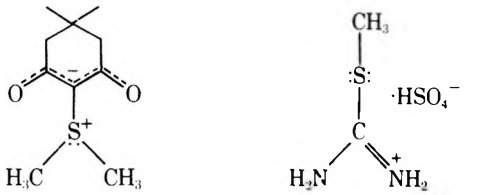
Chart II



that structure. Also, we regard **13** as a more accurate representation of the true structure than **15** because the infrared spectrum of the white solid exhibits an absorption band at 1645 cm^{-1} ($-C=N^+H_2$ stretch). Thus, the known sulfonium ylide **16**[12] does not absorb in that region, but methylthiouronium bisulfate (**17**) does.[13]



13 **14** **15**



16 **17**

The formation of **13** from phenyldimedonyliodone and thiourea provides excellent analogy for the proposed formation of **9** from phenyldimedonyliodone and thiotrione **12**. However, in the case of **9**, the cyclic structure is favored over the dipolar structure, presumably because the carbonyl groups of the thiotrione moiety would inhibit the delocalization of positive charge.

Experimental Section

General. ^1H NMR spectra (60 MHz) were recorded on a Varian Model A-60 NMR spectrometer (relative to internal Me_4Si), infrared spectra on a Perkin-Elmer Model 337 spectrophotometer, and ultraviolet spectra on a Cary-17 uv–visible–ir spectrophotometer. ^1H NMR spectra (300 MHz) were recorded on a Varian Model HR-300 NMR spectrometer at The University of Akron's NMR center. Melting points are uncorrected. GLC analyses were conducted on a Hewlett-Packard Model 5750 gas chromatograph, a 6 ft column of 10% Ucon W-98 on 80–100 mesh silica being utilized. Elemental compositions were determined by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reaction of Phenyldimedonyliodone (1) with Phenyl Isothiocyanate. A solution of **1** (10.98 g, 32.09 mmol) in CH_2Cl_2 (50 ml) and a solution of phenyl isothiocyanate (6.24 g, 46.16 mmol) in CH_2Cl_2 (50 ml) were mixed and allowed to stir for 4.5 days at room temperature. The CH_2Cl_2 was then evaporated in vacuo, and the brown, viscous liquid which remained was resolved by column chromatography on Florisil (250 g). Twenty-one fractions of ca. 300 ml each were collected as the elution solvent was changed in a systematic way: 1 (C_6H_{12}), 2–3 (C_6H_{12}–ether, 50:50), 4 (C_6H_{12}–ether, 20:80), 5–8 (ether), 9 (ether–$CH_3CO_2C_2H_5$, 80:20), 10 (ether–$CH_3CO_2C_2H_5$, 50:50), 11 (ether–$CH_3CO_2C_2H_5$, 20:80), 12–13 ($CH_3CO_2C_2H_5$), 14 ($CH_3CO_2C_2H_5$–CH_2Cl_2, 50:50), 15–16 (CH_2Cl_2), 17 (CH_2Cl_2–CH_3OH, 50:50), 18–21 (CH_3OH). Each fraction was then concentrated and subjected to NMR analysis. Fractions 5–9 gave 1.71 g of reasonably pure **8**, but further resolution of other fractions was necessary before pure materials could be isolated.

Fractions 2 and 3. The crude solid (1.31 g) was divided by hand into colorless crystals (**7**) and yellow crystals (**9**). The yellow material (0.70 g) was chromatographed on Florisil (50 g), six fractions of ca. 300 ml each being collected. The first four fractions (benzene) yielded 0.41 g of **9** while the last two fractions (ether) yielded 0.24 g of **7**.

Fraction 4. The crude solid (0.59 g) was rechromatographed on Florisil (50 g), six fractions of about 300 ml each being collected. The first fraction (benzene) gave nothing, the second fraction (benzene–ether, 90:10) gave 0.23 g of mostly **7**, the third fraction (benzene–ether, 90:10) gave 0.05 g of mostly **7**, and the fourth fraction (ether) gave 0.18 g of **8**.

Fractions 14–17. The crude solids (5.29 g) were combined and triturated with cyclohexane–ether (50:50), and 4.37 g of phenyldimedonyliodone was recovered as a white powder. The washings were concentrated and yielded 0.9 g of a thick, brown liquid which has not been identified.

Fraction 18. This solid–liquid (1.05 g) was washed with ether and combined with the solids (1.24 g) from fractions 19–21. In this way, 2.12 g of a high melting (~290°), highly insoluble, yellow solid was obtained.

Anal. Found: C, 64.29; H, 5.77; N, 5.07; S, 0.28.

The product yields based on the amount of unrecovered **1** (19.317 mmol) follow: **7** (0.52 g, 7.8%), **8** (1.89 g, 35.8%), and **9** (0.41 g, 13.8%).

Purification and Characterization of 8. The crude material was recrystallized from dichloromethane–cyclohexane as white plates: mp 200–201°; uv (CH_2Cl_2) 259 nm (max, ϵ 14179, conjugated benzene ring), 239 (sh, 10672), 271 (sh, 9925), 347 (max, 35149), 334 (sh, 26716); uv (CH_3OH) 260 nm (max, ϵ 13750), 238 (sh, 8945), 271 (sh, 10078), 344 (max, 33164), 331 (sh, 26406), 314 (sh, 11797); ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 6 H), 2.49 (s, 2 H), 2.54 (s, 2 H), 7.38 (t, 1 H), 7.52 (t, 1 H), 7.60 (d, 1 H), 7.83 (d, 1 H), 16.5 (s, 1 H); ^{1}NMR (60 MHz, $CDCl_3$) δ 1.12 (s, 6 H), 2.53 (s, 4 H), sometimes is recorded as a moderately resolved pair of singlets, 7.2–8.0 (complex m, 4 H), 16.5 (broad s, exchanges with D_2O).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; S, 11.73. Found: C, 65.98; H, 5.63; S, 11.55.

Purification and Characterization of 9. The crude material was recrystallized from dichloromethane–cyclohexane as yellow needles: mp 176–178°; ir (KBr) 5.84 (C=O, saturated ketone), 6.04 (C=O, α,β-unsaturated ketone), 6.20 μ (C=C); uv–visible (CH_3OH) 306 nm (max, ϵ 4175), 289 (sh, 3744), 380 (tail, 150); uv–visible (CH_2Cl_2) 292 nm (max, ϵ 4610) 312 (sh, 4082), 380 (tail, 120), 246 (plateau, 1774); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3 H), 1.16 (s, 6 H), 1.23 (s, 3 H), 2.31 (s, 2 H), 2.51 (d, 2 H, $J_{gem} \cong$ 13.5 Hz), 2.60 (s, 2 H), 3.01 (d, 2 H, $J_{gem} \cong$ 13.5 Hz); ^1H NMR (60 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 1.15 (s, 6 H), 1.23 (s, 3 H), 2.30 (s, 2 H), 2.33 (shoulder, 0.5 H), 2.58 (apparent s, 3.5 H), 2.94 (broad apparent s, 1.5 H), 3.18 (broad apparent s, 0.5 H).

Anal. Calcd for $C_{16}H_{20}SO_4$: C, 62.31; H, 6.54; S, 10.40. Found: C, 62.51; H, 6.72; S, 10.74.

Reaction of 1 with Phenyl Isothiocyanate. Yield of Iodobenzene. A solution of **1** (3.0520 g, 8.919 mmol) in CH_2Cl_2 (20 ml) and a solution of phenyl isothiocyanate (1.9510 g, 14.432 mmol) in CH_2Cl_2 (20 ml) were mixed and allowed to stir for 5 days at room temperature. The reaction mixture was then diluted volumetrically to 50 ml with CH_2Cl_2. A 10-ml aliquot was removed, 0.1073 g (0.799 mmol) of durene was added, and the resulting solution was subjected to GLC analysis. Two separate injections yielded an average iodobenzene–durene peak area ratio of 1.247. A known mixture of durene (0.1900 g, 1.416 mmol) and iodobenzene (0.4061 g, 1.991 mmol), when subjected to similar analysis, gave an iodobenzene–durene peak area ratio of 0.917. Thus, the iodobenzene–durene peak area ratio must be multiplied by a factor of 1.533 to give the correct iodobenzene–durene mole ratio. The yield of iodobenzene was, therefore, 85.7%.

The 10-ml GC sample was then combined with the remaining 40 ml of solution, the CH_2Cl_2 was evaporated in vacuo, and the residue was resolved by column chromatography on Florisil. Seven fractions of about 300 ml each were collected and concentrated, and the residues were subjected to NMR analysis. Fractions 1–3 (ether) yielded a mixture of **7**, **8**, and **9** and fractions 4–5 ($CH_3CO_2C_2H_5$) gave 0.71 g of mostly unreacted **1**.

The crude solids from fractions 4 and 5 were combined and washed with ether, and 0.3217 g (0.940 mmol) of **1** was recovered as a white powder. The iodobenzene yield, based on the amount of unrecovered **1**, was 95.76%.

Reaction of Phenyldimedonyliodone (1) with Methyl Isothiocyanate. A solution of **1** (9.156 g, 26.76 mmol) in CH_2Cl_2 (50 ml) and a solution of methyl isothiocyanate (2.46 g, 33.64 mmol) in CH_2Cl_2 (50 ml) were mixed and allowed to stir under nitrogen for 5 days at room temperature. The solvent was then evaporated in vacuo, and the crude product was resolved by column chromatography on Florisil. Nine fractions of ca. 300 ml each were collected, concentrated, and subjected to NMR analysis. The details are given in Table I.

Fraction 2 was resolved into its components by a second chromatography on Florisil with cyclohexane followed by benzene followed by ether as the elution solvents. In this way, 0.160 g of **7** and 0.390 g of **9** was obtained.

Fraction 9 was triturated with ether and 5.873 g of unreacted **1** was recovered.

Table I

Fraction	Solvent	Wt, g	State	Identification
1	Benzene	0.156	Liquid	7 + C_6H_5I
2	Benzene–ether (90:10)	0.570	Solid	7 + 9 (~1:3)
3	Benzene–ether (50:50)	0.699	Solid	Mostly 7
4	Ether	0.233	Solid	Mostly 7
5	Ether	0.065	Solid	Mostly 7
6	Ether	0.016	Solid	7 + unknown
7	$CH_3CO_2C_2H_5$	0.031	Solid	7 + unknown
8	CH_2Cl_2	0.221	Solid	1 + unknown
9	CH_2Cl_2–CH_3OH (50:50)	6.468	Solid	Mostly 1

Hence, the yields of 7 and 9, based on the amount of 1 which had reacted (9.594 mmol), were 35 and 26%.

Reaction of Phenyldimedonyliodone (1) with H_2S. A solution of 1 (10.01 g, 29.25 mmol) in CH_2Cl_2 (120 ml) was saturated with H_2S for 30 min and allowed to stir overnight at room temperature. The solvent was then removed by vacuum evaporation, and the crude yellow-white solid which remained was resolved by column chromatography on Florisil (200 g). Twenty fractions of ca. 300 ml each were collected as the elution solvent was changed in a systematic way: 1 (C_6H_{12}), 2–7 (C_6H_{12}–ether, 90:10), 8–12 (C_6H_{12}–ether, 85:15), 13–14 (C_6H_{12}–ether, 80:20), 15 (C_6H_{12}–ether, 50:50), 16 (ether), 17 (ether–$CH_3CO_2C_2H_5$, 50:50), 18 ($CH_3CO_2C_2H_5$), 19–20 (CH_3OH). Each fraction was then concentrated, and some of them were subjected to NMR analysis. Fractions 4–13 yielded 1.4247 g of relatively pure 9, fractions 2–3 gave 0.3019 g of mostly 9 (contaminated with some iodobenzene), and fractions 14–18 gave 0.7126 g of mostly unknown material contaminated with 9. A second chromatography of that material yielded 0.0830 g of 9. Thus, the total yield of 9 was ~1.8096 g (40%).

Authentic 2-(2-Benzthiazolyl)dimedone (8). This material was prepared by the method of Barnikow.[11] In the first step, dimedone was condensed with phenyl isothiocyanate to give 10 [21%, mp 126–129° (lit.[11] mp 129.5–130°)]. In the second step, 10 was oxidized with bromine in acetic acid to give 8 [53%, mp 197–199° (lit.[11] mp 203–203.5°)]. The NMR and ir spectra of this material are identical with those of 8 obtained from 1 and phenyl isothiocyanate.

Reaction of Phenyldimedonyliodone (1) with Thiourea. A solution of 1 (10.25 g, 29.95 mmol) in CH_2Cl_2 (60 ml) and a solution of thiourea (2.27 g, 29.82 mmol) in absolute ethanol (60 ml) were mixed and allowed to stir for 15 hr at room temperature. The solvents were subsequently evaporated in vacuo, and a red-orange solid remained.

Purification and Characterization of 13. The crude solid was recrystallized from absolute ethanol (150 ml), and two crops of white crystals were obtained: yield 4.23, 0.44 g (67%); mp 170°; ^1H NMR (Me_2SO-d_6) δ 0.98 (s, 6 H), 2.23 (s, 4 H), 3.7 (very broad "singlet," 2 H, H_2O of hydration), 8.28 (very broad singlet, 4 H, $-NH_2$); ir (KBr) 1645 cm^{-1} ($C{=}N^+H_2$); uv (CH_3OH)λ_{max} 266 nm (ϵ 19607).

Anal. Calcd for $C_9H_{14}N_2O_2S{\cdot}H_2O$: C, 46.53; H, 6.94; S, 13.80. Found: C, 46.54; H, 6.93; S, 13.91.

This compound is insoluble in CH_3CN, $CHCl_3$, ether, acetone, and cyclohexane, and for that reason, Me_2SO-d_6 was chosen as the NMR solvent. Sometimes the H_2O resonance appears to be fairly sharp and sometimes very broad. We have no explanation for this behavior.

Registry No.—1, 35024-12-5; 8, 56995-06-3; 9, 56995-07-4; 10, 7721-63-3; 13, 56995-08-5; phenyl isothiocyanate, 103-72-0; iodobenzene, 591-50-4; methyl isothiocyanate, 556-61-6; H_2S, 7783-06-4; thiourea, 62-56-6.

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Thiazolo[3,4-*b*]indazole, a Ring-Fused Tetravalent Sulfur Thiazole System

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Deoxygenation of ethyl 4-(2-nitrophenyl)-2-phenylthiazole-5-carboxylate with $P(OEt)_3$ gave ethyl 3-phenylthiazolo[3,4-*b*]indazole-1-carboxylate, a fused thiazole derivative containing tetravalent sulfur. Cycloaddition of *N*-phenylmaleimide occurred across the thiocarbonyl ylide dipole giving a 1:1 cycloadduct together with the H_2S elimination product, *N*,4-diphenyl-1-ethoxycarbonylpyrido[1,2-*b*]indazole-2,3-dicarboximide. With dimethyl acetylenedicarboxylate, a 1:2 adduct was formed with addition occurring across the azomethine imine dipole. $P(OEt)_3$ deoxygenation of 4-(2-nitrophenyl)-2-phenylthiazole gave, however, 3-phenylthiazolo[5,4-*b*]indole, the same product being obtained by thermolysis or photolysis of the corresponding azide.

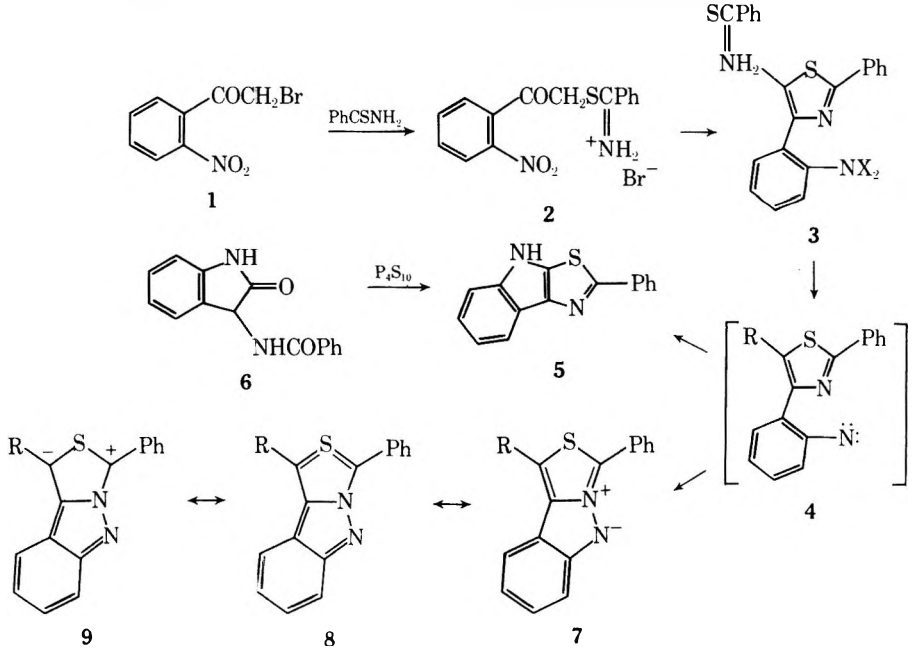
Fused thiophenes containing tetravalent sulfur are of considerable practical and theoretical interest,[2] and recent examples have included the furan,[3] pyrrole,[3,4] and pyrazole[5] ring systems fused to a thiophene nucleus, all of which proved versatile substrates in cycloaddition reactions. Our interests in mesoionic derivatives of the thiazole system,[6] which also may be considered to have some contribution from a canonical form involving a tetravalent sulfur atom, suggested the synthesis of a fused thiazole derivative that would incorporate a tetravalent sulfur atom. Such a system would require fusion at the 3,4 positions and contain a bridgehead nitrogen atom, offering interesting possibilities for the development of ylidic characteristics within the fused ring system. This would provide a new type of "tetravalent sulfur" ring system[7] in addition to the thiabenzenes[8] and 6a-thiathiophthenes[8a,9] for evaluating the importance of dipolar structures or of tetravalent sulfur species to the resonance hybrid.

The usual synthetic routes to the tetravalent sulfur systems[2,4,6] are precluded by the presence of the trigonal nitrogen atom which, however, does provide a basic center susceptible to electrophilic attack. A nitrene cyclization reaction appeared to offer the most direct, feasible route, such intramolecular nitrene cyclizations onto a trigonal nitrogen atom having been utilized in the synthesis of several polyazapentalene derivatives.[10]

The most readily available system would be 3-phenylthiazolo[3,4-*b*]indazole (**7**, R = H) which should be prepared by triethyl phosphite deoxygenation[11] of 4-(2-nitrophenyl)-2-phenylthiazole (**3**, R = H; X = O), this precursor being obtained from 2-bromo-2′-nitroacetophenone (**1**) and thiobenzamide. The isolation of the intermediate **2** in this sequence is worthy of note, as such intermediates have rarely been isolated in the reaction of α-halo ketones with thioamides.[12]

Deoxygenation of aromatic nitro compounds with triethyl phosphite commonly affords products expected from the corresponding nitrenes, although the exact nature of the intermediate is still uncertain.[13] Two products could be anticipated from **4** (R = H), the heteroaromatic betaine **7** (R = H) formed by coordination of the unshared electron pair on nitrogen with the nitrene, or 2-phenylthiazolo[5,4-*b*]indole (**5**), the result of electrophilic attack of the nitrene on the unsubstituted 5-thiazole position. At the time of initiating this work, there were no examples in the literature of C–N bond formation competing with N–N bond formation, but recently, however, several such examples have been reported.[14]

When **3** (R = H; X = O) was heated under reflux in xylene with $P(OEt)_3$ only one product was isolated. Analytical and spectral data (*Experimental Section*) readily established its structure as 2-phenylthiazolo[5,4-*b*]indole (**5**), especially the ν_{NH} ($CHCl_3$) 3460 cm^{-1}. This ring system has been described previously[15] as its 2-methyl derivative but no spectral characteristics were reported and the present structural assignment was confirmed by an alternative synthesis[15] from 2-aminooxindole via 3-benzamidooxindole (**6**) and P_4S_{10}. The intermediacy of the nitrene **4** (R = H) appears likely because of the ready isolation of **5** upon thermolysis or photolysis of 4-(2-azidophenyl)-2-phenylthiazole (**3**, R = H; X = N), obtained from **3** (R = H; X = O) by reduction followed by diazotization and treatment with sodi-



um azide. The azide 3 (R = H; X = N), characterized by its infrared absorption at 2130 cm^{-1} and an $M^{\cdot+}$ 278, had an interesting mass spectrum. The most abundant ion was $[M - N_2]^{\cdot+}$, *m/e* 250, and the remainder of the fragmentation pattern was in accord with the electron-impact induced loss of nitrogen to give 2-phenylthiazolo[5,4-*b*]indole (5). The generation of nitrenes from azides under electron impact is well documented.[16]

The preference for C–H bond insertion over N–N bond formation may be the result of thermodynamic control with the possibility that the N–N bond is made preferentially under kinetic control. The imminium imine thus formed could conceivably redissociate to the nitrene which then reacts to form the observed product, nitrene formation by dissociation of $=N^+-N^-$– being known for some time.[17]

Introduction of a 5 substituent into the thiazole nucleus resulted in reaction of the intermediate nitrene at the thiazole nitrogen atom, a not unexpected result as attack at the 5 position of the thiazole nucleus would generate a tetrahedral center. The choice of a blocking group for the 5 position was somewhat restricted as a methyl group might lead to the corresponding pyridine derivative or product of methyl group migration,[18] and our attempts to prepare the 5-phenyl substituted product was unsuccessful.

Ethyl 4-(2-nitrophenyl)-2-phenylthiazole-5-carboxylate (3, R = COOEt; X = O) was prepared by a reaction sequence from ethyl 2′-nitrobenzoylacetate involving bromination and subsequent reaction with thiobenzamide. 3,5-Diphenyl-1,2,4-thiadiazole and sulfur were also formed along with 3 (R = COOEt; X = O) and, as these two products are also observed from the oxidation of thiobenzamide with a variety of reagents,[19] it appears that the nitro group in either the bromo compound or 3 (R = COOEt; X = O) may act as an oxidizing agent. As the yield of the thiazole was substantially increased by the use of a large excess of thiobenzamide, it appears that the bromo ketone was the more likely oxidant.

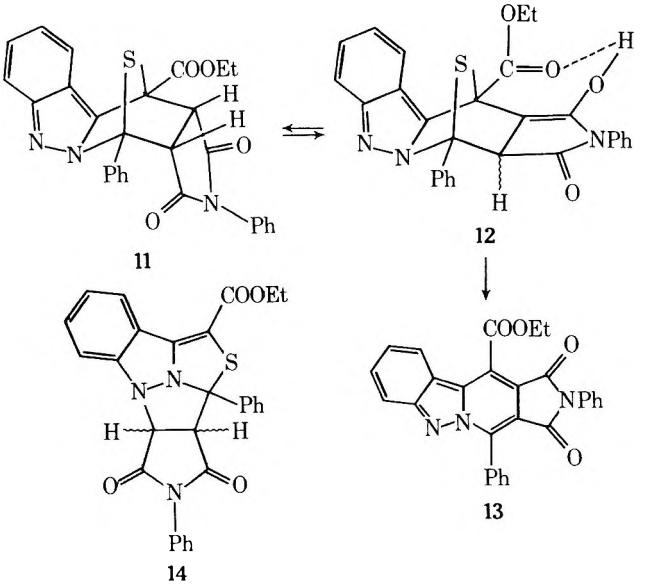
Triethyl phosphite deoxygenation of 3 (R = COOEt; X = O) resulted in the isolation of two products, the major one (24%) being obtained as maroon needles with an intense violet color in solution (λ_{max} 542 nm). This product has been identified as ethyl 3-phenylthiazolo[3,4-*b*]indazole-1-carboxylate (7, R = COOEt). Analytical and mass spectral data established the molecular formula as $C_{18}H_{14}N_2O_2S$, the latter also showing a doubly charged ion at *m/e* 161 (5%) often associated with tetravalent sulfur and other aromatic systems.[4,5,20]

The infrared carbonyl absorption in 7 (R = COOEt) occurred at 1690 cm^{-1}, 15 cm^{-1} lower than that in its precursor 3 (R = COOEt; X = O), indicating that the negative charge is delocalized over the ester group to some extent. This is commonly observed with heteroaromatic betaines with analogous substitution patterns, such as in 4-acetylsydnone[21a] and in *anhydro*-2,3-diphenyl-5-ethoxycarbonyl-4-hydroxythiazolium hydroxide.[21b]

This ring system was found to undergo cycloaddition reactions and, from the several possible ylide structures in the molecule, *N*-phenylmaleimide was found to add across the thiocarbonyl ylide dipole 9. Such an addition is consistent with that observed previously in other tetravalent sulfur systems[4,5] and in this case reaction occurred in 17 hr in refluxing xylene. Two products were isolated from the reaction. The first, obtained in 65% yield, proved to be a 1:1 adduct whose spectral characteristics indicated that it was the enol 12 of the anticipated product 11, with ν_{CO} 1705, 1760 cm^{-1} accompanying a ν_{OH} 3265 cm^{-1}. The NMR spectrum, in addition to the ester absorptions at δ 1.20 and 4.21, showed only a singlet bridgehead methine proton at δ 5.63, aromatic protons as two multiplets at δ 6.99–7.63 and 7.86–8.22, and a D_2O-exchangeable broad proton at δ 12.50 attributed to the enolic OH group.

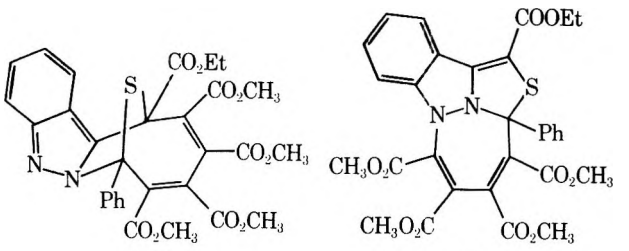
The enolization of the carbonyl group of an imidic cycloadduct has not previously been observed. Models indicate the possibility of stabilizing the enol group through hydrogen bonding with the bridgehead ester function, although this would involve a seven-membered ring system. Unfortunately, approximately the same favorable bond angles and lengths attend intramolecular hydrogen bonding from the cycloadduct regardless of whether the bridgehead proton is cis or trans with respect to the epithio bridge, precluding any assignment of stereochemistry to the cycloadduct. Nonequivalence of the methylene protons is indicated by the methylene resonances which appeared as a complex pattern and may be a consequence of this hydrogen bonding.[22]

The second product (29%) had a molecular composition corresponding to the loss of hydrogen sulfide from the primary cycloadduct 12. Assigned structure 13, it was formed in increased yields at the expense of 12 by increasing the reaction time, and 12 was also converted into 13 by refluxing in xylene or by treatment with methanolic sodium methoxide. Analogous loss of H_2S under these conditions is well established for related bridged-sulfur cycloadducts.[4,22] Formation of the tricyclic derivative 13 by loss of H_2S from the initial 1:1 adduct can only be rationalized in terms of structure 12 for the initial cycloadduct, alternative modes of cycloaddition, such as represented by 14, requiring extensive skeletal rearrangements to accommodate such a loss.



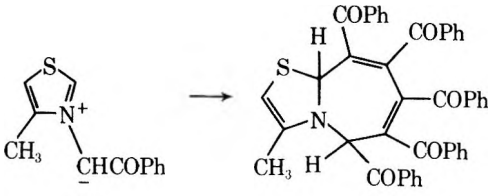
It was anticipated that dimethyl acetylenedicarboxylate would also undergo cycloaddition with 7 (R = COOEt) to give, after extrusion of sulfur from the initial cycloadduct, a pyrido[1,2-*b*]indazole derivative analogous to 13. Instead a 2:1 adduct was obtained (82%), the most plausible structure for which being the epithiodihydroazocinoindazole 15 or the dihydrothiazolodihydrodiazepinoindazole 16, representing an addition of two molecules of dimethyl acetylenedicarboxylate across the thiocarbonyl ylide or the azomethine imine ylide of 7 (R = COOEt), respectively. Although analytical and spectral data clearly establish the formation of a 2:1 adduct, the latter are not sufficiently definitive to allow an unambiguous assignment of structure to be made. However, the ^{13}C pulsed FT spectrum[23] of the adduct provides evidence that lends strong support to structure 16. Apart from the ester groups, structure 15 differs principally from structure 16 in that the former contains two sp^3

carbon atoms at the termini of the epithio bridge whereas the latter has only one sp^3 carbon atom at the original 2 position of the thiazole nucleus. An absorption at 114 ppm and the complete absence of an absorption between 61.62 and 127.49 ppm are consistent with structure **16**.

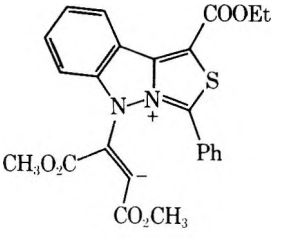


15 **16**

Formation of a 2:1 adduct has also been observed[24] with the thiazolium *N*-ylide **17**, in this case the thiazolo[3,2-*a*]azepine derivative **18** being obtained. An intermediate

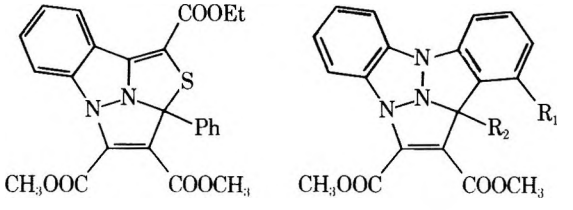


17 **18**

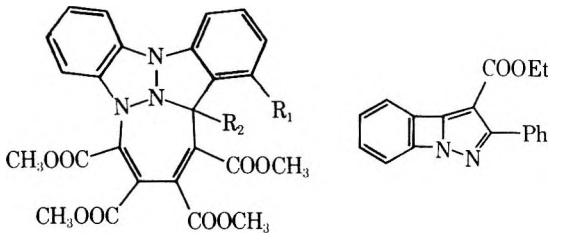


19

such as **19** would be anticipated in the formation of **16**, this 1,4-dipole undergoing condensation with another molecule of dimethyl acetylenedicarboxylate giving what is essentially a 1,7-dipole that undergoes ring closure to the observed product. Introduction of nitrogen atoms into the nucleus of other tetravalent sulfur systems considerably reduces the rate of cycloaddition of dipolarophiles[25] and in this case ring closure of **19** to form the 1:1 adduct **20** is less



20 **21**



22 **23**

favored than condensation with a second molecule of dipolarophile owing to the steric compression required for the fusion of three five-membered rings in a 1:1 adduct. However, the atoms at the points of ring fusion are apparently important in this respect as both a 1:1 adduct **21** and 2:1 adduct **22** are formed in the reaction of a dibenzotriazapentalene with dimethyl acetylenedicarboxylate.[26]

A second product isolated from the deoxygenation of **3** (R = COOEt; X = O) (5%) was shown to have a molecular formula $C_{18}H_{14}N_2O_2$, corresponding to the loss of sulfur from **7** (R = COOEt). Its formation by this route seems unlikely in view of our inability to convert **7** (R = COOEt) into this product on refluxing with triethyl phosphite in xylene. The ester ν_{CO} at 1750 cm^{-1} is 45 cm^{-1} higher than that found in its precursor **3** (R = COOEt; X = O) and 60 cm^{-1} higher than in the tetravalent sulfur system **7** (R = COOEt), indicating reduced electron delocalization over this group. A diazabiphenylene structure, e.g., **23**, seems unlikely since the aromatic multiplets of this product are found between δ 7.21 and 8.42, whereas the chemical shifts of the protons in biphenylene are reported[27] to be considerably upfield at δ 6.7 and 6.6 owing to the lack of effective bond delocalization.

Several improvements in the method of formation of the intermediates for the preparation of **3** (R = H, COOEt) are reported in the Experimental Section. Particularly interesting is the preparation of ethyl 2′-nitrobenzoylacetate from the reaction of 2-nitrobenzoyl chloride with the magnesium enolate of ethyl *tert*-butylmalonate. Heating the acyl malonate with β-napthalenesulfonic acid resulted in a 93% yield of pure product (>95%).

Experimental Section[28]

2′-Nitroacetophenone. This was prepared essentially according to the procedure of Reynolds and Hauser[29] with the following modification. The 150 ml of Et_2O added to the original magnesium ethoxide mixture was replaced by a mixture of 65 ml of anhydrous Et_2O and 85 ml of dry THF. The addition of 2-nitrobenzoyl chloride then resulted in the formation of a soluble magnesium malonate complex which was readily hydrolyzed by dropwise addition of the specified amount of dilute H_2SO_4. Following hydrolysis and decarboxylation of the acylmalonate intermediate, 2′-nitroacetophenone was obtained in 91–93% yield.

4-(2-Nitrophenyl)-2-phenylthiazole (3, R = H; X = O). A solution of thiobenzamide (27.4 g, 0.2 mol) and 2-bromo-2′-nitroacetophenone[30] (24.3 g, 0.1 mol) in 95% EtOH (150 ml) was refluxed for 1 hr. On cooling colorless needles, 25.4 g (90%), mp 97.5–99°, were obtained. Crystallization from MeOH afforded colorless needles: mp 98–99°; ir (KBr) 1530, 1360 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 7.26–8.11 (m, 10, aromatic); $M^{\cdot+}$ *m/e* 282 (19), 121 (100).

Anal. Calcd for $C_{15}H_{10}N_2O_2S$: C, 63.85; H, 3.57; N, 9.92. Found: C, 63.84; H, 3.56; N, 10.03.

When the ethanol solution was warmed gently, a precipitate of the open-chain intermediate **2** was frequently obtained as colorless needles (90%), ir (KBr) 2200–2700 (immonium), 1800 cm^{-1} (CO). This was converted into **3** quantitatively by shaking with a mixture of water, ether, and NEt_3.

Deoxygenation of 4-(2-Nitrophenyl)-2-phenylthiazole (3, R = H; X = O). The thiazole (1.1 g, 0.0029 mol), $P(OEt)_3$ (2 ml, freshly distilled from sodium), and xylene (7 ml) were refluxed under N_2 for 84 hr. The volatile components were removed in vacuo and the residual brown oil chromatographed (silica gel, 60 g, eluted with benzene) to afford, after crystallization from benzene, 2-phenylthiazolo[5,4-*b*]indole (**5**) as pale-yellow, fine, irregular prisms: mp 235–236°; 0.4 g (41%); ir ($CHCl_3$) 3460 cm^{-1} (NH); NMR (Me_2SO-d_6) δ 7.20–8.19 (m, 9, aromatic), 3.48 (br s, exchanged with D_2O, 1, NH); $M^{\cdot+}$ *m/e* 250 (100).

Anal. Calcd for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found: C, 72.20; H, 3.96; N, 11.06.

3-Benzamido-2-oxindole (6). To a solution of 3-aminooxindole hydrochloride[31] (1.73 g, 0.0094 mol) and Et_3N (30 ml) in $CHCl_3$ (70 ml) was added with stirring a solution of benzoyl chloride (1.32 g, 0.0094 mol) in $CHCl_3$ (15 ml). After 5 min the reaction mixture became pasty, and after 30 min it was filtered and washed with $CHCl_3$ to afford a white solid which crystallized from absolute EtOH as fine, colorless, matted needles: 2.25 g (95%); mp 250.5–251.5°; ir (KBr) 3300 (NH), 1730 cm^{-1} (CO); $M^{\cdot+}$ *m/e* 252 (27), 105 (100).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.07; H, 4.82; N, 11.09.

Reaction of 3-Benzamido-2-oxindole with Phosphorus Pentasulfide. A mixture of the above amide (1.26 g, 0.005 mol) and P_4S_{10} (1.11 g, 0.0025 mol) in pyridine (60 ml) was refluxed for 2 hr, reduced in volume to 20 ml by distillation, and poured into ice–water containing dilute NaOH. Upon filtration a cream-colored solid was obtained which crystallized from absolute EtOH as pale-yellow needles: 0.75 g (60%); mp 236–237°; identical[32] in all respects with 2-phenylthiazolo[5,4-*b*]indole (**5**) obtained by deoxygenation of the corresponding nitro compound (**3**, R = H; X = O).

4-(2-Aminophenyl)-2-phenylthiazole (3, R = X = H). A refluxing suspension of 4-(2-nitrophenyl)-2-phenylthiazole (11.3 g, 0.04 mol) and iron powder (76.8 g, 0.136 g-atom) in EtOH (500 ml) was treated dropwise with stirring over 1.5 hr with a solution of concentrated HCl (24 ml) in EtOH (200 ml). Reflux was continued for an additional 1 hr, at the end of which time the reaction mixture was filtered, neutralized with aqueous KOH, concentrated by evaporation, and extracted with $CHCl_3$. The organic layer was filtered to remove iron salts and evaporated to afford a tan solid which crystallized from EtOH as light tan plates, 5.8 g (54%). Work-up of the mother liquors afforded an additional 1.0 g (67% total yield). The combined products were recrystallized from MeOH, affording pale yellow plates: mp 121.5–122.5°; ir (KBr) 3450, 3325 cm^{-1} (NH); NMR ($CDCl_3$) δ 6.51–7.97 (m, 10, aromatic), 5.36 (br s exchanged with D_2O, 2, NH_2); $M^{\cdot+}$ *m/e* 252 (100).

Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.38; H, 4.80; N, 11.11. Found: C, 71.37; H, 4.87; N, 11.02.

4-(2-Azidophenyl)-2-phenylthiazole (3, R = H; X = N). A suspension of 4-(2-aminophenyl)-2-phenylthiazole (2.02 g, 0.008 mol) in concentrated HCl (7 ml) at 0° was treated with a solution of sodium nitrite (0.55 g, 0.008 mol) in H_2O (30 ml). After standing for 1.5 hr at 0°, sodium azide (0.52 g, 0.008 mol) in H_2O (60 ml) was added to the reaction mixture which was stirred for 8 hr at room temperature, at the end of which time the originally bright yellow color had been discharged to leave a white solid which was filtered, washed with H_2O, taken up in acetone, filtered, and evaporated to dryness. Crystallization from MeOH afforded colorless, fine matted needles: 1.1 g (50%); mp 104.5–105° (gas evolution); ir (KBr) 2130 cm^{-1} (N_3); NMR ($CDCl_3$) δ 7.09–7.98 (m, 10, aromatic); $M^{\cdot+}$ *m/e* 278 (16), 250 (100).

Anal. Calcd for $C_{15}H_{10}N_4S$: C, 64.84; H, 3.57; N, 20.12. Found: C, 64.73; H, 3.62; N, 20.13.

Thermolysis of 4-(2-Azidophenyl)-2-phenylthiazole (3, R = H; X = N). A solution of 4-(2-azidophenyl)-2-phenylthiazole (0.10 g, 0.00036 mol) in decalin (7 ml) was refluxed for 28 hr and cooled, giving a deposit of 0.05 g (54%) of light-brown, irregular prisms, mp 231–234.5°, identical[32] in all respects with 2-phenylthiazolo[5,4-*b*]indazole (**5**) obtained by deoxygenation of the corresponding nitro compound **3** (R = H; X = O).

Photolysis of 4-(2-Azidophenyl)-2-phenylthiazole. A solution of the above azide (0.19 g, 0.00067 mol) in benzene (50 ml) was irradiated at 300 nm for 18 hr, some gas evolution being noted. The solvent was removed by evaporation to afford 0.16 g (94%) of light-brown, irregular prisms, mp 236.5–237.5°, identical[32] in all respects with 2-phenylthiazolo[5,4-*b*]indazole (**5**) obtained by deoxygenation of the corresponding nitro compound.

Ethyl 2′-Nitrobenzoylacetate. A three-neck 500-ml round-bottom flask was fitted with a mechanical stirrer, reflux condensor, drying tube, and dropping funnel, and charged with Mg turnings (5.4 g, 0.22 g-atom). To this was added CCl_4 (0.5 ml) and absolute EtOH (5 ml). The ensuing reaction was allowed to run for several minutes, and a solution of anhydrous Et_2O (70 ml) and dry THF (80 ml) was added slowly with stirring. Next a solution of ethyl *tert*-butylmalonate[33] (41.4 g, 0.22 mol) in absolute EtOH (20 ml) and Et_2O (25 ml) was added over the course of 30 min and the mixture refluxed for 4 hr. A solution of 2-nitrobenzoyl chloride[29] (37.0 g, 0.20 mol) in Et_2O (50 ml) was added dropwise with stirring, and the mixture was refluxed for 30 min and left at room temperature overnight. A solution of concentrated H_2SO_4 (25 ml) in H_2O (200 ml) was added, and after stirring for 2 hr, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 75 ml). The combined organic fractions were washed with H_2O (2 × 250 ml) and saturated NaCl (1 × 150 ml), dried (Na_2SO_4), and evaporated to afford 67.7 g of ethyl *tert*-butyl-2′-nitrobenzoylmalonate as a clear yellow oil.

A portion of this oil (17.0 g, 0.55 mol) was heated at 100° (0.1 mm) for 1.5 hr, at the end of which time the small amount of colorless liquid that had distilled was discarded. β-Naphthalenesulfonic acid (0.01 g) was added to the residual yellow oil and heating was resumed at 100° (0.05 mm) for 2 hr to effect decarboxylation. Distillation then afforded ethyl 2′-nitrobenzoylacetate as a pale yellow liquid, bp 170° (0.1 mm): 11.0 g (93% based upon crude nitrobenzoyl malonate, 93% based upon 2-nitrobenzoyl chloride); ir (neat) 1740, 1700 cm^{-1} (CO); NMR ($CDCl_3$) δ 7.48–8.29 (m, 4, aromatic), 4.14 (q, 2, ethyl CH_2), 3.95 (s, 2, CH_2), 1.28 (t, 3, CH_3).

Ethyl 2-Bromo-2′-nitrobenzoylacetate. A solution of Br_2 (3.5 g, 0.022 mol) in CCl_4 (5 ml) was added dropwise with stirring to ethyl 2′-nitrobenzoylacetate (4.74 g, 0.02 mol) in CCl_4 (10 ml). The red color of the Br_2 was discharged instantaneously. Stirring was continued overnight at room temperature, and the mixture was washed with saturated aqueous $NaHSO_3$, then saturated aqueous $NaHCO_3$. The aqueous washings were extracted with $CHCl_3$ and the combined organic extracts were washed with H_2O (2 × 15 ml) and saturated aqueous NaCl, dried (Na_2SO_4), and evaporated to a pale orange oil which was dissolved in hot MeOH and cooled to deposit colorless prisms: 4.5 g (71.3%); mp 66–67.5°; ir (KBr) 1730, 1720 cm^{-1} (CO); NMR ($CDCl_3$) δ 7.44–8.39 (m, 4, aromatic), 5.17 (s, 1, CH), 4.27 (q, 2, CH_2), 1.29 (t, 3, CH_3); $M^{\cdot+}$ *m/e* 318 (0.5), 316 (0.5), 150 (100).

Anal. Calcd for $C_{11}H_{10}BrNO_5$: C, 41.79; H, 3.18; N, 4.43. Found: C, 41.39; H, 3.27; N, 4.44.

Ethyl 4-(2-Nitrophenyl)-2-phenylthiazole-5-carboxylate (3, R = COOEt; X = O). Ethyl 2-bromo-2′-nitrobenzoylacetate (6.32 g, 0.020 mol) in benzene (20 ml) was added dropwise with stirring under N_2 in the dark to a refluxing solution of thiobenzamide (6.0 g, 0.043 mol) in benzene (50 ml). The reaction mixture rapidly turned brown, slowly changing to orange, and eventually fading to pale yellow. Reflux was continued for 1 hr after completion of the addition and stirring was continued at room temperature under N_2 in the dark overnight. Filtration afforded ca. 5.0 g of pale orange solid which was triturated with absolute EtOH to leave a colorless solid which crystallized from CH_3CN as colorless, irregular prisms turning orange, then red upon exposure to light: 2.0 g (28%); mp 196–197°; ir (KBr) 1705 cm^{-1} (CO); NMR ($CDCl_3$) δ 7.52–8.45 (m, 9, aromatic), 4.27 (q, 2, CH_2), 1.19 (t, 3, CH_3); $M^{\cdot+}$ *m/e* 354 (20), 122 (100).

Anal. Calcd for $C_{18}H_{14}N_2O_4S$: C, 61.00; H, 3.98; N, 7.90. Found: C, 60.89; H, 4.10; N, 8.04.

The combined benzene and EtOH washings were concentrated and heated with Et_2O. Filtration afforded a heterogeneous solid which was found to consist mostly of elemental sulfur (ca. 0.8 g). The Et_2O solution, upon cooling, deposited 3.1 g of 3,5-diphenyl-1,2,4-thiadiazole as pink needles, mp 82.5–87°. It crystallized from Et_2O as colorless needles, mp 89–91° (lit.[19] mp 91–92°), $M^{\cdot+}$ *m/e* 238 (100).

$P(OEt)_3$ Deoxygenation of Ethyl 4-(2-Nitrophenyl)-2-phenylthiazole-5-carboxylate (3, R = COOEt; X = O). The nitrophenylthiazole (1.06 g, 0.03 mol) and $P(OEt)_3$ (4 ml, freshly distilled from sodium) in dry xylene (25 ml) were refluxed for 32 hr under N_2. The volatile components were removed by distillation (100°, 0.1 mm) and the reddish residue was chromatographed (silica gel, 25 g, eluted with benzene–$CHCl_3$) to afford a first fraction that crystallized from hexane as colorless, matted needles or colorless plates: 0.042 g (5%); mp 143–144.5°; ir (KBr) 1750 cm^{-1} (CO); NMR ($CDCl_3$) δ 8.01–8.42 (m, 3, aromatic), 7.32–7.62 (m, 5, aromatic), 7.21–7.25 (d of d, 1, aromatic), 4.63 (q, 2, CH_2), 1.44 (t, 3, CH_3); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 290 (100), M − CH_3 275 (26), M − C_2H_5O 245 (7), M − $C_3H_4O_2$ 218 (73), 129 (13), 105 (42), 102 (14).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65; mol wt, 290.32. Found: C, 73.98; H, 4.92; N, 9.43; mol wt, 290.1055 (mass spectroscopy).

The second fraction from the column, ethyl 3-phenylthiazolo[3,4-*b*]indazole-1-carboxylate (**7**, R = COOEt), crystallized from CH_3CN as maroon needles: 0.29 g (24%); mp 168–169°; ir (KBr) 1690 cm^{-1} (CO); λ_{max} ($CHCl_3$) 542 nm (log ϵ 3.92), 375 sh (3.86), 363 (3.90), 322 br sh (4.35), 306 (4.39), 269 (4.23); NMR ($CDCl_3$) δ 8.44–8.79 (m, 3, aromatic), 7.45–7.78 (m, 5, aromatic), 7.08–7.22 (m, 1, aromatic), 4.54 (q, 2, CH_2), 1.53 (t, 3, CH_3); $M^{\cdot+}$ *m/e* 322 (100), 294 (58), 249 (10), 161 (5), 146 (13), 121 (24), 102 (12), 177 (11).

Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 66.87; H, 4.33; N, 8.85.

Reaction of Ethyl 3-Phenylthiazolo[3,4-*b*]indazole-1-carboxylate (7, R = COOEt) with *N*-Phenylmaleimide. The tetravalent thiazole (0.101 g, 0.00031 mol) and *N*-phenylmaleimide (0.150 g, 0.0087 mol) in xylene (15 ml) were refluxed under N_2 for 17 hr, and the resulting solution concentrated to ca. 6 ml. Upon cooling, 1,2,3,4-tetrahydro-*N*,4-diphenyl-1,4-epithio-1-ethoxycar-

bonylpyrido[1,2-*b*]indazole-2,3-dicarboximide (12) separated as colorless prisms, 0.038 g (24%). Preparative thin layer chromatography (silica gel, 5 × 0.5 mm, eluted with benzene–$CHCl_3$–EtOAc, 7:7:1) afforded an additional 0.064 g (42%, total yield 65%) which crystallized as colorless prisms from EtOH: mp 218.5–220° dec (gas evolution); ir (KBr) 3265 (enolic OH), 1760, 1705 cm^{-1} (CO); λ_{max} (MeOH) 347 nm (log ϵ 3.31), 298 sh (3.38), 287 (3.50), 230 sh (3.45), 207 (3.91); NMR ($CDCl_3$) δ 12.50 (br s exchanged with D_2O, 1, enolic OH), 7.86–8.22 (m, 3, aromatic), 6.99–7.62 (m, 11, aromatic), 5.63 (s, 1, CH), 4.21 (m, 2, CH_2), 1.20 (t, 3, CH_3); $M^{\cdot+}$ *m/e* 495 (11), 461 (100).

Anal. Calcd for $C_{28}H_{21}N_3O_4S$: C, 67.86; H, 4.27; N, 8.48. Found: C, 67.45; H, 4.32; N, 8.52.

A second band consisting of *N*,4-diphenyl-1-ethoxycarbonylpyrido[1,2-*b*]indazole-2,3-dicarboximide (13) crystallized from EtOH as fine yellow, matted needles: 0.050 g (29%); mp 267–268°; ir (KBr) 1730, 1705 cm^{-1} (CO); λ_{max} (MeOH) 398 nm (log ϵ 3.87), 293 (4.35), 257 (3.99), 207 (4.26).

Anal. Calcd for $C_{28}H_{19}N_3O_4$: C, 72.87; H, 4.15; N, 9.11. Found: C, 72.72; H, 3.92; N, 9.16.

Base-Catalyzed Elimination of H_2S from *N*-Phenylmaleimide Adduct. To 1,2,3,4-tetrahydro-*N*,4-diphenyl-1,4-epithio-1-ethoxycarbonylpyrido[1,2-*b*]indazole-2,3-dicarboximide (12, 0.025 g, 0.00005 mol) in MeOH (3 ml) was added at room temperature methanolic sodium methoxide [prepared from sodium metal (0.02 g, 0.0087 g-atom) and MeOH (5 ml)]. An immediate dark reddish-brown color slowly faded to yellow, and after 30 min a yellow precipitate was collected by filtration. This material proved to be identical[32] with 13 obtained as described previously, 0.012 g (52%).

Thermolysis of *N*-Phenylmaleimide Adduct. 1,2,3,4-Tetrahydro-*N*,4-diphenyl-1,4-epithio-1-ethoxycarbonylpyrido[1,2-*b*]indazole-2,3-dicarboximide (12, 0.025 g, 0.00005 mol) in xylene (3 ml) was refluxed for 6 days. The solvent was removed by evaporation and the yellow residual solid crystallized from EtOH as fine, yellow, matted needles: 0.017 g (73%), identical[32] with 13 obtained as described previously.

Reaction of Ethyl 3-Phenylthiazolo[3,4-*b*]indazole-1-carboxylate (7, R = COOEt) with Dimethyl Acetylenedicarboxylate. The title thiazole (0.164 g, 0.0005 mol) and DMAD (0.25 g, 0.0018 mol) were refluxed in xylene (10 ml) under N_2 for 30 min. Volatile components were removed by distillation at 100° (0.1 mm), leaving a brown oil which was purified by preparative layer chromatography (silica gel, 4 × 0.75 mm, eluted with benzene–$CHCl_3$–EtOAc, 3:3:1) to give a pale yellow oil which was taken up in hot MeOH, cooled, and induced to crystallize by scratching. The 1:2 adduct 16 was obtained as colorless prisms: 0.252 g (82%); mp 112.5–113.5°; ir (KBr) 1730 cm^{-1} (CO); λ_{max} (MeOH) 265 nm sh (log ϵ 4.21), 225 (4.48); NMR ($CDCl_3$) δ 7.23–7.71 (m, 9, aromatic), 4.27 (q, 2, CH_2), 3.84 (s, 3, OCH_3), 3.80 (s, 6, OCH_3), 3.62 (s, 3, OCH_3), 1.05 (t, 3, CH_3); $M^{\cdot+}$ 606 (20), 533 (100).

Anal. Calcd for $C_{30}H_{26}N_2O_{10}S$: C, 59.40; H, 4.32; N, 4.62. Found: C, 59.10; H, 4.30; N, 4.59.

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Registry No.—2, 56929-93-2; 3 (R = H; X = O), 56929-94-3; 3 (R = H; X = H), 56929-95-4; 3 (R = H; X = N), 56929-96-5; 3 (R = COOEt; X = O), 56929-97-6; 5, 56929-98-7; 6, 56929-99-8; 7 (R = COOEt), 56930-00-8; 12, 56960-33-9; 13, 56930-01-9; 16, 56930-02-0; thiobenzamide, 2227-79-4; 2-bromo-2′-nitroacetophenone, 6851-99-6; 3-aminooxindole hydrochloride, 43012-47-1; benzoyl chloride, 98-88-4; ethyl 2′-nitrobenzoylacetate, 52119-39-8; ethyl *tert*-butylmalonate 759-24-0; 2-nitrobenzoyl chloride 610-14-0; ethyl 2-bromo-2′-nitrobenzoylacetate, 56930-03-1; 3,5-diphenyl-1,2,4-thiadiazole, 4115-15-5; *N*-phenylmaleimide, 941-69-5; dimethyl acetylenedicarboxylate, 762-42-5.

References and Notes

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Macrocyclic Polyether Sulfide Syntheses. Preparation of Thia(crown-6, -7, and -8) Compounds[1,2]

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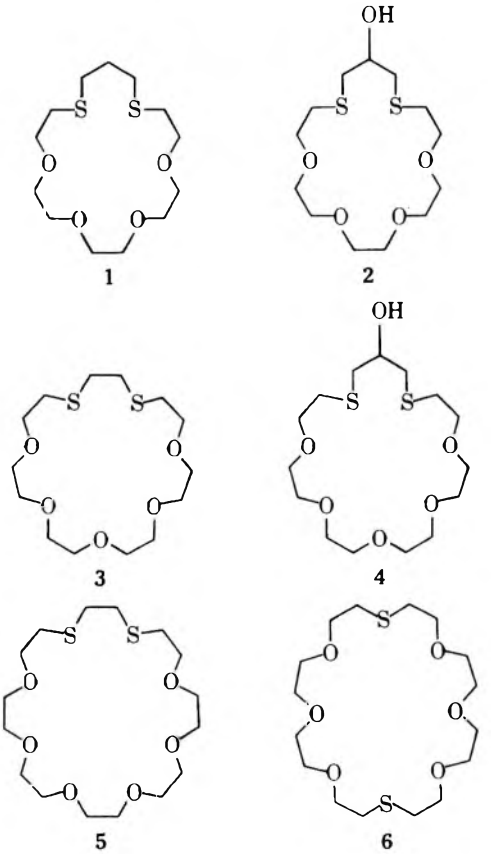
Macrocyclic polyether sulfides have been prepared by treating an oligoethylene glycol dichloride with a dimercaptan as reported in previous papers.[3,4] The following new compounds were prepared: 1,5-dithia(19-crown-6) (**1**); 3-hydroxy-1,5-dithia(19-crown-6) (**2**); 1,4-dithia(21-crown-7) (**3**); 3-hydroxy-1,5-dithia(22-crown-7) (**4**); and 1,4-dithia(24-crown-8) (**5**). 1,13-Dithia(24-crown-8) (**6**) which has previously been reported,[9] was also prepared.

In previous papers[3-5] we have reported the syntheses of sulfur-containing polydentate compounds including the thia(crown-3, -4, -5, -6, and -7) compounds. A calorimetric investigation[6] of the cation complexing properties of several of the thia(crown-5) compounds show them to form much more stable (as measured by log K) complexes in aqueous solution with Ag^+ and Hg^{2+} than with Tl^+ and Pb^{2+}. Also, 2:1 ligand–metal complexes are found for reactions of these cations with thia(crown-3, -4, and -5) ligands. Dalley and coworkers[7] have studied the crystalline structures of three of the thia(crown-4, -5, and -6) compounds. In each case, the larger sulfur atoms were directed away from the ring cavity. We are interested in investigating the cation selectivities of the larger crown rings containing one or at the most two sulfur atoms. We have, therefore, synthesized (see Chart I) thia(crown-6, -7, and -8) compounds

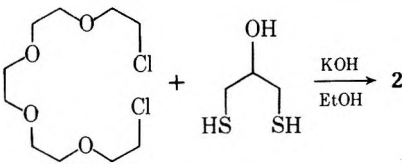
Chart I



with two sulfur atoms, namely, 1,5-dithia(19-crown-6) (**1**),[8] 3-hydroxy-1,5-dithia(19-crown-6) (**2**), 1,4-dithia(21-crown-7) (**3**), 3-hydroxy-1,5-dithia(22-crown-7) (**4**), and 1,4-dithia(24-crown-8) (**5**). In addition, we prepared 1,13-dithia(24-crown-8) (**6**), which was previously reported.[9] The determination of log K, $\Delta H°$, and $\Delta S°$ values for the reactions of these compounds with metal ions is underway. This paper reports on their synthesis.

Results and Discussion

The compounds shown in Chart I were prepared from the appropriate dimercaptans and oligoethylene glycol dichlorides. For example, compound **2** was prepared from 1,3-dimercapto-2-propanol and pentaethylene glycol dichloride.[3,9]



The reactions were carried out in ethanol using potassium or sodium hydroxide as a base. Since the mercaptan is a stronger acid than alcohol or water[10] and the resulting sulfide is a stronger nucleophile than the oxide,[11] we would expect only the sulfide products. Running the reaction at high dilution ensures a good yield of the cycloaddition products.[9] The yields varied from 5% for compound **5** to 24% for compound **1**. Because of their high boiling points, these compounds were isolated by column chromatography.

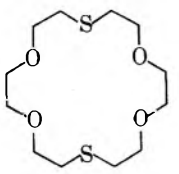
Most of the starting materials used in this study were readily available. However, hexaethylene glycol and heptaethylene glycol were prepared by reacting di- and triethylene glycol dichloride with diethylene glycol and sodium.[12] The yield of these was poor (27–34%).

$$Cl(CH_2CH_2O)_nCH_2CH_2Cl + 2NaOCH_2CH_2OCH_2CH_2OH \longrightarrow HO(CH_2CH_2O)_{n+4}CH_2CH_2OH$$

n = 1 and 2 n = 1 and 2

The structures of all crown products were consistent with those derived from the NMR spectra, elemental analyses, and in most cases molecular weight determinations. The NMR spectra exhibited peaks at δ 2.73 ± 0.01 (triplet, CH_2 α to sulfur but β to oxygen), 2.84 ± 0.01 (singlet, ethylene between sulfur atoms for compounds **3** and **5**), and 3.65 ± 0.05 (CH_2 next to oxygen). In addition the middle CH_2 of the propylene moiety in compound **1** exhibited a peak at δ 1.95. Hydroxy bands were observed in the ir spectra for compounds **2** and **4**.

In the x-ray diffraction structural studies of 1,10-dithia(18-crown-6) (**7**), Dalley and co-workers found that the donor atoms were nearly coplanar and they formed an elliptical cavity. The molecule is located about a center of



7

symmetry with the sulfur atoms directed out of the cavity. The shortest distance across the cavity, 4.6 Å, is between the symmetry-related oxygen atoms.[7]

The important aspect of the structure is the fact that the sulfur atoms are directed away from the cavity. This fact is in harmony with the structure determinations for polyethylene oxide and polyethylene sulfide. Tai and Tadokoro found that polyethylene oxide has a helical form while the polyethylene sulfide has a glide form.[13] They attribute this to differences in bond lengths of the C–O (1.43 Å) and C–S (1.815 Å) bonds and in the van der Waals radii for oxygen (1.52 Å) and sulfur (1.85 Å) atoms. Thus it is understandable that sulfur would be displaced from the normal cavity position of an oxygen atom. This may be beneficial in large thia(crown) compounds. Compound **3**, for example, could have a cavity size similar to that of 18-crown-6 but have quite different cation complexing properties owing to the presence of the sulfur atoms. Work is now in progress to determine the complexing properties of these compounds.

Experimental Section

All infrared (ir) spectra were obtained on a Perkin-Elmer 457 spectrometer. A Varian A-60A spectrometer was used to obtain the nuclear magnetic resonance (NMR) spectra. Elemental analyses and molecular weights were performed by M-H-W Laboratories, Garden City, Mich. Thin layer chromatography R_f values were obtained using Eastman 13181 silica gel sheets with fluorescent indicator and reagent chloroform as eluent.

General Synthesis. All macrocyclic polyether sulfides were prepared by treating oligoethylene glycol dichlorides with the appropriate dimercaptans in base as previously reported.[3,4] We used chloroform to dilute the initial reaction residue rather than ether. The starting materials were used as purchased. The dihalides were prepared from the corresponding glycols:[3,4] 1,11-dichloro-3,6,9-trioxaundecane (from tetraethylene glycol, Eastman Kodak), 1,14-dichloro-3,6,9,12-tetraoxatetradecane (from pentaethylene glycol, Columbia Organic Chemicals), 1,17-dichloro-3,6,9,12,15-pentaoxaheptadecane (from hexaethylene glycol), and 1,20-dichloro-3,6,9,12,15,18-hexaoxaeicosane (from heptaethylene glycol). All the dimercaptans were purchased from Aldrich Chemical Co. except 1,3-propanedithiol, which was made from 1,3-dichloropropane by the method of Urquhart.[14]

1,20-Dihydroxy-3,6,9,12,15,18-hexaoxaeicosane (Heptaethylene Glycol).[12] To diethylene glycol (500 g, excess) at 70°C was added sodium metal (69 g, 3 mol) in parts with stirring under N_2 gas. The heating mantle was removed as the sodium was added and the temperature rose to 180°C during the exothermic reaction. After all the sodium dissolved, the solution was allowed to cool to 110°C and triethylene glycol dichloride (290.2 g, 1.55 mol) was added rapidly. Then the temperature was raised to 170°C until a neutral pH was achieved (1.5 hr). The mixture was cooled to room temperature and filtered through a fritted glass filter. The filtrate was continuously extracted with anhydrous ether on a liquid–liquid extractor equipped with a drying tube (5 days). The ether extract was decolorized with Norit A and the ether was removed on a rotary evaporator. Some diethylene glycol was recovered by distillation, bp 130–140°C (15 mm). The yellow, then later dark-brown, liquid product (95.96 g, 0.29 mol, 19%) was then collected, bp 224–234°C (0.5 mm) [lit. 241–244°C (0.6 mm)].[15] Another run gave a 27% yield. The NMR spectrum exhibited peaks at δ 3.65 (s, 28 H, $HOCH_2CH_2OCH_2$) and 2.95 (s, 2 H, $HOCH_2CH_2O$).

1,17-Dihydroxy-3,6,9,12,15-pentaoxaheptadecane (Hexaethylene glycol).[12] This compound was prepared as above from diethylene glycol, sodium, and diethylene glycol dichloride to give a 34% yield, bp 180–190°C (0.7 mm) [lit. 203–205°C (0.3 mm)].[15] The ir and NMR spectra were consistent with the assigned structure.

Preparation of Thia(crown) Compounds. 1,5-Dithia(19-crown-6) (8,11,14,17-Tetraoxa-1,5-dithiacyclononadecane, 1). 1,14-Dichloro-3,6,9,12-tetraoxatetradecane [15 g, 0.054 mol, bp 90–95°C (0.08 mm)] and 1,3-propanedithiol [5.9 g, 0.055 mol, bp 90°C (95 mm)] were mixed with 200 ml of absolute ethanol and added slowly to a stirred solution of an excess of sodium hydroxide in 400 ml of absolute ethanol. The reaction produced 14 g of residue. The residue (3 g) was purified by chromatography on 60 g of alumina (washed with ethyl acetate and dried at 120°C for 48 hr). The column was eluted with 100 ml of hexane and then with 100-ml portions each of 10% chloroform in hexane (v/v), 20, 30, 40, and 50% chloroform, and then 200 ml of pure chloroform. Product 1 (0.85 g, 24%) was found in the 40% chloroform fraction as a viscous oil: R_f 0.70; NMR δ 3.74 (t, 4 H, OCH_2CH_2S), 3.65 (s, 12 H, OCH_2CH_2O), 2.75, (m, 8 H, CH_2SCH_2), and 1.95 (m, 2 H, $SCH_2CH_2CH_2S$). The other fractions (2.1 g) contained mixtures of starting materials and product. No further work was done on these fractions.

Anal. Calcd for $C_{13}H_{26}O_4S_2$: C, 50.29; H, 8.44; S, 20.65; mol wt, 310.48. Found: C, 50.33; H, 8.62; S, 20.73; mol wt, 320.

3-Hydroxyl-1,5-dithia(19-crown-6) (3-Hydroxy-8,11,14,17-tetraoxa-1,5-dithiacyclononadecane, 2). 1,14-Dichloro-3,6,9,12-tetraoxatetradecane (17 g, 0.062 mol) and 1,3-dimercapto-2-propanol (7.7 g, 0.062 mol) were treated as above, yielding 16.71 g of residue. The product (8%), purified by chromatography, was a viscous, pale yellow oil: R_f 0.61; NMR δ 3.76 (t, 4 H, OCH_2CH_2S), 3.68 (m, 14 H, $SCH_2CH(OH)CH_2S$, OCH_2CH_2O), and 2.84 (m, 8 H, $CH_2SCH_2CH_2O$).

Anal. Calcd for $C_{13}H_{26}O_5S_2$: C, 47.83; H, 8.03; S, 19.64; mol wt, 326.47. Found: C, 47.61; H, 8.30; S, 19.41; mol wt, 315.

1,4-Dithia(21-crown-7) (7,10,13,16,19-Pentaoxa-1,4-dithiacycloheneicosane, 3). 1,17-Dichloro-3,6,9,12,15-pentaoxaheptadecane [20.06 g, 0.0627 mol, bp 159–162°C (0.3 mm), lit. 146.5–148°C (1 mm)[12]] and 1,2-ethanedithiol (5.91 g, 0.0627 mol) were treated as before to give 18.14 g of residue. Compound 3 (10%) was purified by chromatography and was a viscous, pale yellow oil: R_f 0.69; NMR δ 3.66 (m, 20 H, $SCH_2CH_2OCH_2CH_2O$), 2.85 (s, 4 H, SCH_2CH_2S), 2.74 (t, 4 H, SCH_2CH_2O).

Anal. Calcd for $C_{14}H_{28}O_5S_2$: C, 49.38; H, 8.29; S, 18.83; mol wt, 340.50. Found: C, 49.26; H, 8.22; S, 18.62; mol wt, 340.

3-Hydroxy-1,5-dithia(22-crown-7) (3-Hydroxy-8,11,14,-17,20-pentaoxa-1,5-dithiacyclodocosane, 4). 1,17-Dichloro-3,6,9,12-15-pentaoxaheptadecane (32.1 g, 0.10 mol) and 1,3-dimercapto-2-propanol (12.4 g, 0.10 mol) were treated as for compound 1 to yield 54.11 g of residue. Compound 4 (15%) was purified by chromatography and was a viscous, pale yellow oil: R_f 0.60; NMR δ 3.65 (m, 22 H, $SCH_2CH(OH)CH_2S$, $SCH_2CH_2OCH_2CH_2O$), and 2.78 (m, 8 H, $CH_2SCH_2CH_2O$).

Anal. Calcd for $C_{15}H_{30}O_6S_2$: C, 48.62; H, 8.16; S, 17.31; mol wt, 370.53. Found: C, 48.63; H, 8.36; S, 17.49; mol wt, 386.

1,4-Dithia(24-crown-8) (7,10,13,16,19,22-Hexaoxa-1,4-dithiacyclotetracosane, 5). 1,20-Dichloro-3,6,9,12,15,18-hexaoxaicosane [17 g, 0.0468 mol, bp 167–180°C (0.4 mm)] and 1,2-ethanedithiol (4.4 g, 0.0468 mol) were treated as for compound 1 yielding 7.35 g of residue. Product 5 (5%) was purified by chromatography and was a viscous tan oil: R_f 0.67; NMR δ 3.66 (m, 24 H, $SCH_2CH_2OCH_2CH_2O$), 2.85 (s, 4 H, SCH_2CH_2S), and 2.74 (t, 4 H, SCH_2CH_2O).

Anal. Calcd for $C_{16}H_{32}O_6S_2$: C, 49.97; H, 8.39; S, 16.68. Found: C, 49.80; H, 8.40; S, 16.81.

1,13-Dithia(24-crown-8) (4,7,10,16,19,22-Hexaoxa-1,13-dithiacyclotetracosane,[9] 6). Tetraethylene glycol dichloride (31.8 g, 0.137 mol) and tetraethylene glycol dimercaptan[4] (30 g, 0.133 mol) were treated as for compound 1 to yield 30 g of residue. The viscous, pale yellow liquid product (1%) was isolated using a silica gel column and eluting as above: R_f 0.63; NMR δ 3.70 (t, 4 H, OCH_2CH_2S), 3.64 (s, 20 H, OCH_2CH_2O), and 2.77 (t, 8 H, CH_2SCH_2).

Anal. Calcd for $C_{16}H_{32}O_6S_2$: C, 49.97; H, 8.39; S. 16.68. Found: C, 50.22; H, 8.66; S, 16.49.

Registry No.—**1**, 56930-34-8; **2**, 56930-35-9; **3**, 56930-36-0; **4**, 56930-37-1; **5**, 56930-38-2; **6**, 297-13-2; heptaethylene glycol, 5617-32-3; diethylene glycol, 111-46-6; triethylene glycol dichloride, 112-26-5; hexaethylene glycol, 2615-15-8; diethylene glycol dichloride, 111-44-4; 1,14-dichloro-3,6,9,12-tetraoxatetradecane, 5197-65-9; 1,3-propanedithiol, 109-80-8; 1,3-dimercapto-2-propanol, 584-04-3; 1,17-dichloro-3,6,9,12,15-pentaoxaheptadecane, 52559-90-7; 1,2-ethanedithiol, 540-63-6; 1,20-dichloro-3,6,9,12,15,18-he-

xaoxaeicosane, 56930-39-3; tetraethylene glycol dichloride, 638-56-2; tetraethylene glycol dimercaptan, 2781-02-4.

References and Notes

(1) Presented at the 5th International Congress of Heterocyclic Chemistry, Ljubljana, Yugoslavia, July 13, 1975.
(2) Supported by the National Science Foundation Grant GP 33536-X and National Institutes of Health Grant GM 18811.
(3) J. S. Bradshaw, J. Y. Hui, B. L. Haymore, J. J. Christensen, and R. M. Izatt, *J. Heterocycl. Chem.*, **10**, 1 (1973).
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Loss of Water from Ketones in Isobutane Chemical Ionization Mass Spectrometry

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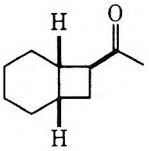
Isobutane CI mass spectra are reported for 38 ketones containing zero, one, or two carbon–carbon double bonds as the only additional functional groups. An enhanced loss of water in these compounds can be correlated with the structural feature that an allylic hydrogen atom be available and able to approach within 2 Å of the carbonyl oxygen. α,β-Unsaturated ketones fail to show enhanced loss of water, even when this feature is present. Experiments with deuterium-labeled ketones demonstrate that scrambling of hydrogen is rapid relative to loss of water.

Earlier examination of the isobutane chemical ionization (CI) mass spectra of the bicyclic ketones **1–6** revealed a noteworthy variation in the intensity of the $(M + 1 - 18)^+$ ions formed on loss of water from the protonated ketone.[1] Significant loss of water occurs only from the unsaturated, endo-substituted ketones **5** and **6**, and we suggested that this result reflected the availability in only these two members of the series of a reactive, allylic hydrogen atom which is accessible to the carbonyl oxygen atom. Through a six-membered (**5**) or seven-membered (**6**) transition state this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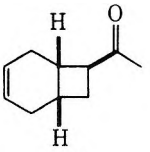
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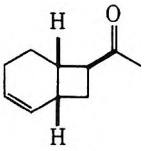
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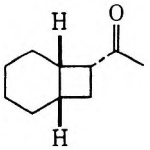
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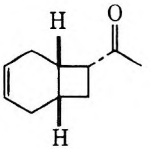
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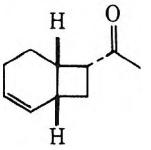
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allylic hydrogen could approach the protonated oxygen atom and be lost subsequently as water. These observations encouraged us to examine the CI mass spectra of a variety of other ketones in order to determine the generality of this process and to study the structural factors influencing it. The results, which are presented in Table I, are discussed below.

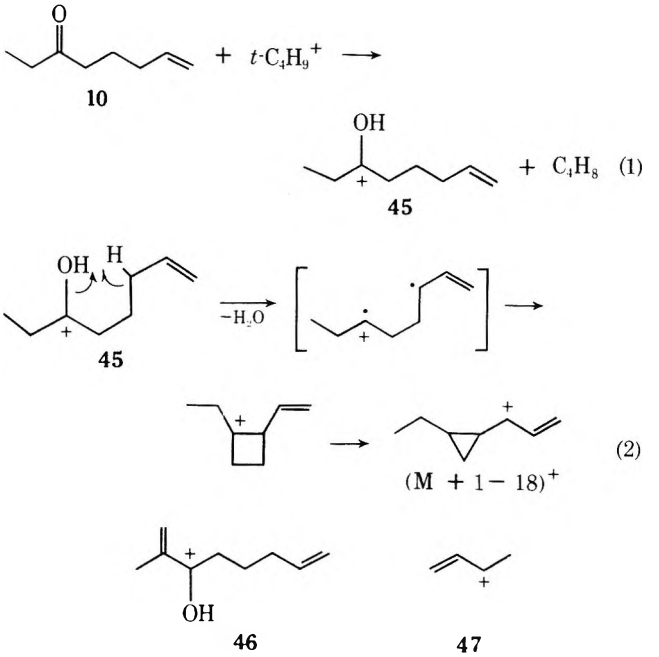
The data in Table I are from the isobutane CI mass spectra of 38 monoketones containing zero, one, or two carbon–carbon double bonds as the only additional functional groups. The results indicate that under these conditions enhanced loss of water can be correlated with three structural requirements. (1) Allylic hydrogens are necessary. Table I contains many pairs of ketones in which the only structural difference involved is the presence or absence of a double bond which provides activation for an appropriately placed (see below) allylic hydrogen. In nearly all cases there is a significant increase in intensity of the $(M + 1 - 18)^+$ ion when allylic hydrogen is present, and many of the ketones lacking the activating double bond show no detectable $(M + 1 - 18)^+$ ion at all.

(2) The allylic hydrogen must be geometrically accessible to the carbonyl oxygen atom. Loss of water occurs only in those ketones of Table I in which allylic hydrogen can approach oxygen closer than 2 Å, as measured on Dreiding models.[2] Thus no $(M + 1 - 18)^+$ ion is seen in **25** or **27**, in which the distance from oxygen to the β allylic hydrogen is ~2.3 or ~2.5 Å, respectively. Furthermore, there is a qualitative correlation between the intensity of the $(M + 1 - 18)^+$ ion and the expected facility with which the two centers can be brought together. Loss of water is greatest with γ allylic hydrogen, which requires a sterically and entropically favorable six-membered transition state. A related effect is apparent in ketones involving more distant allylic hydrogen. In both **22** and **40** a δ allylic hydrogen is present, but the $(M + 1 - 18)^+$ ion is nearly eight times as intense in **22**, in which the activating double bond is situated between the reacting centers rather than beyond the hydrogen atom as it is in **40**. This location of the double bond in **22** presumably facilitates formation of the seven-membered transition state by reduction of the available rotational degrees of freedom in the chain. A similar comparison may be made between **24** and **42**, where the allylic hydrogen is in the ϵ position. It is also noteworthy that for allylic hydrogen more distant than γ there is little effect of increasing number of methylene groups between the allylic hydrogen and the carbonyl group (compare **40**, **42**, **44**).

(3) The presence of a double bond conjugated with the carbonyl group prevents loss of water. This is true whether the double bond is involved in or independent of the allylic activation. Thus, while **10** shows a substantial $(M + 1 - 18)^+$ ion, introduction of an α methylene group to form **11** or **12** effectively suppresses this fragmentation. Mesityl oxide (**33**) and phorone (**34**) provide examples in which allylic activation of a favorably situated γ hydrogen is due to the conjugated double bond, but no significant loss of water occurs.

We have also determined the methane CI mass spectra of most of these ketones. Under these more energetic conditions none of the correlations discussed above is applicable. With methane as the ionizing gas compounds having only saturated hydrogen yield an $(M + 1 - 18)^+$ ion, and α,β-unsaturated ketones behave just as saturated or nonconjugated ketones. Thus, while both methane and isobutane CI mass spectra provide examples of extensive loss of water from ketones, only the milder conditions employing isobutane offer discrimination between saturated and unsaturated systems.

The failure of conjugated ketones to show loss of water in their isobutane CI spectra may result from the fact that on protonation they yield resonance-stabilized ions that are somewhat less reactive. This interpretation can be supported by mechanistic and thermochemical considerations. We suggest that the reaction in which water is lost from the ketones may be represented as shown in eq 1 and 2 for **10**. In



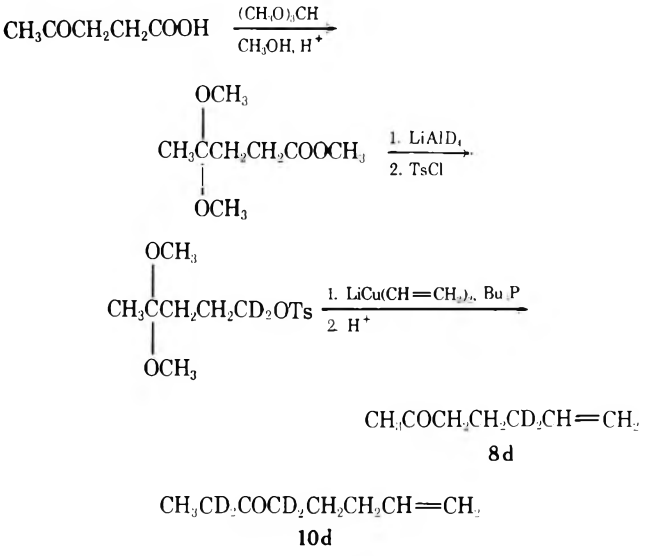
the case of an α,β-unsaturated ketone the ion produced by the reaction analogous to eq 1 may be represented by **46**, which is protonated **11**, and in which the charge is allylically stabilized. From tabulated values of heats of formation[3] one can show that a secondary allylic ion such as 1-buten-3-yl (**47**) is 19 kcal/mol more stable than a secondary alkyl carbonium ion such as 2-butyl. The difference in energies of **45** and **46** will be similar, although not identical because of the stabilizing effect of the hydroxyl group present in these ions. We suggest that the energy of ions such as **46** is sufficiently low markedly to inhibit their further decomposition as represented in eq 2.

The example used in eq 2 permits the formation of an $(M + 1 - 18)^+$ ion wherein stabilization is afforded by both allylic and cyclopropylcarbinyl interaction. For ketones in which the allylic hydrogen is farther removed from the carbonyl group, the cyclic ion analogous to that initially formed in eq 2 will be larger than cyclobutyl, and subsequent reactions of the ions will be different from those represented in eq 2. However, simple mechanisms, generally involving hydride shifts, are available whereby low energy allylic $(M + 1 - 18)^+$ ions may be formed. It should be noted that while these structural requirements suffice to account for nearly all of the results of Table I, there are exceptions. Ketones **36**, **37**, and **38**, all 2-isopropenylcyclohexanones, fail to show significant $(M + 1 - 18)^+$ ions, although by the above criteria they should do so. This structural type appears to involve considerations which are as yet undefined, although one possibility is that the cyclization step (eq 2) here would lead to a strained 1-bicyclo[4.2.0]octyl ion.

Other mechanisms can be written to account for loss of water in the isobutane CI spectra. For example, initial interaction of the required double bond with the protonated carbonyl group is attractive and has plausible analogy in the nucleophilic attack of an olefin on a carbonium ion, a process well known in solution chemistry. However, adoption of any mechanism involving specific participation of the double bond necessarily implies a different mechanism for loss of water in the methane CI spectra of saturated ketones. In the absence of information distinguishing the isobutane and methane processes mechanistically it seems preferable to write a single mechanism applicable to both.

With an interest in demonstrating directly that allylic hydrogen is lost in formation of the $(M + 1 - 18)^+$ ion, we prepared labeled **8d** from levulinic acid as shown in Scheme I, as well as α-labeled **10d** (84% d_4, 15% d_3) by treatment of **10** with potassium carbonate in ethanol-*O*-*d* containing deuterium oxide. Isobutane CI mass spectra of **8d** and **10d** showed approximately statistical loss of HOD, indicating that hydrogen scrambling is rapid relative to loss of water. Such rapid hydrogen scrambling prior to fragmentation precludes use of deuterium-labeled species as mechanistic probes.

Scheme I



Experimental Section

Materials and Equipment. Spectra were determined on samples purified by vapor phase chromatography using a Varian Aerograph Model 700 Autoprep or Model A-90-P3 with one of the following columns: A, 25% QF-1, 10 ft; B, 25% QF-1, 20 ft; C, 25% SE-30, 10 ft; D, 10% SE-30, 15 ft; E, 25% Carbowax 1500, 10 ft; F, 25% Carbowax 20M, 10 ft; G, 25% Carbowax 20M, 20 ft; H, 25% DEGS, 20 ft. All columns were prepared using 60–80 Chromosorb W in 0.375 in. aluminum tubing. The column oven was operated at 85–

Table I
Loss of Water from Ketones in Isobutane Chemical Ionization

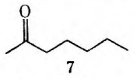
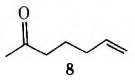
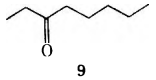
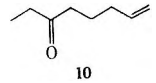
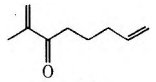
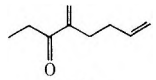
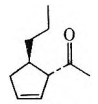
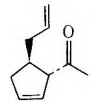
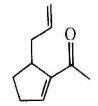
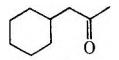
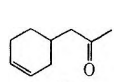
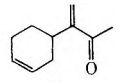
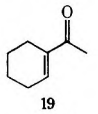
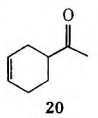
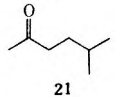
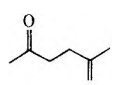
Structure	Mol wt	Rel intensity[a] $(M+1)^+$	Rel intensity[a] $(M+1-18)^+$	100 × $(M+1-18)^+/(M+1)^+$	Other major ions (>0.02) present, (rel intensity)[a]
 7	114	0.92			116 (0.065)
 8	112	0.77	0.174	23	114 (0.040)
 9	128	0.88			130 (0.066)
 10	126	0.75	0.13	17	128 (0.057)
 11	138	0.82	0.003	0.4	140 (0.094) 81 (0.025) 71 (0.024)
 12	138	0.79			140 (0.074) 111 (0.078)
 13	152	0.60	0.004	0.7	155 (0.040) 154 (0.089) 152 (0.038) 151 (0.055) 125 (0.021) 109 (0.084)
 14	150	0.55	0.072	13	152 (0.067) 150 (0.024) 133 (0.072) 107 (0.083)
 15	150	0.73	0.003	0.4	152 (0.069) 150 (0.032) 149 (0.057) 109 (0.033)
 16	140	0.87			142 (0.075)
 17	138	0.51	0.20	39	153 (0.046) 140 (0.046) 81 (0.032) 80 (0.038) 71 (0.027)
 18	152	0.88	0.004	0.4	152 (0.074)
 19	124	0.85			126 (0.062) 124 (0.029)
 20	124	0.79			126 (0.074) 124 (0.040) 81 (0.026) 71 (0.028)
 21	114	0.88	0.007	0.8	116 (0.059)
 22	112	0.61	0.23	37	114 (0.039) 112 (0.020) 95 (0.23)

Table I
(*Continued*)

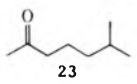
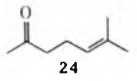
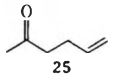
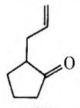
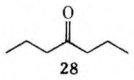
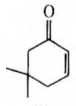
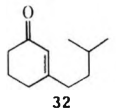
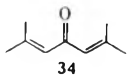
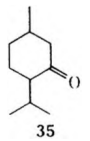
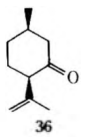
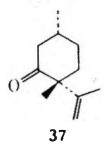
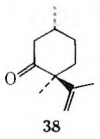
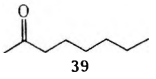
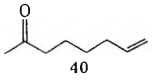
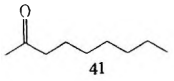
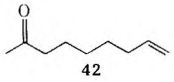
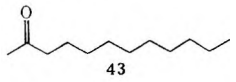
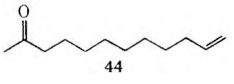
Structure	Mol wt	Rel intensity[a] $(M+1)^+$	Rel intensity[a] $(M+1-18)^+$	100 × $(M+1-18)^+/(M+1)^+$	Other major ions (>0.02) present, (rel intensity)[a]
 23	128	0.80	0.05	5.7	130 (0.065) 111 (0.046) 85 (0.026) 71 (0.041)
 24	126	0.64	0.21	33	128 (0.052) 126 (0.020) 108 (0.022) 71 (0.020) 69 (0.022)
 25	98	0.95			100 (0.045)
 26	126	0.88			128 (0.071) 126 (0.024)
 27	124	0.81			126 (0.073) 124 (0.029) 81 (0.025)
 28	114	0.88			116 (0.056) 71 (0.026)
 29	98	0.90	0.012	1.3	100 (0.059)
 30	112	0.88	0.003	0.3	114 (0.068) 112 (0.026)
 31	124	0.85			126 (0.079) 71 (0.025)
 32	166	0.82			168 (0.096) 71 (0.022)
 33	98	0.79	0.012	1.5	100 (0.047) 98 (0.036) 85 (0.022) 83 (0.028) 71 (0.027)
 34	138	0.72			140 (0.053) 83 (0.20)
 35	154	0.70	0.026	3.7	156 (0.078) 154 (0.027) 112 (0.033) 81 (0.020)
 36	152	0.73	0.004	0.5	154 (0.077) 152 (0.041) 81 (0.022)
 37	166	0.57			181 (0.10) 169 (0.024) 168 (0.077) 166 (0.028) 139 (0.051) 83 (0.024) 81 (0.020)

Table I
(*Continued*)

Structure	Mol wt	Rel intensity[a] (M + 1)+	Rel intensity[a] (M + 1 − 18)+	100 × (M + 1 − 18)+/(M + 1)+	Other major ions (>0.02) present, (rel intensity)[a]
 38	166	0.62			168 (0.063) 166 (0.029) 153 (0.070) 139 (0.033) 83 (0.020)
 39	128	0.93			130 (0.059)
 40	126	0.89	0.042	4.7	128 (0.059)
 41	142	0.92			144 (0.070)
 42	140	0.87	0.040	4.6	142 (0.064) 123 (0.040) 81 (0.022)
 43	184	0.81			186 (0.097) 85 (0.026) 71 (0.020)
 44	182	0.83	0.056	6.8	184 (0.078)

[a] Average of two scans.

200°, and helium carrier gas flow rate was 100–150 ml/min. Unless otherwise noted, ir and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian HR-200 (220 MHz) spectrometer. Solutions were dried over Na_2SO_4; melting points are corrected; boiling points are uncorrected. Mass spectra were obtained with a Du Pont 21-492 mass spectrometer at resolution 1000, source temperature 200°C, and 200 eV ionizing voltage. Samples were introduced via a glass batch inlet system at 200°C. Isobutane and methane reactants were Matheson Instrument Grade gas. The repellers were used to optimize the ion current, and were typically maintained at zero voltage. The pressure of the source could not be measured, but was about 0.5–1.0 Torr based on prior experience. The intensities reported have not been corrected for ^{13}C isotope contributions. Data were obtained with an AEI DS-30 to which our own CI programs have been added. A peak with relative intensity of 0.001 would typically be three times stronger than the computer threshold level.

Ketones **7**, **9**, **16**, **19**, **21–25**, **28–30**, **33–35**, **39**, **41**, and **43** were available commercially. Ketones **14–15**,[4] **17–18**,[4] **20**,[5] **26**,[5] and **27**[4] were on hand from previous investigations. The preparation of ketones **10**,[6] **31**,[7] **32**,[8] **36**,[9] **37–38**,[10] **40**,[11] **42**,[12] and **44**[12] has been previously described; the remaining ketones, **8**, **11**, **12**, and **13**, were synthesized as described below and were obtained as colorless oils.

6-Hepten-2-one (8). This compound was prepared by the method of LeBel and co-workers[11] and in the following way. A solution of levulinic acid (7 g) in 30 ml of dry methanol and 60 ml of methyl orthoformate was treated under nitrogen with 4 ml of acetyl chloride and then allowed to stand at room temperature for 72 hr. It was then poured into pentane containing excess solid anhydrous sodium carbonate and then allowed to stand overnight. Removal of the solid followed by evaporation of the pentane under reduced pressure left an oil (crude methyl levulinate dimethyl ketal) which was dissolved in 50 ml of ether and added dropwise under nitrogen to 2.0 g of lithium aluminum hydride. The reaction mixture was worked up with 15% aqueous sodium hydroxide[13] and the lithium salts were removed by filtration. Concentration of the solution under reduced pressure afforded 4,4-dimethoxy-1-pentanol in good yield; ir 3600–3200 (br), 2950, 2825, 1375 and 1050 cm^{-1}. The crude ketal alcohol was taken up in 25 ml of dry pyridine, 20 g of tosyl chloride in 10 ml of pyridine was added, and the mixture was then allowed to stand at 4° for 6 hr at which time crystals of pyridine hydrochloride were present. The mixture was poured into water and extracted three times with ether. The combined ether layers were washed with saturated sodium bicarbonate, 10% hydrochloric acid, and brine, then dried and evaporated to afford the tosylate: ir 3070, 2990, 2975, 2825, 1580, 1440, 1375, 1190, 1180 and 700 cm^{-1}.

Following the procedure of Johnson[14] a solution of 3 g (0.011 mol) of the tosylate in 5 ml of dry tetrahydrofuran was added to a stirred solution of lithium divinylcuprate tributylphosphine complex (0.020 mol).[15] The mixture was stirred at 0° for 2 hr, poured into saturated ammonium chloride, and then extracted with ether. The ether was dried and the solvent was removed through a Vigreux column. The oily residue was distilled to afford ketone 8 which was identical with an authentic sample:[11] ir 2990, 2980, 1715, 1640, 1380, 1180, 995, and 905 cm^{-1}; NMR δ 1.63 (m, 2 H), 2.01 (m, partially obscured by singlet, 2 H), 2.05 (s, 3 H), 2.36 (t, J = 6 Hz, 2 H), 4.95 (m, 2 H), and 5.71 (m, 1 H).

6-Hepten-2-one-*5,5-d*$_2$ (8d). The labeled ketone was prepared from levulinic acid exactly as ketone 8 except that lithium aluminum deuteride was used: ir 2965, 1715, 1640, 1405, 1360, 1160, 995, and 905 cm^{-1}; NMR δ 1.62 (t, J = 7 Hz, 2 H), 2.05 (s, 3 H), 2.34 (t, J = 7 Hz, 2 H), 4.93 (m, 2 H), 5.68 (dd, J = 15 and 10 Hz, 1 H); mass spectrum m/e 114.1019 (M^+, calcd for $C_7H_{10}D_2O$, 114.1014).

7-Octen-3-one-*2,2,4,4-d*$_4$ (10d). Ketone **10**[6,16] (~175 mg) was treated with a mixture of EtOD (6 ml), D_2O (2 ml), and K_2CO_3 (300 mg) under nitrogen for 24 hr. The mixture was extracted with pentane, dried, and evaporated to an oil. VPC purification on column D afforded ketone **10d**: ir 3080, 2980, 2940, 1720, 1640, 1450, 1400, and 900 cm^{-1}; NMR δ 0.98 (s, 3 H), 1.60 (t, J = 7 Hz, 2 H), 1.98 (m, 2 H), 4.90 (m, 2 H) and 5.67 (m, 1 H); mass spectrum m/e 130.1308 (M^+, calcd for $C_8H_{10}D_4O$, 130.1315).

2-Methylene-7-octen-3-one (11) and 4-Methylene-7-octen-3-one (12). These ketones were prepared from **10** using piperidine hydrochloride and 37% formalin according to a procedure previously described[5] for closely related compounds. Purification on column G yielded analytically pure samples of **12** and **11** in that order. Characterization data for **11**: ir 3075, 2975, 2920, 1685 (s), 1645, 1635, 1450, 1360, 1070, 980, 920. 905 cm^{-1}; NMR δ 1.69 (tt,

$J_1 = J_2$ = 7.5 Hz, 2 H), 1.83 (br s, 3 H), 2.06 (m, 2 H), 2.61 (t, J = 7.5 Hz, 2 H), 4.89–5.03 (m, 2 H), 5.65–5.83 (m, 1 H), 5.68 (m, 1 H), 5.85 (m, 1 H); mass spectrum m/e 138.1072 (M^+, calcd for $C_9H_{14}O$, 138.1044). Characterization data for **12**: ir 3080, 2980, 2940, 1685 (s), 1645, 1630, 1445, 1415, 1375, 1110, 985, 920, 905 cm^{-1}; mass spectrum m/e 138.1056 (M^+, calcd for $C_9H_{14}O$, 138.1044).[16]

Methyl *trans*-5-Propyl-2-cyclopenten-1-yl Ketone (13). A solution of 43 mg of the allyl-substituted ketone **14**[4] was hydrogenated (7 ml of hydrogen) at 1 atm in 2 ml of methanol containing a few milligrams of $Pd/BaSO_4$. Usual work-up and separation on column E afforded **13** as the major product: ir 1710 cm^{-1}; NMR δ 0.92 (t, J = 6 Hz, 3 H), 1.66 (m, 4 H), 1.68 (m, 1 H), 1.77 (m, 1 H), 2.05 (m, 4 H), 2.52 (m, 1 H), and 5.51 (m, 2 H); mass spectrum m/e 152.1201 (M^+, calcd for $C_{10}H_{16}O$, 152.1201).

Acknowledgment. This investigation was supported in part by National Institutes of Health research grant RR-862 from the Division of Research Facilities and Resources and by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**7**, 110-43-0; **8**; 21889-88-3; **8d**, 56960-41-9; **9**, 106-68-3; **10**, 39256-98-9; **10d**, 56960-42-0; **11**, 56960-43-1; **12**, 56960-44-2; **13**, 56960-45-3; **14**, 52358-90-4; **15**, 52502-24-6; **16**, 103-78-6; **17**, 24476-16-2; **18**, 52358-85-7; **19**, 932-66-1; **20**, 7353-76-6; **21**, 110-12-3; **22**, 3240-09-3; **23**, 928-68-7; **24**, 110-93-0; **25**, 109-49-9; **26**, 1187-87-7; **27**, 30079-93-7; **28**, 123-19-3; **29**, 108-94-1; **30**, 583-60-8; **31**, 4694-17-1; **32**, 29843-84-3; **33**, 141-79-7; **34**, 504-20-1; **35**, 10458-14-7; **36**, 17382-43-8; **37**, 23733-70-2; **38**, 57029-74-0; **39**, 111-13-7; **40**, 3664-60-6; **41**, 821-55-6; **42**, 5009-32-5; **43**, 6175-49-1; **44**, 5009-33-6; levulinic acid, 123-76-2; acetyl chloride, 75-36-5; methyl levulinate dimethyl ketal, 52128-61-7; lithium aluminum hydride, 16853-85-3; 4,4-dimethoxy-1-pentanol, 56960-46-4; tosyl chloride, 98-59-9; 4,4-dimethoxy-1-pentyl tosylate, 56960-47-5; lithium aluminum deuteride, 14128-54-2; EtOD; 925-93-9.

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Notes

The α Effect and Ring-Induced Acceleration of Hydrolysis at a Sulfinyl Center. Buffer and Nucleophile Effects in the Hydrolysis of Diphenyl Sulfite

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Received August 1, 1975

Although considerable work on the hydroxide ion and hydronium ion catalyzed hydrolyses of diaryl sulfites, including diphenyl sulfite (**1**), has been described,[1] to date there is a dearth of quantitative information on the susceptibility of the sulfinyl centers in these compounds to reaction with nucleophiles in general. Knowledge of the transition-state properties in the reactions of **1** with nucleophiles is fundamental to an understanding of the large enhancement seen in the value of k_{HO^-} (but not k_{H^+}) when the hydrolysis of catechol cyclic sulfite is compared to that of **1**. In addition, the mechanistic aspects of the sulfitase activity of pepsin attend clarification. In connection with the latter, some studies of the reactions of a series of carboxylate ion with **1** have been made but only over a limited pK range of catalysts. We now wish to report a study of the reactivity of **1** in water containing 9.1% (v/v) of CH_3CN at 25°C over a wide pH span and for a broad range of buffer species. The observed rate constants, k_{obsd}, for the hydrolysis of **1** catalyzed by the more basic buffers (e.g., carbonate) show contributions from first-order terms in hydroxide ion and the free base form of the buffer, but no catalysis by acidic buffer species. Thus, k_B (the second-order rate constant for attack by the free base form of the buffer) is obtained readily as the slope of a plot of the values of k_{obsd} vs. the concentration of buffer present as the free base. The intercept of this plot is the solvolytic rate constant (k_{solv}) for that pH. Less basic buffers (e.g., formate) show contributions to k_{obsd} not only from k_{solv} and k_B but also from catalysis by the acidic forms of the buffer (k_A). In these cases, the values of k_{solv} were obtained as the intercepts at zero buffer concentration of plots of k_{obsd} vs. total buffer concentration. The slopes of such graphs were replotted at a constant total buffer concentration against the mole fraction of buffer present in the free base state to give k_A and k_B, as illustrated in Figure 1 for formate buffer. Similar plots for more basic species such as carbonate showed k_A negligible compared to k_B. Values of k_A and k_B for the nucleophiles studied, along with additional data from the literature, are collected in Table I.

By plotting the values of k_{solv} calculated at zero buffer concentration vs. pH, the pH profile of Figure 2 was constructed for the hydrolysis of **1**. From a comparison with

Table I
Second-Order Catalytic Rate Constants for Basic and Acidic Buffer Catalysis of the Hydrolysis of 1 at 25° in 9.1% (v/v) CH_3CN Solutions[a]

Base	pK_a	k_A, M^{-1} sec^{-1}	k_B, M^{-1} sec^{-1}	Ref
OH^-	15.7[b]		7.93×10^4	This work
anti-α-Morphilino-acetophenone oxime	11.32[d]		$(1.62 \pm 0.13) \times 10^4$	This work
CO_3^{2-}	10.33[b]		51.7 ± 8.3	This work
Maleate	6.15[c]		9.5×10^{-3}	7
Hydroxylamine	6.0[c]		1.68	7
Acetate	4.77[c]		6.2×10^{-3}	7
Formate	3.77[b]	$(1.26 \pm 0.92) \times 10^{-5}$	$(5.74 \pm 0.15) \times 10^{-4}$	This work
Methoxyacetate	3.50[c]		6.35×10^{-4}	7
Chloroacetate	2.86[c]	3.3×10^{-5}	1.4×10^{-4}	7
H_2O	−1.7[b]		2.3×10^{-6}	This work[e]

[a] $\mu = 0.1$ except for morphilinoacetophenone oxime results where $\mu = 0.09$. [b] Taken from C. Long, Ed., "Biochemist's Handbook", Van Nostrand, Princeton, N.J., 1961. [c] Reference 7. [d] J. H. Smith, personal communication. [e] Computed from apparent k_{H_2O} of 1.3×10^{-6} sec^{-1}.

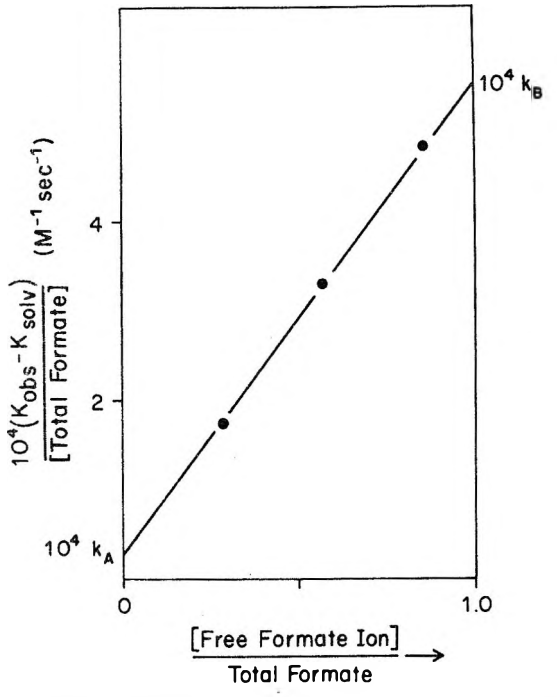

Figure 1. Separation of acidic and base catalytic rate constants in formic buffers for the hydrolysis of 1 at 25°, μ = 0.1, 9.1% (v/v) CH_3CN.

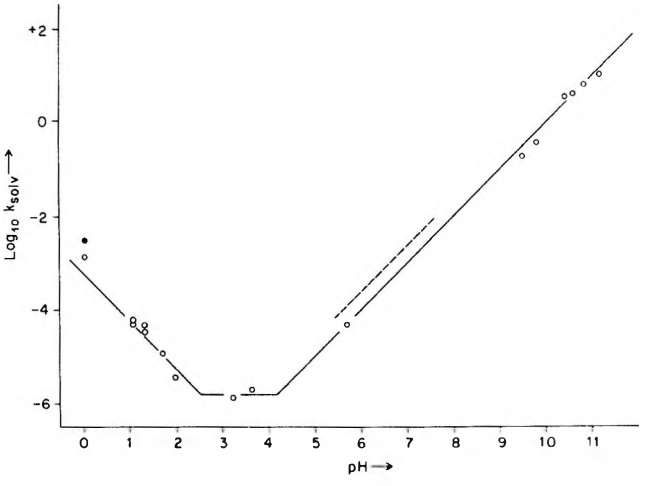

Figure 2. pH dependency of k_{solv} for the hydrolysis of 1 [25°, 9.1% (v/v) CH_3CN, solid line]. For comparison the results of de la Mare et al.[2] are included [25°, 1% (v/v) dioxane, dashed line].

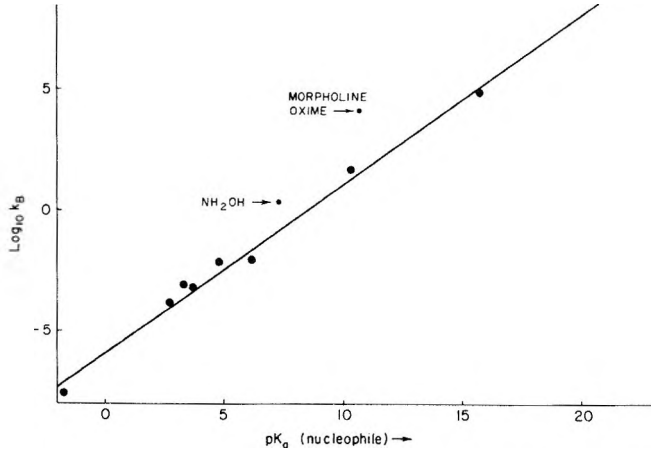

Figure 3. Bronsted plot for nucleophilic catalysis of the hydrolysis of 1. Data from Table I.

published data[2] it can be calculated that changing the medium from 9.1% CH_3CN (present study) to 1% dioxane[2] increases the magnitude of k_{OH^-} by only 2.8-fold. There is a small plateau between pH 3 and 4 seen in Figure 2 which gives the rate constant for the uncatalyzed attack of water on 1, $k_{H_2O} = 1.31 \times 10^{-6}$ sec^{-1} (Table I). In contrast, significant k_{H_2O} terms were not found for the hydrolysis of the alkyl sulfites ethylene sulfite and dimethyl sulfite,[3] an observation explained by the relative leaving tendencies of alcohols and phenols. From the reported value of k_{H_2O} (2.5×10^{-2} sec^{-1} at 25°) for catechol cyclic sulfite[2,4] the rate acceleration for the uncatalyzed hydrolysis of an aromatic five-membered cyclic sulfite as compared to its open-chain analogue[5,6] is computed as greater than 10^4.

Using the data in Table I, a Bronsted plot has been constructed for the k_B constants in the hydrolysis of 1. As can be seen from Figure 3, a line corresponding to eq 1 has been drawn through the points for all the oxygen nucleophiles, only hydroxylamine and *anti*-α-morpholinoacetophenone oximate ion being omitted from the correlation. The carboxylate ions have been shown to react nucleophilically with 1 in a previous study,[7] and based on the common Bronsted correlation it seems likely, though not certain, that a similar mechanism is involved in the reactions of the other oxygen buffers with 1.[8] Hydroxylamine and *anti*-α-morpholinoacetophenone oximate ion[9] react 86 and 133 times as rapidly as predicted on the basis of the Bronsted dependence. This behavior is typical of α nucleophiles but, as far as we are aware, the α effect has not been shown previously to operate at sulfinyl sulfur. Indeed, relatively little information is available in the literature concerning the α effect at sulfur–oxygen centers and that which does exist is solely for sulfonyl derivatives.[10,11]

In summary, the sulfinyl center is highly electrophilic in

diaryl sulfites even without the participation of ring effects. The reactivity of 1 is strongly affected by the nature of the attacking nucleophile and very marked α effects have been observed. Constraint of the sulfite ester group by its incorporation in a five-membered ring causes an even larger acceleration of the uncatalyzed hydrolysis reaction than of the hydroxide ion catalyzed one,[2] as evidenced by a comparison of the reactivity of catechol cyclic sulfite with 1.

Experimental Section

anti-α-Morpholinoacetophenone oxime[9] and freshly distilled diphenyl sulfite[12] were prepared as described in the literature. Morpholine was dried over KOH and distilled through a glass helix packed column (bp 129°). Acetonitrile was fractionally distilled from P_2O_5. All water used was deionized by passage through a Continental mixed-bed ion-exchange column. Water used in stopped-flow experiments was degassed by boiling for several minutes. Inorganic acids and buffer salts were analytical grade.

The reactions of 1 were followed either at 269 nm (pH <10) or at 287 nm (pH >10). The slower reactions were investigated using either Cary 15 or Gilford Model 222 recording spectrophotometers. Fast reactions were followed on a Durrum-Gibson stopped-flow spectrophotometer. Rate data were collected under pseudo-first-order conditions with the concentration of buffer species in large excess over that of the ester. Usually, data were analyzed using plots of log $(A_\infty - A_t)$ vs. time. However, for slower reactions the method of initial rates was adopted.

Acknowledgment. The support of this research by a grant from the National Science Foundation is gratefully acknowledged.

Registry No.—1, 4773-12-0; OH^-, 14280-30-9; CO_3^{2-}, 3812-32-6; H_2O, 7732-18-5; formate, 71-47-6; *anti*-α-morpholinoacetophenone oxime, 57031-42-2.

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(5) While a much higher value of k_{H_2O} (3×10^{-3} sec^{-1}) has been reported previously for 1,[6] the pH of the system studied was not stated, making this measurement questionable, as, even at pH 6, the k_{OH^-} contribution dominates the observed rate (see Figure 2).
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N-*tert*-Butylsulfonylcarbamates from *tert*-Butylsulfinyl Chloride and *N*-Hydroxycarbamates. Reaction Mechanism and Observation of CIDNP

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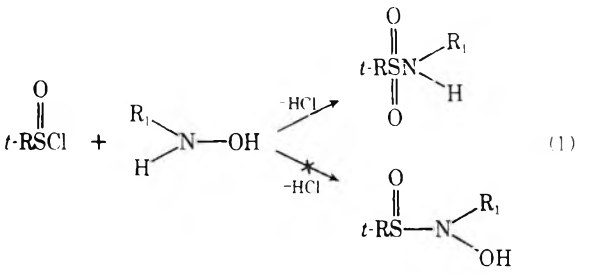
In 1972 Hovius and Engberts[1] reported that the reaction of *tert*-alkylsulfinyl chlorides with hydroxylamines led to formation of *tert*-alkylsulfonamides whereas the expected *N*-hydroxy-*tert*-alkylsulfinamides were not observed (eq 1). Although the mechanism of this oxygen transfer reaction has not been studied, among various possibilities, two mechanisms seem most reasonable: (a) nucleophilic attack of nitrogen on sulfur followed by rearrangement of the *N*-*tert*-alkylsulfinylhydroxylamine to the observed product via a nitrenium ion intermediate[2] and (b) nucleophilic attack of oxygen on sulfur to give an *O*-*tert*-alkylsulfinylhydroxylamine followed by rearrangement to the observed product via nitrogen–oxygen bond cleavage,[3] either heterolytically or homolytically.



(1)

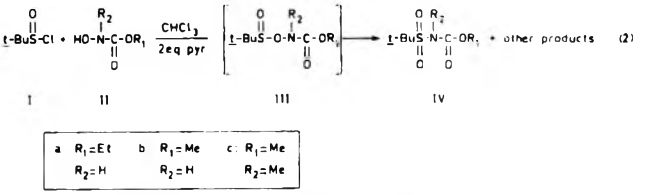
The present investigation was undertaken to determine whether *N*-hydroxycarbamates instead of the hydroxylamines undergo an analogous rearrangement reaction and, if so, whether NMR spectroscopic analysis of the reaction mixture before complete conversion could provide an understanding of the mechanism of the oxygen transfer from nitrogen to sulfur.

Results and Discussion

When *tert*-butylsulfinyl chloride (I) was allowed to react with ethyl *N*-hydroxycarbamate (IIa) in chloroform in the presence of 2 equiv of pyridine,[4] a smooth reaction occurred and ethyl *N*-*tert*-butylsulfonylcarbamate (IVa) was isolated in a yield of 35% after purification by thin layer chromatography. Similarly, reaction of methyl *N*-hydroxycarbamate (IIb) and methyl *N*-hydroxy-*N*-methylcarbamate (IIc) led to the corresponding *N*-*tert*-butylsulfonylcarbamates IVb and IVc in yields of 59 and 33%, respectively, as determined by NMR analysis of the final reaction mixtures. Major side products were characterized as methyl carbamate (VIb, 41%, from IIb), methyl *N*-methylcarbamate (VIc, 56%, from IIc), and *tert*-butylsulfonyl chloride (VIII, 23% from IIb and 41% from IIc).

In view of the smooth reactions of the *N*-hydroxycarbamates, an intermediate nitrenium ion, as implied by mechanism a, is highly improbable because of the destabilizing effect of the electron-attracting ester function attached to nitrogen. In addition, the fast reaction of IIc is difficult to reconcile with nucleophilic attack of nitrogen on sulfinyl sulfur.

In order to test for the occurrence of mechanism b (see eq 2) several NMR experiments were conducted in the



(2)

hope of directly observing intermediate III. Indeed, upon addition of I to a solution of IIb in chloroform-d_1 containing 2 equiv of pyridine, an almost instantaneous shift of the ester *O*-methyl signal from 3.73 to 3.78 ppm was observed together with the appearance of a new *tert*-butyl absorption at 1.29 ppm. This primary product, for which we propose structure IIIb, then slowly rearranges to IVb, the half-

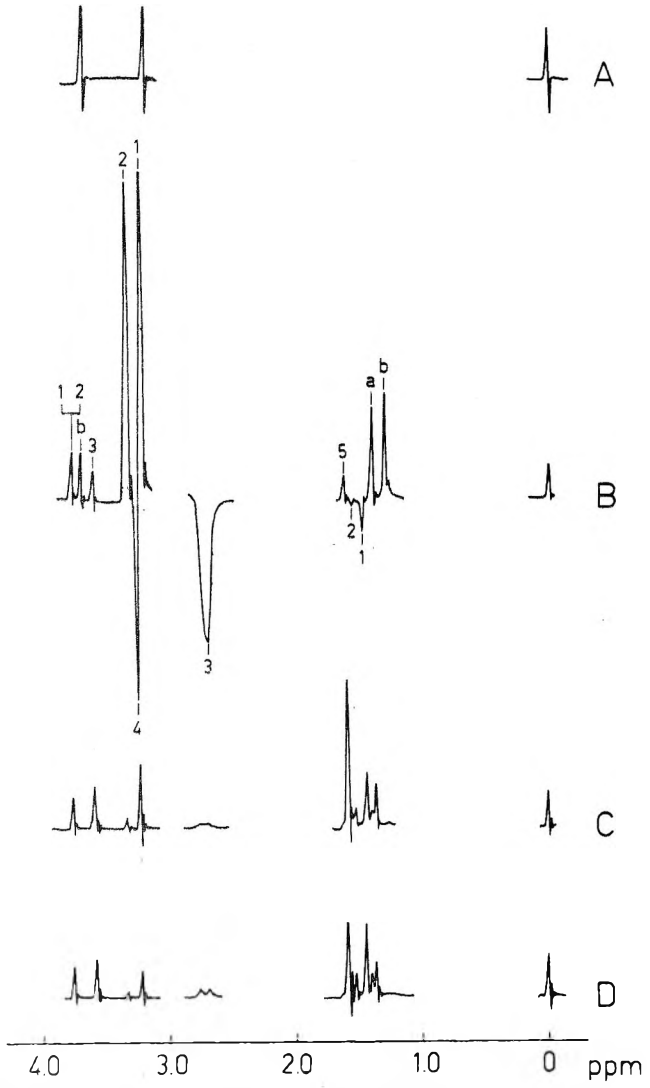


Figure 1. A, IIc in chloroform-d_1; B, CIDNP, 15 sec after addition of I to IIc (signal a is due to excess I, signals b are assigned to IIIc); C, CIDNP, 80 sec after addition of I to IIc; D, spectrum after complete reaction. For the assignment of the transitions 1–5, see Table I.

life of IIIb at probe temperature (ca. 30°) being 75 min. A similar experiment using IIc instead of IIb revealed two important differences. First, the rearrangement of the intermediate IIIc is much faster ($t_{1/2}$ ca. 0.4 min) than that of IIIb. Second, we observe pronounced proton CIDNP (chemically induced dynamic nuclear polarization) effects[5] during conversion of IIIc to the various products in the probe of an NMR spectrometer. We suggest that these results are best accommodated by assuming a thermally induced homolytic cleavage of the nitrogen–oxygen bond of IIIc, resulting in the formation of a radical pair. Apparently, the radical pair from IIIc is sufficiently long lived to allow significant nuclear spin dependent singlet–triplet mixing to occur. Spin selective recombination of this radical pair and diffusion followed by subsequent reaction leads to several products which possess polarized NMR signals (Figure 1). The assignment of transitions 1–5 (Figure 1) to the various reaction products derived from IIc and a description of the CIDNP net effects in the usual nomenclature[5] (A = enhanced absorption, E = emission, N = no polarization) are shown in Table I. The mechanism depicted in Scheme I is proposed to explain the experimental data.[6] The signs (Γ_{ne}) of the CIDNP polarizations are consistent with those predicted by Kaptein's rule[7] for a singlet precursor radical pair. For example, for the NCH_3 peak of

Table I
CIDNP Transitions and Chemical Shifts of Reaction Products Obtained from the Reaction of I with IIc

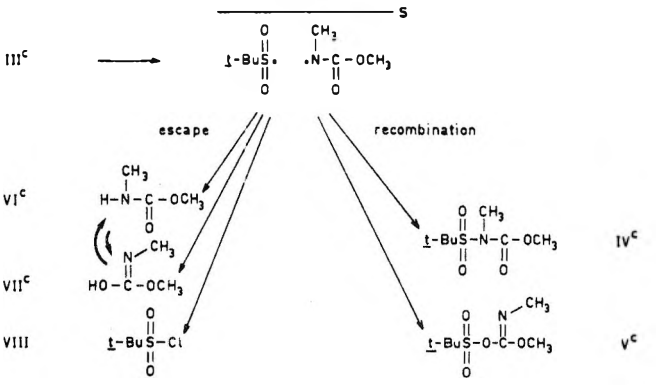
Transition[a]	δ[b] ppm	Proton assignment	CIDNP	Product
1	1.47 (s)	$(CH_3)_3C$	E	IVc
	3.26 (s)	CH_3N	A	IVc
	3.79 (s)	CH_3O	N	IVc
2	1.54 (s)	$(CH_3)_3C$	E	Vc
	3.38 (s)	CH_3N	A	Vc
	3.79 (s)	CH_3O	N	Vc
3	2.74 (s or d)[c]	CH_3N	E	VIc
	3.61 (s)	CH_3O	N	VIc
4	3.32 (s)	CH_3N	E	VII
5	1.60 (s)	$(CH_3)_3C$	A	VIII

[a] See Figure 1. [b] s = singlet, d = doublet. [c] Depending on the concentration of pyridine.

IVc, $\Gamma_{ne} = -+-+ = +$ (A, as observed experimentally) since $g_{\cdot N(CH_3)CO_2CH_3} < g_{t\text{-}BuSO_2\cdot}$[8,9] and $A_{H(NCH_3)}$ is positive. In addition, from the emission found for the *tert*-butyl peak of IVc it may be concluded that $A_{H(t\text{-}BuSO_2)}$ is positive, as expected.

A second recombination product (Vc, yield 11%, Scheme I), which exhibits similar net polarization effects as IVc, is

Scheme I



envisioned to arise as a result of coupling at the carbamoyl oxygen atom. The assignment of structure Vc is based upon NMR and ir spectroscopic data (see Experimental Section) and the formation of this product is reasonable in view of the known resonance interaction in free radicals of the amidyl type.[10]

As expected, the two major escape products, methyl *N*-methylcarbamate (VIc) and *tert*-butylsulfonyl chloride (VIII), showed NMR signals with polarizations opposite to those of the corresponding recombination products.

Finally, it is interesting to note that an emission peak was observed at 3.32 ppm which gradually disappeared until no peak was found after completion of the reaction. We suggest that the emission peak is due to the *N*-methyl group of the imidol VIIc. This product probably originates from escape of the amidyl radical from the initial radical pair followed by hydrogen abstraction by the oxygen atom. Unstable tautomers have been previously detected by CIDNP.[11] Further studies of the behavior of *N*-hydroxy compounds upon treatment with sulfinyl halides are in progress in order to further determine the generality of this type of reaction.

Experimental Section

Elemental analyses were carried out in the Analytical Department of this laboratory under the supervision of Mr. A. F. Hamminga. Melting points were determined using a Reichert melting point apparatus with a microscope attachment. A Varian A-60D spectrometer, using chloroform-d_1 as solvent and Me_4Si as internal standard, was used for the NMR spectra and ir spectra were measured with a Unicam SP 200 instrument.

The starting materials I[12] and IIa–c[13] were prepared according to literature procedures.

Reaction of I with IIa–c. To a stirred solution of 4 mmol of II and 8 mmol of pyridine in 50 ml of chloroform was added 4 mmol of I over a period of 15 min at room temperature. After stirring for an additional 4–6 hr, the chloroform solution was extracted twice with 20 ml of water. The chloroform layer was dried over Na_2SO_4 and the solvent was evaporated. The reaction products were separated by preparative TLC, using silica gel 60 PF and dichloromethane as eluent.

The new compounds IVa–c and Vc are described below; the other reaction products were all identified by comparison (ir and NMR spectral data and, for solids, mixture melting points) with authentic samples. *tert*-Butylsulfonyl chloride (mp 91–93°, lit.[14] 95°) was prepared according to a literature procedure.[14]

Ethyl *N*-*tert*-Butylsulfonylcarbamate (IVa) was obtained in a yield of 35% after crystallization from benzene–petroleum ether (bp 60–80°) as a white solid: mp 84.5–86°; NMR δ 1.27 (t, J = 7 Hz, 2 H, CH_2), 1.47 [s, 9 H, $(CH_3)_3C$], 4.13 ppm (q, J = 7 Hz, ester CH_3); ir (Nujol) 3280 (NH), 1740 (CO), 1325, 1135 (SO_2), 1285 cm^{-1}.

Anal. Calcd for $C_7H_{15}NO_4S$: C, 40.18; H 7.22; N, 6.69; S, 15.32. Found: C, 39.76; H, 7.37; N, 7.17; S, 15.84.

Carbamate IVa was prepared independently in a yield of 35% by using a procedure analogous to that given by Cassidy et al.[15] and starting from 1.3 mmol of *tert*-butanesulfonamide. Ir and NMR spectral data were identical with those given above.

Methyl *N*-*tert*-Butylsulfonylcarbamate (IVb). This carbamate was obtained as described for IVa, yield 59%: white solid: mp 98–101°; NMR δ 1.48 [s, 9 H, $(CH_3)_3C$], 3.79 ppm (s, 3 H, CH_3); ir (CH_2Cl_2) 3280 (NH), 1740 (CO), 1330 and 1130 cm^{-1} (SO_2).

Methyl *N*-Methyl-*N*-*tert*-butylsulfonylcarbamate (IVc). Following the above procedure, this carbamate was isolated as a colorless oil: NMR δ 1.47 [s, 9 H, $(CH_3)_3C$], 3.26 (s, 3 H, NCH_3), 3.79 ppm (s, 3 H, OCH_3); ir (CH_2Cl_2) 1730 (CO), 1345, 1130 (SO_2), 1285, 990, 940, 890 cm^{-1}.

Conversion of IVb into IVc. A freshly prepared solution of diazomethane in ether (ca. 0.2 mmol ml^{-1}) was added at 0° to a solution of 0.092 g (0.47 mmol) of IVb in 10 ml of methanol until the yellow color remained. After stirring for an additional 1 hr at room temperature, the ether and surplus of diazomethane were evaporated to yield IVc in a yield of 90%.

Methyl *N*-methyl-*tert*-butylsulfonyloxycarboximidate (Vc) was a colorless oil, obtained in a yield of 11%: NMR δ 1.54 [s, 9 H, $(CH_3)_3C$], 3.38 (s, 3 H, NCH_3), 3.79 ppm (s, 3 H, OCH_3); ir (CH_2Cl_2) 1720 (C=N), 1345, 1145 (SO_2), 945, 840 cm^{-1}.

CIDNP Experiments. A quartz NMR tube containing 0.030 (0.3 mmol) of IIc and 0.050 g (0.6 mmol) of pyridine in 0.6 ml of chloroform-d_1 was placed in the NMR probe and the spectrum was recorded. Then a slight excess (ca. 0.33 mmol) of I was added and the tube was shaken once. The transitions shown in Figure 1 were obtained by recording the spectrum 15 sec after mixing. After 5 min all signals had obtained normal porportions and no further changes in the NMR spectrum were observed.

Acknowledgment. Stimulating discussions with Dr. R. Kaptein are gratefully acknowledged.

Registry No.—I, 31562-43-3; IIa, 589-41-3; IIb, 584-07-6; IIc, 6092-56-4; IVa, 56908-56-6; IVb, 56908-57-7; IVc, 56908-58-8; Vc, 56908-59-9; VIc, 6642-30-4; VIII, 10490-22-9; diazomethane, 334-88-3.

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Synthesis of $\Delta^{2,2'}$-Bis(1,3-benzodithiolidine) Derivatives and Complex Salts Therefrom with 7,7,8,8-Tetracyanoquinodimethane

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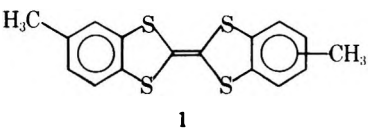
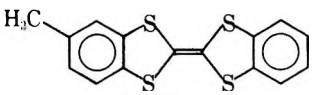
Sharp interest has recently been shown in the design and synthesis of some suitable organic metals[1] and prompts us to report our synthetic results. Several series of the charge-transfer salts including 1,3-dithiolidenes and related selenium analogues have been reported[2–5] and examined for their electrical properties.[2–7] Such charge-transfer salts of appropriate structure can afford organic solids with potential electrical conductivity.[1]

We have found that $\Delta^{2,2'}$-bis(5-methyl-1,3-benzodithiolidene) (1) and 5-methyl-$\Delta^{2,2'}$-bis(1,3-benzodithiolidine) (2)



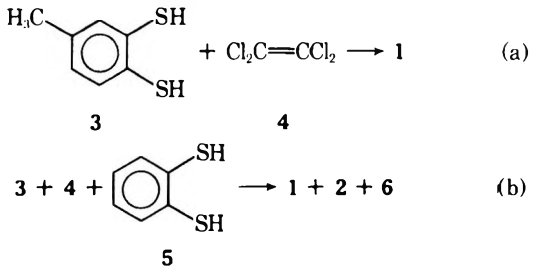
1



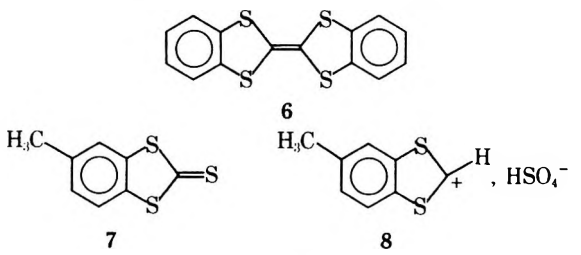
2

can be very conveniently prepared as shown in Scheme I in a and b, respectively. Although the yields are modest (33

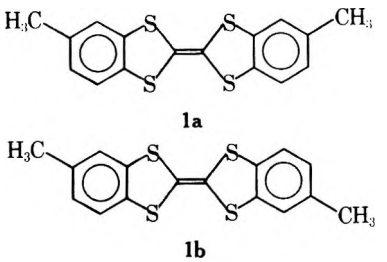
Scheme I



and 15%, respectively) the procedure is *one step* and simple, and the starting materials are commercial. Heretofore, ready access to an *unsymmetrical* benzodithiolidine like **2** has not been published. In spite of the observation that the reaction mixture in b contains **1** and apparently **6** (via mass



spectral analysis) it was possible to fractionally recrystallize out **2** from pyridine. To be sure, no physical or chemical property has permitted an unambiguous assignment of structure for **1** (the CH_3 groups could be in a syn or anti arrangement as in **1a** or **1b**) and a single-crystal x-ray examination seems the only alternative and is currently being investigated. A previous method involved a multistep process to give **1** in lower yield[8] (25% last step only) from **7** prepared by the condensation of **3** with CS_2 in aqueous sodium hydroxide. Desulfurization of **7** via heating with triethyl phosphite produced **1**.[8] Other conceivable approaches to **1** could involve deprotonation with tertiary amines of salts like **8**, potentially available from **7** via one of two published routes.[6,9] However, all attempts proved unfruitful for the preparation of **8**. A similar situation has been noted previously with certain other 1,3-dithiolium salts.[10,11]



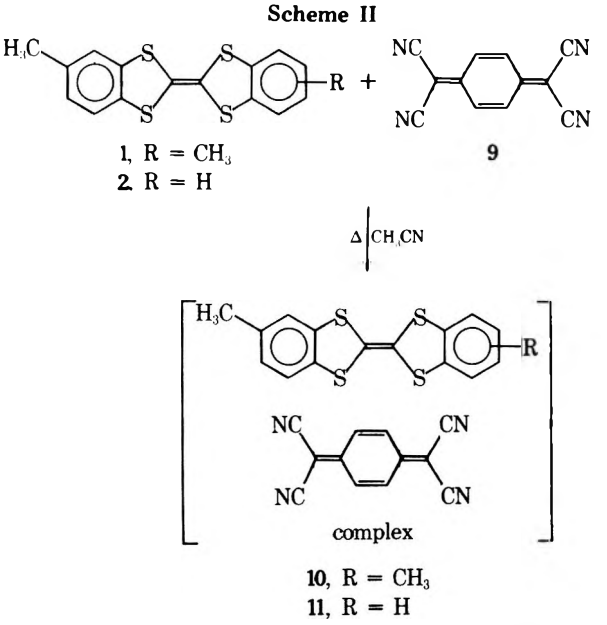
1a

1b

Complexes of **1** and **2** were easily obtained by first dissolving either compound in boiling acetonitrile and filtering the solution. A hot, filtered solution of 7,7,8,8-tetracyanoquinodimethane (**9**) was then freshly prepared. Upon mixing the hot solutions of **1** (or **2**) and **9** there was formed a dark, blue green solution from which, upon cooling, dark crystals formed in good yield (Scheme II). All analytical data support a 1:1 complex for **10** (and **11**).

Preliminary dc conductivity measurements on compacted samples of **10** and **11** were found to give resistivities of 1.28×10^6 and 2.5×10^6 Ω cm, respectively, at room temperature and 1.8 Kbar pressure, well within the range of organic solid state semiconductors.[12,13] The conductance was electronic rather than electrolytic as evidenced by (a) the increase of conductivity with hydrostatic pressure, (b) independence of the conductivity to the direction of long-continued current flow, and (c) its independence of the number of coulombs passed.

Scheme II



10, R = CH_3
11, R = H

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalysis were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

The infrared data were recorded from spectra taken on a Beckman IRA spectrophotometer. KBr disks were used for all spectra. The intensity notations used are vs, s, m, w, b, and vw to indicate bands of very strong, strong, medium, weak, broad, and very weak intensities, respectively. All bands are recorded in wavenumbers (cm^{-1}).

Nuclear magnetic resonance spectra were measured on a Varian XL-100 (15) spectrometer. Tetramethylsilane was used as the internal standard. Chemical shifts are expressed in δ values. Electrical conductivity was determined by a previously reported procedure.[14]

Preparation of $\Delta^{2,2'}$-Bis(5-methyl-1,3-benzodithiolidene) (1). This compound was synthesized by a considerable modification of a procedure used for the synthesis of $\Delta^{2,2'}$-bis(1,3-benzodithiolidene) (**6**) (low yield) from o-benzenedithiol and tetrachloroethylene.[15,16] Several variations in procedure gave positive results but procedure A gave the highest yield most consistently.

A. 3,4-Dimercaptotoluene (**3**, 2 g, 0.012 mol), tetrachloroethylene (**4**, 1 g, 0.006 mol), and *N,N*-diisopropylethylamine (10 ml) were heated under reflux for 7 hr. The color of the reaction mixture changed to yellow after 0.5 hr of heating. After the mixture cooled, it was allowed to stand overnight. A yellow solid formed and was removed by filtration and dissolved in boiling pyridine (30 ml). This hot solution was filtered through a fluted filter paper. The latter contained about 100 mg of Nuchar activated carbon on the surface. Upon cooling, yellow crystals formed and were removed by filtration to weigh 0.7 g (33%).

Two crystallizations from pyridine afforded pure **1** which melted at 260–262° (reported[8] mp 262°). The previous workers[8] recrystallized **1** from benzene, which proved unsatisfactory in our hands.

The infrared spectrum (KBr disk) of **1** showed absorptions at 3000 (vw), 2900 (vw), 1550 (w), 1445 (s), 1370 (w), 1250 (s), 1135 (w), 1115 (s), 1030 (b), 935 (w), 865 (w), 800 (vw), 780 (vs), 690 cm^{-1} (w). The nuclear magnetic resonance spectrum of **1** ($DCCl_3$) showed signals at the following δ values: 7.0–7.30 (6 H, multiplet, aromatic), 1.65 (6 H, sharp singlet, 2 CH_3).

B. 3,4-Dimercaptotoluene (**3**, 1 g, 0.006 mol) and tetrachloroethylene (**4**, 0.5 g, 0.003 mol) were heated under reflux in 15 ml of pyr-

idine for 17 hr. The reaction mixture was allowed to stand at room temperature overnight and then diluted with 4 ml of water. A turbid solution resulted which was cooled in a refrigerator for 3–4 hr. Yellow crystals separated and were filtered and found to weigh 150 mg (15%, mp 255–258°). There was no depression in the melting point of this product after mixing it with a sample of **1** from procedure A. The infrared spectrum (KBr disk) of this product was also identical with that of the authentic sample of **1**.

C. 3,4-Dimercaptotoluene (**3**, 1.2 g, 0.007 mol) and tetrachloroethylene (**4**, 0.6 g, 0.0036 mol) were heated under reflux in 10 ml of dimethylformamide for 7 hr. The reaction mixture was cooled and kept at room temperature overnight. Dark brown needles were formed which were removed by filtration and washed with ethanol (3 × 10 ml). The dried crystals weighed 0.8 g (yield 63%) but melted at 240–250°. The above solid was dissolved in 40 ml of chloroform without warming and then the solution was filtered. The filtrate was cooled in a refrigerator to afford slightly impure 0.4 g of yellow crystals the properties of which were identical in all respects with those for **1** previously prepared. Repeated recrystallization lowered the yield to about that of procedure B.

Synthesis of 5-Methyl-$\Delta^{2,2'}$-bis(1,3-benzodithiolidene) (2). 3,4-Dimercaptotoluene (**3**, 1 g, 0.006 mol) and 1,2-benzenedithiol (**5**, 1 g, 0.007 mol) were added to 20 ml of *N,N'*-diisopropylethylamine and stirred for 2–3 min. To this was added tetrachloroethylene (**4**, 1 g, 0.006 mol) and the contents were again stirred for 2–3 min. The reaction mixture while being stirred was heated under reflux for 12 hr. Upon cooling, the mixture was allowed to stand at room temperature overnight. An orange solid formed which was removed by filtration and dried to weigh 0.9 g (mp 189–210°).

From NMR analysis ($DCCl_3$), it appeared that this solid (mp 189–210°) contained compounds **1** and **2**, the former being estimated at 10–13% in it. However, the mass spectrum indicated that this solid was a mixture of three components: **1** (*m/e* 332), **2** (*m/e* 318), and **6** (*m/e* 304). This mixture was recrystallized from pyridine as below.

The mixture (0.6 g) was dissolved in hot pyridine (30 ml) and then filtered. The filtrate was cooled to room temperature and allowed to stand for 1–2 hr. Fine needles formed and were removed by filtration. This solid contained considerable amount of **1** in it as indicated by its NMR spectrum.

The filtrate was diluted with water until a faint turbidity appeared. This was boiled to clear solution and filtered, and the solution was allowed to stand at room temperature overnight. Orange crystals formed which were removed by filtration and dried. Two more crystallizations afforded 0.2 g (15% yield) of compound **2** which begins to shrink at 190° and melts at 207–210°.

Anal. Calcd for $C_{15}H_{10}S_4$: C, 56.61; H, 3.14; S, 40.25. Found: C, 56.54; H, 3.16; S, 40.46.

The infrared spectrum (KBr disk) shows absorptions at 3000 (vw), 1600 (vw), 1430 (s), 1360 (w), 1260 (w), (w), 1250 (w), 1140 1110 (s), 1020 (w), 930 (w), 875 (w), 800 (s), 770 (s), 750 (s), 690 (w), and 670 cm^{-1} (w).

An NMR spectrum ($DCCl_3$) has signals at the following δ values: 6.80–7.35 (7 H, multiplet, aromatic), 2.30 (3 H, sharp singlet, CH_3).

Synthesis of 5-Methyl-1,3-benzodithiole-2-thione (7). This compound was synthesized by a modification of a previous procedure[15] used for the synthesis of 2-thio-1,3-benzodithiole from the sodium salt of *o*-benzenedithiol. 3,4-Dimercaptotoluene (**3**, 1 g, 0.006 mol) was added to a solution obtained by dissolving sodium hydroxide (0.6 g, 0.015 mol) in 30 ml of water. To this was added carbon disulfide (2.0 g, 0.027 mol), and the reaction mixture was heated at reflux for 4 hr, cooled, and then let stand at room temperature overnight. A yellow solid formed and was filtered. The dried solid weighed 1.2 g and melted at 75–85°. Two recrystallizations from 95% ethanol afford 1.0 g (79% yield) of yellow needles which melted at 85–86° (reported[17] mp 84°).

The NMR spectrum ($DCCl_3$) of **7** (previously unreported) supported its structure with signals at δ 7.08–7.47 (3 H, multiplet, aromatic) and 2.38 (3 H, singlet, CH_3 aromatic). All attempts to convert **7** to **8** by general procedures in the literature[6,9] gave only very complex dark mixtures.

Synthesis of o-Benzenedithiol (5). Compound **5** was synthesized according to a previous procedure[18] except for the following modification.

Cuprous oxide was obtained from 100 g (0.40 mol) of $CuSO_4 \cdot 5H_2O$ according to a previous procedure.[19] The solid was washed with water (2 × 100 ml) and ethanol (2 × 100 ml), followed by decantation. This Cu_2O was filtered under suction and was immediately transferred to a 1-l., round-bottomed flask containing 500 ml of 95% ethanol. To this was added 1-butanethiol (22 g, 0.24 mol) in one lot and the mixture, while being stirred, was heated at reflux for 72 hr. It was filtered to afford 44.4 g of cuprous *n*-butyl mercaptide, slightly wet.

Cuprous *n*-butyl mercaptide (37 g, 0.24 mol) and 1,2-dibromobenzene (24 g, 0.10 mol) were heated in a mixture of quinoline (100 ml) and pyridine (40 ml) for 3.5 hr at 150–170°. The contents, while at 100°, were poured into 1000 g of ice and 200 ml of concentrated HCl. A yellow material formed and the mixture was stirred for 3 hr; then the water was decanted. The remaining mass was extracted with ether (3 × 100 ml.). It was allowed to stand at room temperature overnight and then the ether layer was separated by decantation. The ether layer was washed with 10% HCl (3 × 100 ml), water (3 × 100 ml), concentrated NH_4OH (2 × 100 ml), and then water (2 × 100 ml). After this, the ether layer was dried (K_2CO_3) overnight. The drying agent was filtered and the filtrate was concentrated (rotary evaporation). A yellow oil remained and was distilled at 127–130° (0.35 mm). Light yellow 1,2-bis(*n*-butylthio)benzene weighed 14.2 g (yield 55%) [reported[18a] bp 123–124° (0.3 mm)].

1,2-Bis(*n*-butylthio)benzene (5.1 g, 0.02 mol) was reduced with sodium (1.85 g, 0.08 g-atom) in 80 ml of liquid ammonia as described previously.[17] It afforded o-benzenedithiol (**5**) which weighed 1.5 g (51% yield) and distilled at 96–98° (5 mm) [reported[18b] bp 95° (5 mm)]. Solidification of yellow *o*-benzenedithiol occurred when kept in a refrigerator overnight. It melted at 28–29° (reported[20,21] mp 27–28°).

Synthesis of Charge-Transfer Complex 10. $\Delta^{2,2'}$-Bis(5-methyl-1,3-benzodithiolidene) (**1**, 30 mg, 9×10^{-5} mol) was dissolved by boiling in 110 ml of acetonitrile. The solution was filtered. In another flask, 7,7,8,8-tetracyanoquinodimethane (**9**, 50 mg, 24×10^{-5} mol) was dissolved in 15 ml of acetonitrile by heating and the solution was filtered.

The above filtered solutions of compound **1** and **9** were mixed together while hot. A green solution formed and was allowed to cool to room temperature and then kept at room temperature overnight. Dark needles appeared which were carefully filtered and washed several times with acetonitrile and dried. The yield of **10** was 40 mg (82% yield), mp 291–292°.

Anal. Calcd for $C_{28}H_{16}S_4N_4$: N, 10.44; S, 23.91. Found: N, 10.73; S, 24.27.

The infrared spectrum (KBr disk) of the compound shows absorptions at 3000 (vw), 2240 (s), 1575 (w), 1500 (w), 1425 (w), 1360 (broad), 1160 (s), 1130 (vw), 1100 (s), 855 (vw), 828 (s), 800 (s), 780 (s), 700 (w), 685 cm^{-1} (s). Unfortunately, the low solubility of **10** in all solvents examined prevented ^1H NMR analysis.

Synthesis of Charge-Transfer Complex 11. Compound **2** (20 mg, 9×10^{-5} mol) was dissolved in 50 ml of acetonitrile by boiling and then this solution was filtered. Compound **9** (60 mg, 29×10^{-5} mol) was dissolved in 30 ml of acetonitrile by boiling and then the solution was filtered. Both of these filtered, hot solutions were mixed together in one lot. The mixture was heated gently for 2–3 min and then allowed to stand at room temperature overnight. Blue crystals formed, were filtered, and were washed with acetonitrile (3 × 10 ml). The dried crystals of **11** weighed 30 mg (51% yield) and melted at 272–275°.

Anal. Calcd for $C_{27}H_{14}S_4N_4$: N, 10.64; S, 24.52. Found: N, 10.91; S, 24.75.

The infrared spectrum (KBr disk) showed absorptions at 3000 (vw), 2190 (s), 1575 (w), 1550 (s), 1450 (b), 1390 (b), 1180 (m), 1110 (m), 830 (m), 800 (m), 770 (m), 745 (s), 710 (w), 690 (w), 670 cm^{-1} (w). Again low solubility in all common solvents prevented a ^1H NMR examination.

Acknowledgment. We gratefully acknowledge support of this work by a grant from the 3M Co.

Registry No.—**1**, 41638-48-6; **2**, 57031-43-3; **3**, 496-74-2; **4**, 127-18-4; **5**, 17534-15-5; **7**, 54199-61-0; **9**, 1518-16-7; **10**, 54928-15-3; **11**, 57031-44-4; 1-butanethiol, 109-79-5; 1,2-dibromobenzene, 583-53-9; 1,2-bis(*n*-butylthio)benzene, 53663-38-0.

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Chemistry in Hydrogen Fluoride. Preparation of Aromatic Amides and Thioamides

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The electrophilic substitution reactions of aromatic compounds using a wide variety of substrates, electrophiles, and catalysts have been extensively investigated.[1] The direct introduction of the amide or thioamide moiety into an aromatic ring by electrophilic substitution has received little attention. Gattermann[2] observed formation of aromatic amides by the aluminum chloride catalyzed reaction of aromatic compounds with carbamoyl chloride.[3] More recently, Russian workers[4] observed the formation of aromatic amides in the reaction of aromatic hydrocarbons with alkali metal cyanate in concentrated sulfuric acid in the presence of aluminum chloride.[5] In this note the direct amidation and thioamidation of aromatic compounds with potassium cyanate or potassium thiocyanate using anhydrous hydrogen fluoride as solvent and catalyst are reported.

Aromatic amides were obtained by treating aromatic compounds with dry potassium cyanate in liquid HF at temperatures of 25–100°. The results are presented in Table I. In all cases the only organic materials observed were the monoamides and unreacted substrate with no tar formation. Control experiments demonstrated that the change in isomer ratio with temperature in the case of toluene was not due to isomerization of initially formed species at the higher temperature. With the more reactive aromatic compounds, anisole and toluene, replacement of the cyanate salt with potassium thiocyanate resulted in thioamide formation in high yield and moderate conversion (Table II).

A possible mechanism for the reaction is outlined in Scheme I. In a first step the cyanate salt reacts with HF to generate carbamoyl fluoride (1). Generation of the relative unstable carbamoyl fluoride (1, X = O) from reaction of KOCN with HF has been previously reported.[5] Subsequent acylation of the aromatic by 1 affords the observed products. The ability of HF to function as a Friedel–Crafts catalyst is well known.[1] Alternatively, partial amidation may occur via one or more intermediates in the reversible[5] for-

Scheme I

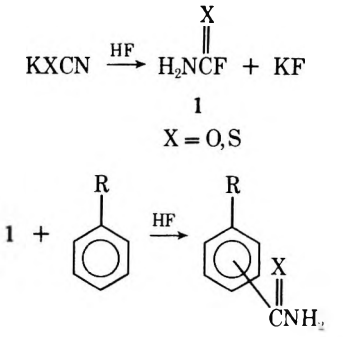

Table I
Reaction of Aromatic Compounds with Potassium Cyanate in HF

Substrate (mol)	Registry no.	KOCN, (mol)	Temp, °C	Conversion,[a] %	Product	Registry no.
Toluene (0.14)	108-88-3	0.030	100	70	45% o-toluamide[b]	527-85-5
					18% m-toluamide[b]	618-47-3
					37% p-toluamide[b]	619-55-6
Toluene (0.054)		0.040	25	50	26% o-toluamide[b]	
					74% p-toluamide[b]	
Benzene (0.17)	71-43-2	0.030	100	63	Benzamide[c]	55-21-0
Anisole (0.74)	100-66-3	0.050	25	42	34% o-anisamide[d]	2439-77-2
					66% p-anisamide[d]	3424-93-9
Naphthalene (0.05)	91-20-3	0.040	25	51	89% 1-naphthamide[e]	2243-81-4
					11% 2-naphthamide[e]	2243-82-5
Chlorobenzene (0.08)	108-90-7	0.040	100	9	Chlorobenzamide[f]	619-56-7
Fluorobenzene (0.08)	462-06-6	0.040	100	20	p-Fluorobenzamide[g]	824-75-9
Pyridine (0.10)	110-86-1	0.050	100			
Aniline (0.05)	62-53-3	0.050	100			
Benzotrifluoride (0.06)	98-08-8	0.05	100			

[a] Based on KOCN. [b] Analyzed by GLC (6 ft × 0.125 in. 10% SE-30 on Chromosorb W column at 175°). [c] Mp 127–128° (lit.[7] mp 132.5–133.5°). [d] Analyzed by NMR, ratios by integration of methoxy singlets. [e] Isomer distribution by GLC analysis (10 ft × 0.25 in. 10% Carbowax on Chromosorb W at 150°) of the methyl esters formed by acid hydrolysis of the crude product, followed by diazomethane. Unreacted naphthalene (3.7 g) was recovered. [f] Mostly para (by NMR), not quantitatively analyzed. [g] Mp 150–152° (lit.[8] mp 152–153°).

Table II
Reaction of Aromatic Compounds with Potassium Thiocyanate in HF

Substrate (g)	KSCN, g, mol	Temp, °C	Conversion,[a] %	Product (g)	Registry no.
Toluene (6.4)	4.9, 0.050	25	36	*p*-Methylthiobenzamide[b] (2.7)	2362-62-1
Anisole (7.6)	4.9, 0.050	25	61	*p*-Methoxythiobenzamide[c] (5.1)	2362-64-3
Benzene (5.5)	4.9, 0.050	25			

[a] Based on potassium thiocyanate. [b] Recrystallized from benzene–petroleum ether, mp 169–171° (lit.[9] mp 172°). [c] Recrystallized from benzene, mp 145–147° (lit.[10] mp 148.5–149.5°).

mation of 1 from KXCN and HF. These species might well have different selectivities. The striking difference in isomer distribution obtained in the reaction with toluene at 25 and 100° might be due to a change in the relative proportion of reactive species with temperature.

Several aspects of the data in Tables I and II deserve further comment. The isomer ratios and relative conversions obtained in the amidation reactions are, in general, normal for electrophilic aromatic substitution reactions.[1] In particular, the exclusive formation of *p*-fluorobenzamide from fluorobenzene is in line with previous observations[6] for this compound. The failure of aniline and pyridine to react is reasonable as their protonation in HF would result in strong deactivation toward electrophilic attack. The exclusive formation of the para isomers with the thiocyanate reagent may reflect a less reactive, more selective nature of this species relative to KOCN, although the greater size of the sulfur reagent relative to the oxygen reagent could account for the exclusive formation of the para isomers.

Experimental Section

General. Potassium cyanate and potassium thiocyanate (Fisher) were dried in a vacuum oven at 105°. Anhydrous hydrogen fluoride was obtained in a cylinder from Air Products and used as received. The aromatic substrates were reagent grade and used without purification. GLC analyses were performed on a Hewlett-Packard 5700 instrument with thermal conductivity detector using the indicated column and conditions. Peak areas are not corrected for relative detector response. Melting points were measured on a Thomas-Hoover melting point apparatus and are corrected.

Caution. Hydrogen fluoride is extremely corrosive to human tissue, contact resulting in painful, slow-healing burns. Laboratory work with HF should be conducted only in an efficient hood with operator wearing full face shield and protective clothing.[11]

Procedure. Reactions at room temperature were run in a 170-ml Kel-F vessel. Higher temperature reactions were run in an 80-ml Hastelloy pressure bomb. Potassium cyanate or thiocyanate (0.03–0.05 mol) and excess aromatic were introduced into the reaction vessel. The vessel was cooled in dry ice–acetone or liquid N_2, evacuated, and charged with 40 g of liquid HF. The vessel was closed, warmed to the reaction temperature, and shaken (Hastelloy bomb) or stirred (Kel-F vessel) for 4 hr. The HF and excess aromatic were removed by aspirator vacuum. The residue was partitioned between water and ether. The ether solution was dried ($MgSO_4$) and concentrated. The residue was analyzed by NMR, ir, and GLC comparison with authentic samples. Results are summarized in Tables I and II.

Registry No.—Potassium cyanate, 590-28-3; HF, 7664-39-3; potassium thiocyanate, 333-20-0.

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Synthesis of Tertiary Amines by Selective Diborane Reduction

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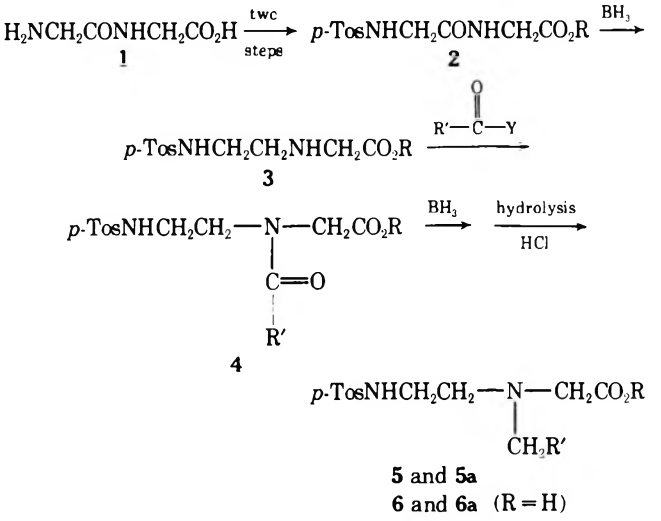
The preparation of tertiary amines containing functionality in the substituent groups has frequently presented a challenge to the synthetic organic chemist. A survey of the literature shows that there are few methods of preparing such tertiary amines and that many of them have limited scope, or poor yield, or both.[1] For example, the reduction of N,N-disubstituted amides with lithium aluminum hydride is one of the more common methods of preparing tertiary amines. The use of this reagent rather severely limits the type of functionality that can be permitted elsewhere in the amide. Also, an aldehyde is often obtained instead of, or along with, the desired amine.[2]

During the past 15 years, diborane has been developed as a reagent for reducing a variety of functional groups.[3] Its usefulness lies in the property that, while most functional groups can be reduced with the reagent, the rates of reduction vary greatly. This permits the reduction of certain groups in a polyfunctional molecule while leaving others intact, if conditions are properly chosen. The relative activity of diborane toward different functional groups is carboxylic acids and amides > olefins > ketones > nitriles > epoxides > esters > acid chlorides.[4] This order of reactivity suggests the possibility of reducing an amide with diborane to obtain an amine while leaving a variety of other functional groups untouched. Thus, with proper protection of a carboxyl function, an amide can be reduced to an amine that carries the carboxyl function.

The purpose of this paper is to suggest a new general approach, shown in Scheme I, to the synthesis of polyfunctional tertiary amines and to report the synthesis of *N*-ethyl-*N*-(2-tosylaminoethyl)glycine hydrochloride (**6a**) using this approach.

In the synthesis of **6a**, the starting material was glycylglycine **1** and it is necessary to protect both the amine and the carboxylic acid functions of this molecule. The amine function was protected by the tosyl group as the tosylamide is known to be inert to diborane reduction.[5] The choice of protecting group for the carboxyl function posed a greater problem.

Scheme I

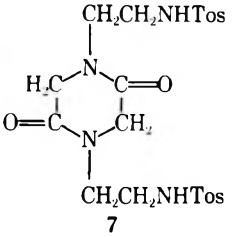


R = pentachlorophenyl, R′ = methyl
Y = acetoxy, a = hydrochloride salt

There are at least two reports of the use of diborane to reduce selectively amido esters[6] or peptides.[7] In the amido ester case, although monoreduction products (amino esters) were obtained, considerable amounts of completely reduced products were found. In the peptide case, the reagent was found to be unsatisfactory because in addition to obtaining the desired material, complete reduction of the peptide occurred and cyclic by-products also were found. In order to prepare a compound such as **5**, it appeared necessary to determine if it was possible to prepare an ester which would be inert to reduction by diborane while the amide was being reduced.

A preliminary investigation of several *N*-tosylglycine esters (ethyl, *tert*-butyl, triphenylmethyl, *p*-nitrophenyl, pentachlorophenyl) indicated that only the pentachlorophenyl ester was stable to excess diborane at room temperature and at 66°, giving no reduction to the *N*-tosylamino alcohol. The ester **2** was prepared from *N*-tosylglycylglycine and pentachlorophenol using dicyclohexylcarbodimide (DDC) as the coupling agent.[8] It was then treated with diborane using a one-hydride excess of BH_3 (calculated on the basis of reduction of amide carbonyl only). At room temperature there was no reduction of the amide carbonyl of **2**, but in refluxing tetrahydrofuran (THF), bp 66°, the amide carbonyl reduced readily to give **3** which was obtained as its relatively insoluble hydrobromide salt in 90% yield (crude). No completely reduced material (the amino alcohol) was found in the reaction mixture.

In the preparation of the *N*-acylamine **4** a problem arose because a diketopiperazine, **7**, formed very easily when **3**



7

was treated with triethylamine or when the free base of **3** was treated with acetic anhydride. To prevent the formation of **7** the free base was acylated without purification and the acetic anhydride was carefully distilled before use. Compound **4** was also unstable, giving **7**, and could not be easily purified.

The amide carbonyl in **4** was readily reduced with diborane at room temperature in excellent yield. Both the hydrochloride salt **6a** and the ester hydrochloride sale **5a** were obtained and were easily separated. Increasing the amount of 6 *N* hydrochloric acid used to decompose the reaction did not seem to change the ratio of **5a** to **6a**. The ester **5** was converted to **6** in near-quantitative yield, 98%, by saponification with sodium hydroxide.

These experimental results show that it is possible to reduce selectively an amide carbonyl in a compound containing both a protected amine and a protected carbonyl group. We suggest that the results from the second reduction (**4** → **5**) indicate that the proper choice of an acylating agent should allow the introduction of a third functional group into a tertiary amine. This would give a tertiary amine containing an amine function in one substituent, a carboxylic acid function in the second, and the third substituent group could contain another functionality unaffected by diborane or else it could be an alkyl group, as it is in the present case.

Experimental Section

General Methods. Thin layer chromatography (TLC) was carried out on Eastman silica gel chromatogram sheets with fluorescent indicator. NMR spectra were obtained using a Varian A-60 spectrometer or a Hitachi Perkin-Elmer R-20 high resolution NMR spectrometer and are reported in parts per million downfield from an internal standard of tetramethylsilane. Ir spectra were obtained using either a Perkin-Elmer 457 or 521 spectrophotometer. Mass spectra were obtained on a Perkin-Elmer 270 mass spectrometer. Solvents were dried over 3A molecular sieves. All melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. The 1 *M* BH_3–THF was purchased from Ventron Corp. and used as obtained. Elemental analyses were obtained by Galbraith Laboratories, Inc. All other chemicals were used as received unless otherwise indicated.

***N*-Tosylglycylglycine.** Tosyl chloride (24.4 g, 0.13 mol) was added in portions with stirring over 0.75 hr to a mixture of glycylglycine (15 g, 0.11 mol), triethylamine (36.6 ml, 0.29 mol), 180 ml of water, and 90 ml of tetrahydrofuran (THF). After the mixture had been stirred for 3 hr at room temperature, the THF was removed in vacuo. The solution was extracted with four 100-ml portions of ether. The aqueous layer was acidified with 12 *N* hydrochloric acid and extracted with three 200-ml portion of ethyl acetate. The extracts were combined, dried over $MgSO_4$, filtered, and reduced in volume. The white solid was filtered, washed with ethyl acetate, and air dried to give 30.3 g of *N*-tosylglycylglycine (85%, mp 172–173.5°, lit. mp 178–179° [9]): ir (Nujol) 3350, 3250, 1725, 1620 cm^{-1}; NMR (Me_2SO-d_6) 2.35 (s, 3, CH_3Ar), 3.40 (d, 2, J = 7 Hz, ($CNCH_2$), 3.69 (d, 2, J = 7 Hz, $SNCH_2$), 7–8.1 ppm (m, 6, Ar, both NH).

***N*-Tosylglycylglycine Pentachlorophenyl Ester (2).** DCC (5.55 g, 0.027 mol) was added to a stirred mixture of *N*-tosylglycylglycine (7.7 g, 0.027 mol) and pentachlorophenol (7.17 g, 0.027 mol) in 200 ml of dry THF with cooling. The reaction mixture was stirred and kept cold for 2 hr and then stirred at room temperature for several days. The reaction mixture was heated to the boiling point, filtered, and refiltered several times through the same funnel to remove the DCC. The filtrate was reduced in volume, diluted with ether, and cooled to give 3.0 g of ester **2**: mp 190–193° dec; ir (Nujol) 3390, 3300, 1775, 1680 cm^{-1}. Further cooling of the filtrate gave 6.4 g of additional ester, mp 210–214° dec, for a total crude yield of 87%. Recrystallization of the combined materials by dissolving them in warm DMF and subsequent filtration into a large volume of ether gave 8.9 g of the ester (64%, mp 204–205° dec).

An analytical sample was prepared by recrystallization from dimethylformamide–ether: mp 210–211° dec; NMR (Me_2SO-d_6) 2.38 (s, 3, CH_3Ar), 3.56 (d, 2, J = 7 Hz, $CNCH_2$), 4.38 (d, 2, J = 7 Hz, $SNCH_2$), 7.32–8.2 (m, 5, Ar, NH), 8.64 ppm (t, 1, J = 6 Hz, NH). Anal. Calcd for $C_{17}H_{13}Cl_5N_2O_5S$ (534.66): C, 38.19; H, 2.45; Cl, 33.16; N, 5.24; S, 6.00. Found: C, 38.15; H, 2.48; Cl, 32.98; N, 5.21; S, 6.24.

***N*-(2-Tosylaminoethyl)glycine Pentachlorophenyl Ester (3).** The experimental apparatus consisted of a three-neck round-bottom flask fitted with a nitrogen inlet, dropping funnel, and con-

denser with drying tube. The reaction mixture was stirred magnetically. All additions were done at ice-bath temperatures and all reactions were carried out under a nitrogen atmosphere.

To the ester **2** (6.2 g, 11.6 mol) suspended in 300 ml of dry THF was added 1 *M* BH_3–THF (20 ml, 20 mmol) in 20 ml of dry THF as rapidly as possible. The reaction mixture was refluxed for 1.5 hr and cooled in an ice bath and 50 ml of acetic acid saturated with HBr(g) was added dropwise. The reaction was stirred at room temperature for 1 hr and filtered to give 5.0 g of the reduced ester **3** HBr, mp 196–197° dec. Reduction in volume of the filtrate and dilution with ether gave an additional 1.6 g of **3** HBr: mp 193–194° dec; 96% total crude yield; ir (Nujol) 3250, 1800 cm^{-1}; NMR (Me_2SO-d_6) 2.43 (s, 3, CHAr), 3.22, 4.00, 4.74 (a series of three singlets which change such that the singlet at 4.74 decreases, the singlet at 4.00 increases, and the singlet at 3.22 becomes a multiplet, as the ester reacts with Me_2SO-d_6, 6, CH_2N), 7.46 and 7.84 (d, 2, J = 9 Hz, Ar), 8.00 (s, 1, $NHSO_2$), 9.4 ppm (s, 2, NH_2^+).

An analytical sample was prepared by recrystallization from a mixture of dimethylformamide–THF–ether to give the pure ester **3** HBr, mp 196.5–197° dec. Anal. Calcd for $C_{17}H_{15}Cl_5N_2O_4S$·HBr (601.60): C, 33.94; H, 2.68; Br, 13.28; Cl, 29.47; S, 5.33. Found: C, 33.84; H, 2.58; Br, 13.43; Cl, 29.57; S, 5.43.

Triethylamine (1.25 ml, 9 mmol) in 75 ml of dry chloroform was added to a stirred suspension of **3** HBr (5.4 g, 9 mmol) in 75 ml of dry chloroform. The reaction mixture was stirred until solution occurred and then concentrated to dryness in vacuo. The residue was warmed gently with 200 ml of benzene and the triethylamine hydrobromide was removed by filtration. The benzene filtrate was concentrated in vacuo to 50 ml to give 4.0 g of the free base **3** (85%, mp 123–125°): ir (Nujol) 3300, 3140, 1785 cm^{-1}.

The free base was unstable and formed the diketopiperazine **7** on attempted purification. A sample of **7** was recrystallized from ethanol–dimethylformamide to give a solid: mp 251–252°; ir (Nujol) 3260, 1635 cm^{-1}. Anal. Calcd for $C_{22}H_{28}N_4O_6S_2$ (**7**) (508.63): C, 51.95; H, 5.55; N, 11.02; S, 12.61. Found: C, 51.96; H, 5.45; N, 11.05; S, 12.77.

***N*-Acetyl-*N*-(2-tosylaminoethyl)glycine Pentachlorophenyl Ester (4).** The base **3** (3.9 g, 7.5 mmol) was stirred in redistilled acetic anhydride (25 ml) until solution occurred. The reaction mixture was then stirred for an additional 2 hr at room temperature. A solid precipitated. The solid was filtered and washed with a small portion of acetic anhydride and then with ether to give 3.0 g of **4** (73%, mp 147–148°): ir (Nujol) 3140, 1786, 1645 cm^{-1}.

***N*-Ethyl-*N*-(2-tosylaminoethyl)glycine Hydrochloride (6a).** The amido ester **4** (1.1 g, 3 mmol) in 40 ml of dry THF was added dropwise to 1 *M* BH_3–THF (3.4 ml, 3.4 mmol) in 15 ml of cold, dry THF. The reaction mixture was stirred at room temperature for 2 hr and then cooled in an ice bath. Hydrochloric acid (0.5 ml, 6 *N*) was added dropwise and the reaction mixture stirred for 1 hr. The solid was filtered and washed with THF to give 0.2 g of the amino acid salt **6a**, mp 154–160° dec. Reduction in volume of the filtrate and dilution with ether gave 0.15–0.20 g more of **6**: ir (Nujol) 3300 (broad), 3060, 1730 cm^{-1}.

The filtrate was concentrated in vacuo. The residue was dissolved in a small volume of THF and diluted with ether to remove the pentachlorophenol. The material that was insoluble in ether was treated with a small portion of THF to give 0.15 g of the amino ester **5**: mp 134–136° dec; ir (Nujol) 3210, 1795 cm^{-1}. Reduction of the filtrate and treatment of the residue with THF–ether gave about 0.1 g of crude **5**.

The amino ester **5** (0.45 g, 0.77 mmol) was saponified with sodium hydroxide (1.54 ml, 1.54 mmol) to give both the amino acid salt **6a**, 0.2 g, ir (Nujol) 1730 cm^{-1}, contains sodium chloride (theory for NaCl 80 mg), and the free amino acid **6**, mp 185–187°, ir (Nujol) 3010, 1650 cm^{-1}, which is a 98% recovery of the material based on recovery of the amino acid salt **6a**.

An analytical sample of **6a** was prepared by recrystallization from 2-propanol: mp 155–161°; ir (Nujol) 3300 (broad), 3050, 1730 cm^{-1}; NMR (Me_2SO-d_6) 1.23 (t, 3, J = 8 Hz, CH_3CH_2), 2.42 (s, 3, CH_3Ar), 3.25 (m, 6, CH_2N), 3.8 (broad t) and 4.1 (s, 2, NCH_2CO), 7.42 and 7.78 (d, 2, J = 9 Hz, Ar), 8.22 ppm (s, 1, SNH). Anal. Calcd for $C_{13}H_{21}N_2O_4ClS$ (336.83): C, 46.36; H, 6.28; Cl, 10.53; N, 8.32; S, 9.52. Found: C, 46.19; H, 6.34; Cl, 10.39; N, 8.28; S, 9.53.

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Registry No.—**1**, 556-50-3; **2**, 57066-12-3; **3**, 57066-13-4; **3** HBr, 57066-14-5; **4**, 57066-15-6; **5**, 57066-16-7; **6**, 57066-17-8; **6a**, 57066-18-9; **7**, 57066-19-0; acetic anhydride, 108-24-7; tosyl chloride, 98-59-9; *N*-tosylglycylglycine, 4703-34-8; pentachlorophenol, 87-86-5.

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Photoreduction of Substituted Benzo[*b*]furans by Aliphatic Amines

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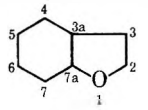
In one of our previous papers we have reported that uv irradiation (254 nm) of benzo[*b*]thiophene in aliphatic amines leads to the corresponding adducts and we have postulated the intermediate formation of an exciplex.[2] In contrast to benzo[*b*]thiophene, no detectable reaction was observed when benzo[*b*]furan was irradiated with uv light in an aliphatic amine.[2] Assuming that the photoexcited heterocycle reacts with the amine via intermediate formation of an exciplex[3,4] in which the heteroaromatic derivative possesses the character of a radical anion, we were able to explain the difference in the photochemical behavior of these two heterocycles as due to the fact that the maximum spin density in the benzo[*b*]furan radical anion is found in the 4 position whereas in the benzo[*b*]thiophene radical anion it is the 2 position where the spin density is the highest.[2] This means that, if a photoreaction between benzo[*b*]furan and an aliphatic amine, HNR_2, were possible, it would lead to the formation of product **1** which would be unstable under the conditions used in our study.[2]

To verify this assumption, we have synthesized some benzo[*b*]furan derivatives in which the spin density of their radical anion is the highest in the 4 position, and we have also prepared some other derivatives whose radical anions have the highest spin density in the 2 position. According to our hypothesis, the former group of compounds should not give any isolable products when irradiated in an aliphatic amine, whereas uv irradiation of the compounds belonging to the latter group is expected to lead to the formation of stable photoproducts.

Table I
Calculated HMO Spin Densities of Radical Anions Derived from Substituted Benzo[b]furans[a]

Position[b]	2,3-Dimethyl	2-Phenyl	3-Phenyl	2,4,7-Trimethyl-3-phenyl	2,3-Diphenyl
1	0.0040	0.0302	0.0236	0.0083	0.0351
2	0.1074	0.1019	0.2257	0.1408	0.1334
3	0.0097	0.0941	0.0295	0.0074	0.0653
3a	0.0735	0.0103	0.0013	0.0297	0.0000
4	0.3018	0.1333	0.1370	0.0122	0.0740
5	0.0605	0.0249	0.0715	0.0554	0.0299
6	0.1009	0.0641	0.0229	0.0123	0.0260
7	0.2972	0.1138	0.1531	0.0172	0.0763
7a	0.0382	0.0002	0.0286	0.0346	0.0002

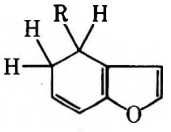
[a] The spin density ρ_r at atom r was approximated by the square of the coefficient of the corresponding atomic orbital in the respective molecular orbital, $\rho_r = c^2_{m+1,r}$, where $c_{m+1,r}$ is the expansion coefficient of the rth atomic orbital in the $(m+1)$st molecular orbital, i.e., the lowest unoccupied π molecular orbital of the parent heterocyclic system. The HMO calculations were made in the usual way using an IBM 360/50 computer. The heteroatom model of the methyl group was used in the calculations and the methyl group was assumed to contribute a pair of electrons to the π system. The following parameters were adopted:[2,5] $\alpha_O = \alpha + 2\beta$; $\alpha_{Me} = \alpha + 2\beta$; $\alpha_{C(Me)} = \alpha - 0.2\beta$; $\beta_{CO} = \sqrt{2}\beta$; $\beta_{CMe} = 0.7\beta$. The highest spin density for each radical anion is underlined. [b] Numbering:



The calculated HMO spin densities of the radical anions of the compounds under study are summarized in Table I.

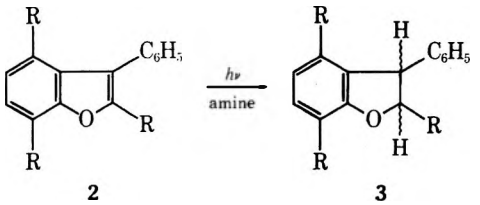
As expected, 2,3-dimethylbenzo[b]furan, which has the highest value of spin density in its radical anion in the 4 position, does not give any identifiable photoproducts when irradiated in n-propylamine or triethylamine, regardless of the presence or absence of methanol (methanol is known to facilitate the photoreaction of benzene with triethylamine[6]). 2-Phenylbenzo[b]furan, which belongs to the same group as 2,3-dimethylbenzo[b]furan, photodimerizes in n-propylamine similarly as in other solvents.[7,8]

On the other hand, 3-phenylbenzo[b]furan (**2a**) and 2,4,7-trimethyl-3-phenylbenzo[b]furan (**2b**), i.e., compounds in which the spin density in their respective radical anions in the highest in the 2 position, are photoreduced to the corresponding 2,3-dihydro derivatives **3a** and **3b**, respectively, when irradiated in an aliphatic amine. Similarly



1

R = H or NR_2



2 3

a, R = H

b, R = Me

as in other solvents, 2,3-diphenylbenzo[b]furan, which belongs to this group as well, undergoes photocyclization when irradiated under these conditions.[9]

The chemical yield of photoreduction of **2a** by aliphatic amines increases when going from a primary amine to a tertiary amine. The yields of 2,3-dihydro-3-phenylbenzo[b]furan (**3a**) in n-propylamine, diethylamine, and triethylamine (with 10% of methanol added) are 10, 20, and 30%, respectively, and thus increase with decreasing ionization potential of the amine (the first ionization potentials of the above amines are 8.78, 8.01, and 7.50 eV, respectively[10]). This finding is consistent with the hypothesis about the intermediate formation of an exciplex during the photoreaction of benzo[b]furan derivatives with an aliphatic amine, at least in the case of those derivatives which undergo photoreduction.

Experimental Section

Materials. 2-Phenylbenzo[b]furan and 3-phenylbenzo[b]furan (**2a**) were synthesized as described in the literature.[11] Previously described procedures were used to prepare 2,4,7-trimethyl-3-phenylbenzo[b]furan[12-14] (**2b**) and 2,3-dimethylbenzo[b]furan.[15]

Instruments and Methods. NMR spectra were obtained with a Jeol C-60HL spectrometer. Mass spectra were determined on an AEI Model MS 12 spectrometer (Laboratoire de Chimie Appliquée de l'Université de Bordeaux I, Bordeaux, France) operating at 70 eV ionizing potential. Preparative gas chromatography was performed on an Autoprep A 700 gas chromatograph using a column of 10% Apiezon L on Chromosorb W (8 ft × 0.375 in.). Gas chromatographic analyses were made on an F & M Model 810 gas chromatograph using a 30% SE column (6 ft × 0.25 in.).

Irradiations were conducted in a quartz vessel using light from a Hanau NN 1544 15-W low-pressure mercury arc lamp. All samples were irradiated for 24 hr and a nitrogen atmosphere was maintained during irradiation. The concentration of the solutions was 1 g of the heterocyclic substrate in 100 ml of n-propylamine, diethylamine, or triethylamine (or a mixture of 90 ml of triethylamine and 10 ml of methanol in the case of the irradiation of **2a** in triethylamine). After evaporation of the solvent, the crude reaction product was filtered through a silica gel column with petroleum ether as eluent and then isolated by preparative gas chromatography. The yields were determined by analytical VPC.

All melting points are uncorrected. Elemental microanalyses were carried out by the Centre de Microanalyse du CNRS, Thiais, France.

Irradiation of 2-Phenylbenzo[b]furan. The dimer of 2-phenylbenzo[b]furan formed during irradiation deposited on the walls of the photochemical vessel (0.51 g, 51%). After recrystallization from benzene, it had mp 283–284°; NMR (dimethyl sulfoxide) δ 4.95 (2 H, s), 6.75 (8 H, m), 7.20 ppm (10 H, m).

Anal. Calcd for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19; O, 8.24. Found: C, 86.19; H, 5.26; O, 8.52.

Irradiation of 3-Phenylbenzo[b]furan. Irradiation of this compound gave 2,3-dihydro-3-phenylbenzo[b]furan (**3a**): mp 35–37° (ethanol); NMR (CCl_4) δ 4.5 (3 H, m), 6.8 (4 H, m), 7.15 ppm (5 H, m); mass spectrum m/e (rel intensity) 196 (M^+, 100), 181 (14), 167 (25), 165 (28), 91 (16). Yields, reduced photoproduct (RP), unreacted starting material (SM): in triethylamine, 30% RP, 70% SM; in diethylamine, 20% RP, 80% SM; in n-propylamine, 10% RP, 90% SM.

Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16; O, 8.15. Found: C, 85.61; H, 6.18; O, 8.12.

Irradiation of 2,4,7-Trimethyl-3-phenylbenzo[b]furan (2b). In this case, an inseparable mixture of *cis*- and *trans*-2,3-dihydro-2,4,7-trimethyl-3-phenylbenzo[b]furan (**3b**) was obtained, in an overall yield of 20% (the unreacted starting material represented 80%) when the reaction was carried out in triethylamine. The two isomers were present in 1:2 ratio, the trans isomer seeming to be the preponderant isomer. NMR of the mixture (CCl_4): δ 1.06 (3 H, d), 1.47 (3 H, d), 1.87 (3 H, s), 2.19 (3 H, s), 4.00 (1 H, d), 4.25 (1 H, d), unresolved between 4.4 and 5.1 (1 H, m), unresolved between 6.3 and 7.25 ppm (7 H, m). Mass spectrum m/e (rel intensity): 238 (M^+, 100), 223 (69), 209 (23), 195 (19). M^+ calcd for $C_{17}H_{18}O$: 238. Found: 238.

Irradiation of 2,3-Dimethylbenzo[b]furan. Under the conditions described above, irradiation of this compound gave no photoreduction. No product could be identified by gas chromatography.

Irradiation of 2,3-Diphenylbenzo[b]furan. The photocyclization of this compound has been described in one of our previous publications.[9]

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Registry No.—**2a,** 29909-72-6; **2a** radical ion (RI), (1−), 57049-55-5; **2b,** 57049-56-6; **2b** RI, (1−), 57049-57-7; **3a,** 57049-58-8; *cis*-**3b,** 57049-59-9; *trans*-**3b,** 57049-60-2; 2-phenylbenzo[*b*]furan, 1839-72-1; 2-phenylbenzo[*b*]furan RI, (1−), 57049-61-3; 2-phenylbenzo[*b*]furan dimer, 57049-62-4; 2,3-dimethylbenzo[*b*]furan, 3782-00-1; 2,3-dimethylbenzo[*b*]furan RI, (1−), 57049-63-5; 2,3-diphenylbenzo[*b*]furan, 13054-95-0; 2,3-diphenylbenzo[*b*]furan RI, (1−), 57049-64-6; *n*-propylamine, 107-10-8; diethylamine, 109-89-7; triethylamine, 598-56-1.

References and Notes

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Cyclobutanones from Cyclopropanone Precursors. Addition of Nitroalkanes to Cyclopropanone Aminals

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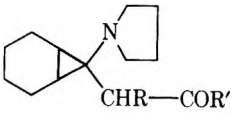
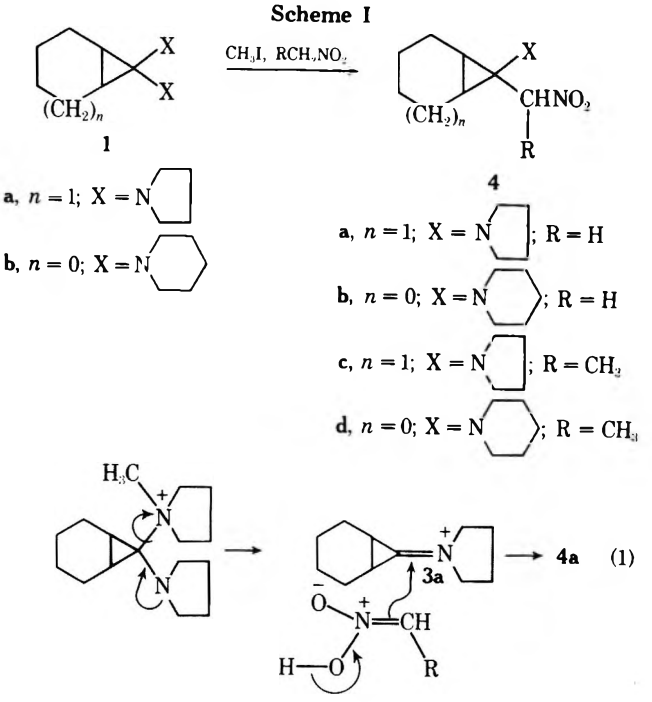
We have previously reported[1] that 1,1-dipyrrolidinocyclopropanes of type 1[3] undergo ready reaction with ketones under mildly acidic conditions to form addition products such as 2. We have now found that these aminals undergo



2

ready alkylation by nitroalkanes under conditions in which the cyclopropyl iminium salts are probable intermediates. The addition takes place on treatment of **1a** or **1b** with excess nitromethane or nitroethane under a nitrogen atmosphere in the presence of methyl iodide at room temperature and leads to derivatives corresponding to **4** (Scheme I). Presumably, the alkylation of **1** with methyl iodide yields a

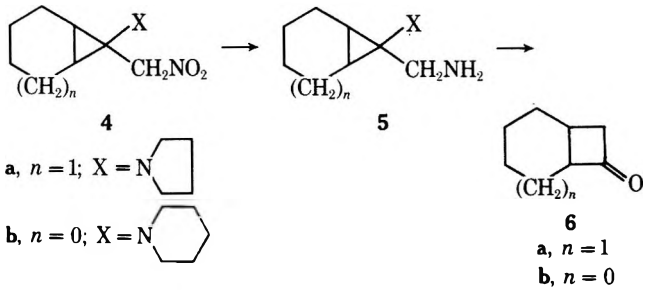
Scheme I



quaternary derivative which then dissociates to an iminium salt such as **3a.** Reaction of the iminium salt with the nitroalkane (through the aci form) leads to **4.**

Reduction of the nitroalkanes with lithium aluminum hydride yields the primary amines **5,** which may serve as substrates for the Tiffeneau–Demjanov ring enlargement (acetic acid and isoamyl nitrite in benzene followed by aqueous work-up)[2] forming fused ring cyclobutanones **6** (Scheme II).

Scheme II



4 5 6
a, $n = 1$
b, $n = 0$

In the work outlined below, this procedure has been adapted for the preparation of bicyclo[4.2.0]octan-7-one (**6a**)[4] and bicyclo[3.2.0]heptan-6-one (**6b**). The structures of these cyclobutanone derivatives were established by spectroscopic methods and by comparison with authentic materials.

Experimental Section

Microanalyses were performed by Dr. R. Rittner of the Olin Mathieson Chemical Co., New Haven, Conn. Infrared spectra were determined on a Perkin-Elmer Model 421 grating spectrophotometer as neat liquids unless otherwise noted. NMR spectra were recorded on Varian Model A-60, A-60A (60 MHz), or Jeolco Minimar 100 (100 MHz) spectrometers, as indicated. Chemical shifts are reported in δ units using tetramethylsilane as the internal standard. Mass spectra were recorded on an AEI Model MS-9 instrument, courtesy of Dr. W. McMurray. Boiling points are uncorrected. VPC analyses and sample preparations were performed with an Aerograph Model A90-P3 instrument. A 12 ft × 0.375 in. 9% SE-30 column packed on 60–80 mesh Anakrom A support was used, column temperature 95–100°C, helium flow rate 60 ml/min. Retention times were as noted below. Sample purity checks were made on a Waters Associates Model ALC-100 analytical liquid chroma-

tograph using chloroform as the solvent and two 2 ft × 0.125 in. columns packed with alumina (activity III). The solvent flow rate was determined by 25% of the pump stroke capacity.

7-Nitromethyl-7-pyrrolidinobicyclo[4.1.0]heptane (4a). A suspension of 11.3 g (48.2 mmol) of 7,7-dipyrrolidinobicyclo[4.1.0]-heptane[3] (**1a**) in 160 ml of nitromethane was heated under nitrogen to 55°C (partial dissolution) with stirring. The heating bath was removed, and 7.00 g (49.3 mmol) of methyl iodide in 45 ml of nitromethane was slowly added over 45 min to the mixture which was stirred overnight. The mixture was taken up in ether (300 ml), washed successively with 10% sodium bicarbonate solution (2 × 100 ml) and saturated sodium chloride solution (2 × 100 ml) and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was distilled at 94–97°C (0.02 mm) to give 8.4 g (78%) of **4a**: ir 2936, 2860, 1543, 1443, 1425, 1377, 1356 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.0–2.1 (m, 14 H), 2.79 (m, 4 H), and 4.28 (s, 2 H); mass spectrum *m/e* 194, 178.

Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.00; H, 8.52; N, 12.53.

7-(1-Nitroethyl)-7-pyrrolidinobicyclo[4.1.0]heptane (4c). To the dipyrrolidino compound **1a** (11.7 g, 50 mmol) was added 150 ml of nitroethane under nitrogen. The mixture was heated on a water bath to 45°C with stirring to dissolve the starting material. The bath was then removed, and methyl iodide (7.1 g, 50 mmol) in 50 ml of nitroethane was added dropwise over 35 min. The reaction mixture was allowed to stir further for 26 hr at room temperature. The mixture was taken up in ether (300 ml), washed successively with dilute sodium bicarbonate solution (2 × 100 ml) and water (3 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Distillation at 115–125°C (0.07 mm) gave 5.4 g (45%) of **4c**: ir (CCl_4) 3014, 2940, 2830, 1553, 1470, 1450, 1375, 1350, 1310 and 1150 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 1.0–2.0 (m, 17 H), 1.29 (emergent doublet, J = 7 Hz), 2.85 (m, 4 H), 5.0 (q, 1 H, J = 7 Hz); mass spectrum *m/e* 208 and 192.

Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.75. Found: C, 65.38; H, 9.12; N, 11.59.

7-Aminomethyl-7-pyrrolidinobicyclo[4.1.0]heptane (5a). 7-Nitromethyl-7-pyrrolidinobicyclo[4.1.0]heptane (**4a**, 7.10 g, 31.6 mmol) in 70 ml of ether was added under nitrogen over 1 hr to a stirred refluxing mixture of 2.7 g (71 mmol) of lithium aluminum hydride and 70 ml of ether. The reaction mixture was stirred for 22 hr at 20°C, cooled in ice, and decomposed cautiously with 2.7 ml of water, 2.7 ml of 15% sodium hydroxide, and 9 ml of water in that order. The mixture was stirred for 1 hr at 20°C and filtered and the precipitated salts washed with ether. The filtrate was dried (Na_2SO_4) and evaporated. The residue was distilled at 62–63°C (0.005 mm) to give 4.8 g (78%) of **5a**: ir 3270, 2925, 2846, 1612, 1453, 1440, 1340, and 1140 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.12 (emergent singlet, disappeared upon addition of D_2O), 0.5–2.1 (group of multiplets, 16 H, contained the emergent singlet), 2.67 (s, 2 H), 2.85 (m, 4 H); mass spectrum *m/e* 194.

Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.14; H, 11.41; N, 14.42. Found: C, 74.00; H, 11.20; N, 14.32.

Bicyclo[4.2.0]octan-7-one (6a). Isoamyl nitrite (2.7 g, 23.1 mmol) in 10 ml of benzene was added to 4.0 g (20.6 mmol) of 7-aminomethyl-7-pyrrolidinobicyclo[4.1.0]heptane (**5a**) and 1.23 g (20.5 mmol) of acetic acid in 30 ml of benzene. The stirred solution was heated to 60–65°C. An initially vigorous gas evolution was observed for 30 min. The reaction was held for 30 min more at 60–65°C. Benzene (20 ml) was added and the solution was washed with 1 *N* hydrochloric acid (2 × 40 ml) and dilute sodium bicarbonate (2 × 40 ml) and dried (Na_2SO_4). After removal of the solvent, the residue was distilled to give at 62–63°C (5 mm) 700 mg (27%) of product (**6a**). After further purification by VPC (retention time 11 min), the ir and NMR spectra were identical with the spectra of the authentic compound.[4]

6-Nitromethyl-6-piperidinobicyclo[3.1.0]hexane (4b). To a stirred suspension of 6,6-dipiperidinobicyclo[3.1.0]hexane[3] (**1b**, 10.0 g, 40 mmol) in 130 ml of nitromethane was added methyl iodide (14.2 g, 100 mmol) in nitromethane (40 ml) at 20°C over 45 min. The reaction mixture was stirred for 3 hr at room temperature. Ether (400 ml) was added; the mixture was washed with dilute sodium bicarbonate solution (3 × 150 ml) and brine (2 × 100 ml) and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on silica gel ($CHCl_3$) to give 4.5 g (50%) of product (**4b**); ir 2936, 2858, 1547, 1439, and 1369 cm^{-1}; NMR (CCl_4, 100 MHz) δ 1.0–2.2 (m, 14 H), 2.2–2.9 (m, 4 H), and 4.24 (s, 2 H); mass spectrum *m/e* 194 and 178.

Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.79; H, 8.91; N, 12.35.

6-(1-Nitroethyl)-6-piperidinobicyclo[3.1.0]hexane (4d). The bis piperidino compound (**1b**, 10 g, 40 mmol) was dissolved in 150 ml of nitroethane under nitrogen at 50°C. Heating was discontinued, and 11.6 g (80 mmol) of methyl iodide in 50 ml of nitroethane was added dropwise with stirring over 1 hr. As the methyl iodide solution was added, a white precipitate formed. Stirring was continued overnight at room temperature. The white solid was removed by filtration, dried under vacuum at 5 mm, and shown by NMR to be *N*-methylpiperidinium methiodide. The liquid phase was diluted with 300 ml of ether, washed with dilute sodium bicarbonate solution (2 × 100 ml) and water (3 × 50 ml), and dried ($MgSO_4$). Removal of solvent in vacuo and distillation [bp ~114°C (0.005 mm)] afforded 2.5 g (26%) of **4d**. Further preparation was done on a 2-mm silica gel TLC plate developed with a 1:1 ether–pentane mixture for the analytical sample: ir 3035, 2925, 2850, 2800, 1540, 1450, 1390, 1370, 1340, 1300, 1275, 1240, 1100, 1030, 860, and 750 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 1.10–1.94 (m, 17 H), 1.43 (emergent doublet, J = 7 Hz), 2.68 (m, 4 H), and 4.85 (q, 1 H, J = 7 Hz); mass spectrum *m/e* 208 and 192.

Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.75. Found: C, 65.37; H, 9.11; N, 11.52.

6-Aminomethyl-6-piperidinobicyclo[3.1.0]hexane (5b). 6-Nitromethyl-6-piperidinobicyclo[3.1.0]hexane (**5a**, 9.3 g, 41.5 mmol) in 20 ml of ether was added under nitrogen over 1 hr to a stirred refluxing mixture of lithium aluminum hydride (3.6 g, 95 mmol) and 90 ml of ether. The reaction was stirred for 20 hr at 20°C, cooled in ice, and decomposed successively with 3.6 ml of water, 3.6 ml of 15% sodium hydroxide, and 11.4 ml of water. The mixture was stirred for 1 hr at 20°C and filtered and the precipitated salt washed with ether. The filtrate was dried (Na_2SO_4), and the solvent evaporated in vacuo. The residue was distilled at 58–59°C (0.003 mm) over a short Vigreux column to give 1.8 g (68%) of **5b**: ir 3285, 3008, 2931, 2857, 2792, 1602, 1450, 1440, 1233, and 1031 cm^{-1}: NMR (CCl_4, 60 MHz) δ 1.17 (emergent singlet, disappeared upon the addition of D_2O), 0.8–2.1 (m, 14 H, contained emergent singlet), 2.63 (s, 2 H), and 2.74 (m, 4 H); mass spectrum *m/e* 194.

Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.37; H, 11.18; N, 14.28.

Bicyclo[3.2.0]heptan-6-one (6b). To a mixture of 6-aminomethyl-6-piperidinobicyclo[3.1.0]hexane (**5b**, 2.0 g, 10.3 mmol) with 0.62 g (10.5 mmol) of acetic acid in 50 ml of benzene was added in one portion isoamyl nitrite (1.35 g, 11.5 mmol) in 20 ml of benzene. The reaction mixture was stirred and slowly heated with an oil bath to 65–70°C. Steady evolution of nitrogen continued for 45 min. The mixture was heated for an additional 15 min and 30 ml of benzene added. The cooled solution was washed with 10 ml of 1 *N* hydrochloric acid and with 10 ml of 7% sodium bicarbonate. The benzene solution was dried ($MgSO_4$) and the solvent removed. Distillation [bp 85–95°C (50 mm)] yielded 286 mg (25%) of **6b**; after further purification by VPC (retention time 7 min) this material was completely identical (ir, NMR) with an authentic sample prepared independently as outlined below. With concentrated nitric acid, the material could be oxidized to glutaric acid.[5]

Independent Preparation of Bicyclo[3.2.0]heptan-6-one (6b). Bicyclo[3.2.0]hept-2-en-6-one[5] (3.7 g, 0.0352 mmol) was hydrogenated (Parr apparatus) over 0.15 g of 5% Pd/C catalyst in 100 ml of methanol at 50 psi. The reaction mixture was filtered through Celite and the methanol removed. The concentrated residue was distilled at 65°C (19 mm) to yield 3.5 g (31.8 mmol, 91%) of pure material (**6b**), homogeneous by VPC assay: ir 2950, 2863, 1775, 1469, 1385, 1312, 1248, 1193, 1126, 1075, 1017, 930, and 915 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.35–2.25 (m), 1.42 (deformed triplet), 1.61 (deformed triplet), 2.89 (m), 3.05–3.39 (series of eight sharp resonances), and 3.55 (m).

Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.13; H, 9.11.

Acknowledgment. This work was supported by Grant GM-07874 from the National Institutes of Health.

Registry No.—**1a**, 23479-84-7; **1b**, 18096-92-9; **4a**, 57031-45-5; **4b**, 57031-46-6; **4c**, 57031-47-7; **4d**, 57031-48-8; **5a**, 57031-49-9; **5b**, 57031-50-2; **6a**, 54211-18-6; **6b**, 13756-54-2; nitromethane, 75-52-5; nitroethane, 79-24-3; bicyclo[3.2.0]hept-2-en-6-one, 13173-09-6.

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Radical Additions of Bromodichloronitromethane to Cyclic Olefins

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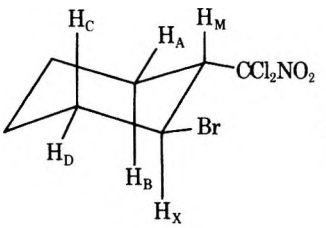
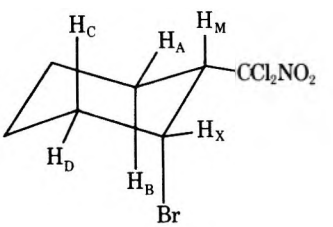
Several investigations have been concerned with free-radical additions of halocarbons, such as bromotrichloromethane,[2] perfluoroalkyl iodides,[3] and bromodicyanomethane,[4] to cyclic olefins. Although tribromonitromethane has been successfully added to several alkenes, the cyclohexene adduct was not isolable.[5] In order to study halonitromethane additions, bromodichloronitromethane was utilized in this investigation.

The photoinitiated addition of bromodichloronitromethane to cyclohexene gave isomeric results similar to that reported for bromotrichloromethane.[2] The major product (13%) was a 40:60 mixture of *cis*- and *trans*-1-bromo-2-(dichloronitromethyl)cyclohexane (I). This ratio



trans-I



cis-I

was an average (±5%) obtained from ten reactions. The chair and configuration seqcis[4] have been assigned to *cis*-1-bromo-2-trichloromethylcyclohexane, while the trans isomer required a twist–boat form to accommodate the vicinal coupling constants.[2] Brace[3] initially observed the twist–boat forms with perfluoroalkyl iodide–cyclohexene adducts. The coupling constants for *cis*-I (see Table I) are very similar to those of *cis*-1-bromo-2-trichloromethylcyclohexane[2] suggesting seqcis configuration. However, the large coupling constants (J_{MB} and J_{XC}) of *trans*-I tend to support a seqtrans form (both bulky groups in equatorial position).

trans-I was crystallized from a quite pure (>95%) isomeric mixture by subjecting it to dry ice conditions. The cis isomer could only be partially purified in this manner.

The reaction mixture could not be directly analyzed by GLC or NMR after solvent removal. Thus, identification of compounds was based on analyses of distillation fractions. The bulk of the reaction mixture was an intractable tar. The components isolated, aside from the isomers of I, were 3-bromocyclohexene (4.5%), bromocyclohexane (2%), and 1,2-dibromocyclohexane (4.4%). Since apparent decomposition of I may occur over extended periods at 25°, as evidenced by product darkening, the origin of the other isolated components has not been established. It must be noted that I is quite stable to redistillation as long as the distilling flask temperature is less than 120°. In all cases the initial product distribution was retained.

Table I
Vicinal Coupling Constants of Bromodichloronitromethane–Cycloolefin Adducts[a]

trans-I	J_{MX} = 10.8; J_{MA} = 4.6; J_{MB} = 9.8; J_{CX} = 9.4; J_{DX} = 4.2
cis-I	J_{MX} = 2.6; J_{MA} = 2.6; J_{MB} = 10.8
trans-II	J_{MX} = 4.0; J_{MA} = 8.0; J_{MB} = 8.0; J_{CX} = 4; J_{DX} = 6

[a] The subscripts designate hydrogens in accordance to the structures portrayed of *trans*- and *cis*-I. Values are in hertz.

Table II
Yields of Bromodichloronitromethane–Cycloolefin Adducts

	Photo-initiated, %	Redox transfer, %
cis-/*trans*-I	13	25
Dibromocyclohexane	4.4	7.5
Bromocyclohexane	2	0
trans-II	18	26
Dibromocyclopentane	2.5	4.7
Bromocyclopentane	3	0

Cyclopentene gave a single adduct (II) in 18% yield. The trans configuration was assigned to II based on the similarity to the vicinal coupling constant (J_{MX}) noted for 1-bromo-2-trichloromethylcyclopentane.[2] Other identifiable components isolated from the distillation fractions were dibromocyclopentane (2%) and monobromocyclopentane (5%).

The reaction of bromodichloronitromethane with cycloheptene and cyclooctene gave 12% 1,2-dibromocycloheptane and 10% 1,2-dibromocyclooctane, respectively. The anticipated adducts were not detected.

Attempts were made to prepare the norbornene adduct, but met with no success. Although precautions were taken to avoid oxygen and light during isolation, decomposition occurred during distillation. Owing to the violent nature of these decompositions and the potential toxicity[6] of the products this area was abandoned.

Since the yields of the photoinitiated reactions were low, and alternate pathways discouraged preparation of the larger cyclic adducts, a redox-transfer procedure utilizing copper chloride–amine was employed. This radical initiation process has been used to good advantage for the addition of haloalkanes to alkenes.[7,8] Application of this procedure to bromodichloronitromethane additions did increase the yield of the desired products, as well as the respective dibromocycloalkanes (see Table II). The viscous tar obtained from the photoinitiated reactions was not evident in this procedure. Again, addition of bromodichloronitromethane to cycloheptene and cyclooctene failed. Only 24% dibromocycloheptane and 20% dibromocyclooctane were recovered from these reactions.

The ratio of *cis*- and *trans*-I in the redox-transfer reaction was identical with that observed after photoinitiation. The NMR patterns of these isomers and *trans*-II were also similar to those obtained previously.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Beckman IR-10 spectrophotometer. NMR spectra were recorded on Varian T-60 and HA-100 spectrophotometers using tetramethylsilane (Me_4Si, O) as internal standard. Gas–liquid chromatographic analyses were obtained from an F & M 5750 research chromatograph. Two columns were found quite useful for elution of the adducts; the first was a 0.25 in. × 6 ft column of 5% SE-30 Glassport M. Column temperature requirements for this column were usually 100° programmed to 180° at 30°/min or

100° isothermal. The second column was a 0.125 in. × 6 ft 20% DEGS–2% H_3PO_4 on Chromosorb W. Temperature requirements were similar to those above. A 0.125 in. × 6 ft SE-30 column was sufficient to resolve 1,2-dibromocycloalkanes, bromocycloalkanes, and 3-bromocyclohexene in the distillation fractions. Bromodichloronitromethane may possess severe toxic properties. All reactions and distillations should be performed in a well-ventilated hood. Protective goggles and gloves must be worn during all operations. Thus, precautions should parallel those of chloropicrin.[9]

Bromodichloronitromethane. The procedure was essentially that of Burk and Davis.[10] Halogenation of nitromethane (73 g) with a mixture of Cl_2 (230 g) and Br_2 (160 g) afforded a 95% total yield of the mixed trihalonitromethanes. Fractional distillation in vacuo through a 12-in. column packed with 0.25 in. glass helices yielded 50 g (20%) of bromodichloronitromethane of 99.5% purity (GLC) having d^{25} 2.073 and bp 52° (22 Torr), together with 84 g (28%) of chlorodibromomethane of 98% purity, d^{25} 2.398, bp 67–69° (22 Torr).

1-Bromo-2-(dichloronitromethyl)cyclohexane (I), Photoinitiation. A solution, containing 20.5 g (0.25 mol) of cyclohexene and 52.3 g (0.25 mol) of bromodichloronitromethane in 500 ml of benzene, was placed in an Ace 500-ml photochemical reactor equipped with a 450-W Hanovia lamp and a Pyrex absorption sleeve. The solution was then sparged with purified nitrogen for 30 min followed by irradiation for 8 hr at 25°. The olefin was monitored by GLC until its disappearance, which usually required 8 hr. The solvent was removed under vacuum at 40°. No residue or tar was present at this stage of isolation. Final fractionation was achieved through a short path column under vacuum. The distillation was terminated when the distilling flask temperature reached 120°. Tar formation was quite evident during this distillation. A total of 9.4 g (13% yield) of I was recovered. Analysis indicated its purity to be 95%. NMR data for I indicated that it was a mixture (40:60) of cis and trans isomers: by 90–92° (0.2 Torr); $n^{20}D$ 1.5369; ir 1590 (asymmetric NO_2) and 1320 cm^{-1} (symmetric NO_2); NMR ($CDCl_3$) δ 2.83 ($HCCl_2NO_2$, cis isomer), 3.24 ($HCCl_2NO_2$, trans isomer), 4.01 (HCBr, trans isomer), and 4.72 (HCBr, cis isomer). Elemental analysis was consistent with the assigned structure.

1-Bromo-2-(dichloronitromethyl)cyclopentane (II), Photoinitiation. A solution containing 17 g (0.25 mol) of cyclopentene and 52.3 g (0.25 mol) of bromodichloronitromethane in 500 ml of benzene was treated in a manner similar to I. Maximum tar formation was also noted above 120° during the final distillation. A total of 12.5 g (18% yield) of II was recovered. Analysis indicated its purity to be 95%. NMR data for II indicated that it was a trans isomer: bp 89–91° (0.5 Torr); $n^{20}D$ 1.5230; NMR δ 3.78 ($HCCl_2NO_2$) and 4.38 (HCBr). Elemental analysis was consistent with the assigned structure.

I and II by Redox-Transfer. A solution containing 0.25 mol of cyclic olefin and 0.25 mol of bromodichloronitromethane was placed in a 250-ml three-neck flask equipped with stirrer, thermometer, and dry ice condensor. A solution of 0.55 g (0.005 mol) of diethylamine hydrochloride and 0.45 g (0.02 mol) of cupric chloride in 20 ml of acetonitrile was added to the reagents. This solution was heated to 80° for 20 hr. Upon cooling the reaction mixture was washed twice with 200 ml of 2 *M* hydrochloric acid followed by a 500-ml water wash. The solution was dried over anhydrous sodium sulfate. It was then distilled through a Vigreux column to remove unreacted reagents and solvent. Final fractionation was achieved utilizing a short-path column. A total of 18.2 g (25% yield) of I and 18.0 g (26%) of II were recovered from the respective reactions. Analytical values of these compounds were identical with those obtained previously.

***trans*-1-Bromo-2-(dichloronitromethyl)cyclohexane.** After distillation of I, 25 g of the high-purity fraction (95%) was placed in a 25-ml flask and allowed to stand in a dry ice–dichloromethane bath for 8 hr. Small crystals were formed after this treatment. The mixture was allowed to stand at 0° for 7 days. The liquid remaining was removed by micropipette. The crystals were washed with 5 × 5 ml of hexane (cooled in dry ice) and dried. Only 1 g of 95% purity *trans*-I was recovered, mp 33–35°.

Acknowledgment. We thank Drs. R. T. Iwamasa, J. Heeschen, and R. Nyquist for NMR and ir spectra as well as Dr. E. Larson and Professor E. Huyser for their helpful suggestions.

Registry No.—*cis*-I, 57049-75-9; *trans*-I, 57049-76-0; *trans*-II, 57049-77-1; cyclohexene, 110-83-8; bromodichloronitromethane, 918-01-4; cyclopentene, 142-29-0.

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Reactions of Azines with Diphenylketene

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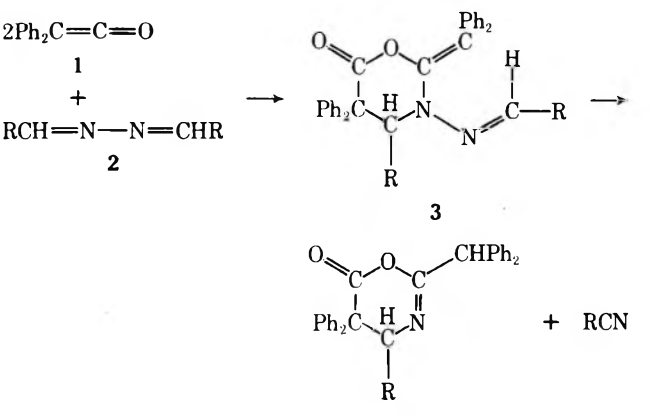
In contrast to extensive studies on the cycloaddition reactions of diphenylketene (**1**) with alkenes, imines, alkadienes, or heterocumulenes,[1] the reaction of **1** with nitrogen analogues of conjugated dienes has been reported[2,3] only with N=C–C=N compounds as dienes. We now report some cycloaddition reactions of **1** with aldehyde azines, RCH=N–N=CHR.

The reaction of **1** with acetaldehyde azine (**2a**) was carried out in refluxing ether for 5 hr, and a white, crystalline product was obtained in a good yield. On the basis of elemental analysis and spectral data shown in Table I, the reaction product was assumed to be 4-methyl-5,5-diphenyl-2-diphenylmethyl-4,5-dihydro-1,3-oxazin-6-one (**4a**), formed by the elimination of 1 mol of acetonitrile from the adduct (**3a**) of 2 mol of **1** and 1 mol of **2a**. At lower temperature (−20°), the expected cycloadduct **3a** was obtained. Compound **3a** was unstable, and decomposed to **4a** and acetonitrile on heating at about 100° or refluxing in ether.



2-4a, R = Me; b, R = Et; c, R = *i*-Pr

Other aliphatic aldehyde azines, propionaldehyde azine (**2b**) and isobutyraldehyde azine (**2e**), also reacted with **1** to

Table I[a]
4-Alkyl-5,5-diphenyl-2-diphenylmethyl-4,5-dihydro-1,3-oxazin-6-one (4)

Compd	R	Yield, %	Mp, °C	Formula	Mass M+	Ir (KBr), cm⁻¹ C=O	C=N	C–O–C	NMR (CCl_4), δ
4a	Me	70	156–157	$C_{30}H_{25}NO_2$	431	1775	1655	1120 1070	7.50–6.64 (m, 20 H), 4.79 (s, 1 H), 4.30 (q, 1 H), 1.00 (d, 3 H)
4b	Et	75	135–138	$C_{31}H_{27}NO_2$	445	1770	1660	1120 1090	7.61–6.65 (m, 20 H), 4.84 (s, 1 H), 4.18 (t, 1 H), 1.24 (m, 2 H), 0.87 (t, 3 H)
4c	*i*-Pr	55	146–148	$C_{32}H_{29}NO_2$	459	1775	1670	1120 1095	7.58–6.73 (m, 20 H), 4.91 (s, 1 H), 4.33 (d, 1 H), 1.33 (m, 1 H), 0.91 (d, 3 H), 0.67 (d, 3 H)

[a] Satisfactory analytical values (±0.35% for C, H, N) for all compounds in this table and Table II were submitted for review. Ed.

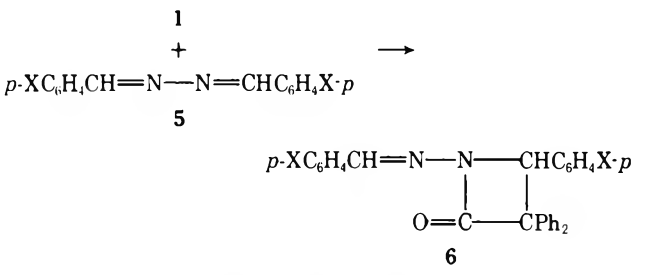
Table II
1-(*p*-X-Benzylideneamino)-4-(*p*-X-phenyl)-3,3-diphenyl-2-azetidinone (6)

Compd	X	Yield, %	Mp, °C	Formula	Mass M+	Ir, cm⁻¹ C=O	C=N	NMR (CCl_4), δ	Uv (EtOH), nm λmax	Log ε
6a	H	53	186–187	$C_{28}H_{22}N_2O$	402	1750	1650	7.88 (s, 1 H) 7.80–6.92 (m, 20 H) 5.89 (s, 1 H)	286 296 308	4.31 4.33 4.17
6b	Me	62	197–199	$C_{30}H_{26}N_2O$	430	1755	1645	7.72 (s, 1 H), 7.69–6.70 (m, 18 H) 5.82 (s, 1 H), 2.23 (s, 3 H) 2.12 (s, 3 H)	291 302 314	4.46 4.48 4.36
6c	MeO	74	187–188	$C_{30}H_{26}N_2O_3$	462	1760	1645	7.72 (s, 1 H), 7.68–6.50 (m, 18 H) 5.80 (s, 1 H), 3.68 (s, 3 H) 3.60 (s, 3 H)	300 312 322	4.50 4.55 4.46
6d	Cl	30	160–161	$C_{28}H_{20}N_2OCl_2$	470 472	1750	1650	7.85 (s, 1 H) 7.77–6.84 (m, 18 H) 5.87 (s, 1 H)	292 304 315	4.49 4.50 4.37

give 4-ethyl- (**4b**) and 4-isopropyl-5,5-diphenyl-2-diphenylmethyl-4,5-dihydro-1,3-oxazin-6-one (**4c**), respectively.

Aromatic aldehyde azines such as benzaldehyde azine (**5a**), *p*-methyl- (**5b**), *p*-methoxy- (**5c**), and *p*-chlorobenzaldehyde azine (**5d**) were allowed to react with **1** in refluxing xylene for 5 hr. Analyses and mass spectra indicated that the products were the adducts of 1 mol of **1** and 1 mol of **5**. The structures of the adducts were confirmed by ir, NMR, and uv spectra (Table II) to be the 2-azetidinone derivatives **6a**, **6b**, **6c**, and **6d**. When the reaction was carried out in refluxing ether or benzene, the yields were lower than those in xylene.

The reactions of **1** with ketone azines gave no adducts, and the starting materials were recovered.



5, 6a, X = H; b, X = Me; c, X = OMe; d, X = Cl

Experimental Section

The ir spectra were recorded on a Hitachi EPI-G2 spectrophotometer, the NMR spectra were taken on a Varian A-60 instrument with tetramethylsilane as an internal standard, the mass spectra were obtained on a Hitachi RMU-7M mass spectrometer, and the uv spectra were determined with a Hitachi EPS-3T spectrophotometer.

4-Alkyl-5,5-diphenyl-2-diphenylmethyl-4,5-dihydro-1,3-oxazin-6-one (4). To a refluxing solution of 0.05 mol of **2** in 100 ml of dried ether, 0.1 mol of **1** was added. After refluxing for 5 hr under a nitrogen atmosphere, the reaction mixture was cooled, and the precipitate thus obtained was recrystallized from CCl_4 to give **4**. The results are shown in Table I.

Intermediates 3a and 3b. To a solution of 4.2 g (0.05 mol) of **2a** in 100 ml of dried ether, 19.4 g (0.1 mol) of **1** was added at −20°, and the mixture was stirred for 2 hr at the same temperature. The precipitate was filtrated under cooling and washed with cold dried ether to give 16.6 g (70%) of **3a**.

When 14.2 g (0.03 mol) of **3a** was heated at about 100°, 1.0 g of colorless liquid distilled, boiling at 80°, which was identified as MeCN by ir spectrum. The solid residue was recrystallized from CCl_4 to give 11.2 g (87%) of **4a**.

Similarly, 18.5 g of **3b** was obtained from 0.05 mol of **2b** and 0.1 mol of **1**, yield 74%, decomposed at about 90° to give **4b** and EtCN.

3a: ir (KBr) 1770, 1630, 1120, 1090 cm⁻¹; NMR (CCl_4) δ 7.48–6.82 (m, 20 H), 6.76 (q, 1 H), 4.90 (q, 1 H), 1.15 (d, 3 H), 1.05 (d, 3 H).

Anal. Calcd for $C_{32}H_{28}N_2O_2$: C, 81.33; H, 5.97; N, 5.93. Found: C, 81.08; H, 6.22; N, 6.07.

3b: ir (KBr) 1760, 1635, 1140, 1125 cm⁻¹; NMR (CCl_4) δ 7.52–6.85 (m, 20 H), 6.67 (t, 1 H), 4.68 (t, 1 H), 2.51 (m, 4 H), 1.08 (t, 3 H), 0.56 (t, 3 H).

Anal. Calcd for $C_{34}H_{32}N_2O_2$: C, 81.57; H, 6.44; N, 5.60. Found: C, 81.33; H, 6.63; N, 5.44.

1-(*p*-X-Benzylideneamino)-4-(*p*-X-phenyl)-3,3-diphenyl-2-azetidinone (6). A mixture of 0.1 mol of **1**, 0.1 mol of **5**, and 100 ml of dried xylene was refluxed for 5 hr under a nitrogen atmosphere, and the solvent was removed by distillation under reduced pressure. The reddish residue was added to ether to precipitate the crude product. Recrystallization from CCl_4 gave **6**. The results are summarized in Table II.

Registry No.—**1**, 525-06-4; **2a**, 592-56-3; **2b**, 15601-98-6; **2c**, 18300-78-2; **3a**, 56930-54-2; **3b**, 56930-55-3; **4a**, 56930-56-4; **4b**, 56930-57-5; **4c**, 56930-58-6; **5a**, 588-68-1; **5b**, 4702-76-5; **5c**, 2299-73-2; **5d**, 3510-48-3; **6a**, 56930-59-7; **6b**, 56930-60-0; **6c**, 56930-61-1; **6d**, 56930-62-2.

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A New Example of Intramolecular 1,5-Hydrogen Transfer during Diazotization Reactions

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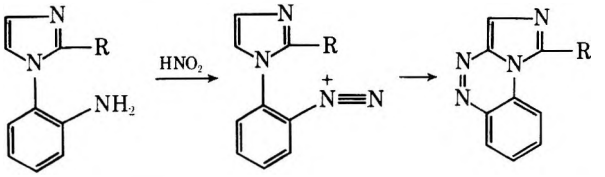
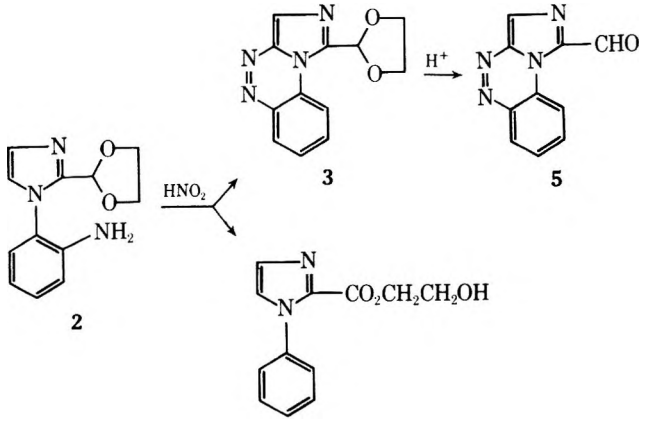
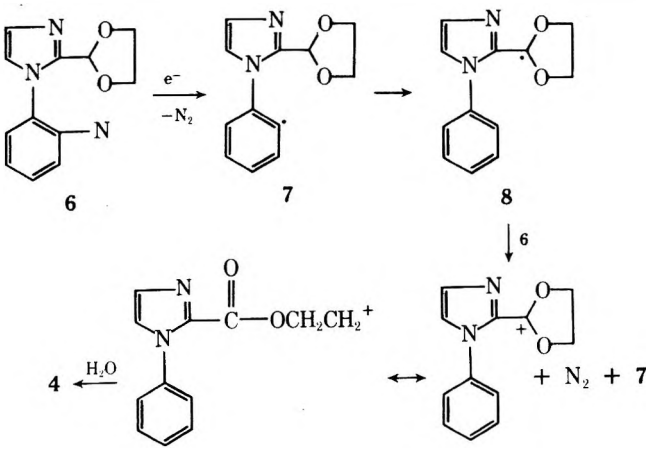
Because of a need for 1-formylimidazo[5,1-c]-1,2,4-benzotriazine (**5**) in other research we considered for its synthesis the method of Pozharskii and co-workers, which involved an intramolecular azo coupling of salts of o-(imidazolyl-1)-phenyldiazonium ion, formed by the diazotization of 1-(o-aminophenyl)imidazoles.[1]



Starting material was the ethylene glycol acetal of 1-(o-aminophenyl)-2-formylimidazole (**2**), which was readily prepared by catalytic hydrogenation of the ethylene glycol acetal of 1-(o-nitrophenyl)-2-formylimidazole (**1**). The diazotization reaction of **2** in diluted H_2SO_4 at 0° yields as major product (52%) the ethylene glycol monoester of 1-phenylimidazole-2-carboxylic acid (**4**) and as minor product (6%) the ethylene glycol acetal of the aldehyde **5** (**3**), from which the desired aldehyde **5** was obtained by acid hydrolysis.



The production of the ester **4** can be explained in terms of a radical chain mechanism, initiated by nitrite ion, which proceeds through an intramolecular 1,5-hydrogen atom transfer from the acetal group to the aryl radical



formed by homolytic cleavage of the $C-N_2^+$ bond; nucleophilic attack by water of carbonium ion **9** produced by reaction of the radical **8** with the diazonium ion **6** gives then the compound **4**.[2]

The mechanism involving radical intermediates is indicated by the adverse effect of oxygen on hydrogen transfer yields; in fact, the diazotization reaction of **2** in diluted H_2SO_4 continuously bubbled with oxygen gas gave only 35% of **4**. This compares with 52% under air.

The reduction by nitrite and intermolecular versions of this type of atom transfer are well established.[3] An example of 1,5-intramolecular hydrogen atom transfer during diazonium ion decomposition was investigated by Cohen and coworkers.[4]

In this case we have ascertained that the 1,5-hydrogen transfer is limited to acetals of type **2**; other 1-(o-aminophenyl)imidazol-2 derivatives such as the 1-(o-aminophenyl)-2-hydroxymethylimidazole and the 1-(o-aminophenyl)-2-methylimidazole[1] give the normal intramolecular azo coupling in high yields. The aldehyde **5** was therefore prepared in better yield by SeO_2 oxidation of 1-hydroxymethylimidazo[5,1-c]-1,2,4-benzotriazine (**10**) obtained by diazotization and azo coupling of 1-(o-aminophenyl)-2-hydroxymethylimidazole.

Experimental Section

Melting points are not corrected. NMR spectra were taken with a Jeol 60-HL spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrometer. Uv spectra were obtained with a Unicam SP 800 spectrophotometer.

1-(o-Nitrophenyl)-2-formylimidazole Ethylene Glycol Acetal (1). 1-(o-Nitrophenyl)-2-formylimidazole[5] (15.2 g, 70 mmol), ethylene glycol (25 ml), and a catalytic amount of p-toluenesulfonic acid were refluxed in C_6H_6 (500 ml) overnight using a Dean-Stark trap to remove the H_2O formed. The solution was cooled to room temperature, washed (aqueous Na_2CO_3), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give yellow crystals (13.1 g, 71%), mp 131–133°.

Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.03; H, 4.31; N, 15.89.

1-(o-Aminophenyl)-2-formylimidazole Ethylene Acetal (2). Compound **1** (5 g, 19.1 mmol) in 150 ml of MeOH and 5% Pd/C (1.5 g) was hydrogenated in a Parr shaker at room temperature and 10 psi pressure for 30 min. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure at 20–25° to give an oil which crystallized from EtOAc to give white needles (3.2 g, 72%), mp 123–125°.

Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.45; H, 5.88; N, 18.01.

1-Formylimidazo[5,1-c]-1,2,4-benzotriazine Ethylene Acetal (3) and Ethylene Glycol Monoester of 1-Phenylimidazole-2-carboxylic Acid (4). The amine **2** (4 g, 17.3 mmol) was dissolved in 80 ml of aqueous H_2SO_4 (1 *M*). The solution was cooled to below 5° with an ice bath. A cold $NaNO_2$ aqueous solution (2.6 g in 12 ml of H_2O) was slowly added with stirring to an end point with KI–starch paper. The solution was allowed to stand at room temperature for 15 min. The solution was neutralized with Na_2CO_3 and extracted with EtOAc. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column; elution with a mixture of EtOAc–MeOH (90:10) gave a first eluate containing the compound **3**. Evaporation of the solvent gave a residue which was recrystallized from EtOAc (0.25 g, 6%): mp 154–156°; uv (95% ethanol) λ_{max} 247 and 372 nm (ϵ 14800 and 5700); ir (Nujol) 1605, 1575, 1160, 1110, 765, and 760 cm^{-1}; NMR [$(CD_3)_2CO$] δ 4.28 (m, 4), 6.58 (s, 1), 7.43 (s, 1, imidazole ring proton), 7.72–8.72 (m, 4, aromatic protons).

Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.35; H, 3.91; N, 22.97.

Elution of the silica gel column with EtOAc–MeOH (80:20) gave a second eluate containing the compound **4**. Evaporation of the solvent gave a residue which was recrystallized from EtOAc (2.1 g, 52%): mp 130–132°; uv (95% ethanol) λ_{max} 260 nm (ϵ 12100); ir (Nujol) 3310 (OH), 1720 (ester C=O), 1310, 1250, 1140, 790, 765, and 695 cm^{-1}; NMR [$(CD_3)_2CO$] δ 3.30, 4.20 (two m, 4,

$-CH_2CH_2O-$), 4.60 (broad s, 1, OH), 7.40 (m, 7, aromatic and heterocyclic protons).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.02; H, 5.21; N, 12.06. Found: C, 61.83; H, 5.03; N, 11.87.

1-Formylimidazo[5,1-*c*]-1,2,4-benzotriazine (5). From 3. A solution of **3** (0.5 g, 2.3 mmol) in 5 ml of diluted H_2SO_4 was heated at 50° for 30 min. The solution was neutralized with Na_2CO_3 and extracted with EtOAc. Evaporation of the solvent gave a residue which was recrystallized from EtOH (0.27 g, 66%): mp 169–171°; uv (95% ethanol) λ_{max} 247 and 372 nm (ϵ 14700 and 5600); ir (Nujol) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_6N_4O$: C, 60.60; H, 3.05; N, 28.27. Found: C, 60.43; H, 2.81; N, 27.95.

From 6. To 25 mmol of the alcohol **6**, dissolved in a mixture of 150 ml of dioxane and 10 ml of H_2O, 90 mmol of finely powdered SeO_2 was added. The reaction mixture was refluxed for 3 days. Se was removed by filtration; evaporation of the filtrate gave a residue which was taken up with H_2O and extracted with EtOAc. Concentration of the organic extracted left a residue which was chromatographed on a silica gel column with EtOAc as eluent. Evaporation of the first fraction of eluate gave **5** as a solid (53%).

1-Hydroxymethylimidazo[5,1-*c*]-1,2,4-benzotriazine (10). The 1-(o-aminophenyl)-2-hydroxymethylimidazole[5] (4 g, 19.5 mmol) was diazotized as the amine **2**. Neutralization of the solution with Na_2CO_3 gave a precipitate which was filtered, washed several times with water, and recrystallized from dioxane (3.2 g, 82%): mp 252–253°; uv (95% ethanol) λ_{max} 247, 262 (s), and 375 nm (ϵ 15600, 12700, and 5700); ir (Nujol) 3160, 1600, 1580, 1150, 1040, 770 cm^{-1}; NMR (trifluoroacetic acid) δ 5.80 (s, 2, $-CH_2-$), 7.90–9.05 (m, 5, aromatic and heterocyclic protons).

Anal. Calcd for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.71; H, 4.23; N, 27.72.

Registry No.—**1**, 56908-89-5; **2**, 56908-90-8; **3**, 56908-91-9; **4**, 56908-92-0; **5**, 56908-93-1; **6**, 56908-94-2; **10**, 56908-95-3; 1-(o-nitrophenyl)-2-formylimidazole, 35015-98-6; ethylene glycol, 107-21-1; 1-(o-aminophenyl)-2-hydroxymethylimidazole, 35016-01-4.

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(2) We are grateful for the suggestion of this mechanism by one of the reviewers.
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A New Synthesis of L-2-Amino-3-oxalylaminopropionic Acid, the *Lathyrus sativus* Neurotoxin[1]

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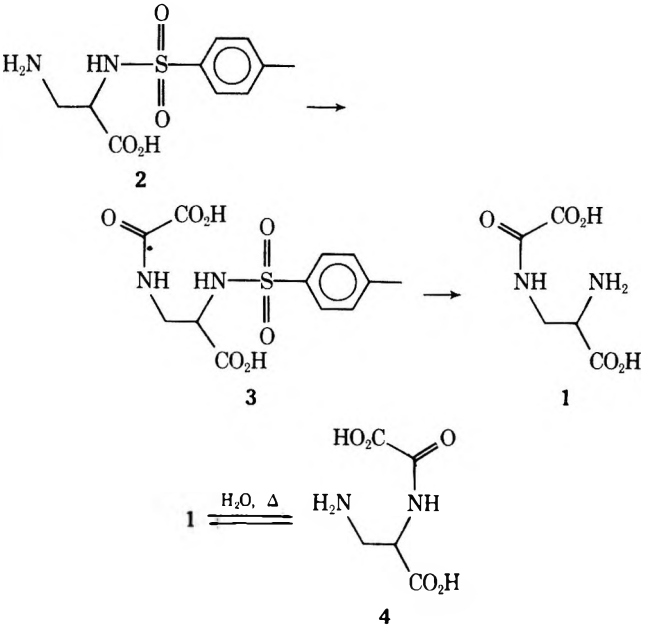
The nonprotein amino acid L-2-amino-3-oxalylaminopropionic acid (**1**) has been suggested[2] to be the neurotoxic principle of the legume *Lathyrus sativus*, consumption of the seeds of which is involved in the etiology of human neurolathyrism.[3] Recent studies indicate that the material is a potent antagonist of L-glutamic acid. The neurotoxin has been shown to inhibit glutamate uptake into certain yeasts[4] and into mitochondria,[5] and to block the physiological mechanism for inactivation of glutamate at the neuromuscular junction of the fleshfly *Sarcophaga bullata*,[6] a synapse at which glutamate is the putative neurotransmitter.

Our continuing investigations in the biochemistry and pharmacology of this material required the development of an efficient and economical source of the neurotoxin. The compound may be obtained in reasonable yields by isolation from seeds of *L. sativus;* the procedure is at best inconvenient and the seed, which must be imported from India, is not generally available. Previous investigations[2,4] have used simple syntheses of the material from the copper chelate of L-2,3-diaminopropionic acid and various oxalate esters. These procedures are economically prohibitive on any reasonably large scale owing to poor yields and the high cost of the starting material.

The synthesis devised in this laboratory starts with L-asparagine, the conversion of which to L-3-amino-2-(*p*-toluenesulfonyl)aminopropionic acid (**2**) via Hofmann degradation of *p*-toluenesulfonyl-L-asparagine[7] has been described.[8] It was found that the utmost care must be exercised to achieve the reported[8] yield for this reaction. An effort to improve the yield of the degradation was unsuccessful: the oxidative rearrangement of amides with lead tetraacetate[9] has been reported to give Hofmann-like products in exceptional yields. At our hands, however, the reaction failed: oxidation of *p*-toluenesulfonyl-L-asparagine in the prescribed manner[9] gave *p*-toluenesulfonamide as the only identifiable product. The oxalylation of **2** proceeds smoothly in dioxane solution, and good yields of **3** are obtained after only the most cursory purification.



Several attempts to remove the toluenesulfonyl blocking group were unsuccessful. Reduction in the usual fashion with sodium and liquid ammonia[10] gave a complex mixture from which the toxin could be isolated in yields of only 2–4%. An alternative method, reduction with sodium naphthalene in tetrahydrofuran,[11] was investigated in some detail, but was equally fruitless. Our attention then turned to a less generally approved procedure, cleavage with hydrobromic acid in acetic acid.[12] This method has failed to obtain wide use in peptide chemistry since the conditions are sufficiently vigorous to cleave peptide bonds. In the present case, it was a method of last resort inasmuch as the desired product **1** is known[13] to convert to the isomeride **4** upon heating in aqueous and presumably other protic media.

The reaction proved to proceed smoothly at 70° to give moderate yields (45–50%) of **1**. As anticipated, there was also formed 2,3-diaminopropionic acid, which has been isolated in yields of up to 23%. The isomerization **1** → **4**, however, was not observed. In retrospect it is clear that the strongly acidic medium essentially irreversibly protonates

the amino group as it is formed, thus preventing nucleophilic attack of the amino group on the oxalyl carboxyl group, presumably the first step in the isomerization.

The neurotoxin prepared by this method is identical in all respects with previously reported material,[2] except for the specific rotation. We have observed $[\alpha]^{24}D$ −19.5° (*c* 2.72, 4 *N* HCl) *vs.* a reported[2] $[\alpha]^{27}D$ −36.9° (*c* 0.66, 4 *N* HCl). Previous workers have given no indication of problems of racemization in the first steps used in our preparation and we have found no change in the rotation when the final cleavage reaction is conducted over periods of 2–16 hr, and at temperatures of up to 100°. Moreover, a sample isolated from *L. sativus* seeds by the reported procedure[2] gave at our hands $[\alpha]^{24}D$ −15.4° (*c* 3.00, 4 *N* HCl). We therefore suggest that the previously reported value is in error.

Experimental Section[14]

L-3-Oxalylamino-2-(*p*-toluenesulfonyl)aminopropionic Acid (3). To a chilled solution of oxalyl chloride (35 ml, 0.4 mol) and 400 ml of dry dioxane was added with vigorous stirring L-3-amino-2-(*p*-toluenesulfonyl)aminopropionic acid (25.8 g, 0.1 mol). The mixture was stirred for 6 hr at room temperature, and the reaction was then quenched by the slow addition of chipped ice. The mixture was evaporated to a small volume, and the oily residue was dried in vacuo. After trituration with dichloromethane, the tarry product slowly solidified. The solid was crushed and washed with additional dichloromethane. There was obtained 27.1 g (82%) of a pale tan powder: mp 187–189° dec; $[\alpha]^{23}D$ +18.1° (c 3.00, methanol); ir (Nujol) 3180, 3130, 1680, 1530, 1235, 1205, 1155, 1080, 955, 817, 745, 714, and 650 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_2O_7S$: C, 43.64; H, 4.27; N, 8.48; S, 9.64. Found: C, 43.57; H, 4.44; N, 8.55; S, 9.59.

A sample of the product (ca. 500 mg) was stirred overnight with 50 ml of methanolic hydrogen chloride (1.25 *N*). The solvent was removed and the residue was crystallized from dichloromethane–petroleum ether (bp 30–60°) to afford the dimethyl ester: mp 113–114.5°; NMR 7.5 (center of AA'BB' pattern, 5 H, aryl and amide H), 5.77 (d, 1 H, J = 7.5 Hz, sulfonamide H), 4.07 (m, 1 H), 3.88 (s, 3 H), 3.68 (m, 2 H), 3.62 (s, 3 H), and 2.40 ppm (s, 3 H).

Anal. Calcd for $C_{14}H_{18}N_2O_7S$: C, 46.92; H, 5.06; N, 7.82; S, 8.95. Found: C, 47.14; H, 5.09; N, 7.87; S, 8.75.

L-2-Amino-3-oxalylaminopropionic Acid (1). A thick-walled pressure bottle was charged with L-3-oxalylamino-2-(*p*-toluenesulfonyl)aminopropionic acid (5.9 g, 18 mmol), phenol (5.2 g), and 100 ml of 32% hydrogen bromide in acetic acid. The bottle was firmly stoppered, and the mixture was heated for 8 hr at 70°. The bottle was then chilled on ice, and the mixture was poured into ca. 600 ml of dry ether. The mixture was chilled for several hours, and the precipitated solids were collected and were washed with additional ether. The hygroscopic product was taken up in water, the solution was filtered with charcoal, and the filtrate was percolated through a 2.5 × 40 cm bed of Dowex 1 × 8 (formate). The column was washed with 1000 ml of water, which was discarded. The product was eluted with 2.5% formic acid; the ninhydrin-positive fractions were pooled and lyophilized. The residue was washed with a small amount of chilled water and acetone, and was air dried to give 1.70 g (49%) of the desired product as the hydrate, mp 206° (dec with gas evolution), $[\alpha]^{24}D$ −19.5° [c 2.72 (anhydrous basis), 4 *N* HCl] [lit.[2] $[\alpha]^{27}D$ −36.9° (c 0.66, 4 *N* HCl)].

Anal. Calcd for $C_5H_8N_2O_5 \cdot H_2O$: C, 30.93; H, 5.19; N, 14.43. Found: C, 30.92; H, 5.15; N, 14.35.

This material was found to be indistinguishable from the natural product isolated by the method of Rao et al.,[2] by chromatography, electrophoresis, and ir. The ir spectra were identical with the published spectrum.[2] The two materials had equal potency when assayed[4] as inhibitors of glutamate transport into yeast cells.

Registry No.—1, 5302-45-4; 2, 21753-19-5; 3, 57016-83-8; 3, dimethyl ester, 57016-84-9; oxalyl chloride, 79-37-8; hydrogen bromide, 10035-10-6.

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(14) Melting points were determined on a Hoover capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded in deuteriochloroform solution on a Varian HA-100 spectrometer; chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ scale). Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Optical rotations were measured in a 1-dm cell on a Zeiss circle polarimeter 0.01°. Microanalyses were performed by J. Nemeth and associates in the Department of Chemistry, University of Illinois. Hydrogen bromide (30–32% in acetic acid) was obtained from Eastman. L-Asparagine hydrate was purchased from Ajinomoto Co., Inc., Tokyo. The preparations of *p*-toluenesulfonyl-L-asparagine and L-3-amino-2-(*p*-toluenesulfonyl)aminopropionic acid were by established methods.

Isolation and Alkaline Decomposition of the Intermediate Pyridinium Salts Occurring in the Pyridine *N*-Oxide Oxidation of α-Halo Esters or Acids

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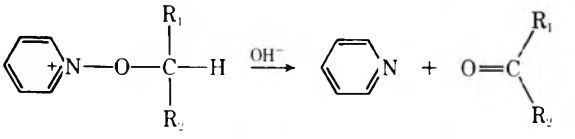
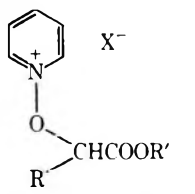
1-Alkoxypyridinium salts are well known; they result from nucleophilic substitution by pyridine *N*-oxide upon alkyl halides, sulfates, or sulfonates and oxonium salts.[1a] Their reactivity toward nucleophiles has been studied by Katritsky et al.[2] In basic solution these salts decompose to a carbonyl compound and the parent pyridine[3] as shown in Scheme I. This reaction can be used either as a carbonyl

Scheme I



compound preparation[1b,4] or as a way of deoxygenating pyridine *N*-oxide in nonreducing conditions.[5]

1-Alkoxypyridinium salts bearing an acid or ester function at the α position of the alkoxy group, such as 1 have not been described yet (though some derivatives of 1-[4-

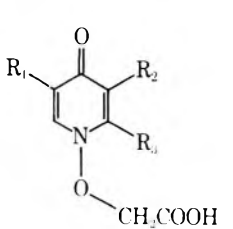


R, R' = H or alkyl

1a, X = Br

b, X = NO_3

c, X = picrate



2

Table I
Reaction of α-Bromo Esters and Acids, RCHBrCOOR′, with Pyridine N-Oxide → Py⁺—ORCHCOOR′X⁻

		X = Br			X = NO_3			NMR of nitrates, ppm						X = picrate
R	R′	Compd	Yield, %	Mp, °C[a]	Compd	Yield, %	Mp, °C[a]	H	R	R′	α	β	γ	Mp, °C[a]
H	Me	3a	78	74.5	3b	82[b]	Oil	5.5 s		3.85 s	9.4	8.3	8.75	118
H	*t*-Bu	4a	31	*c*	4b	60	116	5.3 s		1.5 s	9.3	8.23	8.7	118.5
H	CH_2Ph	5a	33	*c*	5b	43	104	5.5 s		5.3 s 7.47 s	9.34	8.29	8.74	101.5
Me	Me	6a	49	*c*	6b	81[b]	Oil	5.6 q	1.8 d	3.85 s	9.32	8.25	8.72	112
Ph	Me				7b	50	109	6.5 s	7.5 s	3.86 s	9.13	8.15	8.66	110
H	H	8a	62	107	8b	55	129	5.43 s			9.4	8.28	8.74	140
Ph	H	9a	89	103.5	9b	45	115	6.22 s	7.48 s		8.98	8.02	8.52	122

[a] Melting with decomposition. [b] Yield of picrate. [c] Hygroscopic crystals.

Table II
Reaction of α-Bromoacetic Acid with N-Oxides of Substituted Pyridines in the Presence of $AgNO_3$

				NMR, ppm				
Compd	Substituent	Yield, %	Mp, °C[a]	$-CH_2-$	α	β	γ	$-CH_3$
10b	2-Me	55	124	5.37	9.30	8.05	8.55	2.97
11b	3-Me	59	129	5.37	9.16	8.10	8.53	2.62
12b	4-Me	62	129	5.34	9.10	8.02		2.73
13b	2,6-Di Me	50	132	5.17		7.88	8.34	2.90

[a] Melting with decomposition.

oxo-1(*H*)-pyridyl]oxyacetic acid are known,[6] these compounds **2** possess the structure of neutral N-substituted pyridone, but not that of a pyridinium salt).

Nevertheless, the functional salts **1** have been postulated as intermediates in the oxidation of ethyl α-bromoacetate[7] or in the oxidative decarboxylation of either α-halo acids[8] or carboxylic anhydrides[9,10] by means of pyridine *N*-oxide. Reported attempts to isolate such quaternary salts derived from α-halo esters have not been successful,[7] though functional 1-alkoxypyridinium salts have been isolated in other cases, as, for example, in the reaction of α-picoline *N*-oxide with phenacyl bromide.[11]

We wish to report in the present note a convenient procedure for the preparation of the salts **1** and the results of their alkaline degradation.

The isolation of these salts as relatively stable crystalline solids in fairly good yields (see Table I) can be achieved by performing the reaction at 0°. Higher temperature must be avoided, because these compounds are very sensitive to nucleophiles.[2]

α-Bromo esters react in the cold with pyridine *N*-oxide, provided that the former is not fully substituted at the α position. The reaction is facilitated by means of silver nitrate; in this case, pyridinium nitrates which are more easily crystallized are obtained. The latter, having a less nucleophilic anion than the bromides, are more stable, and can be recrystallized from acetone without noticeable decomposition, while, for example, the bromide **3a** undergoes under these conditions a decomposition to methyl bromoacetate and pyridine *N*-oxide.

In the case of the derivatives **7b** the bromide is too unstable to be isolated and the nitrate slowly decomposes to methyl phenylglyoxylate. When bromides or nitrates could not be obtained or when they were too hygroscopic, the pyridinium picrates, which have proved to be more stable, were isolated.

The reaction of pyridine *N*-oxide with α-bromo acids is slower than the reaction with the corresponding esters. Nevertheless, the bromides **8a** and **9a** could be isolated in respectively 62 and 80% yield after 7 days at 4°. In this case too, it is more convenient to prepare the nitrates by working in the presence of silver nitrate.

Table III
Decomposition of Nitrates 4b, 5b, and 7b by Triethylamine in Methanol

Compd	Pyridine yield, %[a]	α-Carbonyl ester yield, %[b]
4b	97.5	97
5b	97.5	89
7b	95	95

[a] Determined by VPC analysis. [b] Gravimetric determination of the 2,4-DNP.

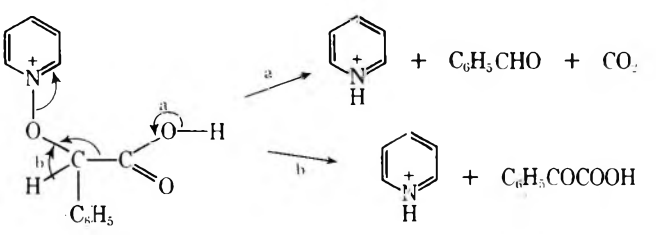
This reaction has been extended to the *N*-oxides of picolines and 2,6-dimethylpyridine as shown in Table II.

The reaction of quaternary salts **4b, 5b,** and **7b** with aqueous 1 *N* sodium hydroxide at room temperature produced pyridine in excellent yield (respectively 97, 95, and 92% in pyridinium picrate) but the resulting α-keto esters were not isolated owing to their hydrolysis by the basic medium.

Best yields of α-carbonyl esters (isolated as 2,4-DNP) are realized by decomposition of the salts with triethylamine in methanolic solution at ambient temperature (see Table III). In the case of the unstable nitrate **7b** this decomposition can take place slowly in the solid state, as previously stated.

Cohen and Song[8] have shown that decomposition of α-halo acids by pyridine *N*-oxide in refluxing benzene, toluene, or xylene is mainly an oxidative decarboxylation (path a in Scheme II) for which they have postulated the intermediacy of salts such as **1**. For example, in the reaction of

Scheme II



excess pyridine *N*-oxide with α-bromophenylacetic acid in refluxing benzene, they obtained principally benzaldehyde (49%) and carbon dioxide (46%); only a small amount (5%) of phenylglyoxylic acid was produced.

In our hands, the salt **9b**, upon treatment by aqueous 1 *N* sodium hydroxide at room temperature, reacted mainly according to path b of Scheme II, providing pyridine (78%), phenylglyoxylic acid (70% as mercuric salt), benzaldehyde (2.5%), and carbon dioxide (2.1%).

Similarly, Cohen and Song obtained formaldehyde (65%) and carbon dioxide (100%) by refluxing in xylene a mixture of chloroacetic acid and pyridine *N*-oxide, while the decomposition of the salt 8b that we performed in aqueous sodium hydroxide yielded up to 37% of glyoxylic acid (determined as calcium oxalate after subsequent oxidation).

The decomposition of the salt **7b** was performed on a batch scale in order to show the potential utility of these salts for α-keto ester synthesis. The intermediate pyridinium salt was not isolated and the reaction was performed in three different modes (see Experimental Section): (1) in equimolecular ratio without silver nitrate, (2) with an excess of pyridine *N*-oxide (1.5–1) and without silver nitrate, (3) in the presence of silver nitrate in equimolecular ratio.

The first two reactions were carried out in boiling methylene chloride while the third one was done in cold acetonitrile followed by fast treatment with triethylamine.

Yields of isolated methyl phenylglyoxylate were respectively (1) 48%, (2) 65%, and (3) 87%. So, this third procedure (3) can be recommended for α-keto ester synthesis from α-bromo esters under very mild conditions; it seems advantageous over the dimethyl sulfoxide oxidation process which has been applied to ethyl bromoacetate by Hunsberger and Tien,[12] and which is not free from side reactions. Although this method has been shown to give ethyl glyoxylate in 70–75% yields, the results were unsatisfactory with *tert*-butyl bromoacetate as reported by Carpino,[13] who isolated only small amounts of the phenylhydrazone of *tert*-butyl glyoxylate.

In conclusion, we show that the intermediate salts produced in the first step of the oxidation of α-halo acid or ester by pyridine *N*-oxide can be isolated; in addition the acid salts can be decomposed in a way that is different from the usual one which has been described in the decarboxylative process. Furthermore the ester salts may be useful intermediates in α-carbonyl ester synthesis.

Experimental Section

The products described in Tables I and II were prepared by one of the following methods. Yields were not optimized and melting points (open capillary) are uncorrected. NMR spectra were obtained on a Jeol C60HL instrument in D_2O solution using TSP (sodium 3-trimethylsilylpropionate-2,2,3,3-d_4) as internal standard. Chemical shifts are reported in parts per million (δ) and are followed by a letter giving the spin multiplicity except for the α, β and γ protons of the pyridine, which give rise to multiplets.[14] Satisfactory analytical data (±0.3% for C, H, N) were reported for the nitrates **4b, 5b, 7b, 8b, 10b, 11b, 12b,** and **13b** and for the picrates issued from **3b, 6b,** and **9b.**

General Procedure for the Conversion of α-Bromo Esters to 1-(1-Alkoxycarbonylalkoxy)pyridinium Bromides 3a–6a. To a solution of pyridine *N*-oxide (0.02 ml) in CH_2Cl_2 (5 ml) cooled to 0°C was added 0.02 mol of α-bromo ester. The mixture was kept at 4°C during 48 hr. In one case (**3a**) crystals appeared spontaneously; they were collected by filtration and washed with ether. In the other cases, crystallization was initiated by adding small amounts of ether.

General Procedure for the Conversion of α-Bromo Acids to the 1-(1-Carboxyalkoxy)pyridinium Bromides 8a and 9a. To a solution of pyridine *N*-oxide (0.02 mol) in CH_2Cl_2 (5 ml) cooled to 0°C was added 0.02 mol of α-bromo acid; the mixture was kept at 4°C during 7 days. Crystals appeared spontaneously; they were collected by filtration and washed with CH_2Cl_2.

General Procedure for the Conversion of α-Bromo Esters to the 1-(1-Alkoxycarbonylalkoxy)pyridinium Nitrates 3b–7b. Pyridine *N*-oxide (0.05 mol) and $AgNO_3$ (0.05 mol) were dissolved in 20 ml of CH_3CN under cooling (down to 0°C). To the stirred solution, 0.05 mol of bromo ester dissolved in 10 ml of CH_3CN was added over a period of 0.5 hr. The mixture was stirred for an additional 24 hr at room temperature (only 4 hr for **7b**). After filtration the precipitated AgBr was washed with acetonitrile. Adding small amounts of ether to the filtrate caused the precipitation of the pyridinium salt, which was collected by filtration and recrystallized from acetone or a mixture of acetone–acetonitrile.

When the nitrates were precipitated as oily products, they were transformed into picrates by treatment with an ethereal solution of picric acid.

General Procedure for the Conversion of α-Bromo Acids to the 1-(1-Carboxyalkoxy)pyridinium Nitrates 8b and 9b. Bromo acid (0.05 mol) dissolved in 20 ml of CH_3CN was added with stirring to a cooled solution of pyridine *N*-oxide (0.05 mol) and $AgNO_3$ (0.05 mol) in 10 ml of acetonitrile. The mixture was stirred for an additional period of 3 hr for **9b** and 24 hr for **8b.** The crystals thus obtained (AgBr and the pyridinium salt) were collected by filtration and washed with aqueous acetonitrile (5–10% H_2O). The filtrate was evaporated under vacuum and the residual product recrystallized from CH_3CN which contained traces of water.

The same procedure was applied to *N*-oxides of substituted pyridines listed in Table II, the additional stirring period being 24 hr.

Decomposition of the Ester Salts 4b, 5b, and 7b by 1 *N* Sodium Hydroxide. A solution of the salt **7b** (1.53 g, 5 mmol) in 50 ml of aqueous 1 *N* sodium hydroxide was allowed to stand for 0.5 hr at room temperature. One-half of the solution was extracted with chloroform (3 × 10 ml). The chloroform extract treated with an ethereal solution of picric acid gave 0.711 g (92%) of pyridinium picrate, mp and mmp 165° after recrystallization from EtOH.

To the second half of the initial solution was added a sulfuric solution of 2,4-dinitrophenylhydrazine and the precipitated 2,4-DNP was isolated in the usual manner. TLC analysis on silica gel showed that this 2,4-DNP was not the derivative of the expected α-keto ester but that of the keto acid resulting from hydrolysis as was confirmed by its melting point, 195–196° (lit.[15] 196–197°).

The same procedure applied to the salt **4b** and **5b** gave respectively a 97 and 95% yield of pyridinium picrate.

Decomposition of the Ester Salts 4b, 5b, and 7b by Triethylamine in Methanol. A 20-ml solution of 1.53 g (5 mmol) of **7b** and 14 ml (10 mmol) of triethylamine was allowed to stand for 0.5 hr at room temperature.

A 10-ml portion of the initial solution was extracted with chloroform (3 × 10 ml); quantitative VPC analysis of an aliquot of the extracts indicated a 95% yield of pyridine.

A 5-ml portion of the initial solution was added to a sulfuric solution of 2,4-dinitrophenylhydrazine. The methyl phenylglyoxylate 2,4-DNP (0.409 g, 95%) was isolated as usual and recrystallized from a mixture of AcOEt–EtOH, mp and mmp 172° (lit.[16] mp 171°).

The same procedure applied to **4b** gave a 97.5% yield in pyridine and a 97% yield in *tert*-butyl glyoxylate 2,4-DNP (0.387 g), mp 116.5°.

Under the same conditions, **5b** afforded a 97.5% yield in pyridine and an 89% yield in benzylglyoxylate 2,4-DNP (0.384 g), mp 191° (lit.[17] mp 190–192°).

Decomposition of 1-(1-Carboxymethoxy)pyridinium Nitrate (8b) by 1 *N* Sodium Hydroxide. A solution of 1.08 g (5 mmol) of **8b** in 50 ml of aqueous 1 *N* sodium hydroxide was allowed to stand for 14 hr. Extraction with chloroform (3 × 10 ml) followed by treatment of the chloroform extract by ethereal picric acid gave 1.25 g (82%) of pyridinium picrate, mp and mmp 165°.

The aqueous solution was then refluxed for 1 hr, allowing the formation of oxalic acid by quantitative oxidation of glyoxylic acid. The cooled solution was then acidified by addition of 10% AcOH. Calcium chloride (0.1 *N*, 100 ml) was added and the resulting mixture was heated with a steam bath for 0.5 hr. The calcium oxalate precipitated was isolated by filtration, washed with water, and dissolved in 100 ml of 10% sulfuric acid. The amount (1.72 mmol, 34.5%) was determined by permanganic titration.

Decomposition of 1-(1-Carboxybenzyloxy)pyridinium Nitrate (9b). A solution of 1.46 g (5 mmol) of **9b** in 20 ml of aqueous 1 *N* sodium hydroxide was allowed to stand for 0.5 hr. Barium carbonate precipitated by addition of 30 ml of aqueous 0.2 *M* barium hydroxide was isolated by filtration, washed with water, and dis-

solved in dilute HCl; sodium sulfamate was added to the chlorhydric solution and the precipitated barium sulfate was isolated as usual. From the amount of barium sulfate obtained (0.0243 g) a 2.1% yield in carbon dioxide was calculated.

The filtrate was then extracted by chloroform (3 × 10 ml) and the combined extracts were diluted to 50 ml. Treatment of 20 ml of this solution by ethereal picric acid gave 0.480 g (78%) of pyridinium picrate, mp and mmp 165° after recrystallization from EtOH; the benzaldehyde content of the above solution was determined by quantitative VPC analysis, which indicated a 2.5% yield.

The remaining aqueous layer was then acidified with dilute HCl and extracted with ether (3 × 10 ml). The residue from evaporation of ether was dissolved in water (10 ml) and an aqueous solution of mercuric acetate was added to the resulting solution. The mercuric salt of phenylglyoxylic acid which precipitated was isolated by filtration, washed, and dried; the salt weighed 0.86 g (70%) and had mp 167° (lit. mp[8] 165–166°).

Preparation of Methyl Phenylglyoxylate. A. By Reaction of Methyl α-Bromophenylacetate with 1 Equiv of Pyridine *N*-Oxide. A solution of pyridine *N*-oxide (5.25 g, 55 mmol) and methyl α-bromophenylacetate (11.9 g, 55 mmol) in methylene chloride (10 ml) was refluxed for 2 hr; 100 ml of a 10% HCl solution was added and the resulting mixture was extracted with ether (3 × 50 ml). Evaporation of the dried extract (Na_2SO_4) and distillation of the oily residue afforded 4.2 g (48%) of methyl phenylglyoxylate, bp 66° (0.5 mm), 2,4-DNP mp 172° (lit.[16] mp 171°).

B. By Reaction of Methyl α-Bromophenylacetate with 1.5 Equiv of Pyridine *N*-Oxide. A solution of pyridine *N*-oxide (10.5 g, 111 mmol) and methyl α-bromophenylacetate (16.8 g, 73 mmol) in methylene chloride (20 ml) was refluxed for 2 hr (TLC examination showed that methyl α-bromophenylacetate had been completely transformed); work-up as above afforded 7.86 g (65%) of methyl phenylglyoxylate.

C. By Reaction of Methyl α-Bromophenylacetate with Pyridine *N*-Oxide in the Presence of Silver Nitrate and Subsequent Decomposition by Triethylamine. A solution of methyl α-bromophenylacetate (17 g, 75 mmol) in acetonitrile (15 ml) was added dropwise, under stirring, to an ice-cooled solution of pyridine *N*-oxide (7.4 g, 78 mmol) and silver nitrate (13.3 g, 78 mmol) in acetonitrile (30 ml). Stirring was continued for an additional 2 hr; the precipitated silver bromide was eliminated by filtration and washed with acetonitrile. To the stirred filtrate, triethylamine was slowly added, and the resulting solution was then acidified by 10% HCl. Work-up as in A afforded 10.8 g (87%) of methyl phenylglyoxylate.

Registry No.—**3a**, 56943-39-6; **3b**, 56943-41-0; **3c**, 56943-42-1; **4a**, 56943-43-2; **4b**, 56943-45-4; **4c**, 56943-46-5; **5a**, 56943-47-6; **5b**, 56943-49-8; **5c**, 56943-50-1; **6a**, 56943-51-2; **6b**, 56943-53-4; **6c**, 56943-54-5; **7b**, 57031-39-7; **7c**, 56943-56-7; **8a**, 56943-57-8; **8b**, 56943-59-0; **8c**, 56943-60-3; **9a**, 56943-61-4; **9b**, 56943-63-6; **9c**, 56943-64-7; **10b**, 109-06-8; **11b**, 108-99-6; **12b**, 108-89-4; **13b**, 108-48-5; methyl α-bromoacetate, 96-32-2; *tert*-butyl α-bromoacetate, 5292-43-3; benzyl α-bromoacetate, 5437-45-6; methyl α-bromopropanoate, 5445-17-0; methyl α-bromobenzeneacetate, 3042-81-7; α-bromoacetic acid, 79-08-3; α-bromobenzeneacetic acid, 4870-65-9; pyridine *N*-oxide, 694-59-7; $AgNO_3$, 7761-88-8; picric acid, 88-89-1; sodium hydroxide, 1310-73-2; 2,4-DNP, 119-26-6; triethylamine, 121-44-8; *tert*-butyl glyoxylate 2,4-DNP, 56943-65-8; methyl phenylglyoxylate, 15206-55-0.

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Lithiation of Methoxyindoles

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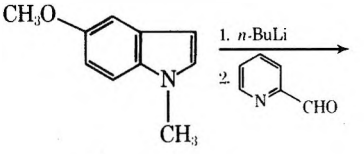
It has been demonstrated that 1-benzenesulfonylindole can be lithiated in the 2 position and that the resulting lithiated intermediate can be used for the synthesis of a variety of 2-substituted indoles.[1,2] This extends earlier studies[3] which had demonstrated selective lithiation of 1-alkylindoles, since the benzenesulfonyl group can be removed readily by hydrolysis.[1] In view of the interest in biologically active methoxyindoles we have now extended lithiation studies to 5- and 6-methoxyindole derivatives.

Lithiation of 1-methyl-5-methoxyindole (1) by *n*-butyllithium in refluxing ether was nonselective as judged by the formation of three isomeric alcohols after reaction with pyridine-2-carboxaldehyde. Two of the products (2 and 3) were obtained as pure crystalline compounds while a third (4) was obtained as an oil slightly contaminated with 2.



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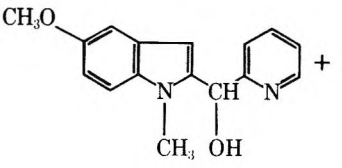

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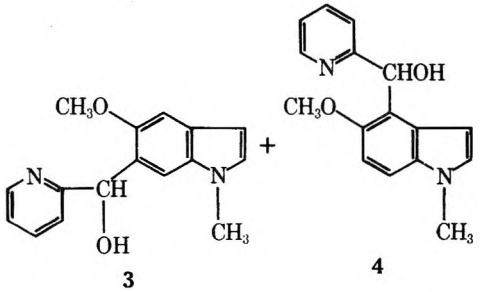

3 4

Product 2 was identified as the 2-substituted product on the basis of a sharp singlet for the indole 3H proton in the NMR. The other major product was assigned structure 3 since the aromatic region reveals two prominent singlets at δ 6.96 and 7.22, indicating that both of the 5 and 6 positions of the ring are substituted. The third product was noncrystalline and a sample purified by chromatography contained ~10% 2. However, the NMR clearly indicated that it was an isomeric product of substitution on the carbocyclic ring since the indole 3H signal appeared as a doublet and the other spectral features were those expected for a 1:1 ad-

duct. Lithiation occurred at 0° using *tert*-butyllithium in THF and the 2 position was selectively lithiated. Compound **2** was isolated in 39% yield and no **3** or **4** could be detected.

1-Benzenesulfonyl-5-methoxyindole (**5**) and 1-benzenesulfonyl-6-methoxyindole (**6**) were prepared readily by reaction of the sodium salts of the corresponding indoles with benzenesulfonyl chloride. Lithiation was effected using *tert*-butyllithium in THF. Lithiation occurred selectively at the 2 position in both compounds and good yields of adducts were obtained on reaction with carbonyl compounds such as pyridine-2-carboxaldehyde, pyridine-3-carboxaldehyde, and 4-acetylpyridine. These results indicate that the benzenesulfonyl group, in addition to serving as a removable N-protecting group, may selectively activate the 2 position of the indole nucleus toward lithiation. The reaction products were identified as 2-substitution compounds on the basis of NMR data. In particular, in each case the readily observable 3H proton appears as a singlet whereas a doublet is observed in indoles lacking 2 substituents. Lithiation of **5** by *n*-butyllithium was also selective when carried out in refluxing ether for a period of 10 hr.

Experimental Section

1-Benzenesulfonyl-5-methoxyindole (5). A solution of sodium methylsulfinylmethide was prepared in the standard way[4] from 0.40 g (1.75 mmol) of sodium hydride and 10 ml of dimethyl sulfoxide. The solution was cooled in an ice bath and 5-methoxyindole (2.0 g, 1.35 mmol) in ether was added dropwise followed by stirring for 1.5 hr. The solution was then cooled to 0° and 2.88 g (1.65 mmol) of benzenesulfonyl chloride was added followed by stirring for 0.5 hr. Water was added and the reaction mixture was extracted with methylene chloride. After drying and evaporation, recrystallization from methylene chloride–hexane gave **5** (3.29, 82%): mp 98–99°; NMR ($CDCl_3$): δ 3.75 (s, 3), 6.53 (d, 1, J = 4 Hz), and 6.8–8.0 (m, 9).

Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.75; H, 4.53. Found: C, 62.85; H, 4.58.

1-Benzenesulfonyl-6-methoxyindole (6) was prepared in a similar manner from 6-methoxyindole,[5] mp 140–142°, 75% yield after recrystallization from methylene chloride–hexane.

Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.72; H, 4.53. Found: C, 62.73; H, 4.55.

1-Methyl-5-methoxyindole (1) was prepared by alkylating the anion prepared as above with methyl iodide, 73% yield, mp 103–104° (lit.[6] mp 103–104°) after recrystallization from methylene chloride–hexane.

Lithiation of 1-methyl-5-methoxyindole with *n*-butyllithium was carried out by refluxing an ether solution containing **1** (0.50 g, 3.1 mmol) and 1 equiv of *n*-butyllithium for 13 hr. After cooling to room temperature an ether solution of pyridine-2-carboxaldehyde was added. The solution was stirred for 0.5 hr and poured into water. The product mixture was extracted and separated by column chromatography. Benzene eluted unreacted **1** (0.18 g, 36%). Ethyl acetate eluted a mixture (0.53 g, 74%) of **2**, **3**, and **4**. The NMR spectrum of the mixture indicated that the ratio was roughly 4:5:1. Pure samples of **2** and **3** were obtained by chromatography on silica gel using 10% ether in benzene for elution followed by recrystallization. Compound **2**: mp 142–143°; NMR ($CDCl_3$) δ 3.55 (s, 3), 3.78 (s, 3), 4.75 (s, broad, 1), 5.95 (s, 1), 6.13 (s, 1), 6.7–7.8 (m, 6) and 8.55 (d, 1, J = 4.5 Hz).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.96; N, 10.45. Found: C, 71.41; H, 6.00; N, 10.41.

Isomer **3**: mp 104–106°; NMR ($CDCl_3$) δ 3.65 (s, 3), 3.83 (s, 3) 6.28 (s, 1), 6.35 (d, 1, J = 3.0 Hz), 6.93 (d, 1 J = 3.0 Hz). 7.0–7.7 (m, 5), and 8.50 (d, 1, J = 4.5 Hz).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97. Found: C, 71.57; H, 5.98.

A fraction containing **2** and a third product was rechromatographed to give **4** as an oil, contaminated by ~10% **2**: NMR ($CDCl_3$) δ 3.60 (s, 3), 3.80 (s, 3), 6.22 (d, 1 J = 3.0 Hz), 6.45 (s, 1), 6.82 (d, 1, J = 3.0 Hz), 6.9–7.7 (m, 5), 8.50 (d, 1, J = 4.0 Hz).

Lithiation of 1-methyl-5-methoxyindole with *tert*-butyllithium was carried out by adding *tert*-butyllithium (1.65 mmol) to a solution of **1** (0.25 g, 1.5 mmol) in tetrahydrofuran (30 ml) at 0°. The solution was then stirred at room temperature for 45 min before being cooled again to 0°. A solution of pyridine-2-carboxaldehyde (200 mg, 1.9 mmol) was added. The usual work-up gave the crude product in which no **3** or **4** could be detected by TLC or NMR. Chromatography afforded recovered **1** (0.085 g) and **2** (0.106 g, 39%).

Lithiation of 1-benzenesulfonyl-5-methoxyindole (5) was effected by addition of 1.25 equiv of *tert*-butyllithium at 0° in THF (25–50 ml) followed by stirring at room temperature for 45 min.

Reaction with **pyridine-3-carboxaldehyde** was carried out by dropwise addition of 0.53 g (1.5 equiv) of the aldehyde in THF (5 ml) at 0° followed by stirring at room temperature for 1.5 hr. After hydrolysis and extraction, chromatography on silica gel gave recovered **5** (0.12 g) and 1-benzenesulfonyl-2-(3-pyridylhydroxymethyl)-5-methoxyindole (1.04 g, 84%): mp 157–158° after recrystallization from methylene chloride; NMR (Me_2SO) δ 3.72 (s, 3), 6.44 (s, 2), 6.7–7.1 (m, 4), 7.2–8.0 (m, 9).

Anal. Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.96; H, 4.57; N, 7.11. Found: C, 63.71; H, 4.56; N, 7.02.

Reaction with pyridine-2-carboxaldehyde was done in a similar manner and gave 20% unreacted **5** and 1-benzenesulfonyl-2-(2-pyridylhydroxymethyl)-5-methoxyindole in 59% yield: mp 140–142° after recrystallization from methylene chloride–hexane; NMR (acetone) δ 3.70 (s, 3), 6.25 (s, 1), 6.65 (broad, 1), 6.85 (m, 1), 6.92 (s, 1), 7.1–8.1 (m, 10), and 8.5 (d, 1).

Anal. Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.96; H, 4.57; N, 7.11. Found: C, 63.73; H, 4.64; N, 7.08.

Lithiation of 1-benzenesulfonyl-5-methoxyindole (5) with *n*-butyllithium was effected by refluxing an ether solution with an equimolar amount of *n*-butyllithium for 10 hr. An ether solution of pyridine-2-carboxaldehyde was added and the mixture stirred at room temperature for 0.5 hr. The usual work-up followed by chromatography separated unreacted starting material from **2** which was identified by its NMR spectrum. There was no evidence of formation of **3** or **4**.

Lithiation of 1-benzenesulfonyl-6-methoxyindole (6) was carried out as described for **5**. The products are described below. Reaction with **pyridine-3-carboxaldehyde** gave 1-benzenesulfonyl-2-(3-pyridylhydroxymethyl)-6-methoxyindole in 70% yield: mp 133–134° after recrystallization from ether–hexane; NMR (acetone) δ 3.82 (s, 3), 6.60 (s, 2), 6.83 (d of d, 1, J = 8.2, 1.5 Hz), 7.1–8.0 (m, 10), and 8.55 (broad, 2).

Anal. Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.96; H, 4.57; N, 7.11. Found: C, 63.86; H, 4.60; N, 7.13.

From pyridine-2-carboxaldehyde, 1-benzenesulfonyl-2-(2-pyridylhydroxymethyl)-6-methoxyindole was obtained in 62% yield after recrystallization from methylene chloride–hexane: mp 123–125°; NMR (acetone) δ 3.80 (s, 3), 6.18 (s, 1), 6.63 (broad s, 1), 6.76 (d of d, J = 8.2, 2.2 Hz), 7.1–8.2 (m, 11), and 8.48 (d, 1, J = 4.5 Hz).

Anal. Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.96; H, 4.57; N, 7.11. Found: C, 63.88; H, 4.59; N, 7.13.

From 4-acetylpyridine, 1-benzenesulfonyl-2-[1-(4-pyridyl)-1-hydroxyethyl]-6-methoxyindole was obtained in 58% yield after recrystallization from chloroform: mp 237–238°; NMR (Me_2SO) δ 1.84 (s, 3), 3.77 (s, 3), 5.93 (s, 1), 6.85 (d of d, 1, J = 9.0, 0.8 Hz), 7.1–7.9 (m, 10), and 8.38 (d, J = 5 Hz).

Anal. Calcd for $C_{22}H_{20}N_2O_4S$: C, 64.71; H, 4.90. Found: C, 64.71; H, 4.97.

Acknowledgment. This work was supported by National Cancer Institute Grant CA-12940.

Registry No.—**1**, 2521-13-3; **2**, 56995-09-6; **3**, 56995-10-9; **4**, 56995-11-0; **5**, 56995-12-1; **6**, 56995-13-2; 5-methoxyindole, 1006-94-6; benzenesulfonyl chloride, 98-09-9; 6-methoxyindole, 3189-13-7; *n*-butyllithium, 109-72-8; pyridine-2-carboxaldehyde, 1121-60-4; *tert*-butyllithium, 594-19-4; pyridine-3-carboxaldehyde, 500-22-1; 1-benzenesulfonyl-2-(3-pyridylhydroxymethyl)-5-methoxyindole, 56995-14-3; 1-benzenesulfonyl-2-(2-pyridylhydroxymethyl)-5-methoxyindole, 56995-15-4; 1-benzenesulfonyl-2-(3-pyridylhydroxymethyl)-6-methoxyindole, 56995-16-5; 1-benzenesulfonyl-2-(2-pyridylhydroxymethyl)-6-methoxyindole, 56995-17-6; 4-acetylpyridine, 1122-54-9; 1-benzenesulfonyl-2-[1-(4-pyridyl)-1-hydroxyethyl]-6-methoxyindole, 56995-18-7

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O-Acylation of Acidic Methylene Compounds

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We would like to report the results on the O-acylation of the relatively acidic methylene compound 1,2-diphenyl-4-butyl-3,5-pyrazolidinedione (phenylbutazone). The previously reported methods[1] which involved acylation in the presence of aqueous sodium hydroxide or triethylamine gave low yields of the *O*-acyl phenylbutazones (**2**) along with some uncharacterized side products. However, these results are not surprising in view of the fact that **2a** undergoes hydrolysis at a rate approaching that of acetic anhydride.[2] Carbon as well as oxygen acylation of the enolate of phenylbutazone is also possible and the C-acylated phenylbutazone may lead to some of the side products. Therefore, it was logical that methods used for preparing mixed anhydrides and *O*-acyl enolates offered the best opportunity for preparing **2**.

A recent innovation in the preparation of mixed anhydrides has been to employ the reaction of the thallium(I) salt of the weaker of the two acids with the acid halide of the stronger acid.[3a] In general, carbon acid thallium(I) salts are insoluble in most reaction solvents and in the case of phenylbutazone the insoluble nature of the thallous salt would ensure that an excess of the acid halide was always present in the reaction medium, conditions also known to maximize O-acylated product in the related reactions of enolate anions with acylating agents.[3b,4]

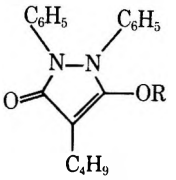
The thallium(I) salt of phenylbutazone (**1**) was a stable, nonhygroscopic white solid. Its infrared spectrum showed loss of all carbonyl bands exhibiting instead a broad absorption centered at 1500 cm^{-1} with a weak shoulder[5] at 1650 cm^{-1}. When **1** was suspended in ether and allowed to react with an acid chloride at room temperature, only one product was observed when the reaction was analyzed by TLC. The ir, uv, and NMR spectra, as well as the elemental analysis of the products were consistent with the corresponding *O*-acyl derivatives of phenylbutazone (**2**) and acid hydrolysis of several of the derivatives prepared regenerated phenylbutazone.

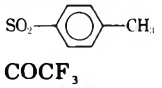
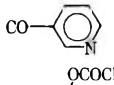
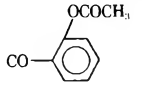
Attempts to prepare **2f** by reaction of **1**, or other salts of phenylbutazone, with nicotinoyl chloride hydrochloride in the presence or absence of an acid scavenger were unsuccessful. Apparently the intermediate acid chloride, generated in situ, preferentially reacted with itself to give an uncharacterized saltlike material faster than it reacted with **1** to give **2f**. Other amino acid chloride hydrochlorides gave similar results so that it was not possible to prepare **2** by the above route when R contained a tertiary amino group.

Therefore, an alternate synthetic scheme was investigated based on the observation of Bourne et al.[6] that 1:1 mixtures of trifluoroacetic anhydride (TFAA) and a carboxylic acid gave the corresponding mixed anhydride and pyridinium trifluoroacetate when the mixtures were allowed to react with pyridine. However, the initial reaction between phenylbutazone and TFAA did not give **2e**, but rather an incompletely characterized adduct that incorporated 1 equiv of TFAA[7] and is considered to be **3**. The NMR spectrum showed an acidic proton at δ 13.6 and loss of the methine hydrogen signal of O=C-CH-C=O centered at δ 3.4, and the ir spectrum showed two strong anhydride-like absorptions at 1830 and 1785 cm^{-1}, as well as complete loss of the carbonyl absorption at 1710 cm^{-1}.

More interesting was the fact that the initial adduct (**3**) could be equilibrated with another anhydride to give a second phenylbutazone adduct which had lost one trifluoroacetyl group and had incorporated the acyl portion of the other anhydride. Thus, **3** was equilibrated with acetic an-

Table I
***O*-Acyl Phenylbutazone Derivatives**

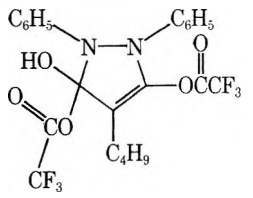


Compd	R	% yield	Mp, °C	Method[a]	Anal. Calcd over found
2a	$COCH_3$	54	49–51	TFAA	Experimental
2b	COC_6H_5	65	116–117.5[a]	Tl (I)	C, 75.70; H, 5.88; N, 6.79 C, 75.92; H, 5.85; N, 6.66
2c	$COC(CH_3)_3$	75	114–115	Tl (I)	Experimental
2d		33	125–126.5	Tl (I)	C, 67.51; H, 5.66; N, 6.06 C, 67.65; H, 5.74; N, 5.89
2e	$COCF_3$				
2f		78	139–141	TFAA	C, 72.62; H, 5.61; N, 10.16 C, 72.39; H, 5.64; N, 9.98
2g		54	85–87[b]	Tl (I)	C, 71.47; H, 5.57; N, 5.95 C, 71.26; H, 5.67; N, 5.82

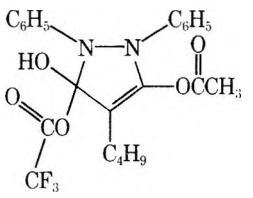
[a] TFAA and Tl (I) stand for the basic method used as exemplified in the Experimental Section for **2a** and **2c**.

hydride and the volatiles were removed in vacuo to give a crystalline adduct assigned structure **4**. Compound **2a** was then obtained by extracting a dichloromethane solution of **4** with 1 equiv of aqueous base and crystallizing **2a** from heptane; **2f** was prepared by the same method.

The infrared spectrum of **4** shows two carbonyl absorptions. One absorption at 1800 cm^{-1} is at the same position as the acetate carbonyl in **2a** and it has been assigned to the acetate carbonyl. The other carbonyl absorption at 1780 cm^{-1} is broad and shifted to longer wavelengths, which suggests that the trifluoroacetate carbonyl is involved in a hydrogen bond. Taken together, these assignments suggest the following structure for the adduct **4**. By analogy one may also infer a similar structure for **3**.



3



4

Experimental Section

General. All melting points were uncorrected. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind., and all analyses were within ±0.3%. TLC were run on Brinkmann polygram sil G/uv_{254}. NMR spectra were recorded on a Varian T-60 spectrometer using Me_4Si as an internal standard. Infrared spectra were recorded on a Beckman IR-33. Trifluoroacetic anhydride and thallium(I) ethoxide were obtained from Aldrich Chemical Co.

1,2-Diphenyl-4-butyl-5-acetyloxy-4-pyrazolin-3-one (2a). Phenylbutazone (5.0 g, 0.016 mol) was dissolved in 15.0 g (0.081 mol) of trifluoroacetic anhydride which was cooled with an ice bath; it usually took about 0.25 hr for all of the phenylbutazone to go into solution. Then the reaction mixture was concentrated in vacuo at room temperature to give **3** as a viscous, clear oil which crystallized when it was cooled in the refrigerator. The crystals were too hygroscopic to handle but NMR and ir spectra of the oil were recorded: ir (neat) 3000–2200 (broad, moderate) (O–H), 1830 (strong, sharp) (C=O), and 1780 cm^{-1} (broad, strong) (C=O); NMR ($CDCl_3$) δ 13.6 (1, 2, OH), 7.5–7.10 (10, m, aromatic H), 2.55–2.2 (2, m, CH_2C=), and 2.2–0.75 (7, m, CH_3 and CH_2). The oil was then allowed to react with 10 ml of acetic anhydride overnight in a tightly sealed flask under a nitrogen atmosphere. The volatile materials were evaporated at room temperature to give a white solid (mp 50–60°), a portion of which was recrystallized from CH_2Cl_2–heptane to give white crystals (mp 63–66°) of **4** whose spectral properties were identical with those of the crude solid: mp 50–60°; ir (KBr) 2800–2200 (broad, moderate) (O–H), 1800 (strong, sharp) (C=O), and 1780 cm^{-1} (broad, strong) (C=O); NMR ($CDCl_3$) δ 11.5 (1, s, OH), 7.55–7.0 (10, m, aromatic H), 2.5–2.1 (s, m, CH_2C=), 2.13 (3, s, CH_3C=O), and 2.1–0.75 (7, m, CH_3 and CH_2).

Anal. Calcd for $C_{23}H_{23}F_3N_2O_5$: C, 59.47; H, 4.99; N, 6.03; F, 12.27. Found: C, 59.54; H. 5.02; N, 6.18; F, 12.24.

The rest of the white solid, mp 50–60°, was dissolved in 120 ml of CH_2Cl_2 and extracted with 75 ml of water containing 1.7 g (0.017 mol) of $KHCO_3$. The CH_2Cl_2 layer was separated and dried over Na_2SO_4 and the CH_2Cl_2 was evaporated in vacuo to give a viscous light-yellow oil. The oil was crystallized from CH_2Cl_2–heptane (20:650) which was concentrated to 350 ml on a hot plate and then cooled in a refrigerator overnight to give 2.10 g (mp 49–51°) of **2a** as fine needles. The mother liquor was concentrated to 200 ml and cooled overnight to give an additional 0.93 g (mp 46–49°) of **2a** as fine needles for a total yield of **2a** of 54%: ir (KBr) 1800 and 1700 cm^{-1} (strong, sharp) (C=O); NMR ($CDCl_3$) δ 7.6–7.0 (10, m, aromatic H), 2.45–2.1 (2, m, CH_2-C=), 2.13 (3, s, CH_3C=O), and 2.0–0.7 (7, m, CH_3 and CH_2).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.97; H, 6.33; N, 7.99. Found: C, 71.79; H, 6.19; N, 8.16.

1,2-Diphenyl-4-butyl-5-pivaloxy-4-pyrazolin-3-one (2c). Thallium(I) ethoxide (2.24 g, 0.009 mol) was dissolved in anhydrous ether (100 ml) and allowed to react with 2.84 g (0.0092 mol) of phenylbutazone. The resulting white suspension was stirred at room temperature for 1 hr, and then it was filtered. The residue was dried in a vacuum desiccator to give 4.55 g (mp 194–202° dec) of the thallium(I) salt of phenylbutazone (**1**).

Anal. Calcd for $C_{19}H_{19}N_2O_2Tl$: C, 44.59; H, 3.74. Found: C, 44.26; H, 3.93.

A suspension of **1** (5.12 g, 0.01 mol) in anhydrous ether (100 ml) was then allowed to react with 1.20 g (0.01 mol) of pivalyl chloride. The resulting suspension was stirred at room temperature for 6 hr. Then it was filtered and the filtrate was concentrated in vacuo. The residue from the concentration of the filtrate was titrated with petroleum ether (bp 30–60°) to give 2.95 g (mp 114–115°, 75% yield) of **2c**: ir (KBr) 1790 and 1660 cm^{-1} (strong, sharp) (C=O); NMR ($CDCl_3$) δ 7.6–6.95 (10, m, aromatic H), 2.40–2.10 (2, m, CH_2C=C), 1.95–0.7 (7, m, CH_3 and CH_2), and 1.20 [9, s, $(CH_3)_3C$].

Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: 73.40; H, 7.06; N, 7.18.

Registry No.—**1**, 57091-21-1; **2a**, 57091-22-2; **2b**, 16006-72-7; **2c**, 57091-23-3; **2d**, 57091-24-4; **2f**, 57091-25-5; **2g**, 42177-40-2; **3**, 57091-26-6; **4**, 57091-27-7; phenylbutazone, 50-33-9; trifluoroacetic anhydride, 407-25-0; acetic anhydride, 108-24-7; thallium(I) ethoxide, 20398-06-5; pivalyl chloride, 3282-30-2; benzoyl chloride, 98-88-4; tosyl chloride, 98-59-9; 3-pyridinecarboxylic anhydride, 16837-38-0; 2-acetoxybenzoyl chloride, 5538-51-2.

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Electrolytic Decarboxylation Reaction. III. Anodic Acetoxylation of Tricyclo[4.4.0.0^{1,5}]decan-4-ones

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The conversion of carboxyl function to acetoxy group has been the subject of many investigations in recent years.[1-5] One of the major difficulties in the reaction is associated with lack of effective methods for preparing carbonium ion at the site of carbon atom attached to carboxyl group. Our interest in exploring the utility of the electrolytic decarboxylation method[6] enables us to investigate the electrochemical acetoxylation to carbonium ion at the C-2 carbon of the tricyclo[4.4.0.0^{1,5}]decan-4-one system. In this report we describe an application of the anodic acetoxylation method to the 2-carboxytricyclo[4.4.0.0^{1,5}]decan-4-ones (**1b** and **7**).

Electrolysis of **1b** in a mixed solvent of AcOH–*t*-BuOH–Et_3N (2:1:0.1) using platinum electrodes at a constant cur-

Table I
Electrolytic Decarboxylation of 1b in Various Solvents

Run	Electrode	Supporting electrolyte (ml)	Solvent (ml)	Current, A/cm²	Applied voltage, V	Temp, °C	Time, hr	Product, %[a] 2	3	4	5	6
1	C	Et_3N (0.04)	Py–H_2O (9:1)	0.03–0.02	20–25	3–5	5	25	10			
2	Pt	Et_2NH (0.03)	MeOH (8)	0.07–0.08	12–15	5–10	2				64	14
3	Pt	Et_3N (0.6)	AcOH-*t*-BuOH (12:6)	0.08	20	5–10	20			67		

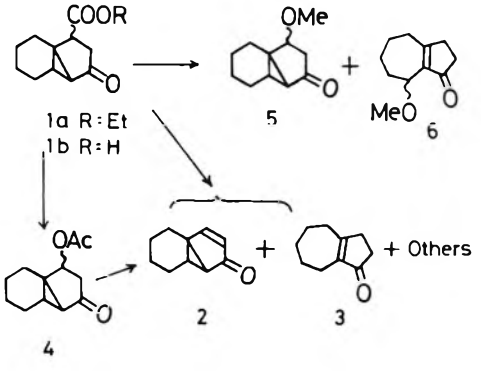
[a] Yields are calculated on isolated products.

Table II
Physical Properties and Elemental Analyses of the Products 2, 3, 4, 5, and 6 obtained by Electrolysis of 1b

Compd	Bp, °C (mm)	Ir, $\nu_{C=O}$	Ir, cm⁻¹ $\nu_{C=C}$	NMR, ppm, δ	Peak, *m/e* (rel intensity)	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
2	153–155 (11)	1697	1569	5.43 (d, 6 Hz, HC=) 7.35 (d, 6 Hz, HC=)	148 (M^+ 47) 91 (100)	$C_{10}H_{12}O$	81.04	8.16	81.05	8.19
3	135–137 (11) [lit.[a] 136 (12)]	1692	1642		150 (M^+, 91), 122 (100)					
4	145–147 (2)	1734		2.06 (s, 3 H, CH_3CO) 2.08 (s, 3 H, CH_3CO)	208 (M^+, 7), 120 (100)	$C_{12}H_{16}O_3$	69.21	7.74	69.33	7.82
5	119–120 (2)	1730		3.21 (s, 3 H, CH_3O) 3.28 (s, 3 H, CH_3O)	180 (M^+, 5) 122 (100)	$C_{11}H_{16}O_2$	73.30	8.95	73.30	9.00
6	118–120 (2)	1695	1642	3.14 (s, 3 H, CH_3O)	180 (M^+, 2) 164 (100)	$C_{11}H_{16}O_2$	73.30	8.95	73.51	8.84

[a] P. Plattner and G. Büchi, *Helv. Chim. Acta*, 29, 1608 (1946).

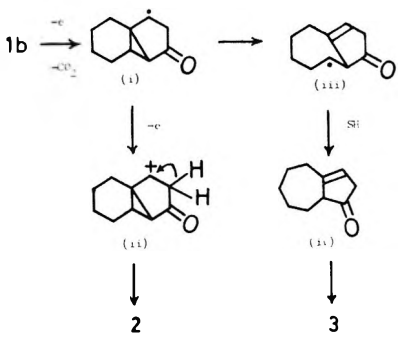
rent of 0.08 A/cm², applied voltage ca. 20 V (1.6–1.7 V vs. SCE), at 5–10° for 20 hr afforded 67% of the acetate **4** as a sole product. The conditions and results of electrolyses of **1b** using diethyl- and/or triethylamines as supporting electrolytes are summarized in Table I. As shown in run 1 (Table I) the electrolysis of **1b** in a mixed solvent of pyridine–H_2O (9:1) using carbon rod electrodes gave a mixture of products **2** and **3** in which the α,β-unsaturated ketone **2** was obtained in 25% yield. Electrolysis of **1b** in methanol using platinum electrodes (run 2) afforded methoxy derivatives **5** and **6** (ca. 5:1) in 78% yield. However, the product-selective electrolysis of **1b** to give the acetate **4** was



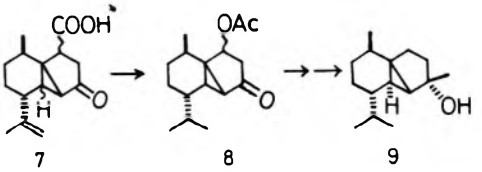
achieved in AcOH-*t*-BuOH (2:1). Properties of the products from **1b** are given in Table II.

It is plausible that the products **2**, **4**, **5**, and **6** may have been produced on electrolysis of **1b** via carbonium intermediates, owing to two-electron discharges on the anode electrode. In contrast to this, it is considered that the ketone **3** would be derived from a radical intermediate (iii) (Scheme I). The result with respect to the preparation of butenolides by electrolytic decarboxylation of β-carboxy-γ-butyrolactones[6a] demonstrates that the electrolysis in the pyridine–Et_3N–H_2O system gives promise of affording a cation intermediate and we are somewhat surprised at the appearance of **3** in the electrolysis medium. As shown in Scheme I, the electrolysis of **1b** (run 1) would proceed by one-electron discharge to yield a key intermediate (i), which is submitted to further anodic oxidation to provide a cation precursor (ii) for **2**.

Scheme I



The method could be applied successfully to a key step of the conversion to (−)-cubebol (**9**) from (−)-carvone.[7] Thus, electrolysis of **7** in the mixed solvent using platinum electrodes at a constant current of 0.08 A/cm², applied voltage ca. 20 V (1.6–1.7 V vs. SCE), at 10° for 20 hr afforded 72% of the acetate **8**, when the electrolysis was carried out without using membrane. In this electrolysis condition hydrogenation to the isopropenyl function of **7** occurred synchronously.



The voltammetric oxidation curves of **1b** and **7** in AcOH–*t*-BuOH–Et_3N using smooth platinum electrodes are shown in Figure 1, demonstrating that in the potential range of 1.6–1.7 V vs. SCE anodic oxidation of the substrates **1b** and **7** proceeded favorably rather than that of acetate anion.

Experimental Section

Melting points and boiling points are uncorrected. NMR spectra were determined with a Hitachi R-24 instrument. Ir spectra were

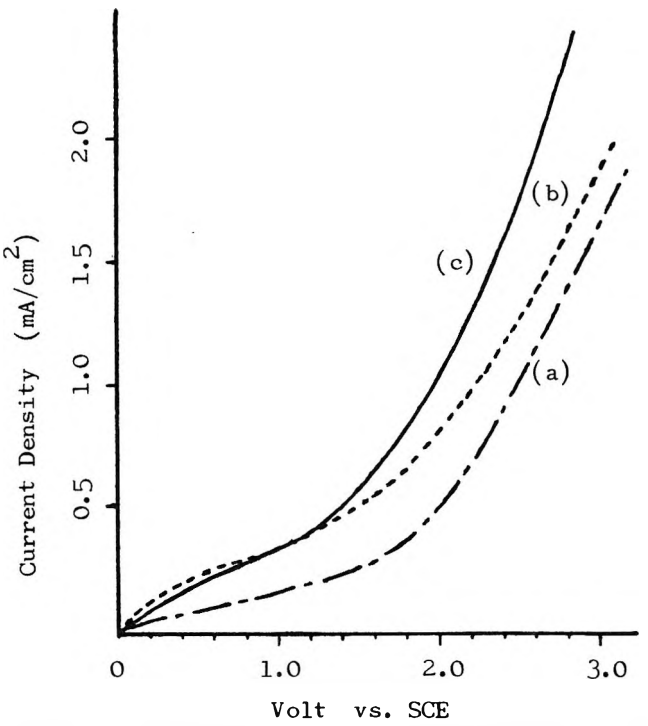


Figure 1. Anodic voltammograms of the acids **1b** and **7** on smooth platinum electrodes in a mixed solvent of AcOH–*t*-BuOH–Et_3N (2:1:0.1) at 15°, sweep rate, 0.05 V/sec: (a) - - - background; (b) - - - - the acid **7** (1.4 *M*); (c) — the acid **1b** (1.1 *M*).

recorded on a Hitachi EPI-S2, with only major absorptions being cited. Mass spectra were obtained on a Hitachi RMS-4 mass spectrometer at 70 eV, with molecular and major fragment ions being cited: *m/e* (rel intensity). Elemental analyses were performed by Mr. Tsutomu Okamoto of our laboratory.

Electrolysis Apparatus. The electrolytic vessel was a water-jacketed beaker, 2.5 cm in diameter and 10 cm high, fitted with a gas lead pipe, a thermometer, a magnetic stirrer, and two smooth platinum (3 cm^2) and/or carbon rod electrodes, being placed parallel to each other 3 mm apart. Current was controlled by manually adjusting the applied voltage as required. The direction of current was changed every 30 sec by means of a commutator.

Ethyl Tricyclo[4.4.0.0^{1,5}]deca-4-one-2-carboxylate (1a). To a stirred solution of 10 ml of dry benzene suspended in 145 mg of NaH (50% mineral oil suspension, washed with anhydrous *n*-hexane before use), 565 mg (2.5 mmol) of the Stobbe half-ester[8] in 5 ml of dry benzene was added dropwise. The mixture was stirred for 1 hr at room temperature and 0.35 ml of oxalyl chloride was added at 5°. The stirring was continued for 1 hr at room temperature and the mixture was filtered under N_2. The residual acid chloride was dissolved in 5 ml of dry benzene. The benzene solution was treated with excess diazomethane at 0°. The mixture was stirred overnight at 0–5°. Removal of the solvent under reduced pressure at 10° and subsequent chromatography over alumina with CH_2Cl_2 gave 570 mg of the diazo ketone, a yellow oil: ir (neat) 2100 (N_2C), 1740 (ester), and 1645 cm^{-1} (diazo ketone); NMR ($CDCl_3$) δ 1.20 (t, J = 6 Hz, 3 H, CH_3), 1.58 (m, 4 H, CH_2), 1.92 (m, 4 H, CH_2), 2.40–2.75 (m, 2 H, CH_2), 3.00–3.30 (m, 1 H, CH), 4.05 (q, J = 6 Hz, 2 H, CH_2), 5.22 (s, 1 H, $COCHN_2$), and 5.50 (m, 1 H, HC=C). Without further purification, the diazo ketone (570 mg, 2.28 mmol) was added to a mixture of 35 ml of benzene and 20 mg of bis(*N*-*n*-propylsalicylideneaminato)copper(II),[9] dried in an oven at 90–100° for 10 min before use, and dissolved in 5 ml of dry benzene with vigorous stirring at 80–81° for 5–6 hr. Then the solvent was removed in a rotoevaporator and the residue was chromatographed over alumina. Elution with 30 ml of *n*-hexane–ether (2:1) monitored by TLC gave 350 mg (62.8%) of **1a**: bp 95° (0.02 mm); ir (neat) 1740 and 1731 cm^{-1} (C=O); NMR (CCl_4) δ 1.10–2.15 (m, 10 H), 1.24 (t, J = 7 Hz, 3 H, CH_3), 2.15–3.20 (m, 3 H), and 4.15 (q, J = 7 Hz, 2 H, CH_2).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.11; H, 8.27.

Hydrolysis of 1a. A mixture of 140 mg (0.658 mmol) of **1a** and 210 mg (3.75 mmol) of KOH in 6 ml of 40% aqueous EtOH was stirred at room temperature for 20 hr. After processing as described in the preparation of **7a**, the crystalline residue (150 mg) was recrystallized from benzene–CH_2Cl_2 (10:1) to give 110 mg (86%) of **1b**: mp 158–159°; ir (Nujol) 3300–3000 (COOH), 1724 (C=O), and 1680 cm^{-1} (COOH); NMR ($CDCl_3$) δ 1.10–2.20 (m, 10 H), 2.20–2.60 (m, 2 H), and 2.80–3.30 (m, 1 H).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.14; H, 7.22.

Electrolysis of 1b in AcOH–*t*-BuOH–Et_3N (Run 3). The acid **1b** (220 mg, 1.13 mmol) was dissolved in a mixed solution of AcOH (12 ml), *t*-BuOH (6 ml), and Et_3N (40 mg). The mixture was electrolyzed at a constant current of 0.08 A/cm^2 (applied voltage ca. 20 V) at 10° for 20 hr. The solvent was removed in a rotoevaporator and the residue was taken up in benzene–ether (1:1). The organic phase was washed with water and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel using *n*-hexane–ether (2:1) to give 158 mg (67%) of **4**.

Electrolysis in Pyridine–H_2O (Run 1). A stirred solution of **1b** (100 mg, 0.52 mmol), Et_3N (0.04 ml), and water (1.0 ml) in pyridine (9.0 ml) was electrolyzed using carbon rod electrodes at a constant current of 0.03–0.02 A/cm^2 at 3–5° for 5 hr. The reaction mixture was concentrated on a rotary evaporator. The residue was taken up in benzene–ether (1:1), washed with aqueous 20% tartaric acid, aqueous $NaHCO_3$, and brine, and dried (Na_2SO_4). Removal of the solvent gave a crude oil (55 mg), which showed four spots on TLC (silica gel, *n*-hexane–ether, 1:1) at the R_f values of 0.30, 0.45, 0.65, and 0.73. The two fractions (R_f 0.30 and 0.45) were separated by preparative TLC, and the structures were assigned as **2** (19.2 mg, 25%) and **3** (7.7 mg, 10%), based on their spectral data and elemental analyses. The other fractions (R_f 0.65 and 0.73) gave ca. 3 mg of unknown oils.

Electrolysis in MeOH (Run 2). A solution of 50 mg (0.26 mmol) of **1b** in 8 ml of dry MeOH containing 0.03 ml of Et_2NH was electrolyzed using platinum electrodes at a constant current of 0.07–0.08 A/cm^2 at 5–10° for 2 hr. The reaction mixture was concentrated and extracted with 10 ml of ether–benzene (3:1). The organic phase was washed with aqueous 20% tartaric acid and water and dried (Na_2SO_4). Removal of the solvent gave a neutral material (42 mg) which was chromatographed over silica gel using *n*-hexane–ether (2:1) to give 30 mg of **5** (64%) and 6.6 mg of **6** (14%). Physical constants together with elemental analyses of **2**, **3**, **4**, **5**, and **6** are shown in Table II.

Electrolytic Acetoxylation of 7. The acid **7**, $[\alpha]^{24}D$ +7.7° (*c* 2.92, $CHCl_3$)[7a] (150 mg, 0.61 mmol), was dissolved in a mixed solution of AcOH (6 ml), *t*-BuOH (3 ml), and Et_3N (20 mg). The mixture was electrolyzed at a constant current of 0.25 A (applied voltage ca. 20 V) at 10° for 20 hr. After work-up in a usual manner, there was obtained 115 mg (72%) of **8**: bp 129–130° (0.005 mm); ir (neat) 1735 (C=O), 1370, 1243, 1028, and 910 cm^{-1}; NMR ($CDCl_3$) δ 0.90–1.20 (m, 9 H, 3 CH_3), 2.07 (s, 3 H, CH_3CO), 5.38–5.65 (m, 1 H, HCOAc); mass spectrum *m/e* (rel intensity) 264 (M^+, 1), 222 (5), 204 (32), 189 (18), 176 (21), 162 (55), 161 (80), 147 (38), and 133 (100); $[\alpha]^{24}D$ +7.7° (c 1.70, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.64; H, 9.20.

Acknowledgment. We gratefully acknowledge financial support from the Ministry of Education, Japan, under the Grant-in-aid for Scientific Research, General Research (B) 047086 (1975).

Registry No.—**1a**, 57065-78-8; **1b**, 57065-79-9; **2**, 57065-80-2; **3**, 769-32-4; **4**, 57065-81-3; **5**, 57065-82-4; **6**, 57065-83-5; **7**, 57065-84-6; **8**, 57065-85-7.

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Reaction of 2-(1,2-Epoxycyclohex-1-yl)cyclohexanone Ketal with Boron Trifluoride Etherate[1]

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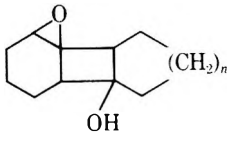
Received June 16, 1975

The formation of substituted furans by the action of acids on α,β-epoxy ketones is known,[3,4] and a recent report by Loubinoux and co-workers[5] indicates that in the presence of boron trifluoride etherate β,γ-epoxy alcohols of the type 1 give good yields of furans.



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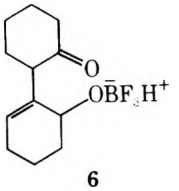
We find that the β,γ-epoxy ketal **2** on treatment with boron trifluoride etherate gives 1,2,3,4,6,7,8,9-octahydrodibenzofuran (**5**) in 43% yield. Scheme I illustrates a possible route, though at this stage it seems difficult to distinguish between the two possible pathways, a and b.

Our result would appear to lend support to the suggestion[5] that epoxy alcohols of the type 1 give rise to furans via ketonic intermediates. Thus, for $n = 2$, the system studied by Loubinoux and co-workers is isomeric with the epoxy ketone **3**, and intermediates **4a** and **4b** are isomeric with their proposed intermediate, **6**.



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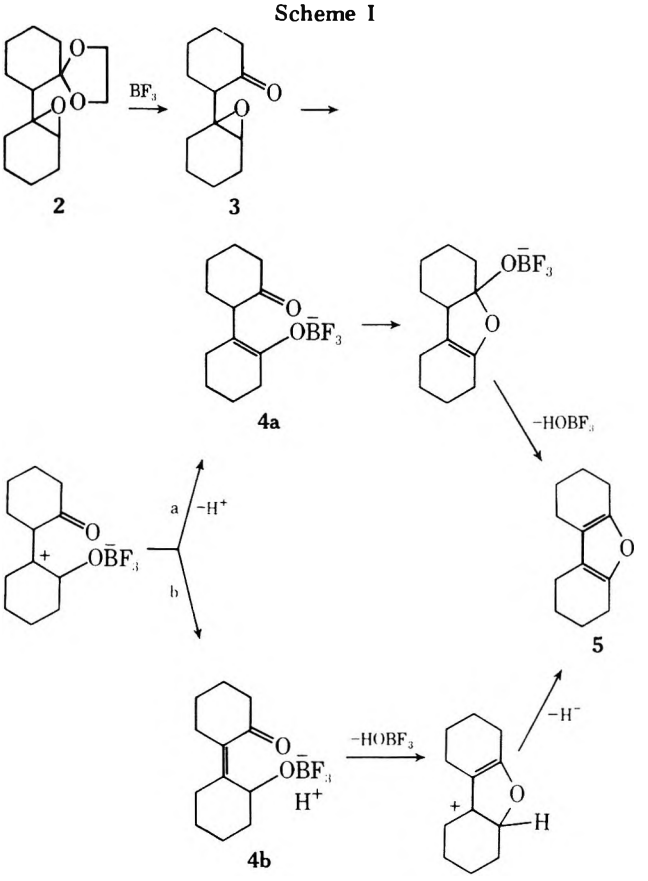
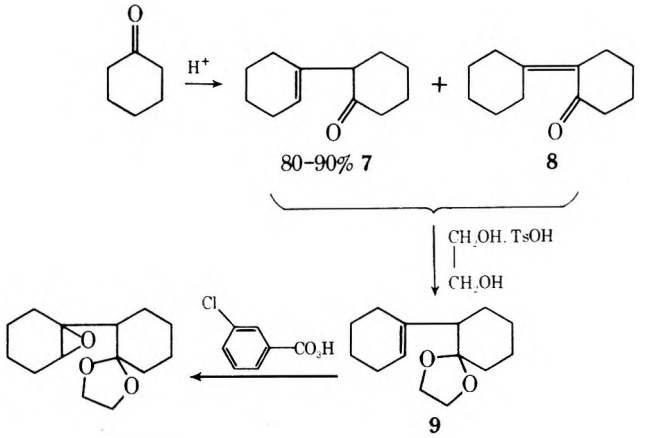
Scheme II outlines the preparation of the title compound.

Self-condensation of cyclohexanone in the presence of 60% H_2SO_4[6] gave 2-(cyclohexen-1-yl)cyclohexanone (**7**), together with a small amount of 2-cyclohexylidenecyclohexanone (**8**). The composition was established by ir and NMR analysis, our results agreeing with those of Wenkert and coworkers.[7] However, VPC failed to reveal the presence of the minor component in the mixture. The many reported investigations[7] of the structure of this condensation product do not appear to include a method for the separation of the isomeric mixture. It has been reported,[8] however, that **7** is the more stable isomer thermally, and thus it seemed possible that **8** might have isomerized to **7** while on the VPC column. Heating the mixture to 140° for varying time

Scheme I



Scheme II

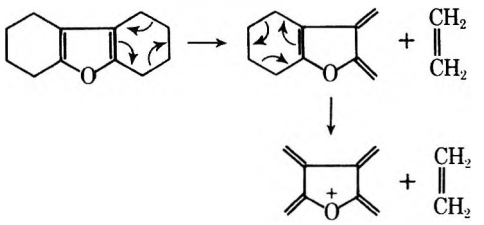


periods did not produce any appreciable change in the isomer ratio as measured by NMR analysis. However, heating with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid over a period of 7 hr gave the ketal **9**, whose NMR spectrum indicated that it consisted of one isomer only, one olefinic hydrogen being present relative to the four hydrogens from the ethylene glycol residue. This migration of the double bond out of conjugation on ketalization has also been observed in the steroid series.[9,10] [Hydrolysis of **9** in 90% acidified methanol gave 2-(cyclohexen-1-yl)cyclohexanone (**7**).] Ketal **9** reacted smoothly with *m*-chloroperbenzoic acid to give **2**.

Treatment of **2** with boron trifluoride etherate, in either methylene chloride or benzene, gave a dark red oil consisting of four (or five) compounds (TLC), of which the major one was 1,2,3,4,6,7,8,9-octahydrodibenzofuran (**5**). The latter was isolated by dry column chromatography on neutral alumina, followed by distillation, and the structure was established by elemental and spectral analysis.

The mass spectrum of 5 proved to be of particular interest. In addition to the previously reported[4] peaks (*m/e* 176, 148, 120, etc.; see Experimental Section) two "metastables" appeared at *m/e* 125 and 97.5. These represent respectively the fragmentation of the parent peak at *m/e* 176 → 148 with loss of 28 mass units, and the *m/e* 148 peak → 120 with loss of 28 mass units. "Exact mass" measurements on the *m/e* 148 and 120 peaks suggested that ethylene is the fragment lost in each case, which leads to the fragmentation pattern indicated in Scheme III.

Scheme III



Experimental Section

Ir spectra were recorded on a Beckman IR 33 spectrometer, NMR spectra were determined on a Varian T-60 spectrometer, and the mass spectra on a Varian CH5 mass spectrometer. Microanalyses were performed on a 185 B Hewlett-Packard C, H, N analyser.

Self-condensation of Cyclohexanone.[6] Technical cyclohexanone (500 g, 5.1 mol) was condensed in the presence of 60% H_2SO_4 according to the procedure of Gault and co-workers.[6] The product was a colorless oil (290 g, 63%): ir (liquid film) 1700 (s), 1670 cm^{-1} (sh); NMR ($CDCl_3$) δ 5.4 (m, 0.8 H), 1.0–3.2 (m, 17 H); mass spectrum parent peak *m/e* 178. Separation of the mixture was attempted, without success, on the following columns: Apiezon, DEGS, XE60, and Carbowax, at temperatures ranging from 180 to 200°. A single, symmetrical peak was observed in every case.

Preparation of Ketal 9.[9] The ketone mixture (8.9 g, 0.05 mol), consisting of 80–90% (7), was added to 165 ml of toluene and 60 ml of freshly distilled ethylene glycol containing 0.1 g of *p*-toluenesulfonic acid, and this mixture was heated with slow distillation for 7 hr, during which time 190 ml of distillate was collected. Fresh toluene was added to maintain the original volume over this period. The organic layer was separated, and, after washing several times with saturated aqueous $NaHCO_3$ and water, the combined aqueous layers were extracted with ether, and the ether layers were washed with water and added to the organic layer. Drying ($MgSO_4$) and removal of the solvent under reduced pressure gave 11.5 g (97%) of a pale yellow oil. Distillation gave a colorless oil: bp 85–89° (0.2 mm); NMR ($CDCl_3$) δ 5.5 (m, 1 H), 3.9 (s, 4 H), 2.2–1.2 (m, 17.2 H). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.08; H, 9.82. Found: 75.38; H, 9.93.

Preparation of 2-(1,2-Epoxycyclohex-1-yl)cyclohexanone Ketal (2).[11] To 11.2 g (0.05 mol) of 7 in 70 ml of methylene chloride in a flask equipped with a thermometer, dropping funnel, stirrer, and condenser was added 11 g (0.054 mol) of *m*-chloroperbenzoic acid in 120 ml of methylene chloride over a period of 20 min. The temperature was maintained at 25° during the addition, and the stirring was continued for a further 1.5-hr period. The excess peracid was destroyed by the addition of a small amount of 10% aqueous sodium sulfite. The methylene chloride solution was then washed with 5% $NaHCO_3$, water, and saturated aqueous NaCl. Drying ($MgSO_4$) and removal of the solvent left 11.2 g (93%) of a colorless oil: mass spectrum parent peak *m/e* 238; NMR ($CDCl_3$) δ 3.9 (s, 4 H), 3.1 (m, 1 H), 2.2–1.2 (m, 17 H). Distillation in a Kugelrohr, pot temperature 145° (3 mm), gave a clear liquid. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24. Found: C, 70.81; H, 9.21.

Reaction of 2 with Boron Trifluoride Etherate.[12] The epoxide 2 (4.8 g, 0.02 mol) in 75 ml of methylene chloride at 5° was treated with 8.4 ml of boron trifluoride etherate (48%, technical) added slowly via a dropping funnel. The mixture was stirred at 5° for a further 0.5 hr, and then 75 ml of water was added rapidly. The organic layer was separated and washed with water (2 × 100 ml), saturated, aqueous $NaHCO_3$ (3 × 100 ml), and water (4 × 75 ml). Drying ($MgSO_4$) and removal of the solvent left a pink oil, which turned dark red in 0.5 hr. [The use of benzene (200 ml) as solvent, and the elimination of the 0.5-hr stirring period after the addition of the boron trifluoride etherate, did not appear to have any appreciable effect on the course of the reaction.] Examination of the crude product by TLC indicated that it contained four (or five) components, one well separated and moving very close to the solvent front. The crude red oil was then chromatographed on 400 g of neutral alumina (Woelm), dry column grade, activity III (20 mm), packed in a 2-in. plastic tube. Ether was used as eluant. The bottom ⅙th of the column, which contained the main component of the mixture, gave, on extraction with ether, 1.5 g (43%) of a pale yellow oil. Distillation [bp ~90° (2 mm), lit.[3] 88–89° (2 mm)] yielded a colorless oil: ir (liquid film) 1600 cm^{-1} (furan ring); NMR ($CDCl_3$) δ 2.0–2.6 (8 H), 1.4–2.0 (8 H); mass spectrum *m/e* 176, 148, 120, 105, 92, 91, 79, 77, 65, 51, 41, 39, and two "metastables" at 125 and 97.5. Exact mass of 148 peak. Calcd for $C_{10}H_{12}O$: 148.088. Found: 148.087. Exact mass of 120 peak. Calcd for C_8H_8O: 120.057. Found: 120.057. (Perfluoroalkane 225 was used as the reference compound.)

Anal. Calcd for $C_{12}H_{16}O$: C, 81.82; H, 9.10. Found: C, 81.62; H, 9.19.

Three other materials were isolated from the column and all were ketonic but none was obtained pure enough to warrant a definite structure assignment.

Hydrolysis of Ketal 2 to 2-(Cyclohexen-1-yl)cyclohexanone (7). Hydrolysis of 2 in 90% boiling MeOH acidified with HCl gave 2-(cyclohexen-1-yl)cyclohexanone (7): ir (liquid film) 1700 cm^{-1}, and very much reduced shoulder (relative to that observed in the initial mixture of ketones produced by the self-condensation of cyclohexanone) at 1670 cm^{-1}; NMR ($CDCl_3$) δ 5.4 (0.96 H), 1.0–3.2 (17.0 H). The relative areas of the proton peaks in the NMR remained unchanged when the material sat at 25° for 6 days.

Registry No.—2, 57090-93-4; 5, 1010-77-1; 7, 1502-22-3; 9, 57090-94-5; cyclohexanone, 108-94-1; boron trifluoride etherate, 109-63-7.

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Demethylation of Labile Aryl Ethers

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As part of a study of structure–activity relationships of certain synthetic estrogens, the carbinols 3-hydroxy-3-(3,4-dimethoxyphenyl)-4-(4-methoxyphenyl)hexane (I) and 3-hydroxy-3,4-bis(4-methoxyphenyl)hexane (II) were prepared. We also wished to prepare the corresponding free

phenols, but found conventional methods of ether cleavage[1,2] to be unsatisfactory. These generally involve heating in the presence of acid and caused dehydration of the carbinols with formation of the corresponding olefins. However, the desired compounds were prepared in good yield by reaction at low temperature with stoichiometric amounts of boron tribromide.[3-5]

Experimental Section

Melting points were taken on a Fisher-Johns apparatus. Infrared spectra (KBr pellet) were recorded on a Perkin-Elmer Model 237 spectrophotometer. Gas chromatography–mass spectrometry was performed using a Perkin-Elmer Model 990 gas chromatograph coupled to an Hitachi RMU-6E mass spectrometer by a modified Watson-Biemann separator. A 180 × 0.2 cm glass column was used, packed with 3% OV-225 on 100–120 mesh Supelcoport. Helium flow rate was 20 ml/min and the column was operated at 190°. Electron impact spectra were recorded at 70 eV.

Demethylation Procedure. A 5% w/v solution of the ether in dry dichloromethane was cooled to −80° and added to a similarly cooled 10% v/v solution of boron tribromide in dichloromethane. One mole of reagent was used for each mole of methoxyl to be cleaved, i.e., 3 mol of reagent per mole of compound I and 2 mol of reagent per mole of compound II. The mixture, protected from moisture by a calcium chloride drying tube, was allowed to warm to room temperature overnight. Water was added to hydrolyze the boron–ether complex and any excess reagent and the phenolic product was extracted into diethyl ether.

I. 3-Hydroxy-3-(3,4-dihydroxyphenyl)-4-(4-hydroxyphenyl)hexane. Crude material was crystallized from benzene–hexane, yield 80%, mp 120°. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33; O, 21.17. Found: C, 71.45; H, 7.20; O, 21.35.

Gas chromatography of the tristrimethylsilyl ether yielded a single peak, retention time 8.8 min.

The mass spectrum of the trimethylsilyl derivative exhibited no molecular ion. Base ion was at *m/e* 500 as a result of loss of water from the molecule. Other prominent ions were at *m/e* 485 (loss of CH_3), 472 (loss of C_2H_4), 295, 205 (hydrogen transfer followed by scission of the molecule between C-3 and C-4 of the hexane chain), 281, 219 (rearrangement followed by scission), 75, 73 (from Me_4Si).

The infrared spectrum of the parent compound exhibited the expected bands due to bonded phenolic OH at ca. 3200 and 1240 cm^{-1} and substituted aromatic CH stretch in the region 1500–1600 cm^{-1}. In addition, a sharp band appeared at 3620 cm^{-1}. This band was absent in the spectrum of 3,4-bis-(4-hydroxyphenyl)hexane (diethylstilbestrol) and may, therefore, be attributed to nonbonded carbinol OH.

II. 3-Hydroxy-3,4-bis(4-hydroxyphenyl)hexane was crystallized from benzene, yield 87%, mp 137°. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; O, 16.76. Found: C, 75.20; H, 7.80; O, 17.00.

Gas chromatography of the bistrimethylsilyl ether yielded a single peak, retention time 6.4 min.

The mass spectrum of the trimethylsilyl derivative was similar in all respects to that of compound I with ions appearing 88 amu lower. Base ion was at *m/e* 412 and other prominent ions appeared at *m/e* 397, 384, 207, 205, 219, 193, 75, and 73.

The infrared spectrum of the parent compound was also similar to that of compound I with differences attributable to the lesser degree of substitution of compound II.

Acknowledgment. This research was supported by the Program for Applied Research on Fertility Regulation, University of Minnesota, under subcontract PARFR-65 to contact AID/csd-3608.

Registry No.—I, 57090-99-0; II, 5331-23-7; 3-hydroxy-3-(3,4-dihydroxyphenyl)-4-(4-hydroxyphenyl)hexane, 57091-00-6; 3-hydroxy-3,4-bis(4-hydroxyphenyl)hexane, 7504-83-8; boron tribromide, 10294-33-4.

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Stereochemistry of the Type II Elimination from 4-*tert*-Butylcyclohexyl Phenylacetate

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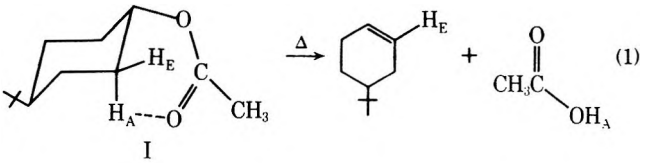
Recently, it has been observed that the stereochemistries of the electron impact induced and pyrolytic elimination of acetic acid from *trans*-4-*tert*-butylcyclohexyl acetate (I) differ.[1] The near-exclusive cis elimination observed in the pyrolysis (eq 1) is related to the greater ease of forcing cis cyclohexyl substituents toward coplanarity than trans substituents.[2] Since the pyrolysis is a concerted elimination, introduction of a double bond into the cyclohexyl ring system must involve a movement toward coplanarity of the eliminated substituents.[2,3] Conversely, it was suggested that the predominantly trans elimination observed in the electron impact induced process (eq 2) was evidence for the nonconcerted nature of this process.[4] In order to test this



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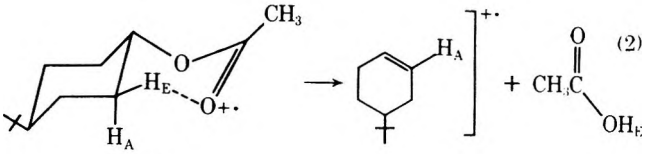


I

hypothesis, it appeared desirable to examine the stereochemistry of a bona fide stepwise unimolecular elimination occurring in an accessible phase. Because of the considerable recent interest in the type II photoelimination from phenylacetates, this reaction was an obvious choice for further investigation.

The photolytic elimination of phenylacetic acid has been suggested to be a syn intramolecular, nonconcerted process proceeding predominantly or exclusively through a singlet state.[5] Thus, the phenylacetates of the stereospecifically labeled alcohols IIa–Va were prepared and irradiated. Mass spectrometry was utilized to establish the isotopic composition of the 4-*tert*-butylcyclohexene product and thus the

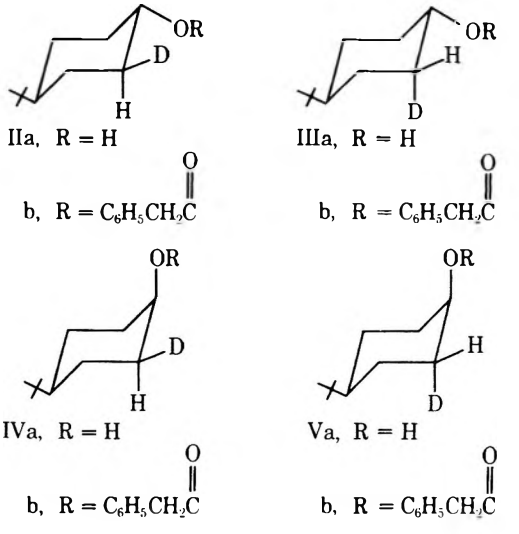


Table I
Isotopic Composition of Phenylacetic Acid Eliminated in the Photolysis of Stereospecifically Labeled 4-*tert*-Butylcyclohexyl Phenylacetates in Hexane at 254 nm

Compd	H loss/D loss [a]
trans-4-*tert*-Butylcyclohexyl phenylacetate-*trans*-2-*d* (IIb)	3.9 ± 0.3
trans-4-*tert*-Butylcyclohexyl phenylacetate-*cis*-2-*d* (IIIb)	8.4 ± 0.5
cis-4-*tert*-Butylcyclohexyl phenylacetate-*cis*-2-*d* (IVb)	1.6 ± 0.2
cis-4-*tert*-Butylcyclohexyl phenylacetate-*trans*-2-*d* (Vb)	>50

[a] Errors are standard deviations from the mean of at least four runs.

stereochemistry of the elimination. The results appear in Table I.

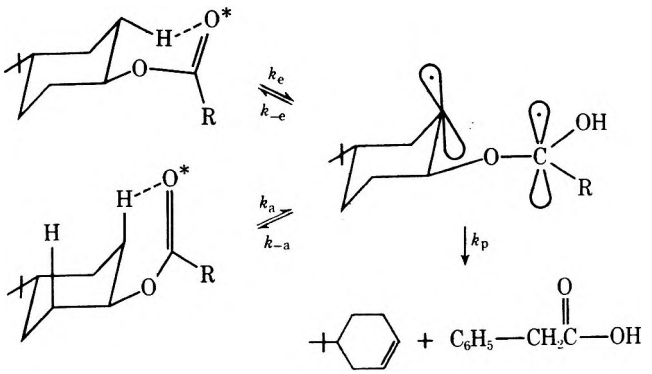
The trans labeled phenylacetate IIb eliminates deuterium ca. twice as frequently as the cis labeled phenylacetate IIIb, consistent with predominant trans elimination.[6] This unusual behavior is not attributable to the intervention of an intermolecular radical-type process. Added 4-methyl-2-pentene has been shown to suppress radical-type products in these systems;[5a,b] photolysis of the labeled phenylacetates IIb and IIIb in the presence of 0.5 *M* 4-methyl-2-pentene gives 4-*tert*-butylcyclohexene of the same isotopic composition as photolysis in the absence of 4-methyl-2-pentene. Further, the complete absence of trans elimination from the axial phenylacetate Vb is most consistent with an intramolecular reaction.

Another explanation for the observed net trans elimination postulates that the stereochemistry of the label is reversed prior to elimination. This possibility is excluded by two observations. The isotopic composition of the alkene produced by the photolysis of either labeled equatorial phenylacetate did not vary significantly as the extent of the reaction was varied from 10% to 80%. Further, photolysis of phenylacetate recovered after photolysis was 80% complete gave alkene of the usual isotopic composition. Thus, the elimination reaction must occur faster than loss of stereochemistry. The photolysis of *trans*-4-*tert*-butylcyclohexyl phenylacetate then provides a rare example of an intramolecular elimination with preferred trans stereochemistry.[7]

These data do not suffice to permit rigorous determination of the exact extent of cis and trans elimination from unlabeled *trans*-4-*tert*-butylcyclohexyl phenylacetate. However, if the gross simplifying assumptions are made that the primary isotope effects for cis and trans elimination are identical, and that secondary isotope effects can be neglected, the data for the labeled compounds IIb and IIIb require $\Phi_{trans\text{-}H}/\Phi_{cis\text{-}H} = 1.8 \pm 0.2$, and $\Phi_{hydrogen}/\Phi_{deuterium} = 1.8 \pm 0.2$. The latter figure is in reasonable agreement with the more rigorously determined isotope effect observed in the elimination proceeding from *cis*-4-*tert*-butylcyclohexyl phenylacetate-*cis*-2-*d* (IVb) ($\Phi_{hydrogen}/\Phi_{deuterium} = 1.6 \pm 0.2$).

Consideration of the formulation of Scheme I provides a possible explanation for the observed stereochemistry. If abstraction of an axial or an equatorial hydrogen atom generates a common biradical intermediate from which product formation and reverse hydrogen transfer occur, the ratio of equatorial hydrogen elimination to axial hydrogen elimination corresponds to k_e/k_a.[8] The half-vacant n orbital of the n,π^* carbonyl group can assume a coplanar relationship[9] with either C–H bond without distortion of the cyclohexyl ring system. The *trans*-decalin-like transition state for abstraction of the equatorial hydrogen appears

Scheme I



strain free. Conversely, a 1,3-diaxial interaction exists between the axial hydrogen at C-6 and the phenylacetyl moiety in the *cis*-decalin-like transition state for axial hydrogen abstraction. Thus, the transition state for cis axial hydrogen abstraction is destabilized relative to the transition state for trans equatorial hydrogen atom abstraction.

These experiments demonstrate a clear dichotomy between the stereochemistries of representative concerted and nonconcerted unimolecular eliminations proceeding through six-membered transition states. If this result proves general, the stereochemistry of elimination from the *trans*-4-*tert*-butylcyclohexyl system may provide a simple test for the concertedness or nonconcertedness of such reactions, a subject of current interest in mass spectrometry[4] and photochemistry.[10]

Experimental Section

The stereospecifically labeled alcohols IIa–Va were prepared as previously described.[1] Conversion to the corresponding phenylacetates IIb–Vb was accomplished by analogy to the procedures of Yarchak, Dalton, and Saunders.[5a]

Photolyses were also conducted according to the general procedures of Yarchak, Dalton, and Saunders.[5a] The phenylacetates were irradiated as thoroughly degassed 0.01 *M* solutions in hexane using an eight-lamp Rayonet preparatory reactor equipped with Rayonet RPR 2537-Å lamps.

The alkene product was isolated by preparative gas chromatography on a Hewlett-Packard F & M Model 5750 containing a 20-ft UCW-98 column operated at 90°. Control experiments demonstrated that the unreacted phenylacetate was not undergoing detectable elimination of phenylacetic acid under the conditions of the gas chromatographic analysis.

The deuterium content of the purified 4-*tert*-butylcyclohexene was determined by analysis of the molecular ion region of the alkene at 70 eV ionizing voltage on an AEI MS-902 mass spectrometer. The calculated ratios of protium loss to deuterium loss varied by less than 10% as the ionizing voltage was varied from 70 eV to threshold.

Acknowledgment. The authors acknowledge support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the Undergraduate Research Participation program of the National Science Foundation.

Registry No.—IIb, 57172-70-0; IIIb, 57172-71-1; IVb, 57172-72-2; Vb, 57172-73-3; phenylacetic acid, 103-82-2.

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(6) The high ratios of hydrogen loss to deuterium loss observed for IIb and IIIb are due to the operation of an isotope effect; photolysis of *trans*-4-*tert*-butylcyclohexyl phenylacetate-2,2,6,6-d_4 proceeded with >98% elimination of phenylacetic acid-d_1.
(7) A referee has suggested that this conclusion is contradicted by the data reported by Saunders et al. (ref 5a) for photoelimination from *cis*- and *trans*-2-methylcyclohexyl phenylacetate. Actually, however, Saunders' data permit no conclusions concerning the preferred stereochemistry of elimination from *trans*-4-*tert*-butylcyclohexyl phenylacetate. For example, *cis*-2-methylcyclohexyl phenylacetate photoeliminates to give ca. 10% 1-methylcyclohexene (trans elimination) and ca. 90% 3-methylcyclohexene (cis and trans elimination). However, since this compound exists largely (80–85%) in the conformer in which the phenylacetate group is axial,[5a] and since the quantum yield for elimination from certain axial phenylacetates is ca. three times greater than that from the corresponding equatorial phenylacetates,[5a] this result has little relevance to the stereochemistry of elimination from an equatorial phenylacetate. *trans*-2-Methylcyclohexyl phenylacetate exists very predominantly in the conformer with an equatorial phenylacetate; photoelimination gives roughly equal amounts of 1-methylcyclohexene (trans elimination) and 3-methylcyclohexene (cis and trans elimination). However, since the relative reactivities of secondary and tertiary hydrogens in this reaction are unknown, conclusions concerning the preferred stereochemistry of elimination from *trans*-4-*tert*-butylcyclohexyl phenylacetate are hazardous. Nevertheless, the relatively large amount of 1-methylcyclohexene observed is indicative of appreciable trans elimination from this system, and fully consistent with the results in this paper.
(8) Alternatively, if alkene formation and/or reverse hydrogen transfer occur from isomeric biradicals, the overall stereochemistry will depend on the relative rates of axial and equatorial hydrogen abstraction, and on the relative rates of reverse hydrogen transfer and alkene formation from each biradical.
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Methoxycarbonylation of Substituted Benzenes. Effect of the Electronic Configuration of Carbon Radicals in Homolytic Substitutions

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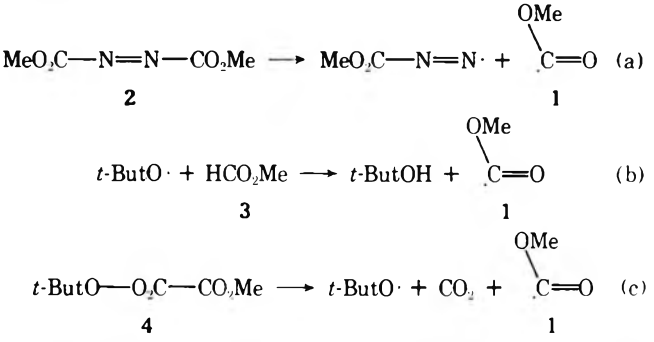
From studies of relative rates and isomer distributions in homolytic substitutions it emerged that one of the factors affecting the polar nature of carbon-centered radicals is the hybridization of the orbital carrying the unpaired electron; because the s orbital has higher electronegativity than the p orbital, it can be expected that the greater the s character of an orbital, the greater will be its electronegativity and hence the lower will be the nucleophilicity of the corresponding radical. Thus for carbon radicals the nucleophilicity should decrease along the series p > sp^3 > sp^2 > sp; substituents linked to the radical carbon atom will modify the polar character and it can be expected that this effect should be more pronounced with π than with σ radicals. Simple alkyl and bridgehead polycyclic alkyl radicals present various degrees of nucleophilicity depending upon their structure, while acetylenic radicals are slightly electrophilic.[1] Radicals produced on carbon having an sp^2 configuration, like phenyl,[2] vinyl,[3] and cyclopropyl,[4] present substantially similar neutral properties; only in the case in which they react with strongly deactivated substrates, like the protonated pyridines, some degree of nucleophilicity can be evidenced, which, however, is much less pronounced than that of simple alkyl radicals.[5] The effect of substituents on σ radicals having an sp^2 configuration has been studied in the case of the phenyl radical; the presence of electron-withdrawing or electron-donating groups makes the resulting aryl radical respectively more electrophilic or more nucleophilic than the phenyl radical.[2]

We report in this paper the results of a study on the methoxycarbonyl radical, $\cdot CO_2Me$, carried out with the aim of investigating the effect of the oxygen functions on the electronic nature of this radical, where the unpaired electron still occupies an sp^2 orbital.[6] Alkoxycarbonyl radicals have been formulated as reaction intermediates[7-11] and have been spectroscopically detected and studied;[12,13] indications that these radicals can effect homolytic substitutions on aromatic[8] and heteroaromatic[14] compounds have also been obtained. In the present investigation methoxycarbonyl radicals, **1**, have been produced in three different ways: (a) the thermal decomposition, at 130°C, of dimethyl azodicarboxylate (**2**); (b) the hydrogen abstraction from methyl formate (**3**) by *tert*-butoxy radicals, photolytically generated at room temperature;[12] and (c) the thermal decomposition,[7] at 65°C, of the methyl *tert*-butylperoxyoxalate (**4**).



Experiments carried out in benzene showed that the substitution product, the methyl benzoate, was formed in every case. Small quantities of toluene were also detected indicating that the radical **1** suffers fragmentation to CO_2 and methyl radicals; in the cases b and c the methyl radicals can obviously be produced also from the *tert*-butoxy radicals.

$$\cdot CO_2Me + C_6H_6 \longrightarrow C_6H_5CO_2Me$$
$$\cdot CO_2Me \longrightarrow CO_2 + Me\cdot$$
$$t\text{-}BuO\cdot \longrightarrow Me_2CO + Me\cdot$$
$$\cdot Me + C_6H_6 \longrightarrow C_6H_5Me$$

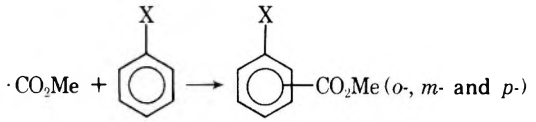
Diphenyl was also formed as a by-product in the reactions b and c, but not from the decomposition of **2**; the formation of this compound has already been reported from the decomposition of the ethyl *tert*-butylperoxyoxalate[7] and of the di-*tert*-butyl peroxide[15] in benzene and has been attributed to the production of phenyl radicals from the reaction of *t*-BuO· with benzene.[16] Finally, from the reactions b and c in benzene traces of dibenzyl were also detected as a result of the dimerization of the benzyl radicals produced from toluene; the dibenzyl obviously constituted the major reaction product when toluene was used as solvent for the studies on the relative reactivities described below. In the thermolysis of dimethyl azodicarboxylate (**2**), other unidentified products were also present and this reaction was therefore not employed for further studies.

In order to evaluate the polar character of methoxycarbonyl radicals, reactions were carried out in several differently substituted benzenes and in an equimolecular mixture of substituted benzenes and benzene; these experiments allowed the reactivity of the various nuclear posi-

Table I
Distribution of Positional Isomers and Relative Reactivities[a] in Aromatic Substitutions of Benzene Derivatives by the Methoxycarbonyl[b] and the Phenyl Radicals

Registry no.	Substrate	·CO_2ME				Yield,[c] %	C_6H_5·			
		o-	*m*-	*p*-	*K*		*o*-	*m*-	*p*-	*K*
108-88-3	C_6H_5Me	56.0	26.9	17.1	1.45	10	60.9	25.1	14.0	1.58[d]
98-06-6	$C_6H_5CMe_3$		64.7	35.3	0.73	13	23.3	51.2	25.5	0.72[d]
108-90-7	C_6H_5Cl	46.8	34.2	19.0	0.85	11	50.0	32.0	18.0[e]	1.0[f]
108-86-1	C_6H_5Br	45.1	37.3	17.6	0.86	10	53.5	31.5	15.0	1.39
93-58-3	$C_6H_5CO_2Me$	35.1	17.9	47.0	2.2	16	57.0	17.5	25.5	1.77[g]
98-86-2	C_6H_5COMe	40.0		60.0	2.3	15	58.0	13.1	28.9	2.2[h]
100-47-0	C_6H_5CN	38.5	13.5	48.0	2.6	20	61.0	12.0	27.0	2.4[h,i]
98-95-3	$C_6H_5NO_2$[j]	77.4		22.6	3.8	21	63.0	10.0	27.0	2.94[f]

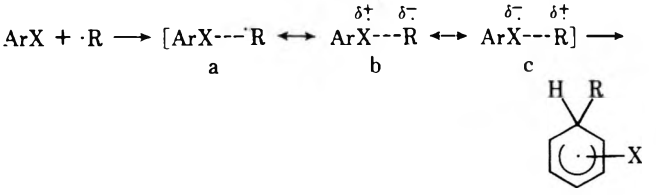
[a] Determined by GLC (see ref 18). [b] The data in the table refer to the ·CO_2Me radical produced from methyl *tert*-butyl peroxyoxalate, at 65° C. The following results were obtained from the photolysis of di-*tert*-butyl peroxide in the presence of HCO_2Me, at room temperature (% ortho, meta, para, and *K* are given in order): $C_6H_5CMe_3$, 0, 64.7, 35.3, 0.73; C_6H_5Cl, 45.8, 54.2 (*m* + *p*), 0.88; $C_6H_5CO_2Me$, 37.0, 15.9, 47.1, not determined; C_6H_5CN, 41.6, 12.1, 46.3, 2.3. [c] Determined from reactions carried out on a preparative scale, as described for benzene. [d] G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. B*, 1413 (1970). [e] C. Shih, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 2600 (1958). [f] D. H. Hey, S. Orman, and G. H. Williams, *ibid.*, 565 (1961). [g] D. H. Hey, F. C. Saunders, and G. H. Williams, *ibid.*, 3409 (1964). [h] This work. The phenylations of C_6H_5COMe and C_6H_5CN have been carried out by aprotic diazotization of aniline. [i] R. Dannley and E. Gregg, *J. Am. Chem. Soc.*, **76**, 2997 (1954), reported 60.0, 10.0, 30.0, 3.7. [j] R. A. McClelland, R. O. C. Norman, and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 578 (1972), reported the isomer ratio of 66, 3, 31 for the methoxycarbonylation of $C_6H_5NO_2$ from the reaction of lead tetraacetate with monomethyl oxalate.



X = Me, CMe_3, Cl, Br, CO_2Me, COMe, CN, NO_2

tions and the total reactivity of a given substrate relative to benzene to be easily determined by gas chromatography from the ratio of substituted methyl benzoates and methyl benzoate. The results are collected in Table I, where the available corresponding values for phenylation are also reported for comparison. The methoxycarbonylbenzenes were obtained in 10–20% yields, depending upon the nature of the aromatic substrate employed. These low yields of conversion are due to concurrent reactions given by the ·CO_2Me radical in this system; one of the most important of these reactions is the above-mentioned fragmentation into carbon dioxide and methyl radicals.

The first characteristic of homolytic methoxycarbonylation which can be revealed from these results is that the degree of ortho substitution results in every case considerably lower than that observed with phenyl radicals; this is particularly evident with *tert*-butylbenzene, where the methyl *o-tert*-butylbenzoate is not formed at all, but is also observed with all the other substituents (with the exception of the nitro group) and is independent from their electronic properties. It can be assumed therefore that steric effects play an important role which can probably be attributed to unfavorable interactions between the substituents and the oxygen atoms linked to the entering carbon radical. This decrease of ortho substitution in respect to phenylation is accompanied by an increase in reactivity of both the meta and para positions in *tert*-butylbenzene; with the other substrates holding electron-withdrawing substituents, however, the meta substitution remains practically unaffected and an increase of the para isomer is observed in every case. With acetophenone and nitrobenzene the meta isomers were not formed at all. These results could be taken as an indication of the preference of the methoxycarbonyl radical for relatively electropositive nuclear positions as a result of a low nucleophilicity. As a matter of fact, over the range of aromatics listed in Table I, the values of the relative reactivities vary only by a factor of 4–5 but it seems indicative that all the substrates holding electron-withdrawing substituents present a slightly greater reactivity toward the ·CO_2Me than the phenyl radicals. It can be assumed that, in the transition state leading to the intermediate cyclohexadienyl radical, some charge transfer from the radical to the substrate or vice versa can take place.



Structure b will contribute with electrophilic radicals, while structure c will assume some importance with nucleophilic radicals. In the latter case the importance of the contribution of polar forms will depend upon the capability of substituents to stabilize the incipient positive charge, and it can be expected that with radicals having an sp^2 configuration, like the ·CO_2Me, the charge separation will play a minor role and will occur only with benzene derivatives holding strongly electron-withdrawing substituents, being completely negligible with the others. It is interesting in this respect to note that in a recent investigation[17] on the polar properties of ethoxy carbonyl radicals, Minisci and co-workers have used protonated pyridines as substrates and have found that the 4-cyano- and 4-acetylpyridines have a reactivity of 18.7 and 6.7 relative to the 4-methylpyridine; owing to the greater electron affinity of these protonated heteroaromatic bases with respect to the benzene derivatives, the charge development in the transition state will assume a greater importance and, as a consequence, the nucleophilic properties of the carbon radicals will be more clearly evidenced.

The results here reported with benzene derivatives show that no substantial changes are produced on the electronic properties of the ·CO_2Me radical by the presence of the oxygen functions; although a certain degree of nucleophilicity can be observed for this radical, its essential behavior does not significantly differ from those of other carbon radicals with similar hybridization, like phenyl, vinyl, and cyclopropyl.

Experimental Section[18]

Monosubstituted benzenes used as substrates, methyl formate and di-*tert*-butyl peroxide, and several substituted methyl benzoates were commercial products; dimethyl azodicarboxylate[19] and

some substituted methyl benzoates were prepared as described in the literature. Methyl *tert*-butylperoxyoxalate was prepared according to the procedure reported[7] for the synthesis of the corresponding ethyl derivative.

Decomposition of Dimethyl Azodicarboxylate in Benzene. A solution of **2** (1 g) in benzene (20 ml) was heated in a sealed tube at 130° for 3 days. The GLC analysis of the reaction mixture showed the presence of toluene in small quantities, and methyl benzoate and other unidentified products in much higher quantities. The solvent was evaporated and the residue was chromatographed through a silica gel column using a mixture of pentane and ether (9:1) as eluent; methyl benzoate (0.25 g) was identified by comparison of its infrared spectrum with that of an authentic sample.

Photolysis of Di-*tert*-butyl Peroxide in Benzene in the Presence of Methyl Formate. A solution of di-*tert*-butyl peroxide (7.3 g) and methyl formate (12 ml) in benzene (200 ml) was put in a cylindrical vessel, surrounded by a water jacket, with a central neck from which the lamp (Hanau P.L. 368) was immersed in the solution. The mixture was magnetically stirred and irradiated for 48 hr and then analyzed by GLC; the main reaction product was methyl benzoate, which was accompanied by small quantities of diphenyl and dibenzyl. The residue after evaporation of benzene was chromatographed under the conditions described above; diphenyl and dibenzyl were eluted first and were identified by comparison with authentic samples. The following fractions contained methyl benzoate (1.3 g).

Decomposition of Methyl *tert*-Butylperoxyoxalate in Benzene. A solution of **4** (3.9 g) in benzene (100 ml) was kept at 65° for 48 hr; analysis by GLC showed the presence of methyl benzoate, diphenyl, and traces of dibenzyl. The solvent was evaporated and the residue chromatographed as described above; diphenyl, dibenzyl, and methyl benzoate (0.5 g) were identified by comparison with authentic samples.[20]

Determination of Isomer Distributions and Relative Reactivities for the Methoxycarbonylation. A. Solutions (0.1 *M*) of **4** in an equimolecular mixture of benzene and monosubstituted benzenes were put in a sealed 2-ml glass tube and kept at 65° for 72 hr and then directly analyzed by GLC without manipulation. Three independent experiments were carried out in every case; the results were reproducible in every case and the averaged values are collected in Table I.

B. Solutions of di-*tert*-butyl peroxide (0.01 mol) and methyl formate (0.01 mol) in equimolecular mixtures of benzene and monosubstituted benzenes (4 ml) were put in a stoppered 5-ml quartz conical flask and irradiated for 72 hr. The reaction mixtures were analyzed as in A. The results are reported in Table I.

When toluene was used as solvent the main reaction product was dibenzyl in both cases. Competitive experiments between benzene and methyl benzoate could not be carried out directly and the relative reactivity of the $C_6H_5CO_2Me$ was therefore determined indirectly using equimolecular mixtures of $C_6H_5CO_2Me$ and C_6H_5CN. The relative reactivity of C_6H_5CN was obtained from the direct competition with benzene and confirmed from the determination of its reactivity relative to acetophenone.

The substituted methyl benzoates formed were also isolated by a combination of column chromatography and preparative GLC from reactions carried out on preparative scale and identified by comparison with authentic samples.

Acknowledgment. Financial support from the CNR, Rome, is gratefully acknowledged.

Registry No.—**1**, 16481-04-2; **2**, 2446-84-6; **4**, 57031-51-3; di-*tert*-butyl peroxide, 110-05-4.

References and Notes

(1) (a) M. I. Perkins in "Free Radicals", J. K. Kochi, Ed., Wiley-Interscience, New York, N.Y., 1973; (b) M. Tiecco in "Free Radical Reactions", W. A. Waters, Ed., Buttersworth, London, in press; (c) J. R. Shelton and C. W. Uzelmeier, *J. Am. Chem. Soc.*, **88**, 5222 (1966); (d) G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. B*, 1413 (1970); (e) P. Spagnolo, L. Testaferri, and M. Tiecco, *ibid.*, 2006 (1971); (f) A. Mangini, P. Spagnolo, D. Tassi, M. Tiecco, and P. Zanirato, *Tetrahedron*, **28**, 3485 (1972); (g) P. Spagnolo, L. Testaferri, M. Tiecco, and P. Zanirato, *Gazz. Chim. Ital.*, **105**, 761 (1975); (h) W. A. Pryor, T. H. Lin, J. P. Stanley, and R. W. Henderson, *J. Am. Chem. Soc.*, **95**, 6993 (1973); (i) W. A. Pryor, W. H. Davis, Jr., and J. H. Gleaton, *J. Org. Chem.*, **40**, 2099 (1975).

(2) (a) R. Ho, T. Migita, N. Morikawa, and O. Simamura, *Tetrahedron*, **21**, 955 (1965); (b) G. H. Williams, "Homolytic Aromatic Substitutions", Pergamon Press, Elmsford, N.Y., 1960.

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(6) P. J. Krusic and T. A. Rettig, *J. Am. Chem. Soc.*, **92**, 722 (1970).

(7) P. D. Bartlett and R. E. Pincock, *J. Am. Chem. Soc.*, **82**, 1769 (1960).

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(9) K. Bartel, A. Goosen, and A. Scheffer, *J. Chem. Soc. C*, 3766 (1971); A. Goosen and A. Scheffer, *ibid.*, 369 (1972).

(10) D. E. Zabel and W. S. Trahanovsky, *J. Org. Chem.*, **37**, 2413 (1972).

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(12) D. Griller and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 747 (1972).

(13) M. J. Perkins and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 297 (1974).

(14) R. Bernardi, T. Caronna, R. Galli, F. Minisci, and M. Perchinunno, *Tetrahedron Lett.*, 645 (1973).

(15) J. H. T. Brook and W. Snedden, *Tetrahedron*, **20**, 1043 (1964).

(16) The rather unfavorable process of hydrogen abstraction from benzene may induce suggestion of an alternative way of formation of biphenyl through the addition of the *tert*-butoxy radical to the benzene followed by dimerization of the resulting cyclohexadienyl radical and nonradical fragmentation of the dimers to *tert*-butyl alcohol and diphenyl; a similar mechanism has already been postulated to explain the formation of diaryls in reactions involving oxygen-centered radicals.[1a,b]

(17) A. Clerici, F. Minisci, and O. Porta, *J. Chem. Soc., Perkin Trans. 2*, 1699 (1974).

(18) Gas chromatographic analyses were performed on a Hewlett-Packard 5700 instrument equipped with a flame ionization detector. Calibrations for area response differences between methyl benzoate and isomeric monosubstituted methyl benzoates were effected for each reactions using the pure samples. The columns used, all on Aeropak 30 (100–120 mesh), follow: 10% Silicone GE XE-60 for the methyl derivatives, 5% Bentone 34 for the halogeno derivatives, and 10% LAC 728 for all the other substituted methyl benzoates; in several cases the results were confirmed using 5% FFAP and 5% SE-30 columns.

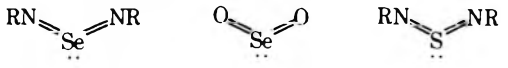
(19) A. Rodgman and J. F. Wright, *J. Org. Chem.*, **18**, 465 (1953).

(20) Other products were obviously formed from the decomposition of **4** in benzene but their complete analysis was not effected in the present investigation; the nature of these more volatile compounds has already been determined from the reaction of the ethyl *tert*-butylperoxyoxalate[7] and their formation is considered not to influence the methoxycarbonylation process.

Allylic Amination of Olefins and Acetylenes by Imido Sulfur Compounds

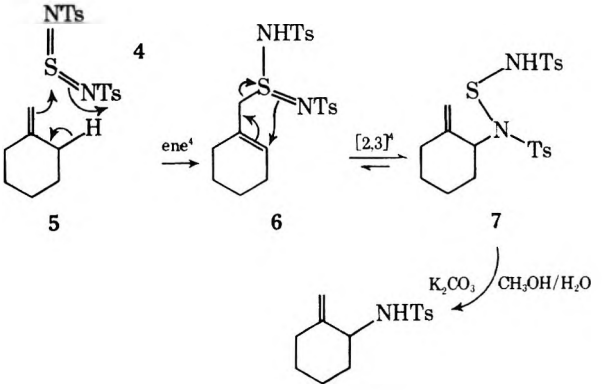
Summary: The sulfur dimide species **4** (TsN=S=NTs) was found to be a powerful enophile in its reactions with simple olefins and acetylenes. Following hydrolysis of the initial ene products, allylic sulfonamides are produced in good yield.

Sir: We have reported that imido selenium compounds (**1**) effect allylic amination of olefins,[1] and thus mimic the well-known allylic oxygenation of olefins by selenium dioxide (**2**). We have now discovered that the analogous sulfur imido compounds (**3**)[2] are also excellent reagents for the al-



1 **2** **3**

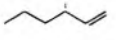
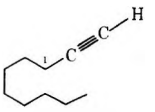
lylic amination of olefins. Thus the deep yellow color of a solution of bis(*p*-toluenesulfonyl)sulfodimide (**4**) in methylene chloride was immediately[3] discharged when an equivalent of methylene cyclohexane (**5**) was added. TLC indicated a single product, and spectroscopic evidence (NMR and ir) suggested that it was principally disulfenamide **7**, perhaps containing some of the initial ene product **6** as a minor component.[5] As indicated in Table I, the reactions of sulfodiimide **4** were also explored with several other olefins and with one acetylene. In each case reaction occurred to produce intermediates analogous to **6** and **7**. These sulfenamide intermediates are easily cleaved to the corresponding allylic sulfonamides (e.g., **8**). As an alternative to the rather slow basic (K_2CO_3) hydrolysis described below, they can be rapidly cleaved by treatment with trimethyl phosphite in methanol at room temperature.



8 (84%)

General Procedure. (Diimide **4**[6] reacts instantly with water; therefore rigorously anhydrous conditions are essential.) To a solution of 278 mg (2.9 mmol) of methylene cyclohexane (**5**) in 2.8 ml of dry CH_2Cl_2 (passed through alumina) was added a solution of 1.11 g (3 mmol) of diimide **4** in 12 ml of CH_2Cl_2 while stirring in an ice-bath under nitrogen. The yellow color of reagent **4** disappeared quickly. The resulting solution was stirred at room temperature for 14 hr and then concentrated to afford an oil. This crude sulfenamide (**7**) was hydrolyzed by stirring at room temperature for 14 hr with 20 ml of a solution consisting of 2.4 g of K_2CO_3, 12 ml of

Table I
Allylic Amination[a]

Example	Olefin or acetylene	Mole ratio of 4/substrate	% yield[b] (mp, °C) Site 1[c]	Site 2[c]
1		1.04	45	
2		1.04	56	3
3		1.12	70 (101–102)	
4		1.04	84 (120–121)	
5[d]		2.06	63[d] (201–202)	
6		1.04	63 (192–193)	
7		1.04	38 (77–78)	33 (68–69)
8		1.55	37 (65–66)	

[a] With the noted differences in stoichiometry in cases 3, 5, and 8, all reactions were carried out on 2.9 mmol of substrate as described in detail for methylene cyclohexane (5). The acetylene (case 8) was slow to react; so the usual 14-hr reaction period was extended to 3 days. The allylic sulfonamide products were characterized by comparison with authentic materials.[1] [b] Yields were determined by isolation, which, in the case of the solid products, involved recrystallization. [c] Site of amination as indicated on the substrate. [d] In this case the bis amide was produced; the sites of amination are indicated by the arrows.

CH_3OH, and 8 ml of H_2O. Then 100 ml of ether was added and the organic phase was washed with 20 ml of a solution made up of two parts 1 *N* aqueous NaOH and one part saturated aqueous NaCl.[7] The ether layer was further washed with water and brine and then dried ($MgSO_4$) and concentrated to give 674 mg of pale yellow crystals. Recrystallization from CCl_4–hexane afforded 648 mg (84%) of the pure allylic sulfonamide **8**, mp 120–121°.

Examination of Table I reveals that these sulfodiimide reagents (**3**) are likely to prove superior to the previously developed selenodiimide reagents (**1**).[1] Of special importance in the case of the sulfur reagent (**4**) is the ease with which the pure products can be isolated without chromatography. At present the Chloramine-T/Se^0 derived reagent (**1**, R = Ts)[1] is much easier to prepare than the sulfur diimide reagent **4**. However, we are trying to develop a convenient in situ method for the generation of **4**.

The present work provides a rare example wherein the discovery of a new reaction in sulfur chemistry was inspired by the prior discovery of the related process in selenium chemistry. It has almost always happened the other way around.

Acknowledgment. We are grateful to the National Institutes of Health (GM21686) for support of this research.

References and Notes

(1) K. B. Sharpless, T. Hori, L. K. Truesdale, and C. O. Dietrich, *J. Am. Chem. Soc.*, submitted for publication.
(2) For an excellent review on the preparation and the reactions of the imides of sulfur dioxide, see G. Kresze and W. Wucherpfennig, *Angew. Chem., Int. Ed. Engl.*, **6**, 149–167 (1964). The Diels–Alder addition of these imido sulfur species (**3**) to 1,3-dienes is well known, but, surprisingly, their facile ene reaction with simple olefins has not been described previously.
(3) In the case of less reactive substrates (e.g., case 1, 3, and 8 of Table I) the yellow color remained even after 14 hr. In these instances excess reagent and even longer reaction times might improve the yields.
(4) This proposed mechanism for formation of **7** is directly analogous to the accepted mechanism for the oxidation of olefins by selenium dioxide: (a) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **94**, 7154 (1972); (b) D. Arigoni, A. Vasella, K. B. Sharpless, and H. P. Jensen, *ibid.*, **95**, 7917 (1973); H. P. Jensen and K. B. Sharpless, *J. Org. Chem.*, **40**, 264 (1975).
(5) Allyl sulfinic acids (i.e., oxygen analogues of **6**) are known to undergo retroene reaction (see ref 2) rather than [2,3] rearrangement. Allyl sulfoxides tend to exist as sulfoxides rather than the 2,3-shifted allyl sulfenate esters [see D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974), and references cited therein]. However, for evidence in support of **7** being the stable side of the [2,3] equilibrium between **6** and **7** in related cases where nitrogen has been substituted for oxygen, see R. S. Atkinson and S. B. Awad, *J. Chem. Soc. D*, 651 (1975), and references cited therein.
(6) Prepared from TsN=S=O as described by W. Wucherpfennig and G. Kresze, *Tetrahedron Lett.*, 1671 (1966). Dry bag techniques were used to avoid contact of **4** with moisture.
(7) The presence of the NaCl in this basic wash allows extraction of *p*-toluenesulfonamide but prevents extraction of the product, which can be a problem in the case of the smaller olefins (e.g., cases 1 and 3). We recommend that this modification of the alkaline wash also be adopted for the selenium-based aminations (see ref 1).

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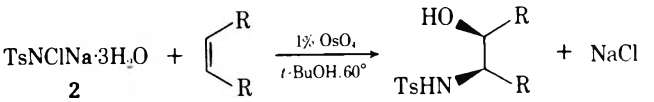
Osmium-Catalyzed Vicinal Oxyamination of Olefins by Chloramine-T

Summary: An osmium-catalyzed procedure which effects cis addition of the hydroxyl (OH) and arylsulfonamide (ArSO_2NH) moieties across an olefinic linkage is described; sixteen different olefin substrates were examined.

Sir: We have reported that *tert*-alkyl imido osmium compounds, such as **1a**, effect stereospecific vicinal oxyamination of olefins.[1] However, this new synthetic transformation suffers from two important limitations. It requires a stoichiometric amount of osmium reagent (**1a**) and it is difficult to remove the *tert*-alkyl group from the products. We have discovered a new procedure which solves both of these problems. The trihydrate of Chloramine-T[2] reacts with olefins in the presence of a catalytic amount of osmium tetroxide to produce vicinal hydroxy *p*-toluenesulfonamides

1a, R = *tert*-alkyl
b, R = Ts



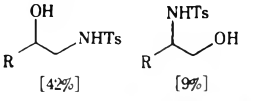
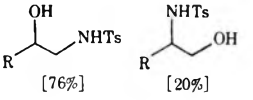
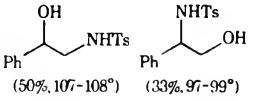
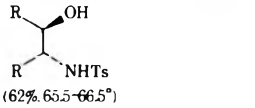
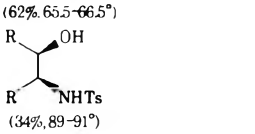
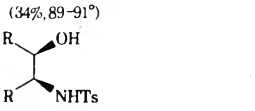
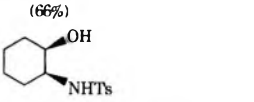
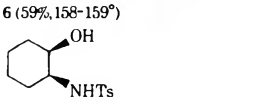
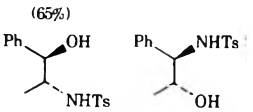
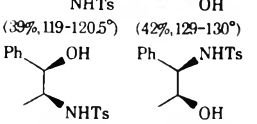
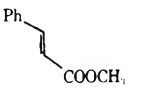
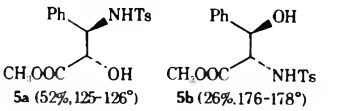
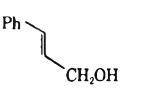
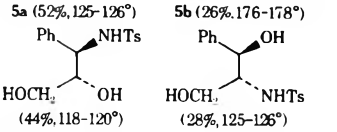
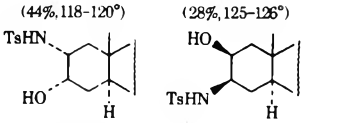
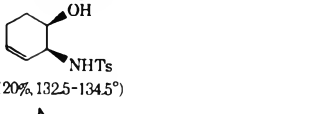
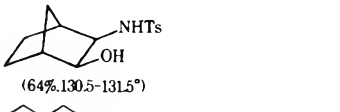
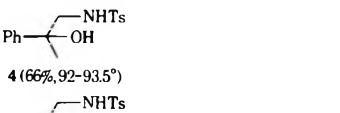
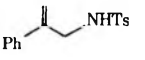
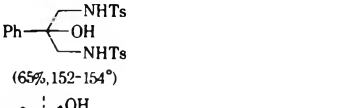
2 **3**

(**3**). This is an aza analogue of the catalytic procedures developed by Hoffman[3] and Milas[4] for vicinal dihydroxylation of olefins. The sulfonyl imido osmium compound **1b** is presumed to be the effective reagent, and it must be continuously regenerated under these conditions. We soon discovered that the process is inhibited by the chloride ion which is released as the reaction proceeds. In the case of 1-decene this inhibition is dramatically overcome by the addition of an equivalent of silver nitrate[5] (compare examples 1 and 2 in Table I). Silver nitrate has a beneficial effect in the case of about half of the olefins listed in Table I. However, we were surprised to find that silver ion can also have a deleterious effect; this effect is so severe in some cases (e.g., 4, 15, 16, 17, and 19 of Table I) that only a trace of the usual hydroxy amide is formed in the presence of silver nitrate. Thus we have developed two general procedures: one without $AgNO_3$ (procedure A) and one with $AgNO_3$ (procedure B). An explanation for the variable effects of silver and chloride ions on these reactions is clearly beyond our current understanding. For almost all of the olefins in Table I both procedures (A and B) were tried; when only one procedure is given it means that it was superior to the other for that substrate.

Procedure A. To 0.59 g (5.0 mmol) of α-methylstyrene in 50 ml of reagent grade *tert*-butyl alcohol was added 1.76 g (6.25 mmol) of Chloramine-T trihydrate (EK) and 0.625 ml (0.05 mmol) of a 0.079 *M* solution of osmium tetroxide in olefin-free hexane. The flask was fitted with a reflux condenser and placed in an oil bath maintained at 60°. The resulting suspension was stirred magnetically until all olefin had disappeared (~15 hr). Then 20 ml of 2.5% aqueous sodium bisulfite was added and the mixture was refluxed for 1.5 hr. The *tert*-butyl alcohol was removed in vacuo, and the residue was taken up in 100 ml of methylene chloride and washed once with 150 ml of water. The suspended osmium-containing impurities were removed from the organic phase by stirring with magnesium sulfate followed by filtration. The solution was then washed once with 50 ml of 1% aqueous sodium hypochlorite solution[6] and then 100 ml of water. The organic phase was dried ($MgSO_4$) and concentrated to give 1.39 g of pale yellow oil[7] which solidified on standing. Recrystallization from ether gave a first crop of 0.87 g of colorless crystals, mp 92–93.5°, and a second crop of 0.14 g of crystals, mp 87–92.5°, for a total yield of 1.01 g (66%) of the hydroxy sulfonamide, **4**. When this same procedure was carried out on a ½-mol scale, 108 g (71%) of hydroxy sulfonamide **4** was produced; for convenience less *tert*-butyl alcohol was used so that the reaction was three times as concentrated as described above.

Procedure B. The procedure is the same as that described above for α-methylstyrene with the following exceptions: (1) the substrate was 0.81 g (5.0 mmol) of methyl cinnamate, (2) in addition to the other reagents 1.06 g (6.25 mmol) of silver nitrate was added, (3) the heterogeneous reaction mixture was stirred at 60°[8] until all olefin was consumed (~20 hr), (4) prior to the usual work-

Table I[a]

Example	Olefin	Procedure, °C, hr	Products[b]
1	1-Decene	A, 60, 3	 [42%] [9%]
2	1-Decene	B, 25, 2	 [76%] [20%]
3	Styrene	B, 25, 15	 (50%, 107-108°) (33%, 97-99°)
4	(*E*)-5-Decene	A, 60, 36	 (62%, 65.5-66.5°)
5	(*Z*)-5-Decene	A, 60, 3	 (34%, 89-91°)
6	(*Z*)-5-Decene	B, 25, 22	 (66%)
7	Cyclohexene	A, 60, 12	 6 (59%, 158-159°)
8	Cyclohexene	B, 25, 6[c]	 (65%)
9		B, 60, 15	 (39%, 119-120.5°) (42%, 129-130°)
10		B, 60, 15	 (26%, 111-113°) (59%, 104-105°)
11		B, 60, 20	 5a (52%, 125-126°) 5b (26%, 176-178°)
12		B, 60, 20	 (44%, 118-120°) (28%, 125-126°)
13	Δ²-Cholestene	B, 60, 20	 (56%, 235-237°) (31%, 185-188°)
14		A, 60, 44	 (20%, 132.5-134.5°)
15		A, 60, 44	 (64%, 130.5-131.5°)
16		A, 60, 15	 (70%, 96-97°)
17		A, 60, 15	 4 (66%, 92-93.5°)
18		A, 60, 72	 (65%, 152-154°)
19		A, 60, 92	 (82%)

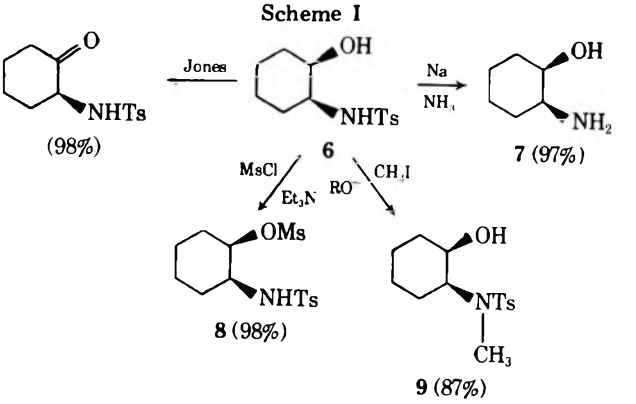
[a] All reactions were performed on a 5-mmol scale as described in detail under procedures A and B. All new compounds exhibited consonant analytical and spectral data. [b] Except in the case of 1-decene where yields (in brackets) were determined by GLC, all yields are for isolated, pure substances. When mixtures were formed, chromatography (on silica gel or basic alumina) was used to separate the regioisomers. When only one hydroxysulfonamide was formed, recrystallization of the crude reaction product was the preferred method of isolation. Melting points are given after the yields. [c] Under these conditions two analogues of Chloramine-T (para-hydrogen and parachloro) also gave with cyclohexene comparable yields of the hydroxysulfonamides related to 6.

up, silver chloride was removed by filtration, and (5) chromatography of the crude product (1.65 g of pale yellow solid) on silica gel gave 0.92 g (52%) of the hydroxy sulfonamide, **5a**, mp 125–126°, and 0.46 g (26%) of the isomer, **5b**, mp 176–178°.

As shown in Scheme I, we have briefly explored some transformations of the hydroxy sulfonamide **6**, derived from cyclohexene. The reduction of **6** to the cis amino alcohol **7** proceeds readily.[9] Because of the acidity of the sulfonamide hydrogen in **6**, the nitrogen can be selectively derivatized (**9**). By means of the mesylate (**8**) and the amino alcohol (**7**) either the oxygen or the nitrogen of these cis vicinal hydroxy amides can be transformed into a leaving group. This should in many cases allow for unique control over the course of molecular rearrangements.

The following olefins either failed to react or gave very low yields of hydroxy sulfonamide: cholesteryl acetate, tetramethylethylene, 1-phenylcyclohexene, cyclohexen-3-one, 1-acetoxycyclohexene, and dimethyl fumarate. In spite of these limitations this new catalytic reaction should prove useful in organic synthesis. It is interesting that in many cases it gives better yields and fewer by-products than the corresponding osmium-catalyzed processes for production of vicinal diols from olefins.[3,4]

Scheme I



Acknowledgment. We are grateful to the National Science Foundation (MP-57-21260) and Hoffmann-La Roche Inc. for support of this research.

References and Notes

(1) (a) K. B. Sharpless, D. W. Patrick, L. K. Truesdale, and S. A. Biller, *J. Am. Chem. Soc.*, **97**, 2305 (1975); (b) K. B. Sharpless, D. W. Patrick, L. K. Truesdale, and S. A. Biller [a full paper on the alkyl imido reagents (**1a**) is in preparation].
(2) It is surprising that Chloramine-T has been so little used in organic synthesis. It is inexpensive and is formally a nitrogen analogue of sodium hypochlorite (NaOCl). Whereas NaOCl is formally a source of ":Ö:", TsNClNa is formally a source of "TsN". We have also found recently that anhydrous TsNClNa reacts with selenium metal to produce a potent reagent for allylic amination of olefins [K. B. Sharpless, T. Hori, L. K. Truesdale, and C. O. Dietrich, *J. Am. Chem. Soc.*, **98**, 269 (1976).
(3) K. A. Hoffmann, *Chem. Ber.*, **45**, 3329 (1912).
(4) N. A. Milas and S. Sussman, *J. Am. Chem. Soc.*, **58**, 1302 (1936).
(5) When $AgNO_3$ is added to a stirred suspension of TsNClNa in *tert*-butyl alcohol at room temperature a new more flocculent precipitate is formed: this solid is the silver salt of Chloramine-T (TsNClAg). TsNClAg was prepared by a known method [G. Wittig and D. Hellwinkel, *Chem. Ber.*, **97**, 789 (1964)] and was found to have the same properties in these reactions as the combination of $AgNO_3$ + TsNClNa.
(6) Commercial bleach was diluted 5 to 1. This treatment converts the *p*-toluenesulfonamide, sometimes a by-product of these oxidations, to Chloramine-T, which is preferentially extracted into the aqueous phase. Although the *p*-toluenesulfonamide can also be extracted with aqueous NaOH, this procedure often removes some of the desired product as well.
(7) These crude products contain surprisingly little diol (usually <2%); recall that on the order of 1% diol is necessarily formed since the catalyst is added as osmium tetroxide. We have found that the solid osmate(VI) ester of pinacol also serves as a catalyst and results in no initial diol formation. However, we prefer to use osmium tetroxide because of the convenience of adding a solution.
(8) These $AgNO_3$ modifications were either run at 60 or at 25° as noted in Table I.
(9) Sodium naphthalene in glyme is also effective for the reductive cleavage of sulfonamides [S. Ji, L. B. Gantler, A. Waring, A. Battisti, S. Bank, and W. D. Closson, *J. Am. Chem. Soc.*, **89**, 5311 (1967)]; this procedure also works well for allylic and benzylic sulfonamides and thus should succeed with most of the hydroxy amides in Table I.
(10) Camille and Henry Dreyfus Teacher-Scholar Grant recipient; Alfred P. Sloan Fellow, 1973–1975.
(11) Rohm and Haas Graduate Fellow, 1974–1975.

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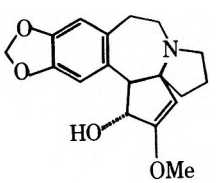
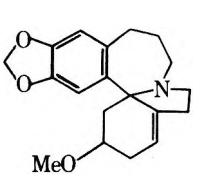
A Biogenetic-Type Approach to Homoerythrina Alkaloids[1]

Summary: A unified synthetic approach to homoerythrina alkaloids via the dibenz[*d*,*f*]azecine **11** has produced the schelhammera-type skeleton **12** and a new homoerysodienone skeleton **13.**

Sir: Recently, attention has been focused on the total synthesis of cephalotaxine[2] **1**, since it is the alkaloidal portion of the antitumor esters[3] of *Cephalotaxus harringtonia*. The presence of schelhammera-type alkaloids[4] such as 3-epischelhammericine **2** in species of *Cephalotaxus*[5] has led



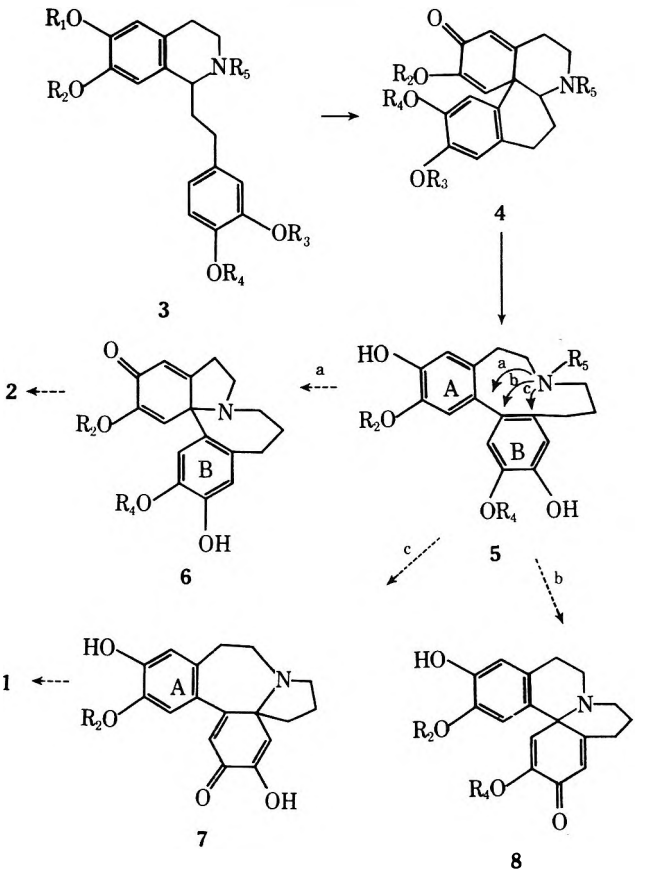
cephalotaxine **1**



schelhammercine **2**

us and others[5a] to the proposal that both the schelhammera-type and *Cephalotaxus* alkaloids are biogenetically related and may be classified as homoerythrina alkaloids. We have been interested in testing in the laboratory a unified approach to homoerythrina skeletons via the substituted phenethylisoquinoline **3** and the pivotal dibenz[*d*,*f*]azecine **5**, shown in Scheme I. It seemed reasonable that compound **5** could be a possible biogenetic precursor[6] to the *Cephalotaxus* (pathway c, Scheme I) and the *Schelhammera* alkaloids (pathway a, Scheme I) as well as the hitherto unknown homoerysodienone skeleton **8** (pathway b, Scheme I). In fact, the dibenz[*d*,*f*]azecine **5** is also a homolog of the alkaloid erybidine.[7] In this communication, we wish to report the synthesis of the dibenz[*d*,*f*]azecine **11** and its oxidative transformation into two homoerythrinadienones **12** and **13.**

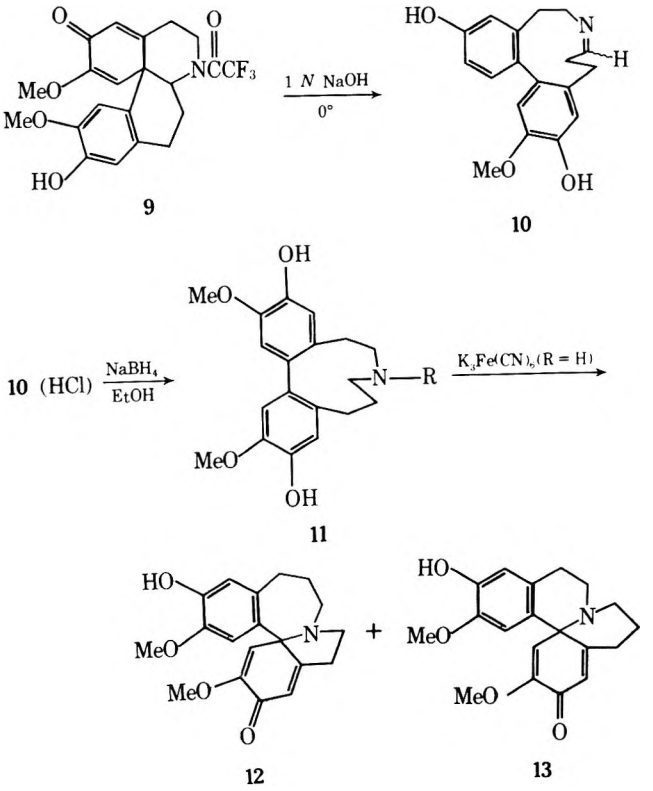
Scheme I



The preparation of the prohomoerythrinadienone derivative **9** from the corresponding phenylethylisoquinoline precursor has been previously described by us.[8] The hydrolytic fragmentation process, which was affected with 1 *N* hydroxide at 0° in methanol, yielded the bisphenolic imine **10** (Scheme II) in quantitative yield. The stereoelectronics of the base-induced bond cleavage requires that the compound **10** initially possess the unusual trans-imine moiety.[9] The bisphenolic imine **10** was converted into its hydrochloride salt (dp 237–239°) with anhydrous hydrogen chloride in ethanol. This imminium chloride was reduced efficiently with sodium borohydride in ethanol to the crystalline bisphenolic amine **11** (R = H, mp 211.5–212.5°).[10] The overall yield from **9** to pure bisphenolic amine **11** was 76%. The preparation of the dibenz[*d*,*f*]azecine **11** constitutes an efficient synthesis[11] of the homoerybidine skeleton which very likely may occur as a natural product.

A variety of oxidative cyclizations were attempted on the free amine **11** (R = H) and its trifluoroacetamide **11** (R =

Scheme II



CH_3CO). It was our original intention to affect the oxidation of the trifluoroacetamide of **11** in order to produce the corresponding diphenoquinone. A suitably substituted dipheno-*p*-quinone could then be transformed into the cephalotaxine precursor **7** via an intramolecular Michael addition of the nitrogen.[5] Attempted oxidation of **11** (R = CH_3CO) with dichlorodicyanoquinone, potassium hexacyanoferrate, silver oxide, or the ferric chloride–DMF complex[12] yielded only starting material. Thallium trifluoroacetate oxidation of the trifluoroacetamide of **11** (R = CH_3CO) produced a dimer (35% yield) derived from oxygen–carbon coupling. Lead tetraacetate oxidation of **11** (R = CH_3CO) in glacial acetic acid produced in high yield a bis-*o*-quinol acetate. The above results reflect the difficulty in oxidizing **11** (R = CH_3CO) to the corresponding dipheno-*p*-quinone, presumably because of the orthogonality of the aromatic rings of **11**. Thus, each aromatic ring of **11** (R = CH_3CO) behaves independently toward oxidation.

In contrast to the oxidations of the trifluoroacetamide of **11**, the free amine **11** (R = H) was cleanly transformed into two cyclized homoerythrina skeletons with potassium hexacyanoferrate in methylene chloride–sodium bicarbonate solution. After preparative layer chromatography on silica gel of the crude reaction mixture, a 45% yield of crystalline dienone **12** (mp 166–167°, from 2-propanol) was isolated along with 15% crystalline homoerysodienone **13** (mp 195.5–197.5°, from 2-propanol) and 35% recovered starting bisphenolic amine **11** (R = H). The isolation of the schelhammera-type skeleton[13] **12** and the new homoerysodienone skeleton **13** is consistent with standard phenolic coupling of the amine nitrogen para to a free hydroxyl group (paths a and b, Scheme I). The ratio of **12** to **13** is probably a good indication of the conformational preference for ring closure via path a vs. closure via path b. That no cephalotaxine precursor (path c) was observed in the above oxidation suggests the absence of a dipheno-*p*-quinone intermediate or a suitably disposed *p*-hydroxy group (**5**, R_4 = H). We are presently exploring the preparation of the biscatechol derivative of **11** and its transformation into a cephalotaxine precursor, via an *o*-quinone.

Acknowledgment. The initial phase of this work was partially supported by an Institutional Research Grant (IN-40K) to The University of Michigan from the American Cancer Society.

References and Notes

(1) A preliminary report of some of this work was presented at the 169th National Meeting of the American Chemical Society, Medicinal Chemistry Division, Philadelphia, Pa., April 1975.
(2) (a) S. M. Weinreb and J. Auerbach, *J. Am. Chem. Soc.*, **97**, 2503 (1975); (b) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *ibid.*, **97**, 2507 (1975).
(3) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972).
(4) (a) J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Aust. J. Chem.*, **22**, 2187 (1969); (b) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *ibid.*, **22**, 2219 (1969); (c) N. Langlois, B. Das, and L. Lacomb, *Bull. Soc. Chim. Fr.*, 3535 (1970).
(5) (a) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972); (b) R. G. Powell and K. L. Mikolajczak, *ibid.*, **12**, 2987 (1973); (c) W. W. Paudler and J. McKay, *J. Org. Chem.*, **38**, 2210 (1973); (d) S. Asada, *Yakugaku Zasshi*, **93**, 916 (1973).
(6) R. J. Parry and J. M. Schwab, *J. Am. Chem. Soc.*, **97**, 2555 (1975). These workers have reported compelling evidence that labeled tyrosine was incorporated into cephalotaxine via an alternative biosynthetic pathway. At the present time, this work does not rule out elements of Scheme I as a possible biogenetic route to other homoerythrina alkaloids.
(7) M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, N.Y., 1972, p 425.
(8) J. P. Marino and J. M. Samanen, *Tetrahedron Lett.*, 4553 (1973).
(9) Analysis of the NMR and ir spectra of **10** could not definitively confirm the trans stereochemistry for the imine. We have also not ruled out the possibility that the initially formed trans amine **10** has isomerized to the cis imine.
(10) All new compounds gave satisfactory elemental analyses and gave NMR, uv, ir, and MS data consistent with the assigned structures.
(11) For a recent and different approach to the dibenz[*d,f*]azecine system, see S. Kano, T. Ogawa, T. Koyomatsu, E. Komiyama, and S. Shibuya, *Tetrahedron Lett.*, 1063 (1974).
(12) S. Tobinaga and E. Kotani, *J. Am. Chem. Soc.*, **94**, 309 (1972).
(13) Dienone **12** was previously prepared by Kametani and Fukumoto in 4.2% yield from a phenethylphenylpropylamine: T. Kametani and K. Fukumoto, *J. Chem. Soc., C*, 2156 (1968).

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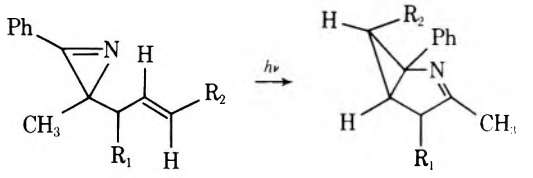
Thermal Rearrangement of Allyl Substituted 2*H*-Azirines to 3-Azabicyclo[3.1.0]hex-2-enes

Summary: The thermal rearrangement of 2-allyl substituted 2*H*-azirines to 3-azabicyclo[3.1.0]hex-2-enes proceeds in high yield. The reactions can best be rationalized in terms of an equilibration of the 2*H*-azirine with a transient vinyl nitrene which subsequently adds to the adjacent π bond.

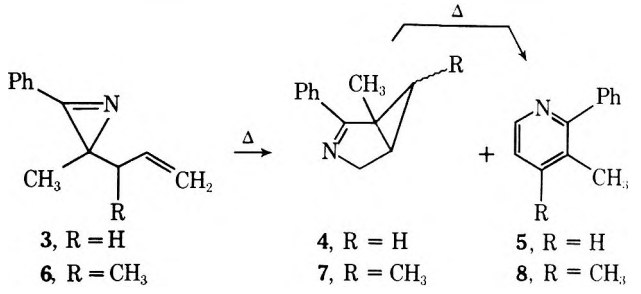
Sir: Photolysis of 2*H*-azirines leads to irreversible ring opening and the formation of nitrile ylides as intermediates.[1,2] These species may be intercepted by a variety of dipolarophiles to form five-membered heterocyclic rings. In certain cases the initially formed 1,3 dipole can be intramolecularly trapped[3] to give novel azabicyclohexenes.[4] For example, irradiation of allyl substituted 2*H*-azirines (**1**) produce 2-azabicyclo[3.1.0]hex-2-enes (**2**) via an unusual 1,1 cycloaddition reaction of the 1,3 dipole.[4] This observation stimulated us to begin a general investigation of the scope and mechanistic details of the intramolecular cyclization of unsaturated azirines. In this communication we wish to report on the thermolysis of a number of allyl substituted

2*H*-azirines and the formation of products previously unobserved in both thermal[5] and photochemical[1,2] azirine decompositions.



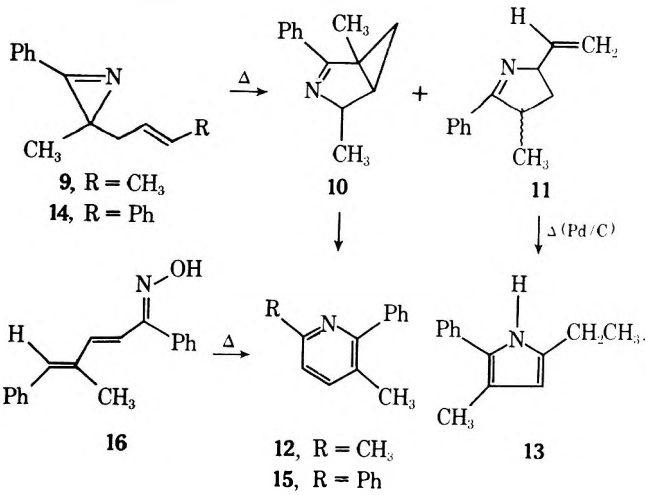
1 2

Thermolysis of 2-phenyl-3-methyl-3-allylazirine[6] (**3**) in toluene at 195° for 180 hr or in the absence of solvent at 250° for 1.5 hr gave 1-methyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**4**, 90%) and 3-methyl-2-phenylpyridine (**5**, 10%). The identity of **4** was determined by its straightforward spectral characteristics[7] as well as its facile conversion into **5** (picrate mp 164–165°)[8] on further heating. Thermolysis of the closely related methyl substituted azirine **6** gave 1,6-dimethyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**7**, 58%) as a 1:1 mixture of endo and exo isomers[9] as well as 3,4-dimethyl-2-phenylpyridine (**8**, 25%) (picrate mp 171–172°).[10] The mixture of exo and endo isomers of **7** were smoothly converted into pyridine **8** on further heating.



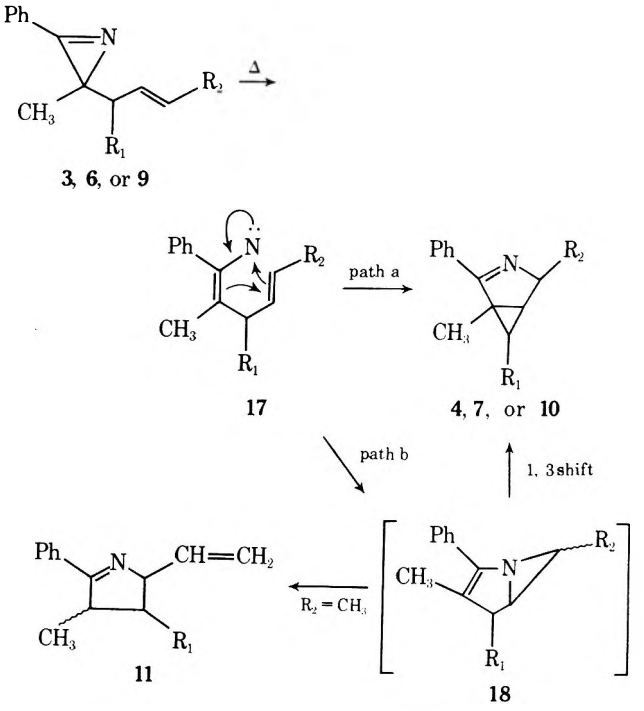
3, R = H; **6**, R = CH_3 — **4**, R = H; **7**, R = CH_3 — **5**, R = H; **8**, R = CH_3

Subjection of azirine **9** to similar pyrolysis conditions gave 1,4-dimethyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene[11] (**10**, 71%), 2-phenyl-3-methyl-5-vinyl-Δ^1-pyrroline[12] (**11**, 23%), as well as a trace amount (<5%) of 3,6-dimethyl-2-phenylpyridine (**12**).[10] The structure of Δ^1-pyrroline **11** was confirmed by refluxing **11** in toluene in the presence of palladium on carbon (5%) for 48 hr. This resulted in the quantitative formation of 2-phenyl-3-methyl-4-ethylpyrrole (**13**). That Δ^1-pyrroline **11** did not arise from 3-azabicyclohexene **10** was shown by heating **10** under conditions similar to those used for the pyrolysis of azirine **9**. Under these conditions **10** was converted exclusively into pyridine **12**. The thermal rearrangement of 2-phenyl-3-methyl-3-cinnamylazirine (**14**) was also studied. Thermolysis of **14** gave 2,6-diphenyl-3-methylpyridine (**15**, 49%) as the only characterizable material. The structure of **15** was verified by comparison with an authentic sample prepared from the thermolysis of oxime **16**. In this case, there were no detectable quantities of a 3-aza substituted bicyclohexene. It would appear as though the initially formed azabicyclohexene is converted into pyridine **15** at a faster specific rate than it is formed.



9, R = CH_3; **14**, R = Ph — **10** — **11** — **16** — **12**, R = CH_3; **15**, R = Ph — **13**

The thermal transformations observed with these systems can best be rationalized in terms of an equilibration of the 2*H*-azirine with a transient vinyl nitrene (**17**) which subsequently rearranges to the final azabicyclohexenes. The products formed on thermal decomposition of 2*H*-azirines generally appear to involve C–N rather than C–C bond cleavage.[13] In some cases, C–N bond cleavage ultimately leads to fragmentation of the three-membered ring with the subsequent formation of a nitrile and carbene[14] and in other cases results in the formation of indoles[15] or pyrroles.[16] One possible route by which the vinyl nitrene can rearrange to the final product (path a) involves attack of the neighboring π system on the electrophilic singlet nitrene followed by bond reorganization. An equally plausible mechanism (path b) involves intramolecular addition of



3, **6**, or **9** — **17** — **4**, **7**, or **10** — **11** — **18**

the nitrene onto the adjacent π bond to give a bicycloaziridine (**18**) as a transient intermediate.[17] This species can subsequently rearrange to the observed product by a 1,3-sigmatropic shift. The allowed concerted thermal 1,3 shift requires an inversion of the migration center, and this seems sterically prohibited in this system. Although a "forbidden" 1,3-suprafacial concerted process cannot be excluded,[18] the rearrangement of **18** to the observed azabicyclohexene probably involves a diradical intermediate by analogy to the results obtained with the parent carbocycle.[19,20] Some evidence favoring path b is provided by the isolation of Δ^1-pyrroline **11** from the thermolysis of **9**. The formation of this product can be rationalized as proceeding via a homo[1,5] hydrogen migration from the endo isomer of bicycloaziridine **18**.[21]

We are continuing to explore the scope and mechanistic details of this novel thermal reaction.

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(6) Azirine **3** was prepared by a modified Neber reaction in which 1-phenyl-2-methyl-4-penten-1-one was treated with dimethylhydrazine according to the general procedure of N. J. Leonard and B. Zwanenburg, *J. Am. Chem. Soc.*, **89,** 4456 (1967). This same approach was used to prepare azirines **6** and **9**. Complete spectroscopic properties of the unsaturated azirines will be given in our full publication.
(7) Compound **4**: uv (cyclohexane) 239 nm (ϵ 11 000); NMR δ 0.45 (t, 1 H, J = 4.0 Hz), 0.96 (dd, 1 H, J = 8.0 and 4.0 Hz), 1.43 (s, 3 H), 1.64 (m, 1 H), 3.75 (dd, 1 H, J = 17.5 and 2.0 Hz), 3.98 (dd, 1 H, J = 17.5 and 5.0 Hz), 7.2–7.8 (m, 5 H); *m/e* 171 (M^+).
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(9) Compound **7**: NMR (endo) δ 0.75 (d, 3 H, J = 6.0 Hz), 1.22 (d, q, 1 H, J = 8.0 and 6.0 Hz), 1.42 (s, 3 H), 1.62 (dd, 1 H, J = 8.0 and 2.0 Hz), 3.56 (dd, 1 H, J = 18.0 and 2.0 Hz), 3.93 (dd, 1 H, J = 18.0 and 7.0 Hz); NMR exo δ 0.70 (p, 1 H, J = 6.0 Hz), 1.19 (d, 3 H, J = 6.0 Hz), 1.25 (dd, 1 H, J = 5.0 and 2.0 Hz), 1.38 (s, 3 H), 3.78 (dd, 1 H, J = 17.0 and 2.0 Hz), 3.94 (dd, 1 H, J = 17.0 and 5.0 Hz).
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(11) Compound **10**: NMR δ 0.48 (t, 1 H, J = 4.0 Hz), 0.96 (dd, 1 H, J = 8.0 and 4.0 Hz), 1.25 (d, 3 H, J = 7.0 Hz), 1.46 (dd, 1 H, J = 8.0 and 4.0 Hz), 1.96 (s, 3 H), 3.87 (q, 1 H, J = 7.0 Hz), 7.2–7.9 (m, 5 H).
(12) Compound **11**: NMR δ 1.16 (two doublets, 3 H, J = 7.0 Hz), 1.90 (m, 1 H), 1.3–1.6 (m, 1 H), 3.36 (m, 1 H), 4.60 (m, 1 H), 4.9–5.3 (m, 2 H), 5.8–6.2 (m, 1 H), 7.0–7.9 (m, 5 H).
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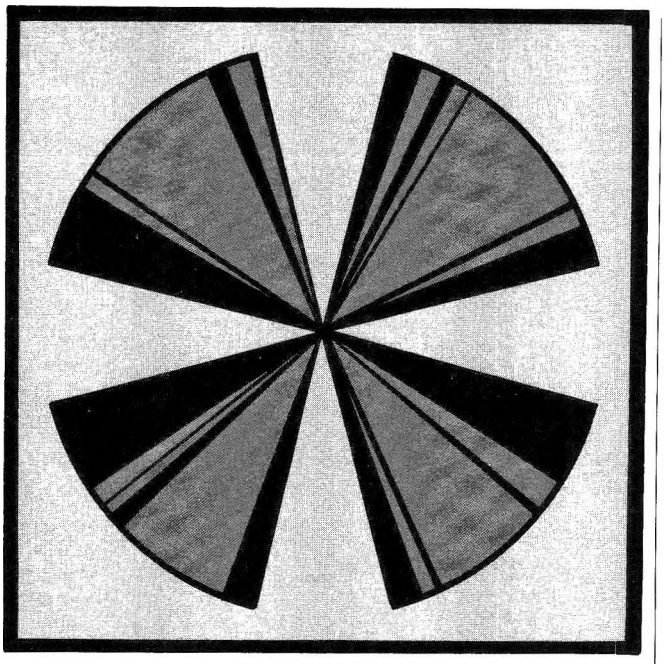

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1) Recent reviews of shift reagents
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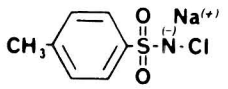
Chloramine-T

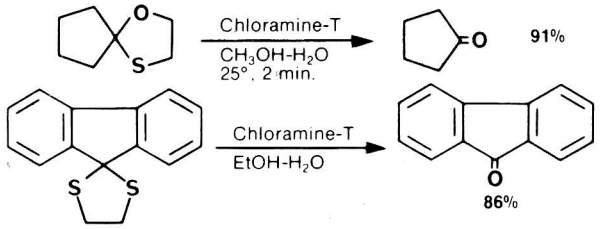
New reagent for the amination of olefins



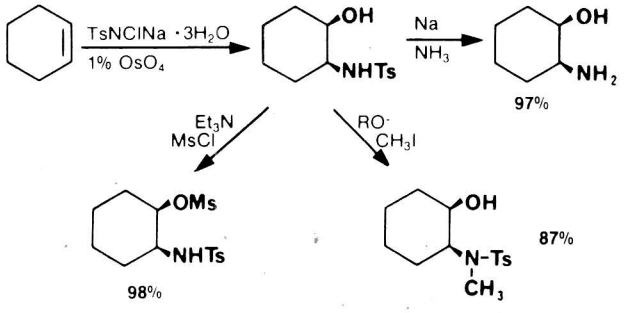
Chloramine-T

Chloramine -T has been known for a long time, and the literature contains many references to its uses as an analytical reagent and as an antibacterial. However, there have been relatively few reports on its use as a synthetic reagent until recently.

It has been shown that **chloramine-T** is an excellent reagent for the mild cleavage of 1,3-oxathiolane- and 1,3-dithiolane-protected carbonyl groups. [1,2]



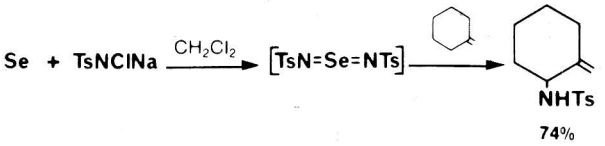
Sharpless and coworkers[3] now report a unique new reaction which effects *cis*-addition of a hydroxyl (OH) group and an arylsulfonamide ($ArSO_2NH$) moiety across an olefinic linkage. Thus, **chloramine-T** (trihydrate) reacts with an olefin in the presence of a catalytic amount of osmium tetroxide to produce the vicinal hydroxy *p*-toluenesulfonamide.[3] The following scheme illustrates the utility of this reaction:



Sharpless *et al.*[4] also report that the reaction of two equivalents of *anhydrous* **chloramine-T** with selenium metal followed by an olefin affords allylic amination products in good yields. It is postulated that the reaction intermediate formed *in situ* is the imidoselenium compound **1**. Most olefins react readily with the imido reagent **1** at or below room temperature. This reagent is more reactive than

Ts-N=Se=N-Ts

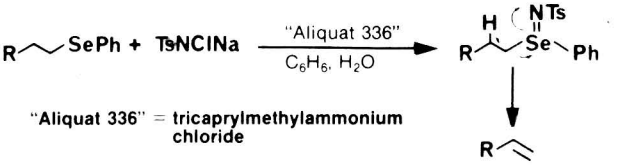
(1)



selenium dioxide. The allylic sulfonamide can be reductively cleaved to the corresponding amine with sodium naphthalene.[5]

Anhydrous chloramine-T is rather difficult to prepare on a large scale, and must be handled with great care to maintain its anhydrous condition.

Chloramine-T, under phase-transfer conditions, provides an improved method for the oxidation-elimination of alkyl phenyl selenides, where the alkyl group is primary.[6] Similarly, the **chloramine-T** phase-transfer system offers some advantages[6] over single-phase methods[7] for the preparation of sulfilimines from sulfides.



"Aliquat 336" = **tricaprylmethylammonium chloride**

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