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THE JOURNAL OF Organic Chemistry

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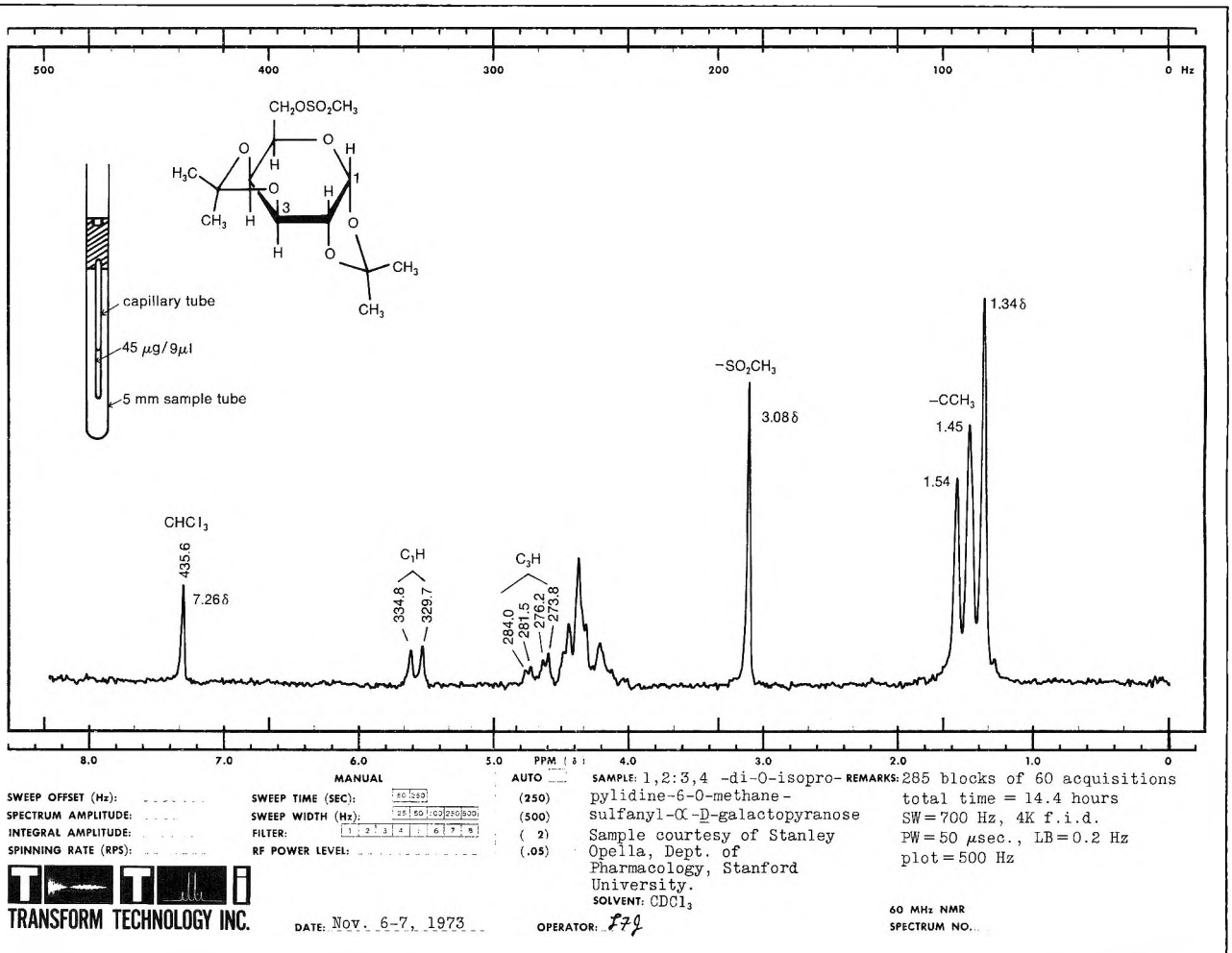

MANUAL | AUTO

SWEEP OFFSET (Hz):
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SPINNING RATE (RPS):

SWEEP TIME (SEC): (250)
SWEEP WIDTH (Hz): (500)
FILTER: (2)
RF POWER LEVEL: (.05)

SAMPLE: 1,2:3,4 -di-O-isopropylidine-6-O-methane-sulfanyl-α-D-galactopyranose
Sample courtesy of Stanley Opella, Dept. of Pharmacology, Stanford University.
SOLVENT: $CDCl_3$

REMARKS: 285 blocks of 60 acquisitions
total time = 14.4 hours
SW = 700 Hz, 4K f.i.d.
PW = 50 μsec., LB = 0.2 Hz
plot = 500 Hz

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60 MHz NMR
SPECTRUM NO.

Analysis of very small samples is best done using a microcell approach. Here, 45 micrograms of a compound with molecular weight 338 was contained in a capillary tube of 1.0 mm I.D. The peak at 3.08δ, although weak after one block of acquisitions, served adequately for the peak register method, which effectively cancels long-term field drift. Signal frequencies and chemical shifts were copied from an oscilloscope display of peak positions using an assigned value of 435.6 Hz for the chloroform peak. The spectrum is very well defined, and demonstrates that overnight FT operation with a T-60A/TT-7 system is quite feasible and very useful for microsample analysis.

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AUTHOR INDEX

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SEPTEMBER 20, 1974

Electrocarboxylation. I.[1] Mono- and Dicarboxylation of Activated Olefins

Donald A. Tyssee* and Manuel M. Baizer

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Received February 26, 1974

Short-lived ($t_{1/2} < 10^{-3}$ sec) anion radicals of activated olefins (CH_2=CHX with X = CO_2CH_3, CN, and acetyl) generated at a mercury cathode under anhydrous conditions react rapidly with carbon dioxide. Further reduction of the radical carboxylate intermediate and subsequent carboxylation results in the formation of substituted succinic acid derivatives. An alternate pathway involves electroreduction of carbon dioxide and subsequent reactions of $CO_2^{\cdot-}$ with unreduced olefin. Under partially aqueous conditions the radical carboxylate intermediate is again formed. However, in the presence of water the anion formed by subsequent reduction of the radical carboxylate reacts preferentially with water. For example, acrylonitrile is converted to 3-cyanopropionic acid. The polarographic behavior of activated olefins in the presence and absence of dissolved carbon dioxide is compared with the products obtained upon bulk electrolysis of activated olefins in the presence of carbon dioxide.

Electrochemical syntheses involving activated olefins have been discussed previously.[2] Two types of behavior are observed, and conditions can be chosen such that one or the other behavior dominates. Electrolysis of activated olefins in aqueous electrolyte solutions at cathodes of low hydrogen overvoltage results in dihydro product. At cathodes

$$CH_2{=}CHX + 2e + 2H_2O \longrightarrow CH_3CH_2X + 2OH^-$$
$$X = \text{electron-withdrawing group}$$

of high hydrogen overvoltage in the presence of aqueous tetraalkylammonium salts, products of electrohydrodimerization are formed. In addition to quenching anionic inter-

$$2CH_2{=}CHX + 2e + 2H_2O \rightarrow X(CH_2)_4X + 2OH^-$$

mediates with water as above, there are several reports in the literature in which carbon dioxide is used as a trapping agent in order to demonstrate the existence of anionic intermediates generated by the electroreduction of neutral organic substrates in anhydrous media.[3]

The work reported here was designed to probe the synthetic utility of reducing activated olefins in the presence of carbon dioxide and to understand the extent to which the behavior under these conditions could be related to the known electrochemistry of activated olefins under aqueous conditions in the absence of carbon dioxide. This paper describes in detail the electrochemical behavior of activated olefins in the presence of dissolved carbon dioxide in both nonaqueous and partially aqueous systems under conditions favoring mono- or dicarboxylation. A subsequent paper[4] describes the electrocarboxylation of activated olefins under conditions favoring either intramolecular cyclization or intermolecular dimerization followed or accompanied by carboxylation.

Results and Discussion

Polarography. The polarographic behavior of the activated olefins subsequently subjected to bulk electrolysis is shown in Table I.

A rapid reaction of the olefin anion radical[5] with carbon dioxide is clearly indicated by a doubling of the diffusion current when carbon dioxide is added to the electrolyte solution at a concentration equivalent to that of the olefin. This is illustrated for a typical monoactivated olefin in Figure 1, in which the polarograms of methyl acrylate in the presence and absence of carbon dioxide are shown. Interaction of the methyl acrylate anion radical generated at the electrode with carbon dioxide diffusing toward the electrode causes the diffusion current for carbon dioxide to be reduced by approximately one-half of the value observed in the absence of a reducible substrate (curves b and c). Thus, less carbon dioxide is available for polarographic reduction.

The pathway most consistent with the polarographic results is as follows.

$$CH_2{=}CHX + e \xrightarrow{E_{1/2}{}^1} [CH_2{=}CHX]^{\cdot-}$$

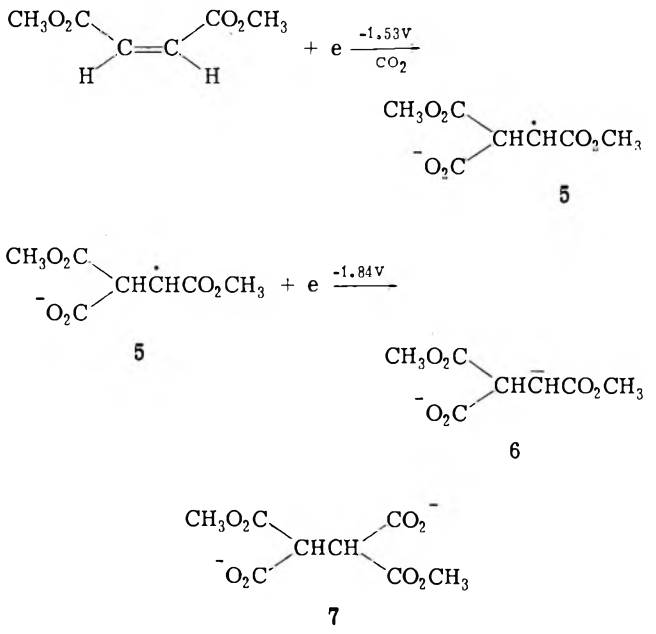
$$[CH_2{=}CHX]^{\cdot-} + CO_2 \longrightarrow {}^-O_2CCH_2\dot{C}HX$$
1 **2**

$${}^-O_2CCH_2\dot{C}HX + e \xrightarrow{E_{1/2}{}^2} {}^-O_2CCH_2\bar{C}HX$$
2 **3**

$${}^-O_2CCH_2\bar{C}HX + CO_2 \longrightarrow {}^-O_2CCH_2CHXCO_2^-$$
3 **4**

$$X = CO_2CH_3, C(O)CH_3, CN$$

Reaction of **1** with carbon dioxide sufficiently disperses the charge in **2** so that the reduction of **2** to **3** can occur (*i.e.*, $|E_{1/2}{}^2| \leq |E_{1/2}{}^1|$). A lower limit for the value of $E_{1/2}{}^2$ of approximately −1.84 V (sce) is suggested from the data for the reduction of dimethyl maleate (Figure 2). In the presence of carbon dioxide, dimethyl maleate is reduced to its anion radical [$E_{1/2}{}^1 = -1.53$ V (sce), $n = 1$] which reacts with carbon dioxide to form the radical carboxylate (**5**). The radical carboxylate (**5**) is stable toward further reduction at this potential, and subsequent reduction of **5** to the carbanion carboxylate (**6**) does not occur until −1.84 V (sce). Reaction of **6** with carbon dioxide gives the ethanetetracarboxylate derivative (**7**). Macroscale electrolyses of



dimethyl maleate on the plateau of the first wave and subsequent reaction of the radical carboxylate (5) are treated in the following paper.[4] Electrolyses on the plateau of the second wave are discussed below.

Bulk Electrolyses. Anhydrous. A series of electrolyses (Hg pool) was carried out under anhydrous conditions in order to confirm the polarographic interpretation of the behavior of activated olefins at low concentrations in the presence of dissolved carbon dioxide. Olefins showing distinct polarographic waves were electrolyzed under controlled potential conditions at a cathode voltage corresponding to the plateau of the reduction wave. The olefin was added in portions to the cathode compartment of the cell so as to maintain a concentration of unreduced olefin in the cell of less than 0.05 *M*. Carbon dioxide was continuously bubbled (1 atm) into the catholyte through a gas dispersion tube. Some of the olefins studied undergo reduction at potentials more negative than that of carbon dioxide. In these cases the electrolyses were run at a constant current with a constant rate of addition of olefin. The rate of addition was selected so as to correspond to the current selected, assuming a two-electron reduction of olefin. The results are presented in Table II.

Table I
Polarographic Behavior of Activated Olefins in the Presence and Absence of Dissolved Carbon Dioxide[a]

Olefin	Registry no.	$-E^1/_2$ (sce)[b]	*n* (N_2)[c]	*n* (CO_2)
Methyl acrylate	96-33-3	2.10	1	2
Methyl methacrylate	80-62-6	2.27	1	*d*
Methyl crotonate	18707-60-3	2.41	1	*d*
Methyl *trans*-β-methoxyacrylate	5788-17-0	2.67	1	*d*
Dimethyl maleate	624-48-6	1.53	1	1
		1.84		1
Acrylonitrile	107-13-1	2.14	1	2
Methacrylonitrile	126-98-7	2.31	1	*c*
Methyl vinyl ketone	78-94-4	1.91	1	2

[a] Polarographic solutions 0.1 *M* $(C_2H_5)_4N^+OTs^-$ in CH_3CN with [olefin] = 10^{-3} *M* and [CO_2] = 10^{-3} *M* by saturation with 1% $CO_2(N_2)$ mixture. [b] $E^1/_2$ *vs.* saturated calomel electrode (sce). Values reported for nitrogen saturated solution. A slight positive shift (*ca.* 0.05 V) was observed when recording polarograms in CO_2 solution. [c] The approximate number of faradays consumed per mole of substrate is given by *n*. This value was obtained by comparison of diffusion currents and in some cases confirmed by coulometry. [d] Wave obscured by CO_2 reduction wave which occurs at *ca.* −2.3 V (sce).[1]

Product yields are expressed as current efficiencies. Assuming the absence of nonelectrochemical routes to the products reported in the table, this number represents the minimum yield based on starting material. Under controlled potential conditions (cpe), minor amounts of dimeric carboxylates were observed.[4] No other major products were detected. Under controlled current conditions (cie), major products observed included oxalic and cyanoacetic acid derivatives. The former arises from reductive coupling of carbon dioxide and the latter from solvent carboxylation.[1] Both products reduce the current efficiency to observed products but not necessarily the chemical yield. Because of the low levels (*i.e.*, 0.05 *M*) at which the electrolyses were carried out, no attempt was made to obtain material balances. Some loss of products probably occurred by electromigration of the products (*i.e.*, dicarboxylate ion) from the cathode to the anode during the electrolysis. Attempts were made to minimize this by adding excess electrolyte to the anode compartment.

Olefins having reduction potentials distinctly separate from that of carbon dioxide (cpe in Table II) give products

Table II
Bulk Electrolyses of Activated Olefins in the Presence of Dissolved Carbon Dioxide[a]

Olefin	$-E^1/_2$ (sce)	Control[b]	Product[c]	Yield, (ce)[d]
Methyl acrylate	2.10	cpe	Trimethyl 1,1,2-ethanetricarboxylate	61
Methyl methacrylate	2.27	cie	Trimethyl 1,2,2-propanetricarboxylate	42
Methyl crotonate	2.41	cie	Trimethyl 1,1,2-propanetricarboxylate	38
Methyl *trans*-β-methoxyacrylate	2.67	cie	Trimethyl 2-methoxy-1,1,2-ethanetricarboxylate	10
Dimethyl maleate	1.84	cpe (second wave)	Tetramethyl 1,1,2,2-ethanetetracarboxylate	31
Acrylonitrile	2.14	cpe	Dimethyl 2-cyanosuccinate	41
Methacrylonitrile	2.31	cie	Dimethyl 2-methyl-2-cyanosuccinate	28
Methyl vinyl ketone	1.91	cpe	Methyl levulinate	22
			Dimethyl 2-acetylsuccinate	16

[a] Electrolyte solution 0.25 *M* $(C_2H_5)_4N^+OTs^-$ in CH_3CN with CO_2 saturation (1 atm) at a Hg pool. [b] cpe = controlled potential electrolysis, cie = controlled current electrolysis (cathode potential = −2.15 V). [c] Catholyte solution treated with methyl iodide to convert tetraethylammonium carboxylates to methyl esters for isolation and characterization: J. H. Wagenknecht, M. M. Baizer, and J. L. Chruma, *Syn. Commun.*, **2** 215 (1972). [d] Yields expressed as current efficiencies (ce), assuming a 2-faraday reduction per mole of product.

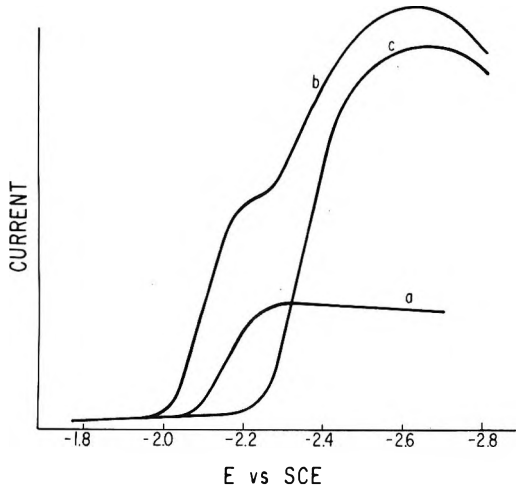
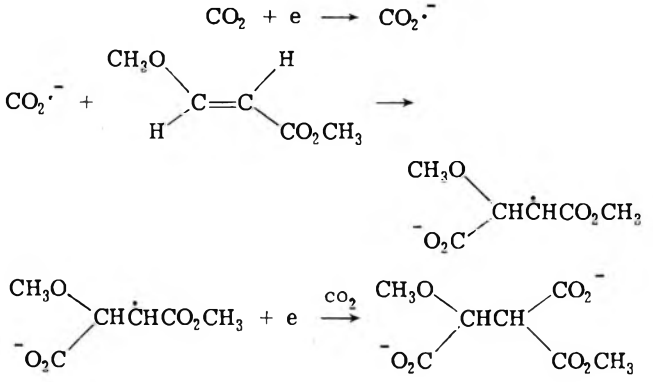


Figure 1. Polarogram of (a) methyl acrylate in acetonitrile saturated with nitrogen and containing 0.1 *M* tetraethylammonium tosylate, (b) methyl acrylate as above, replacing nitrogen by a 1% carbon dioxide–nitrogen mixture, and (c) 1% carbon dioxide–nitrogen mixture only.

consistent with generation of the olefin anion radical and its reaction with carbon dioxide followed by subsequent reduction and further carboxylation.

However, as the reduction potential of the olefin approaches that of carbon dioxide ($E_{1/2} = -2.3$ V), it becomes less clear whether reduced carbon dioxide (*i.e.*, $CO_2\cdot^-$) or the anion radical of the olefin is the primary electrode product which participates in the subsequent chemical reactions (cie in Table II). In the most extreme case, methyl *trans*-β-methoxyacrylate is reduced *ca.* 0.5 V more negative than carbon dioxide and yet undergoes carboxylation. Thus, an alternate pathway exists for the electrocarboxylation of these olefins. The electrocarboxylation (low yield) of



nonelectroactive olefins (norbornadiene and 3,4-dihydropyran) has been reported by us previously.[1] The anion radical of carbon dioxide must unequivocally be involved with these substrates. In addition, certain unsaturated hydrocarbons have been electrocarboxylated: butadiene ($E_{1/2} = -2.6$ V),[6,7] styrene ($E_{1/2} = -2.45$ V),[6b,7] naphthalene ($E_{1/2} = -2.53$ V),[3b,6b,7] and phenanthrene ($E_{1/2} = -2.47$ V).[3b,7] These substances reduce less readily than carbon dioxide and, thus, the participation of $CO_2\cdot^-$ must be considered in these cases. In this connection, Norman, *et al.*,[8] has shown that $CO_2\cdot^-$ and $\cdot CO_2H$ generated by hydrogen abstraction from HCO_2^- and HCO_2H, respectively, undergo typical radical addition reactions.

Bulk Electrolyses. Partially Aqueous. Several attempts were made to moderate the extent of electrocarboxylation to give monocarboxylated products by replacing the anhydrous solvent–electrolyte mixture with a carbon dioxide saturated solution of aqueous tetraethylammonium bi-

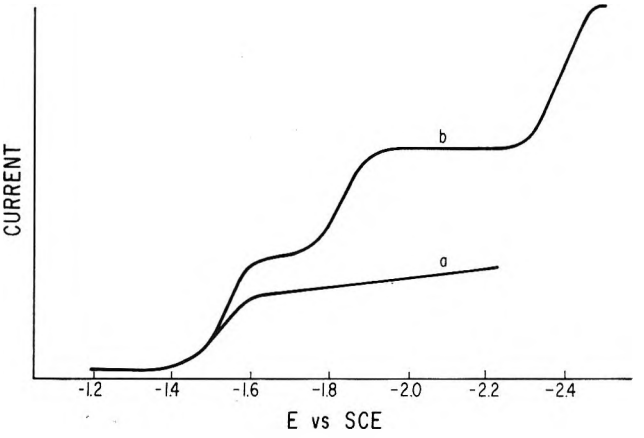


Figure 2. Polarogram of (a) dimethyl maleate in acetonitrile containing 0.1 *M* tetraethylammonium tosylate saturated with nitrogen and (b) replacing nitrogen with 1% carbon dioxide–nitrogen mixture.

carbonate. This system would have the advantage of providing a material (*i.e.*, H_2O) which could be sacrificially consumed at the anode to form noninterfering products (*i.e.*, O_2) and, thus, allow a simple undivided cell to be used. However, no carbon dioxide was incorporated under fully aqueous conditions and products typical of electrohydrodimerization were obtained, *i.e.*,[2b]

cathode: $2CH_2{=}CHX + 2e + 2H_2O \longrightarrow X(CH_2)_4X + 2OH^-$

anode: $H_2O - 2e \longrightarrow {}^1/_2O_2 + 2H^+$

overall cell: $2CH_2{=}CHX + H_2O \longrightarrow X(CH_2)_4X + {}^1/_2O_2\uparrow$

$X = CN, CO_2R$

The desired reaction was realized by adding water at low levels (2.8 *M*) to an aprotic solvent, proceeding as follows.

cathode: $CH_2{=}CHCN + 2e + CO_2 + H_2O \longrightarrow CNCH_2CH_2CO_2^- + OH^-$

anode: $H_2O - 2e \longrightarrow {}^1/_2O_2 + 2H^+$

overall cell: $CH_2{=}CHCN + CO_2 + H_2O \xrightarrow[(2.8\ M)]{\text{propionitrile}} CNCH_2CH_2CO_2H + {}^1/_2O_2\uparrow$

ce = 50%

Because a weak acid (CO_2–H_2O) is being converted to a stronger acid ($CNCH_2CH_2CO_2H$), hydrogen evolution was observed soon after the electrolysis was begun. In order to avoid extensive hydrogen evolution a system was designed (Figure 3) which would provide both for the continuous removal of 3-cyanopropionic acid and reequilibration of the circulating propionitrile with water so as to maintain the desired level of water.[9] Extraction of the electrolyte from propionitrile by water was avoided by the use of the water-insoluble salt, tetrabutylammonium tetrafluoroborate. The acid was isolated by extraction of the aqueous solution after acidification.

In conclusion, carbon dioxide effectively traps anionic electrode intermediates generated by reduction of mono- and diactivated olefins in both anhydrous and partially aqueous environments. Comparison of the polarographic behavior of the olefin in the presence and absence of dissolved carbon dioxide can be used as one criterion of reac-

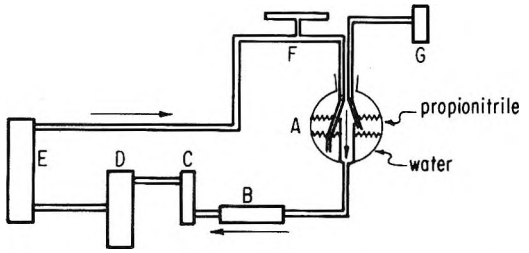


Figure 3. Electrolysis apparatus for monocarboxylation: A, extraction vessel; B, circulating pump; C, flowmeter; D, cooling coil; E, undivided cell containing cadmium cathode and lead oxide anode; F, acrylonitrile inlet; G, carbon dioxide inlet.

tivity provided that there is not interference from the reduction wave of carbon dioxide. The following summarizes the types of reactivity observed.

(1) Activated olefins exhibiting a single two-electron wave in the presence of carbon dioxide are converted under anhydrous conditions to substituted succinic acids provided that the concentration of unreduced olefin is low relative to that of dissolved carbon dioxide.

(2) Activated olefins exhibiting two distinct one-electron waves in the presence of carbon dioxide are converted under anhydrous conditions to α,α' disubstituted succinic acids provided that the potential is maintained on the plateau of the second wave.

(3) Olefins reducing at potentials near or more negative than that of carbon dioxide are also converted to substituted succinic acids under anhydrous conditions. The pathway by which products are obtained is not clear.

(4) Water can be used to moderate the extent of carboxylation. Under partially aqueous conditions β-substituted propionic acids are obtained.

Experimental Section

Equipment. The potentiostat was a Wenking Model 66TS10; the constant-current power supply was a Sorensen DCR300-2.5. Total current passed was measured using a Lectrocount, Royson ENGINEERING Co., Hatboro, Pa. Polarograms were obtained with a Sargent Model XXI polarograph. Nmr spectra were determined at 60 MHz with a Varian A-56/60 or T-60 spectrometer. Analytical glc determinations were made using a Varian Series 1200 gas chromatograph; preparative glc separations employed the Model 770 F & M instrument. The electrolysis cell for the anhydrous electrocarboxylations was a two-compartment H cell, similar to that described previously.[2a] The cell compartments were separated by a 30-mm diameter medium porosity frit. The mercury cathode had an area of 50 cm^2 and the platinum anode an area of 6 cm^2. A combination of mechanical stirring and gas dispersion was employed to mix the catholyte solution. A ground-glass multiport head was fitted to the top of the cathode compartment with provisions for olefin addition, carbon dioxide addition, and system venting through a drying tube. A reference sce was positioned at the mercury surface and as close to the frit as possible.

Reagents and Starting Materials—Reagent-grade acetonitrile was obtained from Matheson Coleman and Bell. The water analysis indicated less than 80 ppm water and, thus, the solvent was used without further purification or drying. Propionitrile was used as commercially obtained. Methyl acrylate, methyl methacrylate, methyl crotonate, dimethyl maleate, acrylonitrile, methacrylonitrile, and methyl vinyl ketone were obtained from commercial sources. They were redistilled and stored with a trace of dissolved hydroquinone prior to being electrolyzed. The preparation of methyl *trans*-β-methoxyacrylate has been described previously.[10] Tetraethylammonium *p*-toluenesulfonate (Aldrich) was recrystallized several times from acetone and dried in a vacuum oven. Tetrabutylammonium tetrafluoroborate was prepared by mixing equimolar amounts of tetrabutylammonium bromide (Eastman) and sodium tetrafluoroborate (Ozark-Mahoning) in water. The solid tetrabutylammonium tetrafluoroborate was isolated by filtration and recrystallized several times from methanol. The carbon dioxide was "bone dry" grade.

Reference Compounds. These were prepared as follows: trimethyl 1,1,2-ethanetricarboxylate by the reaction of sodium dimethyl malonate and methyl bromoacetate;[11] tetramethyl 1,1,2,2-ethanetetracarboxylate by the oxidative coupling of sodium dimethyl malonate;[12] dimethyl 2-cyanosuccinate by the reaction of sodium methyl cyanoacetate and methyl chloroacetate;[13] dimethyl 2-acetylsuccinate by the reaction of sodium methyl acetoacetate and methyl chloroacetate;[14] sodium 3-cyanopropionate by ring opening propiolactone with sodium cyanide.[15] Methyl levulinate was obtained from commercial sources. The spectra and physical properties of all compounds were consistent with those reported.

General Electrolysis Procedure. Dicarboxylation. Depending upon the reduction potential of the activated olefin relative to carbon dioxide, the electrolyses in anhydrous solvents were carried out under conditions of either constant current or constant cathode potential (cie and cpe in Table II). The electrolyte solution [0.25 *M* $(C_2H_5)_4N^+OTs^-$ in acetonitrile] was added to the cell containing the Hg cathode and a properly positioned sce. In addition, 20 g of $(C_2H_5)_4N^+Cl^-$ and 10 ml of 1-octene were added to the anode compartment to provide for a sacrificial anode reaction (*i.e.*, $Cl^- - e \rightarrow \frac{1}{2}Cl_2$). The cell and its contents were cooled to 0° with an external ice bath while the solution was saturated for 15 min with 100% CO_2. For cpe experiments, the potentiostat was set at the desired cathode voltage and 0.06 mol of activated olefin in 10 ml of acetonitrile was added gradually to the catholyte from a

Table III
Analytical and Nmr Spectral Data

Registry no.	Compd	Bp, °C (mm)	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Spectral data, δ ppm[a]
39994-40-6	Trimethyl 1,2,2-propanetricarboxylate	85 (0.4)	49.5	6.48	49.75	6.64	3.78 (6 H, s, OCH_3), 3.71 (3 H, s, OCH_3), 2.97 (2 H, s, CH_2), 1.56 (3 H, s, CH_3)
52003-37-9	Trimethyl 1,1,2-propanetricarboxylate	84 (0.2)	49.5	6.48	50.07	6.72	3.80 (1 H, d, CHX_2), 3.78 (6 H, d, OCH_3),[b] 3.7 (3 H, s, OCH_3), 3.2 (1 H, m, CHX), 1.2 (3 H, d, CH_3)
52003-38-0	Trimethyl 2-methoxy-1,1,2-ethanetricarboxylate	87 (1)	46.15	5.98	46.25	6.03	4.92 (1 H, d, CHX), 3.81 (1 H, d, CHX_2), 3.78 (6 H, s, OCH_3), 3.7 (3 H, s, OCH_3), 3.55 (3 H, s, OCH_3)
52003-39-1	Dimethyl 2-methyl-2-cyanosuccinate	95 (0.2)	51.89	5.95	50.89	5.70[d]	3.85 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 2.85 (2 H, q, CH_2),[c] 1.63 (3 H, s, CH_3)

[a] Solvent $CDCl_3$ with TMS internal standard; X = CO_2CH_3. [b] Nonequivalent CO_2CH_3 due to adjacent asymmetric carbon. Separation *ca.* 1 Hz. [c] Nonequivalent CH_2 due to adjacent asymmetric carbon. [d] Calcd: N, 7.57. Found: N, 7.82.

buret. The rate of addition was such that a maximum current of 0.6 A was passed. The electrolysis was discontinued when the current had fallen to 0.05 A. For cie experiments 0.07 mol of the olefin was taken up in acetonitrile (total volume of 25 ml) and the solution was added to the catholyte at a rate equivalent to 5.6×10^{-3} mol/hr with a syringe pump. A constant current of 0.3 A was maintained [*i.e.*, 0.3 A = (53.6 A hr/mol)(5.6×10^{-3} mol/hr)]. The catholyte was continuously saturated with CO_2 during the electrolyses. The cathode potential was monitored with a sce.

General Electrolysis Procedure. Monocarboxylation. The apparatus employed is shown in Figure 3. The top layer of propionitrile [0.06 *M* in $(C_4H_9)_4N^+BF_4^-$ and 2.8 *M* in H_2O] was circulated through the cell while being saturated with 100% CO_2 for 15 min prior to starting the electrolysis. Acrylonitrile was then added at a rate of 2.43 g/hr to the circulating propionitrile electrolyte solution (continuous CO_2 saturation). A constant current of 2.35 A was maintained [*i.e.*, 2.35 A = (53.6 A hr/mol)(4.38×10^{-2} mol/hr)].

Work-Up and Analyses of Catholytes. The products of electrocarboxylation under anhydrous conditions were converted to their methyl esters by treating the catholyte solution directly with an excess (0.28 mol) of methyl iodide at ice-bath temperatures (*cf.* footnote *c* of Table II). The acetonitrile and excess methyl iodide were removed and the organic products were separated from the electrolyte by benzene–water extraction. If authentic samples were available, analyses were done directly on the benzene-soluble material by glc (internal standards), using one of the following columns and conditions: (a) 6 ft × 0.125 in. S.S. 3% OV-101 on Chromosorb W (80–100 mesh), 150 → 280° at 10°/min; (b) 10 ft × 0.125 in. S.S. 5% FFAP + 1% Carbowax 20M on Chromosorb G (80–100 mesh), 100 → 200° at 10°/min; (c) 10 ft × 0.125 in. S.S. 3% QF-1 on Gas Chrom Q (60–80 mesh), 100 → 200° at 10°/min. Products for which authentic samples were not available were isolated by distillation and/or preparative glc. The following column and conditions were used: 3 ft × 0.75 in. S.S. 30% FFAP + 6% Carbowax 20M on Chromosorb W (60–80 mesh), 200°. The products so obtained were subsequently used for yield determinations by glc (internal standards). Yield data for electrocarboxylations under partially aqueous conditions were obtained by analyzing the aqueous extract by nmr using sodium acetate as an internal standard.

Identification of Products. Products were confirmed by comparing their glc retention lines, mass spectra, nmr spectra, and boiling points. New compounds were identified by their mass spectra, nmr spectra, and elemental analyses. These compounds and the appropriate analytical data are given in Table III.

Acknowledgment. The authors wish to thank Gary Dinkelkamp for his technical assistance.

Registry No.—Carbon dioxide, 124-38-9.

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Electrocarboxylation. II.[1] Electrocarboxylative Dimerization and Cyclization

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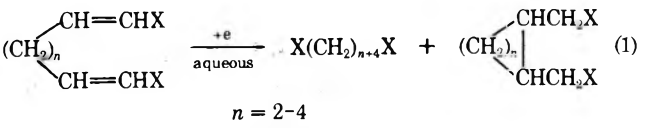
The competitive reactions of electrochemically generated anion radicals of activated olefins with carbon dioxide and unreduced activated olefins have been studied. Dimethyl maleate and carbon dioxide are converted to 1,1,2,3,4,4-hexasubstituted butane derivatives *via* dimerization of electrochemically generated intermediates. Methyl acrylate and carbon dioxide are converted to 1,1,4,4-tetrasubstituted derivatives. The observed product is consistent with a pathway involving reaction of the uncarboxylated methyl acrylate anion radical with unreduced methyl acrylate followed by carboxylation. Electrocarboxylation of the bisactivated olefins, $CH_3O_2CCH{=}CH(CH_2)_nCH{=}CHCO_2CH_3$, gave a variety of cyclic and acyclic products. The influence of n on the product distribution and the mechanistic implications are discussed.

Conditions favorable for the conversion of activated olefins to dicarboxylated monomers have been described previously.[1] At low concentrations of unreduced olefin relative to dissolved carbon dioxide, it was shown that carbon dioxide effectively competes with unreduced olefin as an electrophile toward the activated olefin anion radical.

Under aqueous conditions various types of intra- and intermolecular interactions (*i.e.*, couplings) have been observed when activated or bisactivated olefins are electrochemically reduced.[2] Simple activated olefins are converted to acyclic dimeric products, while bisactivated olefins are converted to combinations of dihydro and cyclic products (eq 1).



(1)

$n = 2\text{-}4$

$X = CO_2C_2H_5$, CN

Table I
Polarographic Behavior of Activated Olefins in the Presence and Absence of Dissolved Carbon Dioxide[a]

Olefin	$-E^1/_2$ (sce)[b]	n (N_2)[c]	n (CO_2)
Dimethyl maleate	1.53	1	1
	1.84		1
Methyl acrylate	2.10	1	2
Dimethyl 2,6-octadiene-1,8-dioate, n = 2	2.24	1	
Dimethyl 2,7-nonadiene-1,9-dioate, n = 3	2.12	1	*d*
Dimethyl 2,8-decadiene-1,10-dioate, n = 4	2.24	1	

[a] Polarographic solutions 0.1 M in $(C_2H_5)_4N^+OTs^-$ in CH_3CN with olefin 10^{-3} M and CO_2 10^{-3} M by saturation with 1% $CO_2(N_2)$ mixture. [b] $E_{1/2}$ *vs.* saturated calomel electrode (sce). Values reported for nitrogen saturated solutions. A slight positive shift was observed when recording polarograms in CO_2 solution. [c] The approximate number of faradays consumed per mole of substrate is given by n. This value was obtained by comparison of diffusion currents and in some cases confirmed by coulometry. [d] Broad wave obscured by CO_2 reduction wave (ca. −2.3 v).

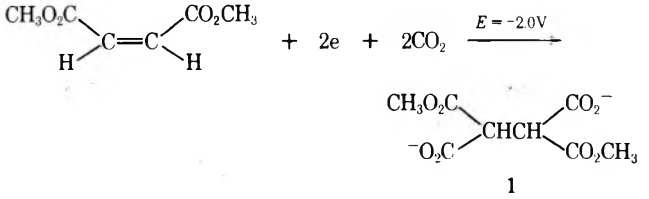
Carboxylative dimerizations have been reported previously by Wawzonek.[3] However, these studies described the reduction of olefins in the presence of carbon dioxide under noncontrolled conditions. The work reported here (1) describes the use of potential control in directing electrocarboxylation toward either monomer dicarboxylation or electrocarboxylative dimerization, (2) examines the influence of excess olefin on the electrocarboxylation process as well as the probable pathway by which dimeric products are obtained, and (3) compares the behavior of bisactivated olefins under carboxylation conditions to that observed in electrolyses under aqueous conditions.

Results and Discussion

Polarography. The polarographic behavior of the activated olefins subsequently subjected to bulk electrolysis is shown in Table I.

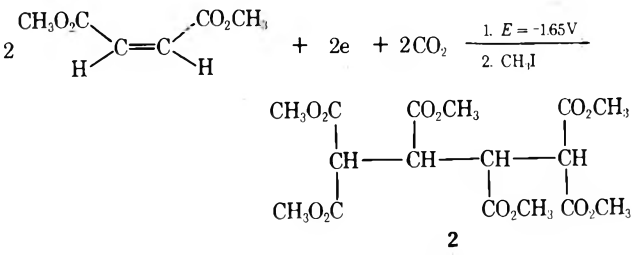
Bulk Electrolyses. General Comments. Product yields are expressed as current efficiencies. Assuming the absence of nonelectrochemical routes to the products reported, this number represents the minimum yield based on starting material. All major products detected were identified and are described below. Some loss of products probably occurred by electromigration of carboxylate ion from the cathode to the anode during the electrolysis. Attempts were made to minimize this by adding excess electrolyte to the anode compartment. No attempts were made to obtain material balances.

Radical Carboxylate Dimerization. The polarogram of dimethyl maleate in the presence of carbon dioxide reveals two plateaus (Figure 1). At cathode potentials more negative than *ca.* −1.8 V (sce) it has been shown that a net two-electron reduction takes place and **1** is obtained.[1]



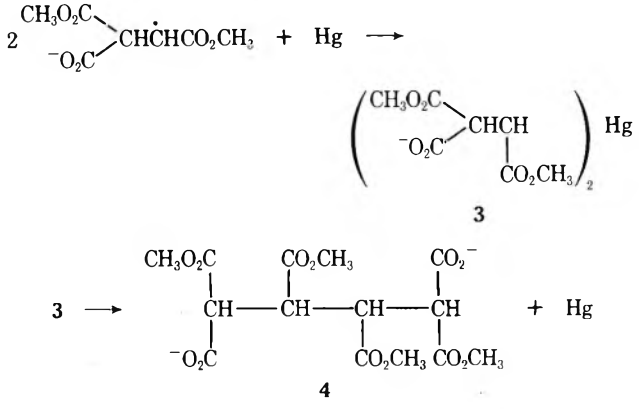
1

Based on the polarogram it should be possible by proper potential control to generate the radical carboxylate and obtain products derived from subsequent reaction of the radical. This was confirmed by electrolyzing a solution of dimethyl maleate and carbon dioxide at a controlled potential (Hg) of −1.65 V (sce) which gave, after esterification, hexamethyl 1,1,2,3,4,4-butanehexacarboxylate (**2**) in 46% current efficiency.



2

Although radical intermediates generated at mercury cathodes often form mercurials,[4] the absence of colloidal mercury in the catholyte is sufficient evidence to eliminate involvement of mercury in the coupling reaction. Thus, there is no significant contribution from the reaction followed by disproportionation of **3** to **4** and mercury.



3

4

Several pathways to **2** can be considered. As suggested by Bard in his studies on the electrochemistry of diactivated olefins,[5] the anion radical of dimethyl maleate (**5**) dimerizes to the dianion, which is then carboxylated (path 1a). A related sequence (path 1b) involves dimerization of the radical carboxylate (**6**). Alternatively, dimeric products are obtained by reaction of either **5** or **6** with unreduced maleate, followed by reduction and carboxylation (path 2). A series of electrolyses with varying initial concentrations of dimethyl maleate showed no variations in yield of **4** (Table II, **2** = **4** as its methyl ester). This eliminates reaction sequences in which unreduced dimethyl maleate participates and, thus, leaves path 1 as the most likely route to dimeric products.

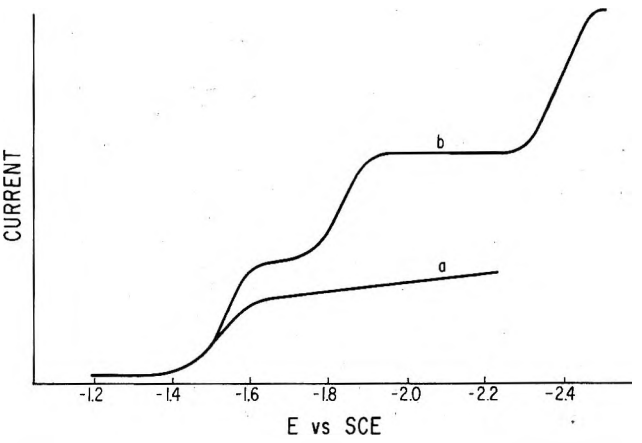
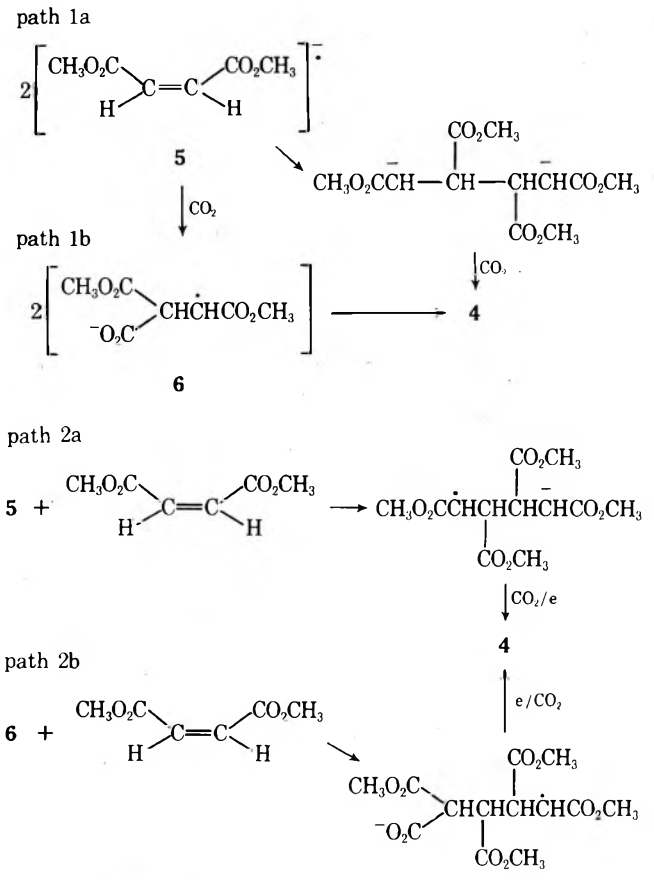
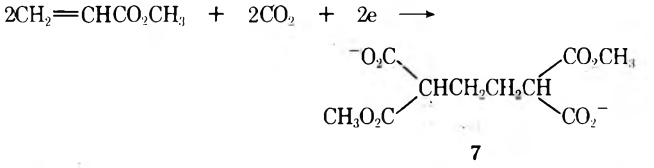


Figure 1. Polarogram of (a) dimethyl maleate in acetonitrile containing 0.1 M tetraethylammonium tosylate saturated with nitrogen and (b) replacing nitrogen with 1% carbon dioxide–nitrogen mixture.

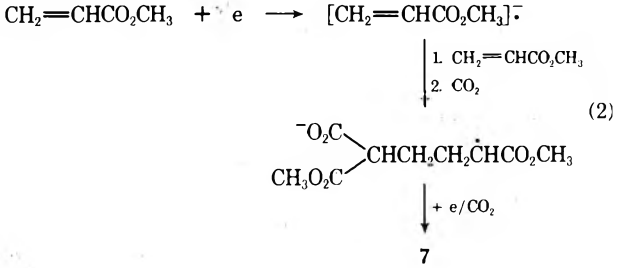


Olefin Anion Radical Reactions. Olefin and Carbon Dioxide Competition. The reaction of olefin anion radicals with carbon dioxide results in products in which carbon dioxide has been added to each of the olefinic carbon atoms.[1] As the concentration of unreduced olefin in the catholyte is increased, a point should be reached at which it competes effectively with carbon dioxide as an electrophile for the anion radical. The polarographic behavior of monoactivated olefins in the presence of carbon dioxide (*i.e.*, a single two-electron wave) does not allow one to predict products expected or the sequence by which they are formed under these conditions.

A series of experiments in which mixtures of methyl acrylate and carbon dioxide were electrolyzed (Table III) indicates that the primary product of electrocarboxylative dimerization of monoactivated olefins is a 1,1,4,4-tetrasubstituted butane derivative (**7**).



Variations of the relative amounts of acrylate and carbon dioxide are consistent with the following pathway to **7** (eq 2). The reduction in current efficiency to dimeric products



(2)

Table II
Bulk Electrolyses of Dimethyl Maleate and Carbon Dioxide at Various Initial Maleate Concentrations[a]

[Maleate]	Yield, % (ce)[b]
0	44
0.14	42
0.31	46
0.62	41

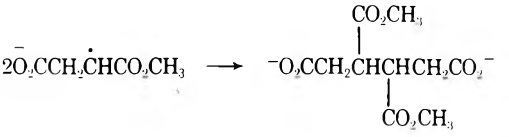
[a] Electrolyte solution 0.25 *M* $(C_2H_5)_4N^+OTs^-$ in CH_3CN with CO_2 saturation (1 atm), −20°. Cathode potential controlled at −1.65 V (sce). Portionwise addition of 2.9 g (0.02 mol) of maleate at total current passed of 0.02 faraday. [b] **4** → **2** with methyl iodide [J. H. Wagenknecht, M. Baizer, and J. L. Chruma, *Syn. Commun.*, **2**, 215 (1972)]; yields expressed as current efficiencies (ce) assuming a 2-faraday reduction per mole of product.

Table III
Electrocarboxylative Dimerization of Methyl Acrylate[a]

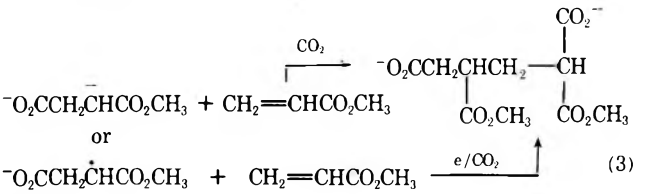
Initial [acrylate], *M*	Current density, mA/cm²	Yield, % (ce),[b] X = CO_2CH_3 X_2CH-CH_2X	X_2CHCH_2-$CHXCH_2X$	$X_2CH(CH_2)_2$-CHX_2
0	20	61	None	None
0.33	20	29	5	28
1.32	20	8	5	47

[a] Electrolyte solution 0.25 *M* $(C_2H_5)_4N^+OTs^-$ in CH_3CN with $[CO_2]$ 0.1 *M*. All but [acrylate] = 0 run at controlled current to less than 20% conversion. Run at [acrylate] = 0 made at controlled potential (−2.1 V) with portionwise addition of acrylate (ref 1). [b] Carboxylate salts converted to methyl esters with methyl iodide [J. H. Wagenknecht, M. M. Baizer, and J. L. Chruma, *Syn. Commum.*, **2**, 215 (1972)]; yields expressed as current efficiencies assuming a 2-faraday reduction per mole of product.

with decreasing concentrations of methyl acrylate supports the contention that the products of electrohydrodimerization of similar substrates under aqueous conditions involve reactions of the olefin anion radical with unreduced olefin.[6] In contrast to the results with dimethyl maleate, there is no evidence for dimerization of either the acrylate anion radical or the radical carboxylate. The latter is supported by the observation that no 1,2,3,4-tetrasubstituted butane derivatives are observed, *i.e.*,

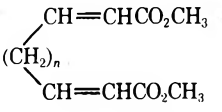


Of minor importance is the following (eq 3), based on the small amounts of tetramethyl 1,1,3,4-butanetetracarboxylate detected.



(3)

Electrocarboxylative Cyclizations. Upon reduction the bisactivated olefins (**8**) may be expected to undergo a variety of electrocarboxylative reactions. In the simplest



8 (*n* = 2-4)

case, each end of the molecule acts independently with the formation of products arising from the successive dicarboxylation of the two activated olefin moieties. However, as the molecular conformations of either the starting materials or reaction path intermediates are altered by variations in n of **8**, intramolecular interactions will compete with carboxylation in much the same way as intermolecular interactions compete with carboxylation in the cases of dimethyl maleate and methyl acrylate described above.

Dimethyl 2,6-Octadiene-1,8-dioate (8, n = 2). Electrocarboxylation of a solution of 8 (n = 2) gave, after esterification with methyl iodide, dimethyl [2,3-bis(methoxycarbonyl)cyclopentyl]malonate (**9**). No other cyclic or acyclic products were detected.

$CH_3O_2CCH{=}CHCH_2CH_2CH{=}CHCO_2CH_3$ (**8** (n = 2)) $\xrightarrow[2.\ CH_3I]{1.\ e/CO_2}$ **9**, 72%

Dimethyl 2,7-Nonadiene-1,9-dioate (8, n = 3). Electrocarboxylation of a solution of 8 (n = 3) gave, after esterification with methyl iodide, tetramethyl 1,2-cyclopentylenedimalonate (**10**). No acyclic products were detected.

$CH_3O_2CCH{=}CHCH_2CH_2CH_2CH{=}CHCO_2CH_3$ (**8** (n = 3)) $\xrightarrow[2.\ CH_3I]{1.\ e/CO_2}$ **10**, 50%

Dimethyl 2,8-Decadiene-1,10-dioate (8, n = 4). Electrocarboxylation of a solution of 8 (n = 4) gave, after esterification with methyl iodide, a mixture of tetramethyl-1,1,2,8-octene-7-tetracarboxylate (**11**), hexamethyl 1,1,2,7,8,8-octanehexacarboxylate (**12**), and tetramethyl 1,2-cyclohexylenedimalonate (**13**).

$CH_3O_2CCH{=}CHCH_2CH_2CH_2CH_2CH{=}CHCO_2CH_3$ (**8** (n = 4)) $\xrightarrow[2.\ CH_3I]{1.\ e/CO_2}$

$(CH_3O_2C)_2CHCH(CO_2CH_3)CH_2CH_2CH_2CH_2CH{=}CHCO_2CH_3$ + **11**, 31%

$(CH_3O_2C)_2CHCH(CO_2CH_3)CH_2CH_2CH_2CH_2CH(CO_2CH_3)CH(CO_2CH_3)_2$ + **12**, 13%

13, 7%

Table IV summarizes the results of the electrohydrocyclization of the same series of bisactivated olefins under aqueous conditions (*cf.* eq 1).[7]

With the exception of dimethyl 2,7-nonadiene-1,9-dioate (**8**, n = 3), the behavior of these olefins differs markedly under the two sets of conditions. The similarity in behavior for 8 (n = 3) can be attributed to the intramolecular interaction between the two olefin moieties in the sequence. Thus, the first electrode intermediate formed is one in which reduction and cyclization are concerted.[2b,7] This is

Table IV
Electrohydrocyclization of Bisactivated Olefins[a]

Olefin (8)	Yield, % (ce) Cyclic	Acyclic
n = 2	41	48
n = 3	100	
n = 4	81–90	

[a] As their ethyl esters. Solvent–electrolyte 50% aqueous $(C_2H_5)_4N^+OTs^-$ at Hg.

reflected by a lower reduction potential for this compound (Table I). Subsequent carboxylations and reduction of **14** leads to the product observed. This sequence is analogous to that in which methyl acrylate is carboxylatively dimerized to a tetrasubstituted 1,1,4,4-butane derivative (eq 2).

$(CH_2)_3(CH{=}CHCO_2CH_3)_2 + e \xrightarrow{-2.12V} [(CH_2)_3(CH{=}CHCO_2CH_3)_2]^{\cdot-}$

14

Dimethyl 2,6-octadiene-1,8-dioate (**8**, n = 2) and dimethyl 2,8-decadiene-1,10-dioate (**8**, n = 4) do not show a polarographic shift indicative of a concerted reduction–ring closure (Table I). Consequently, an acyclic anion radical intermediate (**15**) is formed at the electrode. Under aqueous

8 (n = 2, 4) + e $\xrightarrow{-2.24V}$ $[(CH_2)_n(CH{=}CHCO_2CH_3)_2]^{\cdot-}$

15 (n = 2, 4)

conditions this intermediate is sufficiently long-lived (with respect to protonation) so that ring closure to intermediates of the general type **14** occurs to an appreciable extent. However, in the presence of carbon dioxide, **15** must be carboxylated at a rate exceeding that of ring closure, with the radical carboxylate (**16**, n = 2, 4) being formed. The conformation of **16** (n = 2) (as the radical or anion after reduction) is such that ring closure *via* a 1,5-interaction now occurs more rapidly than carbon dioxide incorporation to give, after esterification, **9**. A similar interaction occurs to a minor extent in the carboxylative dimerization of methyl acrylate (eq 3). The rate of closure of **16** (n = 4) is sufficiently slow (1,7-interaction required), so that the major products (**11** and **12**) are acyclic.

$^-O_2C(CO_2CH_3)CHCH(CH_2)_nCH{=}CHCO_2CH_3$

16 (n = 2, 4)

In conclusion, a variety of inter- and intramolecular interactions have been observed when mono-, di-, and bisactivated olefins are reduced in anhydrous media containing dissolved carbon dioxide. The following summarizes the types of reactivity observed.

(1) Activated olefins exhibiting two distinct one-electron waves in the presence of carbon dioxide are converted to highly substituted adipic acids *via* the dimerization of radical carboxylates provided that the potential is controlled on the plateau of the first wave.

(2) Activated olefins exhibiting a single two-electron wave in the presence of carbon dioxide are converted to α,α'-substituted adipic acids provided that the concentration of unreduced olefins is high relative to that of carbon dioxide. Under these conditions the unreduced olefin com-

Table V
Nmr and Mass Spectral Data

Compd[a]	Nmr, δ, ppm[b]	Mass spectrum,[c] m/e
Hexamethyl 1,1,2,3,4,4-butanehexacarboxylate (2)	4.1 (1 H, d, CHX_2)[d] 3.78 (3 H, s, OCH_3) 3.7 (6 H, s, OCH_3) 3.4 (1 H, d, CHX)[d]	342 ($M^+ - 2CH_3OH$) 314 [$M^+ - (CH_3OH + HCO_2CH_3)$] 283 [$M^+ - (2\ CH_3OH + CO_2CH_3)$] 282 [$M^+ - (2CH_3OH + HCO_2CH_3)$] 244 [$M^+ - (2CH_3OH + 2CO_2CH_3)$]
Tetramethyl 1,1,3,4-butanetetracarboxylate	3.79 (6 H, d, OCH_3)[e] 3.75 (3 H, s, OCH_3) 3.73 (3 H, s, OCH_3) 2.73 (3 H, m, CH_2X, CHX)[f] 2.23 (2 H, m, CH_2)	259 [$M^+ - CH_3O$] 227 [$M^+ - (CH_3O + CH_3OH)$] 199 [$M^+ - (CH_3OH + CO_2CH_3)$]
Dimethyl [2,3-bis(methoxycarbonyl)cyclopentyl]malonate (**9**)	3.78 (6 H, d, OCH_3)[e] 3.73 (3 H, s, OCH_3) 3.69 (3 H, s, OCH_3) 2.67 (2 H, m, CHX)[f] 1.85 (4 H, m, CH_2)	285 ($M^+ - CH_3O$) 284 ($M^+ - CH_3OH$) 256 ($M^+ - CO_2CH_3$) 253 [$M^+ - (CH_3O + CH_3OH)$] 224 [$M^+ - (CH_3OH + HCO_2CH_3)$] 196 ($M^+ - 2HCO_2CH_3$) 185 [$M^+ - HC(CO_2CH_3)_2$] 125 {$M^+ - [HCO_2CH_3 + HC(CO_2CH_3)_2]$}
Tetramethyl 1,2-cyclopentylenedimalonate (**10**)	3.80 (12 H, s, OCH_3) 3.75 (2 H, d, CHX_2)[f] 2.17 (2 H, m, CH) 1.87 (6 H, m, CH_3)	299 ($M^+ - CH_3O$) 267 [$M^+ - (CH_3O + CH_3OH)$] 235 [$M^+ - (CH_3O + 2CH_3OH)$] 199 [$M^+ - HC(CO_2CH_3)_2$] 167 {$M^+ - [CH_3OH + HC(CO_2CH_3)_2]$} 166 [$M^+ - (CH_3OH + Z)$][h] 139 [$M^+ - (CO_2CH_3 + Z)$]
Tetramethyl 1,1,2,8-octene-7-tetracarboxylate (**11**)	7.17 (1 H, m, olefin) 5.95 (1 H, m, olefin) 3.79 (3 H, s, OCH_3) 3.75 (6 H, d, OCH_3)[e] 3.74 (3 H, s, OCH_3) 3.22 (1 H, m, CHX)[f] 2.23 (2 H, m, CH_3Y)[g] 1.49 (6 H, m, CH_3)	313 ($M^+ - CH_3O$) 285 ($M^+ - CO_2CH_3$) 280 ($M^+ - 2CH_3OH$) 248 ($M^+ - 3CH_3OH$) 221 [$M^+ - (2CH_3OH + CO_2CH_3)$]
Hexamethyl 1,1,2,7,8,8-octanehexacarboxylate (**12**)	3.81 (6 H, s, OCH_3) 3.77 (12 H, d, OCH_3)[e] 3.22 (2 H, m, CHX)[f] 1.42 (8 H, m, CH_3)	431 ($M^+ - CH_3O$) 403 ($M^+ - CO_2CH_3$) 398 ($M^+ - 2CH_3OH$) 371 [$M^+ - (CH_3O + CO_2CH_3)$] 366 ($M^+ - 3CH_3OH$) 331 [$M^+ - HC(CO_2CH_3)_2$] 307 [$M^+ - (3CH_3OH + CO_2CH_3)$] 299 (331 $- CH_3OH$) 267 {$M^+ - [2CH_3OH + HC(CO_2CH_3)_2]$} 259 [$M^+ - (CHX_2CH_2X)$][f]

[a] Satisfactory C, H analyses were obtained. [b] Solvent $CDCl_3$ with TMS internal standard. [c] By direct probe or glc–mass spectrum, no molecular ions observed. [d] X = CO_2CH_3, J = 10 Hz. [e] Nonequivalent CO_2CH_3, separation *ca.* 1 Hz. [f] X = CO_2CH_3. [g] Y = olefin. [h] Z = $(HO)(CH_3O)C{=}C(H)(CO_2CH_3)$.

petes with carbon dioxide as an electrophile in the trapping of the activated olefin anion radical.

(3) Bisactivated olefins are electrocarboxylated, the products obtained being a function of the methylene chain length [8 (n = 2–4)]. Intramolecular interactions are observed for 8 (n = 2, 3). The ends of the molecule act independently for 8 (n = 4).

Experimental Section

Equipment. The electrolysis system and instrumentation were the same as those described previously.[1]

Reagents and Starting Materials. Reagent grade acetonitrile (less than 80 ppm water) was obtained from Matheson Coleman and Bell and used without further purification. Methyl acrylate and dimethyl maleate were obtained from commercial sources. They were redistilled and stored with a trace of hydroquinone added. Dimethyl 2,6-octadiene-1,8-dioate [**8**, n = 2, bp 137° (0.6 mm)], dimethyl 2,7-nonadiene-1,9-dioate [**8**, n = 3, bp 126° (0.25 mm)], and dimethyl 2,8-decadiene-1,10-dioate [**8**, n = 4, bp 128° (0.25 mm)] were prepared by the method described previously for the corresponding ethyl esters.[7] Tetraethylammonium *p*-toluenesulfonate (Aldrich) was recrystallized several times from acetone and dried in a vacuum oven. The carbon dioxide was "bone dry" grade.

Reference Compounds. The preparations of trimethyl 1,1,2-ethanetricarboxylate and tetramethyl 1,1,2,2-ethanetetracarboxylate have been described previously.[1] Tetramethyl 1,1,4,4-butanetetracarboxylate (7 as its methyl ester, mp 77°) was prepared as described in the literature.[8] Tetramethyl 1,2,3,4-butanetetracarboxylate[9] (mp 60° from methanol–petroleum ether) was obtained by the transesterification (methanol–*p*-toluenesulfonicacid) of the corresponding ethyl ester prepared by the electrohydrodimerization of diethyl maleate.[10] Tetramethyl 1,1,3,4-butanetetracarboxylate, bp 160° (1 mm), was prepared by the base-catalyzed addition of dimethyl malonate to dimethyl itaconate in a manner similar to that described for the corresponding ethyl ester.[11] Relevant analytical data are given in Table V.

General Electrolysis Procedure. The electrolyte solution [0.25 M $(C_2H_5)_4N^+OTs^-$ in acetonitrile] was added to the cell containing the Hg cathode and a properly positioned sce. In addition, 20 g of $(C_2H_5)_4N^+Cl^-$ and 10 ml of 1-octene were added to the anode compartment to provide a sacrificial anode reaction (*i.e.*, $Cl^- - e \rightarrow \frac{1}{2}Cl_2$). The cell and its contents were cooled to the desired temperature while the solution was saturated for 15 min with 100% CO_2.

Dimethyl Maleate and Methyl Acrylate. The electrocarboxylation of these olefins at initial [olefin] = 0 were done under controlled-potential conditions of −1.65 and −2.1 V, respectively. The olefin, dissolved in acetonitrile, was gradually added to the catholyte. The cell temperature was maintained at −20° for the maleate

reduction and at 0° for the acrylate reduction. Electrolyses in which [olefin] ≠ 0 were run to less than 20% conversion of the initial activated olefin charged to the catholyte so as not to significantly lower the olefin concentration below its desired initial concentration in the cell. A constant-current power supply was employed for these electrolyses.

Bisactivated Olefins. A solution of the olefin (0.015 mol) in acetonitrile was gradually added to the catholyte while potentiostating at −2.2 V (sce). The electrolyses were discontinued when the final current had decayed to the background current observed for carbon dioxide reduction.

Work-Up and Analysis of Catholyte. The products of electrocarboxylation were converted to their methyl esters by treatment with excess methyl iodide (*cf.* footnote *b* of Table II). The acetonitrile and excess methyl iodide were removed and the organic products were separated from the electrolyte by benzene–water extraction. If authentic samples were available, analyses were done directly on the benzene-soluble material by glc (internal standards or known addition methods) using either a 6 ft × 0.125 in. S.S. 3% OV-101 on Chromosorb W (80–100 mesh) or 8 ft × 0.125 in. S.S. 3% OV-17 on Gas-Chrom Q (60–80 mesh) column. Products for which authentic samples were not available were isolated and characterized as described below. Products so obtained were subsequently used for yield determinations by glc.

Isolation and Identification of Products. The relevant analytical data for new compounds obtained during this study are shown in Table V.

Hexamethyl 1,1,2,3,4,4-Butanehexacarboxylate (2). The residue from the benzene extract of the dimethyl maleate electrolysis was taken up in hot methanol; **2** (mp 136–137°) precipitated upon cooling.

Dimethyl [2,3-bis(methoxycarbonyl)cyclopentyl]malonate (9) was isolated by column chromatography (neutral Al_2O_3–benzene) of the benzene-soluble products obtained from the electrolysis of dimethyl 2,6-octadiene-1,8-dioate (**8**, $n = 2$). Attempts to distil the viscous product resulted in decomposition.

Tetramethyl 1,2-cyclopentylenedimalonate (10) was separated from the starting material by column chromatography (neutral Al_2O_3–benzene) of the benzene-soluble residue obtained from the electrolysis of dimethyl 2,7-nonadiene-1,9-dioate (**8**, $n = 3$). Attempts to distil the viscous product resulted in decomposition.

Hexamethyl 1,1,2,7,8,8-octanehexacarboxylate (12) was isolated as a solid by treating the benzene-soluble residue from the electrolysis of dimethyl 2,8-decadiene-1,10-dioate (**8**, $n = 4$) with ice-cold ether (mp 136–137° from methanol).

Tetramethyl 1,1,2,8-Octene-7-tetracarboxylate (11). The ether-soluble residue remaining after precipitation of **12** was adsorbed onto a column of neutral Al_2O_3. Benzene elution gave unreduced **8**, ($n = 4$) and **11**, respectively; **11** is a viscous liquid which decomposed upon attempted distillation.

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Registry No.—**2**, 40853-30-3; **8** ($n = 2$), 4756-84-7; **8** ($n = 3$), 52002-95-6; **8** ($n = 4$), 52002-96-7; **9**, 52002-97-8; **10**, 52002-98-9; **11**, 52002-99-0; **12**, 52003-00-6; dimethyl maleate, 624-48-6; methyl acrylate, 96-33-3; tetramethyl 1,1,3,4-butanetetracarboxylate, 52003-01-7.

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Reactivity of Benzo[*b*]thiophene in Electrophilic Reactions as Determined from Solvolysis Rates[1]

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Electrophilic replacement constants, σ_{Ar}^+, have been obtained for all positions of benzo[*b*]thiophene. The σ_{Ar}^+ values were defined from rate constants for the solvolysis of the six isomeric 1-(benzo[*b*]thienyl)ethyl chlorides in 80% ethanol–water. The positional order of reactivity in the benzo[*b*]thiophene ring was determined to be 3 > 2 > 6 > 5 > 4 > 7. All positions are more reactive than benzene.

Recent studies in these laboratories have determined relative reactivities of several heteroaromatic systems in an "electrophilic side-chain reaction," [3] the solvolysis of 1-arylethyl derivatives.[4-7] A correspondence between solvolytic reactivity and reactivity in electrophilic aromatic substitutions is expected because of the similar electron deficiency developed in the aromatic system in the two types of reactions. In this paper we extend our studies of side-chain reactivity to the benzo[*b*]thiophene ring system and compare the results to literature data concerning the reactivity of benzo[*b*]thiophene in electrophilic reactions.

Aromatic reactivity data can be conveniently generalized by defining σ_{Ar}^+ values for use in the modified Hammett equation introduced by Brown.[8] For the particular electrophilic reaction being considered, a ρ value for the reaction is established from the rate data for substituted benzenes and then σ_{Ar}^+ constants are defined for aromatic systems from rate data obtained under the same conditions. We refer to σ_{Ar}^+ values as "replacement σ^+ values" [9] or "electrophilic replacement constants," rather than "substituent constants," because they signify replacement of the entire benzene ring by another aromatic system instead of the substitution of the aromatic system for one of the phenyl hydrogens. In addition to our studies,[4-7] this approach has been applied to aromatic hydrocarbons by Streitwieser,[10] and to heteroaromatic systems by Hill, *et al.*,[11] by Taylor,[12] by Marino,[13] and by Baker, Eaborn, and Taylor.[14]

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EXPERIMENTAL SECTION[29]

5-(2'-Methylbenzylidene)rhodanine.- o-Methylbenzaldehyde and rhodanine were combined according to the procedure of Chakrabarti, Chapman, and Clarke[30] to give a 94% yield of 5-(2'-methylbenzylidene)rhodanine: mp 202.5-203.5°; nmr (acetone) δ 7.42 (s [broadened at base], 4, ArH), and 7.86 (s, 1, ArCH) (the peak due to $ArCH_3$ is obscured by the acetone peak and its sidebands, and the NH peak could not be detected); UV (95% ethanol) λ_{max} nm/ε: 373/25,800; 274/6200; and 235(sh)/7250.

Anal. Calcd for $C_{11}H_9NOS_2$: C, 56.14; H, 3.86; N, 5.95; S, 27.25. Found: C, 55.97; H, 3.70; N, 5.88; S, 27.04.

β-(2-Methylphenyl)-α-mercaptoacrylic Acid.- This procedure is that used by Julian and Sturgis for similar compounds.[31] A suspension of 5-(2'-methylbenzylidene)rhodanine (43.95 g, 0.187 mol) in aqueous sodium hydroxide (10% w/w, 300 ml) was heated on the steam bath for 30 min. The solution was cooled to 10° and was acidified rapidly by the addition of cold 3 N hydrochloric acid (250 ml). The odor of hydrogen sulfide was apparent after acidification. The creamy white precipitate was filtered, washed with water, and dried to give 29.51 g (81%) β-(2-methylphenyl)-α-mercaptoacrylic acid: mp 115-124° (the broad mp range is probably the result of the product existing as a mixture of the cis and trans isomers[32]); nmr ($CDCl_3$) approximate peak areas are given relative to the area of 3 assigned to the CH_3 peak; exact assignments were not made for all peaks because the product was probably a mixture of isomers) δ 2.33 (s [with broad base and shoulder due possibly to a second peak], 3, CH_3), 4.23 (b, 1, SH), 7.22 (m, 3.5), 7.56 (m, 1), 7.97 (s, 1, β-H), and 9.97 (b, 1, CO_2H).

The product was used without further purification in the preparation of 4-methylbenzo[b]thiophene-2-carboxylic acid.

4-Methylbenzo[b]thiophene-2-carboxylic Acid.- This procedure is patterned after the synthesis of Campaigne and Cline of benzo[b]thiophene-2-carboxylic acid.[33] Crude β-(2-methylphenyl)-α-mercaptoacrylic acid (28.00 g, 0.144 mol) was added to a solution of iodine (146 g, 0.576 mol) in nitrobenzene (500 ml) at 190°. The

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mixture was stirred vigorously for one min, and then was quickly cooled in an ice bath. The product was extracted with dilute sodium hydroxide, sodium bisulfite (110 g) was added, and the alkaline solution was acidified with hydrochloric acid. The precipitated product was filtered, washed with water, and dried to give as a gray powder 17.45 g (63%) of 4-methylbenzo[b]thiophene-2-carboxylic acid: mp 198-200°. The product was purified by sublimation (150°, 0.1 mm) and separately by crystallization from dichloromethane: mp 204-205° [lit.[34] mp 197-198°], nmr (acetone) δ 7.20 (broad d, 1, [overlapping with H-C_6], H-C_5), 7.37 (t, 1, $J_{5,6} \approx J_{6,7} \approx$ 7 Hz, H-C_6), 7.69 (dd, 1, $J_{6,7}$ = 7 Hz and $J_{5,7}$ = 1.5 Hz, H-C_7), 8.15 (s, 1, H-C_3), and 8.43 (b, 1, CO_2H); nmr (nitrobenzene) δ 2.69 (s, CH_3).

Anal. Calcd for $C_{10}H_8O_2S$: C, 62.48; H, 4.19; S, 16.78. Found: C, 62.36; H, 4.19; S, 16.68.

4-Methylbenzo[b]thiophene.- A solution of 4-methylbenzo[b]thiophene-2-carboxylic acid (6.78 g, 0.0353 mol) and powdered cupric oxide (0.50 g) in freshly distilled quinoline (35 ml) was heated at 230° for 30 min. The mixture was cooled, ether (300 ml) was added, and the mixture was filtered. The solution was washed with five 50-ml portions of 2 N hydrochloric acid, then washed twice with 50 ml of water, and then washed with 50 ml of 10% aqueous sodium chloride. The ether solution was dried ($MgSO_4$), and filtered, and the ether was removed on the rotary evaporator. The crude product was redissolved in ether and run through a column of alumina to remove colored impurities. Evaporation of the ether under reduced pressure gave 5.11 g of the crude 4-methylbenzo[b]thiophene. The product was contaminated with methylnaphthalenes which had been present as impurities in the quinoline. Nmr analysis indicated that the methylnaphthalenes constituted ca. 15 mol-% of the product mixture; the remainder was 4-methylbenzo[b]thiophene; nmr ($CDCl_3$) δ 2.64 (s, 3, CH_3), 6.94-7.40 (m, 2, H-C_5 and H-C_6), 7.26 (s, 2, H-C_2 and H-C_3), and 7.60 (dd, 1, $J_{6,7}$ = 7 Hz and $J_{5,7}$ = 2 Hz, H-C_7). Small peaks due to methylnaphthalenes were at δ 2.43-2.60 (CH_3 [less than 15% of total methyl peak area]) and 6.94-7.76 (m, ArH).

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In view of the similarity between the impurities and the product, the separation of the naphthalene material from the benzo[b]thiophene material was delayed until a later step in the synthetic scheme where separation would be easier (benzo[b]thiophene-4-carboxaldehyde was purified).

5-Methylbenzo[b]thiophene (1).- (p-Tolylthio)acetaldehyde diethyl acetal was prepared from p-thiocresol and bromoacetaldehyde diethyl acetal in 80% yield, following the procedure of Elvidge and Foster:[35] bp 120-123°/1.0 mm [lit.[35] bp 168-169°/15 mm].

This cyclization procedure is based on the method of Bhattacharjee, et al.[36]

(p-Tolylthio)acetaldehyde diethyl acetal (20.00 g, 0.0833 mol) in dry chlorobenzene (150 ml) was heated to reflux. While stirring moderately, polyphosphoric acid (160 ml), maintained at 120-150°, was dripped in over 1 hr. The reaction mixture was cooled to 100°, and the chlorobenzene layer was decanted and saved. Water (150 ml) was dripped slowly into the hot acid layer while stirring vigorously. After cooling to 70°, benzene (80 ml) was added. The mixture was stirred vigorously to mix the layers. The benzene layer was decanted, and the extraction was repeated in a separatory funnel. The chlorobenzene and benzene layers were combined, dried ($MgSO_4$), filtered, and the solvents were evaporated under reduced pressure. The residue was distilled to give 9.53 g (77%) 5-methylbenzo[b]thiophene: bp 66-67°/0.6 mm; mp 35-36° [lit.[37] mp 37-38°].

6-Methylbenzo[b]thiophene.- (m-Tolylthio)acetaldehyde acetal was prepared from m-thiocresol and bromoacetaldehyde diethyl acetal in 90% yield, following the procedure of Elvidge and Foster:[35] bp 115-118°/0.8 mm [lit.[35] bp 164-166°/13 mm].

(m-Tolylthio)acetaldehyde diethyl acetal was used in the cyclization procedure described for 1, resulting in an 87% yield of a mixture of the 6- and 4-methylbenzo[b]thiophenes: bp 79-81°/0.8 mm. Nmr analysis showed two methyl peaks, at δ 2.35 and 2.48, indicating a product mixture of 68% 6-methylbenzo[b]thiophene and 32% 4-methylbenzo[b]thiophene, respectively. After one crystalli-

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zation from petroleum ether, the mixture was enriched to 87% 6-methylbenzo[b]thiophene. A number of successive recrystallizations, and reworkings of the filtrates, gave pure 6-methylbenzo[b]thiophene: mp 43.2-44° [lit.[35] mp 42-43°].

7-Methylbenzo[b]thiophene.- (o-Tolylthio)acetaldehyde dimethyl acetal was prepared from o-thiocresol and bromoacetaldehyde dimethyl acetal in 91% yield, following the procedure of Elvidge and Foster:[35] bp 109-111°/0.5 mm [lit.[38] bp 155-160° (bath temp.)/6 mm].

(o-Tolylthio)acetaldehyde was used in the cyclization procedure described for 1, resulting in a 75% yield of 7-methylbenzo[b]thiophene: bp 56-57°/0.6 mm [lit.[35,38] bp 112°/6 mm].

Benzo[b]thiophene-5-carboxaldehyde (2).- The bromination step of this synthesis follows the method of Chapman, et al.[39] A solution of benzoyl peroxide (0.20 g) and 5-methylbenzo[b]thiophene (3.30 g, 0.0223 mol) in dry carbon tetrachloride (70 ml) was heated to reflux while being irradiated by a 250-W electric lamp. N-Bromosuccinimide (3.96 g, 0.0223 mol) was added to the boiling mixture in small portions during 20 min. The mixture was heated under reflux for an additional 90 min, cooled, and filtered from succinimide. The carbon tetrachloride was evaporated under reduced pressure. The crude 5-bromomethylbenzo[b]thiophene was crystallized once from mixed hexanes, yielding 3.60 g (71%).

A solution of the crude 5-bromomethylbenzo[b]thiophene (3.60 g, 0.0158 mole) in dioxane (40 ml) was heated under reflux with 2 N NaOH (40 ml) for 16 hr. After cooling, the solution was extracted with ether, and the combined ether extracts were washed with water three times, washed with 10% aqueous sodium chloride, dried ($MgSO_4$), and filtered. The ether was evaporated under reduced pressure to give 2.12 g (81%) of crude 5-hydroxymethylbenzo[b]thiophene.

A suspension of MnO_2/c[40] (22 g) in benzene (150 ml) was refluxed in an apparatus fitted with a Dean-Stark trap for 30 min to remove water. A solution of the crude 5-hydroxymethylbenzo[b]thiophene (2.12 g, 0.0128 mol) in benzene (30 ml) was added and the

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refluxing was continued for 2 hr. The mixture was then cooled and filtered. The solid residue was shaken with benzene and refiltered. The combined benzene solutions were washed with water, washed with 10% aqueous sodium chloride, dried ($MgSO_4$), and filtered. Evaporation of the benzene under reduced pressure gave 1.85 g (88%) of benzo[b]thiophene-5-carboxaldehyde. From the crude product by column chromatography on silica gel, using 5% benzene-hexanes as the eluent, a pure sample (1.34 g) of benzo[b]thiophene-5-carboxaldehyde was obtained: mp 56-57° [lit.[41] mp 57°] (from hexane).

Benzo[b]thiophene-6-carboxaldehyde.- 6-Methylbenzo[b]thiophene was used in the procedures described for the synthesis of 2, first producing 6-bromomethylbenzo[b]thiophene (71% crude yield), then 6-hydroxymethylbenzo[b]thiophene (80% crude yield), and finally benzo[b]thiophene-6-carboxaldehyde (82% crude yield). Treatment of the crude aldehyde by column chromatography on silica gel, first using 5% benzene-hexanes as the eluent and then 10% benzene-hexanes, gave a colorless product which was crystallized from mixed hexanes to yield a pure sample of benzo[b]thiophene-6-carboxaldehyde: mp 42.5-44° [lit.[41] mp 43°].

Benzo[b]thiophene-7-carboxaldehyde.- 7-Methylbenzo[b]thiophene was used in the sequence described for the synthesis of 2, first producing 7-bromomethylbenzo[b]thiophene (69% crude yield), then 7-hydroxymethylbenzo[b]thiophene (85% crude yield), and finally benzo[b]thiophene-7-carboxaldehyde (86% crude yield). Treatment of the crude aldehyde by column chromatography on silica gel, using 5% benzene-hexanes as the eluent, gave a colorless product which was crystallized from mixed hexanes to yield a pure sample of benzo[b]thiophene-7-carboxaldehyde as white crystals: mp 42-43.5° [lit.[41] mp 42-43°].

Benzo[b]-thiophene-4-carboxaldehyde.- The mixture of 4-methylbenzo[b]thiophene and methylnaphthalenes was oxidized by the procedure described for the synthesis of 2. Two recrystallizations of the aldehyde product mixture from mixed hexanes afforded a pure sample of benzo[b]thiophene-4-carboxaldehyde as yellow crystals: mp 33-34° [lit.[41] mp 34°].

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1-(2-Benzo[b]thienyl)ethanol.- A solution of 1.6 N n-butyllithium in hexane (46.6 ml, 0.0746 mol, Foote Mineral Co.) was added to a solution of benzo[b]thiophene (10.0 g, 0.0746 mol) in anhydrous ether (150 ml) at 0° under a nitrogen atmosphere in a flame-dried flask. The mixture was stirred at 0° for 6 hr, at which time the solution was cloudy and yellow. Acetaldehyde (4.18 ml, 0.0746 mole) in dry ether (30 ml) at 0° was rapidly injected into the reaction mixture, and stirring was continued for 1 hr without further cooling. Water (100 ml) containing NH_4Cl (10 g) was added, the mixture was shaken, the ether layer was removed, and the water layer was extracted three times with 50-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and the ether was evaporated under reduced pressure to give an orange-red oil. The oil was taken up in hot n-hexane, from which crystallized 1-(2-benzo[b]thienyl)ethanol (5.91 g, 44%) as yellow crystals: mp 55-58° [lit.[42] mp 58-58.3°].

1-(3-Benzo[b]thienyl)ethanol.- The procedure of Szmuszkovicz and Modest[43] was used to synthesize 3-bromobenzo[b]thiophene in 72% yield: bp 115-117° (5 mm) [lit.[38] bp 95° (1.5 mm)]. A solution of 1.6 N n-butyllithium in hexane (62 ml, 0.10 mol, Foote Mineral Co.), which had been precooled in a dry ice-acetone bath, was slowly added to a solution of 3-bromobenzo[b]thiophene (21.3 g, 0.10 mol) in anhydrous ether (200 ml), which was cooled by a dry ice-acetone bath around the flame-dried flask protected from moisture by a nitrogen atmosphere. After stirring the cooled solution for 20 min, acetaldehyde (6.9 ml, 0.20 mol) was injected by precooled syringe into the reaction mixture. Stirring was continued for 1 hr while the temperature was controlled by a dry ice-acetone bath. The reaction mixture was quenched with dilute ammonium chloride solution (100 ml). The aqueous and organic phases were separated and the aqueous layer was extracted with 50 ml of ether. The organic layers were combined, dried (Na_2SO_4), and the solvents were removed on the rotary evaporator. Distillation gave 1-(3-benzo[b]thienyl)ethanol as a pale yellow oil: bp 142-144° (2.0 mm); crystallization from mixed hexanes gave white crystals: mp 53.5-55° [lit.[11] mp 43-45°]; nmr ($CDCl_3$) δ 1.57 (d, 3, J = 6 Hz,

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$CHCH_3$), 2.43 (b, 1, OH), 5.10 (q, 1, J = 6 Hz, $CHCH_3$), 7.15-7.41 (m, 3, H-C_2, H-C_5, and H-C_6), and 7.62-7.87 (m, 2, H-C_4 and H-C_7).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.19; H, 5.55; S, 17.78.

1-(5-Benzo[b]thienyl)ethanol (3).- A solution of 3 M methylmagnesium bromide in ether (5.11 ml, 0.014 mol, ALFA Inorganics) was rapidly syringed into a stirred solution of benzo[b]-thiophene-5-carboxaldehyde (1.24 g, 0.0077 mol) in 15 ml of dry ether at 0° under a nitrogen atmosphere in a flame-dried flask. A white precipitate formed immediately. Stirring was continued for 2 hr without further cooling. Aqueous ammonium chloride was added, the mixture was shaken in a separatory funnel, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed with water, washed with aqueous sodium chloride, dried ($MgSO_4$), and filtered. Evaporation of the ether under reduced pressure gave 1.36 g (99%) of 1-(5-benzo[b]-thienyl)ethanol. Nmr analysis indicated complete conversion to the alcohol, with no residual aldehyde or other products present: mp 72.5-74° (mixed hexanes); nmr ($CDCl_3$) δ 1.52 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.18 (b, 1, OH), 4.89 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.10-7.38 (m, 3, H-C_2, H-C_3, and H-C_6), 7.65 (H-C_4 peak overlapping upfield half of H-C_7 doublet), and 7.71 (d, 1, $J_{6,7} \approx$ 7 Hz, H-C_7).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.24; H, 5.89; S, 17.82.

The following alcohols were prepared from the corresponding aldehydes by the procedure described for 3:

1-(4-Benzo[b]thienyl)ethanol.- Yield 89%; mp 37-39° (mixed hexanes); nmr ($CDCl_3$) δ 1.48 (d, 3, J = 6 Hz, $CHCH_3$), 2.68 (b, 1, OH), 5.13 (q, 1, J = 6 Hz, $CHCH_3$), 6.98-7.40 (m, 4, H-C_2, H-C_5, and H-C_6), and 7.64 (dd, 1, $J_{6,7}$ = 6.5 Hz and $J_{5,7}$ = 2.5 Hz, H-C_7).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.18; H, 5.73; S, 17.72.

1-(6-Benzo[b]thienyl)ethanol.- Yield 100%; mp 35-36.5°

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(mixed hexanes); nmr ($CDCl_3$) δ 1.53 (d, 3, J = 6 Hz, $CHCH_3$), 1.93 (b, 1, OH), 4.95 (q, 1, J = 6 Hz, $CHCH_3$), 7.16-7.43 (m, 3, H-C_2, H-C_3, and H-C_5), 7.73 (d, 1, $J_{4,5} \approx$ 8-9 Hz [downfield half obscured by H-C_7 peak], H-C_4), and 7.82 (s, 1, H-C_7).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.11; H, 5.49; S, 17.98.

1-(7-Benzo[b]thienyl)ethanol.- Yield 100%; mp 67-68° (mixed hexanes); nmr ($CDCl_3$) δ 1.62 (d, 3, J = 6 Hz, $CHCH_3$), 2.17 (b, 1, OH), 5.19 (q, 1, J = 6 Hz, $CHCH_3$), 7.16-7.43 (m, 4, H-C_2, H-C_3, H-C_5, and H-C_6), and 7.63 (m, 1, H-C_4).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.31; H, 5.45; S, 18.12

1-(Benzo[b]thienyl)ethyl Chlorides.- The six isomeric 1-(benzo[b]thienyl)ethanols were converted to the chlorides for use in the solvolysis studies. The crude products were used without further purification to avoid possible decomposition in workup procedures. The following procedure for 1-(2-benzo[b]thienyl)ethyl chloride was typical.

Thionyl chloride (1.12 g, 0.0094 mol) in 5 ml of dichloromethane was added to a solution of 1-(2-benzo[b]thienyl)ethanol (1.39 g, 0.0078 mol) in dichloromethane (35 ml). The mixture was heated under reflux for 1 hr, and then cooled to room temperature. Sodium carbonate (1.0 g) and water (0.5 ml) were added, and stirring was continued for 10 min. Magnesium sulfate (ca. 1 g) was added for drying, the mixture was filtered, and the dichloromethane was removed on the rotary evaporator to yield 1.44 g of the crude product. Nmr analysis indicated that 75-80% of the alcohol had been converted to 1-(2-benzo[b]thienyl)ethyl chloride. New peaks in the nmr spectrum were assigned to the aliphatic protons of the chloride (peaks for the aromatic protons overlap inseparable with those from the unreacted alcohol): nmr ($CDCl_3$) δ 1.88 (d, 3, J = 6.5 Hz, $CHCH_3$) and 5.23 (q, 1, J = 6.5 Hz, $CHCH_3$).

Kinetic Procedures.- Solvolysis rates in 80% ethanol-20% water were measured in the static pH method described previously.[6] The first-order rate constants for the solvolyses are listed in Table II, with standard deviations for each kinetic run.

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Table II

Rate Constants for the Solvolysis in 80% Ethanol of 1-(x-Benzo[b]thienyl)ethyl Chlorides

Compd Solvolyzed	T,°C	10^4k, sec^{-1}
2-Benzo[b]thienyl	0.0	4.20±0.01; 4.23±0.01
	25.0	90.4±0.2; 90.5±0.2; 91.6±0.2
3-Benzo[b]thienyl	0.0	12.0±0.0; 12.2±0.0
	25.0	238±0; 240±1; 237±1; 238±1
4-Benzo[b]thienyl	25.0	3.29±0.03; 3.61±0.02; 3.58±0.02
	45.0	31.9±0.2; 32.1±0.3; 33.2±0.2
5-Benzo[b]thienyl	25.0	11.2±0.0
	25.1	11.3±0.0
	44.9	90.6±0.3
	45.0	91.9±0.2; 90.8±0.3
6-Benzo[b]thienyl	0.0	1.43±0.00; 1.39±0.01
	25.0	33.6±0.1; 33.4±0.1
7-Benzo[b]thienyl	25.0	0.513±0.0006; 0.494±0.0006
	44.9	5.03±0.03; 5.06±0.05

Table I
Solvolyses of 1-(Benzo[b]thienyl)ethyl Chlorides in 80% Ethanol–Water at 25°

Aryl group	k, sec^{-1}	σ_{Ar}^+	Registry no.
2-Benzo[b]thienyl	9.11×10^{-3}	−0.49	51830-42-3
3-Benzo[b]thienyl	2.37×10^{-2}	−0.56	51830-43-4
4-Benzo[b]thienyl	3.50×10^{-4}	−0.25	51830-44-5
5-Benzo[b]thienyl	1.12×10^{-3}	−0.34	51830-45-6
6-Benzo[b]thienyl	3.37×10^{-3}	−0.42	51830-46-7
7-Benzo[b]thienyl	5.06×10^{-5}	−0.11	51830-47-8

Table I presents the electrophilic replacement constants determined in the present study for all six of the benzo[b]thiophene positions to which a side chain may be attached. These constants were established from titrimetric rate measurements of the solvolysis in 80% ethanol–water of the six isomeric 1-(benzo[b]thienyl)ethyl chlorides. The first-order rate constants for the solvolyses at 25° are also listed in Table I. The defining ρ value for the reaction was −6.05.[15]

The negative values of the σ_{Ar}^+ constants in Table I indicate that all positions of the benzo[b]thiophene ring are more reactive than a single benzene position in this electrophilic reaction. The positional order of reactivity is 3 > 2 > 6 > 5 > 4 > 7.

Previous kinetic studies of benzo[b]thiophene in electrophilic reactions have been confined to the 2 and 3 positions. Very similar results to those reported here were found by Hill for the solvolysis of 1-(benzo[b]thienyl)ethyl acetates: σ_{Ar}^+ values of −0.46 and −0.54 for the 2 and 3 positions, respectively.[11] Eaborn found that acid cleavage of the 2- and 3-trimethylsilylbenzo[b]thiophenes proceeded at nearly the same rate, with the 3 position reacting 1.15 times faster than the 2 position; these rate measurements give σ_{Ar}^+ values of −0.33 and −0.34 for the 2 and 3 positions.[16] Similarly, the protodetritiation rates showed very little difference between the two positions, although the σ_{Ar}^+ constants are much more similar to those found here than are the protodetrimethylsilylation values; protodetritiation σ_{Ar}^+ constants are −0.61 and −0.62 for the 2 and 3 positions, respectively.[14] A Russian study of protodedeuteration also found little difference in reactivity of the two positions, with the 3 position the faster of the two.[17] A result at variance with the general rule of greater reactivity of the 3 position is the report of σ_{Ar}^+ values from the gas-phase thermolysis of 1-(benzo[b]thienyl)ethyl acetates as being −0.53 for the 2 position and −0.46 for the 3 position.[18] The only other report of greater reactivity of the 2 position over the 3 position concerns Friedel–Crafts isopropylation,[19] for which the anomalous order of reactivity may be explained in terms of rearrangement of the product.[20]

Electrophilic aromatic substitution reactions with benzo[b]thiophene occur predominantly at the 3 position.[20,21] The 3 position has often been reported to be the only position attacked in electrophilic reactions, but careful studies usually reveal the presence of other isomeric products in most reactions. The literature data are not entirely consistent in regard to the relative reactivities of the other positions in benzo[b]thiophene. A review of the literature by Chalvet, Royer, and Dermerseman[22] led them to conclude that the order of reactivity toward electrophiles was 3 ≥ 2 > 6 ≥ 5 ≫ (4,7), which is precisely the order determined from the solvolysis of 1-(benzo[b]thienyl)ethyl chlorides. In a comprehensive review of the literature of benzo[b]thiophene chemistry, Iddon and Scrowston stated that halogenation and acylation reactions usually give a mixture of the 2 and 3 isomers, with the 3 isomer predominating.[20] Nitration also gives the 3 isomer as the major product; however, nitration has been reported to occur at all the ring positions with the relative proportions of the products varying widely in different studies.[20,23–26] The most recent research, by Martin-Smith, *et al.*, indicated that separation of isomeric nitration products of benzo[b]thiophenes by chromatographic methods was incomplete;[26] such difficulties may have contributed to the inconsistencies in the literature.

In summary, the bulk of the data available in the literature agree on a qualitative level with the findings reported in Table I, that the 3 position is more reactive than the 2 position, and that the 3 position is the most reactive site in the benzo[b]thiophene ring. On a quantitative level, there is insufficient information to test the validity of the σ_{Ar}^+ values in linear free-energy relationships. Although Hill[11] concluded that there was no correlation between isomer ratios from electrophilic substitutions and the ratios expected from considering the ρ values for the reactions and the σ_{Ar}^+ values for the 2 and 3 positions of benzothiophene, more recent studies have indicated that the Extended Selectivity Treatment[27] may be profitably applied to thiophenes.[4,13] More recent discussion of the 2 and 3 positions of benzothiophene in this regard[28] indicate some nonlinearity, and therefore a lack of constancy in σ_{Ar}^+ values.

Registry No.—**1**, 14315-14-1; **2**, 10133-30-9; **3**, 51830-48-9; 5-(2′-methylbenzylidene)rhodanine, 50459-52-4; *cis*-β-(2-methylphenyl)-α-mercaptoacrylic acid, 7575-67-9; *trans*-β-(2-methylphenyl)-α-mercaptoacrylic acid, 51830-49-0; 4-methylbenzo[b]thiophene-2-carboxylic acid, 1735-13-3; 4-methylbenzo[b]thiophene, 14315-11-8; (*p*-tolylthio)acetaldehyde diethyl acetal, 51830-50-3; 6-methylbenzo[b]thiophene, 16587-47-6; (*m*-tolylthio)acetaldehyde diethyl acetal, 51830-51-4; 3-bromobenzo[b]thiophene, 7342-82-7; 7-methylbenzo[b]thiophene, 14315-15-2; (*o*-tolylthio)acetaldehyde dimethyl acetal, 51830-52-5; 5-bromobenzo[b]thiophene, 10133-22-9; 5-hydroxymethylbenzo[b]thiophene, 20532-34-7; benzo[b]thiophene-6-carboxaldehyde, 6386-80-7; 6-bromomethylbenzo[b]thiophene, 6179-30-2; 6-hydroxymethylbenzo[b]thiophene, 6179-28-8; benzo[b]thiophene-7-carboxaldehyde, 10134-91-5; 7-bromomethylbenzo[b]thiophene, 10133-24-1; 7-hydroxymethylbenzo[b]thiophene, 51830-53-6; benzo[b]thiophene-4-carboxaldehyde, 10133-25-2; 4-bromomethylbenzo[b]thiophene, 10133-19-4; 4-hydroxymethylbenzo[b]thiophene, 51830-54-7; 1-(2-benzo[b]thienyl)ethanol, 51868-95-2; benzo[b]thiophene, 95-15-8; acetaldehyde, 75-07-0; 1-(3-benzo[b]thienyl)ethanol, 20896-18-8; 1-(4-benzo[b]thienyl)ethanol, 51830-55-8; 1-(6-benzo[b]thienyl)ethanol, 51830-56-9; 1-(7-benzo[b]thienyl)ethanol, 51830-57-0.

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Nucleophilic Reactivity of Peptides toward 2-Acyloxy-*N*-ethylbenzamides. The Utility of Free Peptides as Nucleophiles in Amide Bond Forming Reactions

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The free peptides (Gly-L-Leu-Gly)$_n$, n = 1, 2, 4, and 8, have been found to react slowly but cleanly with DMSO solutions of the *N*-ethylsalicylamide esters of Z(Gly-L-Leu-Gly)$_n$, n = 1, 2, and 4, to yield the sequence polymers, Z(Gly-L-Leu-Gly)$_n$OH, n = 2, 4, 8 and 16. The virtues and limitations of peptide synthesis using suspensions of peptides as nucleophiles are described.

The most commonly encountered amide-forming process in peptide synthesis involves reaction of an activated acyl derivative with a peptide derivative bearing a free N terminus and a blocked C terminus. In certain circumstances, it has been possible to obtain reasonable yields of clean products for coupling reactions in which the C-terminal blocking group of the nucleophilic component is reduced to a simple salt,[1] although difficulties can arise from insolubility and the necessary high basicity of the reaction medium. The simplest possible coupling situation would combine an N-blocked, C-activated peptide with a free, unblocked peptide as nucleophile. In this paper, we demonstrate that high yields of pure products can indeed be obtained with this procedure, provided that certain key conditions are met.

Two serious problems arise if one attempts to employ an amino acid or a free peptide as a reactive amine nucleophile. For all solvents of the aprotic type, the solubility of

$$\underset{\text{crystal}}{\underset{1}{NH_3^+\!\!-\!\!\!-\!\!CO_2^-}} \overset{K_1}{\rightleftharpoons} \underset{\text{solution}}{\underset{2}{NH_3^+\!\!-\!\!\!-\!\!CO_2^-}} \overset{K_2}{\rightleftharpoons} \underset{\text{solution}}{\underset{3}{NH_2\!\!-\!\!\!-\!\!CO_2H}}$$

amino acids and peptides is low, presumably because the strong crystal lattice forces can be compensated for only by a solvent of high dielectric constant which can serve as both hydrogen bond donor and acceptor; on the other hand, in protic solvents, solvated material is present essentially exclusively as the zwitterion **2**, and the magnitude of this effect is essentially independent of chain length.[2]

We were led to attempt the present study through the conjecture that solubility in dipolar aprotic solvents should be lowest for amino acids and should converge to a value characteristic of the particular amide backbone as the peptide size is increased, and through the further conjecture that species larger than dipeptides should be present in solution in dipolar aprotic solvents as the neutral species **3** and not as the zwitterion **2**. If these conjectures are correct, then aminolysis of reactive acyl species should be possible using suspensions of free peptides in solvents such as DMF or DMSO and should occur with increasing ease as one changes the peptide size from small to medium. Should such a procedure be realizable, its mildness and simplicity might prove important advantages when designing coupling reactions between fragments in the 6–12 size range.

1. Results with Gly-L-Leu-Gly Peptides. Since we had previously prepared the peptide Z(Gly-L-Leu-Gly)$_2$OH and found this substance to be readily characterizable,[3] the coupling, Z-Gly-L-Leu-Gly-X with Gly-L-Leu-Gly, seemed an appropriate initial experiment. The active acyl derivative was chosen to be an *N*-ethylsalicylamide ester, despite

its rather low reactivity, since this species is readily available from the corresponding peptide acid, and it is not subject to any rapid decomposition reactions in neutral media.[4] In fact, when the tripeptide in the form of a fine crystalline precipitate was suspended and stirred in a DMSO solution containing 1 equiv of the *N*-ethylsalicylamide ester of Z-Gly-L-Leu-GlyOH for several hours, slow solution was observed, and after 48 hr at 22°, the mixture was homogeneous and no free peptide could be detected by tlc. Upon conventional work-up, a 88–92% yield of pure Z(Gly-L-Leu-Gly)$_2$OH was obtained. The product was obtained in higher yield and in a purer state than by alkaline saponification of the corresponding ethyl ester or by a 3-acyloxy-2-hydroxy-*N*-ethylbenzamide coupling with the tetramethylguanidine salt of Gly-L-Leu-Gly.[5] Investigation of DMF, hexamethylphosphoric triamide, sulfolane, *N*-methylpyrrolidone, or hexafluoroisopropyl alcohol revealed that use of any of these as solvent results in a reduced yield and longer reaction time than is required with DMSO, and all subsequent work was carried out in this solvent.

In an attempt to define the scope of this procedure, we applied it to the couplings, (Gly-L-Leu-Gly)$_n$ + *N*-ethylsalicylamide ester of Z(Gly-L-Leu-Gly)$_n$, where n = 2, 4, and 8. The results obtained are shown in Table I. The products of the latter three reactions are amorphous by X-ray powder pattern and are highly insoluble materials. Satisfactory elemental analyses were observed for all, although the substances were usually obtained as hydrates which retained residual water tenaciously. An independent test of product character was available for the n = 4 and 8 cases through use of radiolabeled starting material. Assuming product homogeneity, one can estimate the molecular weight of the product from its specific activity, and these estimates are reported in the last column of Table I.

The solubilities of HGly-L-Leu-GlyOH and H(Gly-L-Leu-Gly)$_2$OH in DMSO at 22° were found to be 1.1 and 17 mg/ml (4.6×10^{-3} and 3.6×10^{-2} M), respectively. The poor result for an attempted coupling in DMF is directly attributable to poor solubility, for in this solvent, the solubility of Gly-L-Leu-Gly is only 0.07 mg/ml. From these results and the results of yield determinations by isotopic dilution, one can calculate "one-point" rate constants of 0.4 M^{-1} min^{-1} for the [3 + 3] coupling and 0.07 M^{-1} min^{-1} for the [6 + 6] coupling. The former is of the magnitude expected for an unhindered aminolysis reaction of a peptide *N*-ethylsalicylamide ester[6] and therefore supports the conjecture that dissolved Gly-L-Leu-Gly is largely present as the neutral **3** and not as **2**. The fivefold difference in rate constants probably exceeds the error in the determinations and provides evidence for the common view that rates of coupling reactions are slower for reactions of large peptide fragments.

2. Other Cases. The cases just considered are atypical in that the coupling reactions occur between a pair of glycine residues, and are therefore expected to be abnormally rapid. In an attempt to examine a more representative case, we prepared the tripeptide derivative, Boc-L-Ala-L-(γOBz)Glu-L-PheOH, converted it to its *N*-ethylsalicylamide ester, and combined the latter in DMSO solution with L-Ala-L(γOBz)Glu-L-Phe; after a reaction period of 70 hr, the desired N-protected hexapeptide was isolated in 90% yield. Further oligomerization attempts were thwarted by the extreme insolubility of the hexapeptide, obtained by treatment with trifluoroacetic acid.

Oligomers of the sequence HGly-L-Pro-L-AlaOH are of interest as collagen models,[7] and several such species have been reported.[8] Examination of this case provided an especially severe test of our method, since peptides of the form

Table I
Synthesis of Z(Gly-L-Leu-Gly)$_n$ Sequence Polymers

2-[Z-(Gly-L-Leu-Gly)$_n$O]-*N*-ethylbenzamide + H(Gly-L-Leu-Gly)$_n$OH $\xrightarrow[22°]{\text{DMSO}}$ Z(Gly-L-Leu-Gly)$_{2n}$OH

Product	Reaction time, days	Yield, %[a]	—Mol wt— Calcd	Obsd
Z(Gly-L-Leu-Gly)$_2$OH	2	89 (91)		
Z(Gly-L-Leu-Gly)$_4$OH	2	98 (97)	1035[b]	1080
Z(Gly-L-Leu-Gly)$_8$OH	8	58 (79)	2024[b]	2160
Z(Gly-L-Leu-Gly)$_{16}$OH	8	51		

[a] Yields in parentheses were obtained by isotopic dilution. The N-terminal Gly of the free peptide was labeled. [b] Hydrate is formed on work-up.

Table II
Yields and Rate Constants for Ala-Gly Couplings

A. Coupling Reactions with HGly-L-Pro-L-AlaOH and *N*-Ethylsalicylamide Esters

Acyl species	Nucleophile	Reaction time, days	Yield, %
Z-L-Ala	HGly-L-Pro-L-AlaOH	3	98
Z-L-Pro-L-Ala	HGly-L-Pro-L-AlaOH	2.5	92

B. Coupling Reactions of Ala-*N*-ethylsalicylamide Esters with HGlyOEt

Acyl species	Nucleophile	k, M^{-1} min^{-1}
Z-L-Ala	GlyOEt	0.45
Z-L-Pro-L-Ala	GlyOEt	0.50
Z-Gly-L-Pro-L-Ala	GlyOEt	0.45

HGly-ProX-OH are known to undergo formation of the diketopiperazine, Gly-Pro, under very mild conditions.[9] Although a coupling reaction between the *N*-ethylsalicylamide ester of Z-Gly-L-Pro-L-AlaOH and HGly-L-Pro-L-AlaOH was observed, it occurred anomalously slowly, and after 7 days at 22°, an isolated yield of only 54% of pure *Z* hexapeptide was observed. That this result is a peculiarity of this particular combination of active ester and nucleophile is shown by the data of Table II. The tripeptide nucleophile reacts satisfactorily with other C-terminal Ala esters, and the C-terminal tripeptide ester reacts at an expected rate with GlyOEt. (Although the rate constants of Table II, part B are inexact, being based on a "one-point" isotopic dilution for yield, they are sufficient to establish the important point that only the C-terminal amino acid affects the rate constant for reactions with GlyOEt.) The origin of the anomalous behavior of the [3 + 3] case remains unexplained; one possible explanation is unproductive association between the reactants, although it seems unlikely that a substantial effect of this kind could arise with molecules as small as tripeptides.

3. Summary. The above results establish that practical syntheses of large polypeptides can be achieved in DMSO solution using free peptides as nucleophiles. The nucleophile must be a tripeptide or larger, and it must be moderately soluble in DMSO; the activated acyl derivative must be stable in DMSO solution and must be sufficiently reactive to compensate for the low nucleophile concentration. It is clear that the *N*-ethylsalicylamide esters are too unreactive to be practical for peptide coupling reactions of average hindrance; moreover, they are expected to racemize to

the extent of several per cent under these reaction conditions.[10] It is also clear that without a means of controlling peptide solubility, the application of this procedure to a given coupling reaction must be attended by an unacceptable element of unpredictability. The importance of the successful synthesis of a octatetracontapeptide therefore hinges on the possibility of developing new stable, but satisfactorily activated acyl derivatives and side chain protective groups.

Experimental Section

All reagents and solvents were reagent grade. Amino acids were Calbiochem A grade. DMSO and tetramethylguanidine were distilled *in vacuo* from CaH_2. Optical rotations were carried out at 22°, using a Perkin-Elmer Model 141 polarimeter. Radioactive assays were carried out in dioxane-based counting solutions, using a Packard 3375 liquid scintillation spectrometer. Microanalyses were carried out by Scandinavian Microanalytical Laboratories. Unless otherwise indicated, analytical samples were dried for 24 hr at 65° (0.1 mm).

Z-Gly-L-Leu-GlyOH. The tetramethylammonium salt prepared by subjecting a solution of 6.07 g (46.2 mmol) of L-leucine in 42.1 g of 10% tetramethylammonium hydroxide to azeotropic distillation with benzene in a Dean-Stark apparatus was dissolved in 60 ml of DMSO containing 4.84 g (42 mmol) of tetramethylguanidine (TMG) and treated with 15.6 g (42 mmol) of 3-carbobenzoxyglycycloxy-2-hydroxy-*N*-ethylbenzamide under nitrogen. After 6 hr at 20°, the solvent was removed at 0.5 mm, and the residue was distributed between 100 ml each of 1 *N* HCl and ethyl acetate. The aqueous layer was extracted, and the combined organic phase was extracted with 0.5 *N* $NaHCO_3$. Acidification to pH 1 and extraction with ethyl acetate yielded an organic phase which was washed with 0.1 *N* HCl and water, dried, and evaporated. The solid was recrystallized from ethyl acetate to yield a first crop, 15.5 g, mp 143–145°, and a second crop, 0.66 g, mp 141–143°, $[\alpha]^{22}D$ −9.6° (*c* 2.1, EtOH), 97% (lit.[11] 143–144°, −9.5°). The resulting Z-Gly-L-LeuOH was converted to its oily 3-acyloxy-2-hydroxy-*N*-ethylbenzamide ester by reaction of its sodium salt in aqueous pyridine buffer with 11.6 g (46 mmol) of 2-ethyl-7-hydroxybenzisoxazolium fluoroborate, following the procedure previously reported for the ester of Z-Gly-L-PheOH. Addition of this ester in 80 ml of DMSO to a suspension of 3.14 g (42 mmol) of glycine in 25 ml of DMSO containing 9.17 g of TMG was followed 4 hr later by solvent removal and work-up as described above. Recrystallization from ethyl acetate–hexane yielded 13.24 g, mp 108.5–111°, and 0.27 g, mp 165–110°, 94%, $[\alpha]^{22}D$ − 15.2° (c 2.4, DMF) (lit.[12] 110°, −14.7°).

HGly-L-Leu-GlyOH. Hydrogenation in methanol–water solution at 1 atm for 10 hr of Z-Gly-L-Leu-GlyOH over 5% Pd/C gave, after filtration through Celite, washing of catalyst with hot water, concentration, and crystallization from water–EtOH, 92% tripeptide, mp 222–224°, $[\alpha]^{22}D$ −44.6° (*c* 2.0, H_2O) (lit.[13] 214–215°, −43.3°).

2-(Z-Gly-L-Leu-GlyO)-*N*-ethylsalicylamide. A solution of 2.79 g (7.38 mmol) of Z-Gly-L-Leu-GlyOH in 7.0 ml of 1 *N* NaOH, 5 ml of water, 0.7 ml of pyridine, and 15 ml of ethyl acetate was chilled and stirred vigorously as 2.3 g (9.8 mmol) of powdered 2-ethylbenzisoxazolium fluoroborate was added. Ethyl acetate (20 ml) was added, and after 3 min this was followed by 10 ml of 3 *N* HCl. After 15 min, the precipitated ester was collected and washed with 10 ml each of ethyl acetate, 1 *N* HCl, water, and ethyl acetate, and the organic filtrate was extracted with acid, $NaHCO_3$, and water, dried, and evaporated. Recrystallization from acetonitrile yielded 3.32 g, mp 170.5–171.5°, and 0.27 g, mp 169.0–70.0°, total 92.8%, $[\alpha]^{22}D$ −15.7° (c 1.5, DMF). *Anal.* Calcd for $C_{26}H_3N_4O_7$: C, 61.58; H, 6.51; N, 10.64. Found: C, 61.38; H, 6.52; N, 10.52.

Z(Gly-L-Leu-Gly)$_2$OH. To a solution of 2.63 g (5.00 mmol) of 2-(Z-Gly-L-Leu-GlyO)-*N*-ethylbenzamide in 42 ml of dry DMSO was added 1.23 g (5.01 mmol) of HGly-L-Leu-GlyOH as a finely powdered solid. The mixture was stirred magnetically for 45 hr at 22° in a flask equipped with a drying tube. At this time, all solid had dissolved, and the ninhydrin-positive peptide spot had disappeared by tlc. Removal of the solvent at 0.1 mm left an oil which was taken up in ethyl acetate and extracted with 10 ml of 1 *N* HCl. The aqueous extract was back extracted with six 10-ml portions of ethyl acetate. The combined organic extracts were washed with brine and dried briefly over $MgSO_4$. Recrystallization of the residue after evaporation and drying yielded 2.96 g (97.5%) of product, mp 161–165°, $[\alpha]^{22}D$ −20.7° (c 1.5, DMF), identical in all respects with a sample prepared by saponification of Z(Gly-L-Leu-Gly)$_2$OEt (lit.[3] 158–159°, −20.2°, −20.7°).

H(Gly-L-Leu-Gly)$_2$OH. Hydrogenation of Z(Gly-L-Leu-Gly)$_2$OH was carried out as described above, with periodic injections of sufficient water to dissolve product. The crude white solid obtained on work-up was triturated with ethanol and collected, 84%, mp 239–240°, $[\alpha]D$ −34.5° (c 1.2, HOAc). *Anal.* Calcd for $C_{20}H_{36}N_6O_7 \cdot 0.5H_2O$: C, 49.87; H, 7.76; N, 17.45. Found: C, 50.29; H, 7.69; N, 17.32.

2-[Z(Gly-L-Leu-Gly)$_2$O]-*N*-ethhthylbenzamide. A solution of 1.83 g (3.0 mmol) of Z(Gly-L-Leu-Gly)$_2$OH in 27 ml of water and 1.3 ml of pyridine was brought to pH 4.5 with 3 *N* HCl, overlayered with 30 ml of ethyl acetate, and treated with 0.8 g (3.3 mmol) of 2-ethylbenzisoxazolium fluoroborate. After 30 min at 22°, the mixture was worked up in the usual way. Recrystallization from acetonitrile gave 1.80 g (80%) of ester, mp 172–174°, $[\alpha]^{22}D$ −19.9° (*c* 1.5, DMF). *Anal.* Calcd for $C_{37}H_{51}N_7O_{10}$: C, 58.95; H, 6.82; N, 13.01. Found: C, 58.80; H, 7.08; N, 12.91.

Z(Gly-L-Leu-Gly)$_4$OH. In the usual way, 1.063 g (2.25 mmol) of H(Gly-L-Leu-Gly)$_2$OH was suspended in 25 ml of DMSO containing 1.695 g of 2-[Z(Gly-L-Leu-Gly)$_2$O]-*N*-ethylbenzamide. After 48 hr of stirring, the clear solution was concentrated *in vacuo* and the residual oil was triturated with 10 × 15 ml of Et_2O which was discarded. The resulting powder was collected, washed with water and ether, and dried, wt 2.36 g (98.5%), mp 247.5–250°; for analysis the substance was dissolved in 1 *N* $NaHCO_3$, filtered, acidified, collected, and washed with water and EtOAc, mp 244°, $[\alpha]D$ −33.6° (c 1.0, HOAc). *Anal.* Calcd for $C_{48}H_{76}N_{12}O_{15} \cdot 0.5H_2O$: C, 53.86; H, 7.27; N, 15.71. Found: C, 53.96; H, 7.40; N, 15.33.

H(Gly-L-Leu-Gly)$_4$OH·HBr. A solution of 0.192 g of Z(Gly-L-Leu-Gly)$_4$OH in 10 ml of HOAc, saturated with HBr, was allowed to stand at 22° for 45 min and then treated with ether. The resulting gummy solid was washed with ether and recrystallized from methanol–ether to yield 0.479 g (98%) of product. Recrystallization gave mp 174°, $[\alpha]^{22}D$ −17.3° (c 0.7, MeOH). *Anal.* Calcd for $C_{40}H_{71}N_{12}BrO_{13} \cdot 1.5H_2O$: C, 46.40; H, 7.22; N, 16.24; Br, 7.73. Found: C, 46.39; H, 7.33; N, 15.79; Br, 8.21.

2-[Z(Gly-L-Leu-Gly)$_4$O]-*N*-ethylbenzamide. A 0.273-g (0.26 mmol) sample of Z(Gly-L-Leu-Gly)$_4$OH was dissolved in 0.25 ml of 1 *N* NaOH, 0.5 ml of pyridine, and 10 ml of water, and 15 ml EtOAc was added, followed by 85.2 mg (0.36 mmol) of 2-ethylbenzisoxazolium fluoroborate at 0° with stirring. A gel formed almost immediately which was stirred for 1 hr at 22°, filtered, and washed with EtOAc, 2 ml of 1 *N* HCl, water, 0.5 *N* $NaHCO_3$, EtOAc, and water. Drying yielded 0.25 g (81%), mp 236–238° dec. For analysis, the substance was precipitated several times from DMF with ether, mp 238–240°, $[\alpha]D$ −32.0° (c 0.9, HOAc). *Anal.* Calcd for $C_{57}H_{85}N_{13}O_{16} \cdot H_2O$: C, 55.81; H, 7.16; N, 14.85. Found: C, 55.81; H, 7.16; N, 14.45.

Z(Gly-L-Leu-Gly)$_8$OH. To the suspension obtained from 0.310 g (0.25 mmol) of the above HBr salt and 31 mg (0.30 mmol) of triethylamine in 8 ml of DMSO was added 2-[Z(Gly-L-Leu-Gly)$_4$O]-*N*-ethylbenzamide, 0.372 g (0.30 mmol). After 9 days at 22°, the mixture was triturated with ether, and the resulting solid was collected, washed with water, 1 *N* HCl, water, and EtOAc, and then dried to yield 0.496 g (82%). For analysis, the product was precipitated with ether from hexafluoroisopropyl alcohol, mp >250°, $[\alpha]D$ −40° (c 0.1, formic acid) or −55.9° (c 0.15, dichloroacetic acid). *Anal.* Calcd for $C_{88}H_{144}N_{24}O_{27} \cdot 3H_2O$: C, 52.20; H, 7.48; N, 16.61. Found: C, 52.33; H. 7.37; N, 16.54.

H(Gly-L-Leu-Gly)$_8$OH·HBr. The procedure given for the dodecapeptide hydrobromide was followed. Recrystallization from methanol–ether yielded an analytical sample, $[\alpha]D$ −32.1° (c 0.3, HOAc). *Anal.* Calcd for $C_{80}H_{139}N_{24}O_{25}Br \cdot 2H_2O$: C, 49.19; H, 7.39; N, 17.21; Br, 4.09. Found: C, 49.11; H, 7.68; N, 16.68; Br, 4.27.

2-[Z(Gly-L-Leu-Gly)$_8$O]-*N*-ethylbenzamide. To a solution of 57.0 mg (0.05 mmol) of Z(Gly-L-Leu-Gly)$_8$OH in 6 ml of water, 3 ml of acetonitrile, 0.03 ml of 1 *N* NaOH, and 1.5 ml of pyridine was added 15.3 mg of 2-ethylbenzisoxazolium fluoroborate. A gel formed, 15 ml of EtOAc was added, and the slurry was stirred for 30 min, whereupon 6 ml of 1 *N* HCl was added and the mixture was filtered. Washing of the solid with water, EtOAc, and ether followed by drying yielded 37.5 mg (61%) of ester. Using isoxazolium salt, tritiated in the 5 and 7 positions, 5.9×10^{-3} μCi/mmol, ester with specific activity 6.5×10^{-3} μCi/mmol was obtained. For analysis, the ester was triturated in boiling acetonitrile and then precipitated with ether from hexafluoroisopropyl alcohol, $[\alpha]D$ −63.5° (c 0.69, dichloroacetic acid). *Anal.* Calcd for $C_{97}H_{153}N_{25}O_{28}$·

Table III
Properties of Peptide Derivatives

A. Free Peptides

Registry no.	Peptide[a]	Preparation	Yield, %	[α]D, deg		C	H	N
51876-87-0	1. Ala (γOBz)-Glu-Phe	BOC derivative + TFA Crystallized from MeOH–H_2O	80	+18.2 (c 0.8, HOAc)				
						$C_{24}H_{29}N_3O_6$		
					Calcd	63.28	6.42	9.22
					Found	63.04	6.45	8.92
837-83-2	2. Gly-Pro-Ala	*Z* derivative + H_2/Pd	78	−181 (*c* 0.1, H_2O) Lit.[8] −177				

B. 2-Acyloxy-*N*-ethylbenzamide Esters

Registry no.	Acid	Purification	Yield, %	Mp, °C	[α]D, deg		C	H	N
51933-26-7	1. Boc-Ala(γOBz)-Glu-Phe	$CHCl_3$–hexane	87	97–98	−39 (*c* 0.6, HOAc)				
							$C_{38}H_{46}N_4O_9$		
						Calcd	64.93	6.60	7.97
						Found	64.83	6.50	7.78
51876-88-1	2. Boc-(Ala(γOBz)-Glu-Phe)$_2$	CH_3CN	64		−30.4 (*c* 0.3, HOAc)				
							$C_{62}H_{73}N_7O_{14}\cdot H_2O$		
						Calcd	64.28	6.54	8.47
						Found	64.11	6.44	8.39
52022-29-4	3. Z-Gly-Pro-Ala	CH_2Cl_2–petroleum ether	98	105–106	−102 (*c* 1, HOAc)				
							$C_{27}H_{34}N_4O_7$		
						Calcd	61.82	6.15	10.68
						Found	61.66	6.01	10.85
51876-89-2	4. Z-Pro-Ala	EtOAc	90	130–133	−119 (*c* 0.5, HOAc)				
							$C_{25}H_{29}N_3O_6$		
						Calcd	64.22	6.01	8.80

C. Peptide Acids and Esters

Registry no.	Product	Preparation	Yield, %	Mp, °C	[α]D, deg	Purification		C	H	N
51876-90-5	1.- Boc-Ala-(γOBz)Glu-PheOH	From Boc-Ala-(γOBz)Glu + Phe, method of ref 5	64	88–90	−11 (*c* 1, HOAc)	MeOH–water				
							$C_{29}H_{37}N_3O_8$			
							Calcd	62.69	6.71	7.56
							Found	62.19	6.69	7.42
51876-91-6	2. Boc(Ala-(γ-OBz)Glu-Phe)$_2$OH	Method of this paper	90 (crude)		−21 (*c* 1.5, HOAc)	Gel from MeOH				
							$C_{53}H_{64}N_6O_{13}\cdot 0.5H_2O$			
							Calcd	63.49	6.62	8.38
							Found	63.40	6.61	8.43
5891-41-8	3. Z-Gly-Pro-AlaOH	Z-Gly + Pro-Ala method of ref 5	88	147–149	−117 (−120) (*c* 1, MeOH)	EtOH–petroleum ether				
51876-92-7	4. Z-Ala-Gly-Pro-AlaOH	Method of this paper Z-Ala + Gly-Pro-Ala	48		−86.7 (3.2, HOAc)	EtOAc–ether				
							$C_{21}H_{28}N_4O_7\cdot 1.5H_2O$			
							Calcd	53.03	6.58	11.78
							Found	53.43	6.18	11.74
51876-93-8	5. Z-Pro-Ala-Gly-Pro-AlaOH	Method of this paper Z-Pro-Ala + Gly-Pro-Ala	92	166–170, 190	−133 (*c* 0.9, HOAc)	CH_3CN				
							$C_{26}H_{35}N_5O_8\cdot 0.5H_2O$			
							Calcd	56.30	6.55	12.63
							Found	56.31	6.31	12.53
51876-94-9	6. Z-Pro-Ala-Gly-OEt	See text	87	148–149	−95.4 (*c* 1, HOAc)	EtOAc–petroleum ether				
							$C_{20}H_{27}N_3O_6$			
							Calcd	59.24	6.72	10.36
							Found	59.25	6.60	10.31
51876-95-0	7. Z-Gly-Pro-Ala-Gly-OEt	See text	70	143–145	−98.4 (*c* 0.7, HOAc)	EtOAc–petroleum ether				
							$C_{22}H_{30}N_4O_7$			
							Calcd	57.12	6.55	12.12
							Found	57.21	6.36	12.08

[a] All amino acids have the L configuration.

H_2O: C, 54.55; H, 7.33; N, 16.40. Found: C, 53.91; H, 7.33; N, 16.40.

Z(Gly-L-Leu-Gly)$_{16}$OH. A suspension of 21.0 mg (9.8 μmol, of the above ester and 19.8 mg (9.6 μmol) of H(Gly-L-Leu-Gly)$_8$OH·HBr in 0.25 ml of DMSO containing 1.05 mg (10 μmol) of triethylamine was stirred for 24 hr, at which point a gel formed and a further 0.1 ml of solvent was added. After 8 days, the mixture was triturated with water, and the gel was collected, washed with water and ethyl acetate, and dried to yield 21.6 mg (57%). This extremely insoluble substance was triturated in a mortar with ether and dried *in vacuo*. *Anal.* Calcd for $C_{168}H_{280}N_{48}O_{51}\cdot 10H_2O$: C, 50.83; H, 7.63; N, 16.94. Found: C, 51.17; H, 7.84; N, 16.55.

Determination of Solubility and Yield by Isotopic Dilution. Example. A weighed sample of [1-^{14}C]-Gly-L-Leu-Gly, 0.74 μCi/mmol, was suspended in 2 ml of solvent in a sealed ampoule in a 30° bath. At 30-hr intervals, samples were filtered and aliquots of the filtrate were counted. In DMF, after 27, 41, and 75 hr, 455, 400, and 451 dpm/ml were observed corresponding to 6.8, 6.0, and 6.7 mg/ml.

Yields by isotopic dilution were determined by adding labeled product to the initial reaction mixture and recrystallizing the recovered product to constant activity.

Other Peptide Derivatives. Table III reports properties for other peptides prepared in this study. Detailed experimental procedures may be found in Z. Bernstein, Ph.D. Dissertation, Massachusetts Institute of Technology, 1971.

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Registry No.—Z-Gly-L-Leu-GlyOH, 16295-38-8; L-leucine, 61-90-5; 3-carbobenzoxyglycyloxy-2-hydroxy-*N*-ethylbenzamide, 16859-24-8; Z-Gly-L-LeuOH, 1421-69-8; 3-carbobenzoxyglycylleucyloxy-2-hydroxy-*N*-ethylbenzamide, 51876-76-7; glycine, 56-40-6; HGly-L-Leu-GlyOH, 2576-67-2; 2-(Z-Gly-L-Leu-Gly)-*N*-ethylsalicylamide, 51876-77-8; $Z(Gly\text{-}L\text{-}Leu\text{-}Gly)_2OH$, 51876-78-9; $H(Gly\text{-}L\text{-}Leu\text{-}Gly)_2OH$, 2576-71-8; 2-[$Z(Gly\text{-}L\text{-}Leu\text{-}Gly)_2O$]-*N*-ethylbenzamide, 51876-79-0; $Z(Gly\text{-}L\text{-}Leu\text{-}Gly)_4OH$, 51876-80-3; $H(Gly\text{-}L\text{-}Leu\text{-}Gly)_4OH\cdot HBr$, 51876-81-4; 2-[$Z(Gly\text{-}L\text{-}Leu\text{-}Gly)_4O$]-*N*-ethylbenzamide, 51876-82-5; $Z(Gly\text{-}L\text{-}Leu\text{-}Gly)_8OH$, 51876-83-6; $H(Gly\text{-}L\text{-}Leu\text{-}Gly)_8OH\cdot HBr$, 51876-84-7; 2-[$Z(Gly\text{-}L\text{-}Leu\text{-}Gly)_8O$]-*N*-ethylbenzamide, 51876-85-8; $Z(Gly\text{-}L\text{-}Leu\text{-}Gly)_{16}OH$, 51876-86-9; TFA, 76-05-1.

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Photobenzidine Rearrangements. V. Mechanistic Aspects. Rearrangement of Mixtures of Different *N,N'*-Dimethylhydrazo Aromatics, and the Nature of the Excited State[1-3]

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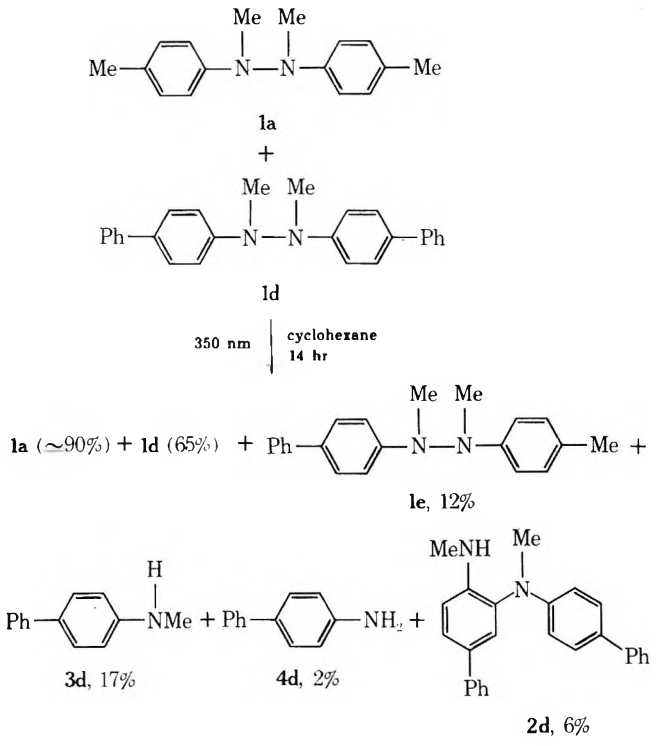
Quantum yields of rearrangement of *N,N'*-dimethyl-*p*-hydrazotoluene (**1a**) to the o-semidine (**2a**) under irradiation in cyclohexane solution at 298 nm were unaffected by the triplet quencher, 1,3-cyclohexadiene. None of **2a** could be detected in the products of irradiation at 335 ± 2.5 nm in the presence of the triplet sensitizer, xanthone. The rearrangement appears to occur in the singlet excited state. Irradiation of a mixture of **1a** and *N,N'*-dimethyl-*p*-hydrazobiphenyl (**1d**) at 350 nm led to the formation of a new hydrazo compound, 4-phenyl-*N,N',4'*-trimethylhydrazobenzene (**1e**). Irradiation of a mixture of *N,N'*-dimethyl-*p*-hydrazoanisole (**1b**) and *N,N'*-dimethylhydrazomesitylene (**1c**) at 300 nm also gave a new hydrazo compound, *N,N'*-2,4,6-pentamethyl-4'-methoxyhydrazobenzene (**1f**). Irradiation of **1f** at 300 nm led to the formation of **1b** and **1c**. Crossed rearrangement products (*i.e.*, crossed semidines) were not found. It is proposed that although radicals are probably involved in the formation of scission products (*N*-methylarylamines), the formation of o-semidines may be intramolecular, and the formation of new hydrazo compounds may involve biomolecular, four-center reactions.

In contrast with acid-catalyzed and thermal reactions of hydrazo aromatics,[4,5] little is known about photochemical ones. The few studies that have been made show that hydrazobenzene and ring-substituted hydrazobenzenes are dehydrogenated by irradiation in solution,[6-8] whereas *N,N'*-dimethylhydrazobenzenes rearrange.[6,9] No mechanistic details are known about these rearrangements, however, and the present paper describes our attempts to obtain some understanding of them. We have tried to find if the photochemical rearrangements are intra- or intermolecular and, also, whether they occur in the singlet or triplet excited state. For the former purpose we have carried out rearrangements of mixtures of hydrazo compounds and of one unsymmetrical hydrazo compound and have searched for "crossover" rearrangement products. For the latter purpose we have measured the fluorescence and phosphorescence characteristics of several of the hydrazo compounds, to establish singlet and triplet state characteristics, and have made quantum yield measurements for rearrangement of a representative compound, *N,N'*-dimethyl-*p*-hydrazotoluene (**1a**) in the absence and presence of triplet quenchers.

Results

Irradiation of Mixtures of Hydrazo Aromatics. A. *N,N'*-Dimethyl-*p*-hydrazotoluene (1a) and *N,N'*-Dimethyl-*p*-hydrazobiphenyl (1d). Although **1a** rearranges slowly when irradiated at 300 nm (19% yield after 10 hr),[9] it did not rearrange after 14 hr of irradiation at 350 nm in cyclohexane solution. On the other hand, **1d** rearranged quite readily under the latter conditions. When a mixture of **1a** and **1d** was irradiated in cyclohexane solution at 350 nm for 14 hr at room temperature, almost 90% of the **1a** and 65% of the **1d** were recovered. Rearrangement of **1d** to the o-semidine (**2d**) and scission to *N*-methyl-4-aminobiphenyl (**3d**) and 4-aminobiphenyl (**4d**) occurred also. At the same time a new hydrazo aromatic (**1e**) was formed, too (Scheme I).

Scheme I



Scheme II

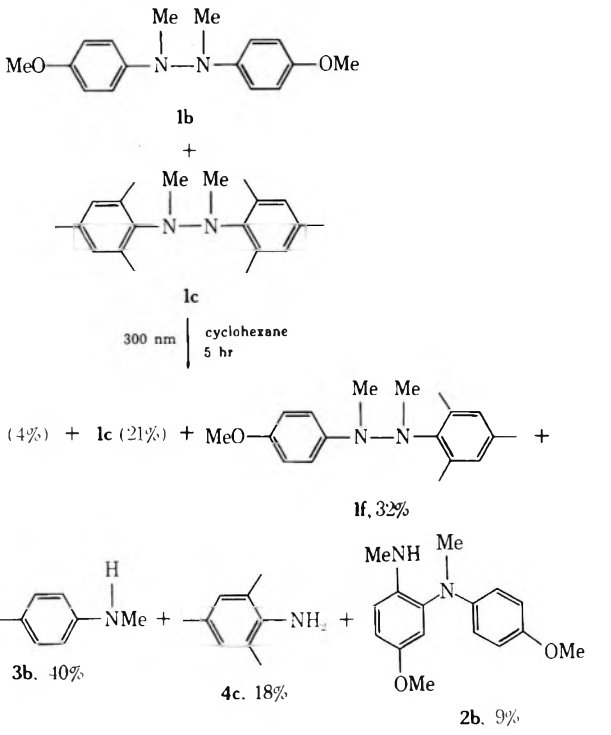
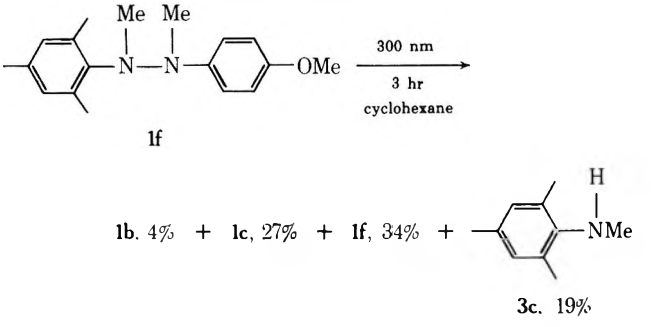


Table I
Quantum Yields of Formation of 2a from 1a in the Presence and Absence of 1,3-Cyclohexadiene (Q)

$[Q] \times 10^2 M$	$[1a]_0 \times 10^2 M$	$\Phi \times 10^3$	Φ_0/Φ
0	1.5	5.98[a]	
4.66	1.5	5.33[a]	1.12
8.24	1.5	6.18[a]	0.97
9.15	1.5	4.56[a]	1.31
0	2.0	39.6[b]	
2.65	2.0	38.0[b]	1.04

[a] Photolysates were separated by Eastman Chromagram sheet 6060, silica gel with fluorescent indicator, and the *o*-semidine was removed with cyclohexane (spectrograde). Work-up conditions were standardized. [b] Photolysates were separated by tlc on Brinkmann GF-254 silica gel and the *o*-semidine was removed with chloroform.

Scheme III



Authentic **1e** was synthesized, compound **2d** is known from our earlier work,[9] and **3d** and **4d** were suitably identified.

B. *N*-*N*′-Dimethyl-*p*-hydrazoanisole (1b) and *N*,*N*′-Dimethylhydrazomesitylene (1c). When **1b** is irradiated it rearranges to the *o*-semidine (**2b**), while irradiation of **1c** causes scission to *N*-methylmesitylamine (**3c**) and mesitylamine (**4c**).[9] When a mixture of **1b** and **1c** in cyclohexane solution was irradiated at 300 nm for 5 hr at room temperature 4% of the **1b** and 21% of the **1c** were recovered. The *o*-semidine (**2b**), a new hydrazo compound (**1f**), and a number of scission amines were also obtained (Scheme II). Compound **1f** was synthesized for comparison with the compound isolated from this experiment, and for irradiation in solution by itself. All of the other products were known and suitably identified.

Irradiation of *N*,*N*′,2,4,6-Pentamethyl-4′-methoxyhydrazobenzene (1f). Irradiation in cyclohexane solution at 300 nm for 3 hr at 19° gave **1b** (4%), **1c** (27%), **1f** (recovered, 34%), and scission amine **3c** (19%) (Scheme III). *N*-Methyl-*p*-anisidine (**3b**) was not observed in this experiment.

Luminescence and Quenching Experiments. From fluorescence and phosphorescence data the singlet (E_{S_1}) and triplet (E_T) energies of several of the *N*,*N*′-dimethylhydrazo aromatics were calculated. They were found to be in the range 81–88 and 57–66 kcal/mol, respectively (see Experimental Section). One compound, *N*,*N*′-dimethyl-*p*-hydrazotoluene (**1a**), was chosen for detailed quantum yield work. It was found that the quantum yield of formation of the *o*-semidine (**2a**) was not affected by the presence of the triplet-state quencher 1,3-cyclohexadiene. Ratios of Φ_0/Φ were close to 1 for four different concentrations of quencher (Table I). No **2a** was formed when a solution of **1a** and xanthone (E_T = 74 kcal/mol) was irradiated at 335 ± 2.5 nm.

Discussion

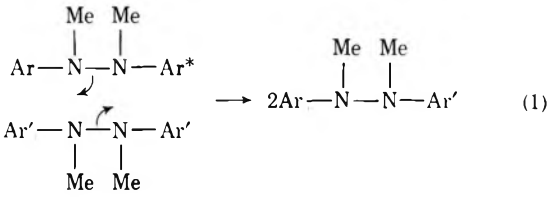
The luminescence and quenching results (Table I) indicate that the rearrangement of **1a** to **2a** occurs in the singlet excited state or from singlet-state precursors rather than the triplet state. This would place then the rearrangement of **1a** among some other photoreactions of hydrazo and azo compounds. That is, the photodehydrogenation of hydrazobenzenes to azobenzenes[6-8] appears to be a singlet-

state reaction.[8] The photodecomposition of 1,4-diaryl-1,4-dimethyl-2-tetrazenes to *N,N'*-dimethylhydrazoarenes also appears to be a singlet-state reaction,[10] and the role of singlet states in the photodecomposition of azo compounds has recently been summarized and discussed by Engel and Bartlett.[11]

Mechanistic details of the photorearrangement are not yet clear. It is probable that *N*-methylarylamino radicals are formed because *N*-methylarylamines are among the photoproducts. It is not known, though, that it is recombination of these radicals which leads to rearrangement products. Irradiation of a mixture of **1b** and **1c** did not lead to a "crossed" rearrangement product. The *o*-semidine **2b** was obtained, but although **1c** itself cannot rearrange (*i.e.*, there is no analog, **2c**), no rearrangement product corresponding to half of each of **1b** and **1c** was found, although if one had been formed in small amount it could have gone unnoticed. Instead, a new hydrazo compound (**1f**) was formed (Scheme II).

Most interestingly, when a mixture of **1a** and **1d** was irradiated under conditions in which **1d** absorbed over 97% of the incident light, another new hydrazo compound (**1e**) was obtained. Again, a crossed rearrangement product was not found, but, again, may have escaped our finding.

These results suggest that the new hydrazo compounds may be formed by a nonradical route. Collision of an excited hydrazo molecule with another hydrazo molecule could, through a four-center process, lead in principle to a molecule of a new hydrazo compound (eq 1). Such a process, if it



(1)

occurs, would not appear to involve energy transfer also. None of the rearrangement or scission products, for example, of **1a** was found, whereas those of **1d** (**2d** and **3d**) were. That is, excited **1a** does not seem to have been formed. Under appropriate irradiation conditions **1a** will, of course, rearrange readily.[9]

In line with the formation of a new hydrazo compound from each of the two mixture experiments is the formation of two symmetrical hydrazo compounds (**1b** and **1c**) from an unsymmetrical one (**1f**). *o*-Semidines were again not found, suggesting once more that the hydrazo-forming reaction may be a four-center one, *i.e.*, the reverse of eq 1. The yields of **1b** and **1c** were unequal (4 and 27%), but this may have been caused by the difficult separation and isolation problems encountered.

The overall picture emerging from these photoreactions is that *N,N'*-dialkylhydrazobenzenes rearrange (in contrast with the unalkylated parents) and probably intramolecularly, but this is as yet by no means certain.

Experimental Section

Hydrazo compounds **1a–d** were described earlier.[9]

4-Methyl-4'-phenylazobenzene (5e). A mixture of 5.7 g (47.1 mmol) of *p*-nitrosotoluene[12] and 8 g (47.3 mmol) of 4-aminobiphenyl in 40 ml of ethanol and 10 ml of acetic acid was boiled for 30 min. On cooling, 7.0 g (54%) of **5e**, mp 138–141°, crystallized. Recrystallization from ethanol gave mp 144.5–145°.

Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.8; H, 5.92; N, 10.3. Found: C, 83.7; H, 6.21; N, 10.4.

4-Methyl-4'-phenylhydrazobenzene (6e). A suspension of 5 g (18.3 mmol) of **5e** in a mixture of 50 ml of pyridine, 15 ml of acetic acid, and a small amount of acetone was kept on an ice bath. Small amounts of zinc powder were added until the solution was colorless. The filtrate was poured into 400 ml of ice water and the precipitate obtained was dried under vacuum, giving 4.7 g (17.2 mmol, 94%) of 4-methyl-4'-phenylhydrazobenzene (**6e**): mp 105–106° dec; nmr (CCl_4) δ 2.18 (s, 3), 5.17 (s, 1), 5.25 (s, 1), 6.35, 6.58, and 6.75 (3 d, 6), 7.15 (m, 7).

4-Phenyl-*N,N',4'*-trimethylhydrazobenzene (1e). To a cold solution of 4.5 g of **6e** in 80 ml of dry THF was added 8 ml of *n*-butyllithium solution (commercial, 90% in hydrocarbon). The red solution was stirred until hydrogen evolution ceased, and 10 ml of methyl iodide was added dropwise. After stirring for a further 45 min, 100 ml of ether was added, and the solution was washed with 3 × 100 ml of water, dried over K_2CO_3, and evaporated to give 6.7 g of yellow oil. This was crystallized from *n*-hexane containing a very small amount of ether to give 4.2 g (85%) of **1e**: mp 52–54°; nmr (CCl_4) δ 2.17 (s, 3), 2.83 (s, 6), 6.46 and 6.75 (2 d, 6), 7.11 (m, 7).

Anal. Calcd for $C_{21}H_{22}N_2$: C, 83.4; H, 7.33; N, 9.26. Found: C, 83.6; H, 7.37; N, 9.45.

***N,N',2,4,6*-Pentamethyl-4'-methoxyhydrazobenzene (1f).** This was prepared by methylation of the azo compound (**5f**). 4-Methoxyphenylhydroxylamine (**7**), mp 86–94°, was prepared by the reduction of *p*-nitroanisole with zinc and NH_4Cl.[13] Oxidation of **7** with aqueous ferric chloride gave *p*-nitrosoanisole (**8**) as a green oil (lit. mp 23°). A solution of 4.8 g (35 mmol) of **8** and 5.0 g (37 mmol) of mesidine (**4c**) in a mixture of 50 ml of ethanol and 35 ml of acetic acid was boiled for 1 hr and stirred at room temperature for 2 hr. The ethanol was removed under reduced pressure, ether was added, and the solution was washed with 2 × 100 ml of saturated $NaHCO_3$ and 3 × 100 ml of 10% HCl, dried over $MgSO_4$, and evaporated to give 6.9 g of brown oil. Chromatography on a silica gel column using 95:5 petroleum ether–ether gave 3.4 g (38%) of 4-methoxy-2',4',6'-trimethylazobenzene (**5f**): mp 65–66° (methanol); nmr (CCl_4) δ 2.30, 2.40 (2 s, 9), 3.82 (s, 3), 6.92, 6.97 (m, 4), 7.93 (d, 2).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.6; H, 7.13; N, 11.0. Found: C, 75.3; H, 7.18; N, 11.3.

A solution of 5.06 g (19.8 mmol) of **5f** in dry THF was stirred under nitrogen with 1.2 g (43.5 mmol) of sodium for 23 hr, and 13 ml of methyl iodide was added dropwise at 0°. After stirring at room temperature for 4 hr the solution was filtered and evaporated to give a residue which was extracted by trituration with ether. The ether solution was evaporated and the orange-yellow solid was crystallized from ether–methanol, giving 3 g (10.5 mmol, 53%) of **1f**: mp 110–111°; nmr (CCl_4) δ 2.18, 2.20 (2 s, 9), 2.83, 2.88 (2 s, 6), 3.70 (s, 3), 6.75 (m, 6).

Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.1; H, 8.51; N, 9.85. Found: C, 76.2; H, 8.27; N, 10.0.

Irradiation Equipment and Method. Irradiations were carried out with a Rayonet reactor "Merry-Go-Round" Model Type RS. The top opening of the reactor was connected to the output of an air conditioner by flexible conduit so that the whole of the inside of the reactor could be flushed continuously with cold air. In this way an ambient temperature of 15–25° was maintained. Irradiation at 300 and 350 nm means that banks of 300- and 350-nm lamps were used. Solutions for irradiation were degassed by three cycles of freeze–thaw technique and were sealed before being placed in the reactor. Silica vessels were used for 300-nm and Pyrex vessels were used for 350-nm irradiations. Cyclohexane solvent was from Eastman Kodak, spectrograde, and was used without further treatment.

Irradiation of *N,N'*-Dimethyl-*p*-hydrazotoluene (1a), *N,N'*-Dimethyl-*p*-hydrazobiphenyl (1d), and a Mixture of 1a and 1d. Control Experiments. Three tubes were used. One contained 240 mg (1.0 mmol) of **1a** in 150 ml of cyclohexane. The second contained 364 mg (1.0 mmol) of **1d** in 150 ml of cyclohexane. The third contained a mixture of 48 mg (0.20 mmol) of **1a** and 73 mg (0.20 mmol) of **1d** in 30 ml of cyclohexane, and was wrapped in aluminum foil to prevent access of light. The purpose of wrapping was to test the stability of the mixture to the reactor environment. The three tubes were irradiated with 350-nm lamps for 14 hr, opened, and examined by tlc on Eastman Kodak Chromagram sheets 6060 silica gel, using as solvent a mixture of 55 ml of *n*-hexane, 10 ml of benzene, 5 drops of ethanol, and 10 drops of acetone. The solution from **1a** showed only one spot corresponding to **1a**. However, column chromatography on alumina (Fisher, 80–200 mesh) gave 207 mg (86%) of **1a** and 23 mg (9.6%) of *N*-methyl-*p*-toluidine (**3a**). The solution from **1d** showed four spots corresponding to **1d**, the o-semidine (**2d**), *N*-methyl-4-aminobiphenyl (**3d**), and 4-aminobiphenyl (**4d**). The solution containing **1a** and **1d**

showed spots of **1a** and **1d** only. Column chromatography gave quantitative separation and recovery of the two components. No scission or rearrangement products were observed.

Irradiation of a Mixture of 1a and 1d. A solution of 311 mg (1.29 mmol) of **1a** and 365 mg (1.0 mmol) of **1d** in 150 ml of cyclohexane was irradiated at 350 nm for 14 hr. Evaporation of the solvent and trituration of the solid residue with *n*-hexane left 176 mg (48%) of **1d.** The hexane solution was chromatographed on an alumina column, using petroleum ether, mixtures of petroleum ether–ether, and finally ether as the eluent. A total of 66 75-ml fractions was collected. Fractions 1–26 (petroleum ether) gave 313 mg (100%) of crude **1a,** from which by trituration with cold ethanol was obtained 227 mg (73%) of **1a,** mp 64.5–65.5°, mmp with **1a** 64.5–66.5°. Fractions 27–37 (95:5 petroleum ether–ether) gave 38 mg (12.5%) of a yellow oil whose nmr and mass spectrum (parent peak *m/e* 302) corresponded with those of **1e.** Crystallization gave mp 48.5–50.5° (ethanol). Fractions 38–41 (90:10) gave 5.2 mg of a three-component mixture which was discarded. Fractions 42–49 (90:10) gave 77.6 mg of yellow solid from which trituration with ethanol gave 62 mg of **1d,** mp 177–178°. The total recovery of **1d,** therefore, was 65%. Fractions 50–54 (90:10) and 55–66 (85:15) gave 23 mg (6.4%) of the o-semidine **2d,** as shown by tlc, nmr, crystallization to give mp 168–169.5° (ethanol–chloroform), and undepressed mixture melting point with authentic **2d.**[9] Elution of the column with 1 l. of solvent (60:40) gave 61 mg (17%) of **3d** as shown by tlc, nmr, benzenesulfonyl derivative, mp 150–152°, and undepressed mixture melting point.[9] Final wash of the column with 400 ml of ether gave 8.4 mg (2%) of **4d,** as shown by tlc.

Irradiation of *N,N'*,2,4,6-Pentamethyl-4'-methoxyhydrazobenzene (1f). A solution of 500 mg (1.76 mmol) of **1f** in 200 ml of cyclohexane was irradiated at 300 nm for 3 hr at 15–20°. Removal of solvent gave 650 mg of brown solid which was chromatographed on alumina as described above. Fractions 1–3 (petroleum ether) gave 70 mg (27%) of an oil which was crystallized from ethanol to give **1c,** mp 117–118°, mmp with authentic **1c** 117–118°. Fractions 10–12 (95:5) gave a solid from which by trituration with cold methanol was obtained 170 mg (34%) of **1f,** mp and mmp 115–116°. Evaporation of the methanol gave 50 mg (19%) of an oil, shown by nmr and benzenesulfonyl derivative (mp and mmp 117–119°) to be *N*-methylmesitylamine (**3c**). Fractions 18 and 19 (90:10) gave 28 mg of an oily solid, from which trituration with cold methanol gave 10 mg (4.0%) of **1b,** mp 105–106°, mmp with authentic **1b**[9] 104–105.5°. Other fractions gave a total of 160 mg of unidentified oils.

Irradiation of a Mixture of *N,N'*-Dimethyl-*p*-hydrazoanisole (1b) and *N,N'*-Dimethylhydrazomesitylene (1c). A solution of 300 mg (1.09 mmol) of **1b** and 500 mg (1.69 mmol) of **1c** in 450 ml of cyclohexane was irradiated at 300 nm for 5 hr at 15–25°. Chromatography was carried out on a basic alumina (Alcoa F-20) column. Elution with 500 ml of petroleum ether gave 104 mg (21%) of **1c,** mp and mmp 115–116°. Elution with 500 ml of 90:10 petroleum ether–ether mixture gave 200 mg (32%) of **1f,** mp 111–112°, identified by nmr, elemental analysis, and comparison with authentic **1f.** Elution with 500 ml of 85:15 mixture gave 84 mg (18%) of mesitylamine (**4c**), identified by its dibenzenesulfonyl derivative, mp and mmp 178.5–179.5°.[9] Elution with 500 ml of 80:20 mixture gave 44 mg of residue from which trituration with petroleum ether gave 14 mg (4%) of **1b,** identified by nmr, melting point, and mixture melting point (103–104°). Elution with 500 ml of 70:30 mixture gave 24 mg of unidentified oil. Further elution with 500 ml of 70:30 mixture gave 27 mg (9%) of the o-semidine **2b,** identified by nmr.[9] Finally, elution with 500 ml of ether gave 120 mg (40%) of *N*-methyl-*p*-anisidine (**3b**), identified by nmr.

Extinction Coefficients of 1a and 1d. These compounds have similar spectra but quite different absorbancies. For **1a,** at λ_{max} 296 nm, ϵ is 4.7×10^4. Values of ϵ at 5-nm intervals were calculated, and are given as λ ($\epsilon_{(1a)}$, $\epsilon_{(1d)}$): 320 (435, 14,250), 325 (79, 7170), 330 (13, 2590), 335 (3, 732), 340 (2, 198), 345 (~1–2, 54), 350 (~1–2, 17). It was calculated from the lamp output characteristics supplied by Rayonet and the transmission of Pyrex glass that in the irradiation of the mixture of **1a** and **1d** (see above) with a 350-nm lamp 97% of the light between 320 and 350 nm was absorbed by **1d.**

Singlet and Triplet Energies of *N,N'*-Dimethylhydrazo Compounds. Fluorescence spectra of these compounds in cyclohexane and phosphorescence spectra in either ethanol or cyclohexane were taken at 77°K with an Aminco-Bowman spectrophotofluorometer. An estimate of the fluorescence 0–0 band was made from the point of intersection of fluorescence excitation and emission bands. An estimate of the lowest singlet energy (E_{S_1}) was made either from the 0–0 band or as the average of E_a and E_s, where E_a is the energy at the absorption maximum and E_s the energy at the fluorescence emission maximum.[14] An estimate of the triplet energy (E_T) was made from the phosphorescence band. Values of E_{S_1} were, for **1a, 1b, 1c, 1d,** and **1f,** 88, 81, 88, 84, and 85 kcal/mol. Values of E_T were, for **1a, 1b, 1d,** and **1f,** 66, 63, 57, and 64 kcal/mol. The difference between E_{S_1} and E_T for each compound indicates that in each case π–π^* excitation occurred. It is recognized that these methods of measuring excitation energies are not exact. Attempts were made to obtain a high-resolution phosphorescence spectrum of **1a** for the precise calculation of E_T from the 0–0 phosphorescence band, but sufficient resolution could not be obtained.[15] Knowledge of E_T was necessary for planning the triplet quenching experiments. Triplet lifetimes were measured from phosphorescence decays plotted on an *x–y* recorder, and were, for **1a, 1b,** and **1d,** 1.6, 1.2, and 3.7 sec. Phosphorescence of **1c** was too weak for making triplet data measurements.

Triplet Quenching of 1a. Quantum yields for the formation of the o-semidine (**2a**) were measured. Three milliliters of a degassed and sealed solution of **1a,** with or without quencher, in cyclohexane was irradiated at 298 nm for 8 hr at 18–20° in a Bausch and Lomb monochromator. The instrument slits were set for a 10-nm band pass. The solution was evaporated, and the residue was dissolved in 1 ml of cyclohexane and streaked on a silica gel tlc plate. The **2a** band was removed and assayed by uv spectroscopy. Light intensities were measured before and after irradiation by the method of Hatchard and Parker.[16] Results using 1,3-cyclohexadiene (E_T = 54 kcal/mol)[17] as quencher (Q) are given in Table I.

Triplet Sensitization of 1a (Attempted). Monochromatic Irradiation. Four milliliters of a solution which was 1.02×10^{-3} *M* in xanthone (E_T = 74 kcal/mol) and 1.5×10^{-2} *M* in **1a** was degassed, sealed, and irradiated at 335 ± 2.5 nm for 9 hr in a Bausch and Lomb monochromator, Model 33-86-07. The solution was cooled externally by circulating water at 20°. After irradiation the solution was evaporated at room temperature in a rotary evaporator and the residue was taken up in ethanol and spotted on a silica gel sheet (Eastman Chromagram 6060). Development with a mixture of 40 ml of cyclohexane, 15 ml of benzene, and 0.3 ml of acetone, and monitoring with authentic samples, showed the presence of **1a** (R_f 0.46), and *N*-methyl-*p*-toluidine (**3a,** R_f 0.26). No trace of the *o*-semidine)**2a,** R_f 0.43) was seen. An unknown compound, R_f 0.36, λ_{max} (ethanol) 253 and 301 nm, was formed. Compound **2a** has λ_{max} 247 and 303 nm, and **1a** has λ_{max} 253 and 298 nm. Authentic **2a** was added to the product mixture and was readily separated from these three compounds by tlc. Two-directional tlc also failed to show the presence of **2a** in the product mixture.

The absorbance of xanthone at 335 nm is approximately 550 times greater than that of **1a,** so that under the conditions used ample opportunity existed for excitation of xanthone and energy-transfer from excited xanthone to **1a** (E_T = 66 kcal/mol).

Registry No.—**1a,** 30724-66-4; **1b,** 30724-67-5; **1c,** 30788-04-6; **1d,** 30788-03-5; **1e,** 52032-51-6; **1f,** 52032-52-7; **2a,** 30724-68-6; **2b,** 30745-00-7; **2d,** 30724-70-0; **3a,** 623-08-5; **3b,** 5961-59-1; **3c,** 13021-14-2; **3d,** 3365-81-9; **4c,** 88-05-1; **4d,** 92-67-1; **5e,** 30821-46-6; **5f,** 52032-53-8; **6e,** 52032-54-9; **7,** 4546-20-7; **8,** 1516-21-8; *p*-nitrosotoluene, 623-11-0.

References and Notes

(1) Supported by Grant D-028 from the Robert A. Welch Foundation.
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Enamide Photochemistry. Formation of Oxyprotoberberines by the Elimination of Ortho Substituents in 2-Aroyl-1-methylene-1,2,3,4-tetrahydroisoquinolines[1]

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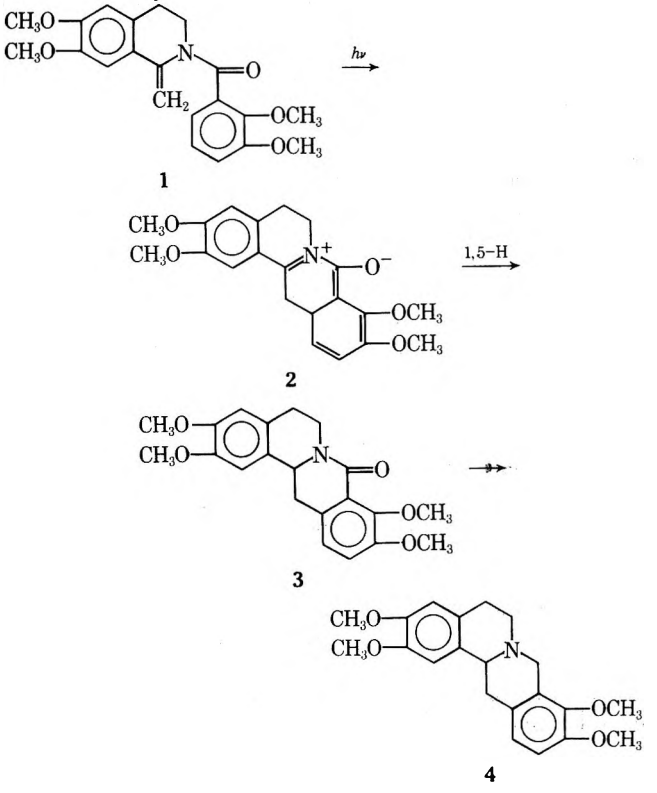
The synthesis of ortho-substituted 2-aroyl-1-methylene or ethylidene enamides was accomplished and their photochemistry investigated. Irradiation of these enamides results in an azatriene–azacyclohexadiene cyclization followed by elimination of an ortho substituent to form oxyprotoberberines in good yield. A wide variety of ortho substituents has been found to be capable of elimination: methoxyl, acetoxyl, nitro, halo, and thiomethyl. Polysubstitution does not seem to affect the reaction, since D-ring substituted oxyprotoberberines can also be formed. The reaction has been extended to form 13-methyloxyprotoberberines. Nonoxidative photocyclization was used to form phenanthridones from 2-methoxybenzanilides, but not all benzanilides react.

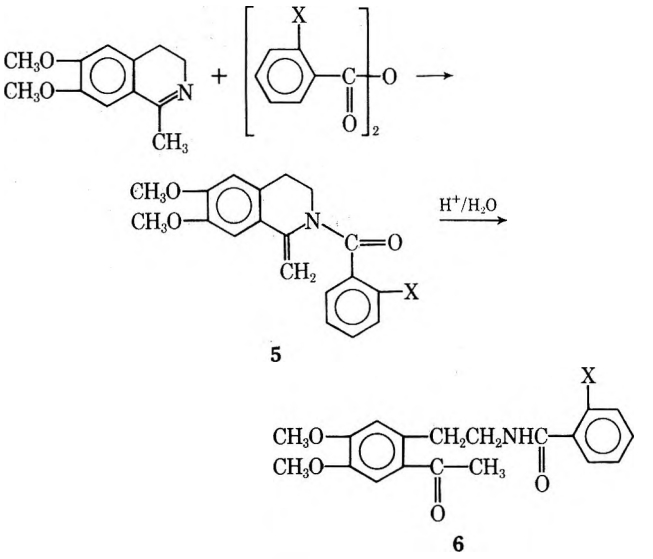
Previous studies on the photochemistry of enamides has shown this chemical grouping to be reactive photochemically and capable of undergoing synthetically useful reactions. Simple enamides undergo a facile [1,3]-acyl shift to give vinylogous amides in high yield.[2] When the enamide has been included as part of an isoquinoline ring system, irradiation has given rise to a variety of isoquinoline alkaloids.[3] Among the alkaloid nuclei synthesized photochemically are dehydroaporphines and aporphines,[4] oxyprotoberberines,[5] protoberberines, and tetrahydroprotoberberines,[6] benzophenanthridines,[7] and 8-oxoberbines.[8] In order to extend the usefulness of enamide photochemistry in the synthesis of isoquinoline alkaloids, the synthesis of 2-aroyl-1-methylene-1,2,3,4-tetrahydroisoquinolines and a study of their photochemistry were undertaken.

Results and Discussion

Based on analogy with the photocyclization and photoacylation reactions of enamides,[5,6] it was postulated that synthesis of enamide **1** and irradiation would lead to an intermediate **2** which would undergo a [1,5]-hydrogen shift to generate the 8-oxoberbine **3**. Reduction of the 8-oxoberbine **3** would then give the tetrahydroprotoberberine alkaloids with the natural oxygenation pattern **4**.[9]

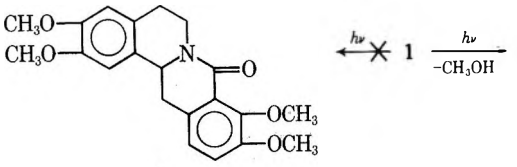


Initial attempts at synthesizing the enamides by a 1-*N*,*N*-diethylaminopropyne coupling reaction of equimolar amounts of acid and imine were unsuccessful, giving only low yields and several by-products. The best method found was to preform the acid anhydride in benzene using the ynamine,[10] adding the dihydroisoquinoline and refluxing. Work-up by aqueous and bicarbonate extraction gave the enamides **5** as nicely crystalline compounds. The enamides **5** are stable in the absence of acid; however the presence of acid causes hydrolysis to the acetylamide **6**.[11] The 1-methylene enamides **5** have two characteristically low-field exomethylene resonances in the nmr. In the eight methylene enamides studied, the first resonance occurs between δ 5.13 and 5.33, and the second between δ 4.54 and 4.80, presumably due to shielding by the aroyl group.



The first enamide studied was the tetramethoxy **1**. Irradiation of **1** in benzene with a medium pressure mercury lamp gave a clean conversion into a single highly fluorescent compound **7**, which was isolated in 85% yield. The compound isolated was not the expected **3**, but rather the oxyprotoberberine **7**. The nmr spectrum of **7** shows the absence of the low-field resonances attributable to the exomethylene protons. There is a low-field resonance at δ 8.02 for an aromatic proton ortho to a carbonyl, as part of a total of six aromatic protons. Most significant was the pres-

ence of only three of the initial four methoxy groups. The mass spectrum confirmed the loss of methanol with a parent peak at *m/e* 337 (97.1%). Other significant peaks were the loss of a methoxyl methyl group [*m/e* 322 (100%)] and a further loss of two hydrogens [*m/e* 320 (18.9%)]. The uv spectrum of **7** was characteristic of oxyprotoberberines.[5] On the basis of the physical evidence, **7** was assigned the 2,3,12-trimethoxy-8-oxyprotoberberine structure indicated.



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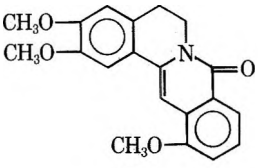

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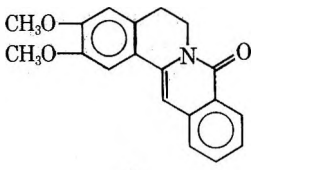
To test the generality of this photoelimination, a series of ortho aroyl-substituted enamides **5** was synthesized and irradiated. The 2-fluoro derivative **5a** (X = F) was irradiated in degassed *tert*-butyl alcohol in a Rayonet photoreactor with 3000 Å lamps to yield 2,3-dimethoxy-8-oxyprotoberberine **8** in 85% yield. The structural elucidation proceeded as for **7**. Additionally, an authentic sample of **8** was prepared by the intramolecular photoacylation of the carbamate **9**.[12] The irradiation of **9**, in ethanol, gave **8** as the major product, in addition to significant amounts of *N*-carbethoxy-6,7-dehydronornuciferine (**10**), and the hydrate **11**.



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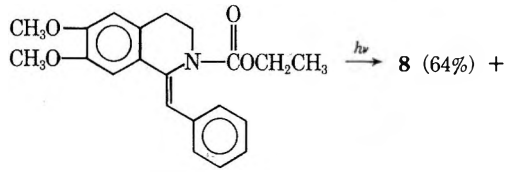

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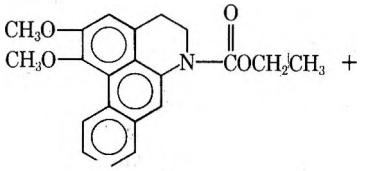

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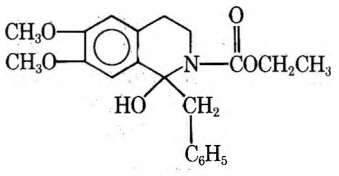


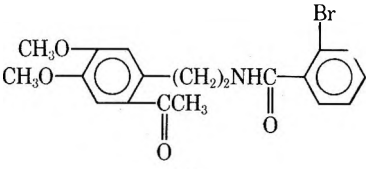
11 (17%)

The results for the enamides studied are collected in Table I. All of the enamides **5a–f** cyclized smoothly to the oxyprotoberberine **8**, without side products, except **5b** and **5c**.[13] In these enamides, photocyclization and elimination generate hydrogen chloride and hydrogen bromide, respectively. These strong mineral acids catalyze the addition of trace amounts of water to the enamide double bond to form the amides **6**. This amide was fully characterized for X = Br, **12**, as this type of compound had previously been prepared in the *N*-acyl series.[11] The amide **12** can exist in the open form **12a** or the closed form **12b**. The ir spectrum shows an acetophenone carbonyl at 1660 cm^{-1} and a secondary amide at 3280, 1640, and 1610 cm^{-1}, while the nmr spectrum shows only a single methyl resonance at δ 2.33. On this basis, the amide is better represented in the open form **12a**. On the other hand, in the double bond hydration of **9**, the ring remains closed in **11** as evidenced by the absence of ketone absorptions other than the carbamate carbonyl (1710 cm^{-1}) in the ir spectrum, and the presence of a hydroxyl absorption at 3340 cm^{-1}. Again, the nmr spectrum showed the presence of only one isomer.

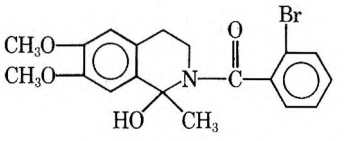
Table I
The Elimination of Ortho Substituents to Form Oxyprotoberberines[a]

Enamide	Product (% yield)	Remarks
1 (49619-28-5)	**7** (85) (52050-41-6)	
5a (X = F) (52050-38-1)	**8** (85) (32255-47-3)	
5b (X = Cl) (49619-29-6)	**8** (50)	
5c (X = Br) (49619-30-9)	**8** (50)	38% **12** (52050-42-7)
5d (X = O_2CCH_3) (49619-27-4)	**8** (76)	
5e (X = SCH_3) (52050-39-2)	8 (55)	
5f (X = NO_2) (49619-31-0)	**8** (17)	20% **5f** recovered
13 (49619-32-1)	**14** (85) (10211-78-6)	
15 (52050-40-5)	**16** (69) (26665-00-9)	

[a] Registry no. are in parentheses beneath compounds.



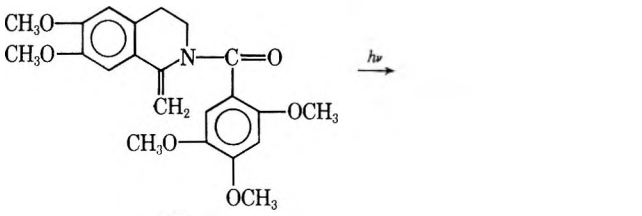
12a



12b

Polymethoxyl substitution was investigated to determine whether photoelimination could be of use in the synthesis of polyoxygenated oxyprotoberberines. The pentamethoxy enamide **13** was synthesized and then irradiated in *tert*-butyl alcohol where it was smoothly converted in 85% yield to the known tetramethoxyoxyprotoberberine **14**.[14] Based on this limited sample (**1** and **13**), it appears that polyfunctionality does not have much of an effect on the reaction nor on its rate compared with monosubstituted enamides.

The presence of a C-13 methyl group is a fairly common feature in the berbine alkaloids.[9] In order to extend the enamide photoelimination to prepare C-13 methyl oxyprotoberberines, it was necessary to synthesize 1-ethylidene enamides. The ethylidene enamide **15** was conveniently



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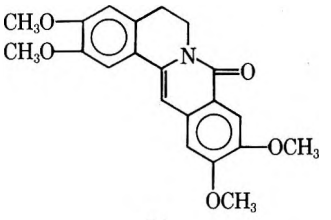

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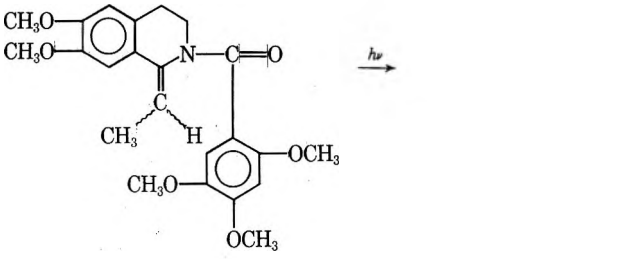
prepared from 1-ethyl-3,4-dihydro-6,7-dimethoxyisoquinoline and the anhydride of arasonic acid. Enamide **15**, as prepared, exists as a mixture of ethylidene isomers, which is indicated by the appearance of two pairs of doublets in the nmr for the ethylidene methyl resonance at δ 1.70 and 1.41 in a ratio of 2:1. Irradiation of this mixture in *tert*-butyl alcohol for 12 hr gave the 13-methyloxyprotoberberine **16** in 69% yield. The oxyprotoberberine **16** showed the



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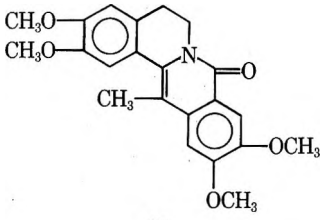

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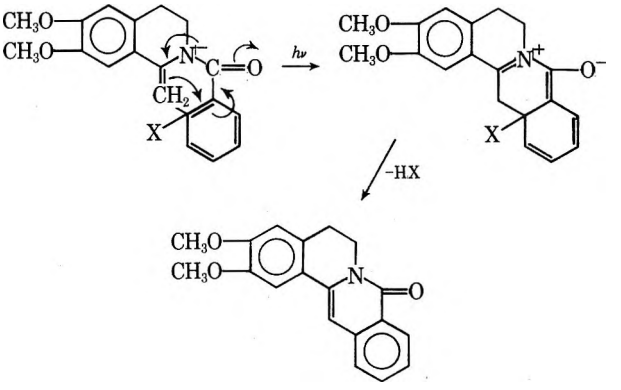
same physical properties as the C-13 unsubstituted compounds and the nmr spectrum showed the C-13 methyl resonance as a singlet at δ 2.64.

A plausible mechanism for the photoelimination reaction of the enamides proceeds from viewing the enamide as an aza analog of a hexatriene. Irradiation then gives the aza analog of a hexatriene–cyclohexadiene interconversion.[15] This is borne out in the enamide photoacylation reactions,[5] protoberberine synthesis,[6] and other nonoxidative cyclizations.[1,7,16] Then irradiation of the aroyl enamides (**4**) would cause the azacyclohexadiene formation at the ortho substituent according to Scheme I. Elimination of HX and electron redistribution generates the oxyprotoberberine. There is not much analogy in the literature for the elimination of ortho substituents in photocyclizations. The loss of halogen[17] and methoxyl[18] groups from diphenyl ethers to form dibenzofurans has been observed. The photolysis of ortho haloaromatic systems has been systematically exploited.[19] The problem arises for the *o*-chloro and o-bromo enamides of whether the photocyclization is as depicted in Scheme I or whether a simple homolysis or heterolysis of the carbon–halogen bond occurs. There is, at present, no way to decide between these alternatives. Photofragmentation is clearly unlikely in the remainder of the cases studied as, for example, with fluorine substitution, the energy of the carbon–fluorine bond is above that available to the molecule from the wavelength of the absorbed light and would be unlikely to fragment.[20] In the other enamides, *e.g.*, **1, 5d, 5e, 13,** photofragmentation would lead to phenoxy or thiophenoxy radicals and reactions characteristic of these, which is clearly not in accord with the observed facts.[21] For these reasons, we prefer the mechanism of cyclization followed by elimination of the elements of HX as outlined in Scheme I. The reaction appears to be very general. All the enamides, where X is a suitable leaving group, photocyclized and aromatized without side products in good to excellent yields.

Scheme I



Several other fully aromatic enamides were studied to see whether the photoelimination would occur in the fully aromatic systems. It is known that photolysis of o-bromo and *o*-iodo anilides gives acceptable yields of phenanthridones.[22] The reaction has been postulated to proceed through a radical mechanism.[23] It was of interest to see whether the reaction could proceed through a cyclized intermediate with elimination of a suitable leaving group. With this in mind, the benzanilide **17** was synthesized and irradiated.[24,25] Irradiation of **17** either at 3000 or 2537 Å gave no detectable phenanthridone **18,** starting material being recovered.[26] Equivalent results were obtained with 2-acetoxybenzanilide **19.**[27] However, when the trimethoxybenzanilide **20** was irradiated, a slow conversion to the phenanthridone **21** took place in 55% yield. The mass spectrum of **21** confirmed the loss of methanol and **21** possesses the typical phenanthridone uv spectrum.[5] The results of the benzanilide irradiations are collected in Table II.

Irradiation of the *N*-methyl derivative **22** also gave a smooth conversion to the *N*-methylphenanthridone **23.** The nmr spectrum of **23** indicated the loss of a methoxyl methyl group. The C-1 and C-10 protons in **23** appear as a low-field multiplet and singlet at δ 8.13 and 7.91, respectively, indicating distortion of the protons from coplanarity. A similar situation exists in phenanthrene.[28] The mass spectrum of **23** indicated the loss of methanol with a parent at *m/e* 269 (100%). The uv spectrum was essentially the same as **21.**

The tetramethoxybenzanilide **24** was also studied and irradiation at 2537 and 3000 Å, as well as acetone sensitization, gave no indication of reaction and **24** was recovered.

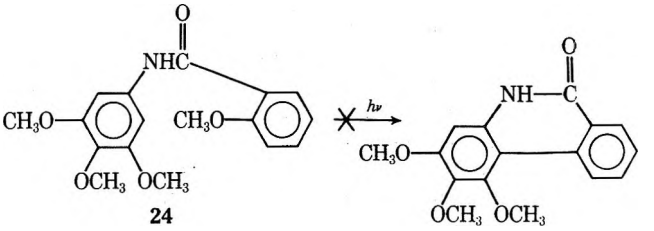


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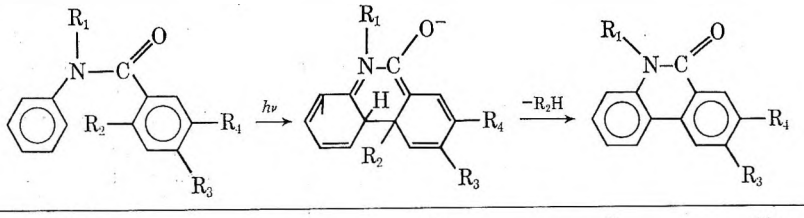
Table II
The Elimination of Ortho Substituents to Form Phenanthridones[a]

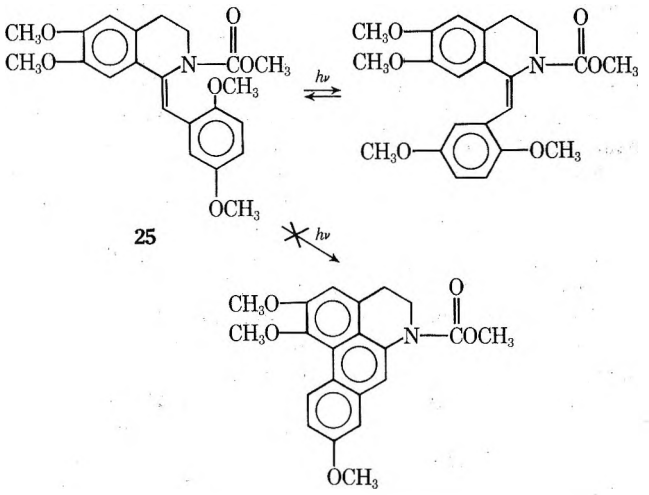


Benzanilide	R_1	R_2	R_3	R_4	Phenanthridone	Yield, %
17 (6833-21-2)	H	OCH_3	H	H	**18**	0
19 (6005-59-0)	H	O_2CCH_3	H	H	**18**	0
20 (50879-52-2)	H	OCH_3	OCH_3	OCH_3	**21** (50879-53-3)	55
22 (52050-43-8)	CH_3	OCH_3	OCH_3	OCH_3	**23** (52050-44-9)	41

[a] Registry no. in parentheses beneath compounds.

From a consideration of the results with the benzanilides, it can be seen that ortho substituents can be eliminated in a nonoxidative cyclization. However, the reaction does not appear to be as general as in the isoquinoline enamides, and no clear trends can be gleaned from this limited sample.

The final system studied was the benzylidene enamide **25**, with the aim of producing dehydroaporphine carbamates **26** under nonoxidative conditions. This had previously been observed to occur with o-chloro, bromo-, and iodo substituents.[4b,c,e,29]



25 **26**

The elimination of ortho substituents in the stilbene–phenanthrene conversion is uncommon but known: chloro, bromo, iodo, methyl, carboxyl, and methoxyl having been reported.[30] It was felt that the combination of the stilbene and enamide systems would offer a greater chance of success for forming dehydroaporphines. However, irradiation of **25** gave only a cis/trans isomeric mixture under varying conditions.[4d]

From a consideration of the above results, it appears that cyclization and elimination in a 6π-electron enamide array can occur. When one of the enamide double bonds is not part of an aromatic system, as in the methyleneisoquinolines, cyclization and elimination is especially facile. However, when both double bonds are aromatic, as in the benzanilides, cyclization and elimination can occur but the reaction is not facile and appears to be dependent on substitution pattern.[30a]

Experimental Section

Melting points were taken on a Thomas-Hoover Uni-melt capillary apparatus and are uncorrected. Infrared spectra were run in KBr unless otherwise noted, and ultraviolet and visible spectra were run in methanol unless otherwise indicated. A Varian Associates A-60, T-60, or HA-100 spectrometer was used to record nmr spectra. All spectra were run in deuteriochloroform with tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were run on either an A.E.I. MS-9 or MS-30. Microanalyses were performed by the Searle Laboratories Microanalytical Department, Mr. E. Zielinski, Director.

3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline.[31] *N*-Acetylhomoveratrylamine (50 g) in refluxing toluene was stirred magnetically, and 40 ml of phosphorus oxychloride was slowly added. After the initial exothermic reaction, the mixture was refluxed a further 0.5 hr and allowed to cool while stirring was continued. Usually 80 g of dihydroisoquinoline salt crystallized. Treatment of 15 g of dihydroisoquinoline salt with aqueous base and chloroform extraction yielded approximately 9 g of free base.

2-(2,3-Dimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (1). 2,3-Dimethoxybenzoic acid (17 g, 0.094 mol) (Aldrich) was suspended in 300 ml of benzene and brought to reflux and 25 ml of solvent removed (Dean-Stark trap). The suspension was cooled to room temperature and 6 g (8 ml, 0.054 mol) of 1-*N*,*N*-diethylaminopropyne (Fluka) was added. The suspension immediately dissolved to give a reddish solution of the benzoic anhydride. Dihydroisoquinoline salt (18 g) was added to 25 g of sodium hydroxide in 500 ml of water, and the resulting solution of free base was extracted with chloroform (2 × 250 ml) and the chloroform extract dried (sodium sulfate). Removal of the chloroform gave approximately 11 g of crystalline free base. The dihydroisoquinoline was taken up in 50 ml of pyridine and added to the anhydride solution in benzene. The resulting mixture was refluxed 1 hr and allowed to stand overnight. The solution was poured into 1 l. of water and washed further with water (2 × 1 l.). The benzene solution was dried with sodium sulfate and evaporated to a syrup. The syrup was dissolved in ether, and stirred magnetically, whereupon 14.5 g (0.039 mol, 73%) of the enamide, **1**, mp 120–122°, crystallized as a white solid: λ_{max} 200 nm (ϵ 37,000), 244 (min, 12,000), 264 (16,000), 306 (7000), 316 (6000); γ_{max} 1650, 1615, 1585, 1520 cm^{-1}; nmr δ 6.61 (m, 5 H), 5.30 (broad s, 1 H), 4.80 (very broad s, 1 H), 4.03 (t, 2 H), 3.88 (s, 3 H), 3.85 (s, 6 H), 3.78 (s, 3 H), 2.92 (t, 2 H).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.95; H, 6.27; N, 3.89.

2-(2-Fluorobenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (5a). *o*-Fluorobenzoic acid (Aldrich), 18.5 g (0.13 mol), 6.8 g of 1-*N*,*N*-diethylaminopropyne (0.06 mol), and 9 g of dihydroisoquinoline treated as above gave 8.1 g (0.021 mol, 41%) of the enamide **5a** as a white crystalline solid: mp 112–115° (ethyl acetate–petroleum ether); λ_{max} 220 nm (ϵ 29,500), 230 (sh, 23,000), 243 (min, 11,000), 262 (17,000), 287 (min, 6000), 304 (7500), 314 (sh, 6000); γ_{max} 1640, 1625, 1520 cm^{-1}; nmr δ 6.96 (s, 1 H), 6.61 (s, 1 H), 7.0–7.5 (m, 4 H), 5.26 (broad s, 1 H), 4.54 (broad s, 1 H), 4.08 (t, 2 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 2.92 (t, 2 H).

Anal. Calcd for $C_{19}H_{18}FNO_3$: C, 69.71; H, 5.54; N, 4.28. Found: C, 69.50; H, 5.65; N, 4.31.

2-(2-Chlorobenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (5b). *o*-Chlorobenzoic acid (Aldrich), 21 g (0.132 mol), 6.8 g (0.061 mol) of 1-*N*,*N*-diethylaminopropyne, and 9 g (0.044 mol) of dihydroisoquinoline were treated as above to yield 6.45 g (0.019 mol, 43%) of enamide **5b** as a white crystalline solid: mp 143–144° (ethyl acetate–ether); λ_{max} 229 nm (sh, ϵ 29,500), 245 (min, 10,000), 265 (14,200), 289.5 (min, 5000), 305 (7000), 317 (sh, 5500); γ_{max} 1650, 1635, 1615, 1605, 1520 cm^{-1}; nmr δ 7.29 (m, 4 H), 6.98 (s, 1 H), 6.63 (s, 1 H), 5.32 (broad s, 1 H), 4.67 (broad s, 1 H), 4.09 (t, 2 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 2.95 (t, 2 H).

Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.37; H, 5.28; N, 4.07. Found: C, 66.66; H, 5.24; N, 3.92.

2-(2-Bromobenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (5c). **5c** was prepared from 26.5 g (0.132 mol) of *o*-bromobenzoic acid, 0.061 mol of 1-*N*,*N*-diethylaminopropyne, and 9 g of (0.044 mol) of dihydroisoquinoline as detailed above. Crystallization from ether gave 11.5 g (0.030 mol, 68%) of the enamide **5c:** mp 146–147°; λ_{max} 220 nm (ϵ 35,000), 230 (sh, 26,000), 245 (min, 11,000), 264 (14,500), 289 (min, 4500), 305 (7000), 315 (sh, 6500); γ_{max} 1650, 1635, 1615, 1520 cm^{-1}; nmr, δ 7.52 (m, 1 H), 7.27 (m, 3 H), 6.97 (s, 1 H), 6.63 (s, 1 H), 5.33 (broad s, 1 H), 4.67 (broad s, 1 H), 4.14 (t, 2 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.95 (t, 2 H).

Anal. Calcd for $C_{19}H_{18}BrNO_3$: C, 58.77; H, 4.67; N, 3.61. Found: C, 58.70; H, 4.65; N, 3.57.

2-(2-Acetoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (5d). **5d** was synthesized from 23.8 g (0.132 mol) of acetylsalicylic acid, 10 g of 1-*N*,*N*-diethylaminopropyne, and 12 g (0.059 mol) of dihydroisoquinoline as detailed above. Crystallization from 150 ml of ether gave 15.7 g (0.043 mol, 73%) of enamide **5d:** mp 108–110°; λ_{max} 220 nm (ϵ 30,000), 231 (sh, 23,000), 244 (min, 11,000), 263 (16,000), 289 (min, 5500), 304 (7000), 314 (sh, 7000); γ_{max} 1770, 1647, 1635 (sh), 1610, 1515 cm^{-1}; nmr δ 7.30 (m, 4 H), 6.97 (s, 1 H), 6.63 (s, 1 H), 5.26 (d, $J \simeq 1.5$ Hz, 1 H), 4.57 (d, $J \simeq 1.5$ Hz, 1 H), 4.12 (t, 2 H), 3.86 (s, 6 H), 2.94 (t, 2 H), 1.72 (s, 3 H).

Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.42; H, 5.84; N, 3.80.

2-(2,4,5-Trimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (13). **13** was synthesized from 2,4,5-trimethoxybenzoic acid (Aldrich), 28 g (0.132 mol), 0.061 mol of 1-*N*,*N*-diethylaminopropyne, and 9 g (0.44 mol) of dihydroisoquinoline as above. Crystallization from ethyl acetate–ether gave 12.7 g (0.032 mol, 73%) of enamide **13:** mp 222–225°; λ_{max} 230 nm (sh, ϵ 31,000), 247 (min, 14,000), 263 (16,500), 284 (min, 9000), 304 (12,500), 316 (sh, 9000); γ_{max} 1630, 1615, 1510 cm^{-1}; nmr, δ 6.97 (s, 1 H), 6.87 (s, 1 H), 6.63 (s, 1 H), 6.37 (s, 1 H), 5.13 (d, $J \simeq 1$ Hz, 1 H), 4.72 (d, $J \simeq 1$ Hz, 1 H), 4.06 (broad s, 2 H), 3.90 (s, 3 H), 3.86 (s, 6 H), 3.64 (s, 3 H), 3.37 (s, 3 H), 3.07 (t, 2 H).

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.05; H, 6.41; N, 3.55.

2-(2-Methylthiobenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (5e). 2-Methylthiobenzoic acid was prepared from *o*-mercaptobenzoic acid (Eastman Kodak) and dimethyl sulfate, according to the literature.[32] The enamide was prepared from 2-methylthiobenzoic acid (16.8 g, 0.10 mol), 5.55 g of 1-*N*,*N*-diethylaminopropyne (0.05 mol), and 9 g (0.044 mol) of dihydroisoquinoline. Work-up as detailed above gave 6.3 g of **5e** (0.018 mol, 41%): mp 117–118°; λ_{max} 220 nm (ϵ 34,000), 242 (min, 14,000), 260 (17,500), 290 (min, 6000), 304 (7500), 314 (sh, 6000); nmr δ 7.22 (m, 4 H), 6.98 (s, 1 H), 6.63 (s, 1 H), 5.27 (d, $J \simeq 1.5$ Hz, 1 H), 4.77 (d, $J \simeq 1.5$ Hz, 1 H), 4.08 (t, 2 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 2.94 (t, 2 H), 2.42 (s, 3 H).

Anal. Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.96; N, 3.94; S, 9.02. Found: C, 67.62; H, 6.08; N, 3.89; S, 9.40.

2-(2-Nitrobenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (5f). **5f** was synthesized from 22 g (0.132 mol) of o-nitrobenzoic acid (Aldrich), 6.8 g (0.061 mol) of 1-*N*,*N*-diethylaminopropyne, and 10.6 g dihydroisoquinoline (0.052 mol) as above. The mixture was refluxed 1 hr and allowed to stand overnight. Methanol (50 ml) was added and a violent reaction ensued. The solvent was removed at vacuum aspirator pressure to give a black gummy mass. The gum was taken up in 500 ml of methylene chloride and washed with water (2 × 1 l.) and 5% potassium carbonate (500 ml). The solution was dried with sodium sulfate, treated with activated carbon, and filtered to give a light orange solution. The solution was evaporated and the residue crystallized from methylene chloride–ethyl acetate to give 13.85 g (0.039 mol, 75%) of bright yellow plates of the enamide **5f:** mp 189–190°; λ_{max} 230 nm (sh, ϵ 25,500), 243 (min, 14,000), 264 (18,000), 290 (min, 7000), 305 (8500), 316 (7000); γ_{max} 1635, 1625 (sh), 1610, 1575, 1520 cm^{-1}; nmr δ 8.10 (m, 1 H), 7.44 (m, 3 H), 7.03 (s, 1 H), 6.63 (s, 1 H), 5.23 (m, 1 H), 4.57 (s, 1 H), 4.14 (m, 2 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 2.98 (t, 2 H).

Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.68; H, 5.24; N, 7.89.

2-(2,4,5-Trimethoxybenzoyl)-1-ethylidene-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (15). **15** was prepared from 2,4,5-trimethoxybenzoic acid, 16.5 g (0.080 mol), 4.3 g of 1-*N*,*N*-diethylaminopropyne, and 1-ethyl-3,4-dihydro-6,7-dimethoxyisoquinoline (0.039 mol) (prepared from *N*-propionoylhomoveratrylamine as detailed for *N*-acetylhomoveratrylamine) to give 5.7 g of enamide **15** (0.015 mol, 38%): mp 131–133°: λ_{max} 244 nm (min, ϵ 16,000), 258 (18,000), 282 (min, 9000), 300 (12,500); γ_{max} 1620, 1520 cm^{-1}; nmr δ 6.30–7.00 (m, 4 H), 5.0–5.7 (very broad multiplet, 1 H), 3.3–4.2 (m, 17 H), 2.90 (t, 2 H), 1.70 (d, $J \simeq 8$ Hz, 2 H), and 1.41 (d, $J \simeq 8$ Hz, 1 H). The ethylidene methyl resonances at δ 1.70 and 1.41 indicated a mixture of ethylidene isomers in the ratio of approximately 2:1.

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 67.06; H, 6.37; N, 3.45.

Irradiation of 2-(2,3-Dimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (1). The enamide 1 (1.0 g) was dissolved in 200 ml of dry benzene and irradiated, under nitrogen, through Pyrex, with a 450-W medium pressure mercury arc (Hanovia 679A). After 4.5 hr, tlc examination indicated consumption of starting material and formation of a single highly fluorescent compound. The solvent was removed and the residue crystallized from methanol to give 775 mg of 2,3,12-trimethoxy-8-oxyprotoberberine (**7**): mp 219–220°; λ_{max} 220 nm (ϵ 38,000), 238 (min, 16,500), 248 (18,500), 253 (18,000), 267 (sh, 10,500), 285 (min, 7000), 304 (sh, 11,000), 316 (sh, 15,000), 330 (21,000), 340 (20,000), 361 (25,000), 388 (20,000); γ_{max} 1650, 1615, 1600 cm^{-1}; nmr δ 8.02 (d, $J \simeq 8$ Hz, 1 H), 6.9–7.4 (m, 4 H), 6.72 (s, 1 H), 4.37 (t, 2 H), 3.95 (s, 6 H), 3.90 (s, 3 H), 2.91 (t, 2 H).

Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.14; H, 5.65; N, 4.11.

Irradiation of 2-(2-Fluorobenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline. The enamide **5a** (1.0 g) was dissolved in 600 ml of *tert*-butyl alcohol in a quartz vessel and degassed by three freeze–thaw cycles in a Dry Ice–isopropyl alcohol bath. The degassed solution was irradiated for 2 hr in a Rayonet Preparative Photoreactor (Southern New England Ultraviolet Model RPR-208).[33] Removal of the solvent on a rotary evaporator gave 830 mg of 2,3-dimethoxy-8-oxyprotoberberine (**8**), mp 181–182° (methanol). The mother liquor indicated the presence of a small amount of starting material as the only other compound. The oxyprotoberberine **8** exhibits: λ_{max} 220 nm (ϵ 35,000), 226 (31,000), 240 (sh, 18,000), 256 (12,000), 283 (min, 6000), 304 (sh, 11,000), 317 (sh, 16,000), 331 (20,000), 350 (sh, 14,500), 368 (8000); γ_{max} 1650, 1615, 1600, 1520 cm^{-1}; nmr δ 8.52 (d, $J \simeq 8$ Hz, 1 H), 7.26–7.84 (m, 4 H), 6.94 (s, 1 H), 6.82 (s, 1 H), 4.38 (t, 2 H), 4.02 (s, 3 H), 3.95 (s, 3 H), 2.94 (t, 2 H).

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.28; H, 5.78; N, 4.34.

Irradiation of 2-(2-Bromobenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline. The enamide **5c** (1.0 g) was irradiated as indicated for the 2-fluoro enamide. Removal of the majority of the solvent on a rotary evaporator and addition of methanol gave 400 mg of *N*-2-bromobenzoyl-2-acetyl-4,5-dimethoxyphenylethylamine (**12**): mp 158–160°; λ_{max} 228 nm (ϵ 15,500), 250 (min, 2500), 273 (5500), 302 (3000); γ_{max} 3280, 1660, 1640, 1610 cm^{-1}; nmr δ 7.34 (m, 3 H), 7.25 (s, 1 H), 6.89 (s, 1 H), 3.97 (s, 3 H), 3.94 (s, 3 H), 3.70 (t, 2 H), 3.15 (t, 2 H), 2.23 (s, 3 H).

Anal. Calcd for $C_{19}H_{20}BrNO_4 \cdot H_2O$: C, 51.67; H, 5.02; N, 3.17. Found: C, 51.21; H, 5.18; N, 3.45.

The yellow mother liquor was evaporated and the residue was dry column chromatographed on 150 g of E. Merck silica, deactivated with 12 ml of water. The dry column was developed with 12:88 ethyl acetate–benzene to give 400 mg of the oxyprotoberberine **8**.

1-Benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline. This was prepared from *N*-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide[34] according to the method of Tschesche, *et al.*[35]

1-Benzylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (9).[12] 1-Benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline (13.4 g, 0.061 mol) was dissolved in 250 ml of dry benzene and 10 ml of Hünig's base (*N*,*N*-diisopropylethylamine) and

to this solution was added 10 ml of ethyl chlorocarbonate in 25 ml of benzene. The mixture was allowed to stand overnight and filtered from a precipitate, and the solution was evaporated to an oil. The oil was crystallized (2×) from methanol to give 8.28 g (0.023 mol, 38%) of **9**: mp 122–124°; mol wt 353 (mass spectrum, calcd 353); λ (EtOH) 229 nm (ε 20,000), 302 (sh, 20,000), 322 (22,000); γ_{max} ($CHCl_3$) 1680, 1250 cm^{-1}; nmr δ 7.1–7.7 (m, 6 H), 6.77 (s, 1 H), 6.57 (s, 1 H), 3.6–4.2 (m, 4 H), 3.90 (s, 3 H), 3.83 (s, 3 H), 2.87 (t, 2 H), 0.77 (t, 3 H).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.54; H, 6.63; N, 4.25.

Irradiation of 1-Benzylidene-2-carbethoxy-6,7-dimethoxyisoquinoline (9). A solution of **9** (1.00 g) in 150 ml of absolute ethanol was irradiated through a Vycor filter, with a 450-W mercury arc for 120 hr. Dry nitrogen was passed through the solution for 0.5 hr prior to the irradiation and during the irradiation. Evaporation of solvent gave 1.36 g of residue which was chromatographed on 40 g of Florisil. Elution with benzene gave 0.20 g of *N*-carbethoxy-6a,7-dehydronornuciferine: mp 131–132°; mol wt 351.1471 (mass spectrum, calcd 351.1440); λ (EtOH) 249 nm (ε 48,700), 259 (47,500), 308 (12,200), 320 (12,200), 352 (1900), 370 (1900); γ ($CHCl_3$) 1670, 1240 cm^{-1}; nmr δ 9.41–9.74 (m, 1 H), 6.7–7.0 (m, 4 H), 6.97 (s, 1 H), 4.24 (q, 2 H), 4.00 (t, 2 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 2.07 (t, 2 H), 1.27 (t, 3 H).

Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.87; H, 6.15; N, 3.98.

Continued elution with methylene chloride containing 0.25% methanol gave 0.55 g of **8**. Elution with methanol–chloroform (1:99) gave 0.19 g of 1-benzyl-2-carbethoxy-1,2,3,4-tetrahydro-1-hydroxy-6,7-dimethoxyisoquinoline (**11**) as a noncrystalline oil: mol wt 371.1730 (mass spectrum, calcd 371.1733); λ (EtOH) 227 nm (ε 17,500), 275 (6600), 303 (8000); γ_{max} (CCl_4) 3340, 1710, 1250 cm^{-1}; nmr δ 7.22 (s, 6 H), 6.72 (s, 1 H), 5.20–5.50 (-OH, 1 H), 4.14 (s, 2 H), 4.04 (q, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.31 (t, 2 H), 2.93 (t, 2 H), 1.16 (t, 3 H).

Irradiation of 2-(2,4,5-Trimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline. The enamide **13** (2.0 g) was prepared for irradiation and irradiated for 3.5 hr as described for the 2-fluoro enamide above. Removal of the *tert*-butyl alcohol solvent at the aspirator gave a residue which upon crystallization from ether gave 1.5 g of 2,3,11,12-tetramethoxy-8-oxyprotoberberine (**14**): mp 187–188°; λ_{max} 220 nm (ε 28,000), 227 (31,000), 245 (min, 18,500), 262 (24,000), 286 (min, 5000), 306 (sh, 11,500), 318 (sh, 15,500), 332 (18,500), 346 (sh, 17,500), 362 (10,500); γ_{max} 1650, 1615, 1600, 1515 cm^{-1}; nmr δ 7.80 (s, 1 H), 7.20 (s, 1 H), 6.94 (s, 1 H), 6.80 (s, 1 H), 6.72 (s, 1 H), 4.37 (t, 2 H), 3.94 (s, 9 H), 3.88 (s, 3 H), 2.91 (t, 2 H).

Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.48; H, 6.02; N, 4.02.

Irradiation of 2-(2,4,5-Trimethoxybenzoyl)-1-ethylidene-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. The enamide **15** (1.0 g) was irradiated in ethyl acetate for 12 hr as described above for the 2,3-dimethoxybenzoyl enamide **1**. The solvent was reduced to small volume and diluted with petroleum ether, whereupon 516 mg of 2,3,10,11-tetramethoxy-13-methyl-8-oxyprotoberberine (**16**), mp 213–215°, crystallized: λ_{max} 230 nm (ε 35,000), 244 (min, 20,000), 262 (28,000), 286 (min, 5500), 328 (24,000), 360 (sh, 10,500); γ_{max} 1645, 1615, 1595, 1515 cm^{-1}; nmr δ 7.94 (s, 1 H), 7.16 (s, 1 H), 7.11 (s, 1 H), 6.83 (s, 1 H), 4.30 (t, 2 H), 4.06 (s, 6 H), 3.98 (s, 3 H), 3.95 (s, 3 H), 2.87 (t, 2 H), 2.64 (s, 3 H).

Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 68.97; H, 6.21; N, 3.91.

The residue for the crystallization was found to contain appreciable oxyprotoberberine and was submitted to dry column chromatography on 150 g of CC-7 silica, deactivated with 12 ml of water, and developed with 4:96 ethanol–benzene to yield an additional 120 mg of oxyprotoberberine **16**.

2-Methoxybenzanilide (17). **17** was prepared from aniline and *o*-methoxybenzoyl chloride (Kodak).[24]

Irradiation of 2-Methoxybenzanilide (17). A solution of **17** (1.0 g) in 200 ml of methanol in a quartz vessel was irradiated in a Rayonet photoreactor with 3000 Å lamps for 18 hr. No reaction was detected. The same solution was then irradiated for 20 hr with 2537 Å lamps and starting material was recovered.

2-Acetoxybenzanilide (19). **19** was prepared from salicyloyl chloride and aniline according to the literature.[26]

Irradiation of 2-Acetoxybenzanilide (19). A solution of 250 mg of **19** in 190 ml of ethyl acetate was irradiated under nitrogen with a 450-W mercury lamp (Pyrex filter) for 21 hr. There was no indication of reaction by tlc and starting material was recovered.

2,4,5-Trimethoxybenzanilide (20). **20** was prepared from 2,4,5-trimethoxybenzoyl chloride (53.7 mmol) and 5.0 g (53.7 mmol) of aniline in 10 ml of pyridine and 50 ml of chloroform at 0°. After standing for 0.5 hr, the solution was extracted with water, dilute hydrochloric acid, and dilute sodium carbonate. The chloroform solution was dried with sodium sulfate and the solvent removed. The residue was crystallized from methanol–water: mp 151–152°; λ_{max} 222 nm (ε 25,500), 240 (min, 12,000), 270 (16,500), 293 (min, 11,000), 311 (14,500); γ_{max} 3360, 1650, 1610, 1600 cm^{-1}; nmr δ 7.0–7.8 (m, 6 H), 6.50 (s, 1 H), 3.98 (s, 3 H), 3.91 δ (s, 6 H).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.14; H, 5.97; N, 5.01.

Irradiation of 2,4,5-Trimethoxybenzanilide (20). A solution of 500 mg of **20** in 190 ml of ethyl acetate was irradiated under nitrogen, through Pyrex, with a 450-W medium pressure mercury lamp. After 20 hr of irradiation a substantial precipitate had formed. The ethyl acetate was removed and the residue combined with the precipitate and the whole recrystallized from hot dimethylformamide to give 245 mg of **21**, 8,9-dimethoxyphenanthridone: mp 300–302°; mol wt 255 [mass spectrum (100%), calcd 255]; λ_{max} 225 nm (ε 22,000), 245 (sh, 43,000), 250 (46,000), 261 (min, 18,000), 264 (20,000), 280 (9500), 287 (min, 8500), 293 (9000), 299 (min, 8000), 305 (9000), 315 (min, 6500), 320 (8000), 328 (min, 5000), 335 (8000); γ_{max} 3180, 3120, 3040, 1660, 1610, 1520, 1510 cm^{-1}; nmr (saturated sol in dimethylformamide) δ 7.2–8.2 (m, 7 H), 4.11 (s, 3 H), 3.98 (s, 3 H).

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.79; H, 5.21; N, 5.58.

***N*-Methyl-2,4,5-trimethoxybenzanilide (22).** 2,4,5-Trimethoxybenzoyl chloride (11.6 g, 53.7 mmol) in 25 ml of chloroform was added to a solution of 4.9 g (46.8 mmol) of *N*-methylaniline in 10 ml of pyridine and 25 ml of chloroform at 0°. After standing for 0.5 hr, the chloroform solution was washed with distilled water, dilute hydrochloric acid, and dilute sodium bicarbonate. The chloroform layer was dried with sodium sulfate and the solvent removed. Crystallization from methanol–water gave 10.2 g (33 mmol, 71%) of **22**: mp 137–139°; λ_{max} 227 nm (ε 31,000), 275 (min, 8500), 297 (12,500); γ_{max} 1640, 1620, 1600, 1520, 1500 cm^{-1}; nmr δ 7.11 (s, 5 H), 6.80 (s, 1 H), 6.25 (s, 1 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 3.55 (s, 3 H), 3.44 (s, 3 H).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.64; H, 6.30; N, 4.88.

Irradiation of *N*-Methyl-2,4,5-trimethoxybenzanilide (22). A solution of 150 mg of **22** in 190 ml of ethyl acetate was irradiated, under nitrogen, through Pyrex, with a 450-W medium pressure mercury arc for 12 hr. The ethyl acetate solution was concentrated to a small volume whereupon 56 mg of 8,9-dimethoxy-5-methylphenanthridone (**23**), mp 219–220°, crystallized. Removal of the ethyl acetate and crystallization from methanol–water gave back starting benzanilide.

8,9-Dimethoxy-5-methylphenanthridone (**23**) shows: mol wt 269 [mass spectrum (100%), calcd 269]; λ_{max} 222 nm (ε 20,000), 246 (sh, 48,000), 252 (50,000), 264 (20,000), 276 (min, 9500), 281 (10,000), 286 (min, 9500), 293 (10,500), 301 (min, 9000), 305 (9500), 316 (min, 6500), 321 (8000), 329 (min, 5000), 336 (8000); γ_{max} 1650, 1620, 1595, 1530 cm^{-1}; nmr δ 8.13 (m, 1 H), 7.91 (s, 1 H), 7.58 (s, 1 H), 7.15–7.55 (m, 3 H), 4.08 (s, 3 H), 4.03 (s, 3 H), 3.82 (s, 3 H).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61. Found: C, 71.57; H, 5.40.

2,3′,4′,5′-Tetramethoxybenzanilide (24). 3,4,5-Trimethoxyaniline (Aldrich) (5 g) was dissolved in pyridine and cooled in an ice bath. To this solution was added 6 g of 2-methoxybenzoyl chloride (Eastman Kodak) in 25 ml of methylene chloride and the resulting mixture stirred for 1 hr. The mixture was dissolved in 300 ml of methylene chloride and extracted with 5% potassium carbonate and dilute hydrochloric acid and washed with water. The methylene chloride solution was dried with sodium sulfate, and solvent removed at the aspirator. Crystallization from methanol gave 6.8 g of amide **24**: mp 110–115°; γ 3340, 1655, 1610, 1550, 1515 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}O_5N$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.52; H, 5.96; N, 4.31.

Irradiation of 2,3′,4′,5′-Tetramethoxybenzanilide (24). (a) The amide (1.0 g) was dissolved in 350 ml of *tert*-butyl alcohol and irradiated, through Pyrex and under nitrogen, with a 450-W medium pressure mercury arc for 6.5 hr. Upon removal of solvent starting material was recovered. (b) The amide (1.0 g) was dissolved in 450 ml of *tert*-butyl alcohol and irradiated in a quartz vessel in the Rayonet photoreactor with 2537 Å lamps for 28 hr. Removal of solvent gave back starting material. (c) The amide (1.0 g) was dis-

solved in 500 ml of acetone and irradiated with 3000 Å lamps, under argon, for 48 hr. Evaporation of acetone gave back starting material.

1-(2,5-Dimethoxybenzylidene)-2-carbomethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (25). 1-(2,5-Dimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (15 g, 0.044 mol) was added to a preformed solution of 10 ml of methyl chloroformate in 25 ml of pyridine and 100 ml of benzene. The mixture was brought to reflux under nitrogen for 1 hr. The solution was cooled and washed three times with water. Removal of solvent and crystallization from ether gave 10.8 g (0.027 mol, 61%) of the benzylidene carbamate **25**: mp 144–145°; λ_{max} 256 nm (min, ϵ 7500), 295 (s, 13,000), 327 (16,000); γ_{max} 1705, 1605, 1520 cm^{-1}; nmr δ 7.28 (s, 1 H), 7.05 (s, 2 H), 6.82 (s, 2 H), 6.63 (s, 1 H), 4.02 (t, 2 H, obscured by $-OCH_3$'s), 3.95 (s, 3 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.75 (s, 3 H), 3.34 (broad s, 3 H), 2.92 (t, 2 H).

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.28; H, 6.10; N, 3.50.

Irradiation of 1-(2,5-Dimethoxybenzylidene)-2-carbomethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (25). (a) The carbamate (1.0 g) was dissolved in 250 ml of benzene and irradiated, under nitrogen, with a 450-W medium pressure mercury arc (Pyrex) for 2.5 hr. Removal of solvent and crystallization from ether gave back a cis/trans mixture of the starting carbamate. (b) The carbamate (1.0 g) was dissolved in 200 ml of ethanol and irradiated as above for 8 hr. Removal of solvent gave back a cis/trans mixture of the starting carbamate. The evidence for a cis/trans mixture is the absence of either phenanthrene or oxyprotoberberine bands in the uv, and the appearance of the ester methyl group as two broad singlets at δ 3.33 and 3.38 in the ratio of 1:2. There were also eight methoxyl signals instead of the initial four.

Registry No.—**9**, 22185-92-8; **10**, 13555-30-1; **11**, 52050-45-0; **24**, 52050-46-1; **25**, 52050-47-2; 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline, 4721-98-6; *N*-acetylhomoveratrylamine, 6275-29-2; 2,3-dimethoxybenzoic acid, 1521-38-6; 1-diethylaminopropyne, 4231-35-0; *o*-fluorobenzoic acid, 445-29-4; *o*-chlorobenzoic acid, 118-91-2; *o*-bromobenzoic acid, 88-65-3; acetylsalicylic acid, 50-78-2; 2,4,5-trimethoxybenzoic acid, 490-64-2; 2-(methylthio)benzoic acid, 3724-10-5; *o*-nitrobenzoic acid, 552-16-9; 1-ethyl-3,4-dihydro-6,7-dimethoxyisoquinoline, 51665-55-5; 1-benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline, 4876-00-0; *N*-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide, 4876-02-2; ethyl chlorocarbonate, 541-41-3; 3,4,5-trimethoxyaniline, 24313-88-0; 2-methoxybenzoyl chloride, 21615,34-9; 1-(2,5-dimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline, 52050-48-3; methyl chloroformate, 79-22-1.

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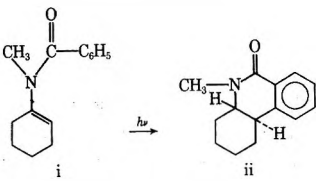

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(30a) Note Added in Proof. Since the submission of this manuscript, two further examples of cyclization and elimination of ortho substituents to form aromatic systems have been described. I. Ninomiya, H. Takasugi, and T. Naito [*Heterocycles*, **1**, 17 (1973)] have described the synthesis of tetrahydroprotoberberine alkaloids utilizing the elimination of an *o*-methoxy group in methyleneisoquinoline enamide. R. G. F. Giles and M. V. Sargent [*J. Chem. Soc., Chem. Commun.*, 215 (1974)] have described the synthesis of a large variety of phenanthrenes using *o*-methoxy-substituted stilbenes.
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Enamide Photochemistry. Formation of 8-Oxoberbines from 2-Aroyl-1-methylene-1,2,3,4-tetrahydroisoquinolines[1]

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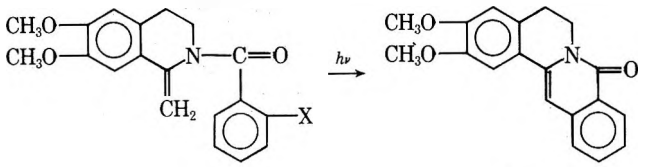
Irradiation of 2-aroyl-1-methylene-1,2,3,4-tetrahydroisoquinoline enamides **3** under degassed conditions yields 8-oxoberbines **4** in excellent yields. A wide variety of substituents is not affected by the reaction conditions. Methoxyl-, acetoxyl-, methylenedioxy-, chloro-, methyl-, and phenyl-substituted enamides have been successfully cyclized. Irradiation in the presence of air of the acetoxy enamide **3e** yields the oxyprotoberberine **6**. Alternatively dehydrogenation by dichlorodicyanobenzoquinone of the 8-oxoberbines forms the oxyprotoberberines **9** in good yield. Reduction of the 8-oxo group with either lithium aluminum hydride or sodium bis(methoxyethoxy)aluminum hydride furnishes the berbine alkaloid bases **10**. The naturally occurring berbine xylopinine (**10b**) has been synthesized in this manner from the corresponding 8-oxoberbine (**4b**).

The use of enamides to form isoquinoline alkaloids photochemically has proved to be very fruitful.[2] The use of ortho-substituted aroyl-1-methyleneisoquinolines **1** to generate oxyprotoberberines **2** has been described.[3] It was felt



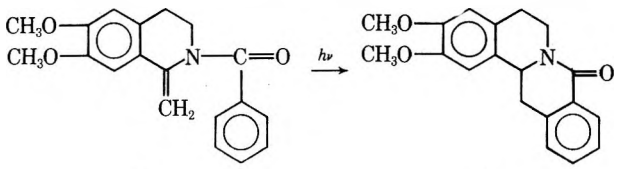
1 **2**

that if the ortho positions in the aroyl group were unsubstituted, then a [1,5]-hydrogen shift would generate 8-oxoberbines which could be easily reduced to the berbine alkaloids. In a further extension of our studies in this area, it has been found that aroyl enamides could be smoothly cyclized to 8-oxoberbines, and the photoproducts transformed into other benzylisoquinoline alkaloid structures.[4]

Results

The aroyl enamides **3** are conveniently prepared by treating 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline with either the appropriate aroyl chloride or, in most cases, with the aroyl anhydride. The anhydrides were prepared *in situ* in very high yield using the ynamine condensation method.[5] The enamides **3** all showed two pairs of doublets in the nmr for the exocyclic methylene protons. The enamides are crystalline compounds with the exception of the acetylvanilloyl derivative **3e** and are stable in the absence of acid.[6]

Irradiation of a thoroughly degassed *tert*-butyl alcohol solution of the benzoyl enamide converted **3a** into a single photoproduct **4a** which was isolated in 96.7% yield. The photoproduct **4a** showed the disappearance of the exo-



3a **4a**

methylene protons in the nmr and the loss of one aromatic proton. The nmr spectrum showed, on the other hand, a one-proton multiplet for a proton ortho to a carbonyl at δ 8.17 and a two-proton multiplet between δ 4.65 and 5.15. This new resonance is assigned to the 13a-methine hydrogen and the equatorial 6 proton which a model shows to be coplanar between 1.8 and 2.2 Å removed from the carbonyl.[7] This downfield two-proton multiplet is characteristic of all 8-oxoberbines thus far synthesized. The 13-equatorial proton resonates in the same area as the 5,6-ethylene bridge between δ 2.7 and 3.5. The nmr evidence indicates that the 8-oxoberbine tetracyclic ring system is essentially flat, analogous to yohimbine.[8] The uv spectrum had become much simpler than **3a**, indicative of the loss of the extended conjugation. On this basis, **4a** was postulated as 2,3-dimethoxy-8-oxoberbine, a compound which had been previously prepared.[9,10]

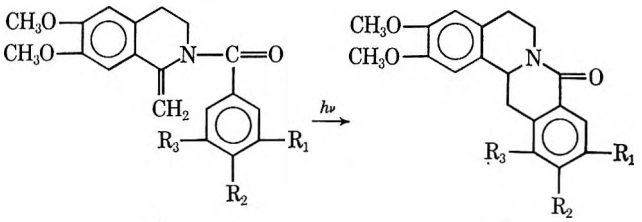
The 8-oxoberbines synthesized are collected in Table I. It can be seen that a wide variety of meta and para substituents can be accommodated in the photocyclization including methoxyl, methylenedioxy, alkyl, halo, and phenyl substituents. The yields are uniformly good. The most significant observation is that phenolic hydroxyl groups, masked as the acetate, can be easily introduced.

Enamide **3e** was readily prepared from acetylvanilloyl chloride and 5,6-dihydro-6,7-dimethoxy-1-methylisoquinoline. This was the only enamide that could not be crystallized, and was particularly prone to hydrolysis. As a result, a preparation of the crude enamide was degassed in *tert*-butyl alcohol, containing a few drops of triethylamine to retard hydrolysis, and irradiated to give a 45% yield of the acetoxy-8-oxoberbine **4e**. The yield of **4e** would undoubtedly be much higher if the enamide were crystalline and capable of rigorous purification. This promises to be a particularly advantageous method for preparing polyhydroxy 8-oxoberbines and their derivatives. Acid-catalyzed transesterification in methanol, under nitrogen, gave the phenolic compound **5** in 95% yield.

The irradiation of the acetoxy enamide **3e** under nondegassed conditions was also studied. When the crude enamide **3e** was irradiated in ethyl acetate in a Pyrex vessel open to the atmosphere, a rapid reaction occurred leading to a highly fluorescent compound **6** in 65% yield, a trace of **4e**, and the hydrolysis product **7** of the enamide **3e**. The photoproduct **6** was identified as the cyclized and dehydrogenated oxyprotoberbine by virtue of its characteristic uv spectrum and the mass spectrum, which confirmed the loss of a mole of hydrogen.[3] Exposure of solutions of the 8-oxoberbines to air in the laboratory results in complete conversion to the oxyprotoberberine in a matter of days. Acid-catalyzed transesterification gave the phenolic oxyprotoberberine **8** in 77% yield.

The ready dehydrogenation of **4e** indicated that dehydrogenation of the other 8-oxoberbines **4** by high potential quinones would be feasible.[11] The reaction of 8-oxoberbines **4** with 2,3-dichloro-5,6-dicyanobenzoquinone was

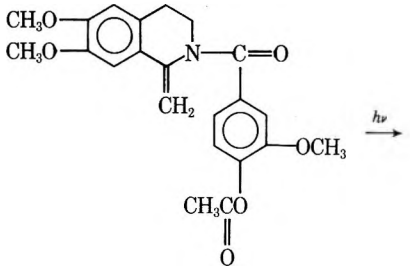
Table I
Photochemical Formation of 8-Oxoberbines[a]



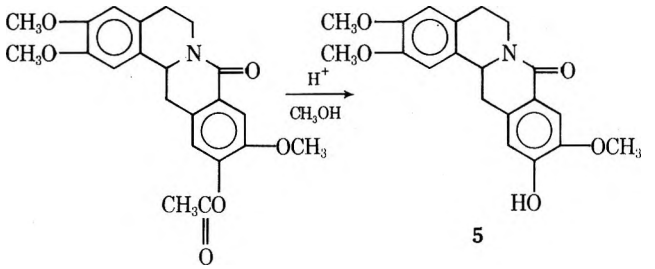
3 4

Enamide	R_1	R_2	R_3	8-Oxoberbine	Yield, %
3a (52050-53-0)	H	H	H	**4a** (1876-67-1)	96.7
3b (41173-78-8)	OCH_3	OCH_3	H	**4b** (52050-59-6)	93.5
3c (52050-54-1)	—OCH_2O—		H	**4c** (52050-60-9)	75
3d (49619-33-2)	OCH_3	OCH_3	OCH_3	**4d** (49619-37-6)	70
3e (52050-55-2)	OCH_3	O_2CCH_3	H	**4e** (52050-61-0)	45
3f (52050-56-3)	H	CH_3	H	**4f** (52050-62-1	85
3g (52050-57-4)	H	Cl	H	**4g** (52124-31-9)	76
3h (52050-58-5)	H	Ph	H	**4h** (52050-63-2)	76

[a] Registry no. are in parentheses beneath compounds.



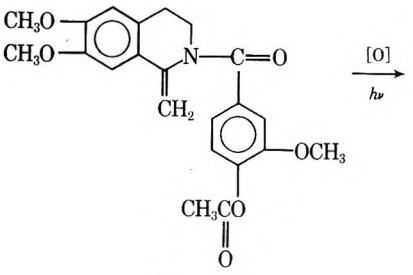
3e



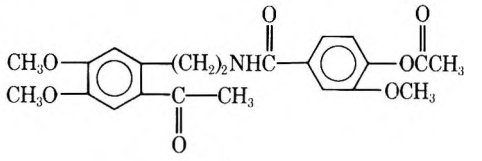
4e 5

found to virtually be instantaneous, generating the oxyprotoberberines **9**. The oxyprotoberberines **9** synthesized are collected in Table II.

Two methods were used to reduce 8-oxoberbines to the tetrahydroprotoberberine (berbine), reduction with lithium aluminum hydride in tetrahydrofuran and sodium bis(methoxyethoxy)aluminum hydride in benzene. In general, reductions with $LiAlH_4$ gave inferior yields and less clean products than reduction with the other hydride reagent. For instance, reduction of 2,3,10,11,12-pentamethoxy-8-oxoberbine **4d** with $LiAlH_4$ gave, in 67% yield, 2,3,10,11,12-pentamethoxyberbine **10d** which could not be crystallized and was isolated as its hydrochloride salt. On the other hand, reduction with sodium bis(methoxyethoxy)aluminum hydride gave a 90% yield of **10d** as a crystalline compound.



3e



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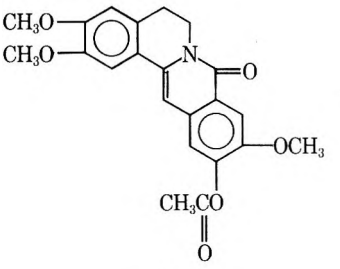

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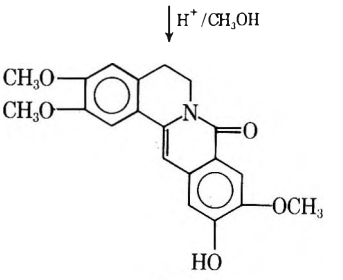

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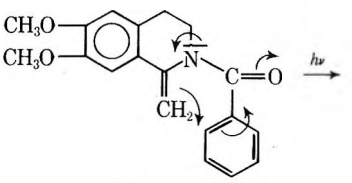
Reduction of **3b** gave the naturally occurring *dl*-xylopinine in 85% yield.[12] Reduction of the acetoxy 8-oxoberbine **4e** gave the phenolic berbine **10e** (2-*O*-methylcoreximine) in 62% yield. Acetylation with acetic anhydride and pyridine using 4-dimethylaminopyridine as catalyst gave the acetoxyberbine **11**.[13] The berbines synthesized are collected in Table II.

Discussion

The photochemistry of conjugated enamides is dominated by the aza analog of the hexatriene–cyclohexadiene ring closure. This has been demonstrated in the isoquino-



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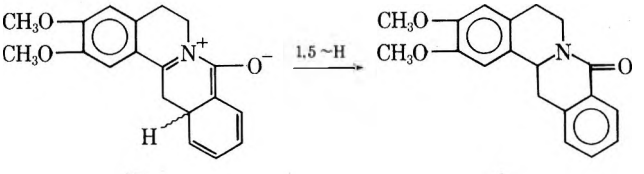
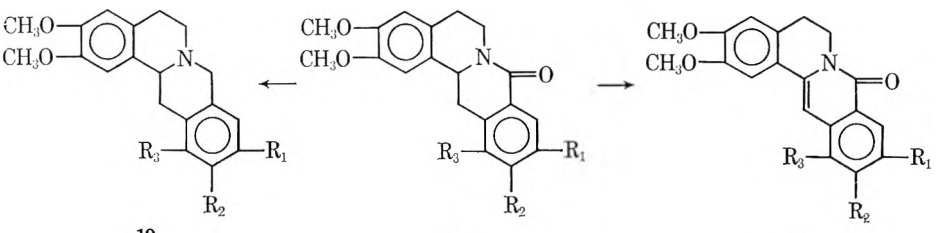


12 4

Table II
Derivatives of 8-Oxoberbines[a]



10 4 9

Berbine	Yield, %		R_1	R_2	R_3	Oxyprotoberberine	Yield, %
10b (4216-86-8)	85	**4b**	OCH_3	OCH_3	H		
10c (24314-66-7)	73[b]	**4c**	—OCH_2O—		H	**9c** (19716-62-2)	79
10d (23837-66-3).	92	**4d**	OCH_3	OCH_3	OCH_3	**9d** (23837-65-2)	60
10e (52050-64-3)	62[c]	**4e**	OCH_3	$OC(=O)CH_3$	H	**6** (52050-68-7)	65
10f (52050-65-4)	95	**4f**	H	CH_3	H	**9f** (52050-69-8)	80
10g (52050-66-5)	53	**4g**	H	Cl	H	**9g** (52050-70-1)	70
10h (52050-67-6)	60	**4h**	H	Ph	H	**9h** (52050-71-2)	72

[a] Registry no. are in parentheses beneath compounds. [b] M. Tomita and J. Niimi, *Yakugaku Zasshi*, **79**, 1023 (1959). [c] R_1 = —OCH_3, R_2 = —OH.

line series by the formation of oxyprotoberberines[14] and protoberberines.[15] The synthesis of 8-oxoberbines from enamides can be viewed as an electrocyclic ring closure to give the intermediate **12** which then undergoes a [1,5]-hydrogen shift to generate the 8-oxoberbine **4**. When the ortho position of the aroyl group is occupied by a substituent which is capable of acting as a leaving group, elimination occurs to give an oxyprotoberberine.[3]

The synthesis of 8-oxoberbines is a very convenient reaction proceeding from readily synthesized enamides and generating the oxoberbine in excellent yields. A wide variety of substituents has been found to be stable to the irradiation conditions extending the utility of the photocyclization. Particularly noteworthy is the synthesis of the acetoxy compound **4e** from vanillic acid and the dihydroisoquinoline. This promises to be an effective method for preparing phenolic berbines simply and conveniently with the hydroxy group masked as the acetate. Reduction with hydride reagents gives the berbines in excellent yields, while dehydrogenation of the 8-oxoberbines either with air or high potential quinones gives excellent yields of the oxyprotoberberines.

Experimental Section

General. Melting points were taken on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. Infrared spectra were run in KBr unless otherwise noted, and ultraviolet and visible spectra were run in methanol. A Varian Associates A-60, T-60, or HA-100 spectrometer was used to record nmr spectra. All spectra were run in deuteriochloroform containing tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were run on an A.E.I. MS-30 mass spectrometer by the Searle Laboratories Mass Spectrometry Department, Dr. Jeremy Hribar, Director. Microanalyses were performed by the Searle Laboratories Microanalytical Department, Mr. E. Zielinski, Director.

2-Benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3a). A suspension of 16 g of benzoic acid (0.132 mol) was stirred magnetically in 350 ml of dry benzene while 8.5 ml of 1-*N*,*N*-diethylaminopropyne (0.066 mol) was added. The reaction mixture warmed spontaneously, turned orange-red as benzoic anhydride formed, and went into solution. After 0.5 hr, a solution of 9.0 g of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline[16] (0.044 mol) in 50 ml of pyridine was added. The resulting solution is blanketed with nitrogen and brought to reflux for 1 hr. The reaction mixture was cooled to room temperature and then extracted with distilled water (3 × 500 ml). The organic phase was dried with sodium sulfate and the solvent removed on a rotary evaporator. Crystallization from ether–petroleum ether gave 8.4 g (0.027 mol, 61%) of 2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (**3a**): mp 121–124°; uv 230 nm (sh, ϵ 23,000), 243 (min, 11,500), 263 (18,500), 290 (min, 6000), 304 (7250), 314 (sh, 6000); ir 1655, 1635 (sh), 1615 cm^{-1}; nmr δ 7.30 (m, 5 H), 7.03 (s, 1 H), 6.70 (s, 1 H), 5.27 (d, $J \simeq 1.5$ Hz, 1 H), 4.47 (d, $J \simeq 1.5$ Hz, 1 H), 4.12 (t, 2 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 2.97 (t, 2 H).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.50; H, 6.24; N, 4.36.

2-(3,4-Dimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3b). A solution of 3,4-dimethoxybenzoic anhydride was prepared from 24 g (0.132 mol) of 3,4-dimethoxybenzoic acid (Aldrich) and 8.5 ml of 1-*N*,*N*-diethylaminopropyne and treated with 10 g of dihydroisoquinoline as described for **3a** to give 14.9 g (0.040 mol, 82%) of **3b**: mp 134–137°; uv 231 nm (sh, ϵ 29,000), 245 (min, 14,000), 265 (21,000), 295 (11,250), 315 (sh, 7000); ir 1630 cm^{-1}; nmr δ 7.03 (m, 3 H), 6.84 (s, 1 H), 6.68 (s, 1 H), 5.28 (d, $J \simeq 1$ Hz, 1 H, C=CH_2), 4.46 (d, $J \simeq 1$ Hz, 1 H, C=CH_2), 4.10 (t, 2 H), 3.92 and 3.90 (s, 9 H), 3.78 (s, 3 H), 2.95 (t, 2 H).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.26; H, 6.40; N, 3.78.

2-(3,4-Methylenedioxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3c). A suspension of 22 g of piperonylic acid (0.132 mol) was suspended in 400 ml of refluxing benzene and 25 ml of solvent removed (Dean-Stark trap). The hot suspension was allowed to cool slightly and 9 ml of 1-*N*,*N*-diethylaminopropyne was added. The exothermic reaction caused the solvent to reflux. After cooling to room temperature, piperonylic anhydride crystallized. To the suspension of the anhydride in benzene was added 13 g (0.063 mol) of dihydroisoquinoline in 100 ml of benzene and 50 ml of pyridine. The mixture was held at reflux, under nitrogen, for 7 hr. Upon cooling, 50 ml of methanol was added; the mixture was stirred for 1 hr and then extracted with water (3 × 500 ml) and 5% potassium carbonate solution. The organic phase was dried with sodium sulfate and the sodium sulfate washed with methylene chloride. Removal of solvent and crystallization from ethyl acetate–ether gave 11.4 g (0.032 mol, 51%) of **3c**: mp 133–135°; ir 1640, 1625 (sh), 1615 cm^{-1} (sh); uv 232 nm (sh, ϵ 24,000), 244 (min, 11,500), 265 (18,000), 285 (min, 10,000), 300 (12,000), 314 (sh, 8000); nmr δ 7.00 (m, 3 H), 6.75 (s, 1 H), 6.63 (s, 1

H), 5.90 (s, 2 H, $-OCH_2O-$), 5.12 (d, $J \simeq 1.5$ Hz, 1 H, $C=CH_2$), 4.46 (d, $J \simeq 1.5$ Hz, 1 H, $C=CH_2$), 4.07 (t, 2 H), 3.90 (s, 6 H, OCH_3), 2.93 (t, 2 H).

Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.94; H, 5.52; N, 3.94.

2-(3,4,5-Trimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3d). Compound **3d** (11.15 g, 0.028 mol, 64%) was prepared from 28 g (0.132 mol) of 3,4,5-trimethoxybenzoic acid (Mallinckrodt), 6.8 g (8.5 ml, 0.061 mol) of 1-*N*,*N*-diethylaminopropyne, and 9 g (0.044 mol) of dihydroisoquinoline as described above for **3a**. Compound **3d** shows: mp 107–109°, uv 243 nm (min, 12,000), 265 (19,000), 302 (8000), 315 (sh, 5500); ir 1635, 1615, 1595, 1520 cm^{-1}; nmr δ 7.06 (s, 1 H), 6.72 (s, 3 H), 5.31 (d, $J \simeq 1$ Hz, 1 H, $C=CH_2$), 4.56 (d, $J \simeq 1$ Hz, 1 H, $C=CH_2$), 4.13 [t, 2 H, $-CH_2NC(=O)-$], 3.95 (s, 3 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.62 (s, 6 H), 3.00 (t, 2 H, $=CCH_2CH_2N$).

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.24; H, 6.27; N, 3.30.

2-(4-Acetoxy-3-methoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3e). A suspension of 10 g of acetylvanillic acid was stirred in 20 ml of toluene, 20 ml of thionyl chloride and 0.5 ml of dimethylformamide for 16 hr. The solvents were removed; 50 ml of benzene was added and evaporated and the residue crystallized from petroleum ether to give 9 g of the acid chloride. A solution of 10.0 g of the dihydroisoquinoline in 250 ml of toluene and 20 ml of pyridine was stirred with 9.0 g acetylvanilloyl chloride, under nitrogen, for 20 min, when tlc indicated complete reaction. The solution was washed with water (3 × 500 ml) and dried to a light yellow solution. Evaporation of the solvent gave 12.0 g of **3e** as a gum which could not be crystallized from ethyl acetate, ether, or petroleum ether, nor from methanol nor methanol–water. The enamide **3e** shows: uv 230 nm (ϵ 20,000), 261 (12,500), 290 (8000); ir 1770, 1640, 1515 cm^{-1}; nmr δ 6.65–7.85 (m, 5H), 5.32 (d, $J \simeq 1.5$ Hz, 1 H), 4.52 (d, $J \simeq 1.5$ Hz, 1 H), 4.10 (q, 2 H), 3.90 (s, 9 H), 3.02 (q, 2 H), 2.33 (s, 3 H).

The enamide **3e** had to be used as prepared due to its facile hydrolysis to *N*-[β-(2-acetyl-4,5-dimethoxyphenyl)ethyl]-4-acetoxy-3-methoxybenzamide (**7**): mp 129–131° (methanol–water); uv 230 nm (ϵ 30,000), 260 (min, 9500), 275 (11,000), 310 (sh, 5000); ir 3340 (NH), 1780 (C_6H_5OAc), 1695 [$C=OCH_3$], 1675 (sh, HNC=O), 1640, 1615 cm^{-1}; nmr δ 6.65–8.00 (m, 6 H), 3.88 (s, 6 H), 3.85 (s, 3 H), 3.67 (m, 2 H), 2.92 (m, 2 H), 2.60 (s, 3 H), 2.28 (s, 3 H).

Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.38; H, 6.08; N, 3.17.

2-(4-Methylbenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3f). The enamide was synthesized from 4.0 g (19.5 mmol) of dihydroisoquinoline base and 3.4 g of *p*-toluoyl chloride (21 mmol) in 100 ml of methylene chloride and 7 ml of pyridine for 16 hr. Extraction with distilled water (3 × 500 ml) and drying of the organic phase with sodium sulfate gave 4.25 g (13 mmol, 67%) of **3f**: mp 137–138° (ether–petroleum ether); uv 220 nm (end, ϵ 39,000), 244 (min, 13,500), 263 (25,000), 290 (min, 7000), 303 (7500), 313 (sh, 6000); ir 1645, 1625, 1525 cm^{-1}; nmr δ 7.0–7.5 (m, 5 H), 6.68 (s, 1 H), 5.27 (d, $J \simeq 1.5$ Hz, 1 H), 4.44 (s (d, $J \simeq 1.5$ Hz, 1 H), 4.09 (t, 2 H), 3.88 (s, 6 H), 2.95 (t, 2 H), 2.35 (s, 3 H).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.24; H, 6.57; N, 4.38.

2-(4-Chlorobenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3g). The enamide **3g** was prepared from 8.8 g of *p*-chlorobenzoyl chloride (10% excess) and 9.3 g (0.045 mol) of dihydroisoquinoline in 90 ml of dioxane and 10 ml of pyridine at room temperature, under nitrogen. After 17 hr, 500 ml of chloroform was added and the organic layer was washed with water (2 × 500 ml) and then dried (Na_2SO_4). Evaporation of the solvents and crystallization from ether gave 12.4 g (0.036 mol, 80%) of **3g**: mp 159–162°, uv 220 nm (end, ϵ 32,000), 230 (sh, 26,500), 248 (min, 14,000), 264 (17,500), 290 (min, 7000), 303 (7500), 315 (sh, 5000); ir 1655, 1645, 1615, 1520 cm^{-1}; nmr δ 7.36 (m, 4 H), 7.03 (s, 1 H), 6.69 (s, 1 H), 5.28 (d, $J \simeq 1.5$ Hz, 1 H), 4.40 (d, $J \simeq 1.5$ Hz, 1 H), 4.12 (t, 2 H), 3.90 (s, 6 H), 2.97 (t, 2 H).

Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.37; H, 5.28; Cl, 10.31; N, 4.07. Found: C, 66.00; H, 5.35; Cl, 10.62; N, 4.07.

2-(4-Phenylbenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3h). 4-Phenylbenzoyl chloride (Aldrich), 10 g, was added to 6.7 g (0.033 mol) of dihydroisoquinoline in 20 ml of pyridine and 100 ml of dioxane. After stirring at room temperature for 2 hr, the mixture was poured into 500 ml of chloroform and washed with distilled water (3 × 500 ml). The organic phase was dried (sodium sulfate) and evaporated to a tan solid. The solid was triturated with ether and dried to give 9.5 g (0.025 mol, 76%) of **4h**: mp 103–107° (methanol–water), uv 232 nm (sh, ϵ 20,000), 241 (min, 15,500), 270 (32,000), 295 (sh, 20,000); ir 1635, 1615, 1520 cm^{-1}; nmr δ 8.27 [d, $J \simeq 8$ Hz (secondary splitting), 1 H], 7.25–7.80 (m, 8 H), 7.06 (s, 1 H), 6.70 (s, 1 H), 5.34 (d, $J \simeq 1.5$ Hz, 1 H), 4.54 (d, $J \simeq 1.5$ Hz, 1 H), 4.17 (t, 2 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.00 (t, 2 H).

Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.95; H, 5.95; N, 3.62.

Irradiation of 2-Benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3a). A solution of 1.0 g of **3a** in 600 ml of *tert*-butyl alcohol in a quartz irradiation vessel was subjected to four vacuum freeze–thaw cycles in a Dry Ice–isopropyl alcohol bath for degassing purposes. The degassed solution was irradiated for 1.5 hr with eight 3000 Å lamps in a Southern New England Ultraviolet Co. Rayonet preparative photochemical reactor. [The 3000 Å lamps also emit appreciably at 2537 Å. This energy could be absorbed by the molecule due to the transparency of the quartz irradiation vessel.] The solvent was removed at the aspirator and the residue crystallized from methanol, in two crops, to give 967 mg of 2,3-dimethoxy-8-oxoberbine **4a** (5,6,13,13a-tetrahydro-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 143–145°; uv 229 nm (ϵ 18,000), 254 (6500), 264 (5500), 279 (6000); ir 1660, 1520 cm^{-1}; nmr δ 8.17 (m, 1 H), 7.34 (m, 3 H), 6.75 (s, 1 H), 6.73 (s, 1 H), 4.65–5.15 (m, 2 H), 3.91 (s, 6 H), 2.7–3.5 (m, 5 H). The analytical sample was recrystallized from ethyl acetate–petroleum ether.

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.46; H, 6.19; N, 4.48.

Irradiation of 2-(3,4-Dimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3b). A solution of 2.0 g of **3b** in 600 ml of *tert*-butyl alcohol is degassed and irradiated, as above, for 2.5 hr. The solvent was removed and the residue crystallized from ether to give, in two crops, 1.87 g of 2,3,10,11-tetramethoxy-8-oxoberbine **4b** (5,6,13,13a-tetrahydro-2,3,10,11-tetramethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 188–189°; uv 223.5 nm (ϵ 42,000), 249 (min, 7500), 263 (9000), 270 (9250), 280 (min, 7500), 285 (8000), 290 (8500), 302 (6000); ir 1650, 1615, 1600, 1520 cm^{-1}; nmr δ 7.65 (s, 1 H), 6.74 (s, 3 H), 4.67–5.17 (m, 2 H), 3.93 and 3.90 (s, 12 H), 2.67–3.33 (m, 5 H).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.92; H, 6.38; N, 3.79.

2,3-Dimethoxy-9,10-methylenedioxy-8-oxoberbine (4c). Enamide **3c** (2.0 g) in 600 ml of *tert*-butyl alcohol is degassed and irradiated for 2.5 hr. Solvent removal and crystallization from ethyl acetate–ether gave 1.50 g of **4c** (5,6,13,13a-tetrahydro-2,3-dimethoxy-8*H*-benzo-[*a*][1,3]-benzodioxolo[5,6-*g*]quinolizin-8-one): mp 174–178°; uv 225 nm (ϵ 41,000), 265 (7250), 273 (7500), 291 (8000), 305 (7500); nmr δ 7.58 (s, 1 H), 6.72 (broad s, 3 H), 5.99 (s, 2 H), 4.65–5.05 (m, 2 H), 3.86 (s, 6 H), 2.50–3.10 (m, 5 H).

Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.72; H, 5.61; N, 3.90.

2,3,10,11,12-Pentamethoxy-8-oxoberbine (4d). A solution of 4.0 g of **3d** in *tert*-butyl alcohol was degassed and irradiated, as above, for 5 hr. The solvent was removed and the residue dissolved in ethyl acetate–ether and filtered from a slight precipitate. Scratching induced the crystallization of 2.8 g of **4d** (5,6,13,13a-tetrahydro-2,3,10,11,12-pentamethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 127–30°; uv 220 nm (end, ϵ 38,000), 246 (min, 7000), 265 (9000), 290 (5500), 304 (2500); ir 1655, 1600, 1525, 1515 cm^{-1}; nmr δ 7.55 (s, 1 H), 6.74 (s, 1 H), 6.68 (s, 1 H), 4.5–5.0 (m, 2 H), 3.95, 3.92, 3.89 (s, 15 H), 2.5–3.5 (m, 5 H).

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.96; H, 6.42; N, 3.32.

11-Acetoxy-2,3,10-trimethoxy-8-oxoberbine (4e). A solution of 6.0 g of the freshly prepared, noncrystalline enamide **3e** in 300 ml of *tert*-butyl alcohol, to which a few drops of triethylamine had been added to retard hydrolysis, was degassed as above and irradiated for 12 hr. The solvent was removed and the residue crystallized from methanol to give 1.55 g of **4e** in two crops. The residue from the mother liquor was chromatographed on 250 g of silica; elution with ethyl acetate–methylene chloride (1:3 and 1:1) gave an additional 1.10 g of **4e** (11-acetoxy-5,6,13,13a-tetrahydro-2,3,10-trimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 166–167°; uv 235 nm (ϵ 17,500), 260 (sh, 8500), 275 (6000), 280 (6250), 285 (6500), 290 (7000), 299 (min, 5500), 306 (5750), 318 (min, 5000), 334 (5500); nmr δ 7.59 (s, 1 H), 6.96 (s, 1 H), 6.65 (s, 2 H), 4.58–5.10 (m, 2 H), 3.89 (s, 9 H), 2.70–3.20 (m, 5 H), 2.32 (s, 3 H).

Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.24; H, 5.91; N, 3.45.

3-Hydroxy-2,3,10-trimethoxy-8-oxoberbine (5). A solution of 411 mg of **4e** in 75 ml of methanol and 103 mg of *p*-toluenesulfonic

acid monohydrate was refluxed under nitrogen for 18 hr. Tlc inspection indicated approximately 25% reaction and an additional 300 mg of tosyl acid was added and refluxed for a further 8 hr. Upon cooling of the solution, 250 mg of **5** crystallized. Concentration of the solution yielded an additional 96 mg: mp 243–244°; uv 224 nm (41,000) 246 (min, 9500), 267 (14,250), 290 (9500), 304 (7500), 330 (4000); ir 3300, 1650, 1600, 1530 cm^{-1}; nmr (DMSO-d_6) δ 9.59 (broad s, 1 H, phenolic H), 7.45 (s, 1 H), 6.98 (s, 1 H), 6.78 (s, 2 H), 4.75 (m, 2 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 2.5–3.5 (m, 5 H, partially obscured by DMSO-solvent peak).

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.35; H, 5.87; N, 4.10.

11-Chloro-2,3-dimethoxy-8-oxoberbine (4g). A solution of 6.0 g of the enamide **3g** in 600 ml of *tert*-butyl alcohol was degassed and irradiated as above for 16 hr. Removal of solvent and crystallization from ether gave 5.10 g of **4g** (11-chloro-5,6,13,13a-tetrahydro-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 219–220°; uv 233 nm (ϵ 21,500), 258 (sh, 9500), 267 (sh, 7500), 280 (6500), 290 (sh, 5500); ir 1655, 1610, 1530 cm^{-1}; nmr δ 8.02 (d, $J \simeq$ 8 Hz, 1 H), 7.33 (dd, $J \simeq$ 8 Hz, 1.5 Hz, 1 H), 7.25 (broad s, 1 H), 6.70 (s, 2 H), 4.67–5.08 (m, 2 H), 3.90 (s, 6 H), 3.10 (m, 2 H), 2.88 (broad s, 3 H).

Anal. Calcd for $C_{19}H_{18}NO_3Cl$: C, 66.37; H, 5,28; N, 4.07. Found: C, 66.65; H, 5.34; N, 4.17.

2,3-Dimethoxy-11-methyl-8-oxoberbine (4f). A solution of 3.5 g of **3f** in 600 ml of *tert*-butyl alcohol was degassed and irradiated for 4.5 hr as described above. Removal of solvent gave a gum which could be crystallized from ethyl acetate–ether to give 2.1 g of **4f**. Dry column chromatography of the mother liquor residue gave an additional 536 mg of **4f** (5,6,13,13a-tetrahydro-2,3-dimethoxy-11-methyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 151–152°; uv 225 (min, 18,000), 233 (18,500), 254 (10,000), 265 (8000), 280 (6500), 290 (sh 5500); ir 1655, 1620, 1520 cm^{-1}; nmr δ 8.05 (d, $J \simeq$ 8 Hz, 1 H), 7.00–7.33 (m, 2 H), 6.73 (broad s, 2 H), 4.67–5.10 (m, 2 H), 3.91 (s, 6 H), 2.75–3.25 (m, 5 H), 2.40 (s, 3 H).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.19; H, 6.54; N, 4.33.

2,3-Dimethoxy-11-phenyl-8-oxoberbine (4h). A solution of 4.0 g of **3h** in 300 ml of *tert*-butyl alcohol was degassed and irradiated for 12 hr. Removal of the solvent and crystallization from methanol gave 3.05 g of **4h** (5,6,13,13a-tetrahydro-2,3-dimethoxy-11-phenyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 136–138°; uv 220 nm (end, 29,500), 244 (min, 11,000), 278 (27,500), 334 (3750); ir 1670, 1620, 1530, 1520, cm^{-1}; nmr δ 8.22 (d, $J \simeq$ 8 Hz, 1 H), 7.15–7.85 (m, 7 H), 6.75 (s, 1 H), 6.70 (s, 1 H), 4.65–5.15 (m, 2 H), 3.40 (s, 3 H), 3.37 (s, 3 H), 2.75–3.35 (m, 5 H).

Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.73; H, 5.94; N, 3.39.

Irradiation of 3e under Nondegassed Conditions. A solution of 6.0 g of the noncrystalline enamide **3e** was dissolved in 300 ml of ethyl acetate containing a few drops of triethylamine to retard hydrolysis. The solution was stirred magnetically and irradiated through Pyrex with a Hanovia 450-W medium pressure mercury arc for 9 hr. During the irradiation, 650 mg of a precipitate of 11-acetoxy-2,3,10-trimethoxyoxyprotoberberine **6** formed. Filtration of the precipitate and concentration of the solution, followed by dilution with petroleum ether gave an additional 3.05 g of **6**: mp 185–187°; uv 223 nm (ϵ 43,000), 261 (sh, 13,000), 282 (min, 5000), 306 (sh, 13,500), 332 (25,000), 356 (sh, 14,000), 370 (sh, 9500); ir 1770, 1655, 1615, 1520 cm^{-1}; nmr δ 7.86 (s, 1 H), 7.23 (s, 2 H), 6.75 (s, 2 H), 4.28 (t, 2 H), 3.97 (s, 3 H), 3.94 (s, 6 H), 2.92 (t, 2 H), 2.35 (s, 3 H); mass spectrum *m/e* 395 (parent, 31%), 367 (–CO, 11), 353 (–$OCCH_3$, 95), 338 (–$OCCH_3$, CH_3, 100), 310 (–CO, –$OCCH_3$, 41), 74 (22), 59 (49), 42 (93).

Despite repeated recrystallizations, a satisfactory analysis for **6e** could not be obtained. However, the mass spectrum, conversion to **8**, and the other data indicate the correct structure.

Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35; N, 3.54. Found: C, 64.98; H, 5.41; N, 3.41.

11-Hydroxy-2,3,10-trimethoxyoxyprotoberberine (8). A solution of 250 mg of **6** in 50 ml of methanol containing a few milligrams of *p*-toluenesulfonic acid monohydrate was refluxed for 24 hr. Upon cooling, 170 mg of **8** (5,6-dihydro-11-hydroxy-2,3,10-trimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one) crystallized: mp 267–268°; uv 226 nm (ϵ 34,000), 245 (min, 24,500), 265 (34,000), 288 (min, 6500), 330 (27,000), 358 (sh, 16,000); ir 3180, 1650, 1615, 1590, 1520 cm^{-1}; nmr (DMSO-d_6) δ 7.61 (s, 1 H), 7.45 (s, 1 H), 7.11 (s, 1 H), 7.03 (s, 1 H), 6.92 (s, 1 H), 4.23 (t, 2 H), 3.90 (s, 6 H), 3.84 (s, 3 H), 2.90 (t, 2 H).

Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.92; H, 5.56; N, 3.83.

General Procedure for DDQ Dehydrogenation of 8-Oxoberbines. A 1% solution of 8-oxoberbine in either benzene or toluene is treated with a weight equivalent of dichlorodicyanobenzoquinone for 0.25 to 0.50 hr. The precipitated hydroquinone is filtered and the dehydrooxyprotoberberine isolated by chromatography on a short alumina column.

2,3-Dimethoxy-10,11-methylenedioxyoxyprotoberberine (9c). 8-Oxoberbine **4c** (500 mg) dehydrogenated as described above gave 383 mg of **9c** (5,6-dihydro-2,3-dimethoxy-8*H*-benzo[*a*][1,3]-benzodioxolo[5,6-*g*]quinolizin-8-one): mp 204–205° (ether–petroleum ether); uv 227 nm (ϵ 38,000), 245 (min, 17,500), 265 (25,000), 288 (min, 5500), 333 (25,000), 364 (sh, 12,000); ir 1655, 1620, 1585, 1515 cm^{-1}; nmr δ 7.72 (s, 1 H), 7.17 (s, 1 H), 6.81 (s, 1 H), 6.68 (s, 2 H), 6.00 (s, 2 H), 4.32 (t, 2 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 2.88 (t, 2 H).

Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.18; H, 4.94; N, 4.17.

2,3,10,11,12-Pentamethoxyoxyprotoberberine (9d). Compound **4c** (500 mg) was dehydrogenated with DDQ as described above to give 300 mg of **9d** (5,6-dihydro-2,3,10,11,12-pentamethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 170–171° (ethyl acetate–petroleum ether); uv 228 nm (ϵ 32,500), 249 (min, 23,000), 260 (25,000), 287 (min, 6500), 306 (sh, 12,500), 320 (sh, 19,000), 334 (24,000); ir 1650, 1605, 1520 cm^{-1}; nmr δ 7.53 (s, 1 H), 7.33 (s, 1 H), 7.11 (s, 1 H), 6.77 (s, 1 H), 4.39 (t, 2 H), 4.05 (s, 3 H), 4.01 (s, 9 H), 3.95 (s, 3 H), 2.95 (t, 2 H).

Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5,83; N, 3.52. Found: C, 66.33; H, 5.88; N, 3.62.

2,3-Dimethoxy-11-methyloxyprotoberberine (9f). A solution of 8-oxoberbine **4f** (500 mg) is dehydrogenated with DDQ to give 400 mg of **9f** (5,6-dihydro-2,3-dimethoxy-11-methyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 169–170° (ethyl acetate–petroleum ether); uv 220 (ϵ 36,000), 226 (sh, 32,000), 235 (sh, 29,000), 249 (sh, 21,000), 257 (18,000), 282 (min, 4500), 302 (sh, 11,000), 316 (sh, 18,000), 330 (25,000), 344 (22,500), 362 (15,000); ir 1660, 1630, 1620 (sh), 1605, 1525 cm^{-1}; nmr δ 8.35 (d, $J \simeq$ 8 Hz, 1 H), 7.33 (s, 1 H), 7.28 (s, 1 H), 7.25 (d, 1 H), 6.82 (s, 1 H), 6.75 (s, 1 H), 4.36 (t, 2 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 2.92 (t, 2 H), 2.47 (s, 3 H).

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.65; H, 6.01; N, 4.40.

11-Chloro-2,3-dimethoxyoxyprotoberberine (9g). A solution of compound **4g** (1.00 g) was dehydrogenated with DDQ to 700 mg of **9g** (11-chloro-5,6-dihydro-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]-quinolizin-8-one): mp 220–221°; uv 227 nm (ϵ 29,500), 238 (28,000), 258 (sh, 16,000), 266 (sh, 11,000), 283 (min, 4000), 334 (25,500), 350 (sh, 21,000), 366 (sh, 13,000); ir 1665, 1615, 1520 cm^{-1}; nmr δ 8.30 (d, $J \simeq$ 8.5 Hz, 1 H), 7.15–7.60 (m, 3 H), 6.73 (s, 2 H), 4.31 (t, 2 H), 3.97 (s, 3 H), 3.92 (s, 3 H), 2.92 (t, 2 H).

Anal. Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.49; H, 4,83; N, 4.14.

2,3-Dimethoxy-11-phenyloxyprotoberberine (9h). Compound **4h** (400 mg) was dehydrogenated to give 360 mg of **9h** (5,6-dihydro-2,3-dimethoxy-11-phenyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 187–189°; uv 220 nm (end, ϵ 32,000), 238 (min, 18,000), 274 (37,000), 304 (min, 14,000), 322 (sh, 20,000), 335 (27,500), 362 (sh, 13,500), 376 (10,000); ir 1655, 1620, 1520 cm^{-1}; nmr δ 7.25–7.75 (m, 8 H), 6.92 (s, 1 H), 6.75 (s, 1 H), 4.40 (t, 2 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 2.93 (t, 2 H).

Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.20; H, 5.67; N, 3.46.

2,3,10,11-Tetramethoxyberbine (Xylopinine) (10b). A solution of 500 mg of 2,3,10,11-tetramethoxy-8-oxoberbine **4b** in 65 ml of dry benzene was reduced, under nitrogen, with 2 ml of a 70% solution of sodium bis(methoxyethoxy)aluminum hydride in benzene (Aldrich Red-al) for 16 hr. The reaction mixture was quenched by careful addition of saturated Rochelle salt. The organic layer was separated and the salt solution extracted with methylene chloride (2 × 50 ml). The combined organic extracts were dried with sodium sulfate and the solvent removed. Crystallization from ether–petroleum ether gave 400 mg of *dl*-xylopinine (**10b**): mp 142–143°; ir 1610, 1515 cm^{-1}; uv 224 nm (ϵ 16,000), 251 (min, 750), 280 (8000), 284 (8000), 289 (7000); nmr δ 6.63 (s, 1 H), 6.57 (s, 1 H), 6.52 (s, 1 H), 6.47 (s, 1 H), 3.84 (s, 3 H), 3.80 (s, 9 H), 2.9–3.7 (m, 9 H).

2,3-Dimethoxy-10,11-methylenedioxyberbine (10c). To a solution of 792 mg of 8-oxoberbine **4c** in 50 ml of dry tetrahydrofuran was added 500 mg of lithium aluminum hydride and the mix-

ture was refluxed for 16 hr. After cooling to room temperature the excess $LiAlH_4$ is destroyed with ethyl acetate and the mixture poured into distilled water. The aqueous solution was extracted with chloroform (3 × 200 ml), and the organic extracts were dried with sodium sulfate. Removal of solvent gave a gum which was crystallized from 5 ml of methanol to give 325 mg of **10c:** mp 155–156°; uv 220 nm (end, ϵ 15,000), 232 (sh, 11,000), 255 (min, 1000), 289 (8500); ir 1620, 1530, 1510 cm^{-1}; nmr δ 6.75 (s, 1 H), 6.64 (s, 2 H), 6.55 (s, 1 H), 5.90 (s, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.5–3.75 (m, 9 H).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.70; H, 6.24; N, 4.13. Found: C, 70.56; H, 6.40; N, 3.93.

The mother liquor which was found to contain appreciable amounts of **10c** was added to 25 ml of ethyl acetate and 3 ml of hydrogen chloride saturated isopropyl alcohol. The combined solvents were removed to give the crude hydrochloride as a light tan solid. The solid was suspended in 25 ml of refluxing ethyl acetate and filtered to give 244 mg of 2,3-dimethoxy-10,11-methylenedioxyberbine hydrochloride: mp 263–265°, ir 1620, 1530, 1505 cm^{-1}.

Anal. Calcd for $C_{20}H_{21}NO_4 \cdot HCl \cdot 0.5H_2O$: C, 62.41; H, 6.02; N, 3.64. Found: C, 62.13; H, 6.00; N, 3.44.

2,3,10,11,12-Pentamethoxyberbine (10d). A solution of 250 mg of **4d** is reduced as described for **4b** to give 220 mg of **10d:** mp 117–120° (methanol–water); uv 227 nm (sh, ϵ 19,500), 252 (min, 1000), 281 (5500), 290 (sh, 3500); ir 1530, 1520, 1505 cm^{-1}; nmr δ 6.83 (s, 1 H), 6.64 (s, 1 H), 6.46 (s, 1 H), 3.92, 3.88, 3.85 (s, 15 H), 2.5–3.7 (m, 9 H).

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.73; H, 7.19; N, 3.61.

11-Hydroxy-2,3,10-trimethoxyberbine (10e). A solution of 535 mg of **4e** is reduced as described for **4b.** Crystallization from ethyl acetate–petroleum ether gave 286 mg of **10e:** mp 227–229°; uv 200 nm (end, ϵ 15,500), 252 (min, 1000), 285 (8000), 303 (min, 1500), 317 (2000); ir 1615, 1515 cm^{-1}; nmr (DMSO-d_6) δ 6.90 (s, 1 H), 6.69 (s, 1 H), 6.65 (s, 1 H), 6.60 (s, 1 H), 3.75 (s, 3 H), 3.73 (s, 6 H), 2.5–3.7 (m, 9 H).

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.20; H, 6.79; N, 4.00.

11-Acetoxy-2,3,10-trimethoxyberbine (11). To a suspension of 173 mg of **10e** in 0.8 ml of acetic anhydride, 1 ml of pyridine, and 8 ml of methylene chloride was added a few crystals of 4-dimethylaminopyridine. The suspended solid immediately dissolved to a light yellow solution. After standing for 16 hr, excess methanol was added and the solvents removed. The residue was partitioned between water and methylene chloride. The organic layer was dried with sodium sulfate and removed at the aspirator. Crystallization from ether–petroleum ether gave 172 mg of **11:** mp 139–141°; uv 220 nm (end, ϵ 14,000), 250 (min, 750), 276 (4500), 280.5 (5000), 285.5 (5000); ir 1770, 1625, 1525 cm^{-1}; nmr δ 6.87 (s, 1 H), 6.73 (s, 1 H), 6.69 (s, 1 H), 6.64 (s, 1 H), 3.87 (s, 6 H), 3.80 (s, 3 H), 2.5–3.7 (m, 9 H), 2.30 (s, 3 H).

Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.57; H, 6.76; N, 3.63.

2,3-Dimethoxy-11-methylberbine (10f). The 8-oxoberbine **4f** (500 mg) was reduced as described for **10b** to yield 450 mg of **10f** as a light tan solid: mp 116–118° (methanol–water); uv 220 nm (end, ϵ 18,500), 232 (sh, 9000), 251 (min, 1500), 277 (5000), 284 (4500), 290 (4000); ir 1620, 1525, 1515 cm^{-1}; nmr δ 6.97 (s, 3 H), 6.78 (s, 1 H), 6.63 (s, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 2.5–3.8 (m, 9 H), 2.30 (s, 3 H).

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.74; H, 7.66; N, 4.68.

11-Chloro-2,3-dimethoxyberbine (10g). A solution of 500 mg of **4g** in 50 ml of dry tetrahydrofuran was reduced with 300 mg of $LiAlH_4$ for 1.5 hr. The excess $LiAlH_4$ was destroyed with a saturated Rochelle salt solution and the aqueous extracted with methylene chloride (2 × 250 ml). The organic phase was dried with sodium sulfate and the solvent removed. Crystallization from methanol–water gave 250 mg of **10g:** mp 128–130°; uv 220 nm (end, ϵ 19,000), 280 (6000); ir 1525 cm^{-1}; nmr δ 6.83–7.34 (m, 3 H), 6.75 (s, 1 H), 6.66 (s, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.67–4.00 (m, 2 H), 2.5–3.5 (m, 7 H).

Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11 N, 4.25. Found: C, 69.04; H, 6.26; N, 4.27.

2,3-Dimethoxy-11-phenylberbine (10h). The oxoberbine **4h** (370 mg) was added to 370 mg of $LiAlH_4$ in 50 ml of THF under nitrogen and the mixture stirred. After 16 hr the solution was a light green. The excess $LiAlH_4$ was destroyed with saturated Rochelle salt solution and the aqueous layer was extracted with methylene chloride (4 × 60 ml). The combined organic extracts were dried with sodium sulfate and evaporated. The residue was crystallized from methanol–water to give 215 mg of **10h:** mp 119–121°; uv 220 nm (end, ϵ 29,000), 232 (min, 16,000), 253 (20,000), 280 (sh, 9500), 290 (5000); ir 1530, 1520 cm^{-1}; nmr δ 7.0–8.2 (m, 8 H), 6.80 (s, 1 H), 6.65 (s, 1 H), 3.58–4.09 (m, 2 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.59 (m, 1 H), 2.34–3.34 (m, 6 H).

Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.59; H, 6.77; N, 3.97.

Registry No. —**5,** 52050-72-3; **7,** 52050-73-4; **8,** 52050-74-5; **11,** 52050-75-6; benzoic acid, 65-85-0; 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline, 4721-98-6; 3,4-dimethoxybenzoic acid, 93-07-2; piperonylic acid, 94-53-1; 3,4,5-trimethoxybenzoic acid, 118-41-2; acetylvanillic acid, 10543-12-1; *p*-toluoyl chloride, 874-60-2; *p*-chlorobenzoyl chloride, 122-01-0; 4-phenylbenzoyl chloride, 14002-51-8.

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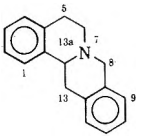

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Synthesis of Cyclopentano-1,2,3,4-tetrahydroisoquinolines. Novel Heterocyclic Systems

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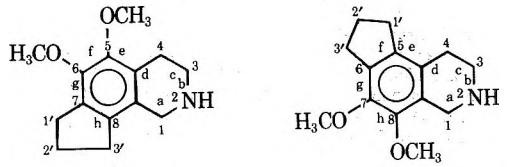
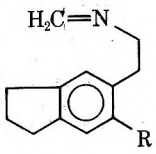
The synthesis of the previously unreported dimethoxy-substituted 5,6-cyclopentano[*f*]- and 7,8-cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinolines is described. Following numerous attempts to synthesize these new ring systems from various indan derivatives using standard isoquinoline ring closures, a procedure involving the acid-catalyzed Pictet-Spengler closure of the Schiff base of 4,5-dimethoxy-6- (and 7-) aminoethylindan was developed. The use of the chemical shift reagent $Eu(DPM)_3$ was of particular importance in the elucidation of the structures of the intermediate 4,5-dimethoxyindan-6- (and 7-) aldehydes (**11** and **10**).

Our continued interest in heterocycles of medicinal interest[1] has more recently prompted an investigation of the synthesis of the previously unreported tricyclic cyclopentano-1,2,3,4-tetrahydroisoquinolines having the cyclopentane ring at the 7,8 (*h*) (**1**) and 5,6 (*f*) (**2**) positions. The initial approach involved attempts to synthesize the cited compounds by the addition of the nitrogen-containing ring to an indan system by way of a Pictet–Spengler type ring closure of compound **3** shown below. Attempts were also made to effect ring closure on the acetamido analog **4** using the Bischler–Napieralski method.



1

2



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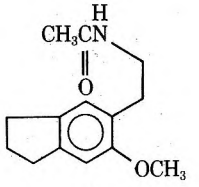


4

R = CH_3, OCH_3

Repeated attempts varying conditions of temperature, time, and solvent as well as closing reagent yielded no identifiable ring-closed product. However, utilization of the Pictet–Spengler reaction on 4,5-dimethoxyindan (**9**) yielded the sought products in respectable yields. The overall reaction sequence starting from 2,3-dimethoxybenzaldehyde is shown in Scheme I. Assignment of the position of the aldehyde grouping in the isomeric aldehydes **10** and **11** was made on the basis of their nmr spectra. The solid aldehyde **10**, which crystallized from the isomeric mixture, showed signals (CCl_4) at δ 2.02 (m, 2, CH_2), 2.84 (t, 2, CH_2), and 3.15 (t, 2, CH_2) corresponding to the methylenes of the cyclopentane ring at positions 2, 3, and 1, respectively. Addition of a chemical shift reagent $Eu(DPM)_3$ very clearly separated these methylene signals to produce peaks at δ 2.66 (m, 2, 2-CH_2), 3.61 (t, 2, 3-CH_2), 4.66 (t, 2, 1-CH_2). The liquid aldehyde (**11**) on the other hand showed only two signals for the methylenes of the cyclopentane ring; one at δ 2.04 (m, 2, 2-CH_2) and a second complex signal at 2.52–3.22 (4, 1- and 3-CH_2). On addition of the shift reagent the complex peak at δ 2.52–3.22 was better defined into a triplet (3.48) accounting for the methylenes at positions 1 and 3.

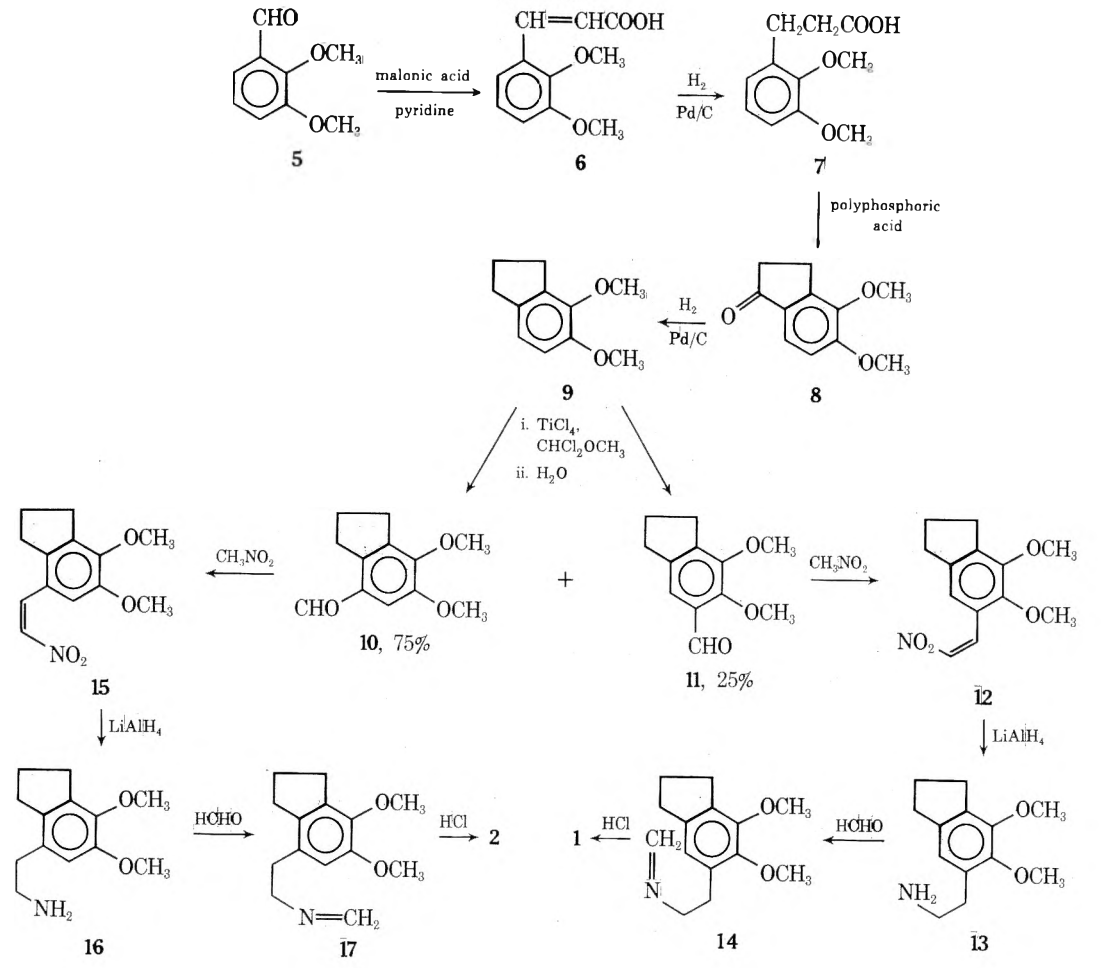
Attempts were also made to correlate the signals for the methoxyl groupings using 2,3-dimethoxybenzaldehyde (2,3-DMB) and 3,4-dimethoxybenzaldehyde (3,4-DMB) as reference compounds. As anticipated, the methoxyls of 2,3-DMB were separated (CCl_4) (6 Hz) to a greater extent than the methoxyls of 3,4-DMB (singlet at 2.20). Addition of $Eu(DPM)_3$ resulted in a shift which magnified the separation to the extent of 28 Hz for the methoxyls of 2,3-DBM and 4 Hz for the 3,4-DMB methoxyl protons. It was expected that a similar situation might be apparent with compounds **10** and **11**. The methoxyl signals indeed were separated to a greater extent (4 Hz) in **11** (*cf.* 2,3-DMB) than in **10** (2 Hz) (*cf.* 3,4-DMB). Addition of the shift reagent however did not produce results comparable to the dimethoxybenzaldehydes (33 Hz for **10**; 14 Hz for **11**) presumably due to the additional substitution on the aromatic ring resulting in steric hindrance to the binding of the shift reagent.

Examination of the aldehyde protons of **10** and **11** in conjunction with the aldehyde protons of 2,3-DMB and 3,4-DMB provided further evidence for the assignments of **10** and **11**. In both 3,4-DMB and **11** the aldehyde signal was located downfield from the aldehyde of 2,3-DMB and **10** (δ 10.5 and 10.24 *vs.* 9.76 and 9.90, respectively), further supporting the analogous location of the aldehyde in **10** with 2,3-DMB and **11** with 3,4-DMB. The aromatic signals in **10** and **11** were not of great significance in the structural assignment.

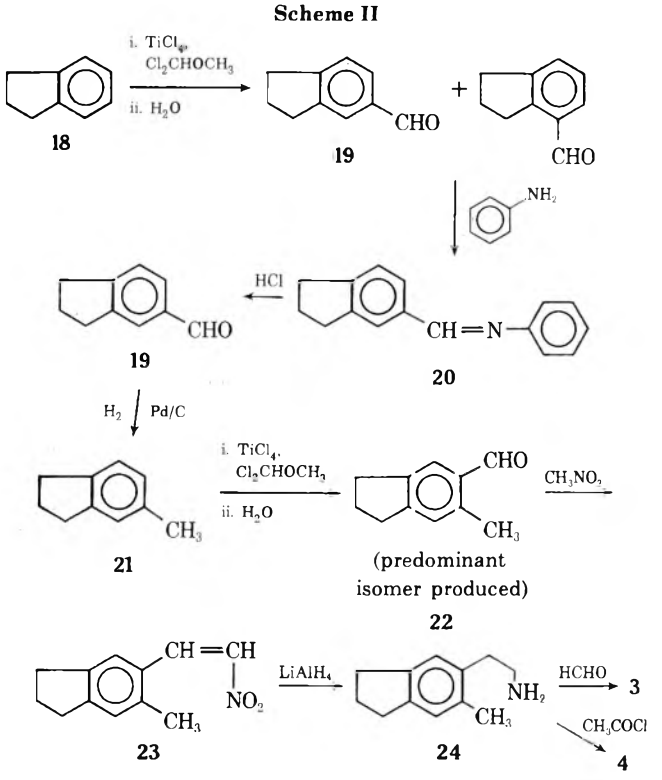
The aldehydes were converted to the nitrovinyl derivatives[2] which on $LiAlH_4$ reduction in high dilution[3] gave the corresponding dimethoxyaminoethylindans (**13** and **16**). Formation of the intermediate Schiff base (**14** and **17**) using formaldehyde followed by the Pictet–Spengler acid-catalyzed ring closure yielded the hydrochloride salt of the desired 7,8-cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline (**1**) and 5,6-cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline (**2**). The absence of aromatic protons in the nmr spectrum in addition to microanalytical and ir spectral data confirmed the successful ring closures.

The preparation of compounds **3** and **4** (where R = CH_3) was achieved from indan as shown in Scheme II. The identity of the isolated anilide[4] **20** was determined by hydrolysis to the known aldehyde[4] **19**. Nmr data confirmed the location of the aldehyde grouping: δ 7.35 [d, 1, CH= (7)], 7.69 [d, 1, CH= (6)], 7.74 [s, 1, CH= (4) overlapped with CH= (6)]. Reduction of **19** to the methyl derivative **21** followed by a second formylation yielded **22**. Confirmation of the structure of **22** was made from a comparison of the nmr spectrum of **22** with that of **21**. Compound **21** showed the 4, 6, and 7 protons as a multiplet at about δ 7.08. Aldehyde **22**, however, showed as expected one proton at δ 7.08 (4 proton) and one at 7.58 (7 proton). Coupled with a downfield shift of the methyl signal (δ 2.68) these data clearly indicated the location of the CHO grouping at the 6 position. Treatment of **22** with nitromethane followed by reduction

Scheme I



Scheme II



with $LiAlH_4$ yielded the desired aminoethylindan (**24**) which readily gave the imine **3** and acetamide **4**. The preparation of **3** and **4** where R = OCH_3 was accomplished by a modified procedure involving the use of *N*-methylformanilide[5] to introduce the aldehyde grouping.

Experimental Section

All melting points were determined on a Swissco melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-33 infrared spectrophotometer. Vapor phase chromatograms were recorded on a Varian Autoprep model 700 chromatograph. Nmr spectra were recorded on Varian A-60 and Perkin-Elmer R24 spectrometers. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn., and Chemalytics, Tempe, Ariz.

4,5-Dimethoxy-1-indanone (8). 2,3-Dimethoxybenzaldehyde (**5**) was treated with malonic acid in pyridine according to the procedure of Koo, *et al.*,[6] to yield 2,3-dimethoxycinnamic acid (**6**). Low pressure (45 psi) hydrogenation of **6** (25.0 g) over Pd/C (1.75 g) in glacial acetic acid afforded quantitative yields of β-(2,3-dimethoxyphenyl)propionic acid (**7**). Treatment of **7** with polyphosphoric acid at 60° according to the procedure of Koo[7] yielded 4,5-dimethoxy-1-indanone (**8**), mp 71–72° (lit.[7] 74–75°).

4,5-Dimethoxyindan (9). A mixture of 52.6 g (0.275 mol) of **8**, 3.00 g of 5% Pd/C, 100 ml of glacial acetic acid, and 20 drops of concentrated HCl was hydrogenated at 45 psi and room temperature until hydrogen uptake ceased. Following filtration of the used catalyst, two methods may be used to work up the reaction.

A. The acid was neutralized with dilute NaOH and the product extracted from the aqueous phase with ether. The ether was removed by distillation and crude **9** was distilled under reduced pressure, bp 133–135° (15 mm) [lit.[8] bp 124–125° (14 mm)] yielding 42.0 g (86.4%) of clear liquid. Infrared analysis showed the absence of carbonyl absorption.

B. Most of the acetic acid was removed on the rotary evaporator and the remaining liquid was distilled as before giving **9** with no significant difference in yield from that obtained in A.

4,5-Dimethoxy-7-indanaldehyde (10). To a solution of 10.0 g (0.056 mol) of **9**, 24.0 g (0.126 mol) of titanium tetrachloride, and

104 ml of CH_2Cl_2 in a 250-ml 3-necked flask fitted with a thermometer and condenser and magnetically stirred, 11.0 g (0.096 mol) of α,α-dichloromethyl methyl ether was added rapidly dropwise at 0°. Hydrogen chloride gas was liberated during the course of the reaction. After vigorous evolution of HCl had subsided, the reaction solution was allowed to slowly warm to room temperature and was stirred for 1–2 hr. The solution was refluxed for 6 hr and cooled and the reaction mixture poured over 200 ml of ice and water (ether and salt were added at this point to increase the volume of the organic phase, to invert the two layers and to break emulsions). The organic phase was washed with 2 × 100 ml of 8% $NaHCO_3$ solution and 1 × 100 ml of water and dried over Na_2SO_4. After removal of the solvent by distillation, the mixture of aldehyde isomers was distilled under high vacuum [bp 115–126° (0.28 mm)] giving 10.2 g of the aldehydes (88%). The 7-position aldehyde (**10**) which crystallized from the liquid was filtered This process was repeated several times by seeding the filtrate followed by cooling. Gas chromatography showed the white crystalline solid to be one component of the two component mixture. In this way 4.24 g of white solid was obtained, mp 41–44°, yield 38.5%. A small sample was recrystallized from petroleum ether to obtain material for elemental analyses. The nmr spectrum (CCl_4) showed signals at δ 2.02 (m, 2, J = 8.0 Hz, 2-CH_2), 2.84 (t, 2, J = 8.0 Hz, 3-CH_2), 3.15 (t, 2, J = 8.0 Hz, 1-CH_2), 3.79 (s, 3, 4-OCH_3), 3.82 (s, 3, 5-OCH_3), 7.05 (s, 1, 8-H), 9.90 (s, 1, CHO).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.98; H, 6.84. Found: C, 70.03; H, 6.66.

4,5-Dimethoxy-7-nitrovinylindan (15). To a 100-ml 3-necked round-bottom flask fitted with a condenser and thermometer and magnetically stirred was added 12.97 g (0.063 mol) of **10**, 3.00 g (0.039 mol) of ammonium acetate, 13.0 ml (0.292 mol) of CH_3NO_2, and 40 ml of glacial acetic acid. This was heated for 1–2 hr at 112°. As the reaction solution began to cool the entire solution solidified. After this was cooled in an ice bath and the solvent was removed by filtration, the solid was washed with a small volume of acetic acid giving fine yellow needles (9.55 g) after thorough drying. The filtrate was poured into 300 ml of ice and water which precipitated a slightly gummy, yellow-brown solid. This gave an additional 1.43 g of crystalline solid after drying and crystallizing from methanol giving a total yield of 10.98 g (70%). An analytical sample melted at 128–130°: nmr ($CDCl_3$) δ 2.16 (m, 2, 2-CH_2), 3.02 (t, 4, 1- and 3-CH_2), 3.87 (s, 3, 4-OCH_3), 3.93 (s, 3, 5-OCH_3), 6.91 (s, 1, 6-H), 7.49 (d, 1, J = 14 Hz, =$CHNO_2$), 8.10 (d, 1, J = 14 Hz, **CH**=$CHNO_2$).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.79; H, 6.12; N, 5.53.

4,5-Dimethoxy-7-aminoethylindan (16). To a slurry of 15.0 g (0.395 mol) of $LiAlH_4$ and 500 ml of anhydrous ether in a 5-l. 3-necked flask fitted with a condenser, mechanical stirrer, and dropping funnel was added 20.0 g (0.084 mol) of **15** dissolved in 2 l. of ether. The addition was made over a period of ~4 hr while refluxing the ether slurry. When addition was complete, refluxing was continued for an additional 1–2 hr. After the addition of 20 g of Celite and then 70 ml of water slowly, dropwise, with cooling in an ice bath, the supernatant ether was decanted and the salts were washed with fresh ether several times, followed by decantation and finally filtration. The solvent was removed by distillation and more thoroughly on the rotary evaporator. Cooling in an ice bath gave 15.91 g (90%) of a slightly yellow solid: mp 45–48°; ir (liquid film) 1605 (aromatic C=C and NH_2), 3190, 3300, 3370 cm^{-1} (NH_2). High vacuum distillation gave an analytical sample.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.32. Found: C, 70.22; H, 8.49; N, 6.18.

7,8-Dimethoxycyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline Hydrochloride (2). To 11.1 ml of formalin in a round-bottom flask heated at 60–70° and magnetically stirred was added 10.95 g (0.049 mol) of **16** (dissolved in 22 ml of methanol) rapidly dropwise. After 50 min of heating, the solvent was thoroughly removed on the rotary evaporator. The ir spectrum showed absence of primary amine stretching vibrations at 3190, 3300, and 3370 with a weakening in intensity of the peak at 1605 cm^{-1}. This material was dissolved in 55 ml of 23% HCl and heated on the water bath with stirring at 50–60° for 30 min. The water–acid solvent was removed on the evaporator and the residue was dried overnight in a vacuum oven giving a hard solid which yielded 11.14 g (84.1%) of **2** when crystallized from acetonitrile–absolute alcohol: mp 232–235° dec; nmr ($CDCl_3$) δ 2.10 (m, 2, 2′-CH_2), 2.82 (m, 4, 1′- and 3′-CH_2), 3.42 (broad m, 2, 1-CH_2), 3.79 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 4.30 (broad s, 2, > $^+NH_2$), and absence of an aromatic proton signal.

Anal. Calcd for $C_{14}H_{20}NO_2Cl$: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.58; H, 7.36; N, 5.33; Cl, 13.29.

4,5-Dimethoxy-6-indanaldehyde (11). The 6-indanaldehyde was obtained by high vacuum (20–50μ) fractional distillation of the mixture of aldehydes remaining after repeated crystallization and filtering of the 7-aldehyde, **10**. The 6-aldehyde distilled as a pure substance in the first fractions followed by a mixture of the aldehydes and finally the pure 7-aldehyde. The 6-aldehyde was a liquid at room temperature but crystallized when refrigerated. An approximate mp (11°) was obtained from the temperature of a mixture of the solid in equilibrium with the liquid; nmr (CCl_4) showed δ 2.04 (m, 2, 2-CH_2), 2.52–3.22 (m, 4, 1- and 3-CH_2), 3.87 (s, 3, 5-OCH_3), 3.94 (s, 3, 4-OCH_3), 7.32 (s, 1, 7-H), 10.24 (s, 1, CHO).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.13; H, 6.87.

4,5-Dimethoxy-6-nitrovinylindan (12). In a 2-l. 3-necked flask fitted with a condenser and thermometer and magnetically stirred, 126.7 g (0.613 mol) of **11**, 29.3 g (0.380 mol) of ammonium acetate, 127 ml (2.82 mol) of nitromethane, and 390 ml of acetic acid were heated at 112° for 45 min. After cooling in the refrigerator and scratching with a glass rod the solution crystallized. After filtering and washing with a few ml of cold acetic acid the product was dried under vacuum overnight and recrystallized from methanol yielding 104.4 g (68%) of yellow needles: mp 103.5–104.5°; nmr ($CDCl_3$) δ 2.12 (m, 2, 2-CH_2), 2.92 (m, 4, 2- and 3-CH_2), 3.95 (s, 3, 4-OCH_3), 3.99 (s, 3, 5-OCH_3), 7.16 (s, 1, 7-H), 7.76 (d, 1, J = 14 Hz, **CH**=$CHNO_2$), 8.24 (d, 1, J = 14 Hz, CH=**CH**NO_2).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.45; H, 6.17; N, 5.84.

4,5-Dimethoxy-6-aminoethylindan (13). To 9.2 g (0.242 mol) of $LiAlH_4$ in 400 ml of anhydrous ether was added 12.17 g (0.048 mol) of **12** in 1 l. of anhydrous ether dropwise over a period of 4 hr while refluxing; this was followed by refluxing for a further 2 hr. After the addition of 15 g of Celite and decomposition of excess $LiAlH_4$ with 40 ml of H_2O (while cooling in an ice bath), the ether was decanted and the salts were washed twice with ether, followed by decantation and finally filtration. The ether was removed by distillation and the product distilled yielding 7.42 g (68%): bp 101–103° (75 μ); ir (liquid film) 1576 (NH_2 and aromatic C=C), 3180, 3240, and 3365 cm^{-1} (NH_2).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.32. Found: C, 70.68; H, 8.71; N, 6.35.

5,6-Dimethoxycyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1). To 7.42 ml of formalin in a 100-ml boiling flask, 7.42 g (0.033 mol) of **13** in 15 ml of methanol was added dropwise with magnetic stirring and warming. After heating at 70–75° for 45 min, the mixture was rinsed into a separatory funnel with 3 × 50 ml of benzene. The benzene layer was washed with 3 × 100 ml of water and then the benzene was thoroughly removed on the evaporator. The ir spectrum showed absence of NH stretching and weakening of intensity of the band at 1576 cm^{-1}. This material weighed 8.72 g and was dissolved in 39 ml of 23% HCl followed by heating at 50–60° for 30 min. The aqueous acid was removed on the rotary evaporator yielding an oily, viscous substance which was dried in a vacuum oven in the presence of P_2O_5. A tacky hygroscopic solid was obtained which was crystallized from ether–ethanol giving fine needles, mp 215.5–216.5°. Further experimentation showed acetonitrile–ethanol to be a better recrystallization solvent. The nmr spectrum ($CDCl_3$ + D_2O) gave signals at δ 2.09 (m, 2, 2′-CH_2), 2.49–3.59 (m, 8, 3, 4, 1′ and 3′-CH_2), 3.79 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 4.16 (s, 2, 1-CH_2), and absence of an aromatic proton signal.

Anal. Calcd for $C_{14}H_{20}NO_2Cl$: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.47; H, 7.33; N, 5.15; Cl, 13.36.

5-Indanaldehyde (19). A solution of indan (**18**, 50 g, 0.423 mol) and 300 ml of CH_2Cl_2 were cooled to 0° in an ice–salt bath before 106.5 g (0.562 mol) of titanium tetrachloride was poured in. After additional cooling, 64.35 g (0.560 mol) of α,α-dichloromethyl methyl ether was added rapidly dropwise allowing the evolution of HCl gas to subside before removing the ice bath and stirring for 30 min. The mixture was poured over 600–700 ml of ice and water, well shaken, and then washed with water, 200 ml of 10% Na_2CO_3 solution, and finally with water. Often ether was added to invert the phases before washing. The solvent was evaporated and the residual dark oil was distilled under high vacuum giving a major fraction, 38.42 g (84%), bp 132–133° (15–16 mm). Gas chromatography showed the presence of two components with similar retention times in a ratio of ~20:80. The compounds were assumed to be the 4- and 5-aldehydes, the 5-aldehyde being present in greatest quantity and having the longest retention time. They were separated by formation of the anilide, and identified by recrystallization from acetonitrile followed by hydrolysis of the crystalline product. This

yielded a liquid which gave a single peak on the gas chromatograph which corresponded to the compound with greatest retention time. The anilide gave a melting point, 85–86°, which agreed with the value for 5-indanaldehyde anilide.[4] The literature does not mention the formation of an isomeric mixture during an alternate complex synthesis of **19**. The nmr spectrum ($CDCl_3$) gave signals at δ 2.16 (m, 2, 2-CH_2), 2.99 (t, 4, 1- and 3-CH_2), 7.35 (d, 1, J = 9 Hz, 7-H), 7.69 [d, 1, J = 9 Hz, CH= (6)], 7.74 [s, 1, CH= (4) overlapped with CH= (6)].

5-Methylindan (21). Low pressure (45 psi) hydrogenation of 16.78 g (0.115 mol) of **18** over 2.5 g of 5% Pd/C in 30 ml of glacial acetic acid and 25 drops of concentrated HCl yielded the desired compound. After Celite was added to the reaction mixture and filtration, the filtrate was made basic with 40 g (1 mol) NaOH in 300 ml of water at 0°. This was extracted with 3 × 90 ml of ether; the ether solution was washed with water, dried over Na_2SO_4, and concentrated. The concentrated liquid was distilled at atmospheric pressure, bp 197–198° [lit.[9] bp 74° (11 mm)], yielding 12.70 g (84%) of clear liquid. The nmr spectrum ($CDCl_3$) gave signals at δ 2.04 (m, 2, 2-CH_2), 2.33 (s, 3, CH_3), 2.89 (t, 4, 1- and 3-CH_2), 7.03 (m, 3, =CH).

5-Methyl-6-indanaldehyde (22). To 12.70 g (0.096 mol) of **21** in 55 ml of CH_2Cl_2 at 0° was added 24.70 (0.132 mol) of titanium tetrachloride. After cooling, 13.30 g (0.134 mol) of α,α-dichloromethyl methyl ether was added rapidly dropwise. After the evolution of HCl gas had subsided, the reaction mixture was poured over 225 ml of ice and water in a separatory funnel. Additional CH_2Cl_2 was added and the organic phase was washed with 100 ml of water followed by 2 × 100 ml of 10% $NaHCO_3$ solution. The precipitate which formed in the organic phase was dissolved by addition of ether. After washing again with 200 ml of water and drying over Na_2SO_4 the solvent was evaporated and the remaining dark liquid was distilled giving a clear liquid: bp 152–154° (18 mm); 10.51 g (68%); nmr (CCl_4) δ 2.06 (m, 2,2-CH_2), 2.57 (s, 3, CH_3), 2.90 (t, 4, 1- and 3-CH_2), 7.02 (s, 1, 4 =CH), 7.52 (s, 1, 7 =CH).

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.54. Found: C, 82.19; H, 7.55.

5-Methyl-6-nitrovinylindan (23). To 8.00 g (0.050 mol) of **22** in a round-bottom flask fitted with a condenser, magnetically stirred and heated in an oil bath, was added 13.00 g (0.213 mol) of CH_3NO_2, 1.25 g (0.016 mol) of ammonium acetate, and 27 ml of glacial acetic acid. After the solution was heated at an oil bath temperature of 95° for 18 hr, the flask was cooled to room temperature, scratched with a glass rod, and refrigerated. A crystalline product (6.06 g, 55%) was obtained by filtering, reducing the volume of the filtrate, and collecting additional material. Recrystallization from methanol gave an analytical sample: mp 84.5–86.5°; nmr ($CDCl_3$) δ 2.05 (m, 2, 2-CH_2), 2.42 (s, 3, 5-CH_3), 2.90 (t, 4, J = 7 Hz, 1- and 3-CH_2), 7.13 (s, 1, 4-H), 7.36 (s, 1, 7-H), 7.45 (d, 1, J = 13 Hz, =$CHNO_2$), 8.28 (d, 1, J = 13 Hz, C**H**=$CHNO_2$) (the doublet at 7.45 overlapped the singlet at 7.36).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.24; N, 6.69.

5-Methyl-6-aminoethylindan (24). To 10.3 g (0.271 mol) of $LiAlH_4$ and 295 ml of anhydrous ether in a 2-l. 3-necked flask fitted with a 500-ml dropping funnel, condenser with drying tube, and a mechanical stirrer, 13.54 g (0.066 mol) of **23** in 590 ml of anhydrous ether was added dropwise over a period of 4.5 hr at reflux temperature. Refluxing was continued for 2 hr and the mixture was allowed to stand overnight. After 6.0 g of Celite was added, excess hydride was decomposed by the slow dropwise addition of 37 ml of water with stirring and cooling. The white salts were washed several times with ether followed by decantation each time and finally filtration. Removal of the ether by distillation gave a liquid which distilled at 160–162° (15.5 mm) yielding 10.32 g (89.1%) of **22**. Elemental analyses were obtained for the hydrochloride salt of **24**, mp 229–231°.

Anal. Calcd for $C_{12}H_{18}NCl$: C, 68.07; H, 8.56; N, 6.61; Cl, 16.74. Found: C, 68.15; H, 8.48; N= 6/62: Cl, 16.61.

5-Methoxy-6-aminoethylindan. 5-Indanol was methylated with dimethyl sulfate according to the procedure of Hunsberger, *et al.*,[5] and subsequently formylated to yield 5-methoxy-indan-6-aldehyde by way of the Vilsmeir–Haack reaction. The preparation of 5-methoxy-6-aminoethylindan was achieved by reaction with nitromethane to form the nitrovinyl derivative by way of the general procedures outlined by Gairaud.[2] Reduction of this compound with $LiAlH_4$ as described in the preparation of **16** gave the desired product, bp 119–120° (0.3 mm) [lit.[10] bp 115–120° (0.03 mm)]. Our experience with the nitrovinyl derivative yielded a compound with a significantly higher melting point (92–94°) than the reported value for this compound (83–85°[10]).

1-Acetamido-2-(5-methoxy-6-indanyl)ethane (4). To 6.99 g (0.037 mol) of 5-methoxy-6-aminoethylindan in 51 ml of dry dimethylformamide, 4.7 g (0.046 mol) of acetic anhydride in 18.8 ml of benzene was added dropwise at 0° under nitrogen. The solution was slowly warmed to room temperature and stirred overnight and the solvent was removed on the rotary evaporator yielding a slightly yellow oil which solidified on cooling. Crystallization of the crude material (8.67 g) from ethyl acetate gave 5.60 g (71%) of pure material, mp 106–107°.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.32; H, 8.13; N, 6.00.

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Registry No.—**1** hydrochloride, 51932-54-8; **2** hydrochloride, 51932-55-9; **4**, 51932-56-0; **8**, 6342-80-9; **9**, 51932-57-1; **10**, 51932-58-2; **11**, 51932-59-3; **12**, 51932-60-6; **13**, 51932-61-7; **14**, 51932-62-8; **15**, 51932-63-9; **16**, 51932-64-0; **17**, 51932-65-1; **18**, 496-11-7; **19**, 30084-91-4; **21**, 874-35-1; **22**, 51932-66-2; **23**, 51932-67-3; **24**, 51932-68-4; **24** hydrochloride, 51932-69-5; 4-indanaldehyde, 51932-70-8; 5-indancarboxanilide, 51932-71-9; 5-methoxy-6-aminoethylindan, 13203-59-3.

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Pentacyclodecane Chemistry. XI. Low-Temperature Proton Magnetic Resonance and Other Studies on the Nature of the Secondary and Tertiary Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-yl (1,3-Bishomocubyl) Cations[1]

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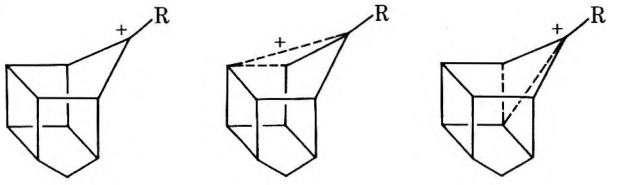
Reaction of 6-methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-*anti*-6-ol (**10**) with fluorosulfonic acid–sulfur dioxide at −50° gave the ring-opened allylic 3-methyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-yl cation (**21**). *anti*-6-Chloropentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (**14**) was synthesized by a photochemical ring closure; attempts to prepare the corresponding secondary cation **1** by the reaction of **14** with antimony pentafluoride or the reaction of the corresponding alcohol **8** with fluorosulfonic acid–antimony pentafluoride gave either decomposition products or the protonated alcohol. Oxymercuration–reduction of 6-methylenepentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (**11**) gave the alcohols, 6-methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-*syn*-6-ol (**9**) and **10**, in a 50:50 ratio. The acid-catalyzed addition of formic acid to olefin **11** and the acid-catalyzed equilibration of the formate **15** of the syn alcohol **9** at 27° gave the formate **15** and the formate **16** of the anti alcohol **10** in a 61:39 ratio, respectively. The *p*-nitrobenzoates **20** and **19** of alcohol **9** and of 6-phenylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-ol (**18**), respectively, were prepared, and a brief examination of their hydrolysis reactions was made. The relationship of these reactions to the problem of the nature of 1,3-bishomocubyl cations is discussed.

Previous papers of this series have described our efforts to determine the nature of the 1,3-bishomocubyl cation which is involved in solvolytic and related reactions.[1,2] Stereochemical and kinetic data seem most consistent with bridged ions, **3** and **5**, in the secondary system, but the classical ion **1** has not been ruled out.[1,2]

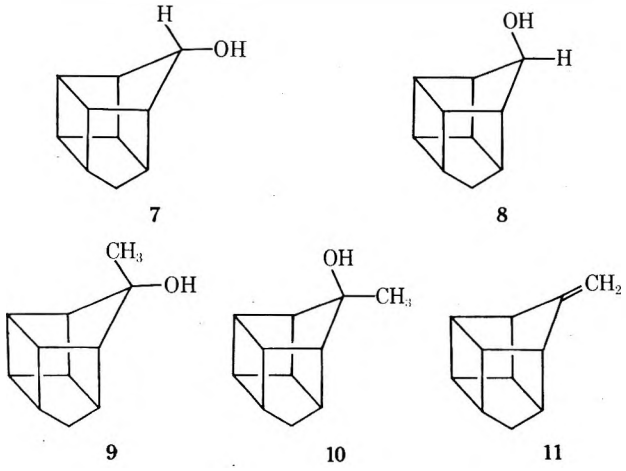


1, R = H; **2**, R = CH_3 **3**, R = H; **4**, R = CH_3 **5**, R = H; **6**, R = CH_3

The data on reactions which formally involve the tertiary carbonium ion **2** also are ambiguous with respect to the possible involvement of bridged ions such as **4** and **6**.[1,2d] This paper describes our attempts to observe, by nmr, the secondary and tertiary 1,3-bishomocubyl cations in strong acid media in an effort to gain additional insight into the nature of these carbonium ions. Also reported are several other reactions which relate to the same question.

Results

The stereospecific syntheses of the requisite alcohols **7–9** have been described previously.[1,2a,b,d] The anti tertiary alcohol **10** was obtained only in a 56:44 mixture with the syn isomer **9** by epoxidation of the olefin **11** followed by hydride reduction.[1,2d] The isomer **10** was obtained pure by fractional crystallization.[1]



7 **8** **9** **10** **11**

Attempts were made to take greater advantage of the slight inherent steric preference for attack on the one-carbon bridge of the 1,3-bishomocubyl skeleton from the anti direction[1,2b] by using the large mercury atom in oxymercuration reactions. Oxymercuration of the olefin **11** followed by sodium borohydride reduction proceeded to give a 50:50 mixture of the alcohols **9** and **10**. The complete lack of stereoselectivity does not necessarily indicate the absence of unbalanced steric effects in **11**, but could indicate a thermodynamic rather than kinetic distribution of products. The equilibrium distribution of alcohols **9** and **10** and of **7** and **8** is 50:50.[1,2b] This thermodynamic distribution probably arises by an equilibration of the initially formed mercurinium ions, a reaction which is well documented.[3] It has been shown, however, that in many cases oxymercuration is highly stereoselective and that the effects of equilibration can be minimized by using very short reaction times.[4] In our work reaction times as short as 1 min failed to alter the ratio of isomeric alcohols. Apparently the equilibration of the mercurinium ions is extremely fast. It was suggested that an equilibration effect can be overcome by carrying out the reaction in acetic acid.[5] This method presumably causes an acetate ligand to be transferred directly from mercury to carbon by an SNi-type process. Application of this technique in our work also failed to alter the isomer ratio.

Treatment of either the syn or anti isomers **9** and **10** with fluorosulfonic acid at −78° gave complex but identical nmr spectra at −30° (see Experimental Section). When a sample of the syn hydroxy isomer **9** was treated with fluorosulfonic acid–sulfur dioxide at −78° the spectrum at −50° was different (Figure 1). At −30° the spectrum was not the same as that obtained at −30° in fluorosulfonic acid alone; all the original absorptions had broadened. Lowering the temperature did not regenerate the original spectrum. When the sample was warmed to −10° the spectrum deteriorated rapidly, finally becoming a broad absorption at 4–1 ppm.

All attempts at preparation of the secondary pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-yl cation **1** (or a characterizable derived ion) from the alcohol **8** were futile. Dissolution of **8** in fluorosulfonic acid alone or in fluorosulfonic acid–

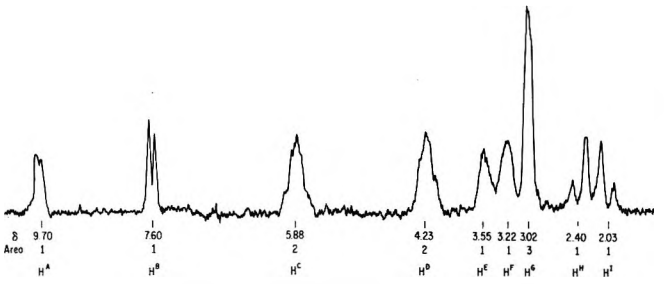
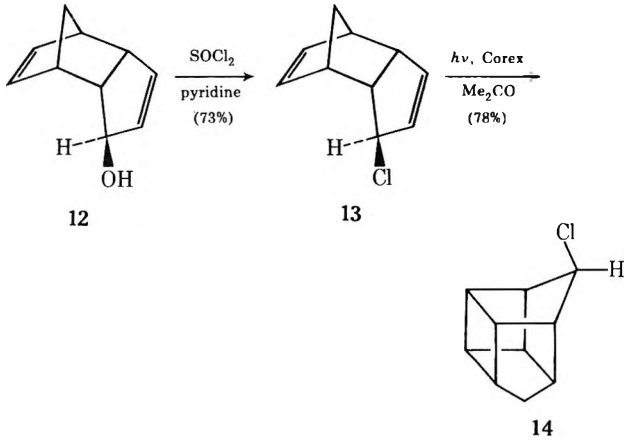


Figure 1. Nmr spectrum of species derived from alcohol **9** in fluorosulfonic acid–sulfur dioxide at −50°.

antimony pentafluoride in liquid sulfur dioxide at −78° gave a very dark solution. The nmr spectra of these solutions (−30°) and the alcohol **8** (in $CDCl_3$) were very similar, the main difference being that the proton of the carbinol carbon (C-6) was shifted downfield by about 1.1 ppm in the strong acid solutions. Ice water hydrolysis of the alcohol **8**–acid mixture gave only the starting alcohol **8**; none of the epimeric syn alcohol **7** was detected.

Secondary cations have been generated by reaction of an alkyl fluoride[6] or chloride, etc.,[7] with antimony pentafluoride and observed by nmr spectroscopy. A halogenated derivative of 1,3-bishomocubane was needed in order to attempt the generation of the secondary cation **1** by reaction of the halogenated derivative with antimony pentafluoride. Attempts to replace the hydroxyl group of the alcohol **8** with a chlorine atom were unsuccessful.

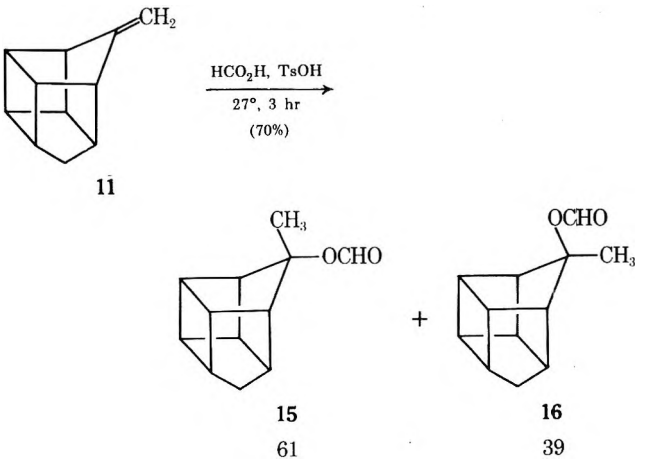
The anti chloride **14** was prepared from the anti allylic chloride **13** by photochemical ring closure.[8] The chloride **13** was synthesized by reaction of the anti allylic alcohol **12** with thionyl chloride in pyridine. The stereochemistry of



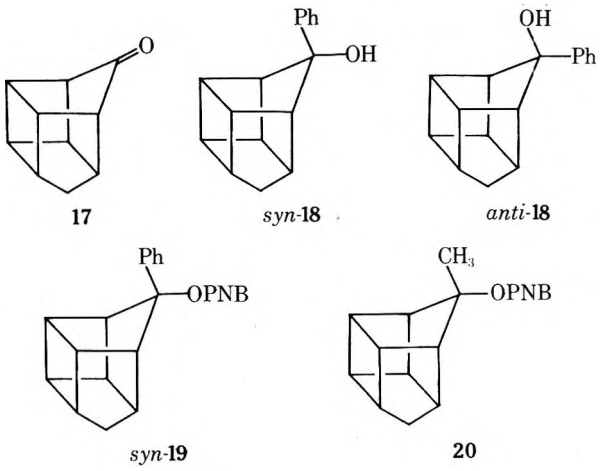
chlorides **13** and **14** was determined readily by nmr spectroscopy: **13** by comparison with **12** and the syn epimer of **12**, and **14** by comparison with the corresponding alcohol **8**, its epimer **7**, and other derivatives.[2b,9]

The product which resulted from the addition of *anti*-pentacyclodecyl chloride (**14**) to antimony pentafluoride in sulfur dioxide at −78° produced an nmr spectrum (at −50°) which showed only a weak, broad, unresolved absorption at 5–1 ppm. Similar results were obtained with **14** in antimony pentafluoride–sulfur dioxide–sulfuryl fluoride at −80°.

The authentic formate esters **15** and **16** were prepared from the corresponding alcohols **9** and **10** by reaction with acetic–formic anhydride. The *p*-toluenesulfonic acid catalyzed addition of formic acid to the olefin **11** produced a 61:39 mixture of syn and anti formates **15** and **16**, respectively. However this product distribution apparently was thermodynamically controlled; subjection of the syn formate **15** to the reaction conditions also gave a 61:39 product (**15**:**16**) distribution. The olefin **11** was insoluble in formic acid, thereby precluding an attempt at the homogeneous uncatalyzed addition. Heating either the syn (**9**) or anti (**10**) tertiary alcohol in refluxing formic acid (~100°) for 4 hr gave the same mixture of product formates (~35%) and decomposition products. None or very little of the unrearranged formates **15** and **16** was formed. The product mixture appeared to consist mainly of rearranged secondary formates, tentatively assigned as 1,4-bishomocubyl[2b] derivatives.



Phenylmagnesium bromide and the ketone **17** gave a mixture of phenylcarbinols, *syn*-**18** and *anti*-**18**. The exact



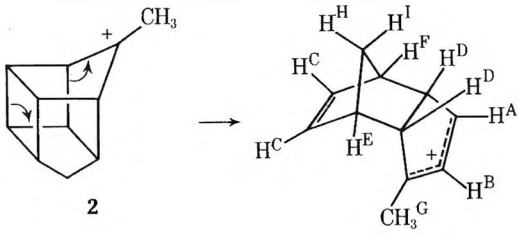
composition of this mixture could not be determined readily. It was apparent that one isomer predominated by at least a 4:1 ratio as determined by comparing infrared and nmr spectra of the crude reaction mixture and the purified major isomer which was isolated easily by recrystallization. The major isomer presumably was the syn hydroxy compound *syn*-**18**; this assignment was based on the analogy of the methyl Grignard reaction, methyllithium addition, and hydride reductions[1,2b] of the ketone **17**.

The *p*-nitrobenzoate ester, presumably *syn*-**19**, of the purified phenyl carbinol was prepared by a standard procedure, as was the methyl-substituted derivative **20**. The phenyl-substituted *p*-nitrobenzoate **19** was relatively unreactive in 60% aqueous dioxane; at 85°, 80% was recovered after 16 hr. At 115°, hydrolysis of **19** was nearly complete in 72 hr. The product (91%) was probably a mixture of the syn and anti isomers of the phenyl carbinol **18** based on spectroscopic data. The spectra indicated a more nearly equal distribution of the syn and anti isomers than was formed in the Grignard reaction with the ketone **17**. However, the exact isomer distribution could not be determined. The methyl-substituted *p*-nitrobenzoate **20** was resistant to sol-

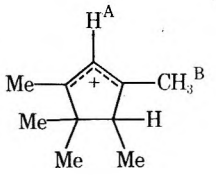
volysis in 60% aqueous dioxane at 100°. After 240 hr, 91% of the starting ester was recovered.

Discussion

The low-temperature (−30 or −50°) pmr spectra which were obtained after dissolving the tertiary alcohols **9** and **10** in fluorosulfonic acid are not consistent with the cation **2**. The low-field absorption at 9.7 ppm (−50°) is consistent with a proton on a carbon atom which bears considerable positive charge, but not a full positive charge.[6] The allylic cation **21** is a possible structure for the species that produced the spectrum in Figure 1. The protons corresponding



2 **21**

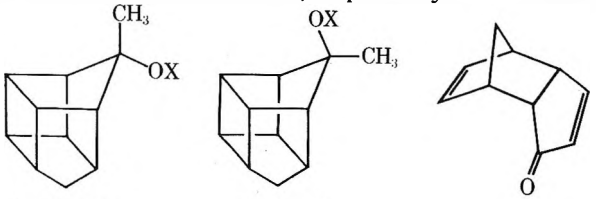


22

to those listed in Figure 1 are shown on the structure of **21**. For comparison purposes, the cyclopentenyl cation **22** in 96% sulfuric acid exhibited proton resonances at 7.62 ppm for H^A and 2.93 ppm for H^B.[10] Ion **21** must be regarded as a tentative assignment for the species derived from alcohol **9** in fluorosulfonic acid–sulfur dioxide, since attempts to isolate a derived alcohol by hydrolysis with ice in liquid sulfur dioxide[6] gave only a black, carbonaceous material. Ion **21** appears to be the simplest structure which is qualitatively in accord with the nmr spectrum and is easily derivable from the parent ion **2**.

The magnitude of the chemical shift of the proton on the carbinol carbon (C-6) of the secondary alcohol **8** in deuteriochloroform and fluorosulfonic acid is consistent with the formation of a protonated alcohol. The signal for the proton on the hydroxyl-bearing carbon atom of isopropyl alcohol (Me_2CHOH) appeared at 4.00 ppm[11] in deuterated chloroform solution, while in fluorosulfonic acid–antimony pentafluoride–sulfur dioxide at −60° this proton ($Me_2CHOH_2^+$) appeared at 5.5 ppm.[12] Similar results with other alcohols have been observed by Olah and coworkers.[13] In general they found that primary and secondary alcohols reacted with fluorosulfonic acid–antimony pentafluoride to give only the protonated alcohols[12] or monosulfates.[13] The only exceptions to this rule were *exo*-2-norbornanol and benzhydrol, both of which gave well-resolved nmr spectra of the corresponding carbonium ions.[13] In these cases cations are formed presumably because they are stable.

Acetolysis of the tosylates **23** and **25** gave 63–75 and 25–37% of the acetates **24** and **26**, respectively.[1,2d] The difference in behavior of the cationic species generated by the acetolyses of these tosylates at 45° and the reaction of the alcohol **9** in fluorosulfonic acid–sulfur dioxide at −50° is attributed mainly to the much longer lifetime of the ion generated by the latter route. In the solvolyses the ion's lifetime is too short to allow appreciable ring opening to occur. The driving force for the ring opening probably is relief of strain in the pentacyclic ring system (16.4 kcal/mol for the hypothetical **17** → **27** process[14]).



23, X = Ts
24, X = Ac

25, X = Ts
26, X = Ac

27

The *p*-toluenesulfonic acid catalyzed addition of acetic acid to the olefin **11** at ~25° gave a 68:32 mixture of acetates **24** and **26**, respectively.[1] The addition of formic acid to the olefin **11** was of interest, since one would predict the intermediate cation's positive charge to be more localized in this more polar medium than in acetic acid. If we assume, for example, that a single cation is involved in the acetic acid addition reaction, and that this cation has structure **4** in which **2** is the major resonance contributor and a localized secondary cation is the minor contributor, then the structure of the cation involved in the formic acid addition reaction should be more nearly like **2** with less contribution from the secondary resonance form. This prediction is based on the higher solvation energy associated with a localized positive charge as in **2** when compared with the more diffuse positive charge in a bridged ion[15] such as **4** (or **6**). Thus one might predict a syn:anti formate ratio (**15**:**16**) that was closer to 20:80 than to the 68:32 ratio observed for the acetates **24** and **26**. The 20:80 ratio was that observed for the syn and anti attack on the ketone **17** by metal hydrides and organometallic reagents.[1,2b] In addition the tosylate anion should have less effect (less ion pairing) in formic acid, which is a more highly ionizing medium than is acetic acid. However, the 61:39 ratio of syn (**15**) to anti (**16**) formates, obtained from the addition of formic acid to the olefin **11** in the presence of *p*-toluenesulfonic acid at 27°, apparently is the equilibrium ratio of the two formates. Treatment of the authentic syn formate **15** under the same reaction conditions gave the same mixture of formates. Since the kinetic product distribution from the formic acid–olefin **11** reaction was not determined, nothing can be said about the character of the presumed cationic intermediate **2**, **4**, or **6** in this reaction. Interestingly the corresponding tertiary acetate esters **24** and **26** were stable at 45° in acetic acid which contained 1 equiv of *p*-toluenesulfonic acid. The mechanism for isomerization of the formates **15** and **16** probably involves protonation followed by the loss of formic acid, and reversal of these processes. The reasons for the isomerization in formic acid and the stability of the acetates **24** and **26** in acetic acid are probably the greater protonating ability of the *p*-toluenesulfonic acid–formic acid mixture and the higher dielectric constant of formic acid compared with acetic acid (58.5 *vs.* 6.15[16]). The formation of charged intermediates, such as **2** and the protonated esters, would be lower energy processes in the higher dielectric medium.

Experimental Section

General. Melting points were taken in capillary tubes and were uncorrected. Boiling points were uncorrected. Infrared spectra were obtained by Mr. F. L. Beman and coworkers with a Perkin-Elmer 337 grating infrared spectrophotometer. Nmr spectra were obtained by Mr. Beman and coworkers with a Varian A-60 analytical spectrometer operating at 60 MHz. All chemical shifts (δ) are relative to internal tetramethylsilane (positive when downfield from the reference). Mass spectral analyses were carried out by Dr. L. A. Shadoff and coworkers with a magnetically scanning 90° sector spectrometer, an electron ionizing voltage of 75 eV, and a sample inlet temperature of 200°. High-resolution mass spectra were obtained with a CEC 21-110B spectrometer that had a variable-temperature direct probe sample introduction system. Gas chro-

matographic analyses were carried out with a F and M 500 temperature-programmed gas chromatograph. Elemental analyses were determined by Mr. R. B. Nunemaker and coworkers.

Oxymercuration of 6-Methylenepentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (11). A. In Water. The olefin 11[1] (18.7 g, 0.13 mol) was added dropwise over a period of 5 min to a stirred solution of mercuric acetate (41.5 g, 0.13 mol) in 130 ml of water and 130 ml of tetrahydrofuran which was cooled in an ice bath. The clear solution was stirred for an additional 5 min, and 130 ml of 3 *M* sodium hydroxide solution followed by 130 ml of a solution 3 *M* in sodium hydroxide and 0.5 *M* in sodium borohydride were added at a rate sufficient to maintain the temperature below 25°. The solution was stirred for another 10 min and saturated with sodium chloride. The organic layer was separated and dried (Na_2SO_4). The tetrahydrofuran was removed under vacuum to give 19.5 g (93%) of a 50:50 mixture (by nmr[1]) of syn and anti alcohols **9** and **10**. Control experiments carried out on a small scale (10 mmol of olefin and 10 mmol of mercuric acetate) utilizing shorter total reaction times (5, 1 min) gave consistently good yields (>90%), but did not change the ratio of isomeric alcohols.

B. In Acetic Acid. To a stirred solution of mercuric acetate (1.75 g, 5.5 mmol) in 15 ml of acetic acid was added the olefin **11** (0.72 g, 5.0 mmol). The mixture was stirred for 5 min and poured into 125 ml of 5.6 *M* sodium hydroxide solution. The temperature rose to 60–70° and was maintained at this temperature for 15 min. Ten milliliters of a solution 3 *M* in sodium hydroxide and 0.5 *M* in sodium borohydride was added. The solution was stirred for an additional 5 min, cooled, extracted with ether, and dried (Na_2SO_4). The solvent was removed under vacuum to give 0.6 g of a waxy solid. Nmr analysis of the product indicated that it consisted of a mixture of syn and anti alcohols (~67%) **9** and **10** (~50:50) and unhydrolyzed syn and anti acetates (~33%) **24** and **26** (~50:50).

Low-Temperature Nmr Spectra of *syn*- (9) and 6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-*anti*-6-ol (10) in Fluorosulfonic Acid. These spectra were obtained by adding concentrated solutions (~0.1 g/0.1 ml) of the alcohol[1] in chloroform to ~1 ml of fluorosulfonic acid at −7°. The small amount of chloroform was used as an internal reference[12] at 7.27 ppm. Both syn (**9**) and anti (**10**) alcohols gave identical spectra at −30°; a singlet at 9.83 (1 H), a doublet at 8.07 (1 H, J = 5 Hz), a broad absorption at 5.37 (1 H), singlets at 3.67 (1 H), 3.27 (3 H), 2.97 (1 H), and 2.79 (1 H), a broad singlet at 2.28 (2 H), and two doublets centered at 1.48 (1 H) and 0.64 ppm (1 H) (J = 12 Hz). Areas of these peaks could be determined only approximately, since some decomposition caused broad absorption at 4–1 ppm. As the temperature of these solutions was raised to −10° the spectra quickly degenerated into low-lying broad absorption between 4 and 1 ppm. The original spectra were not regenerated as the temperature was lowered again.

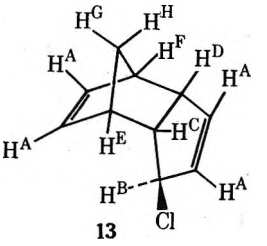
A different spectrum was obtained when the syn alcohol **9** was dissolved in FSO_3H–SO_2 at −78°, and the spectrum was recorded at −50° (Figure 1). The solution was warmed to −30°; the spectrum degenerated, but did not revert to the spectrum obtained originally at −30° in FSO_3H alone. When the solution was warmed to −10°, the spectrum decayed to a broad absorption between 4 and 1 ppm, and did not sharpen when the solution was cooled.

When the acid–cation solution at −50° was hydrolyzed according to the procedure of Olah and coworkers,[6] by pouring the solution into ice–SO_2 at −78°, only an ether-insoluble, carbonaceous tar was formed.

Low-Temperature Nmr Spectra of *anti*-Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-ol (8) in Fluorosulfonic Acid. This spectrum was obtained by adding ~1 ml of fluorosulfonic acid at −78° to 0.1 g of the alcohol 8[2b] at −78°. The solid alcohol dissolved very slowly when the mixture was shaken. A small amount (~10 mg) of tetramethylammonium fluoroborate was added as an internal reference (3.1 ppm[17]). The spectrum was obtained at −30° and consisted of a singlet at 5.4 (1 H), overlapping multiplets at 3.0 and 2.9 (8 H), and two unsymmetrical doublets centered at 1.8 and 1.4 ppm (1 H each, $J \simeq$ 12 Hz). The spectrum quickly degenerated when the sample was warmed to −10°.

A good spectrum was also obtained in antimony pentafluoride–fluorosulfonic acid–sulfur dioxide. In this case a mixture of 1.1 ml (15 mmol) of fluorosulfonic acid and 0.5 ml (7 mmol) of antimony pentafluoride was cooled to −20° with stirring. Approximately 10 ml of sulfur dioxide was condensed into this mixture, which was then cooled to −78°. The alcohol 8 (1.5 g, 10 mmol) was added slowly to the stirred solution as a solid. After the mixture was stirred at −78° for 1 hr, most of the solid had dissolved. The nmr spectra at −50 to −10° were identical with the one obtained above but did not degenerate at −10° in a period of 15 min. The total acid–SbF_5–alcohol solution was poured onto ~200 g of ice. The main product was an ether-insoluble green solid. The soluble portion was taken up in ether, washed with water, and dried. Evaporation of the solvent and sublimation of the residue afforded 0.25 g (17%) of alcohol. Analysis by nmr indicated only the starting isomer 8.

***endo,anti*-5-Chlorotricyclo[5.2.1.0^{2,6}]deca-3,8-diene (13).** Thionyl chloride (15.6 g, 0.13 mol) was added to a stirred solution of *endo,anti*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ol (**12**)[18] (16.0 g, 0.11 mol) in 300 ml of dry ether, and the solution was stirred at ~25° for 15 min. No apparent reaction ensued. Pyridine (25 ml, 0.31 mol) was added dropwise to the mixture with immediate formation of the hydrochloride salt. After the mixture was stirred at ~25° for 1 hr, enough water (100 ml) was added to dissolve all the solids, and the ether layer was separated and washed with water. Drying, evaporating, and distilling the residue afforded 13.2 g (73%) of the allylic chloride **13**: bp 60–64° (1 mm); n^{25}D 1.5324; ν_{max} (neat) 3070 (m, =CH), 2970 (s), 2910 (m) and 2875 (m) (CH), 1615 (w, cyclopentenyl C=C), 1580 (w, norbornenyl C=C), 1345 (s), 772 (s), 726 cm^{-1} (s, *cis*-CH=CH–); nmr spectrum (CCl_4) a multiplet at 6.3–5.4 with an intense singlet at 5.90 and another maximum at 5.59 (4.0 H, H^A), a multiplet at 4.33–4.15 with a maximum at 4.25 (H^B, 0.9 H), a multiplet at 3.6–3.2 with maximum intensity at 4.41 (1.0 H, H^C or H^D), a multiplet at 3.3–2.7 with an intense maximum at 3.07 and a weaker maximum at 2.85 (3.1 H, H^D or H^C, H^E, H^F), and two slightly overlapping unsymmetrical doublets of triplets centered at 1.59 (H^G, J_{GH} = 8.2, $J_{EG,FG}$ = 1.6 Hz) and 1.36 ppm (H^H, J_{GH} = 8.1, $J_{EH,FH}$ = 1.2 Hz) (2.0 H total); mass spectrum *m/e* 66 ($C_5H_6^+$), 115 (M$^+$ − HCl, CH_3), 128 (M$^+$ − HCl, H_2), 129 (M$^+$ − HCl, H), 130 (M$^+$ − HCl), 131 (M$^+$ − Cl), 166 and 168 (M$^+$).

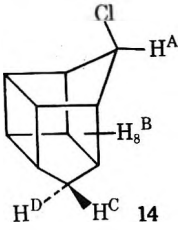


13

Anal. Calcd for $C_{10}H_{11}Cl$: nuclidic mass, 166.0549. Found: nuclidic mass, 166.0531.

The chloro compound **13** was unstable and turned dark in a few days.

***anti*-6-Chloropentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (14).** A solution of 10.0 g (60 mmol) of the allylic chloride **13** in 150 ml of distilled acetone was purged with oxygen-free nitrogen for 2 hr. This solution was irradiated through a Corex filter with a 450-W Hanovia medium-pressure mercury arc lamp in an immersion reactor. The progress of the reaction was followed by gc analysis on a 10 ft × 0.25 in. column packed with 20% Apiezon L on Chromosorb WAW at 225° with a helium flow of 40 ml/min. The product chloride **14** had a retention time of 11.0 min, and the starting material **13** eluted at 9.5 min. After 4 hr there was greater than 99% reaction, and the irradiation was stopped. The solvent was removed under vacuum, leaving ~10 g of a brown oil. Distillation of the residue afforded 7.8 g (78%) of a slightly yellow, partly crystalline oil: bp 58–60° (0.5 mm); n^{20}D 1.5351; ν_{max} (neat) 2980 (s) and 2870 (m) (CH), 1290 (s), 1265 (s), 790 (s), 750 cm^{-1} (s); nmr spectrum (CCl_4) a singlet at 4.20 (0.9 H, H^A), a multiplet at 3.3–2.1 with maxima at 2.80 and 2.62 (8.0 H, H^B), an unsymmetrical doublet at 1.69 (1.0 H, H^C, J_{CD} = 11.1 Hz), and an unsymmetrical doublet centered at 1.27 ppm (1.1 H, H^D, J_{CD} = 10.9 Hz); mass spectrum *m/e* 38 ($C_3H_2^+$), 51 ($C_4H_3^+$), 66 ($C_5H_6^+$), 77 ($C_6H_5^+$), 91 ($C_7H_7^+$), 100 and 102 ($C_5H_5Cl^+$), 115 (M$^+$ − HCl, CH_3), 116 (M$^+$ − HCl, CH_2), 128 (M$^+$ − HCl, H_2), 129 (M$^+$ − HCl, H), 130 (M$^+$ − HCl), 131 (M$^+$ − Cl), 166 and 168 (M$^+$).



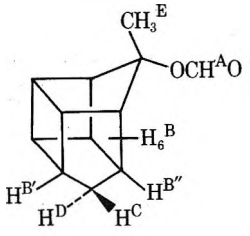
14

Anal. Calcd. for $C_{10}H_{11}Cl$: C, 72.06; H, 6.67; nuclidic mass, 166.0549. Found: C, 72.4; H, 6.94; nuclidic mass, 166.0536.

Low-Temperature Nmr Spectra of Chloride 14 in Antimony Pentafluoride. A solution was made up from 2 ml of sulfur dioxide and 0.2 ml of antimony pentafluoride at −78°. To this stirred solution at −78°, 0.2 ml of chloride **14** was added slowly as a fine spray from a syringe. The dark red solution was stirred at −78° for 15 min and transferred quickly *via* a cold pipette to an nmr tube at −78°. The nmr spectrum was run at −50°; one low-intensity absorption band from ~5 to 1 ppm was observed. Because no reference material was present the position of this band is accurate to no more than 1 ppm.

Essentially the same results were obtained when the spectrum was obtained at −80°. Here the solvent consisted of a ~50:50 mixture of sulfur dioxide and sulfuryl fluoride. Approximately the same quantities of acid, solvent, and halide were used; the same type of spectrum was obtained.

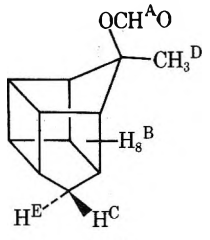
6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-*syn*-6-yl Formate (15). A solution of acetic–formic anhydride in acetic acid was prepared according to the procedure of Stevens and van Es.[19] The acetic–formic anhydride solution (0.75 ml, 5.6 mmol) was added dropwise to the stirred syn alcohol **9**[1] (94% pure, 6% **10**) (150.5 mg, 0.928 mmol) at 0–5° over a period of ~5 min. The resulting solution was stirred at 0–5° for another 10 min and then at 24–25° for 7 days. The light yellow solution was poured into a solution of 100 ml of water and 50 ml of 5% aqueous sodium bicarbonate solution. The aqueous mixture was extracted with methylene chloride (4 × 15 ml), and the organic extract was washed with water (2 × 30 ml). After being dried ($CaSO_4$), the methylene chloride was evaporated under vacuum to give 136.1 mg (77%) of the syn formate **15** (94% pure by nmr, 6% **16**) as a yellow oil: ν_{max} (neat) 2970 (s) and 2860 (m) (CH), 2740 (w, COH), 1725 (s, C=O), 1450 (m) and 1375 (m) (CH_3), 1172 (s, CO), 825 cm^{-1} (m); nmr spectrum ($CDCl_3$) a singlet at 8.06 (1.0 H, H^A), a multiplet at 3.04–2.54 with maxima at 2.81



15

and 2.71 (7.9 H, H^B), two unsymmetrical doublets of triplets centered at 1.66 (H^C, J_{CD} = 11.3, $J_{B'C,B''C}$ = 1.1 Hz) and 1.35 (H^D, $J_{B'D,B''D}$ = 1.1 Hz) (2.1 H total), and a singlet at 1.27 ppm (3.0 H, H^E); mass spectrum of mixture of formates **15** and **16** given later.

6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-*anti*-6-yl Formate (16). As described in the preceding experiment, the acetic–formic anhydride solution (0.29 ml, 2.2 mmol) was allowed to react with the anti alcohol **10**[1] (97% pure, 3% **9**) (58.3 mg, 0.359 mmol). Work-up as above gave 38.8 mg (57%) of the anti formate **16** (96% pure by nmr, 4% **15**) as a colorless oil: ν_{max} (neat) 2975 (s) and 2860 (m) (CH), 2740 (w, COH), 1725 (s, C=O), 1450 (m) and 1380 (m) (CH_3), 1172 (s, CO), 942 cm^{-1} (m); nmr spectrum ($CDCl_3$) a singlet at 7.91 (1.0 H, H^A), a multiplet at 3.00–2.50 with maxima at 2.82



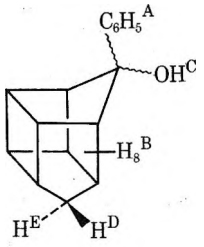
16

and 2.73 (7.7 H, H^B), an unsymmetrical doublet centered at 1.66 (H^C) overlapping a singlet at 1.56 (H^D) (4.3 H total), and an unsymmetrical doublet centered at 1.31 ppm (1.0 H, H^E, J_{CE} = 11.2 Hz).

***p*-Toluenesulfonic Acid Catalyzed Addition of Formic Acid to Olefin 11.** To the olefin **11** (144.1 mg, 0.999 mmol) was added 7.0 ml of formic acid (97+%); the olefin appeared to be largely insoluble. *p*-Toluenesulfonic acid monohydrate (189.5 mg, 0.996 mmol) was added; after the mixture was shaken at ~25° for several minutes the olefin dissolved (0.143 *M* olefin **11**, 0.142 *M* *p*-toluenesulfonic acid). The solution was maintained at 27 ± 1° for 3 hr. The solution turned pale green almost immediately, and became gradually darker as the reaction progressed. At the end of 3 hr the dark blue-green solution was poured into 100 ml of cold water. The aqueous mixture was extracted with methylene chloride (5 × 10 ml), and the combined extracts were washed with 20 ml of 5% aqueous sodium bicarbonate solution and 35 ml of water. After being dried ($CaSO_4$), the methylene chloride was evaporated under vacuum to give 132.2 mg (70%) of a mixture of formates **15** and **16** as a nearly colorless oil. Nmr analysis indicated a composition of 61 ± 1% syn formate **15** and 39 ± 1% anti formate **16** (by electronic integration and planimeter area measurements of the formate proton singlets). The remainder of the nmr spectrum and the infrared spectrum also were consistent with this composition. The mass spectrum showed significant ion peaks at *m/e* (probably structure assignment of ion, and order of intensity, most intense = 1, etc., given): 43, CH_3CO^+, 5; 66, $C_5H_6^+$, 2; 77, $C_6H_5^+$, 11; 78, $C_6H_6^+$, 10; 79, $C_5H_3O^+$ or $C_6H_7^+$, 9; 91, $C_7H_7^+$, 7; 95, $C_5H_4(CH_3)O^+$, 8; 96, $C_5H_4(CH_3)OH^+$, 1; 124, $C_5H_4(CH_3)OCHO^+$, 4; 129, $C_{10}H_9^+$, 3; 144, $M^+ - HCO_2H$, 6; 145, $M^+ - OCHO$, 12; 145, $M^+ - CH_3$, CO, very weak; 162, $M^+ - CO$, very weak; 175, $M^+ - CH_3$, very weak; 190, M^+, ~0.2% of base peak.

***p*-Toluenesulfonic Acid Catalyzed Isomerization of Formate 15.** A 0.147 *M* solution of *p*-toluenesulfonic acid in formic acid was prepared by dissolving *p*-toluenesulfonic acid monohydrate (278.8 mg, 1.466 mmol) in 10.0 ml of 97+% formic acid. A solution of the syn formate **15** (94% pure, 6% **16**) (136.1 mg, 0.715 mmol) in 5.0 ml of the 0.147 *M* *p*-toluenesulfonic acid solution in formic acid (0.143 *M* **15**) turned green within a few minutes, and was maintained at 27 ± 1° for 3 hr. The deep blue-green solution was worked up as in the preceding experiment to give 70.2 mg (52%) of a 61 ± 2:39 ± 2 mixture of formates **15** and **16**, respectively.

6-Phenylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-ol (18). Phenylmagnesium bromide was prepared by the addition of 10.7 g (68.4 mmol) of bromobenzene in 20 ml of ether to 1.82 g (75 g-atoms) of magnesium turnings under a nitrogen atmosphere. After the reaction started an additional 25 ml of ether was added; the solution refluxed spontaneously for 20 min. To this solution was added a solution of 5.00 g (34.2 mmol) of the ketone **17** in 30 ml of ether, and the solution was refluxed for an additional 2 hr. A few milliliters of water was added, and the mixture was poured into 100 ml of 20% aqueous ammonium chloride solution. The organic layer was separated, washed with water (3 × 100 ml), and dried (Na_2SO_4). The solvent was removed under vacuum to give 7.2 g of crude product. After four recrystallizations from hexane, the white crystals of **18** had constant mp 96–98°; ν_{max} (CCl_4) 3615 (m, free OH), 3450 (m, br, bonded OH), 3070 (m) and 3035 (m) (=CH), 2980 (s) and 2860 (m) (CH), 1505 (m) and 1455 cm^{-1} (m) (C=C); ν_{max} (CS_2) 766 (s), 761 (s), and 695 cm^{-1} (s) (Ph); nmr spectrum ($CDCl_3$) a singlet at 7.30 with minor multiplet bands at 7.5–7.1 (5.0



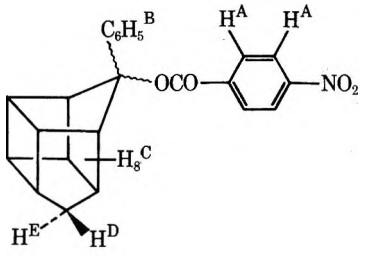
18

H, H^A), a multiplet at 3.4–3.1 with maximum intensity at 3.25 (1.0 H, one of H^B protons), a multiplet at 3.1–2.3 with maxima at 2.91 and 2.58 (6.9 H, seven of H^B protons), a singlet at 1.98 (1.0 H, H^C), an unsymmetrical doublet centered at 1.72 with further ill-defined splitting (1.0 H, H^D, J_{DE} = 11.6 Hz), and an unsymmetrical doublet centered at 1.42 ppm (1.0 H, H^E); mass spectrum *m/e* 66 (weak, $C_5H_6^+$), 91 ($C_7H_7^+$), 105 (base peak, $PhCO^+$), 119 (PhC_2H_2O), 158 ($M^+ - C_5H_6$), 206 ($M^+ - H_2O$), 209 ($M^+ - CH_3$), 224 (M^+).

Anal. Calcd for $C_{16}H_{16}O$: C, 85.67; H, 7.19; mol wt, 224. Found: C, 85.73; H, 7.24; mol wt, 224 (mass spectrometry).

Comparison of the nmr and infrared spectra of the crude reaction mixture with those of the purified material **18** indicated the crude product to contain at least 80% of the isomer which was isolated in purified form (presumably the syn OH); the remainder may have been the epimer.

6-Phenylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-yl *p*-Nitrobenzoate (19). To a solution of 1.50 g (6.7 mmol) of the alcohol 18 in 40 ml of pyridine was added 1.37 g (7.4 mmol) of *p*-nitrobenzoyl chloride. The solution was stirred at ~25° for 48 hr. The solution was poured into 200 ml of water and extracted with methylene chloride (4 × 25 ml). The combined extracts were washed with water (2 × 10 ml), 0.1 *N* hydrochloric acid (100 ml), and again with water. The solution was dried (Na_2SO_4), and the solvent was evaporated to yield 2.4 g of yellow solid. Recrystallization from methanol–ethanol afforded 2.2 g (88%) of crystals of **19**: mp 139.5–141.5°; ν_{max} (CCl_4) 3070 (m) and 3040 (m) (=CH), 2985 (s) and 2870 (m) (CH), 1730 (s, C=O), 1620 (m, C=C), 1535 (s, NO_2), 1505 (m) and 1455 (m) (C=C), 1360 cm^{-1} (m, NO_2); ν_{max} (CS_2) 1275 (s, CO), 720 (s), 698 cm^{-1} (s, Ph); nmr spectrum ($CDCl_3$) a singlet at 8.20 (4.0 H, H^A), a multiplet at 7.6–7.1 with maximum intensity at 7.33 (5.0

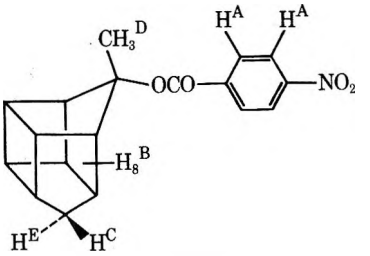


19

H, H^B), a multiplet at 3.8–3.5 with maximum intensity at 3.62 (1.0 H, one of H^C protons), a multiplet at 3.5–3.3 with maximum intensity at 3.40 (1.0 H, one of H^C protons), a multiplet at 3.3–2.4 with maxima at 3.11, 2.84, and 2.63 (6.0 H, six H^C protons), an unsymmetrical doublet centered at 1.78 (1.0 H, H^D, J_{DE} = 11.3 Hz), and an unsymmetrical doublet centered at 1.44 ppm (1.0 H, H^E, J_{DE} = 11.4 Hz); mass spectrum *m/e* 77 ($C_6H_5^+$), 150 ($O_2NC_6H_4CO^+$), 206 ($M^+ - O_2NC_6H_4CO_2H$), 223 ($M^+ - O_2NC_6H_4CO$), 307 ($M^+ - C_5H_6$), 373 (M^+).

Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75; mol wt, 373. Found: C, 74.06; H, 5.06; N, 3.86; mol wt, 373 (mass spectrometry).

6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-*syn*-6-yl *p*-Nitrobenzoate (20). To a solution of 1.50 g (9.25 mmol) of the syn alcohol 9[1,2d] in 10 ml of ether and 1 ml of pyridine was added 1.86 g (10 mmol) of *p*-nitrobenzoyl chloride. The solution was stirred for 48 hr at ~25°. Ether (50 ml) was added and the solution was washed with water (3 × 50 ml). After being dried (Na_2SO_4), evaporation of the solvent afforded 2.75 g of yellow solid. Recrystallization from methonol gave 2.2 g (77%) of pale yellow crystals of **20**: mp 110–112°; ν_{max} (CCl_4) 2980 (s) and 2870 (m) (CH), 1730 (s, C=O), 1620 (m, C=C), 1535 (s, NO_2), 1455 (m) and 1385 (m) (CH_3), 1360 cm^{-1} (m, NO_2); ν_{max} (CS_2) 1283 (s) and 1276 cm^{-1} (s) (CO); nmr spectrum ($CDCl_3$) a singlet at 8.26 (3.9 H, H^A), a multiplet at 3.2–2.6



20

with maximum intensity at 2.81 (8.0 H, H^B), an unsymmetrical doublet centered at 1.69 (1.1 H, H^C, J_{CE} = 11.2 Hz), and an intense singlet at 1.40 (H^D) partially overlapping the stronger low-field branch of an unsymmetrical doublet centered at 1.36 ppm (H^E) (4.0 H total); mass spectrum *m/e* 129 ($M^+ - CH_3$, $O_2NC_6H_4CO_2H$), 144 ($M^+ - O_2NC_6H_4CO_2H$), 150 ($O_2NC_6H_4CO^+$), 161 ($M^+ - O_2NC_6H_4CO$), 245 ($M^+ - C_5H_6$), 311 (M^+).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50; mol wt, 311. Found: C, 69.17; H, 5.48; N, 4.62; mol wt, 311 (mass spectrometry).

Hydrolysis of Phenyl *p*-Nitrobenzoate 19. A. At 115°. A solution of 0.748 g (2.0 mmol) of the ester **19** in 80 ml of a 60% dioxane–40% water (by volume) mixture (0.025 *M* **19**) was placed in a glass pressure bottle, heated to reflux, sealed, and heated at 115 ± 5° for 72 hr. The solution was cooled, and the solvent was removed under vacuum. The residual orange solid was dissolved in 50 ml of ether, washed successively with 50 ml of a 5% sodium bicarbonate solution and 50 ml of water, and dried (Na_2SO_4). Evaporation of the ether afforded 0.42 g (91%) of an orange oil. The infrared spectrum was identical with that of the purified alcohol **18** except for some very weak bands in the fingerprint region. The nmr spectrum also was quite similar to that of the alcohol **18** except that the aromatic proton absorption was a multiplet and the methylene region was quite complex. These data indicate that the product probably is a mixture of syn and anti isomers of **18**.

B. At 85°. The reaction in part A was duplicated except that the solution was heated at 85 ± 1° for 16 hr. The solution was cooled, and the solvent was removed under vacuum to give a pale yellow solid. This solid was dissolved in methylene chloride, and the solution was washed successively with water, sodium bicarbonate solution, and water. After being dried, the methylene chloride was evaporated under vacuum to give 0.60 g (80% recovery) of a white solid, which was identified as the starting ester by its infrared and nmr spectra. No significant amount of other products could be detected from the spectra.

Attempted Hydrolysis of Methyl *syn*-*p*-Nitrobenzoate 20. A solution of 0.934 g (3.0 mmol) of the ester **20** in 60 ml of a 60% dioxane–40% water (by volume) mixture (0.05 *M* **20**) was placed in a glass pressure bottle, heated to reflux, sealed, and heated at 100 ± 5°. After 240 hr the reaction mixture was cooled, and the solvent was removed under vacuum. The residual yellow solid was dissolved in 50 ml of ether, washed with 5% sodium bicarbonate solution, and dried (Na_2SO_4). Evaporation of the ether afforded 0.85 g (91%) of yellow crystals. The infrared and nmr spectra were identical with those of the starting material. There was no evidence for the presence of any hydrolysis products.

Acknowledgment. The authors wish to thank Professor D. G. Farnum for helpful discussions.

Registry No.—**8**, 13351-15-0; **9**, 51965-68-5; **10**, 52021-57-5; **11**, 51965-69-6; **12**, 24529-79-1; **13**, 51965-70-9; **14**, 51965-71-0; **15**, 51965-72-1; **16**, 52021-58-6; **17**, 15584-52-8; *syn*-**18**, 51965-73-2; *anti*-**18**, 52021-59-7; *syn*-**19**, 51965-74-3; **20**, 51965-75-4; *p*-nitrobenzoyl chloride, 122-04-3

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3-Methylenebicyclo[2.1.0]pentane-1-carbonitrile and 3-Vinylbicyclobutane-1-carbonitrile

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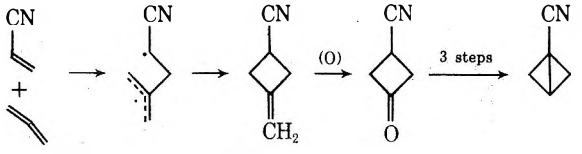
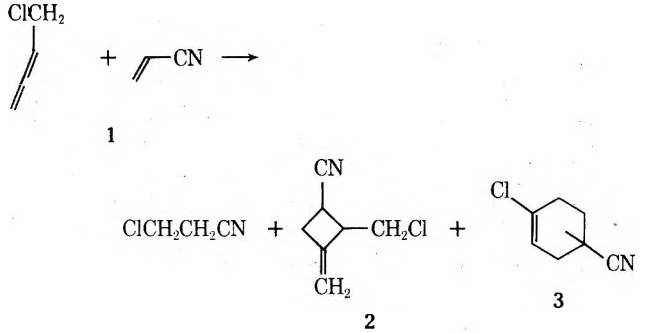
4-Chloro-1,2-butadiene reacted with acrylonitrile at 210–225° and autogenous pressure to yield the [$_\pi$2 + $_\pi$2] cycloadduct, 2-chloromethyl-3-methylenecyclobutanecarbonitrile (2). The equilibrium constants allene + acrylonitrile ⇄ 3-methylenecyclobutanecarbonitrile were calculated for various temperatures by assigning infrared fundamentals to the latter and calculating the thermodynamic properties of each component. The yield of cycloadduct was not limited by equilibrium considerations. Dehydrochlorination of 2 with potassium *tert*-butoxide in ether gave 3-methylenebicyclo[2.1.0]pentanecarbonitrile (4). This polymerized readily. This sequence represents the synthesis of a new bicyclic monomer in two steps from industrially available materials. Vinylmagnesium chloride added to 3-cyanocyclobutanone to yield 3-vinyl-3-hydroxycyclobutanecarbonitrile (5). Reaction of 5 with triphenylphosphine in carbon tetrachloride occurred with partial allylic rearrangement to give tertiary chloride 6 and primary chloride 7. Dehydrochlorination of 6 afforded 3-vinylbicyclobutanecarbonitrile (8); this polymerized readily. Dehydrochlorination of 7 gave a mixture of 8 and 3-vinyl-2-cyclobutene-1-carbonitrile (9).

Synthesis of 3-Methylenebicyclo[2.1.0]pentane-1-carbonitrile. In earlier work, we have synthesized and polymerized bicyclobutane-1-carbonitrile[1-7] and bicyclo[2.1.0]pentane-1-carbonitrile,[8] each containing a C–C single bond of high p character. Further development in this new field of ring-opening polymerization through strained C–C single bonds requires facile syntheses from readily available starting materials. For two compounds of this class, our present work describes convenient syntheses, one from industrially available materials.

Cycloaddition of 4-Chloro-1,2-butadiene ("Isochloroprene") to Acrylonitrile. Our earlier, rather lengthy synthesis of bicyclobutane-1-carbonitrile began with the biradical cycloaddition of allene to acrylonitrile.[9] In the

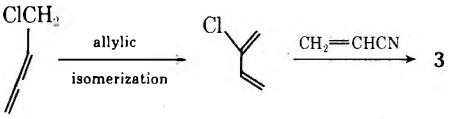


present work we have utilized 4-chloro-1,2-butadiene (chloromethylallene, "isochloroprene," 1) in the acrylonitrile cycloaddition reaction. The isochloroprene is easily obtained by the 1,4-addition of hydrogen chloride to monovinylacetylene.[10] Four compounds were obtained from the reaction with acrylonitrile. A little 3-chloropropionitrile, proba-



bly formed by generation of HCl in some unknown fashion, followed by addition to acrylonitrile, was obtained as the first fraction. The second fraction contained the remaining three components. Two of these were the desired cis and trans cycloadducts 2. Although a cycloadduct bearing the chloromethyl group on the *exo*-methylene carbon was expected as well, comparison of our cycloaddition product with authentic material (see below) showed its absence.

The fourth compound crystallized from the second fraction on storage. From its melting point of 53–54° and its nmr spectrum (one vinyl H), this was the Diels–Alder adduct 3 of chloroprene to acrylonitrile (lit.[11] mp 51°). Evi-



dently isochloroprene isomerizes to chloroprene (2-chloro-1,3-butadiene) and then undergoes the Diels–Alder reaction with acrylonitrile. Whether this isomerization occurs thermally or is catalyzed by traces of impurities is not known at present.

Reaction conditions were varied to optimize the yield of cycloadduct 2. Best results were obtained in sealed glass ampoules heated under pressure-equalizing conditions within a rocker bomb. A limited amount of benzene served as solvent, and a substantial quantity of 2,5-di-*tert*-butylhydroquinone was the inhibitor. Conversions of 40–45% were obtained at 210–225° during reaction periods of 3–8 hr. These conditions are similar to those used for the cycloaddition of allene itself to acrylonitrile.[9] Higher temperature and longer reaction times led in our hands to tar or charred material.

The [$_\pi$2 + $_\pi$2] cycloadduct mixture could be separated cleanly from the [$_\pi$2 + $_\pi$4] product by preparative gas chromatography if required; however, separation of the individual cis and trans isomers of the former has not been accomplished. Because 3 is inert to the basic conditions used in the next step (see below), the mixture of 2 and 3 could be used as such.

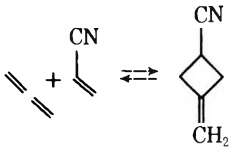
Calculation of the Equilibrium Constants for Cycloaddition of Allenes to Acrylonitrile. We were interested in knowing whether the cycloaddition of a typical allene to acrylonitrile reached equilibrium under our conditions, or whether the conversion was controlled by kinetic factors. In a previous investigation of the cycloaddition of ethylene to acrylonitrile to give cyclobutanecarbonitrile,[12] this problem was approached by assigning the fundamental infrared absorptions of the components and calculating their thermodynamic properties. The same procedure has been used here. The heat of formation of 3-methylenecyclobutanecarbonitrile was taken from the paper of Hall and Baldt.[3] The laser Raman and mid-infrared spectra were measured and the fundamental frequencies were identified (Table I). With the help of these identifications,

Table I
Fundamental Vibrations for 3-Methylenecyclobutanecarbonitrile

Type of vibration	Fundamental vibration frequency, cm^{-1}	Description
A_1 (13); A′	510	C–CN stretching
	612	Ring deformation
	910	Ring deformation
	1005	Ring breathing
	1225	CH_2 wagging (α)
	1410	Olefinic CH_2 deformation
	1430	CH_2 deformation (β)
	1440	CH_2 deformation (α)
	1689	C=C stretching
	2244	C≡N stretching
	2900	CH_2 stretching (α)
	2995	CH_2 stretching (β)
	3080	Olefinic CH_2 stretching
A_2 (5); A″	640	CH_2 rocking (α)
	950	Olefinic CH_2 twisting
	1200	CH_2 twisting (β)
	1200	CH_2 twisting (α)
	2900	CH_2 stretching (anti, α)
B_1 (10); A″	260	C–CN wagging
	490	C=C in-plane bending
	690	Ring deformation (anti)
	840	Ring stretching (anti)
	1160	CH_2 wagging (β)
	1200	CH_2 wagging (α)
	1325	Olefinic CH_2 rocking
	1450	CH_2 deformation (α)
	2900	CH_2 stretching (α)
	3080	Olefinic CH_2 stretching
B_2 (8); A′	195[a]	Ring puckering
	275	C–CN rocking
	370	C=C out-of-plane bending
	690	CH_2 rocking (α)
	780	CH_2 rocking (β)
	880	Olefinic CH_2 out-of-plane wagging
	1055	CH_2 stretching (a, α)
	2950	CH_2 stretching (a, β)
Total 36		

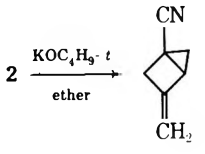
[a] Estimated from the observed far-infrared transitions as the harmonic frequency needed to represent the contributions to the thermodynamic functions of the ring-puckering vibration.

the thermodynamic quantities were calculated (Table II). They were insensitive to the effect of the ring puckering angle in the range 0–30° on the moments of inertia. The free energies and equilibria of the reaction of allene with acrylonitrile were calculated as follows.



$$\Delta G^\circ_T = -28{,}870 + 47.38T$$

Dehydrochlorination of 2. Cycloadduct **2** was rapidly dehydrochlorinated by sublimed potassium *tert*-butoxide in ether to give 3-methylenebicyclo[2.1.0]pentane-1-carbonitrile (**4**) in 50% yield.



4

Table II
Thermodynamic Properties of 3-Methylenecyclobutanecarbonitrile

Assumptions: Symmetry C_s, $\sigma = 1$; electronic contributions negligible; all vibrations are harmonic oscillations; ring puckering angle 30°; $\Delta H^\circ_{f,g,298} = +60.27$ kcal mol^{-1}

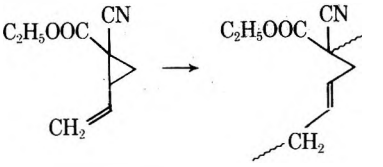
Molecular parameters: $I_A = 0.921134 \times 10^{-38}$ g cm^{-2}; $I_B = 0.552016 \times 10^{-37}$ g cm^{-2}; $I_C = 0.603078 \times 10^{-37}$ g cm^{-2}; Mol wt 93.120

Temp, °K	$(H_T^\circ - E_0^\circ)/T$[a]	H°_T[b]	$(G^\circ - E_0^\circ)/T$[a]	G_T°[b]	S°	C_p
0	0	65.45	0	65.45	0	0
298.2	14.91	69.90	−62.35	46.86	77.25	25.96
400	18.75	72.96	−67.26	38.55	86.01	33.89
500	22.46	76.68	−71.85	29.53	94.31	40.46
600	25.93	81.00	−76.25	19.70	102.17	45.84
700	29.09	85.82	−80.49	9.11	109.58	50.26

[a] Cal mol^{-1} deg^{-1}. [b] kcal mol^{-1}.

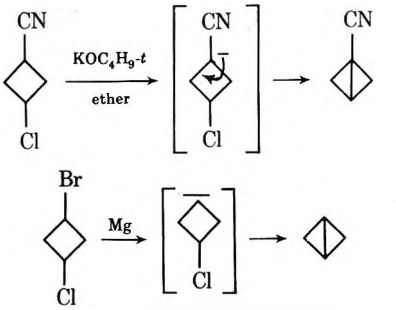
No substantial difference in the reactivity of the cis–trans isomers of **2** was noted. The Diels–Alder adduct **3** was inert under these conditions. After cycloadduct **2** had reacted to the extent of ~95%, the mixture was worked up and compound **4** was separated by vacuum distillation from unreactive **3**. Nitrile **4** polymerized rapidly under ambient conditions or at 0° (probably caused by light and/or air) to a glassy solid. Accordingly this new monomer was stored at −80° in the presence of inhibitors.

Synthesis of 3-Vinylbicyclobutane-1-carbonitrile. Monomer **4** contains a vinylcyclopropanecarbonitrile moiety incorporated into a bicyclic structure. This moiety has been shown by Lishanskii and his colleagues[13] to be polymerizable even in acyclic cases. In this work, for purposes of

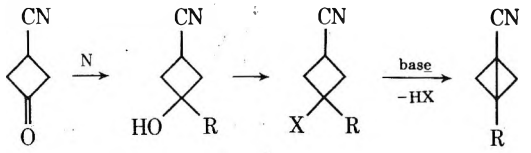


comparison, a second bicyclic monomer containing this moiety has been synthesized.

Addition of Vinylmagnesium Chloride to 3-Cyanocyclobutanone. Bicyclobutane syntheses in this series[1,2] have involved the generation of a carbanion on the cyclobutane ring in a 1,3 relationship to a leaving group. If an activating group (CN, $COOCH_3$) were present at C_1, abstraction of H^+ by strong bases yielded the requisite carbanion; if none were present,[14] abstraction of positive halogen by metals served the same purpose. Our present route to 3-



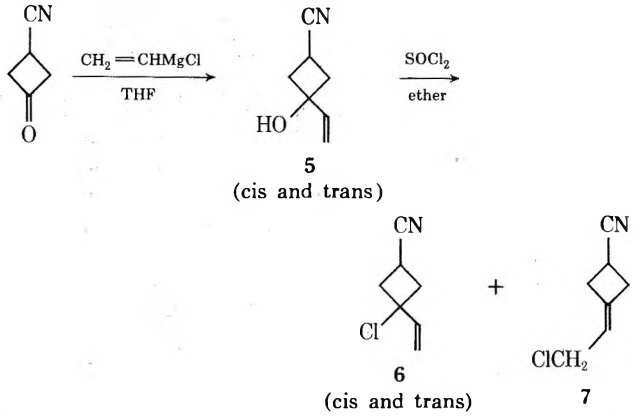
vinylbicyclobutane-1-carbonitrile utilized the former of these modes. 3-Cyanocyclobutanone, available as described above, has already been shown to be a prolific source of the required 1,3-disubstituted cyclobutanes. Attack of a nucleophile R^- at carbonyl, conversion of the resulting hydroxyl to a leaving group X, and elimination have been



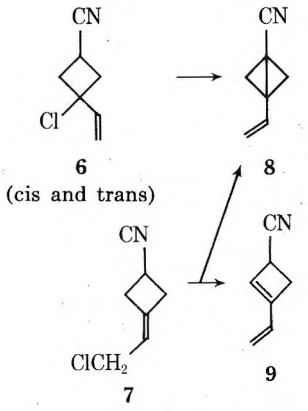
R = CN, C_6H_5
X = Cl, $OSO_2C_6H_5$

demonstrated for two cases. We have carried out this sequence with R = vinyl. Addition of vinylmagnesium chloride to 3-cyanocyclobutanone in tetrahydrofuran at −25 to −30° proceeded smoothly in yields of 85–90%.

Replacement of Hydroxyl by Chlorine. Although it is reputed to be the reagent favoring SNi[1] reaction,[15] thionyl chloride in ether converted cyano alcohol to an allylically rearranged mixture of chlorides **6** and **7**. Triphenylphosphine in carbon tetrachloride led to a similar, but much cleaner, mixture in 70% yield. Sieja[14] encountered a similar allylic rearrangement in his synthesis of 1-vinylbicyclobutane. The primary chloride **7** could be separated by fractional distillation from the cis–trans mixture of tertiary isomers **6**. Spectral and gas chromatographic studies of the rearranged product **7** indicated that it was different from the isomeric [$_\pi2 + _\pi2$] cycloadduct **2** described above, and confirms the absence of **7** from the cycloaddition reaction mixture.



Dehydrochlorination of 6 and of 7. The dehydrochlorination of tertiary chloride **6** and primary chloride **7** was carried out with potassium *tert*-butoxide in ether as before. The tertiary chlorides gave a 90% yield of 3-vinylbicyclobutanecarbonitrile (**8**). The primary chloride gave a mixture of **8** and 3-vinyl-2-cyclobutenecarbonitrile (**9**) in about equal amounts, for a combined yield of 60%. These could not be separated by fractional distillation or glc, but were clearly visible by nmr spectroscopy. This differs from Sieja's results; both his tertiary and primary chlorides gave only 1-vinylbicyclobutane.



The new bicyclobutane monomer **8**, like other bicyclobutane-1-carbonitriles,[1,2] underwent ready polymerization (probably by light and air) and was stored at −80° in the presence of inhibitor.

Discussion

Synthesis of 3-Methylenebicyclo[2.1.0]pentane-1-carbonitrile. Like allene itself, 4-chloromethyallene has been found to cycloadd readily to acrylonitrile. The reason why only **2**, and not **7**, is formed in this reaction is not clear at present. A referee has suggested that the regiospecificity may be due to higher odd-electron localization on the internal end of the allylic radical.[16] The cycloadduct has been obtained in conversions of 40–50%. That this is limited by side reactions, rather than by equilibrium considerations, is clear from the thermodynamic data obtained. Thus for the allene–acrylonitrile cycloaddition, the temperature at which $\Delta G° = 0$ is 336°. These calculations should apply to 4-chloromethyallene as well.

In our earlier work[12] on the ethylene–acrylonitrile reaction, $\Delta G° = 0$ at 175°, and cycloadduct could be obtained at temperatures well above that value. These calculations suggest that increased conversions and reaction rates should be achievable if side reactions could be minimized, possibly in a vapor-phase reactor.

The practical significance of these results is that a novel monomer has been synthesized in two steps from industrially available chemicals.

Synthesis of 3-Vinylbicyclobutane-1-carbonitrile. The facile synthesis of monomer **8** provides another example of the generality of the synthesis. The only departure from previous results lies in the dehydrochlorination of primary chloride **7** to a mixture of **8** and **9**. Possibly the inductive effect of the 1-cyano group activates the β hydrogen as well as α hydrogen to attack by base.

Polymerization studies of **8**, and also of **4**, will be described at a later date.

Experimental Section

All boiling points and melting points were uncorrected. Capillary melting points were determined on a Thomas-Hoover melting point apparatus. Infrared spectra were determined with a Perkin-Elmer Model 337 spectrophotometer in KBr or between NaCl plates. Nmr spectra were obtained on a Varian T-60 spectrometer. Mass spectral data were collected on a Hitachi Perkin-Elmer RMU-6E double-focusing instrument at an ionization potential of 70 eV. All gas–liquid chromatography, analytical and preparative, was done on a Varian Aerograph 1700 instrument using the following columns: (A) 3% SE-30 on 80–100 mesh Chromosorb W AW/DMCS HP, 5 ft × 0.25 in., (B) 15% Fluorosilicon QF-1-0065 on 80–100 mesh Anakron SD, 5 ft × 0.25 in., (C) 5% Carbowax 20 M on 80–100 mesh Chromosorb W AW/DMCS, 5 ft × 0.25 in. Elemental analyses were performed by Galbraith Laboratories.

Isochloroprene (4-Chlorobutadiene-1,2) (1). The procedure of Carothers, Berchet, and Collins[10] was followed. Separation of the desired allene derivative from the by-product chloroprene (2-chlorobutadiene-1,3) was accomplished with a 3-ft glass helix-filled column. The isochloroprene, bp 86–88° (700 mm), was stored in a refrigerator over 2,5-di-*tert*-butylhydroquinone inhibitor.

3-Methylene-2-chloromethylcyclobutanecarbonitrile (2). All experiments in this series were carried out at the University High Pressure Laboratory.

Heavy-walled glass tubes with interior diameters of 25–30 mm and with a constriction at the neck about 3 in. below the mouth were prepared. In a typical experiment, a tube was charged with 10 g of isochloroprene, 20 g of acrylonitrile, and 0.5 g of 2,5-di-*tert*-butylhydroquinone. The resulting mixture contained the nitrile and the chloride in a molar ratio of 4:1. To this mixture was added 15 ml of benzene as a diluent, and the contents of the tube were degassed. This was accomplished by freezing the mixture in a Dry Ice–acetone bath, reducing pressure in the tube to 0.3–0.2 mm, and alternately thawing and refreezing the contents until no gas bubbles were observed escaping in the liquid state. The cycle was usu-

ally repeated three or four times. While the mixture was frozen and under reduced pressure, the tube was sealed by heating at the constriction until the walls slowly collapsed. The tube was then subjected to temperatures of 180–200° for 10–15 hr, after which time it was opened and the darkened, slightly viscous liquid was poured into 200 ml of anhydrous ethyl ether. This precipitated acrylonitrile oligomers and polymers. Filtration and concentration of the filtrate on the rotary evaporator yielded 9 g of yellow liquid. Distillation of this residue through the spinning-band column resulted in two fractions. The first component, 2.3 g, bp 29–30° (1.2 mm), was shown by glc to be composed of one compound, which was shown spectrally to be 3-chloropropionitrile: ir superimposable on that of authentic 3-chloropropionitrile found in Sadtlers Collective Indices; nmr ($CDCl_3$) τ 6.0 (triplet, 2 H, α cyano), 6.9 (triplet, 2 H, α chloro).

The second fraction from the spinning-band column was collected at a head temperature of 46–56° (0.1 mm). This fraction was shown by glc to contain three components. Separation of these compounds by preparative gas–liquid chromatography was accomplished and both materials were analyzed.

3-Methylene-2-chloromethylcyclobutanecarbonitrile (Cis and Trans) (2) had ir (NaCl) 2250 (CN), 1625 cm^{-1} (C=C); nmr ($CDCl_3$) τ 4.7 (broad singlet, 2 H, olefinic), 6.0)multiplet, 3 H, α to cyano and chloro), 6.8 (multiplet, 3 H, chloromethyl and methine α to chloromethyl); mass spectrum *m/e* 141, parent peak (calcd mol wt, 141).

Anal. Calcd for C_7H_8NCl: C, 59.34; H, 5.69; N, 9.88; Cl, 25.09. Found: C, 59.40; H, 5.63; N, 9.84; Cl, 25.31.

1-Chloro-1-cyclohexene-4-carbonitrile (3). On standing at below 0° temperature for several days, the mixture of cycloadducts contained a crystalline precipitate. Filtration and recrystallization from hot hexane afforded pure crystals, mp 53–54°. Preparative glc of the binary mixture that constituted fraction 2 of the spinning-band distillation showed that the compound having the longer retention time was identical with the solid recrystallized from hexane: ir (KBr) 2250 (CN), 1660 (olefinic), 740 cm^{-1} (CCl); nmr ($CDCl_3$) τ 4.4 (multiplet, 1 H, olefinic), 7.3 (multiplet, 1 H, α to cyano), 7.5 (multiplet, 4 H, α to double bond), 8.0 (multiplet, 2 H, C-5 methylene); mass spectrum *m/e* 141, parent peak (calcd mol wt, 141).

Anal. Calcd for C_7H_8NCl: C, 59.34; H, 5.69; N, 9.88; Cl, 25.09. Found: C, 59.21; H, 5.74; N, 9.79; Cl, 25.20.

3-Methylenebicyclo[2.1.0]pentane-1-carbonitrile (4). The mixture of cycloadducts **2** and **3**, 1.5 g (106 mmol), was dissolved in 20 ml of anhydrous ethyl ether, placed in an ice–methanol bath, and chilled to −8°. A gentle nitrogen bleed was applied and 1.3 g (115 mmol) of potassium *tert*-butoxide was added all at once. The color of the resulting mixture darkened to a brownish purple and the temperature rose to 3–4° before beginning to fall. At this point, 1.0 g of powdered CO_2 was added to the reaction mixture followed by 2–3 ml of saturated potassium chloride solution. Filtration of the slurry of salt and drying over $MgSO_4$ was followed by rotary evaporation and distillation. The distillate, 0.6 g, bp 38–56° (0.1 mm), was found to contain a new lower boiling component along with the unreacted Diels–Alder adduct. Separation of the two substances was accomplished through preparative glc and the new compound, present in 80% yield based on starting reactive adduct, was analyzed: ir (NaCl) 2250 (CN), 1660 cm^{-1} (C=C); nmr ($CDCl_3$) τ 5.0 (doublet, 2 H, olefinic), 6.8 (multiplet, 2 H, cyclobutylmethylene), 8.0 (triplet, 3 H, cyclopropyl); mass spectrum *m/e* 105, parent peak (calcd mol wt, 105).

Anal. Calcd for C_7H_7N: C, 80.03; H, 6.66; N, 13.30. Found: C, 80.13; H, 6.78; N, 13.22.

3-Hydroxy-3-vinyl-1-cyclobutanecarbonitrile (5) Vinylmagnesium chloride was prepared from magnesium turnings and vinyl chloride.[17] We found it necessary to heat the mixture of vinyl chloride, magnesium turnings (ground), and THF to 60° before reaction could be sustained. The reagent, when stored under nitrogen at room temperature, was stable for months. The concentration of the solution of Grignard reagent in THF was determined by acidification with known acid (excess) followed by back titration with standard NaOH. The Grignard reagent, 50 ml of 2.0 *M* solution, was placed in a 250-ml three-necked flask fitted with a motor-driven stirrer, 50-ml addition funnel, and gas inlet adaptor. The flask and contents were cooled to −30° in a controlled Dry Ice–acetone bath. A solution of 5.3 g (0.056 mol) of 3-cyanocyclobutanone in 30–40 ml of dry THF was placed in the addition funnel and added dropwise to the Grignard reagent over a period of 30–45 min. After addition was complete, stirring was continued for 2 hr while the temperature was maintained at −30°. At this point about 15 ml of saturated KCl solution was added to the mixture (carefully!). Formation of a light yellow crystalline precipitate was observed during the addition of the salt. The resulting organic layers were washed with 5 ml of saturated KCl, dried over $MgSO_4$, and rotary evaporated to a clear yellow-orange residue. Distillation in a short-path distillation apparatus afforded 4.1 g (60%) of a clear, colorless distillate: bp 70–73° (0.1 mm); ir (NaCl) 3420 (OH), 2240 (CN), 1630 cm^{-1} (C=C); nmr ($CDCl_3$) τ 3.8–4.2 (multiplet, 1 H, vinyl), 4.5–4.9 (multiplet, 2 H, vinyl), 6.0 (singlet, 1 H, hydroxyl), 7.4 (broad singlet, 5 H, cyclobutyl). Deuteration of the sample resulted in the disappearance of the singlet at τ 6.0 while leaving the remainder of the spectrum virtually unchanged. The mass spectrum of the vinyl alcohol behaved anomalously, giving repeatedly a parent peak of *m/e* 220 (calcd mol wt, 123); we were unable to account for this. The overwhelming majority of the data, however, assures us that the compound we have is 3-hydroxy-3-vinyl-1-cyclobutanecarbonitrile.

Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.28. Found: C, 68.35, H, 7.47; N, 11.28.

3-Chloro-3-vinyl-1-cyclobutanecarbonitrile (6) and 3-(β-chloroethylidene)-1-cyclobutanecarbonitrile (7). A solution of 26 g (0.1 mol) of triphenylphosphine in 75 ml of CCl_4 was placed in a 200-ml round-bottomed flask fitted with an air-cooled reflux condenser and Teflon-coated magnetic stirring bar. To this solution was added 6.0 g (0.05 mol) of 3-hydroxy-3-vinyl-1-cyclobutanecarbonitrile (**5**). The mixture was stirred and brought to 60–65° and maintained at this temperature for 24 hr. At the end of this period the reaction mixture was added to 30 ml of cold hexane, effecting the precipitation of much of the triphenylphosphine oxide. Filtration and rotary evaporation yielded 9 g of reddish, clear liquid. When this liquid was placed under full oil pump vacuum and the residual carbon tetrachloride removed, more of the triphenylphosphine oxide precipitated. At this point an additional 10 ml of hexane was added to the thick slurry and the filtration and rotary evaporation were repeated. Distillation of this second residue yielded 4.9 g (71%) of clear, colorless liquid, bp 53–56° (0.08 mm). Gas–liquid chromatography indicated that three new components were present in addition to a small amount of unreacted alcohol. The two components of shorter retention time were the cis and trans isomers of tertiary chloride **6**; the component of longest retention time was primary chloride **7**. Spinning-band distillation was used to separate the isomeric 3-chloro-3-vinyl-1-cyclobutanecarbonitriles (**6**) from the higher boiling **7**. We were, however, unable to separate the isomeric tertiary chlorides from each other.

3-Chloro-3-vinyl-1-cyclobutanecarbonitrile (6) had ir (NaCl) 2200 (CN), 1550 and 1620 (C=C), 757 cm^{-1} (CCl); nmr ($CDCl_3$) τ 3.8–4.1 (multiplet, 1 H, vinyl), 4.6–4.9 (multiplet, 2 H, vinyl), 7.1 (singlet, 5 H, ring protons); mass spectrum *m/e* 141, parent peak (calcd mol wt, 141).

Anal. Calcd for C_7H_8NCl: C, 59.31; H, 5.65; N, 9.90; Cl, 25.10. Found: C, 59.35; H, 5.63; N, 9.83; Cl, 24.93.

3-(β-Chloroethylidene)-1-cyclobutanecarbonitrile (7) had ir (NaCl) 2240 (CN), 1630 (C=C), 750 cm^{-1} (CCl); nmr ($CDCl_3$) τ 4.4–4.7 (multiplet, 1 H, methylene), 6.0 (doublet, 2 H, chloromethyl), 6.9 (broad singlet, 5 H, ring H's); mass spectrum *m/e* 141 parent peak (calcd mol wt, 141).

Anal. Calcd for C_7H_8NCl: C, 59.31; H, 5.65; N, 9.90; Cl, 25.10. Found: C, 59.13; H, 5.74; N, 10.04; Cl, 25.27.

3-Vinylbicyclobutanecarbonitrile (8). A solution of 1.0 g (71 mmol) of 3-vinyl-3-chlorocyclobutanecarbonitrile (cis–trans mixture) in 30 ml of anhydrous ethyl ether was placed in a 50-ml three-necked round-bottom flask fitted with a nitrogen gas inlet adaptor and Teflon-coated magnetic stirring bar. The flask and its contents were then cooled to −6° in an ice–methanol bath. At this point 1.0 g (88 mmol) of potassium *tert*-butoxide was added to the flask all at once. The color of the mixture instantly became a dark brownish purple and the temperature rose from −6° to about 4° over a 3-min period. Over the next 4–5 min the temperature tapered off and began to drop. At this point the reaction mixture was treated with 1.0 g of powdered CO_2 and approximately 2 ml of saturated KCl solution. The resulting slurry of salts was rapidly filtered, and the filtrate was dried over a little magnesium sulfate and concentrated on the rotary evaporator. Distillation of the residue yielded 0.7 g (92%) of a clear, colorless liquid: bp 45–48° (0.08 mm); ir (NaCl) 2210 (CN), 1550 and 1610 cm^{-1} (C=C); nmr ($CDCl_3$) τ 3.8–4.2 (multiplet, 1 H, vinyl), 4.5–4.8 (multiplet, 2 H, vinyl), 7.6 (singlet, 2 H, ring protons), 8.4 (singlet, 2 H, ring protons), the last two signals (τ 7.6 and 8.4) are attributed to the exo and endo protons, respectively; mass spectrum *m/e* 105, parent peak (calcd mol wt, 105).

Anal. Calcd for C_7H_7N: C, 80.02; H, 6.66; N, 13.30. Found: C, 79.97; H, 6.83; N, 13.02.

A 15% solution of **8** in sulfolane yielded polymer when subjected to uv radiation for 8 hr at room temperature.

3-Vinyl-1-cyanocyclobut-2-ene (9) 3-(β-Chloroethylidene)cyanocyclobutane, 1.0 g (71 mmol), was dissolved in 15 ml of anhydrous ethyl ether. The resulting solution was placed in a 50-ml three-necked round-bottomed flask fitted with a nitrogen gas inlet adaptor and a 0.5-in. magnetic stirring bar (Teflon coated). The flask and contents were then cooled to −7° in an ice–methanol bath. At this point, 1.0 g (88 mmol) of potassium *tert*-butoxide was introduced into the flask all at once. The color of the solution turned dark brownish purple as the temperature rose slightly above 0°. After 10–12 min the temperature began to fall and the reaction mixture was worked up by adding *ca.* 0.5 g of powdered CO_2 and 1–2 ml of saturated KCl solution. The resulting slurry of salts was filtered and the filtrate was dried over a little $MgSO_4$ and distilled. The distillate (0.8 g), collected over a temperature range of 37–63° (0.1 mm), was found to contain, in addition to 20% unreacted starting material, a 55:45 (glc) mixture of two new lower boiling components. These two substances were separated from the unreacted chloride and their nmr spectrum was taken. When the spectrum (nmr) of pure 3-vinylbicyclobutanecarbonitrile was compared with that of the mixture of products of this reaction, it was evident that the conjugated diene **9** was present along with the bicyclic isomer. The yield of diene based on a 45:55 diene to bicyclic ratio was about 29%: nmr ($CDCl_3$) τ 6.5 (broad multiplet, 1 H, α to cyano), 7.0 (multiplet, 2 H, methylene), 3.5–4.8 (multiplet, 4 H, olefinic protons) (absorptions caused by 3-vinylbicyclobutane-1-carbonitrile not mentioned).

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Registry No.—**1**, 25790-55-0; *cis*-**2**, 51934-00-0; *trans*-**2**, 51934-01-1; **3** (4-CN), 31865-09-5; **4**, 51934-02-2; *cis*-**5**, 51934-03-3; *trans*-**5**, 51934-04-4; *cis*-**6**, 51934-05-5; *trans*-**6**, 51934-06-6; **7**, 51934-07-7; **8**, 51934-08-8; **9**, 52003-46-0; acrylonitrile, 107-13-1; vinyl chloride, 75-01-4; 3-cyanocyclobutanone, 20249-16-5.

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Pyrimido[5,4-*e*]-*as*-triazines. VII. Synthesis of 7-Aza Analogs of Pteroic and Folic Acids[1]

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An investigation of the preparation and stability of dihydropyrimido[5,4-e]-*as*-triazines indicated that electron-donating groups in the dihydro-*as*-triazine ring promoted the air oxidation of these compounds to the corresponding heterocyclic derivatives. Work was also carried out in the preparation and reactions of a number of substituted anilinoacetonitriles. Conversion of [*p*-(ethoxycarbonyl)anilino]acetonitrile (**6a**) and diethyl *p*-[(cyanomethyl)amino]benzoyl-L-glutamate (**6c**) to the corresponding ethyl imidates and condensation of the latter with 2,5-diamino-4-(benzylthio)-6-hydrazinopyrimidine (**7**) provided directly ethyl *p*-[[[7-amino-5-(benzylthio)-pyrimido[5,4-*e*]-*as*-triazin-3-yl]methyl]amino]benzoate (**10a**) and the corresponding diethyl L-glutamate (**10b**), respectively. Nucleophilic replacement of the benzylthio group of **10a** with the appropriate reagent gave the 5-oxo (**11a**, ethyl 7-azapteroate), the 5-thione (**12a**), and the 5-amino (**13a**) derivatives. Similarly, **10b** was converted to the 5-oxo (**11c**, 7-azafolic acid) and 5-thione (**12c**) derivatives. Reaction of **10b** with sodium azide lead to the corresponding diethyl ester of the 5-amino derivative (**13b**).

Previously, we reported the development of synthetic methods for the preparation of 4-substituted 2-amino-7-azapteridines (5-substituted 7-aminopyrimido[5,4-e]-*as*-triazines).[2] Further modification of these procedures have now provided methods for the preparation of 7-azapteroic and 7-azafolic acids and related compounds.[3] These compounds, especially 7-azafolic acid and the corresponding 4-thio compound, are of interest as potential substrates for the folic reductase enzyme, which on interaction might produce biologically interesting 7-aza derivatives that are analogs of the tetrahydrofolate coenzymes.[4]

Earlier we showed that reaction of **2a** with NaSH not

only replaced the benzylthio group but also reduced the *as*-triazine ring to give the dihydro derivative **1a.**[5] To obtain information on the preparation and stability of dihydro-7-azapteridines containing a methylene function in the triazine ring, the reactions of some simple derivatives were investigated. The cyclization of **3**[6] in hot HOAc gave a mixture of products in which the desired **1b** was shown to be the major component by its pmr spectrum. Treatment of **1b** with NaSH gave a product which, after reprecipitation from a basic solution with acid, analyzed correctly for **1c** but was shown by its pmr spectrum to be a 7:3 mixture of **1c** and **2b.** Alkylation of this mixture with benzyl chloride gave both **1d** and **2c,** which were separated by recrystallization. Reaction of **2c** with NaSH and isolation of the product directly from the reaction medium by acidification gave only the dihydro derivative **1c** as determined by its pmr spectrum. However, reprecipitation of this sample from a basic solution with acid gave a 7:3 mixture of **1c** and **2b,** the same as that obtained in the reaction of **1b** with NaSH described above. These results indicated that the presence of the methyl group does not interfere with the reduction of the *as*-triazine ring but does promote the air oxidation of **1c** when compared with **1a,** which can be reprecipitated unchanged from a basic solution with acid.[5]

The preparation of the desired analogs were attempted by two routes. One involved the alkylation of a *p*-aminobenzoyl side-chain moiety with a preformed halomethyl-7-azapteridine intermediate. The products of these reactions have been difficult to characterize, and the results of this work will be reported at a later date. The successful route involved the condensation of a 5-amino-4-hydrazinopyrimidine with the imidate derived from an anilinoacetonitrile type intermediate. The known **6a**[7] was prepared in good yield by a new method, which involved the alkylation of **4a** with cyanomethyl *p*-toluenesulfonate in EtOAc. Similarly, treatment of methyl *p*-(methylamino)benzoate (**4b**)[8] and diethyl *p*-aminobenzoyl-L-glutamate (**4c**)[9] with this reagent in refluxing dioxane gave, respectively, **6b** and **6c.** The latter was purified by column chromatography and recrystallization and was obtained in low yield. The preparation of **6c** by treatment of **4c** successively with $HOCH_2SO_3Na$ ($NaHSO_3$ and CH_2O) and KCN was unsuccessful.[7]

Initially, we considered the conversion of the cyanomethyl compounds to the corresponding ortho esters, which would be used as intermediates in the cyclization of 5-amino-4-hydrazinopyrimidines to 7-azapteridines. Treatment of the simple cyanomethyl compound **6d**[10] in Et_2O with ethanolic HCl gave only its hydrochloride salt rather than the imidate **5a.** In contrast, the conversion of **6d** to the acyl derivative **6e** and treatment of this product with ethanolic HCl gave **5b.** Under the same conditions that were successful for the preparation of **6e,** acylation of **6a** to give **6f** was unsuccessful, apparently because of the reduced basicity of the amino group. However, treatment of **6a** in Et_2O with ethanolic HCl provided directly the hydrochloride salt of the imidate **5c.** Conversion of this salt to the corresponding ortho ester was attempted in EtOH, but this reaction appeared to give mainly the hydrochloride salt of the corresponding acetic acid derivative based on elemental analysis. To eliminate from consideration the presence of HCl in **5c,** the method of Kim and McKee for the preparation of this compound was investigated.[7] This method involved the base-catalyzed addition of EtOH to **6a** to give **5c.**[11] After neutralization with acetic acid, refluxing the solution of **5c** evolved NH_3, presumably to give the ortho ester, which was successfully condensed with **7.** Further investigation showed that the condensation of **7** with the *in situ* formed imidate **5c** also gave the desired product (see below). Unexpectedly, treatment of **6b** under similar conditions to give **5d** and condensation of the latter *in situ* with **7** gave no 7-azapteridine. The isolated product analyzed closely for a ring-opened derivative **9,** which could not be cyclized in an acid medium. Similarly, reaction of 5-amino-4-chloro-6-hydrazinopyrimidine[5] with **5c** apparently gave a ring-opened amidrazone intermediate that also could not be cyclized under acidic, neutral, and basic conditions. Although not enough work was carried out to determine the cause of these unsuccessful reactions, the imidate intermediate can react with the hydrazino group either by replacement of the alkoxy group[12] or by exchange amination with the amino group.[13] However, both types of pyrimidine intermediates produced by these reactions should undergo cyclization although the product resulting from exchange amination might do so more readily.[14]

A solution of **5c** prepared as described above was condensed with **7** at room temperature to give **10a,** no doubt formed by air oxidation of the intermediate dihydro derivative **8a.** Reaction of **10a** with $KHCO_3$ in aqueous DMSO at 90° gave ethyl 7-azapteroate (**11a**). Under these conditions, no hydrolysis of the benzoate ester function was observed. The interaction of **10a** with NaSH in aqueous DMF at 80° gave the thione **12a.** The isolation of the heteroaromatic compound from this reducing medium is attributed to the

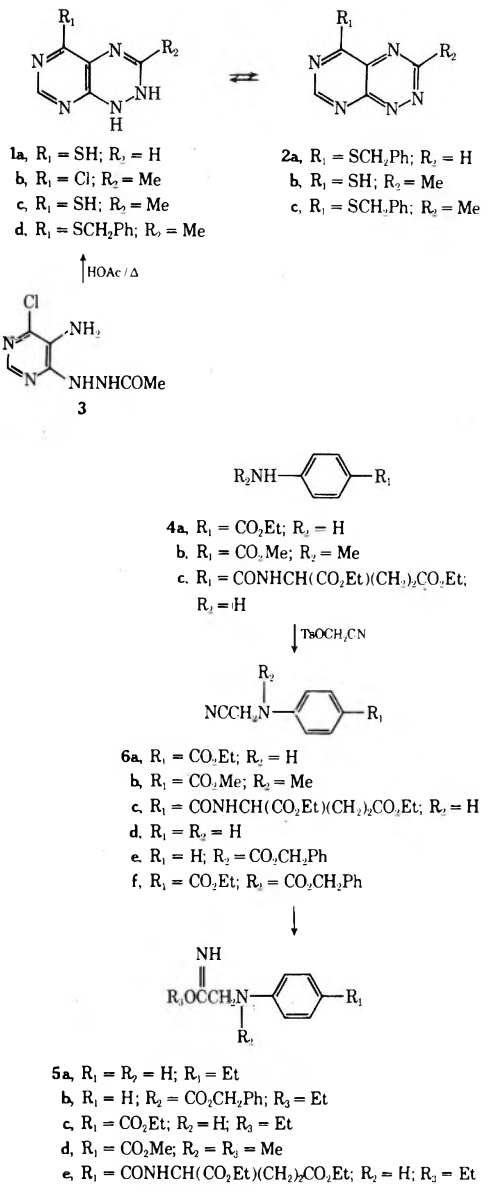

Table I

Compd	Uv absorption[a] spectra at pH 7, λ_{max}, nm ($\epsilon \times 10^{-3}$)	Ir absorption[b] spectra in KBr, selected bands, cm^{-1}	Pmr spectral assignments,[c] chemical shifts, δ (rel area)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1c	254 (10.4), 298 (5.16), 339 (6.96), 415 (3.62)[d,e]	1645	1.59 (3, CH_3), 6.47, 8.77 (1, 1, NH),[f] 7.47 (1, CH), ~13 br (NH)[f,g]	$C_6H_7N_5S$	39.77	3.89	38.65	39.66	3.69	38.50
1d	357 (5.34)[d,e]	1660	1.53 (3, CH_3), 3.26 (H_2O), 4.29 (2, CH_2), 7.27 (6, C_6H_5, NH[f]), 7.61 (1, CH), 8.62 (1, NH)[f]	$C_{13}H_{13}N_5S \cdot 0.33H_2O$	56.30	4.97	25.25	56.27	5.06	25.29
2c	240 (11.1), 263 sh (5.88), 391 (6.40)[d,e]	1595, 1540	3.10 (3, CH_3), 4.66 (2, CH_2), 7.40 (5, C_6H_5), 9.28 (1, CH)	$C_{13}H_{11}N_5S$	57.98	4.12	26.00	58.05	4.13	25.95
10a	242 (14.3), 281 sh (26.2), 299 (29.8), 420 (7.68)[h]	1695, 1640	1.25 (3, CH_3), 4.20 q (2, CH_2O), 4.52 (2, CH_2S), 4.78 d [2, CH_2N (J = 6.0 Hz)], 7.18, 7.37, 7.87 [12, C_6H_4 (C_6H_5, NH[f]), NH_2[f]]	$C_{22}H_{21}N_7O_2S$	59.05	4.73	21.91	58.94	4.85	21.95
10b	232 (26.4), 289 (19.8), 373 (8.85)[d,e]	1725, 1630	1.17 (6, CH_3), 2.04, 2.41 (CH_2-CH_2), 4.06 (4, CH_2Me), 4.39 (1, CHN), 4.52 (2, CH_2S), 4.77 d [2, CH_2N (J = 5.6 Hz)], 6.95 t (1, HNC), 7.17, 7.38 (9, C_6H_4, C_6H_5), 7.88 br (2, NH_2),[f] 8.17 d [1, HNCO (J = 7.0 Hz)][f]	$C_{29}H_{32}N_8O_5S$	57.60	5.33	18.53	57.22	5.40	18.61
11a	266 (24.7), 287 sh (21.7), 387 (4.87)[i]	1690, 1640	1.25 (3, CH_3), 4.20 q (2, CH_2O), 4.79 (2, CH_2N), 7.53 br (NH, NH_2),[f] 7.22 (C_6H_5)	$C_{15}H_{15}N_7O_3 \cdot HCl$	47.69	4.27	25.92	47.31	3.98	26.09
11c	272 (22.2), 377 (4.35)[d]	1700, 1650	2.04, 2.34 (CH_2CH_2), 3.35 (H_2O), 4.36, 4.74 br (3, CHN, CH_2N), 7.18, 7.32 br, 8.08 d [9, C_6H_4, (NH_2, NH, NH), NHCO (J = 8.0 Hz)], ~12 br (2, OH)	$C_{18}H_{18}N_8O_6 \cdot 1.5H_2O$	46.06	4.51	23.87	45.85	4.31	24.10
12a	299 (26.9), 378 sh (4.18), 443 (6.18)[d]	1685, 1635	1.23 (CH_3), 4.17 q (CH_2O), 4.71 (CH_2N), 7.15 (C_6H_5), 7.3 br (NH_2),[f] 7.67 br (NH)[f,j]	$C_{15}H_{15}N_7O_2S \cdot H_2O$	47.99	4.56	26.12	48.23	4.84	26.00
12b	291 (24.8), 360 (4.67), 440 (5.17)[d]	1725, 1640	1.17 (CH_3), 2.04, 2.51 (CH_2-CH_2), 4.06 (CH_2Me), 4.38 (CHN), 4.74 (CH_2N), 7.17 (C_6H_5), 7.27 br, 8.15 br (NH, NH_2)[f,j]	$C_{22}H_{26}N_8O_5S \cdot HCl$	47.95	4.94	20.34	47.58	5.02	20.16

12c	270 sh (22.3), 284 (22.8), 377 (4.78), 432 (4.45)[d]	1710, 1660, 1645	2.01, 2.32 (CH_2CH_2), 3.4 (H_2O), 4.34, 4.72 (3, CHN, CH_2N), 7.14, 8.05 d [9 (C_6H_4, NH_2,[f] NH,[f] NH^f), NHCO (J = 8.0 Hz)], ~11 (2, OH)[f]	$C_{18}H_{18}N_8O_5S\cdot H_2O$	45.38	4.23	23.52[k]	45.18	4.10	23.57[k]
13a	275 sh (26.4), 298 (31.7), 403 (5.03)[h]	1685, 1640	1.27 (3, CH_3), 3.27 (H_2O), 4.22 q (2, CH_2O), 4.77 d [2, CH_2N (J = 6.0 Hz)], 6.92, 7.04, 7.30 (7, NH,[f] NH_2,[f] C_6H_4), 8.19 br (2, NH_2)[f]	$C_{15}H_{16}N_8O_2\cdot H_2O$	50.28	5.06	31.27	50.63	4.61	31.05	
13b	267 (27.3), 287 sh (24.6), 393 (5.90)[d]	1730, 1640	1.18 (6, CH_3), 2.05, 2.43 (CH_2-CH_2), 3.3 (H_2O), 4.19 q, 4.35, 4.76 (7, CH_2O, CHN, CH_2N), 7.25, 8.25 [10 (C_6H_4, NH_2,[f] NH^f), NH^f]	$C_{22}H_{27}N_9O_5\cdot 0.75H_2O$	51.71	5.62	24.67	51.96	5.29	24.28	
14b	280 (22.4), 364 (4.81)[d]	1725, 1665, 1640		$C_{22}H_{25}N_{11}O_5\cdot 1.75H_2O$	47.61	5.18	27.76	47.70	4.86	27.66	

[a] Cary Model 14 and 17 spectrophotometers. [b] Perkin-Elmer Model 521 and 621 spectrophotometers. [c] Pmr spectra of samples were determined on DMSO-d_6 solutions (3–6% w/v) on a Varian A-60A and XL-100-15 spectrometers with TMS as an internal reference; peak positions quoted in the case of multiples are measured from the approximate center, and the relative peak areas are given to the nearest whole number. [d] The sample was dissolved in a mixture containing 8% DMSO and 92% MeOH. [e] Determined in 0.1 *N* HCl. [f] Exchanged for deuterium on addition of D_2O. [g] This product was a 7:3 mixture of **1c** and **2b** in which **2b** showed δ 2.99 (CH_3), 8.32 (CH). [h] Determined in a mixture of 8% DMSO and 92% MeOH. [i] The sample was dissolved in 0.1 *N* NaOH and diluted with pH 7 buffer. [j] Relative peak areas were inconsistent. [k] Calcd: S, 6.73. Found: S, 6.90.

presence of the electron-releasing aminomethyl function in the triazine ring since the corresponding compound without this moiety gave only a dihydro derivative.[2] Incomplete reaction was obtained when **10a** was treated with NaSH in H_2O at 80°. The product obtained under these conditions was identified by the pmr spectrum as the benzoic acid derivative of **12a.** Replacement of the benzylthio group of **10a** to give **13a** was effected with 10% ethanolic NH_3 in warm DMAC. Treatment of **10a** with NaN_3 in aqueous DMSO at room temperature appeared to give the tetrazolo compound **14a.** This compound was not obtained pure, and the conversion of **14a** *via* reduction of the corresponding azido tautomer to **13a** was not attempted.

Addition of ethanol to the cyano group of **6c** in the presence of sodium ethoxide gave the imidate **5e.** The solution of **5e** was neutralized and condensed *in situ* with **7** to give **10b,** presumably formed *via* air oxidation of the corresponding dihydro derivative **8b.** Treatment of an aqueous DMSO solution of **10b** with $KHCO_3$ at 90° replaced the benzylthio group to give crude **11b.** Saponification of the ester groups of **11b** to give **11c** at room temperature with oxygen-free NaOH was slow and required two 18-hr treatments to complete the hydrolysis. Reaction of **10b** with NaSH in refluxing EtOH gave the diethyl ester of the thione **12b,** which was saponified in the absence of oxygen with NaOH to give **12c.** Thin layer chromatography data indicated that hydrolysis of the thioamide moiety of **12c** occurred slowly in dilute NH_4OH to give mainly 7-azafolic acid (**11c**). The preparation of **13b** from **10b** and ethanolic NH_3 was eliminated from consideration as this reagent might also convert the ester functions to amides. For this reason, **10b** was reacted with NaN_3 to give a mixture of **13b** and **14b** which were separated. The isolation of **13b** directly from the reaction mixture is in agreement with the observation that 4-azido-7-azapteridines are readily converted to 4-amino-7-azapteridines.[15] The structure of **14b** is based on the absence of an azido absorption band in its infrared spectrum. Hydrolysis of the ester groups of **13b** to give **13c** was attempted under the same conditions that were suc-

cessful for the preparation of **11c** and **12c**, but the pmr spectrum of the recovered material indicated that little or no saponification occurred.

Although the activities (ED_{50}) of the folic acid analogs (**11c** and **12c**) were similar to that of methotrexate when tested against *Streptococcus faecium* ATCC 8043, no activity was observed in preliminary tests against L1210 leukemia cells implanted intraperitoneally in mice.

The uv and pmr spectra and selected bands in the ir spectra for the new compounds are presented in Table I.

Experimental Section[16]

5-Chloro-1,2-dihydro-3-methylpyrimido[5,4-*e*]-*as*-triazine (1b). A solution of **3** (2.4 g) in glacial HOAc (50 ml) was refluxed for 2 hr and evaporated to dryness *in vacuo*. The resulting residue was washed with Et_2O and dried *in vacuo* over P_2O_5: yield, 2.2 g. A sample of the crude product was recrystallized three times from EtOAc. The pmr spectrum (DMSO-d_6) of the resulting sample showed a three-component mixture of which 74% was the desired product **1b**. In later experiments, the crude product first isolated was used in the preparation of **1c**.

1,2-Dihydro-3-methylpyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione (1c). A. A mixture of crude **1b** (3.4 g) and hydrated sodium hydrosulfide (3.4 g) in EtOH (700 ml) was refluxed for 1 hr and evaporated to dryness *in vacuo*. This residue was dissolved in H_2O, and the resulting solution was acidified to pH 5 (paper) with dilute HCl. The solid that precipitated was collected by filtration and stirred for 1 hr in C_6H_6 (500 ml) and then for 30 min in EtOH (50 ml) to give practically pure **1c**: yield, 1.9 g (57%). Further purification was obtained by reprecipitation of a portion of this sample (0.90 g) from a NaOH solution with dilute HCl. The resulting product was dried *in vacuo* over P_2O_5 at 110°: yield, 0.65 g (72% recovery); mp >264°. The pmr spectrum indicated that this sample was a 7:3 mixture of **1c** and **2b**.

B. Treatment of **2c** (100 mg) as described above gave, after acidification to pH 5, only **1c**: yield, 51 mg. None of **2b** was observed in the pmr spectrum (DMSO-d_6) of this product. However, reprecipitation of a portion of this sample (32 mg) from a NaOH solution with dilute HCl gave a sample (20 mg) which was shown to be about a 7:3 mixture of **1c** and **2b** by its pmr spectrum (DMSO-d_6).

5-(Benzylthio)-1,2-dihydro-3-methylpyrimido[5,4-*e*]-*as*-triazine (1d) and 5-(Benzylthio)-3-methylpyrimido[5,4-*e*]-*as*-triazine (2c). A solution of **1c** (1.0 g) in 0.2 *N* NaOH (28 ml) containing benzyl chloride (0.65 ml) was stirred at room temperature for 5 hr. The solid that precipitated was collected by filtration, dried *in vacuo* over P_2O_5, and extracted with hot C_6H_6 (30 ml). On cooling, the extract deposited a small amount of solid that was removed by filtration. The filtrate was concentrated to about one-half volume and on standing deposited **1d**: yield, 0.30 g (20%); mp 145–146°.

The C_6H_6 filtrate from above was evaporated to dryness *in vacuo*, and the residue was washed with H_2O. The resulting solid was dried (P_2O_5) and recrystallized from hexane to give **2c**: yield, 0.46 g (31%); mp 125–126°.

Ethyl [*N*-Benzyloxycarbonyl)anilino]ethanimidate Hydrochloride (5b). A solution of **6e** (0.57 g) in Et_2O (35 ml) containing absolute EtOH (0.15 ml) and excess anhydrous HCl was cooled at 5° for 48 hr. The hygroscopic precipitate was collected by filtration and washed with fresh Et_2O: yield, 0.08 g (11%).

Anal. Calcd for $C_{18}H_{20}N_2O_3$·HCl: C, 61.98; H, 6.07; N, 8.03. Found: C, 61.70; H, 6.30; N, 8.32.

Ethyl [*p*-(Ethoxycarbonyl)anilino]ethanimidate Hydrochloride (5c). A solution of **6a** (1.0 g) in Et_2O (100 ml) containing 10 ml of 22% ethanolic HCl was cooled at 5° for 18 hr. The resulting hydrochloride salt was collected by filtration and washed with fresh Et_2O: yield, 0.32 g (21%); mp ~95° with presoftening (capillary tube).

Anal. Calcd for $C_{13}H_{18}N_2O_3$·HCl: C, 54.45; H, 6.68; N, 9.77. Found: C, 54.46; H, 6.40; N, 10.00.

[*p*-(Ethoxycarbonyl)anilino]acetonitrile (6a). A mixture of **4a** (36 g) and cyanomethyl *p*-toluenesulfonate (21 g) in ethyl acetate was refluxed with stirring for 48 hr. The cooled mixture was filtered, the residue was washed with ethyl acetate, and the combined filtrate and wash was evaporated to dryness *in vacuo*. The resulting oil was extracted with ether (500 ml), and the solid obtained by evaporation of the extract was recrystallized from CCl_4: yield, 16 g (79% based on cyanomethyl *p*-toluenesulfonate); mp 92–93° (lit.[7] mp 92–93.5°); ν_{max} 2235 cm^{-1} (CN).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.70; H, 5.91; N, 13.57.

[*p*-(Methoxycarbonyl)-*N*-methylanilino]acetonitrile (6b). A solution of **4b** (2.0 g) and cyanomethyl *p*-toluenesulfonate (2.5 g) in dioxane (30 ml) was refluxed for 72 hr. The cooled reaction mixture was filtered to remove some solid material (0.17 g), the filtrate was evaporated to dryness *in vacuo*, and the resulting oil was extracted by stirring with Et_2O. After the separation of the solid (1.4 g), the Et_2O solution was washed with 1 *N* NaOH (3 × 20 ml portions), dried ($MgSO_4$), and evaporated to dryness *in vacuo* to yield an oil (2.5 g). A solution of the oil in Et_2O (25 ml) was diluted with hexane (25 ml) and refrigerated to deposit crude **6b**: yield, 1.1 g; mp 77° with presoftening from 32°. Two additional reprecipitations of the product from Et_2O–hexane gave pure **6b**: yield, 0.23 g (18.6%); mp 82°; ν_{max} 2230 cm^{-1} (CN); pmr (DMSO-d_6) δ 3.05 (3, CH_3N), 3.81 (3, CH_3O), 4.65 (2, CH_2), 7.47 (4, C_6H_4).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.36; H, 5.92; N, 13.73.

Dilution of the combined Et_2O–hexane filtration from above with hexane followed by refrigeration gave recovered crude **6b**: yield, 0.61 g; mp ~33–49°.

Diethyl *p*-[(Cyanomethyl)amino]benzoyl-L-glutamate (6c). A mixture of **4c** (45 g) and cyanomethyl *p*-toluenesulfonate (27 g) in dioxane (350 ml) was refluxed for 120 hr and evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ and poured onto a 3-l. fritted-glass funnel containing silica gel H (375 g). The funnel was washed with $CHCl_3$ to give fractions I (17 g, 1500 ml) and II (19 g, 8500 ml) and with EtOAc to give fraction III (7 g, 2000 ml). Fractions I and II were combined and eluted ($CHCl_3$) from a silica gel H (350 g) column to give a crude oily product (6.6 g), which was washed with Et_2O to give a solid: yield, 3.6 g; mp 90–92°. For analyses a sample (124 mg) was recrystallized from a mixture of C_6H_6 and hexane: mp 95°; ν_{max} 2250 cm^{-1} (CN); pmr (DMSO-d_6) δ 1.18 (6, CH_3), 2.09, 2.43 (CH_2CH_2), 4.07, 4.32 [7, CH_2O (CHN, CH_2N)], 6.7 (br, 1, NH), 7.24 (4, C_6H_4), 8.32 [d, 1, NH (J = 8.0 Hz)].

Anal. Calcd for $C_{18}H_{23}N_3O_5$: C, 59.82; H, 6.41; N, 11.63. Found: C, 59.58; H, 6.37; N, 11.37.

Fraction III was eluted with $CHCl_3$ from a coarse silica gel 60 column to give an oily product which was then washed with Et_2O to give a solid: yield, 2.8 g. This sample melted with softening from 80°.

The residue obtained from evaporation of the combined Et_2O washes was eluted with $CHCl_3$ from a silica gel H (80 g) column to give an additional amount of crude oily product: yield, 1.0 g.

[*N*-(Benzyloxycarbonyl)anilino]acetonitrile (6e). A solution of **6d** (1.0 g)[10] in dioxane (25 ml) containing pyridine (0.61 ml) and benzyloxycarbonyl chloride (1.3 g) was stirred at room temperature for 5 hr. After filtration the filtrate was evaporated to dryness, and the resulting residue was extracted with ether. Addition of anhydrous HCl in Et_2O to the filtrate gave a precipitate that was discarded. The filtrate was washed (H_2O), dried ($MgSO_4$), and evaporated *in vacuo* in a tared flask: yield, 0.67 g (33%); pmr (DMSO-d_6) δ 4.78 and 5.17 (CH_2), 7.35 (C_6H_5).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.22; H, 5.29; N, 10.34.

Ethyl *p*-[[[7-Amino-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazin-3-yl]methyl]amino]benzoate (10a). A solution of **6a** (4.0 g) in absolute EtOH (40 ml) containing NaOEt (0.17 g) was stirred at room temperature for 18 hr. followed by neutralization with glacial HOAc (0.16 ml). This solution was added to a suspension of **7** (4.0 g)[2] in dioxane (200 ml). The resulting dark solution was stirred in an open flask (cotton plug) at room temperature for 18 hr to deposit **10a**, which was collected by filtration and washed with $CHCl_3$ (1500 ml): yield, 2.8 g (42%). For analyses a sample was reprecipitated from a DMSO solution with H_2O and dried *in vacuo* over P_2O_5 at 78°, mp >264°.

Diethyl *N*-[*p*-[[[7-Amino-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazin-3-yl]methyl]amino]benzoyl]-L-glutamate (10b). A solution of **6c** (3.61 g) in EtOH (50 ml) containing NaOEt (0.1 g) was stirred at room temperature for 18 hr followed by neutralization with HOAc (0.1 ml). This solution was added to a solution of **7** (2.62 g)[2] in dioxane (200 ml) and whole was stirred in an unstoppered flask (cotton plug) at room temperature for 72 hr. After the solution was evaporated to dryness, the resulting residue was washed successively by stirring with H_2O (3 × 500 ml portions) and Et_2O (100 ml) to give crude **10b**: yield, 4.9 g (81%). A portion (500 mg) of this sample was recrystallized twice from EtOH to give the pure product: yield, 85 mg; mp 151°. From the filtrates 353 mg of crude **10b** was recovered.

Ethyl *p*-[[(7-Amino-5(6*H*)-oxopyrimido[5,4-*e*]-*as*-triazin-3-yl)methyl]amino]benzoate Hydrochloride (Ethyl 7-Azapteroate) (11a). A solution of **10a** (250 mg) in DMSO (25 ml) containing $KHCO_3$ (250 mg) and H_2O (0.5 ml) was heated with stirring at 90° for 18 hr. The cooled mixture was diluted with 1 *N* HCl (2.5 ml) and H_2O (400 ml) and chilled for 18 hr. The resulting precipitate was collected by filtration, dissolved in 0.1 *N* NaOH (10 ml), and acidified to pH 3 (paper) with 0.1 *N* HCl. The product that precipitated was collected by filtration and dried *in vacuo* over P_2O_5 at 110°: yield, 77 mg (37%); mp >264°. Chlorine analysis indicated that this sample was a partial hydrochloride salt. A portion of the sample was stirred in 1 *N* HCl for 1 hr to give the monohydrochloride salt, mp >264°.

***N*-[*p*-[[7-Amino-5(6*H*)-oxopyrimido[5,4-*e*]-*as*-triazin-3-yl)methyl]amino]benzoyl]-L-glutamic Acid Sesquihydrate (7-Azafolic Acid) (11c).** A solution of crude **10b** (1.68 g) in DMSO (30 ml) containing $KHCO_3$ (3.37 g) and H_2O (17 ml) was heated with stirring at 90° for 18 hr and diluted with 1 *N* HCl (51 ml) and H_2O (750 ml). The precipitate (0.75 g) was collected by filtration, washed with Et_2O (100 ml), and dissolved in oxygen free 0.2 *N* NaOH (100 ml). After 18 hr at room temperature, the solution was acidified with dilute HCl (~pH 3, paper) and the precipitate (0.55 g) was collected under N_2. The pmr spectrum of this product showed that ester hydrolysis was about 85% complete. Retreatment of this product with 0.2 *N* NaOH for 18 hr gave **11c**: yield, 0.40 g (30.5%). This sample soften at about 240° but melted >264°. Elemental analysis showed the absence of chloride.

Ethyl *p*-[[(7-Amino-5(6*H*)-thioxopyrimido[5,4-*e*]-*as*-triazin-3-yl)methyl]amino]benzoate (12a). A solution of 10a (0.54 g) in DMF (20 ml) containing hydrated NaSH (0.54 g) and H_2O (3.5 ml) was heated with stirring at 80° for 2 hr and evaporated to dryness *in vacuo*. This residue was washed with H_2O (85 ml), and the wash was extracted with Et_2O (3 × 35 ml portions) and acidified with 1 *N* HCl. The product (0.40 g) was collected by filtration and reprecipitated from 1 *N* NH_4OH by the addition of dilute HCl (pH ~3, paper). The solid was collected by filtration, extracted successively by stirring with C_6H_6 (50 ml) and EtOH (5 ml), and dried *in vacuo* over P_2O_5 at 78°: yield, 0.18 g (40%); mp ~264°. Elemental analysis indicated the absence of chlorine.

Diethyl *N*-[*p*-[[(7-Amino-5(6*H*)-thioxopyrimido[5,4-*e*]-*as*-triazin-3-yl)methyl]amino]benzoyl]-L-glutamate Monohydrochloride (12b). A mixture of **10b** (2.1 g) and hydrated sodium hydrosulfide (1.0 g) in ethanol (200 ml) was refluxed for 3 hr, cooled to room temperature, and filtered through a Celite pad. The filtrate was evaporated to dryness *in vacuo*, the residue was stirred with water (650 ml), and the resulting mixture was filtered through a Celite pad. The filtrate was adjusted to pH 3.5 (paper) with 1 *N* hydrochloric acid, and the resulting gelatinous precipitate was collected by filtration, washed successively with ether (120 ml) and benzene (120 ml) and dried *in vacuo* over P_2O_5: yield, 0.92 g (48%); melting point indefinite. This sample underwent softening and decomposition from about 164°.

Concentration of the filtrate from above to ~¼ volume gave an additional crop of product: yield, 0.18 g (yield, 9.4%). The total yield was 57.4%.

***N*-[*p*-[[(7-Amino-5(6*H*)-thioxopyrimido[5,4-*e*-]-*as*-triazin-3-yl)methyl]amino]benzoyl]-L-glutamic Acid Monohydrate (12c).** Sodium hydroxide (0.2 *N*, 94 ml) was boiled to expel oxygen and cooled to room temperature under N_2. A solution of **12b** (0.91 g) in this medium was stirred at room temperature for 24 hr, filtered, and acidified to pH 3.4 (paper) with 1 *N* HCl. After the gelatinous precipitate was allowed to stand in the medium for 3 hr, the solid was collected by filtration and stirred with a 1:1 mixture of ethanol and water (120 ml) for 30 min. The solid was collected by filtration and dried *in vacuo* over P_2O_5: yield, 0.51 g (65%); melting point indefinite. This sample underwent softening and decomposition from 255°.

A sample of the product dissolved in dilute NH_4OH showed on tlc after 2 weeks mainly **11c** and several minor spots, one of which corresponded to *p*-aminobenzoic acid.

Ethyl *p*-[[(5,7-Diaminopyrimido[5,4-*e*]-*as*-triazin-3-yl)methyl]amino]benzoate (13a). A solution of **10a** (223 mg) in DMAc (20 ml) containing 10% ethanolic NH_3 (10 ml) was heated at 60° for 5 hr. The resulting mixture was cooled, and the product was collected by filtration and dried *in vacuo* over P_2O_5 at 140°. This sample analyzed correctly for a partial hydrate of **13a**: yield, 105 mg (61%); mp >264°. The monohydrate was obtained by reprecipitation of this sample from DMSO with H_2O, which was dried *in vacuo* over P_2O_5 at 78°.

The reaction filtrate gave an additional 65 mg of crude **13a**.

Diethyl *N*-[*p*-[[(5,7-Diaminopyrimido[5,4-*e*]-*as*-triazin-3-yl)methyl]amino]benzoyl]-L-glutamate Hydrate (4:3) (13b) and Diethyl *N*-[*p*-[[(5-Aminotetrazolo[5′,1′:6,1]pyrimido[5,4-*e*]-*as*-triazin-8-yl)methyl]amino]benzoyl]-L-glutamate Hydrate (4:7) (14b). A solution of **10b** (0.80 g) in DMSO (10 ml) containing H_2O (1 ml) and sodium azide (0.20 g) was heated at 80° for 2 hr and diluted with H_2O (90 ml). The resulting mixture was cooled; the solid was collected by filtration, washed with Et_2O (20 ml) to remove benzyl disulfide, and then with 1:1 EtOH–H_2O (10 ml), and dried *in vacuo* over P_2O_5 at 78° to give **13b**: yield, 0.20 g (29.6%); melting point indefinite. This sample underwent softening and decomposition from 140°.

The reaction filtrate was evaporated to dryness *in vacuo*, and the resulting residue was washed with Et_2O and hot MeCN to give a solid. From the MeCN wash crude **10b** (0.11 g) was recovered. The MeCN insoluble residue was dissolved in H_2O and adjusted to pH 3–4 (paper) with 1 *N* HCl to give a precipitate of **14b**: yield, 0.10 g (13.6%); melting point indefinite. This sample underwent softening and decomposition from ~200°.

Acknowledgments. The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute, who performed most of the microanalytical and spectral determinations reported.

Registry No.—**1b,** 51934-15-7; **1c,** 51934-16-8; **1d,** 51934-17-9; **2b,** 51934-18-0; **2c,** 51934-19-1; **3,** 7597-91-3; **4a,** 94-09-7; **4b,** 18358-63-9; **4c,** 51934-20-4; **5b** HCl, 51934-21-5; **5c** HCl, 51934-22-6; **6a,** 22433-08-5; **6b,** 51934-23-7; **6c,** 51043-64-2; **6d,** 3009-97-0; **6e,** 51934-24-8; **10a,** 35171-06-3; **10b,** 51043-66-4; **11a,** 35171-24-5; **11a** HCl, 51934-25-9; **11c,** 51043-68-6; **12a,** 35171-08-5; **12b** HCl, 51934-26-0; **12c,** 51934-27-1; **13a,** 35171-07-4; **13b,** 51934-28-2; **14b,** 51934-29-3.

References and Notes

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(16) Melting points were determined on a Kofler-Heizbank apparatus.

Synthesis of 2-Aminomethyldipyrrylmethanes

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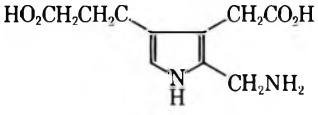
The synthesis of 2-aminomethyl-3,4′-(β-carboxyethyl)-4,3′-carboxymethyldipyrrylmethane and of 2-aminomethyl-3,3′-(β-carboxyethyl)-4,4′-carboxymethyldipyrrylmethane is outlined. The condensation of ethyl 2-methyl-3-formyl-5-ethoxycarbonyl-4-pyrroleacetate with benzyl hydrogen malonate afforded a benzyl acrylate which was reduced and esterified to a benzyl 2-methyl-3-pyrrolepropionate. The latter was transformed by oxidation with sulfuryl chloride into its 2-formyl derivative, whose oxime was reduced to afford the 2-aminomethyl-3-pyrrolepropionic acid. Cyclization of the amino acid followed by sodium benzylate transesterification allowed the synthesis of benzyl 3-(benzyloxycarbonylmethyl)pyrrolohexahydroazepin-6-one-2-carboxylate, which was then converted into methyl pyrrolohexahydroazepin-6-one-3-acetate. The 2-bromomethyl- or 2-chloromethylpyrroles derived from the 2-methyl-3- (or 4-) methoxycarbonylmethyl-4- (or 3-) β-methoxycarbonylethyl-5-benzyloxycarbonylpyrroles were prepared. Condensation of the halomethylpyrroles with the pyrrolohexahydroazepinone afforded the corresponding 5′-benzyloxycarbonyldipyrrylmethane lactams. Hydrogenolysis, decarboxylation, and saponification of the ester groups and the seven-membered lactam ring afforded the 2-aminomethyldipyrrylmethanes.

The chemical mechanism underlying the enzymatic polymerization of porphobilinogen (1) to uroporphyrinogen III is a fertile field for biosynthetic speculations.[1] As yet, no open-chain polypyrrolic intermediates have been isolated and identified from the enzymatic reaction that could help clarify the nature of this metabolic process. The synthesis of the four possible dipyrrylmethanes **2–5** formally derived from the self-condensation of two units of porphobilinogen was hence undertaken. Once the synthetic dipyrrylmethanes are obtained they will be used to study their enzymatic and chemical behavior in the process of uroporphyrinogen biosynthesis.



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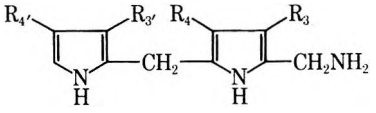


2, $R_3 = R_{3'} = CH_2CO_2H$; $R_4 = R_{4'} = CH_2CH_2CO_2H$

3, $R_3 = R_{4'} = CH_2CO_2H$; $R_4 = R_{3'} = CH_2CH_2CO_2H$

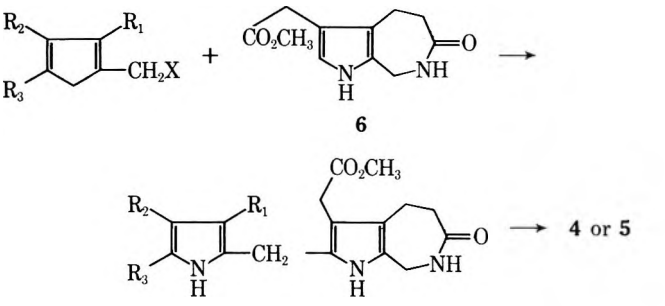
4, $R_3 = R_{4'} = CH_2CH_2CO_2H$; $R_4 = R_{3'} = CH_2CO_2H$

5, $R_4 = R_{3'} = CH_2CH_2CO_2H$; $R_4 = R_{4'} = CH_2CO_2H$

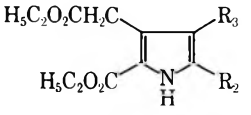
The synthesis of the dipyrrylmethanes **2** and **3** and several of its enzymatic and chemical properties obtained during the course of studies on uroporphyrinogen biosynthesis were already reported.[1–6] The enzymatic incorporation of dipyrrylmethane **4** into uroporphyrinogen III, as well as some of its chemical properties of relevance for the study of uroporphyrinogen III biosynthesis, was discussed elsewhere.[4,7] In this paper we will discuss the synthetic method used to obtain the dipyrrylmethanes **4** and **5**. The sequence was based on the condensation of properly activated and protected 2-halomethylpyrroles with a seven-membered pyrrole lactam **6** to obtain the corresponding dipyrrylmethane lactams (Scheme I). It was then expected that the cleavage of the protecting groups and the saponification of the lactam ring would afford the dipyrrylmethanes **4** and **5**.

The seven-membered pyrrole lactam **6** was prepared according to the following sequence. The diethyl ester aldehyde **7**, prepared by a Vilsmaier–Haak formylation of ethyl 5-ethoxycarbonyl-4-pyrroleacetate, was condensed with

Scheme I



benzyl hydrogen malonate, affording the benzyl 3-pyrroleacrylate **8**. The benzyl hydrogen malonate was obtained by partial saponification of dibenzyl malonate. Reduction with hydrogen of the acrylate resulted in the simultaneous cleavage of the benzyl ester group and reduction of the acrylic side chain. No specific hydrogenation conditions of the double bond could be found which should avoid the hydrogenolysis of the benzyl ester. The resulting 3-pyrrolepropionic acid **9** was transformed into its benzyl ester **10** by treatment with distilled diazotoluene, and the latter was oxidized to the corresponding aldehyde **11** by reaction with sulfuryl chloride. The transformation of the aldehyde **11** into its oxime **12** and the catalytic hydrogenation of the latter allowed the synthesis of the 2-aminomethyl-3-pyrrolepropionic acid **13**.



7, $R_2 = CH_3$; $R_3 = CHO$

8, $R_2 = CH_3$; $R_3 = CH{=}CHCO_2CH_2C_6H_5$

9, $R_2 = CH_3$; $R_3 = CH_2CH_2CO_2H$

10, $R_2 = CH_3$; $R_3 = CH_2CH_2CO_2C_6H_5$

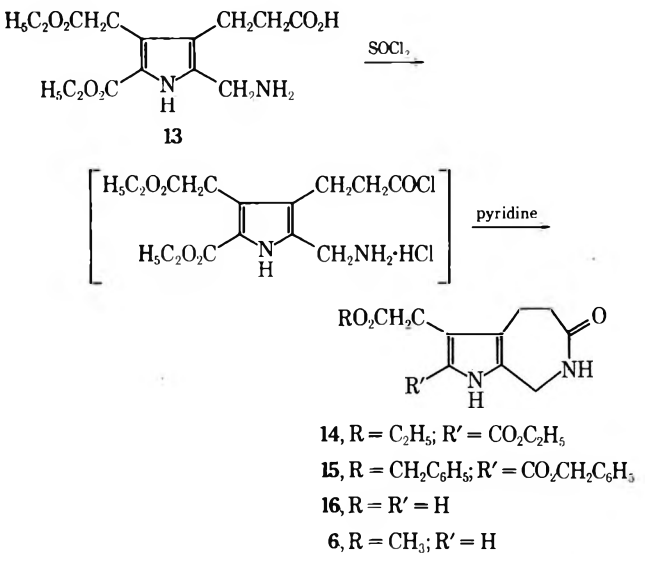
11, $R_2 = CHO$; $R_3 = CH_2CH_2CO_2CH_2C_6H_5$

12, $R_2 = CH{=}NOH$; $R_3 = CH_2CH_2CO_2CH_2C_6H_5$

The cyclization of a 2-aminomethyl-3-pyrrolepropionic derivative to yield a seven-membered pyrrole lactam is not a spontaneous process as is the case with a 2-aminomethyl-3-pyrroleacetic acid derivative. While in the latter case a six-membered pyrrole lactam was spontaneously obtained after esterification of the acetic acid residue,[1] a 2-amino-

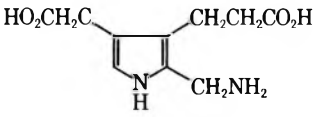
methyl-3-pyrrolepropionate remained mainly in the open form even after heating at 100°. By heating the amino acid **13** above its melting point only a small amount of the desired lactam was obtained. Efficient cyclization could, however, be obtained after transformation of the propionic acid residue into its chloride with thionyl chloride. By dissolving the crude chloride hydrochloride in pyridine the cyclization reaction takes place spontaneously and the diethyl pyrrolehexahydroazepinone **14** was obtained in 50% yield (Scheme II).

Scheme II



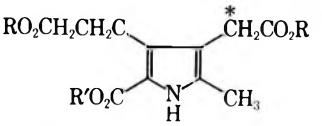
14, R = C_2H_5; R′ = $CO_2C_2H_5$
15, R = $CH_2C_6H_5$; R′ = $CO_2CH_2C_6H_5$
16, R = R′ = H
6, R = CH_3; R′ = H

Transesterification of **14** with sodium benzylate afforded the dibenzyl ester **15.** The benzyl ester groups were cleaved by hydrogenolysis and the 5-carboxypyrrole lactam was decarboxylated by heating in water at 100° for a short time. The decarboxylation was best carried out in a vacuum-sealed vessel, since the pyrrole lactam **16** was sensitive to heating in air. By treating the lactam **16** with diazomethane, the methyl pyrrolehexahydroazepinone-3-acetate **6** was obtained. The lactam could be kept at 5° during several months without decomposition. It was saponified to isoporphobilinogen (**17**) when dissolved in a 2 *N* potassium hydroxide solution and kept at room temperature during 72 hr.



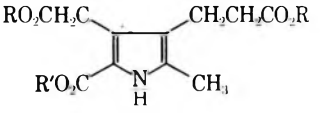
17

The synthesis of the conveniently substituted 2-halomethylpyrroles necessary for the synthesis of the dipyrrylmethane lactams (Scheme I) made use of selective transesterification reactions based on Kenner's experience with simple pyrroles[8] and on our results with complex pyrroles.[1] The triethyl esters **18** and **19** were used as convenient starting materials for this purpose. They could be prepared by simple and reproducible reaction sequences.[9,10] Treibs' approach[10] was particularly suited, since it allowed the synthesis of the triethyl ester **18** labeled with ^{14}C at the position (*), using [^{14}C]-formaldehyde. The triethyl ester **18** was transformed into the tribenzyl ester **21** by treatment of the triacid **20** obtained by saponification of **18** with distilled diazotoluene, or by transesterification of the triethyl ester **18** with benzyl alcohol in the presence of a small amount of sodium benzylate. The tribenzyl ester **21** was transesterified back with sodium methylate in methyl alcohol to the dimethyl benzyl ester **22** which was thus obtained in 80% yield.



18, R = R′ = C_2H_5
20, R = R′ = H
21, R = R′ = $CH_2C_6H_5$
22, R = CH_3; R′ = $CH_2C_6H_5$

The transesterification of the isomeric triethyl ester **19** with sodium benzylate in benzyl alcohol only afforded an inseparable mixture of esters. However, when the triacid **23** obtained by saponification of **19** was treated with diazotoluene, the tribenzyl ester **24** was easily obtained. The tribenzyl ester **24** could not be transesterified with sodium methylate in methyl alcohol, since under different conditions of reaction time and heating periods it only afforded mixtures of dibenzyl methyl and dimethyl benzyl esters which could not be efficiently separated. A reproducible reaction sequence was then found by the partial saponification of the tribenzyl ester **24** to the monobenzyl ester **25** with potassium hydroxide in benzyl alcohol, followed by treatment of the diacid with ethereal diazomethane. The dimethyl benzyl ester **26** thus obtained in 25% overall yield from the tribenzyl ester was found to be pure by tlc analysis and could be used in the further reaction sequence.



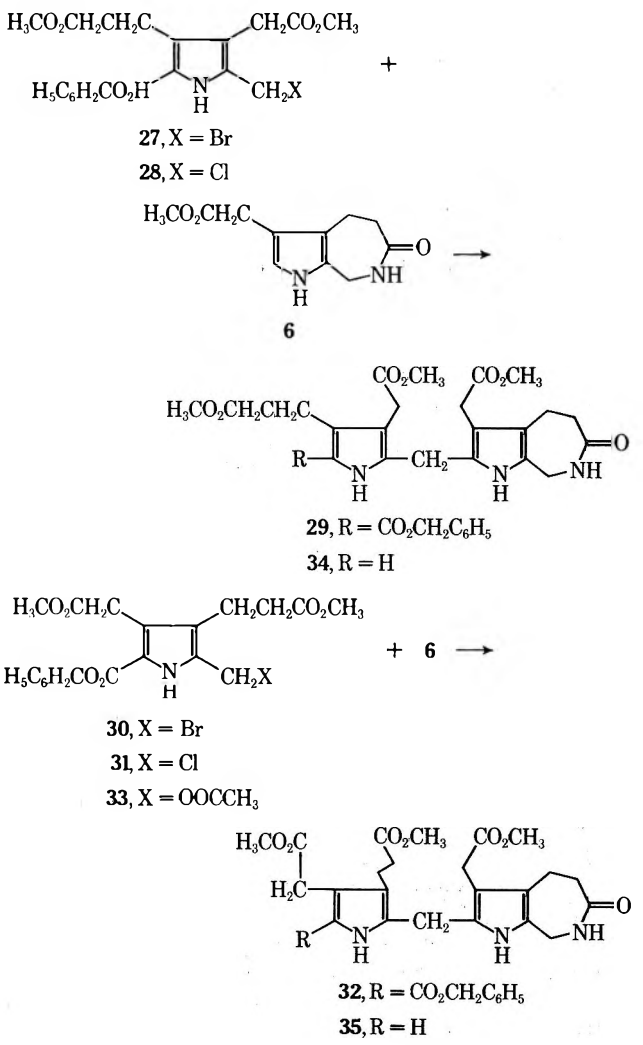
19, R = R′ = C_2H_5
23, R = R′ = H
24, R = R′ = $CH_2C_6H_5$
25, R = H; R′ = $CH_2C_6H_5$
26, R = CH_3; R′ = $CH_2C_6H_5$

Reference should be made here to the procedures described by MacDonald and coworkers[2] and later by Battersby and coworkers,[3] who transesterified the triethyl esters **18** and **19** using large amounts of sodium benzylate in benzyl alcohol, and obtained the 5-benzyloxycarbonylpyrrole diacids as the main reaction products and the tribenzyl esters as the secondary reaction products. In our experience, the monobenzyl diacids obtained by the aforementioned procedures always contained the dibenzyl monoacid derivatives (as judged by tlc analysis), whose complete removal resulted in extremely poor yields of the pure monobenzyl acid.

Dipyrrylmethane lactams have been prepared by condensation of 2-aminomethylpyrroles[1] or of 2-halomethylpyrroles[2,3] and pyrrole lactams. The condensation of 2-aminomethylpyrroles[1] with the lactam **6** failed to give the expected dipyrrylmethanes. The 2-bromomethyl derivative **27** was obtained by bromination of **22** under ultraviolet light and was condensed with the pyrrole lactam **6** in acetic acid containing sodium acetate. The dipyrrylmethane **29** was obtained in 29% yield (Scheme III). The analogous 2-chloromethyl derivative **28,** obtained as a solid and stable compound by the action of sulfuryl chloride on **22,** reacted in an analogous manner to give the dipyrrylmethane **29** in 41% yield. The reactions were carried out in a sealed vessel under air exclusion and no other definite reaction products

could be identified. By reaction of the 2-bromomethylpyrrole **30** with the pyrrole lactam **6** under the same reaction conditions, the dipyrrylmethane **32** was obtained in 37% yield. When the 2-chloromethylpyrrole **31** was used, the dipyrrylmethane **32** was obtained in 28% yield, along with the 2-acetoxymethylpyrrole **33,** formed in 19% yield. When the condensations of the 2-bromomethylpyrroles with the pyrrole lactam were carried out in pyridine at 90–100°, the dipyrrylmethanes were obtained in much lower yields. The attempted condensation of the 2-acetoxymethylpyrrole **33** with the pyrrole lactam **6** under the usual reaction conditions afforded only traces of the dipyrrylmethane **32** and the major part of **33** was recovered unchanged.

Scheme III



The transformation of the 5′-benzyloxycarbonyldipyrrylmethanes **29** and **32** into the 5′-free derivatives followed the sequence outlined in our former work.[1] Hydrogenolysis of **29** and **32** resulted in formation of the 5′-carboxydipyrrylmethanes, which were decarboxylated by a short heating at 220° under high vacuum. The obtained dipyrrylmethanes **34** and **35** were purified by chromatography and saponified to the 2-aminomethyl derivatives **4** and **5.** The saponification of the dipyrrylmethane lactams **34** and **35** was carried out by dissolving them in a 2 *N* potassium hydroxide solution in 50% ethanol and by keeping the solutions at room temperature during 72 hr. This procedure was previously used to carry out the saponifications of the dipyrrylmethane lactams leading to **2** and **3,** and was later successfully used by other groups.[3,11] The saponification procedure for dipyrrylmethane lactams using a hot ethanolic potassium hydroxide solution[2] led to saponification of the ester groups, but the resulting potassium salt still contained much unsaponified lactam, as evidenced by tlc on cellulose using lutidine–0.7 *N* ammonium hydroxide (10:7 v/v) as a solvent.

The 2-aminomethyldipyrrylmethanes **4** and **5** were very unstable substances, as could be expected from their structures, and were directly used in solution for the ulterior enzymatic and chemical studies. Heating the dipyrrylmethane **4** at 37° and pH 7.4 afforded exclusively uroporphyrin II, while the dipyrrylmethane **5** was transformed under the same reaction conditions into a mixture containing 85% of uroporphyrin I and 15% of uroporphyrin III or IV.

Experimental Section[12]

Benzyl Hydrogen Malonate. A solution of 29 g (0.5 mol) of potassium hydroxide in 300 ml of benzyl alcohol was added to a solution of 142 g (0.5 mol) of dibenzyl malonate in 300 ml of benzyl alcohol and the solution was stirred overnight. The potassium salt which separated was filtered and dissolved in water and the solution was extracted with ether (3 × 100 ml), adjusted to pH 2 with concentrated hydrochloric acid, and repeatedly extracted with ether (3 × 100 ml). The ethereal extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness, and the residue was crystallized from benzene–cyclohexane: 39 g (94%); mp 38–40°; nmr ($CDCl_3$) 2.88 (s, 2, CH_2CO_2H), 3.99 (s, 2, $CH_2C_6H_5$), 6.72 ppm (br, 5, C_6H_5).

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.8; H, 5.2. Found: C, 61.8; H, 5.3.

Ethyl 5-Methyl-4-formyl-3-(ethoxycarbonylmethyl)-2-pyrrolecarboxylate (7). A solution of 3.37 g of ethyl 5-ethoxycarbonyl-4-pyrroleacetate[9] dissolved in 23 ml of dry dimethylformamide was added under moisture exclution conditions to a mixture of 15 ml of dimethylformamide and 8.1 ml of phosphorus oxychloride kept at 0–5°. The resulting solution was heated at 75° during 1 hr with continuous stirring and then cooled, adjusted to pH 8 with concentrated sodium hydroxide, and further heated at 75° during 15 min. The mixture was then poured into ice–water (100 ml), and the reaction product was extracted with chloroform. The dried (Na_2SO_4) extracts were evaporated to dryness *in vacuo* and the residue was crystallized from methanol–water: 3.4 g (91%); mp 152° (lit.[9] mp 151–152°); nmr ($CDCl_3$) 1.3, 1.4 (t, J = 8 Hz, CH_2CH_3), 2.5 (s, 3, CH_3), 4.25 (m, 6, CH_2CH_3, CH_2CO), 10 ppm (s, 1, CHO).

Benzyl 2-Methyl-4-(ethoxycarbonylmethyl)-5-ethoxycarbonyl-3-pyrroleacrylate (8). A solution of 12 g of the aldehyde **7,** 35 g of benzyl acid malonate, and 0.5 ml of piperidine in 40 ml of pyridine was heated at 90° during 15 hr, followed by heating under reflux during 2 hr. The mixture was poured over ice (300 ml), adjusted to pH 2 with concentrated hydrochloric acid, and extracted repeatedly with chloroform (5 × 100 ml). The dried (Na_2SO_4) chloroform extracts were evaporated to dryness, the residue was dissolved in 60 ml of methanol, and 20 ml of water was added in small portions with continuous cooling while crystallization was achieved. The solid **8** was filtered and dried (6 g), the filtrates were evaporated to dryness, and the residue, dissolved in 2% methanol in benzene, was filtered through a silica gel column prewashed and later eluted with the same solvent. The acrylate **8** was eluted first (R_f, 0.40, benzene–2% methanol) and collected after evaporation of the elution solvent to dryness. An additional 6 g of **8** was thus obtained: total yield 67%; mp 78–80°; uv max 259 nm (ϵ 17,200), 321 (19,900); nmr ($CDCl_3$) 1.3 (m, 6, CH_3CH_2), 2.35 (s, 3, CH_3), 3.95 (s, 2, CH_2CO), 4.2 (m, 4, CH_2CH_3), 5.2 (s, 2, $CH_2C_6H_5$), 6.0 (d, 1, J = 15 Hz, =CHCO), 7.3 (br, 5, C_6H_5), 7.65 ppm (d, 1, J = 15 Hz, pyrr–CH=).

Anal. Calc. for $C_{22}H_{25}NO_6$; C, 66.1; H, 6.3; N, 3.5. Found: C, 66.3; H, 6.1; N, 3.6.

2-Methyl-5-(ethoxycarbonyl)-4-(ethoxycarbonylmethyl)-3-pyrrolepropionic Acid (9). A solution of 3.4 g of the benzylacrylate **8** was dissolved in 100 ml of ethanol and reduced with hydrogen at 50 psi during 2 hr over an equal weight of 10% palladium on charcoal. The catalyst was filtered, the solvent was evaporated *in vacuo,* and the residue was crystallized from ethanol–water: 2.4 g (90%); mp 123–125°; nmr (TFA) 1.4, 1.45 (t, 6, J = 7 Hz, CH_3CH_2), 2.3 (s, 3, CH_3), 2.75 (m, 4, CH_2CH_2), 4.0 (s, 2, CH_2CO), 4.4 ppm (m, 4, CH_2CH_3).

Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.8; H, 6.7; N, 4.5. Found: C, 58.0; H, 6.8; N, 4.4.

Benzyl 2-Methyl-5-(ethoxycarbonyl)-4-(ethoxycarbonylmethyl)-3-pyrrolepropionate (10). The pyrrolepropionic acid **9** (4 g) was dissolved in 50 ml of methanol and an excess of freshly distilled diazotoluene was added in small portions until persistence of a pink color. The excess of reagent was destroyed with acetic acid, the solution was evaporated to dryness *in vacuo*, and the residue was crystallized from cyclohexane: 4 g (78%); mp 66–68°; nmr ($CDCl_3$) 1.2, 1.3 (t, 6, CH_3CH_2), 2.1 (s, 3, CH_3), 2.55 (m, 4, CH_2CH_2), 3.7 (s, 2, CH_2CO), 4.15 (m, 4, CH_2CH_3), 5.0 (s, 2, $CH_2C_6H_5$), 7.2 (br, 5, C_6H_5).

Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.8; H, 6.7; N, 3.5. Found: C, 65.7; H, 6.6; N, 3.6.

Benzyl 2-(Ethoxycarbonyl)-3-(ethoxycarbonylmethyl)-5-formyl-4-pyrrolepropionate (11). A solution of 2.4 g (6 nmol) of the benzyl ester **10** in 30 ml of anhydrous methylene chloride was cooled at 2–3° under moisture exclusion, and 0.96 ml (12 nmol) of sulfuryl chloride was added in small portions. The mixture was kept with continuous stirring at room temperature during 30 min. The solvent was evaporated to dryness *in vacuo*, 4 g of sodium acetate dissolved in 100 ml of water was added, and the mixture was heated at reflux during 5 min. It was then cooled, the supernatant aqueous solution was discarded, and the oily residue was dissolved in 120 ml of hot ethanol and reprecipitated by addition of 150 ml of water: 2.1 g (83%); mp 70–73°; nmr ($CDCl_3$) 1.2, 1.4 (t, J = 7 Hz, 6, CH_2CH_3), 2.8 (m, 4, CH_2CH_2), 3.75 (s, 2, CH_2CO), 4.2 (m, 4, CH_2CH_3), 5.0 (s, 2, CH_2Bz), 7.2 (br, 5, C_6H_5), 10 ppm (s, 1, CHO).

Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.6; H, 6.0; N, 3.4. Found: C, 63.5; H, 6.0; N, 3.5.

Benzyl 2-(Ethoxycarbonyl)-3-(ethoxycarbonylmethyl)-5-formyl-4-pyrrolepropionate Oxime (12). A solution of 330 mg of hydroxylamine hydrochloride in 3 ml of ethanol was added to a second solution of 106 mg of sodium in 40 ml of ethanol. The formed precipitate was centrifuged, 1.36 g of aldehyde **11** was added, and the solution was heated under reflux for 45 min. The solution was cooled, poured over 300 ml of ice water, and kept during 15 hr at 5°. The solid was filtered and crystallized from methanol–water, 1.25 g (89%), mp 97–99°.

Anal. Calcd for $C_{22}H_{26}N_2O_7$: C, 61.4; H, 6.05; N, 6.5. Found: C, 61.2; H, 6.15; N, 6.7.

Ethyl 2-Aminomethyl-3-(carboxyethyl)-4-(ethoxycarbonylmethyl)-5-pyrrolecarboxylate (13). A solution of 1.25 g of the oxime **12** in 100 ml of glacial acetic acid was reduced with hydrogen over 1 g of 10% palladium on charcoal at 50 psi. The catalyst was filtered, the solvent was evaporated to dryness *in vacuo*, and the oily residue was crystallized from anhydrous ethanol: 0.61 g (50%); mp 177–179°; nmr (TFA) 1.4 (6, m, CH_3CH_2), 2.9 (br, 4, CH_2CH_2), 4.1 (br, 2, CH_2CO), 4.6 (m, 6, CH_2CH_3, $CH_2NH_3^+$), 7.4 ppm (br, 3, NH_3^+).

Anal. Calcd for $C_{15}H_{22}N_2O_6$: C, 55.2; H, 6.7; N, 8.6. Found: C, 55.1; H, 6.8; N, 8.8.

Ethyl 3-(Ethoxycarbonylmethyl)pyrrolohexahydroazepin-6-one-2-carboxylate (14). The amino acid **13** (0.45 g) was dissolved in 9 ml of freshly distilled thionyl chloride and the mixture was stirred overnight under moisture exclusion conditions. The solvent was completely evaporated to dryness, and the solid residue was dissolved in 9 ml of cold anhydrous pyridine. The solution was kept during 1 hr at 3–5° followed by 30 min at room temperature, 50 ml of water was added, the solution was extracted with chloroform (3 × 10 ml), and the chloroform extracts were evaporated *in vacuo*. The residue was filtered through a silica gel column (10 × 1 cm) prewashed with 10% methanol in chloroform and eluted with the same solvent. The lactam **14** was the only product eluted and was crystallized from methanol: 0.21 g (50%); mp 191–193°; uv max 280 nm (ϵ 21,700); ir 3350 (NH), 1745 (CO ester), 1690 (CO ring ester), 1665 cm^{-1} (CO amide); nmr (TFA) 1.0, 1.2 (t, J = 6 Hz, 6, CH_3CH_2), 3.0 (br, 4, CH_2CH_2), 3.8 (s, 2, CH_2CO), 4.25 (m, 4, CH_2CH_3), 4.5 (br, 2, CH_2NH).

Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.4; H, 6.5; N, 9.1. Found: C, 58.4; H, 6.3; N, 9.0.

Benzyl 3-(Benzyloxycarbonylmethyl)pyrrolohexahydroazepin-6-one-2-carboxylate (15). Diethyl lactam **14** (1.7 g) was added to a solution of 42 mg of sodium in 100 ml of benzyl alcohol, the mixture was heated under anhydrous conditions and 100° during 2 hr, 20 ml of benzyl alcohol was distilled off *in vacuo* and replaced with fresh benzyl alcohol, and the mixture was heated for an additional 4 hr at 100°. The solvent was then evaporated to dryness *in vacuo*, and the residue was redissolved in 50 ml of chloroform, which was washed with 5 ml of water and evaporated to dryness. The residue was crystallized from ethanol: 1.2 g (50%); mp 169–171°; nmr ($CDCl_3$), 2.75 (br, 4, CH_2CH_2CO), 3.8 (s, 2, CH_2CO), 4.2 (br, 2, CH_2NH), 5.1 (s, 2, $CH_2C_6H_5$), 5.3 (s, 2, ring $CH_2C_6H_5$), 7.35 (br, 10, C_6H_5).

Anal. Calcd for $C_{25}H_{24}N_2O_5$: C, 69.4, H, 5.5; N, 6.5. Found: C, 69.4; H, 5.6; N, 6.4.

Methyl Pyrrolohexahydroazepin-6-one-3-acetate (6). A solution of 0.3 g of benzyl lactam **15** in 50 ml of glacial acetic acid was reduced with hydrogen over 300 mg of 10% palladium on charcoal at 50 psi during 2 hr. The catalyst was filtered and the solution was freeze-dried. The residue was suspended in 60 ml of deaerated water in a vacuum-sealed vessel, and the mixture was heated at 100° during 45 min. The solution was freeze-dried. The residue was shown to be pure lactam **16** (R_f 0.66) when examined by paper chromatography [Whatman No. 1, 1-butanol–acetic acid–water (4:1:5)]. Too unstable to be crystallized, it was dissolved in methanol and treated with an excess of ethereal diazomethane at 5°. The solvent was evaporated *in vacuo*, and the residue was filtered through a short column of silica gel prewashed with 10% methanol in chloroform which eluted the lactam **6** as the only product: 0.108 g (70%); mp 135–138°; ir 1750 ($COOCH_3$), 1653 cm^{-1} (CO amide); nmr (pyridine-d_5) 2.75 (s, 4, CH_2CH_2), 3.35 (s, 2, CH_2CO), 3.45 (s, 3, OCH_3), 4.25 (d, J = 6 Hz, 2, CH_2NH), 6.6 ppm (br, 1, H_5).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.3; N, 12.6. Found: C, 59.4; H, 6.3; N, 12.5.

Ehrlich's reaction was positive in the cold.

Isoporphobilinogen (17). A solution of 41 mg of lactam **6** in 0.5 ml of 2 *N* potassium hydroxide was kept at room temperature during 72 hr. The solution was acidified to pH 4 with glacial acetic acid, cooled at 5°, and filtered. Isoporphobilinogen was collected and dried: 35.7 mg (80%); mp 190° (capillary tube) (lit.[13] mp 192–195°); R_f 0.49 [Whatman No. 1, butanol–acetic acid–water (4:1:5)]; nmr (D_2O, pH 7 with Na_2CO_3) 2.6 (m, 4, CH_2CH_2), 3.5 (s, 2, CH_2CO), 4.2 (s, 2, CH_2NH_2), 6.7 ppm (s, 1, H_5).

Benzyl 2-Methyl-3-(benzyloxycarbonylmethyl)-4-(benzyloxycarbonylethyl)-5-pyrrolecarboxylate (21). Procedure A. A suspension of 1.1 g of the acid **20**[14] in 200 ml of methanol was treated with an excess of freshly distilled diazotoluene[15] at room temperature until esterification was complete. The excess of diazotoluene was destroyed with acetic acid, the solvent was evaporated to dryness *in vacuo*, and the residue was crystallized from cyclohexane: 1.8 g (77%); mp 106–108° (lit.[2] mp 108°); nmr ($CDCl_3$) 2.1 (s, 3, CH_3), 2.75 (m, 4, CH_2CH_2), 3.4 (s, 2, CH_2CO), 4.97, 5.01 (s, 4, $CH_2C_6H_5$), 5.2 (s, 2, ring $CO_2CH_2C_6H_5$), 7.2 (br, 15, C_6H_5).

Anal. Calcd for $C_{32}H_{31}NO_6$: C, 73.1; H, 5.9; N, 2.7. Found: C, 73.0; H, 5.8; N, 2.7.

Procedure B. Triethyl ester **18**[10] (3 g) was dissolved in 300 ml of benzyl alcohol and 36 mg of sodium was added. The mixture was heated at 150° during 6 hr *in vacuo* (20 mm), the solvent was then evaporated to dryness under high vacuum, and the residue was crystallized from methanol. The product was recrystallized from the same solvent, affording 1.5 g (33%) of the tribenzyl ester **21**. The product was pure by tlc (chloroform–1% methanol). The same tlc analysis indicated that a dibenzyl monoethyl ester remained in the mother liquors.

Benzyl 2-Methyl-3-(methoxycarbonylmethyl)-4-(methoxycarbonylethyl)-5-pyrrolecarboxylate (22). Tribenzyl ester **21** (3 g) was dissolved in 300 ml of anhydrous methanol, 40 mg of sodium was added, and the mixture was heated under reflux during 90 min. The solution was evaporated to half volume and poured over 1000 ml of ice water. After the solution was kept at 5° during 12 hr, it was filtered and the product was recrystallized from cyclohexane: mp 78° (lit.[3] mp 78.5–79.5°); uv max 286 nm (ϵ 19,000); 1.6 g (80%); nmr ($CDCl_3$) 2.2 (s, 3, CH_3), 2.7 (m, 4, CH_2CH_2), 3.4 (s, 2, CH_2CO), 3.55, 3.6 (s, 3, 3, OCH_3), 5.2 (s, 2, $CH_2C_6H_5$), 7.3 ppm (s, 5, C_6H_5).

Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.3; H, 6.2; N, 3.8. Found: C, 64.4; H, 6.2; N, 3.9.

Benzyl 2-methyl-3-(benzyloxycarbonylethyl)-4-(benzyloxycarbonylmethyl)-5-pyrrolecarboxylate (24) was obtained following procedure A used in the synthesis of **21**. From 2 g of the triacid **23**[9] was obtained 2.7 g (70%) of the tribenzyl ester: mp 94–96° (cyclohexane) (lit.[2] mp 92–93°); nmr ($CDCl_3$) 2.1 (s, 3, CH_3), 2.55 (m, 4, CH_2CH_2), 3.8 (s, 2, CH_2CO), 4.98, 5.02 (s, 4, $CH_2C_6H_5$), 5.18 (s, 2, ring $CH_2C_6H_5$), 7.25, 7.27 ppm (br, 15, side chain C_6H_5 and ring C_6H_5).

Anal. Calcd for $C_{32}H_{31}NO_6$: C, 73.1; H, 5.9; N, 2.7. Found: C, 73.0; H, 5.8; N, 2.7.

Benzyl 2-Methyl-3-(methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-5-pyrrolecarboxylate (26). To a solution of

160 mg of potassium hydroxide in 20 ml of benzyl alcohol was added 500 mg of the tribenzyl ester **24**, and the mixture was heated at 100° during 12 hr under moisture exclusion conditions. The solution was cooled and extracted with water (3 × 20 ml), and the aqueous solution was washed with ether and then adjusted to pH 3 with concentrated hydrochloric acid. The precipitated diacid **25** was filtered, dried in vacuo, suspended in methanol, and esterified by addition of an excess of ethereal diazomethane. The ether–methanol solution was evaporated to dryness and the product was crystallized from benzene–cyclohexane: 72 mg (25%); mp 111°; pure by tlc (chloroform–2% methanol) (lit.[3] mp 113–116°); nmr ($CDCl_3$) 3.5, 3.6 (s, 3, 3, OCH_3), 5.2 (s, 2, $CH_2C_6H_5$), 7.2 (s, 5, C_6H_5).

Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.3; H, 6.2; N, 3.8. Found: C, 64.3; H, 6.2; N, 3.7.

2-Chloromethyl-3-(methoxycarbonylmethyl)-4-(2-methoxycarbonylethyl)-5-benzyloxycarbonylpyrrole (28). To a solution of 420 mg of dimethyl benzyl pyrrole **22** in 5 ml of anhydrous dichloromethane kept at 5° was added 0.088 ml of sulfuryl chloride under moisture exclusion conditions. The mixture was stirred during 45 min at room temperature, the solvent was evaporated *in vacuo* at 30°, and the residue was redissolved in 5 ml of dry methylene chloride and evaporated again *in vacuo*. The residue was crystallized from benzene–hexane: 400 mg (87%); mp 108–111° (in literature[3] described as amorphous and unstable); nmr ($CDCl_3$) 2.7 (m, 4, CH_2CH_2), 3.5, 3.6, 3.65 (s, 8, CH_2CO, OCH_3), 4.6 (s, 2, CH_2Cl), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 (br, 5, C_6H_5).

Anal. Calcd for $C_{20}H_{22}NO_6Cl$: C, 59.0; H, 5.4; N, 3.4. Found: C, 58.9; H, 5.4; N, 3.5.

Methyl 2-(3′-Methoxycarbonylmethyl-4′-β-methoxycarbonyl-5′-benzyloxycarbonyl-2′-pyrrylmethyl)pyrrolohexahydroazepin-6-one-3-acetate (29). Procedure A. A solution of 280 mg of bromine in 6 ml of carbon tetrachloride was added to 447 mg of the benzyl dimethyl ester **22** dissolved in 6 ml of the same solvent contained in a quartz vessel. The mixture was stirred while being irradiated with a Hanovia ultraviolet lamp during 35 min. The solvent was then evaporated *in vacuo* to dryness, the residue was extracted with boiling hexane (3 × 25 ml), and the extracts were pooled and concentrated *in vacuo* to dryness. The residual solid **27** (271 mg, 50%) had nmr ($CDCl_3$) 2.8 (m, 4, CH_2CH_2), 3.55 (s, 2, CH_2CO), 3.65, 3.7 (s, 6, OCH_3), 4.58 (s, 2, CH_2Br), 5.5 (s, 2, $CH_2C_6H_5$), 7.4 ppm (br, 5, C_6H_5), and was pure for further work-up. It was dissolved in 6 ml of glacial acetic acid containing 1% of sodium acetate, 135 mg of pyrrole lactam **6** was added, and the mixture was heated during 40 min at 90° in a vessel sealed under vacuum (0.3 mm). After the heating period was completed, the vessel was cooled and opened and the reaction mixture was freeze-dried. The residue was dissolved in a small volume of chloroform containing 3.5% of methanol and filtered through a tlc silica gel column (20 × 2 cm) prewashed and then eluted with the same solvent. The dipyrrylmethane **29** was eluted as the exclusive product and was crystallized from methanol–water: 105 mg (29%); mp 184–186°; uv max (ethanol) 284 nm (ε 39,000); ir 1670 (CO lactam), 1710 (CO benzyl ester), 1740 (CO side-chain esters), 3400 cm^{-1} (NH amide); nmr (pyridine-d_5) 2.9 (br, 4, ring CH_2CH_2), 3.1 (m, 4, side-chain CH_2CH_2CO), 3.4, 3.47, 3.5 (s, 13, CH_2CO, OCH_3), 4.2 (s, 2, pyrr–CH_2–pyrr), 4.3 (d, J = 6 Hz, 2, CH_2NH), 5.3 (s, 2, $CH_2C_6H_5$), 7.3 ppm (br, 5, C_6H_5).

Anal. Calcd for $C_{31}H_{35}N_3O_9$: C, 62.7; H, 5.9; N, 7.1. Found: C, 62.7; H, 5.9; N, 7.0.

Procedure B. A mixture of 260 mg of the chloromethyl derivative **28** and 130 mg of the lactam **6** was dissolved in 10 ml of glacial acetic acid containing 1% of sodium acetate and the mixture was heated in a vacuum-sealed vessel at 100° during 30 min. Subsequent work-up was identical with that described under procedure A, and afforded dipyrrylmethane **29** (141 mg, 41%) as the exclusive reaction product. The substance was pure when examined by tlc (chloroform–3.5% methanol). Ehrlich's reaction was negative. It was revealed as an intense orange spot when submitted to bromine vapors.

Methyl 2-(3′-Methoxycarbonylethyl-3′-methoxycarbonylmethyl-5′-benzyloxycarbonyl-2′-pyrrylmethyl)pyrrolohexahydroazepin-6-one-3-acetate (32). Procedure A. The 2-bromomethylpyrrole **30** was obtained following the technique described for the isomer **27**. From 373 mg of the dimethyl benzyl pyrrole **26** was obtained 271 mg (60%) of the 2-bromomethylpyrrole **30**: nmr ($CDCl_3$) 2.7 (m, 4, CH_2CH_2CO), 3.6, 3.7 (s, 6, OCH_3), 3.8 (s, 2, CH_2CO), 4.5 (s, 2, CH_2Br), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 ppm (br, 5, C_6H_5). Manipulation of the substance led to its gradual decomposition; hence it was used directly for the condensation reaction. The 2-bromomethylpyrrole (271 mg) and the pyrrole lactam **6** (135 mg) were condensed in an acetic acid–sodium acetate solution following the technique described for the synthesis of **29**. The dipyrrylmethane **32** thus obtained was purified by filtration through a tlc silica gel column (20 × 2 cm) using chloroform–4% methanol as a solvent. The dipyrrylmethane was crystallized from methanol–water: 134 mg (37%); mp 111–114°; ir 1680 (CO amide), 1700 (CO ring ester), 1740 (CO side-chain ester), 3450 cm^{-1} (NH amide); nmr (pyridine-d_5) 2.7 (br, 8, CH_2CH_2), 3.35 (s, 2, C_4 CH_2CO), 3.55, 3.6 (s, 9, OCH_3), 3.8 (br, 4, pyrr–CH_2–pyrr, C_4 CH_2CO), 4.1 (d, J = 6 Hz, 2, CH_2NH), 5.2 (s, 2, $CH_2C_6H_5$), 7.3 ppm (br, 5, C_6H_5).

Anal. Calcd for $C_{31}H_{35}N_3O_9$: C, 62.7; H, 5.9; N, 7.1. Found: C, 62.8; H, 5.9; N, 7.0.

The substance was pure by tlc using various solvents. It was revealed as a bright orange spot when exposed to bromine vapors.

Procedure B. The 2-chloromethylpyrrole **31** was obtained following the technique described for the isomer **28**. From 210 mg of the dimethyl benzyl pyrrole **26** was obtained 207 mg (90%) of **31**: mp 87–89° (chloroform–hexane); nmr ($CDCl_3$) 2.6 (m, 4, CH_2CH_2), 3.6, 3.65 (s, 6, OCH_3), 3.8 (s, 2, CH_2CO), 4.6 (s, 2, CH_2Cl), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 ppm (br, 5, C_6H_5). It was too unstable to allow the preparation of an analytical sample. It was dissolved (192 mg) in 8 ml of an acetic acid–sodium acetate solution and condensed with 96 mg of lactam **6** as described for the synthesis of **29**. The residue obtained after evaporation of the acetic acid was filtered through a tlc silica gel column (20 cm × 2 cm) using chloroform–4% methanol as eluent. Two substances were eluted. One (tlc, R_f 0.25, chloroform–4% methanol) was dipyrrylmethane **32** (72 mg, 28%); the second (tlc, R_f 0.80, chloroform–4% methanol) was the 2-acetoxymethylpyrrole **33** (40.8 mg, 19%), nmr ($CDCl_3$) 2.1 (s, 3, CH_3CO), 2.6 (m, 4, CH_2CH_2), 3.6, 3.7 (s, 6, OCH_3), 3.8 (s, 2, CH_2CO), 5.0 (s, 2, CH_2Ac), 5.3 (s, 2, $CH_2C_6H_5$), 7.3 (br, 5, C_6H_5). It was revealed on tlc as a red spot when exposed to bromine vapors.

Methyl 2-(3′-Methoxycarbonylmethyl-4′-β-ethoxycarbonylethyl-2′-pyrrylmethyl)pyrrolohexahydroazepin-6-one-3-acetate (34). The monobenzyldipyrrylmethane **29** (210 mg) was dissolved in 20 ml of glacial distilled acetic acid and reduced with hydrogen over 100 mg of 10% palladium on charcoal at 50 psi during 90 min. The catalyst was removed, the solution was freeze-dried, and the residue (160 mg, 90%) was melted at 220° (0.1 mm) under nitrogen and kept as a molten mass during 60 sec. The residue was dissolved in a small volume of chloroform–4% methanol and filtered through a 20 × 2 cm column of tlc silica prewashed with the same solvent. After evaporation of the solvent the dipyrrylmethane **34** was obtained in pure form: 70 mg (47%); mp 134–136° (from methanol); ir 1690 (CO amide), 1720, 1740 (CO esters), 3400 cm^{-1} (NH amide); nmr (pyridine-d_5) 2.9 (br, 8, CH_2CH_2), 3.45, 3.55, 3.57, 3.60 (s, 13, OCH_3, CH_2CO), 4.1 (s, 2, pyrr–CH_2–pyrr), 4.25 (d, J = 6 Hz, 2, CH_2NH), 6.6 ppm (br, 1, C_5H).

Anal. Calcd for $C_{23}H_{29}N_3O_7$: C, 60.1; H, 6.3; N, 9.1. Found: C, 60.0; H, 6.3; N, 8.9.

The substance was homogeneous on tlc analysis. Erhlich's reaction was positive in the cold, (uv max 560 nm, shifting to 490 nm after heating at 60°). It gave an orange spot on tlc when exposed to bromine vapors, R_f 0.70 (tlc, chloroform–4% methanol).

Methyl 2-(3′-β-methoxycarbonylethyl-4′-methoxycarbonylmethyl-2′-pyrrylmethyl)pyrrolohexahydroazepin-6-one-3-acetate (35) was obtained following the same procedure described for isomer **34**. From 200 mg of **32** was obtained 66 mg (46%) of **35**, homogeneous by tlc (chloroform–4% methanol). The substance could not be recrystallized, although it crystallized after a hexane wash: mass spectrum m/e (rel intensity) 459 (M^+, 100), 400 ($M - CO_2CH_3$, 30), 386 ($M - CH_2CO_2CH_3$, 50, possible β-cleavage[16]), 372 ($M - CH_2CH_2CO_2CH_3$, 50, β-cleavage[16]), 235 (M − pyrrole lactam **14** ion − 2 H, 50), 222 (pyrrole lactam **14** ion originated in the C_5 H* formation during bridge cleavage from methylene with $C_{3'}$*$CH_2CH_2CO_2CH_3$, 50); nmr (pyridine-d_5) 2.9 (br, 8, CH_2CH_2), 3.5 (s, 2, C_4 CH_2CO), 3.6, 3.65 (s, 12, OCH_3, $C_{4'}$ CH_2CO), 4.1 (s, 2, pyrr–CH_2–pyrr), 4.3 (d, J = 6 Hz, 2, CH_2NH), 6.75 (br, 1, $H_{5'}$); R_f 0.50 (tlc, chloroform–4% methanol).

2-Aminomethyl-3,4′-(β-carboxyethyl)-4,3′-carboxymethyldipyrrylmethane (4).[17] Dipyrrylmethane **34** (30 mg) was dissolved in a mixture of 0.25 ml of perdeuterioethanol and 0.25 ml of 4 *N* potassium deuteroxide. The solution was kept at room temperature for 72 hr and the gradual saponification of **34** was monitored by following the changes in the nmr spectrum as proposed in our former dipyrrylmethane synthesis.[1] The hexadeuterioethanol was eliminated after 48 hr and replaced by deuterium oxide. The $C_{5'}$-H signal at 6.2 ppm (δ 0 for sodium 4,4-dimethyl-4-silapentane-1-sulfonate) exchanged rapidly and faded after 24 hr. This

susceptibility to electrophilic attack of the 5′-free dipyrrylmethanes was already described by us[1] and later confirmed by others.[3] After 72 hr saponification was complete: nmr 2.7 (m, 8, CH_2CH_2), 3.5 (br, 4, CH_2CO), 3.7 (br, 2, pyrr–CH_2–pyrr), 4.0 (br, 2, CH_2NH_2). The substance was rapidly transformed into porphyrins by manipulation. Addition of an acid resin (IRC-H^+ or IRA 120-H^+) allowed adjustment of the solution to pH 7. This solution could be kept at −10° during 1 week with no decomposition and was used for chemical or enzymatic studies. Ehrlich's reaction was positive in the cold.

2-Aminomethyl-3,3′-(β-carboxyethyl)-4,4′-carboxymethyldipyrrylmethane (5) was obtained as described above for dipyrrylmethane **4**. The dipyrrylmethane **35** (36 mg) was dissolved in 0.4 ml of 2 *N* potassium deuterioxide in 50% perdeuteriomethanol. The saponification was complete after 72 hr. The $C_{5'}$ H (6.0 ppm, 0.20) was not completely exchanged after that period, nmr (δ 0 for DSS) 2.7 (m, 8, CH_2CH_2), 3.5 (br, 4, CH_2CO), 3.75 (br, 2, pyrr–CH_2–pyrr), 3.9 (br, 2, CH_2NH_2). After the solution was adjusted to pH 7 with IRA 120-H^+ resin, it could be freeze-dried and kept without decomposition at −15° during 1 week. Ehrlich's reaction was positive in the cold.

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Registry No.—**4**, 39649-89-3; **5**, 51911-89-8; **6**, 51911-90-1; **7**, 6122-77-6; **8**, 51911-91-2; **9**, 51911-92-3; **10**, 51911-93-4; **11**, 51911-94-5; **12**, 51911-95-6; **13**, 51911-96-7; **14**, 51911-97-8; **15**, 51911-98-9; **17**, 526-51-2; **18**, 17266-35-2; **20**, 51911-99-0; **21**, 38252-54-9; **22**, 50622-64-5; **23**, 51912-00-6; **24**, 38252-61-8; **26**, 50622-78-1; **27**, 50622-66-7; **28**, 50622-68-9; **29**, 51912-01-7; **30**, 51912-02-8; **31**, 51912-03-9; **32**, 51912-04-0; **33**, 51912-05-1; **34**, 51912-06-2; **35**, 51990-01-3; benzyl hydrogen malonate, 616-75-1.

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Studies on β-Lactams. XXXVI. Monocyclic Cis β-Lactams *via* Penams and Cephams[1]

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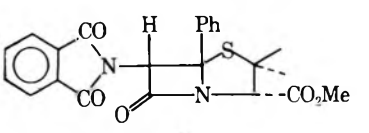
A stereospecific synthesis of monocyclic cis β-lactams has been devised which involves Raney nickel hydrogenolysis of readily accessible penams and cephams. The reaction of various acid chlorides and cyclic imines in presence of a base led to the stereospecific synthesis of a number of 6-substituted penams and 7-substituted cephams with *E* configuration with respect to the β-lactam substituents. These bicyclic β-lactams or their sulfoxides could be desulfurized under mild conditions and in good yields to 1,3,4-trisubstituted cis 2-azetidinones. No convincing rationale is obvious for the exclusive formation of bicyclic β-lactams of *E* configuration by this method.

The synthesis of bicyclic β-lactams became a desirable goal from the time it was first suspected that penicillin had a fused thiazolidine-β-lactam structure.[2] The discovery that cephalosporin C is a fused dihydrothiazine β-lactam made the preparation of bicyclic β-lactams even more attractive. Sheehan and coworkers[3] were the first to synthesize penams (for example 1) by the action of certain acid chlorides on thiazolines in presence of triethylamine.

We introduced the use of α-azidoacyl chlorides for the synthesis of α-azido-β-lactams[4] and several 6-azidopenams[5,7] and 7-azidocephams[6] (for example **2** and **3**) were synthesized in our laboratory in the course of the total synthesis of a 6-epipenicillin ester.[7] Various other penams and cephams have been prepared in different laboratories[8] and



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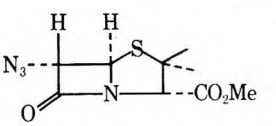

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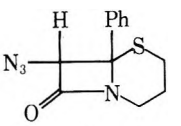

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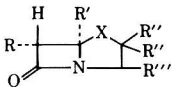
cephalosporins[9] and 4-mercapto-2-azetidinones[10,11] have been synthesized using the "acid chloride method."

Table I.

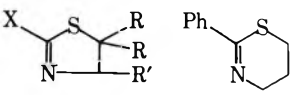


Compd	R	R′	R″	R‴	X	Mp, °C	Yield, %	Formula[a]	Spectral data
6a	MeO	Ph	H	H	S	80–81	90	$C_{12}H_{13}NO_2S$	Ir 1770 cm^{-1}; nmr τ 2.53 (s, 5 H), 5.11 (s, 1 H, 6-H), 5.68 (m, 1 H, 3-H), 6.78 (m, 3 H, 3-1H and 2-2H)
6b	PhO	Ph	H	H	S	132–134	70	$C_{17}H_{15}NO_2S$	Ir 1770 cm^{-1}; nmr τ 2.9 (br, 10 H, 2 Ar), 4.5 (s, 1 H, 6-H), 5.65 (m, 1 H, 3α-H and 2-2H)
6c	N_3	Ph	H	H	S	65–67	70	$C_{11}H_{10}N_4OS$	Ir 2105 (azide), 1773 cm^{-1}; nmr τ 2.55 (s, 5 H), 5.07 (s, 1 H, 6-H), 5.67 (m, 1 H, 3-H), 6.75 (m, 3 H, 3-H and 2-2H)
6d	N_3	Ph	Me	H	S	103–104	87	$C_{13}H_{14}N_4OS$	Ir 2.28 (azide), 1786 cm^{-1}; nmr τ 2.58 (s, 5 H), 4.98 (s, 1 H, 6-H), 5.92 (d, 1 H, 3-H, J = 12.5 Hz), 7.05 (d, 1 H, 3-H, 2-CH_3), 8.56 (s, 3 H, 2-CH_3)
6e	MeO	$C_6H_4CO_2CH_2Ph$-*p*	H	H	S	102–103	70	$C_{20}H_{19}NO_4S$	Ir 1770, 1748 cm^{-1} (ester CO); nmr τ 1.9 (d, 2 H, J = 8 Hz), 2.5 (d, 2 H, J = 8 Hz), 2.6 (br, 5 H), 4.61 (s, 2 H, OCH_2), 5.13 (s, 1 H, 6-H), 5.7 (m, 1 H, 3-H), 6.8 (m, 3 H, 3-H and 2-2H), 6.81 (s, 3 H, OCH_3)
6f	PhO	$C_6H_4CO_2CH_2Ph$-*p*	H	H	S	84–86	63	$C_{25}H_{21}NO_4S$	Ir 1788, 1724 cm^{-1} (ester CO); nmr τ 2 (d, 2 H, J = 8 Hz), 2.9 (br, m, 12 H), 4.48 (s, 1 H, 6-H), 4.7 (s, 2 H, $COCH_2$), 4.67 (m, 1 H, 3-H), 6.86 (m, 3 H, 3-H and 2-2H)
6g	PhO		H	H	S	95	70	$C_{15}H_{13}NO_3S$	Ir 1792 cm^{-1}; nmr τ 2.5–3.11 (m, 6 H), 3.41–3.68 (m, 2 H), 4.47 (s, 1 H), 5.48–5.75 (m, 1 H), 6.43–7.08 (m, 3 H)
6h	PhO	Ph	H	H	SO	108–109	80	$C_{17}H_{15}NO_3S$	Ir 1783 cm^{-1}; nmr τ 2.85 (m, 10 H), 4.25 (s, 1 H, 6-H), 5.66 (m, 1 H, 3-H), 6.65 (m, 3 H, 3-H and 2-2H)
6i	MeO	$C_6H_4CO_2CH_2Ph$-*p*	H	H	SO	180–181	95	$C_{20}H_{19}NO_5S$	Ir 1779, 1730 cm^{-1} (ester CO); nmr τ 1.83 (d, 2 H, J = 8Hz), 2.53 (d, 2 H, J = 8 Hz), 4.6 (s, 2 H, OCH_2), 4.84 (s, 1 H, 6-H), 5.7 (m, 1 H, 3-H), 6.67 (m, 3 H, 3-H and 2-2H), 6.65 (s, 3 H, OCH_3)
6j	MeO	Ph	H	H	SO_2	142–144	80	$C_{12}H_{13}NO_4S$	Ir 1808 cm^{-1}; nmr τ 2.6 (s, 5 H), 4.87 (s, 1 H, 6-H), 5.67 (m, 1 H, 3-H), 6.67 (s, 3 H, OCH_3), 6.6 (br m, 3 H, 3-H and 2-2H)

6k	MeO	$C_6H_4CO_2CH_2Ph$-*p*	H	H	SO_2	113–114	90	$C_{20}H_{19}NO_6S$	Ir 1776, 1709 cm^{-1} (ester CO); nmr τ 1.97 (d, 2 H, J = 8 Hz), 2.48 (d, 2 H, J = 8 Hz), 2.6 (s, 5 H, phenyl), 4.61 (m, 2 H, OCH_2), 5.83 (m, 1 H, 3-H), 6.7 (s, 3 H, OCH_3), 6.65 (m, 3 H, 3β-H and 2-2H)
7a	MeO	H	H	CO_2Et	S	61–63	11	$C_9H_{13}NO_4S$	Ir 1770, 1739 cm^{-1} (ester CO); nmr τ 4.85 (d, 1 H, 6 H, J = 1.5 Hz), 4.95 (m, 1 H, 3-H), 5.47 (d, 1 H, 5-H, J = 1.5 Hz), 5.73 (q, 2 H, OCH_2, J = 7 Hz), 6.45 (s, 3 H, OCH_3), 6.53 (m, 2 H, 2-2H), 8.7 (t, 3 H, CH_3, J = 7 Hz)
7b	MeO	Ph	Me	CO_2CHPh_2	S	110–111	90	$C_{23}H_{21}NO_4S$	Ir 1739 (ester CO), 1770 cm^{-1}; nmr τ 2.3 (m, 2 H), 2.7–2.75 (m, 13 H, aromatic), 5.22 (s, 1 H, 6-H), 5.32 (s, 1 H, 3-H), 6.95 (s, 3 H, OCH_3), 8.33 (s, 3 H, 2-CH_3), 9.02 (s, 3 H, 2-CH_3)

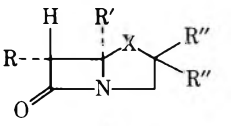
[a] All of the solid penams described in this table gave satisfactory (within ±0.4% of the theoretical value) C, H, and N analyses. In most of the cases they were also analyzed for S.

Recently we have discussed some aspects of the mechanism and stereochemistry[12] of the reaction of imines, acid chlorides, and bases to give β-lactams. We report here on some studies where the imine component in this type of reaction was either a thiazoline (**4**) or a dihydrothiazine (**5**).[13] The 6-substituted penams (**6, 7**) and the 7-substituted cephams (**8**) were obtained by the general reaction shown in eq 1. Some of the penams and cephams were converted to the corresponding sulfoxides and sulfones for characterization purposes because of better crystallinity of these derivatives.

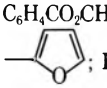


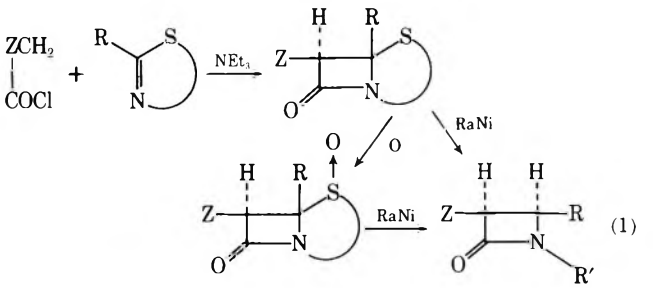
4 **5**

a, R = H; R′ = H; X = Ph
b, R = H; R′ = CO_2H; X = Ph
c, R = Me; R′ = CO_2Et; X = Ph
d, R = Me; R′ = CO_2H; X = Ph
e, R = Me; R′ = H; X = Ph
f, R = H; R′ = H; X = $C_6H_4CO_2CH_2Ph$-*p*
g, R = H; R′ = H; X = 
h, R = Me; R′ = CO_2CHPh_2; X = Ph
i, R = H; R′ = CO_2Et; X = H



6

a, R = MeO; R′ = Ph; R″ = H; X = S
b, R = PhO; R′ = Ph; R″ = H; X = S
c, R = N_3; R′ = Ph; R″ = H; X = S
d, R = N_3; R′ = Ph; R″ = Me; X = S
e, R = MeO; R′ = $C_6H_4CO_2CH_2Ph$-*p*; R″ = H; X = S
f, R = PhO; R′ = $C_6H_4CO_2CH_2Ph$-*p*; R″ = H; X = S
g, R = PhO; R′ =  ; R″ = H; X = S
h, R = PhO; R′ = Ph; R″ = H; X = SO
i, R = MeO; R′ = $C_6H_4CO_2CH_2Ph$-*p*; R″ = H; X = SO
j, R = MeO; R′ = Ph; R″ = H; X = SO_2
k, R = MeO; R′ = $C_6H_4CO_2CH_2Ph$-*p*; R″ = H; X = SO_2



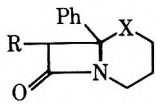
(1)

In the synthesis of penams the yield of β-lactams was low when X = H in the thiazoline (**4**);[7,14] the yield increased sharply when X = aryl or ester.[5,15] In general, cephams were formed in higher yield than the corresponding penams.

In the synthesis of monocyclic β-lactams by the "acid chloride method" it is usual to get a mixture of both cis and trans stereomers—often the trans isomer predominates.[12,16] In one case, however, only the cis β-lactam was formed.[17]

The synthesis of bicyclic β-lactams from thiazolines and

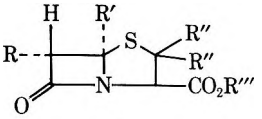
Table II.



Compd	R	X	Mp, °C	Yield, %	Formula[a]	Spectral data
8a	MeO	S		63		Ir 1770 cm^{-1}; nmr τ 2.59 (s, 5 H), 5.31 (s, 1 H), 5.72–5.90 (m, 1 H), 6.94 (s, 3 H), 6.78–7.42 (m, 3 H), 8.0–8.33 (m, 2 H)
8b	PhO	S	130–131	81	$C_{18}H_{17}NO_2S$	Ir 1770 cm^{-1}; nmr τ 2.3–3.45 (m, 10 H), 4.6 (s, 1 H), 5.66–6.0 (m, 1 H), 6.7–7.27 (m, 3 H), 8.0–8.3 (m, 2 H); M^+ at *m/e* 311
8c	MeO	SO	130	80	$C_{13}H_{15}NO_3S$	Ir 1751 cm^{-1}; nmr τ 2.62 (s, 5 H), 4.90 (s, 1 H), 5.76–6.06 (m, 1 H), 6.51–7.67 (m, 4 H), 6.80 (s, 3 H), 8.32–8.68 (m, 1 H)
8d	PhO	SO	138–139	88	$C_{18}H_{17}NO_3S$	Ir 1776 cm^{-1}; nmr τ 2.77–3.33 (m, 10 H), 4.20 (s, 1 H), 5.70–6.03 (m, 1 H), 6.50–7.67 (m, 4 H), 8.3–8.82 (m, 1 H); M^+ at *m/e* 327

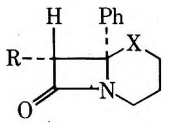
[a] The compounds described in this table gave satisfactory (within ±0.4% of the theoretical value) C, H, and N analyses.

dihydrothiazines was characterized by stereospecificity—a single stereoisomer was formed in each instance. In the case of the 5-unsubstituted penam (**7a**) the size of the coupling (J = 2 Hz) between H-5 and H-6 indicated the trans stereochemistry of the β-lactam, but for the other penams and cephams the stereochemistry was not so obvious. The compounds (**6a, 6e, 6j, 6k, 6l, 8a**), however, were found to belong to a special category—the signal for the methoxy protons appeared at τ 6.65–6.94, that is at ~0.45–0.70 ppm higher field than usual. This upfield shift is indicative of the cis relationship between the methoxy group and the aromatic ring and "*E*" stereochemistry as in this configuration the methoxy protons lie in the shielding cone of the phenyl ring. The nmr spectra of the other penams and cephams do not reveal their stereochemistry. Therefore, we took recourse to desulfurization of these compounds with Raney nickel. Reductive desulfurization has been reported to proceed with retention of configuration.[18] We reconfirmed this in two different ways. Firstly, we desulfurized the trans β-lactam **9** with deuterated Raney nickel. The product (**10**) showed ~70% deuterium incorporation by



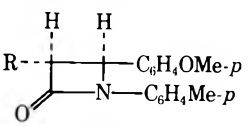
7

a, R = MeO; R′ = H; R″ = H; R‴ = Et
b, R = MeO; R′ = Ph; R″ = Me; R‴ = $CHPh_2$



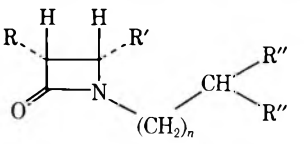
8

a, R = MeO; X = S
b, R = PhO; X = S
c, R = MeO; X = SO
d, R = PhO; X = SO



9, R = $PhCH_2S$
10, R = D

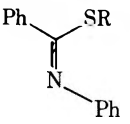
mass spectroscopy and trans relationship of the protons at C-3 and C-4 was preserved. Secondly, Raney nickel desulfurization of 8a led to the monocyclic β-lactam **11c** which was found to be cis by nmr spectroscopy as would be expected on the basis of its *E* stereochemistry.



11

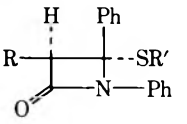
a, R = PhO; R′ =  ; R″ = H; n = 1
b, R = MeO; R′ = Ph; R″ = H; n = 2
c, R = PhO; R′ = Ph; R″ = H; n = 2

Application of the desulfurization technique to the other penams (**6g**) and cephams (**8b**) or their sulfoxides (**6i**,[18] **8c, 8d**) also gave cis β-lactams—thus demonstrating their *E* configuration in each case. The currently held views[12,19] regarding the mechanism of β-lactam formation from acid chlorides and imines do not provide any convincing rationale for the exclusive formation of bicyclic β-lactams of *E* configuration from thiazolines and dihydrothiazines. It may be added that monocyclic β-lactams **13** from thioimidates, such as **12**, also show the same stereospecificity.

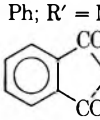


12

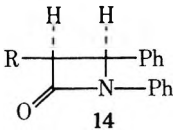
a, R = CH_3
b, R = CH_2Ph
c, R = $CH_2C_6H_4NO_2$-*p*



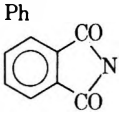
13

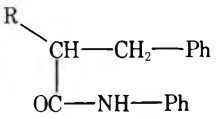
a, R = PhO; R′ = Me
b, R = PhO; R′ = CH_2Ph
c, R = PhO; R′ = $CH_2C_6H_4NO_2$-*p*
d, R = MeO; R′ = Me
e, R = Ph; R′ = Me
f, R =  ; R′ = Me

Raney nickel desulfurization to cis β-lactams **14** was observed to form side products (**15**) in some cases.



14

a, R = PhO
b, R = OMe
c, R = Ph
d, R = 



15

a, R = H
b, R = OMe

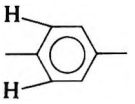
Monocyclic cis β-lactams derived from penicillins are currently attracting considerable attention for the partial synthesis of cephalosporins.[20,21] A few monocyclic β-lactams have also been discovered in nature.[22] In view of these developments, our method for preparing variously substituted monocyclic *cis*-β-lactams by the desulfurization of readily synthesized penams and cephams is of potential value to medicinal chemists. There is an added interest in monocyclic β-lactams since we have recently discovered that some of them show antibiotic activity.[1a]

Experimental Section

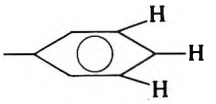
The ir spectra were recorded on a Perkin-Elmer Infracord spectrophotometer calibrated with polystyrene film at 1603 cm^{-1}. The pmr spectra were obtained on a Varian A-60A spectrometer operating at 60 MHz using TMS as an internal standard. The mass spectra were measured on a Hitachi Perkin-Elmer RMU-7 mass spectrometer at 70 eV using an all glass heated inlet system. Thin layer chromatography (tlc) was performed on silica G plates and spots were developed with iodine vapors or aqueous $KMnO_4$ solution. Elemental analyses were performed by A. Bernhardt, Max Planck Institute, Mülheim, W. Germany. Melting points were determined in open capillary tubes and are uncorrected.

4-Carboxy-2-phenyl-2-thiazoline (4b). This compound was synthesized by the method of Sheehan and coworkers:[23] mp 123–124°; nmr ($CDCl_3$) τ 0.44 (s, 1 H), 2.10 (m, 2 H), 2.54 (m, 3 H), 4.58 (t, 1 H), 6.28 (d, 2 H).

2-Phenyl-2-thiazoline (4a). 4-Carboxy-2-phenyl-2-thiazoline (**4b,** 32 g, 0.154 mol) was heated under reduced pressure (1.5 mm). When the bath temperature was raised to 180°, evolution of carbon dioxide started and the desired product began to distil over which was collected at 95–100° (1.5 (1.5 mm) [lit.[24] bp 105–107° (2 mm), 275–280° (740 mm)]: yield 28.5%; nmr ($CDCl_3$) τ 2.05 (m, 2 H, a), 2.55 (m, 3 H, b), 5.56 (t, 2 H, 4-CH_2), 6.66 (t, 2 H, 5-CH_2).

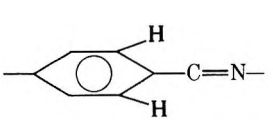


a

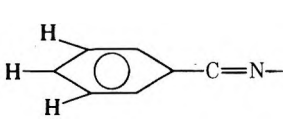


b

5,5-Dimethyl-2-phenyl-2-thiazoline (4e). 5,5-Dimethyl-2-phenyl-2-thiazoline-4-carboxylic acid (**4d,** 46.0 g, 0.195 mol) obtained by the hydrolysis of ethyl 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylate (**4c**)[25] was heated to 120° (0.25 mm). Effervescence due to the evolution of carbon dioxide was noticed and 5,5-dimethyl-2-phenyl-2-thiazoline (**4e**) was collected at 120° (0.25 mm) (35.5 g, 76%): ν_{max} 1610 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.11 (m, 2 H, c), 2.59 (m, 3 H, d), 5.9 (s, 2 H, 4-CH_2), 8.51 (s, 6 H, 5-2CH_3); mass spectrum M^+ at *m/e* 191.

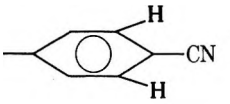


c

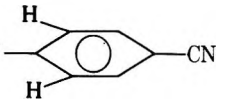


d

Benzyl 4-Cyanobenzoate. 4-Cyanobenzoic acid (34 g, 0.231 mol) was suspended in 200 ml of anhydrous ether in a 1-l. flask equipped with a dropping funnel. A solution (600 ml) of 28.04 g of phenyldiazomethane[26] was added. The yellowish pink color of the phenyldiazomethane solution disappeared immediately on reaction. After the addition of the phenyldiazomethane solution was completed, the reaction mixture was refluxed for 16 hr. Evaporation of the solvent gave the crude ester (55 g) which was dissolved in 300 ml of methylene chloride. This solution was washed successively with 50 ml of saturated $NaHCO_3$ and 2 × 100 ml of water, dried ($MgSO_4$), and stripped of the solvent to give the product (53 g, 96.5%). This material was used for subsequent reactions without further purification: mp 44–46°; ν_{max} 2252 (–CN), 1760 cm^{-1} (ester carbonyl); nmr ($CDCl_3$) τ 1.93 (d, 2 H, e), 2.45 (d, 2H, f), 2.6 (br, 5 H, phenyl), 4.67 (s, 2 H, CH_2); mass spectrum M^+ at *m/e* 234.

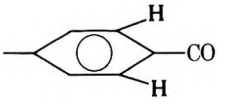


e

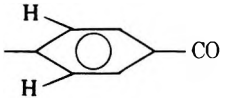


f

2-(*p*-Benzyloxycarbonylphenyl)-2-thiazoline (4f). In a 500-ml round-bottom flask equipped with a condenser and a drying tube were placed benzyl 4-cyanobenzoate (59 g, 0.25 mol) and cysteamine (20 g, 0.25 mol). The mixture was heated for 18 hr at 150° without solvent and the melt was cooled and extracted with 300 ml of methylene chloride. Evaporation of the solvent from the extract left a viscous material (78 g) which was passed through a column of Florisil (80 g, mesh 60–100) and eluted with benzene–hexane (1:1) mixture. The first 200 ml of the eluant gave the desired compound (59 g, 80%). This material was used without purification for the next operation. A portion was purified by distillation under reduced pressure, the fraction distilling at 210° (0.5 mm) which was essentially pure title compound solidified on standing: mp 67–69°; ir (Nujol) ν_{max} 1709 (ester carbonyl), 1610 cm^{-1} (C=N); nmr ($CDCl_3$) τ 1.87 (d, 2 H, $J_{A_2B_2}$ = 8 Hz, g), 2.11 (d, 2 H, $J_{A_2B_2}$ = 8 Hz, h), 2.61 (s, 5 H, phenyl), 4.63 (s, 3 H, OCH_2), 5.51 (t, 2 H, J = 8 Hz, 4-2H), 6.6 (t, 2 H, J = 8 Hz, 5-2H); mass spectrum M^+ at *m/e* 297.

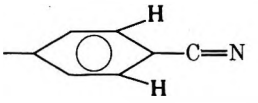


g

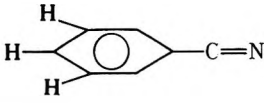


h

Benzhydryl 5,5-Dimethyl-2-phenyl-2-thiazoline-4-carboxylate (4h). In a 500-ml round-bottom flask equipped with a condenser and a drying tube was taken a solution of 6 g (0.025 mol) of **4d** in 200 ml of anhydrous ether. Freshly prepared diphenyldiazomethane[27] (5.95 g, 0.0255 mol) in 200 ml of ether was then added dropwise at room temperature with constant stirring. After the addition of the diphenyldiazomethane, the solution was refluxed for 48 hr and then the solvent was evaporated to give essentially the pure product (10 g). An analytical sample of the thiazoline ester was prepared by crystallization from methylene chloride–petroleum ether: mp 114–116°; ir ν_{max}^{Nujol} 1745 (ester C=O), 1605 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.13 (m, 2 H, i), 2.65 (br, 13 H, j and two phenyls), 2.97 (s, 1 H, Ph_2CH), 5.05 (s, 1 H, 4-H), 8.27 (s, 3 H, 5-CH_3), 9.73 (s, 3 H, 5-CH_3); mass spectrum M^+ at *m/e* 401.



i

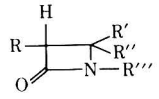


j

Anal. Calcd for $C_{25}H_{23}NO_2S$: C, 74.81; H, 5.73; N, 3.49; S, 7.98. Found: C, 74.63; H, 5.75; N, 3.67; S, 7.97.

Ethyl 2-Thiazoline-4-carboxylate (4i). Through a solution of L-cysteine ethyl ester hydrochloride (50 g) in 500 ml of methanol was passed ammonia gas at room temperature at moderate rate for 15 min. The precipitated ammonium chloride was filtered off. Evaporation of methanol under reduced pressure gave L-cysteine ethyl ester which was dissolved in 200 ml of absolute ethanol containing 50 mg of *p*-toluenesulfonic acid and the solution was refluxed. To this refluxing solution was added 150 ml of triethyl orthoformate dropwise over a period of 0.5 hr. The reaction mixture was refluxed for an additional 3 hr. The solvent was then evaporated under reduced pressure and the viscous residue was dissolved in 200 ml of methylene chloride and washed with 3 × 75 ml of water and dried ($MgSO_4$). Evaporation of CH_2Cl_2 yielded the *N*-formylcysteine ethyl ester as a viscous oil (29 g) which was not

Table III.



Compd	R	R′	R″	R‴	Stereochemistry	Mp, °C	Yield, %	Formula[a]	Spectral data[b]
9	$PhCH_2S$	C_6H_4OMe-*p*	H	C_6H_4Me-*p*	Trans	118–119	56	$C_{24}H_{23}NO_2S$	Ir 1727 cm^{-1}; nmr τ 2.79–3.27 (m, 13 H), 5.45 (d, 1 H, J = 2 Hz), 6.08 (s, 1 H), 6.11 (d, 1 H, J = 2 Hz), 6.25 (s, 3 H), 7.75 (s, 3 H)
11a	PhO		H	C_2H_5	Cis	109–110	60	$C_{15}H_{15}NO_3$	Ir 1748 cm^{-1}; nmr τ 2.5–3.15 (m, 6 H), 345–3.62 (m, 2 H), 4.50 (d, 1 H, J = 4.5 Hz), 4.81 (d, 1 H, J = 4.5 Hz), 6.25, 7.10 (m, 2 H), 8.89 (t, 3 H)
11b	MeO	Ph	H	C_3H_7-*n*	Cis	Colorless oil	50		Ir 1745 cm^{-1}; nmr τ 5.29 (d, 1 H, J = 4 Hz), 5.39 (d, 1 H, J = 4 Hz), 5.39 (d, 1 H, J = 4 Hz), 7.0 (s, 3 H)
11c	PhO	Ph	H	C_3H_7-*n*	Cis	109–110	40	$C_{18}H_{19}NO_2$	Ir 1745 cm^{-1}; nmr τ 2.57–3.21 (m, 10 H), 4.46 (d, 1 H, J = 4.5 Hz), 4.98 (d, 1 H, J = 4.5 Hz), 6.3–7.31 (m, 2 H), 8.3–8.75 (m, 2 H), 9.1 (t, 3 H, J = 7 Hz)
13a	PhO	SCH_3	Ph	Ph		192	64	$C_{22}H_{19}NO_2S$	Ir 1770 cm^{-1}; nmr τ 2.15–3.18 (m, 15 H, aromatic), 4.40 (s, 1 H, 3-H), 7.88 (s, 3 H, SCH_3); M^+ at *m/e* 361
13b	PhO	SCH_2Ph	Ph	Ph		154–155	71	$C_{28}H_{23}NO_2S$	Ir 1764 cm^{-1}; nmr τ 2.1–3.22 (m, 20 H), 4.57 (s, 1 H), 6.19 (s, 2 H)
13c	PhO	$SCH_2C_6H_4NO_2$-*p*	Ph	Ph		138–139	81	$C_{28}H_{22}N_2O_4S$	Ir 1767 cm^{-1}; nmr τ 1.90–3.30 (m, 19 H), 4.5 (s, 1 H), 6.06 (AB q, 2 H, J = 13 Hz)
13d	MeO	SCH_3	Ph	Ph		126	90	$C_{17}H_{17}NO_2S$	Ir 1748 cm^{-1}; nmr τ 2.11–2.02 (m, 10 H), 5.12 (s, 1 H, 3-H), 6.75 (s, 3 H, OCH_3), 7.94 (s, 3 H, SCH_3)
13e	Ph	SMe	Ph	Ph		169–170	76	$C_{22}H_{19}NOS$	Ir 1745 cm^{-1}; nmr τ 2.03–2.97 (m, 10 H), 4.95 (s, 1 H, 3-H), 7.82 (s, 3 H, SCH_3)
13f		SMe	Ph	Ph		208–209	69	$C_{24}H_{18}N_2O$	Ir 1787, 1757, 1720 cm^{-1}; nmr τ 2.03–3.0 (m, 14 H), 4.26 (s, 1 H, 3-H), 7.82 (s, 3 H, SCH_3)

14a[c]	PhO	Ph	H	Ph	Cis	192–193	50	$C_{21}H_{17}NO_2$	Ir 1757 cm^{-1}; nmr τ 4.46 (d, 1 H, J = 5 Hz), 4.64 (d, 1 H, J = 5 Hz)
14b[c]	MeO	Ph	H	Ph	Cis	141–142	60		Ir 1754 cm^{-1}; nmr τ 2.63–3.0 (m, 10 H), 4.8 (d, 1 H, J = 5 Hz), 5.20 (d, 1 H, J = 5 Hz), 5.28 (d, 1 H, J = 5 Hz), 6.81 (s, 3 H)
14c[d]	Ph	Ph	H	Ph	Cis	184–185	57		Ir 1742 cm^{-1}; nmr τ 2.47–3.0 (m, 15 H), 4.17 (d, 1 H, J = 6 Hz), 4.99 (d, 1 H, J = 6 Hz)
14d		Ph	H	Ph	Cis	218–219	61	$C_{23}H_{16}N_2O_3$	Ir 1781, 1760, 1722 cm^{-1}; nmr τ 2.42–2.95 (m, 14 H), 4.34 (d, 1 H, J = 5 Hz), 5.5 (d, 1 H, J = 5 Hz)

[a] All of the new β-lactams described in this table gave satisfactory (within ±0.4% of the theoretical value) C, H, and N analyses. [b] Infrared spectra in Nujol; the band at 1745–1805 cm^{-1} is due to β-lactam CO. Nmr spectra in $CDCl_3$. M^+ peak for nominal mass reported for compounds **6a–k, 7a, b.** [c] Reference 12a. [d] Reference 28.

purified further: ν_{max} 3300 (amide NH), 1739 (ester C=O), 16.75 cm^{-1} (amide C=O).

N-Formylcysteine ethyl ester (34 g) was distilled from 100-ml round-bottom flask at 120° (0.3 mm). The distillate was pure **4i** (17.5 g, 57.4%): ν_{max} 1742 cm^{-1} (ester C=O); nmr ($CDCl_3$) τ 1.97 (d, 1 H, J = 2 Hz, 2-H), 4.83 (m, 1 H, $J_{1,4}$ = 2 Hz, $J_{4,5}$ = 7 Hz, 4-H), 5.7 (q, 2 H, J = 7 Hz, OCH_2), 6.38 and 6.53 (2 s, 2 H, 5-2H), 8.67 (t, 3 H, J = 7 Hz, CH_3).

Preparation of Penams and Cephams. 6-Methoxy-5-phenylpenam (6a). In a 1-l. flask equipped with a condenser, a pressure-equalized dropping funnel, and a nitrogen-inlet tube were placed 2-phenyl-2-thiazoline (6.52 g, 0.025 mol), methoxyacetyl chloride (4.34 g, 0.025 mol), and 750 ml of methylene chloride. This solution was maintained at reflux while a solution of triethylamine (4.04 g, 0.025 mol) in 125 ml of methylene chloride was slowly added dropwise over a period of 7–9 hr. After the addition was completed the reaction mixture was refluxed for an additional 17 hr. Evaporation of the solvent gave a yellowish solid which was extracted with 2 × 500 ml of diethyl ether. The ethereal extract was washed with water and dried ($MgSO_4$). Removal of ether left a light red, viscous oil, 9.3 g (99.3%), which showed a strong band at 1773 cm^{-1} (β-lactam C=O) in the ir spectrum. This crude product was dissolved in methylene chloride and filtered through Florisil (80 g, 60–100 mesh); the first 200 ml of the eluent gave the desired bicyclic β-lactam (8.5 g, 90.7%). Crystallization of the β-lactam from benzene–hexane gave pure **6a.**

The penams (**6b–g** and **7a,b**) were also prepared by this general method using the appropriate acid chloride and the thiazoline.

The reaction of the dihydrothiazine **5** with methoxyacetyl chloride and phenoxyacetyl chloride in the presence of NEt_3 afforded the cephams **8a** and **8c,** respectively.

Preparation of Penam and Cepham Sulfoxides. 6-Phenoxy-5-phenylpenam 1-Oxide (6h). A solution of **6b** (0.9 g, 0.003 mol) and *m*-chloroperoxybenzoic acid (0.52 g, 0.003 mol) in 150 ml of anhydrous ether was stirred at room temperature for 15 hr. Ether was evaporated and the product dissolved in 100 ml of methylene chloride. *m*-Chlorobenzoic acid formed during the reaction was neutralized with 20 ml of 10% $NaHCO_3$ solution. The organic layer was washed with 2 × 50 ml of water, dried ($MgSO_4$), and filtered. Evaporation of the solvent gave a white crystalline solid which on recrystallization from methylene chloride–petroleum ether afforded 0.75 g of **6h.**

Using the same general procedure the penam sulfoxide **6j** was obtained from the corresponding penam. In a similar manner the cephams **8a** and **8b** gave the sulfoxides **8c** and **8d,** respectively.

Preparation of Penam Sulfones. 5-(*p*-Carbobenzyloxyphenyl)-6-methoxypenam 1,1-Dioxide (6k). A mixture of **6i** (0.38 g, 0.001 mol) and *m*-chloroperoxybenzoic acid (0.17 g, 0.001 mol) in 100 mol of CH_2Cl_2 was stirred at room temperature for 48 hr. The reaction mixture was washed with $NaHCO_3$ solution followed by water and dried ($MgSO_4$). Removal of the solvent and recrystallization of the residue from methylene chloride–hexane gave 0.36 g of **6k.**

The penam **6a** could be converted directly to the sulfone **6j** by using 2 *M* proportions of *m*-chloroperoxybenzoic acid.

The spectral data on the penams, their sulfoxides, and sulfones are reported in Table I. The data on cephams are recorded in Table II.

***trans*-1-(*p*-Tolyl)-3-benzylthio-4-(*p*-anisyl)azetidin-2-one (9).** To a solution of *S*-benzylthioglycolyl chloride (6.88 g, 0.02 mol) in 300 ml of CH_2Cl_2 was added under stirring a mixture of *p*-anisylidene-*p*-toluidine (4.50 g, 0.02 mol) and Et_3N (2.50 g, 0.025 mol) in 100 ml of CH_2Cl_2 over a period of 2 hr and contents were further stirred for 10 hr. CH_2Cl_2 solution was washed with $NaHCO_3$ solution followed by water and dried ($MgSO_4$), and solvent was removed. The residue was crystallized from methylene chloride–hexane to give 4.35 g.

Using similar reaction conditions the Schiff bases **12a–c** on treatment with appropriate acid chlorides afforded the β-lactams **13a–f.**

***trans*-1-(*p*-Tolyl)-3-deuterio-4-(*p*-anisyl)azetidin-2-one (10).** To a solution of **9,** (1.90 g, 0.005 mol) in 100 ml of MeOD containing 50 ml of D_2O was added Raney nickel (15 g) previously washed thrice with D_2O. The reaction mixture was refluxed for 10 hr and worked up as described for **9** to give 0.88 g (65%) of **10:** mp 70–71°; ir (Nujol) 1742 cm^{-1} (β-lactam CO); nmr ($CDCl_3$) τ 2.70–3.26 (m, 8 H), 5.12 (d, 1 H, J = 2 Hz), 6.27 (s, 3 H), 7.15 (d, 1 H, J = 2 Hz), 7.79 (s, 3 H); mass spectrum M^+ at *m/e* 268.

The procedure described below for synthesizing **11a** is typical of the desulfurization carried out on other β-lactams.

cis-**1-Ethyl-3-phenoxy-4-(2-furyl)azetidin-2-one (11a).** To a solution of **6g** (1.44 g, 0.005 mol) in 300 ml of acetone was added 30 g of Raney nickel (W-7) and the contents were refluxed on a steam bath for 10 hr. After filtration, the acetone solution was concentrated under vacuum and the residue obtained was crystallized from methylene chloride–hexane to furnish crude **11a** which was further purified by chromatography over a column of Florisil using benzene as eluent to give 60% yield of the pure title compound.

Using the same reaction conditions **8c** was converted to **11b**. Similarly the cis monocyclic β-lactam **11c** could be prepared *via* the desulfurization of the cepham **8b** or its sulfoxide **8d**.

Similarly the desulfurization of **13a, 13b** or **13c** resulted in the formation of **14a**. Also the cis β-lactams **14b, 14c,** and **14d** were formed by the Raney Ni treatment of the methylthio β-lactams **13d, 13e,** and **13f,** respectively.

The analytical and spectral data for all the monocyclic β-lactams are given in Table III.

S-**Methylthiobenzanilide (12a)** was prepared by the method of May,[30] mp 63–64°.

S-**Benzylthiobenzanilide (12b).**[31] To a solution of thiobenzanilide (4.26 g, 0.02 mol) in 50 ml of 10% KOH was added benzyl chloride (2.52 g, 0.02 mol), the contents were stirred at room temperature for 10 hr and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and dried ($MgSO_4$), and the solvent was removed to give an oil: ν_{max} 1603 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.71–3.32 (m, 15 H, aromatic H), 5.79 (s, 2 H, SCH_2); mass spectrum M^+ at *m/e* 303.

S-(*p*-**Nitrobenzyl)thiobenzanilide (12c).** A suspension of thiobenzanilide (8.52 g, 0.04 mol) and *p*-nitrobenzyl bromide (8.64 g, 0.04 mol) in 100 ml of 10% KOH was stirred for 12 hr at 85°. The contents were cooled and extracted with CH_2Cl_2 (3 × 75 ml), washed with water, and dried ($MgSO_4$), and the solvent was removed under vacuum. Recrystallization of the residue from benzene–hexane gave 12.3 g (88.5%) of **12c:** mp 98–99°; ν_{max} 1613 cm^{-1} (C=N); nmr ($CDCl_3$) τ 1.75–45 (m, 14 H), 5.67 (s, 2 H).

Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.96; H, 4.60; N, 8.05. Found: C, 68.71; H, 4.75; N, 8.25.

Registry No.—4a, 2722-34-1; **4b,** 19983-15-4; **4d,** 51932-22-0; **4e,** 37950-61-1; **4f,** 51932-23-1; **4g,** 14117-27-2; **4h,** 51932-24-2; **4i,** 51932-25-3; **5,** 6638-35-3; **6a,** 51932-26-4; **6b,** 37958-31-9; **6c,** 52019-83-7; **6d,** 52019-84-8; **6e,** 51932-27-5; **6f,** 51932-28-6; **6g,** 51932-29-7; **6h,** 51932-30-0; **6i,** 52022-26-1; **6j,** 51932-31-1; **6k,** 51932-32-2; **7a,** 51932-33-3; **7b,** 51932-34-4; **8a,** 37958-33-1; **8b,** 37958-32-0; **8c,** 51932-35-5; **8d,** 51932-36-6; **9,** 38395-81-2; **10,** 51932-37-7; **11a,** 38395-85-6; **11b,** 37958-36-4; **11c,** 37958-35-3; **12a,** 52019-85-9; **12b,** 52019-86-0; **12c,** 51932-38-8; **13a,** 52019-87-1; **13b,** 38395-82-3; **13c,** 38395-83-4; **13d,** 51932-39-9; **13e,** 51932-40-2; **13f,** 52019-88-2; **14a,** 33812-92-9; **14b,** 33812-89-4; **14c,** 16141-50-7; **14d,** 29834-35-3; benzyl 4-cyanobenzoate, 18693-97-5; 4-cyanobenzoic acid, 619-65-8; cysteamine, 60-23-1; diphenyldiazomethane, 883-40-9; L-cysteine ethyl ester hydrochloride, 868-59-7; *N*-formylcysteine ethyl ester, 52022-27-2; methoxyacetyl chloride, 38870-89-2; *S*-benzylthioglycolyl chloride, 7031-28-9; *p*-anisylidene-*p*-toluidine, 3246-78-4; thiobenzanilide, 636-04-4; benzyl chloride, 100-44-7; *p*-nitrobenzyl bromide, 100-11-8; phenoxyacetyl chloride, 701-99-5; azidoacetyl chloride, 30426-58-5; phenylacetyl chloride, 103-80-0; phthalimidoacetyl chloride, 6780-38-7.

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Synthesis and Cycloaddition Reactions of Fluorenethione S-Benzoylimide

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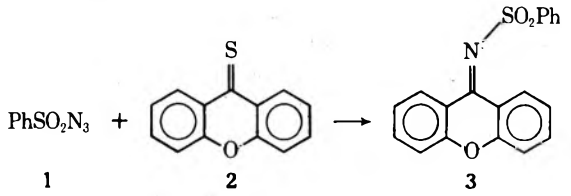
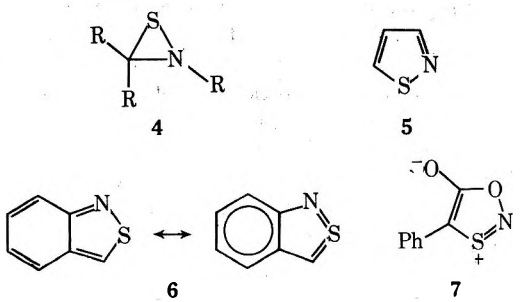
Reaction of N-(trimethylsilyl)benzamide with sulfur dichloride afforded benzamide-N-sulfenyl chloride, which reacted rapidly with diphenyldiazomethane at −30° to give N-benzoylchlorodiphenylmethanesulfenamide. Treatment of the latter with triethylamine at −78° resulted in the formation of 2,2,5-triphenyl-1,3,4-oxathiazole, and no evidence was obtained to support the intermediacy of benzophenthione S-benzoylimide in this reaction. Reaction of the above sulfenyl chloride with 9-diazofluorene at −30° gave N-benzoyl-9-chlorofluorenesulfenamide, which with triethylamine at −78° resulted in the formation of fluorenethione S-benzoylimide which could be isolated as a metastable solid at room temperature; however, in solution at *ca.* −30°, an electrocyclic ring closure to 5′-phenylspiro[fluorene-9,2′-[1′,3′,4′]oxathiazole] resulted. When this thione S-imide was treated with N-isobutenylpyrrolidine at −78° there was obtained 2′-benzoyl-3′-pyrrolidine-4′,4′-dimethylspiro[fluorene-9,5′-[1′,2′]isothiazolidine] while reaction with N-propenylpiperidine afforded 2′-benzoyl-3′-piperidine-4′-methylspiro-[fluorene-9,5′-[1′,2′]isothiazolidine]. The thione S-imide was also found to react with the terminal double bond of 1-diethylaminobutadiene to give 2′-benzoyl-3′-(*trans*-N-ethenyldiethylamine)spiro[fluorene-9,5′-[1′,2′]isothiazolidine] and an unstable sulfonium ylide, 2-phenyl-4-fluorenylide-5-methyl-6-diethylamino-1,4,3-oxathiazine, was obtained from the reaction with 1-(diethylamino)-1-propyne.

Among the heterocumulenes containing a central tetravalent (d-orbital participation) sulfur atom related to sulfur dioxide shown in Table I, only thione S-imides[2] represented an unknown[3] entity. Pedagogically, thione S-imides could be derived from the addition of a nitrene to a thione; however, the only reported reaction which might have mechanistically followed this course was the thermal decomposition of benzenesulfonyl azide (**1**) in the presence of xanthione (**2**), which only gave the imine **3**.[4] Electrocyclic



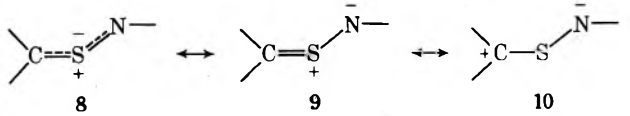
1 **2** **3**

opening of thiaziranes (**4**) would also constitute synthesis of this heterocumulene, although the only reaction in which **4** was possibly an intermediate provided no products which could be rationalized as derived from a thione S-imide.[5] In an electronic sense perturbed examples of this grouping appear in isothiazoles (**5**) and more particularly in thioanthranil (**6**) and 4-aryl-1,3,2-oxathiazolium 5-oxides (**7**).



4 **5** **6** **7**

The stability of thione S-imides would be expected to be dependent on the relative contributions of the canonical structures **8**–**10** with a substituent unperturbed thione S-



8 **9** **10**

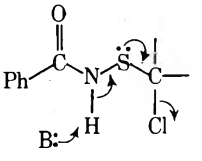
imide charge distribution most closely approximated by structure **9**. We wish to report the details of the synthesis

Table I
Heterocumulenes Containing Tetravalent Sulfur

$R_2C{=}S{=}CR_2$, thione ylides[1]	RN=S=NR, sulfur diimides
$R_2C{=}S{=}NR$, thione S-imides	RN=S=O, N-sulfinylamines
$R_2C{=}S{=}O$, sulfines	O=S=O, sulfur dioxide

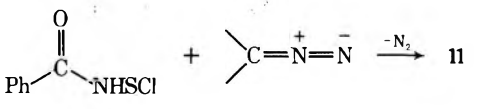
of this new functional group with substitution patterns stabilizing contributor **8**.

An attractive if not challenging synthetic approach to this functional group would focus on a base-promoted 1,3-dehydrohalogenation of a suitably substituted sulfenamide **11** as an ultimate step. A synthetically flexible reaction



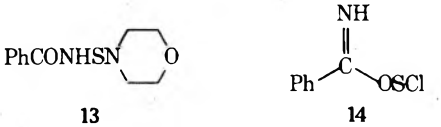
11

envisioned for the production of **11** would involve **12** and a diazo compound, a step for which considerable precedent



12

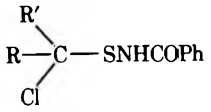
may be found.[6] The reaction of N-(trimethylsilyl)benzamide[7] with sulfur dichloride in ether–pentane solution at 0° gave in good yield **12**, mp 105–108° dec, whose 1670-cm^{-1} (C=O) absorption in the infrared and reaction with morpholine to produce[8] **13** substantiates the assigned structure rather than the alternative **14**. Treatment of **12**



13 **14**

with diphenyldiazomethane in THF solution at −30° afforded the rather unstable N-benzoylchlorodiphenylmethanesulfenamide (**15a**), mp 114–117 dec, in low yield. Triethylamine reacted rapidly with **15** in THF solution at −78° without visible formation of a colored intermediate to yield 1 equiv of triethylamine hydrochloride and 2,2,5-tri-

phenyl-1,3,4-oxathiazole (**16a**), mp 118–120°, which displayed infrared absorptions at 1605 (C=N) and 1575 cm^{-1}



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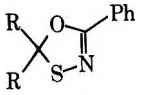
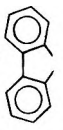


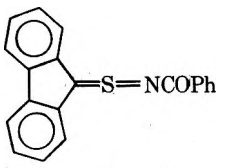
16

a, R, R′ = Ph

b, R, R′ = 

c, R = H; R′ = CO_2Et

(C=C) along with a mass spectrum which was most informative with fragment ions at *m/e* 182 ($C_{13}H_{10}O^+$) and 103 ($C_7H_5N^+$). Since all attempts to trap an intermediate thione *S*-imide during the dehydrohalogenation of **15a** failed, attention was directed toward stabilization by a fluorenyl substituent. In this case the required chlorosulfenamide **15b**, mp 114–116° dec, was obtained in good yield by an analogous reaction with diazofluorene and when submitted to the action of triethylamine in THF at −78° gave a deep red (λ_{max} 484 nm) solution of 9-fluorenethione *S*-benzoylimide (**17**).

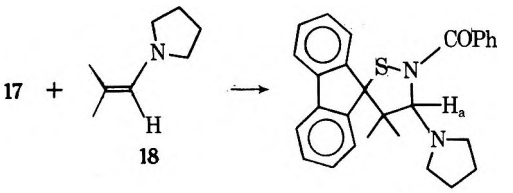


17

Unlike sulfines[9] (R_2CSO), passage of anhydrous HCl into the THF solution of **17** at −78° resulted in the rapid reformation of precursor **15b**. When a solution of **17** was allowed to warm to *ca.* −30° the color was discharged and the electrocyclic closure product, 5-phenylspiro[fluorene-9,2′-[1′,3′,4′]oxathiazole] (**16b**), mp 100–103° dec, was isolated. The latter product had an infrared spectrum similar to that of **16a** with mass spectral ions at *m/e* 196 ($C_{13}H_8S^+$), 180 ($C_{13}H_8O^+$), and 103 ($C_7H_5N^+$). Furthermore, on standing at 30° for 14 days **16b** decomposed to give fluorenone, benzonitrile, and sulfur.[10] Although **17** underwent cyclization at temperatures greater than −30° in solution, it could be isolated as metastable crystals at room temperature which underwent instantaneous transformation to **16b** upon the slightest amount of mechanical deformation.

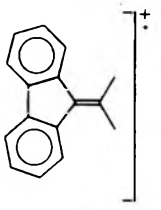
With substantial evidence at hand that the intermediate from the dehydrohalogenation was 9-fluorenethione *S*-benzoylimide, attention was turned to a search for cycloaddition reactions. Initial studies revealed that the cycloadditive reactivity of **17** at 30° for the capture of electrophiles such as phenyldiazomethane or diphenyl ketene, and nucleophiles such as vinyl ethers and ketene acetals, was not sufficient to compete against internal cyclization. However, **17** reacted rapidly with the more nucleophilic alkenes, enamine and ynamines, at −78°.

When **17**, generated *in situ* at −78° in a THF solution, was treated with *N*-isobutenylpyrrolidine (**18**) the solution decolorized immediately and there was obtained 2′-benzoyl-3′-pyrrolidine-4′,4′-dimethylspiro[fluorene-9,5′-[1′,2′]isothiazolidine] (**19**) as the only isolable product. The nmr spectrum of **19** displayed an aromatic multiplet at δ 7.47 (13 H), a singlet for H_a at δ 5.62 (1 H), and nonequivalent methyl singlets at δ 1.66 (3 H) and 0.58 (3 H) as well as pyrrolidine ring multiplets at δ 3.23 (4 H). The infrared



18 19

spectrum contained a tertiary amide C=O absorption at 1635 cm^{-1} and the mass spectrum revealed a molecular ion at *m/e* 440 and fragments at *m/e* 206 and 202 corresponding to **20** and **21** and the major ions resulted from cleavage of the ring system into its chemical precursors (*m/e* 315 and 125).



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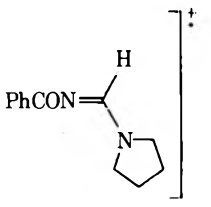
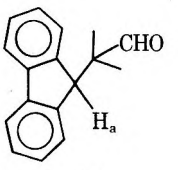


21

The possibility of **19** having a structure analogous to **37** or **38** may be discounted, since the ultraviolet spectrum of the adduct is not characteristic of fluorenyl sulfonium ylides.[13] A structure analogous to **36** is improbable, since the C=O absorption for acyl iminosulfuranes has been observed at 1600–1540 cm^{-1} in the infrared.[14] Since the C=N linkage may show infrared absorptions in the range 1690–1630 cm^{-1}, spectral data do not adequately distinguish between a five-membered ring adduct and a seven-membered ring structure such as **40**; however, sufficient chemical evidence was also obtained to support an isothiazolidine ring structure. Hydrolysis of **19** in 2 *N* sodium hydroxide afforded 9-isobutyraldehydefluorene (**22**) and benzamide as



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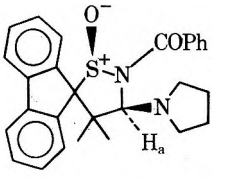
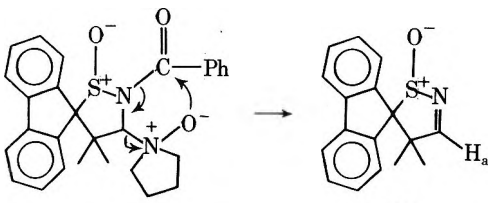


23

the only isolable products and the structure of the former is based on observed nmr singlets for the aldehydic proton at δ 9.78, for H_a at δ 6.83, and for the methyl groups at δ 1.01 while the infrared spectrum displayed an aldehyde C=O absorption at 1725 cm^{-1}. Oxidation of **19** with 1 equiv of *m*-chloroperbenzoic acid provided 2′-benzoyl-3′-pyrrolidine-4′,4′-dimethylspiro[fluorene-9,5′-[1′,2′]isothiazolidine] 1′-oxide (**23**) in moderate yield. The mass spectrum of **23** was consistent with the structure shown and the infrared spectrum contained a C=O absorption at 1665 cm^{-1} and a strong S=O absorption at 1290 cm^{-1}. The nmr spectrum was similar to that of **19** except for a downfield shift of 0.32 ppm for H_a, 0.19 ppm for the lower field methyl, and 0.08 ppm for the higher field methyl. The addition of excess *m*-chloroperbenzoic acid resulted in the formation of 4′,4′-dimethylspiro[fluorene-9,5′-[1′,2′]dihydroisothiazole] 1′-oxide (**24**) in 64% yield. This oxidative elimination may be the result of decomposition of the intermediate *N*-oxide **25**, as shown.

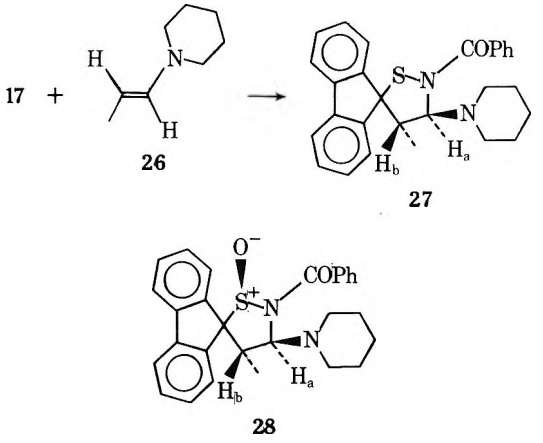
The nmr spectrum of **24** displayed a multiplet at δ 7.46 (9 H) composed of the fluorenyl ring protons and H_a and, in addition, singlets at δ 1.67 (3 H) and 0.96 (3 H) accounted for the nonequivalent methyl groups. The infrared spec-



25 24

trum displayed a C=N stretching absorption at 1595 cm^{-1} and the mass spectrum exhibited a molecular ion at *m/e* 281 with principal fragments at *m/e* 233 ($C_{17}H_{15}N^+$) and 206 ($C_{16}H_{14}^+$). The oxidative elimination to give **31** confirms the structure assigned to **19** and **23,** since the only other possible adduct capable of this elimination mechanism would have a structure analogous to **37.**

Although the reaction of heterocumulenes with enamines possessing β hydrogens often leads to acyclic adducts, treatment of **17** with *N*-propenylpiperidine (**26**) at −78° resulted in the exclusive formation of 2′-benzoyl-3′-piperidine-4′-methylspiro[fluorene-9,5′-[1′,2′]isothiazolidine] (**27**) in good yield. The nmr spectrum of **27** displayed signals centered at δ 7.46 (m, 13 H), 5.60 (d, 1 H, J = 8 Hz, H_a), 3.17 [m, 5 H, H_b and $(CH_2)_2N$], 1.59 [s, 6 H, $(CH_2)_3$], and 0.56 (d, 3 H, J = 6.5 Hz, CH_3). Although **27** is tentatively assigned as having a trans relationship for H_a and H_b, the possibility cannot be eliminated that it actually possesses cis stereochemistry, since the coupling constant of H_a, H_b is intermediate in the ranges expected for cis or trans isomers of flexible five-membered rings. The infrared spectrum of **27** was similar to that of **19,** having a C=O stretching absorption at 1637 cm^{-1}, and the mass spectrum exhibited a molecular ion at *m/e* 440.

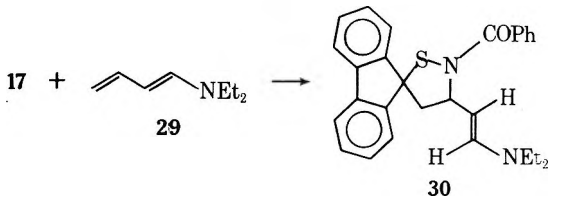


26 27

28

Compound **27** was also readily oxidized with *m*-chloroperbenzoic acid to 2′-benzoyl-3′-piperidine-4′-methylspiro-[fluorene-9,5′-[1′,2′]isothiazolidine] 1′-oxide (**28**), albeit in lower yield than the oxidation of **19** to **23.** The infrared spectrum of **28** was similar to that of **23,** containing C=O and S=O stretching absorptions at 1665 and 1295 cm^{-1}, respectively. The nmr spectrum displayed signals at δ 7.60 (m, 13 H, aromatic), 5.78 (d, 1 H, J = 8.5 Hz, H_a), 3.32 [m, 5 H, H_b and $(CH_2)_2N$], 1.55 [s, 6 H, $(CH_2)_3$], and 0.77 (d, 3 H, J = 7 Hz, CH_3). The cis relationship of the oxide function to H_b is tentatively assigned based on the observed nmr downfield shift of H_b and the H_a, H_b coupling constant.

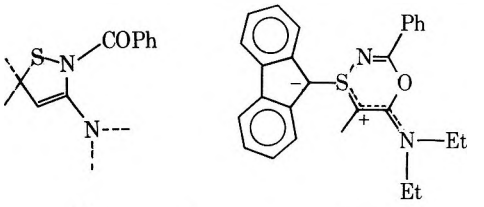
In an attempt to determine if **17** would behave as a dienophile in a manner similar to sulfines,[15] **17** was treated with 2,3-dimethylbutadiene, but no reaction occurred below −30° and only the oxathiazole **16b** was isolated. The thione *S*-imide did react rapidly at −78° with 1-diethylaminobutadiene (**29**); however, no 1,4 cycloadducts were detected. The only product was 2-benzoyl-3′-(*trans*-*N*-ethenyldiethylamino)spiro[fluorene - 9,5′ - [1′,2′]isothiazolidine] (**30**), which was isolated in 37% yield. Since attempts



29 30

to purify **30** for complete analysis were unsuccessful, the structure assigned is based primarily on its nmr and ir spectrum (see Experimental Section). Furthermore, the ultraviolet absorption spectrum of **30** was very similar to those of adducts **19** and **27.**

Based on the isothiazolidine adducts obtained from the reaction of **17** with enamines, the reaction with ynamines might possibly yield dihydroisothiazoles such as **31.** However, when 1-(diethylamino)-1-propyne was added to a THF solution of **17** at −78°, 2-phenyl-4-fluorenylidine-5-methyl-6-diethylamino-1,4,3-oxathiazine (**32**) was the only adduct isolated. The fluorenyl ylide **32** was a yellow, crys-



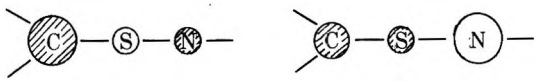
31 32

talline solid which decomposed in solution at room temperature or at the melting point (125–126°). The ultraviolet spectrum was similar to that of 9-dimethylsulfonium fluorenylidine,[16] displaying λ_{max} (ϵ) at 242 (20,500), 253 (25,900), 261 (33,600), 278 (12,500), 327 (9450), 311 (9770), and 375 nm (5800). The nmr spectrum contained aromatic protons centered at δ 7.58 (m, 13 H), a methyl singlet at δ 2.72 (3 H), and nonequivalent *N*-ethyl groups as quartets at δ 3.75 (2 H, J = 7.3 Hz) and 3.60 (2 H, J = 7.3 Hz) and triplets at 1.54 (3 H, J = 7.3 Hz) and 1.06 (3 H, J = 7.3 Hz). The infrared spectrum of **32** was transparent between 1600 and 2900 cm^{-1} and had C=C and C=N absorptions at 1590, 1525, and 1500 cm^{-1} and suggests that the charge-delocalized structure **32** is the best representation of the structure, since no characteristic enamine C=C absorption between 1630 and 1660 cm^{-1} appears. Upon thermal decomposition **32** affords benzonitrile, a trace of difluorenylidine, and a plethora of other products which have not been identified.

A mechanistic rationalization of the formation of such diverse cycloadducts from **17** should depend upon the following considerations. In the family of sulfur 1,3 dipoles ($X=S^+-Y^-$), those with appropriate stabilizing substituents would be expected to have a lower order of electrophilic reactivity toward alkene cycloaddends than other dipoles where the central atom has a higher electronegativity. The electrophilic center will be sulfur in the case of electron-withdrawing substitution at both termini but a considerable amount of the sulfur positive change would undergo leakage onto carbon if this center were substituted with electron-donating substituents (*cf.* **9** *vs.* **10**). Electron-rich but very asymmetric cycloaddends in nonconcerted charge-controlled[17] addition reactions to such thione *S*-imides should establish initial bond formation to sulfur in the former case and possibly carbon in the latter case. This initial sulfur–cycloaddend union is also enhanced by the large sul-

fur (but not as large as carbon, see (Chart I) LUMO coefficient in that frontier orbital (with electron-rich dipolarophiles such LUMO control[18] of the dipole is expected).

Chart I
Estimated Frontier Orbitals of R_2CSNR



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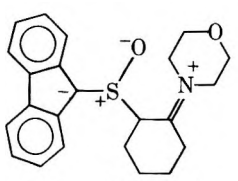
The observed formation of **33** from fluorenethione *S*-oxide and *N*-cyclohexenylmorpholine supports this argument, as also observed in the case of sulfines.[19] Therefore it



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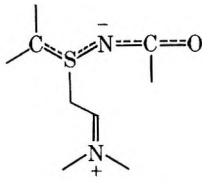

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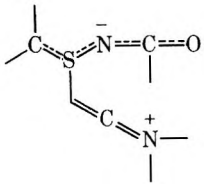
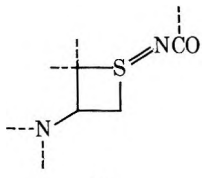


35

may be concluded that nonconcerted cycloaddition reactions of *N*-acyl thione *S*-imides with electron-rich alkenes (NC=C) or alkynes (NC≡C) which proceed *via* the dipolar intermediate, **34** or **35**, would provide ultimate cycloadducts such as **36, 37,** or **38** (or as the dehydro equivalent).



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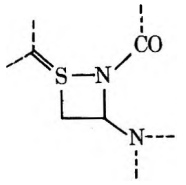

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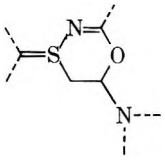

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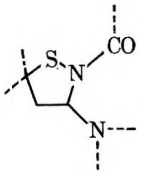

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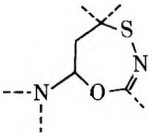


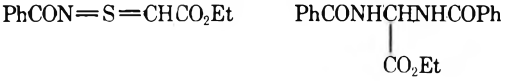
40

For concerted cycloaddition reactions of acyl thione *S*-imides with electronically asymmetric alkenes the $[_\pi 2 + _\pi 4]$ combinations (**38** and **39**) would be expected. Finally, the formation of adduct **40** requires antarafacial addition in a concerted reaction and is electrostatically unfavorable in the initial step of a charge-controlled nonconcerted reaction.

At first inspection it would appear that these two types of cycloadducts obtained represent the two symmetry allowed [2 + 4] possibilities from a concerted cycloaddition. However, it is difficult to reconcile the remarkably different pathway regioselectivity demonstrated by an enamine *vs.* an ynamine. Orbital control of such concerted cycloadditions requires that the interaction energy (inversely proportional to the LUMO–HOMO cycloaddends energy difference) be minimized and the interacting frontier orbitals have phase-compatible and large coefficients for union. With dipole LUMO control[18] expected in this case a cycloadduct of the type **39** should be preferred and formed from enamines with a smaller interaction energy than from ynamines (the HO orbitals of alkynes are lower in energy than those of the corresponding alkenes). However, the interaction energy is also dependent upon coulombic terms and from such charge-separation considerations (charge control) the concerted formation of cycloadducts such as **38** would be favored. The course followed by the two regioisomeric cycloadditions here may reflect the interplay between orbital and charge control from minor electronic variations in one cycloaddend.

Finally, a nonconcerted cycloaddition mechanism involving the intermediate **34** (for enamines) or **35** (for ynamines) might be involved. The smaller S–C–C angle (owing to a central carbon atom of higher hybridization state) in the case of **34** than that of **35** permits closure of **34** to **19** or **27** while **35** is restricted to the less strained cyclization to **32.** A Stevens rearrangement of **37** involving either a radical[20] or polar intermediate[21] would yield the isolated isothiazolidines.[22] Further expansion of **32** to ring systems such as **40** by such a mechanism is energetically blocked by the increased strength of the C–S ring bond due to the electron-releasing amino substituent.

To extend this synthetic route to other thione *S*-imides, **12** was treated with ethyl diazoacetate in THF at 30°, which afforded in low yield the unstable sulfenamide, **15c,** mp 111–116° dec. Dehydrohalogenation of **15c** with triethylamine in THF led to the formation of a colored intermediate (probably the thione *S*-imide **41**) with a comparably long life-time even at 30°. However, attempts to isolate **41**



41 **42**

by removal of the solvent led to a complex mixture of products only one of which was obtained crystalline and had spectral and analytical characteristics which suggest structure **42.**

Studies on the synthesis of thione *S*-imides *via* the intermediary reaction of **12** with other diazo compounds met only with disappointments. Diazo functions substituted with strong electron-withdrawing groups (such as diazodimethylmalonate and diazoanthrone) failed to react with **12** and the reaction of more nucleophilic 9-diazoxanthone with **12** resulted in the formation of benzonitrile, *N,N'*-thiobisbenzamide, and 9-xanthone azine.

Experimental Section[23]

***N*-(Trimethylsilyl)benzamide.** *N*-(Trimethylsilyl)benzamide was prepared by modification of the procedure of Derkach and Smetankina.[7] Freshly distilled (bp 58–59°) chlorotrimethylsilane (21.7 g, 0.20 mol) was added dropwise over a period of 1 hr under nitrogen to 24.2 g (0.20 mol) of benzamide and 22.3 g (0.22 mol) of triethylamine in 150 ml of anhydrous ether and 75 ml of anhydrous THF. When the addition was complete, stirring was continued for 2 hr and then the precipitated triethylamine hydrochloride was removed by filtration. After the precipitate was washed with two 50-ml portions of anhydrous ether the combined filtrate was concentrated with a rotary evaporator under reduced pressure to a colorless oil. Vigorous stirring of the oil with dry hexane caused the crystallization of 38 g (98%) of *N*-(trimethylsilyl)benzamide, mp 62–65° (lit.[7] mp 63–65°).

Benzamide-*N*-sulfenyl Chloride (12). *N*-(Trimethylsilyl)-benzamide (38 g, 0.196 mol) in 175 ml of anhydrous ether was added dropwise under nitrogen over a 3-hr period to 30.3 g (0.294 mol) of freshly distilled sulfur dichloride in 35 ml of anhydrous ether and 50 ml of pentane maintained at 0°. After about one-third had been added, a yellow precipitate began to separate from the reaction mixture. When the addition was complete, the reac-

tion mixture was stirred at 0° for an additional 6 hr. Pentane (175 ml) was then added and the reaction mixture was cooled to −30° for 1 hr. The precipitate which had separated from the solution was collected by filtration under a nitrogen atmosphere and dried under reduced pressure at 0° to yield 30.9 g (84%) of benzamide-*N*-sulfenyl chloride (**12**) as bright yellow microneedles: mp 105–108° dec; λ_{max} (THF) 209 nm (ϵ 7070), 237 (12,900), and 350 (140); ir ($CHCl_3$) 3200 (NH) and 1670 cm^{-1} (C=O); nmr (DMSO-d_6) δ 11.66 (s, 1 H), 7.97 (m, 2 H), and 7.50 (m, 3 H).

Anal. Calcd for C_7H_6NOSCl: C, 44.80; H, 3.22; N, 7.46; S, 17.09. Found: C, 44.68 H, 3.29; N, 7.52; S, 17.13.

Compound **12** has been kept for 3 months without appreciable deterioration if it was tightly sealed under an inert atmosphere and stored below 0°.

***N,N'*-Thiobenzamidemorpholine (13).** Benzamide-*N*-sulfenyl chloride (3 g, 0.016 mol) in 10 ml of anhydrous THF was added dropwise over a period of 20 min under nitrogen to 2.8 g (0.032 mol) of morpholine in 25 ml of THF maintained at −78°. When the addition was complete, stirring was continued for an additional 1 hr. The precipitated morpholine hydrochloride (1.94 g, 98%) was removed by filtration and the filtrate was concentrated with a rotary evaporator under reduced pressure to a yellow oil. The oil was dissolved in a minimum volume of hot benzene–hexane; and upon cooling, 2.08 g of *N,N'*-thiobenzamidemorpholine (**13**) separated as colorless plates. When the mother liquor was concentrated to half volume and allowed to stand for 12 hr an additional 0.175 g of **13** crystallized to give a total yield of 2.25 g (59%): mp 117–118°; ir ($CHCl_3$) 3410 and 3300 (NH) and 1680 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.12 (s, 1 H), 7.81 and 7.43 (m, 5 H), 3.62 (m, 4 H), and 3.17 (m, 4 H); mass spectrum (70 eV) *m/e* (rel intensity) 238 (33), 121 (73), 105 (100), 86 (44).

Anal. Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76; S, 13.45. Found: C, 55.52; H, 5.98; N, 11.73; S, 13.35.

Compound **13** was also prepared by the dropwise addition of 10 g (0.065 mol) of morpholine-*N*-sulfenyl chloride under nitrogen to 9.3 g (0.065 mol) of the sodium salt of benzamide (prepared by the addition of benzamide to an equimolar amount of sodium hydride in refluxing DME) suspended in 150 ml of DME. When the addition was complete, the solution was filtered and the filtrate was concentrated with a rotary evaporator under reduced pressure to a yellow powder. Recrystallization from benzene–hexane gave 7.1 g (46%) of **13**, mp 117–118°, both pure and when admixed with the above product.

***N,N'*-Thiobenzamideaniline.** Benzamide-*N*-sulfenyl chloride (2 g, 0.011 mol) in 15 ml of anhydrous THF was added dropwise over a period of 45 min under nitrogen to 2.05 g (0.022 mol) of aniline in 15 ml of THF at −78°. When the addition was complete the reaction mixture was stirred for an additional 1 hr, and was then warmed to 30°. The precipitated aniline hydrochloride (1.30 g, 92%) was removed by filtration and the filtrate was concentrated with a rotary evaporator under reduced pressure to a dark residue. The residue was dissolved in ether and decolorized with Norit, and the ether was removed under reduced pressure to give a colorless powder. Two crystallization from benzene–hexane gave 1.43 g (54%) of *N,N'*-thiobenzamideaniline as colorless needles: mp 148–150° dec; ir ($CHCl_3$) 3490 (broad, NH), 1675 (C=O), and 1600 cm^{-1} (C=C); nmr (DMSO-d_6) δ 10.12 (s, 1 H), 8.39 (s, 1 H), 7.93 (m, 2 H), and 7.15 (m, 8 H); mass spectrum (70 eV) *m/e* (rel intensity) 244 (4), 121 (77), 105 (100), 93 (64).

Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.90; H, 4.95; N, 11.47; S, 13.13. Found: C, 63.71; H, 5.02; N, 11.38; S, 13.22.

***N*-Benzoylchlorodiphenylmethanesulfenamide (15a).** Diphenyldiazomethane[24] (1.03 g, 0.0053 mol) in 10 ml of anhydrous THF was added dropwise over a period of 30 min under nitrogen to 1.0 g (0.0053 mol) of benzamide-*N*-sulfenyl chloride in 25 ml of THF maintained at −30°. When the evolution of nitrogen had ceased (*ca.* 10 min after the addition was complete) the solvent was removed with a rotary evaporator under reduced pressure. The resulting residue was dissolved in a minimum volume of anhydrous ether and cooled to −30°. After standing overnight, 0.178 g (11%) of *N*-benzoylchlorodiphenylmethanesulfenamide (**15a**) had separated as light yellow needles: mp 114–117° dec; ir ($CHCl_3$) 3410 (NH) and 1675 cm^{-1} (C=O); nmr (acetone-d_6) δ 7.34 (m, 6 H) and 6.83 (m, 10 H).

Compound **15a** rapidly decomposed upon exposure to moisture or if allowed to stand at room temperature. Noticeable decomposition had also occurred after 3 days at −30°. The instability of **15a** precluded elemental analysis.

Treatment of 15a with Triethylamine. Isolation of 2,2,5-Triphenyl-1,3,4-oxathiazole (16a). Triethylamine (0.59 g, 0.0053 mol) was added in one portion to 1.87 g (0.0053 mol) of **15a** under a nitrogen atmosphere at −78°. Although a precipitate of triethylamine hydrochloride formed immediately, no color changes were observed. After warming to 30° the triethylamine hydrochloride was removed by filtration and the filtrate was concentrated with a rotary evaporator under reduced pressure. The resulting residue was crystallized from ether–hexane to give 0.52 g (31%) of 2,2,5-triphenyl-1,3,4-oxathiazole (**16a**) as colorless plates: mp 118–120°; ir ($CHCl_3$) 1605 (C=N) and 1575 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.98 (m, 2 H) and 7.38 (m, 13 H); mass spectrum (70 eV) *m/e* (rel intensity) 182 (9.2), 103 (100).

Anal. Calcd for $C_{20}H_{15}NOS$: C, 75,68; N, 4.76; N, 4.41; S, 10.10. Found: C, 75.53; H, 4.81; N, 4.45; S, 9.95.

Attempted Trapping of Benzophenthione *S*-Benzoylimide. A THF solution (35 ml) of 1.87 g (0.0053 mol) of **15a** and 0.664 g (0.0053 mol) of *N*-isobutenylpyrrolidine maintained at −78° under a nitrogen atmosphere was treated in one portion with 0.59 g (0.0053 mol) of triethylamine. After warming to 30°, the precipitated triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated with a rotary evaporator under reduced pressure. An infrared spectrum of the resulting residue revealed that the only product present was 2,2,5-triphenyl-1,3,4-oxathiazole (**16a**).

***N*-Benzoyl-9-chloro-9-fluorenesulfenamide (15b).** 9-Diazofluorene[25] (3.06 g, 0.016 mol) in 20 ml of anhydrous THF was added dropwise over a period of 1 hr under nitrogen to 3.0 (0.015 mol) of benzamide-*N*-sulfenyl chloride in 50 ml of THF maintained at −30°. When the addition was complete, stirring was continued until the evolution of nitrogen had ceased (*ca.* 15 min), and then the THF was removed with a rotary evaporator under reduced pressure. The resulting residue was dissolved in anhydrous ether and cooled to −30°. After 4 hr the light yellow crystals that had separated from the solution were collected. Washing the crystals with three 25-ml portions of anhydrous ether gave 4.28 g (76%) of *N*-benzoyl-9-chloro-9-fluorenesulfenamide (**15b**) as colorless needles: mp 114–116° dec; ir (KBr) 3280 (NH) and 1660 cm^{-1} (C=O); nmr (DMSO-d_6) δ 8.10 (s, 1 H) and 7.48 (m, 13 H).

Anal. Calcd for $C_{20}H_{14}NOSCl$: C, 68.27; H, 4.01; N, 3.98; S, 9.11. Found: C, 68.36; H, 4.10; N, 3.94; S, 9.19.

Although **15b** decomposes upon exposure to moisture or if allowed to stand over a 2-day period at 30°, it has been stored for up to 2 months without appreciable decomposition at −30°.

Treatment of 15b with Triethylamine. Isolation of 5-Phenylspiro[fluorene-9,2'-[1',3',4']oxathiazole] (16b). Triethylamine (0.283 g, 0.0028 mol) was added in one portion to 1.0 g (0.0028 mol) of **15b** maintained at −78° under nitrogen. The precipitated triethylamine hydrochloride was removed from the resulting red reaction mixture by rapid filtration at −78°. The colored filtrate was then allowed to warm slowly to 30° and at *ca.* −30° the solution decolorized. The THF was removed with a rotary evaporator under reduced pressure, and the resulting residue was recrystallized from ether–hexane at −30° to give 0.0283 g (46%) of 5'-phenylspiro[fluorene-9,2'-[1',3',4']oxathiazole] (**16b**) as colorless needles, mp 100–103° dec. An analytical sample was prepared by a second recrystallization from ether–hexane: mp 102–103° dec; uv max (dioxane) 213 nm (ϵ 34,000), 230 (50,200), 237 (46,400), 278 (17,800), 287 (shoulder, 16,200), and 306 (shoulder, 9670); ir ($CHCl_3$) 1605 (C=N) and 1575 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.58 (m, 13 H); mass spectrum (70 eV) *m/e* (rel intensity) 315 (20), 196 (9.2), 180 (100), 135 (32), 103 (19).

Anal. Calcd for $C_{20}H_{13}NOS$: C, 76.16; H, 4.15; N, 4.44; S, 10.17. Found: C, 76.06; H, 4.22; N, 4.38; S, 10.24.

Upon standing at room temperature over a 2-week period **16b** decomposed to give benzonitrile, 9-fluorenone, and sulfur and the former two components were separated by column chromatography over Florisil and identified by comparison with authentic samples.

Isolation of Fluorenethione *S*-Benzoylimide (17). Compound **15b** (0.350 g) was dissolved in 10 ml of anhydrous THF and cooled to −78° under a nitrogen atmosphere. Triethylamine (0.110) was added by syringe and the solution was filtered under nitrogen into a receiving flask which was also at −78°. After an aliquot was removed for uv analysis, 15 ml of dry hexane was added to the red filtrate, causing the precipitation of fluorenethione *S*-benzoylimide (**17**) as red needles. The crystals were collected at −78° under a nitrogen atmosphere and allowed to warm slowly to 30°. Although the crystals appeared to be stable at this temperature, any mechanical deformation resulted in the instantaneous transformation to 5'-phenylspiro[fluorene-9,2'-[1',3',4']oxathiazole] (**16b**).

Reaction of 17 with Anhydrous HCl. An anhydrous THF solution (35 ml) of fluorenethione *S*-benzoylimide (**17**), which had been prepared *in situ* from 3.16 g (0.009 mol) of **15b** and 0.91 g (0.009 mol) of triethylamine at −78°, was treated with a slow stream of anhydrous HCl until the red color of **17** had dissipated. After warming to 30° the precipitated triethylamine hydrochloride was removed by filtration and the filtrate was concentrated with a rotary evaporater under reduced pressure. The resulting residue was recrystallized from anhydrous ether to give 2.6 g (82%) of *N*-benzoyl-9-chloro-9-fluorenesulfenamide (**15b**), mp 114–116° dec on admixture with an authentic sample.

Reaction of 17 with *N*-Isobutenylpyrrolidine. 9-Diazofluorene[24] (5.11 g, 0.027 mol) in 50 ml of anhydrous THF was added dropwise over a period of 1 hr under nitrogen to 5.0 g (0.027 mol) of benzamide-*N*-sulfenyl chloride in 100 ml of THF maintained at −30°. When the addition was complete and the evolution of nitrogen had ceased, the solution was cooled to −78° and 2.96 g (0.029 mol) of triethylamine was added at once. To the resulting red reaction mixture was added 3.66 g (0.029 mol) of *N*-isobutenylpyrrolidine[26] which caused the solution to decolorize immediately. After warming to room temperature the precipitated triethylamine hydrochloride (3.57 g, 96%) was removed by filtration and the filtrate was concentrated with a rotary evaporator to a brown viscous oil. The crude residue was triturated with 800 ml of anhydrous ether and the ethereal solution was decanted from an insoluble brown tar. The volume of the ether was reduced to 300 ml with a rotary evaporator under reduced pressure and the solution was then allowed to stand at −30°. After 24 hr, 6.60 g of 2′-benzoyl-3′-pyrrolidine-4′,4′-dimethylspiro[fluorene-9,5′-[1′,2′]isothiazolidine] (**19**) was collected as colorless plates. When the mother liquor was concentrated to a volume of 100 ml and allowed to stand at −30°, an additional 0.93 g of **19** crystallized to give a total yield of 7.53 g (64%): mp 185–187° dec; λ_{max} ($CHCl_3$) 228 nm (ϵ 25,300), 265 (15,400), and 310 (2890); ir ($CHCl_3$) 1635 (C=O) and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.47 (m, 4 H), 1.66 (s, 3 H) and 0.58 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 440 (1.2), 315 (65), 206 (10), 202 (8.4), 135 (100), 125 (62).

Anal. Calcd for $C_{29}H_{28}N_2OS$: C, 76.32; H, 6.40; N, 6.36; S, 7.28. Found: C, 76.11; H, 6.59; N, 6.40; S, 7.14.

Hydrolysis of 19. Compound **19** (0.440 g, 0.001 mol) was dissolved in 35 ml of THF and 25 ml of a 2 *N* sodium hydroxide solution. After stirring for 24 hr at 30° the reaction mixture was neutralized with concentrated hydrochloric acid and then extracted with 50 ml of chloroform. The chloroform extract was dried with magnesium sulfate and concentrated with a rotary evaporator under reduced pressure. The resulting residue was dissolved in 25 ml of ether, 10 ml of hexane was added, and the ether was slowly evaporated under reduced pressure until crystallization began. The recrystallizing flask was then allowed to stand at −30°, and after 24 hr, 0.032 g of colorless needles was collected by filtration and subsequently identified as benzamide by mixture melting point with an authentic sample. The filtrate was concentrated with a rotary evaporator under reduced pressure to yield a light yellow oil which upon chromatography on 10 g of florisil using methylene chloride as the eluent afforded a colorless oil which was crystallized from hexane to give colorless needles of 9-isobutyraldehydofluorene (**22**, 0.021 g, 10%): mp 143–146°; ir ($CHCl_3$) 1725 (aldehyde C=O) and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 9.78 (s, 1 H), 7.55 (m, 8 H), 6.83 (s, 1 H), and 1.01 (s, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 236 (2.9), 207 (16), 165 (100); exact mass, 236.118 (calcd. 236.120).

Oxidation of 19 with 1 Equiv of *m*-Chloroperbenzoic Acid. Purified *m*-chloroperbenzoic acid[27] (0.230 g, 0.0013 mol) in 5 ml of methylene chloride was added to 0.605 g (0.0013 mol) of **19** in 10 ml of methylene chloride maintained at 0°. When the addition was complete the reaction mixture was warmed to 30° and stirred for 48 hr. At the end of this period the reaction mixture was cooled to 0° and the precipitated *m*-chlorobenzoic acid was removed by filtration. The filtrate was extracted with 25 ml of a 5% aqueous sodium thiosulfate solution followed by 25 ml of water. The methylene chloride extract was then dried with magnesium sulfate and concentrated with a rotary evaporator under reduced pressure. The resulting residue was dissolved in 35 ml of anhydrous ether, and then 10 ml of hexane was added and the solution was slowly concentrated with a rotary evaporator under reduced pressure. When crystals began to separate from the solution, the flask was removed from the rotary evaporator and allowed to stand at −30°. After 16 hr, 0.320 g (56%) of 2′-benzoyl-3′-pyrrolidine-4′,4′-dimethylspiro-[fluorene-9,5′-[1′,2′]isothiazolidine] 1′-oxide (**23**) was collected as colorless needles: mp 210–213° dec; λ_{max} ($CHCl_3$) 235 nm (ϵ 28,300), 270 (19,300), and 280 (shoulder, 16,200); ir ($CHCl_3$) 1665 (C=O), 1600 (C=C), and 1290 cm^{-1} (S=O); nmr ($CDCl_3$) δ 7.61 (m, 13 H), 5.94 (s, 1 H), 3.31 (m, 4 H), 1.85 (s, 3 H), 1.80 (m, 4 H), and 0.66 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 456 (2.1), 250 (100), 206 (44), 105 (65).

Anal. Calcd for $C_{28}H_{28}N_2O_2S$: C, 73.65; H, 6.18; N, 6.14; S, 7.02. Found: C, 73.54; H, 6.22; N, 6.08; S, 7.07.

Oxidation of 19 with Excess *m*-Chloroperbenzoic Acid. Purified *m*-chloroperbenzoic acid[27] (0.78 g, 0.0045 mol) in 15 ml of methylene chloride was added dropwise over a period of 10 min to 1.0 g (0.002 mol) of **19** in 15 ml of methylene chloride maintained at 0°. When the addition was complete the reaction mixture was warmed to 30°, and after 24 hr, tlc [silica gel, $CHCl_3$–hexane (4:1 v:v)] indicated the presence of unreacted **19**, compound **23**, and a third unknown component. An additional 0.25 g of *m*-chloroperbenzoic acid was added to the reaction mixture and stirring was continued for 72 hr at 30°. At the end of this period the reaction mixture was cooled to 0° and the precipitated *m*-chlorobenzoic acid was removed by filtration. The filtrate was extracted with 25 ml of a 5% aqueous sodium thiosulfate solution, 25 ml of a 10% aqueous sodium bicarbonate solution, and 25 ml of water. The methylene chloride extract was dried with magnesium sulfate and concentrated with a rotary evaporator under reduced pressure. The resulting residue was recrystallized from methylene chloride–hexane, affording 0.362 g (64%) of 4′,4′-dimethylspiro[fluorene-9,5′-[1′,2′]dihydroisothiazole] 1′-oxide (**24**) as colorless microneedles: mp 168–169°; λ_{max} ($CHCl_3$) 241 nm (ϵ 12,800), 272 (15,100), and 282 (shoulder, 12,800); ir ($CHCl_3$) 1595 (C=N) and 1295 cm^{-1} (S=O); nmr ($CDCl_3$) δ 7.46 (m, 9 H), 1.67 (s, 3 H), and 0.96 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 381 (2.1), 280 (6.9), 233 (9.3), 206 (100), 191 (92), 165 (83).

Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.56; H, 5.37; N, 4.98; S, 11.40. Found: C, 72.37; H, 5.41; N, 4.90; S, 11.35.

Reaction of 17 with *N*-Propenylpiperidine. 9-Diazofluorene[25] (2.05 g, 0.011 mol) in 15 ml of anhydrous THF was added dropwise over a period of 1 hr under nitrogen to 2.0 g (0.011 mol) of benzamide-*N*-sulfenyl chloride in 35 ml of THF maintained at −30°. When the addition was complete and the evolution of nitrogen had ceased the solution was cooled to −78° and 1.11 g (0.011 mol) of triethylamine was added at once. To the resulting red reaction mixture was added 1.5 g (0.012 mol) of *N*-propenylpiperidine,[28] which caused the solution to decolorize immediately. After warming to 30°, the precipitated triethylamine hydrochloride (1.51 g, 99%) was removed by filtration and the filtrate was concentrated with a rotary evaporater under reduced pressure. After the last traces of solvent had been removed, an nmr of the residue revealed that only the trans isomer of the adduct was present. The residue was dissolved in 200 ml of anhydrous ether, and the solution was clarified by filtering through a Celite pad. The volume of the ether was reduced with a rotary evaporator under reduced pressure to *ca.* 125 ml and the solution was then allowed to stand at −30°. After 24 hr, 3.15 g of 2′-benzoyl-3′-piperidine-4′-methylspiro[fluorene-9,5′-[1′,2′]isothiazolidine] (**27**) was collected as colorless plates. When the mother liquor was concentrated to a volume of *ca.* 50 ml, an additional 0.325 g of **27** was obtained to give a total yield of 3.47 g (71%): mp 159–161° dec; λ_{max} ($CHCl_3$) 242 nm (ϵ 28,800), 263 (16,600), and 310 (3000); ir ($CHCl_3$) 1637 (C=O) and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.46 (m, 13 H), 5.60 (d, 1 H, J = 8 Hz), 3.17 (m, 5 H); mass spectrum (70 eV) *m/e* (rel intensity) 440 (1.3), 287 (46), 192 (35), 165 (30), 105, (100), 84 (38).

Anal. Calcd for $C_{28}H_{28}N_2OS$: C, 76.32; H, 6.40; N, 6.36; S, 7.28. Found: C, 76.28; H, 6.47; N, 6.33; S, 7.33.

Oxidation of 27 with *m*-Chloroperbenzoic Acid. Purified *m*-chloroperbenzoic acid[27] (0.160 g, 0.0009 mol) in 10 ml of methylene chloride was added dropwise over a period of 20 min to 0.410 g (0.0009 mol) of **27** in 15 ml of methylene chloride maintained at 0°. When the addition was complete, the solution was stirred at 0° for 24 hr. At the end of this period, the reaction mixture was diluted to a volume of 50 ml with methylene chloride and extracted with 50 ml of a 10% aqueous sodium thiosulfate solution, 50 ml of a 10% aqueous sodium bicarbonate solution, and 50 ml of water. The methylene chloride extract was dried with magnesium sulfate and concentrated with a rotary evaporator under reduced pressure. After attempts to crystallize the resulting residue were unsuccessful it was chromatographed on 10 g of Florisil. Eluting with hexane–methylene chloride (2:1 v:v) afforded 0.140 g (34%) of 2′-benzoyl-3′-piperidine-4′-methylspiro[fluorene-9,5′-[1′,2′]isothiazolidine] 1′-oxide (**28**), mp 206–212° dec. An analytical sample was prepared by recrystallization from ether–hexane to give **28** as colorless rods: mp 218–219° dec; λ_{max} ($CHCl_3$) 247 nm (ϵ 18,000), 274

(12,400), and 284 (shoulder, 10,700); ir ($CHCl_3$) 1665 (C=O), 1600 (C=C), and 1295 cm^{-1} (S=O); nmr ($CDCl_3$) δ 7.60 (m, 13 H), 5.78 (d, 1 H, J = 8.5 Hz), 3.32 (m, 5 H), 1.55 (s, 6 H), and 0.77 (d, 3 H, J = 7 Hz); mass spectrum (70 eV) m/e (rel intensity) 456 (1.3), 408 (4.2), 289 (97), 274 (100), 192 (42), 124 (61), 84 (26).

Anal. Calcd for $C_{28}H_{28}N_2O_2S$: C, 73.65; H, 6.18; N, 6.14; S, 7.02. Found: C, 73.51; H, 6.20; N, 6.08; S, 7.14.

Reaction of 17 with 1-Diethylaminobutadiene. 9-Diazofluorene[25] (1.05 g, 0.011 mol) in 15 ml of anhydrous THF was added dropwise over a period of 1 hr under nitrogen to 2.0 g (0.011 mol) of benzamide-*N*-sulfenyl chloride in 35 ml of THF maintained at −30°. When the addition was complete and the evolution of nitrogen had ceased, the solution was cooled to −78° and 1.11 g (0.011 mol) of triethylamine was added at once. To the resulting red reaction mixture was added 1.40 g (0.011 mol) of 1-diethylaminobutadiene,[29] which caused the solution to decolorize immediately. After warming to 30°, the precipitated triethylamine hydrochloride (1.41 g, 92%) was removed by filtration and the filtrate was concentrated with a rotary evaporator under reduced pressure. The resulting dark brown residue was triturated with 250 ml of anhydrous ether. The ethereal solution was decolorized with Norit and then it was concentrated on a rotary evaporator under reduced pressure to a volume of *ca.* 75 ml. After standing at −30° for 16 hr, 1.79 g (36%) of 2′-benzoyl-3′-(*trans*-*N*-ethenyldiethylamino)spiro-[fluorene-9,5′-[1′,2′]isothiazolidine] (**30**) had crystallized from the solution as colorless plates: mp 123–124° dec; λ_{max} ($CHCl_3$) 247 nm (ϵ 18,500), 264 (19,100), and 311 (4410); ir ($CHCl_3$) δ 7.51 (m, 13 H), 6.51 (d, 1 H, J = 13.5 Hz), 5.70 (m, 1 H, J = 8 Hz), 4.42 (d of d, 1 H, $J_{b,d}$ = 13.5, $J_{d,c}$ = 5.5 Hz,) 3.07 (q, 4 H, J = 7.5 Hz), 2.92 (m, 2 H), and 1.11 (t, 6 H, J = 7.5 Hz).

Reaction of 17 with 1-(Diethylamino)-1-propyne. 9-Diazofluorene[25] (2.05 g, 0.011 mol) in 15 ml of anhydrous THF was added dropwise over a period of 1 hr under nitrogen to 2.0 g (0.011 mol) of benzamide-*N*-sulfenyl chloride in 35 ml of THF maintained at −30°. When the addition was complete and the evolution of nitrogen had ceased, the solution was cooled to −78° and 1.11 g (0.011 mol) of triethylamine was added. To the resulting red reaction mixture was added 1.22 g (0.011 mol) of 1-(diethylamino)-1-propyne . Within 5 min the solution had become orange and it was allowed to warm to room temperature. A yellow precipitate was collected by filtration and was found to weigh 0.651 g greater than the theoretical amount of triethylamine hydrochloride. The filtrate was concentrated with a rotary evaporator under reduced pressure to yield a brown oil. Attempts to obtain a crystalline product from the oil were unsuccessful; however, distillation of the oil in a Hickmann still (bath temperature, 50°, 3 mm) afforded a colorless liquid which was identified as benzonitrile by infrared spectral comparison with an authentic sample.

An nmr spectrum of the yellow precipitate indicated the presence of triethylamine hydrochloride and a 1:1 adduct of **17** and 1-(diethylamino)-1-propyne. The precipitate was washed with 100 ml of water and 0.398 g of an insoluble yellow-orange powder, mp 121–124° dec, was collected. The adduct was recrystallized by dissolving the powder in a minimum volume of methylene chloride–hexane followed by slowly concentrating the solution with a rotary evaporator under reduced pressure until crystallization began. In this manner, 0.211 g (4.5%) of 2-phenyl-4-fluorenylide-5-methyl-6-diethylamino-1,4,3-oxathiazine (**32**) was collected as yellow needles: mp 125–126° dec; λ_{max} ($CHCl_3$, 0°) 242 nm (ϵ 20,500), 253 (25,900), 261 (33,600), 278 (shoulder, 12,500), 327 (9450), 311 (9770), and 375 (shoulder, 5800); ir (KBr) 1590, 1525, and 1500 cm^{-1} (C=C and C=N); nmr ($CDCl_3$, −30°) δ 7.58 (m, 13 H), 3.75 (q, 2 H, J = 7.3 Hz), 2.72 (s, 3 H), 1.54 (t, 3 H, J = 7.3 Hz), and 1.06 (t, 3 H, J = 7.3 Hz).

Anal. Calcd for $C_{27}H_{26}N_2OS \cdot CH_2Cl_2$: C, 65.75; H, 5.52; N, 5.48; S, 6.26. Found: C, 65.97; H, 5.28; N, 5.23; S, 6.18.

Although **32** was stable in the crystalline state and in solution below 0°, it rapidly decomposed at the melting point or in solution at room temperature. Upon decomposition **32** gave benzonitrile and a trace of difluorenylidene as the only identifiable products.

Reaction of Benzamide-*N*-sulfenyl Chloride with 9-Diazoxanthene. 9-Diazoxanthene[30] (2.0 g, 0.010 mol) in 20 ml of anhydrous THF was added dropwise over a period of 1 hr under nitrogen to 1.80 g 0.010 mol) of benzamide-*n*-sulfenyl chloride in 35 ml of THF maintained at −78°. Rapid evolution of nitrogen ensued, and as the addition progressed a precipitate formed. When the addition was complete the reaction mixture was filtered to give 0.182 g of an orange powder, mp 282–284°, which was subsequently identified as 9-xanthoneketazine by mixture melting point with an authentic sample. The filtrate was concentrated with a rotary evaporator under reduced pressure to afford a brown residue from which benzonitrile and *N,N*-thiobisbenzamide were obtained as the only isolable products.

***N*-Benzoyl-α-chloro-α-carbomethoxymethansulfenamide (15c).** To ethyl diazoacetate (0.6 g, 0.0053 mol) in 10 ml of dry THF was added dropwise over a period of 20 min at 30° benzamide-*N*-sulfenyl chloride (1.0 g, 0.0053 mol) in 25 ml of dry THF under a nitrogen atmosphere. Evolution of nitrogen began immediately and continued rapidly throughout the addition. Removal of the solvent under reduced pressure and crystallization of the residual oil from ether–hexane at −30° gave 0.115 g of the sulfenamide as colorless needles: mp 111–116 dec; ir ($CHCl_3$) 3410 (NH), 1740 (ester C=O), and 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz), 4.25 (q, 2 H, J = 7 Hz), 5.48 (s, 1 H), 6.30 (broad s, 1 H), and 7.60 (m, 5 H).

Compound **15c** rapidly decomposed upon exposure to moisture or if allowed to stand at room temperature and this instability precluded elemental or mass spectral analysis.

Treatment of 15c with Triethylamine. At −78° a THF solution of *N*-benzoyl-α-chloro-α-carboethoxymethanesulfenamide was prepared from benzamide-*N*-sulfenyl chloride (1.0 g, 0.0053 mol) and ethyl diazoacetate (0.6 g, 0.0053 mol) was described above. To this solution at −78° was added triethylamine (0.6 g, 0.0059 mol) which caused immediate formation of a deep red color. After removal of the precipitated triethylamine hydrochloride (0.6 g, 82%) by filtration the red solution was allowed to warm to 30°, after which time (2 hr) the color faded to a light yellow. After removal of the solvent under reduced pressure the yellow semisolid residue was crystallized from THF–hexane at −30° to afford 0.115 g of a crystalline product: mp 209–210°; ir (KBr) 3300 (NH), 1740 (ester C=O), and 1640 cm^{-1} (amide C=O); nmr (DMSO-d_6) δ 1.20 (t, 3 H, J = 7 Hz), 4.20 (q, 2 H, J = 7 Hz), 6.15 (m, 1 H), 7.60 (m, 7 H); mass spectrum (70 eV) m/e (rel intensity) 324 (2), 253 (47), 121 (20), 105 (100).

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.66; H, 5.35; N, 8.64. Found C, 6.43; H, 5.58; N, 8.40.

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Registry No.—**12,** 39593-81-2; **13,** 51933-55-2; **15a,** 39593-82-3; **15b,** 39593-83-4; **15c,** 51933-56-3; **16a,** 51933-57-4; **16b,** 51933-58-5; **17,** 39593-85-6; **18,** 2403-57-8; **19,** 39593-87-8; **22,** 52022-28-3; **23,** 39593-89-0; **24,** 39593-91-4; **26,** 7182-09-4; **27,** 39593-88-9; **28,** 39593-90-3; **29,** 14958-13-5; **30,** 51933-63-2; **32,** 52022-30-7; **42,** 51933-59-6; *N*-(trimethylsilyl)benzamide, 1011-57-0; morpholine, 110-91-8; morpholine-*N*-sulfenyl chloride, 2958-89-6; sodium salt of benzamide, 39536-32-8; *N,N*′-thiobenzamideaniline, 51933-60-9; aniline, 100-46-9; diphenyldiazomethane, 883-40-9; triethylamine, 121-44-8; 9-diazofluorine, 832-80-4; 1-(diethylamine)-1-propyne, 4231-35-0; 9-diazoxanthene, 51933-61-0; ethyl diazoacetate, 623-73-4.

References and Notes

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New Monohemiaminal Derivatives of Thiobinupharidine and Thionuphlutine B. Role of Circular Dichroism and Mass Spectrometry in Ascertaining the Position of the Hemiaminal Function[1]

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Spectral properties of four monohemiaminals belonging to the thiaspirane class of nuphar alkaloids are compared and employed in the structure elucidation of three of these compounds. The new monohemiaminals are 6′-hydroxythiobinupharidine and 6-hydroxythionuphlutine B, both isolated from *N. luteum*, and 6′-hydroxythionuphlutine B, prepared from 6,6′-dihydroxythionuphlutine B. The nmr showed that the hemiaminal group in each of the three monohemiaminals was located at one of two C-6 positions. Distinction of a C-6 from a C-6′ hemiaminal was made chiefly by (1) deuteride reduction to singly labeled thiaspirane followed by a mass spectral analysis for the extent of *m/e* 178 to 179 shift; and (2) the CD of the monohemiaminals in acid solution. Singly deuterated thiaspiranes which were labeled at C-6 resulted in *m/e* 178 shifting to 179 by more than 90%. In contrast, thiaspiranes singly labeled at C-6′ resulted in only a 10% shift of *m/e* 178 to 179. The CD of all the C-6′ hemiaminals in acid solution showed positive CD bands in the region of 260–280 nm but the CD of 6-hydroxythiobinupharidine and 6-hydroxythionuphlutine B show positive and negative CD bands, respectively, in the 290–310-nm region.

Two bishemiaminal derivatives of the C_{30} thiaspirane type of Nuphar alkaloid have been reported.[2] These are 6,6′-dihydroxythiobinupharidine (**1**)[3] and 6,6′-dihydroxythionuphlutine B (**2**). A monohemiaminal derivative, 6-hydroxythiobinupharidine (**3**), has also been reported.[5,6] Chief among the methods for ascertaining the number of the hemiaminal functions was a borodeuteride reduction followed by a mass spectral analysis for the presence of a d_1- or d_2-labeled C_{30} thiaspirane. The location of the hemiaminal groups was determined by nmr, which readily allowed a distinction between a C-6 hemiaminal on the one hand and a C-4 or C-10 hemiaminal on the other. However, the distinction between two C-6 positions (C-6 and C-6′) in a monohemiaminal was somewhat more complex because of the symmetry characteristics of the thiaspirane skeleton and it was necessary to rely on subtle differences between α- and β-thiohemiaminals[7] and their stereochemistry. Thus in the case of the monohemiaminal, **3**, the nearly complete replacement of the hemiaminal hydroxyl by equatorial deuterium through sodium borodeuteride hydrogenolysis was the result which necessitated the attachment of the hydroxyl at C-6, not C-6′, since the replacement of hydroxyl by deuterium at C-6′ was known to occur in a completely axial fashion.[5]

Application of CD to α-thioimmonium ions, or α-thiohemiaminals in acid solution, led to the establishment of the absolute configuration of thiobinupharidine and thionuphlutine B[8] and simultaneously gave supporting evidence for the position of the hemiaminal function in 6-hydroxythiobinupharidine. However, the CD results alone did not furnish independent evidence for the presence of a C-6 hemiaminal, as opposed to a C-6′ hemiaminal, since the CD properties of β-thiohemiaminals and β-thioimmonium ions were not known. We have now isolated and prepared two new β-thiohemiaminals and isolated a new α-thiohemiaminal belonging to the thiobinupharidine and thionuphlutine B series. We illustrate here how several spectral characteristics of α- and β-thiohemiaminals differ. However, we emphasize how the CD of these compounds and comparative mass spectra of singly labeled thiaspiranes prepared from the monohemiaminals can be utilized in determining the hemiaminal position in samples obtained in 2–5-mg amounts.

6′-Hydroxythiobinupharidine (4). This compound was isolated from *N. luteum*. Its mass spectrum revealed a parent ion peak at *m/e* 510 which corresponded to a monohemiaminal derivative of a C_{30} thiaspirane type of nuphar alkaloid. The ir revealed the presence of a hydroxyl group. The appearance of Bohlmann bands[9] in the ir indicated the presence of a trans-fused quinolizidine. Since the hydroxyl group could be reduced by hydride reducing agents and hemiaminal derivatives of quinolizidines do not show Bohlmann bands,[10] the evidence for the presence of both hydride-reducible hydroxyl and a trans quinolizidine ring system revealed the dual amine–hemiaminal character of this alkaloid. Conversion of the new monohemiaminal to an am-

Table I
Proton Chemical Shifts[a] in the Nmr of Thiobinupharidine and Thionuphlutine B Hemiaminals

Compd	Proton: CH_3	CH_2S	CH_2N, H_{eq}: C-6	CH_2N, H_{eq}: C-6′	HC(OH)N: C-6	HC(OH)N: C-6′	3F[b]CH: C-4	3F[b]CH: C-4′	3-Furyl: α	3-Furyl: β
6,6′-Dihydroxythiobinupharidine (1)	0.82	2.46[c]			4.01[d]	4.26[e]	3.73	3.61	7.35	6.40
6-Hydroxythiobinupharidine, (3)	0.88	2.20[c]		2.96	3.98[d]		3.70	2.92	7.22 7.30	6.34
6′-Hydroxythiobinupharidine (4)	0.92	2.53[c]	2.83			4.25[e]	2.94	3.62	7.35	6.36
6,6′-Dihydroxythionuphlutine B (2)	0.87	2.52[c]			4.10[f]	3.92[f]	3.4–3.7			6.27 6.47
6-Hydroxythionuphlutine B (8)	0.88	2.32[c]		2.88	4.08[d]		3.55		7.27	6.22 6.41
6′-Hydroxythionuphlutine B (14)	0.89	2.53[c]	2.70			3.94[g]	2.95	3.50	7.30	6.20 5.43

[a] In parts per million from TMS (δ 0.0) in $CDCl_3$. [b] 3F = 3-furyl. [c] AB quartet, J = 11.0–12.0 Hz. [d] Singlet. [e] Doublet, J = 4 Hz. [f] Multiplet. [g] Doublet, J = 2 Hz.

monium–immonium diperchlorate supported the presence of amine and hemiaminal groups. The melting point of this diperchlorate was different from that obtained earlier from 6-hydroxythiobinupharidine.[5]

The sodium borodeuteride reduction of the new monohemiaminal gave a singly labeled thiobinupharidine which was identified by comparative specific rotations, melting points, ir, nmr, and mass spectra. An admixture melting point determination showed no depression. Hydride reduction to unlabeled thiobinupharidine, **6**, would have sufficed to identify the stereoisomeric type of thiaspirane. However, the use of sodium borodeuteride was considered advantageous because we wished to have sufficient labeled material for extensive comparison of the mass spectra of C-6 and C-6′ deuterated thiobinupharidines (see below). Mass spectral differences possibly could allow a determination of the position of the deuterium and thus the position of the hydroxyl group in the precursor monohemiaminal. The singly labeled sample used for comparison was prepared from 6,6′-dihydroxythiobinupharidine. The latter was reduced first with sodium borodeuteride and the resulting 6-hydroxythiobinupharidine-6′-d_1 (**5**), the only monohemiaminal detected in the reaction product, was separated from the mixture of products. The mass, nmr, and uv spectra of this C-6′ labeled hemiaminal were identical with the spectra of 6-hydroxythiobinupharidine except for the absorption bands which would be expected to change as a result of the presence of deuterium. Reduction of the C-6′ labeled hemiaminal with sodium borohydride gave thiobinupharidine-6′-d_1 (**7**). Since 6′-hydroxythiobinupharidine and 6,6′-dihydroxythiobinupharidine both had been reduced to the same labeled thiobinupharidine, it was clear that the first named compound belonged to the thiobinupharidine series.

Significantly, the nmr of the newly isolated hemiaminal displayed a doublet at δ 4.25 which collapsed to a singlet upon addition of deuterium oxide. The chemical shift of this proton was the same as the chemical shift of one of two similar carbinyl hemiaminal protons of 6,6′-dihydroxythiobinupharidine. The nmr also showed an equatorial proton α to nitrogen at δ 2.83. Thus the hemiaminal was not located at C-10, C-10′, C-4, or C-4′, but at C-6 or C-6′. The principal resonances are summarized in Table I along with corresponding data for bishemiaminals and other monohemiaminals of the thiobinupharidine and thionuphlutine B series. As can be seen in Table I, the chemical shift of each monohemiaminal carbinyl proton corresponds to one of two chemical shifts for the pair of similar protons in the bishemiaminals. The carbinyl hemiaminal proton assignments in the thiobinupharidine series are based on the previously reported[5] independent evidence which locates the hemiaminal function in 6-hydroxythiobinupharidine at the C-6 rather than the C-6′ position. These assignments and those in the thionuphlutine B series are supported by the work described below.

Not only do the nmr of 6- and 6′-monohemiaminals show differences, but the mass spectra do also. The *m/e* 178 peak is one of the principal peaks, and is often the base peak, in the mass spectra of the thiaspirane alkaloids.[11] However, 6-hydroxythiobinupharidine shows a weak peak at *m/e* 178 but a much stronger peak at *m/e* 176. The order of peak intensities is reversed in the mass spectrum of 6′-hydroxythiobinupharidine . As shown in Figure 1, the chief source

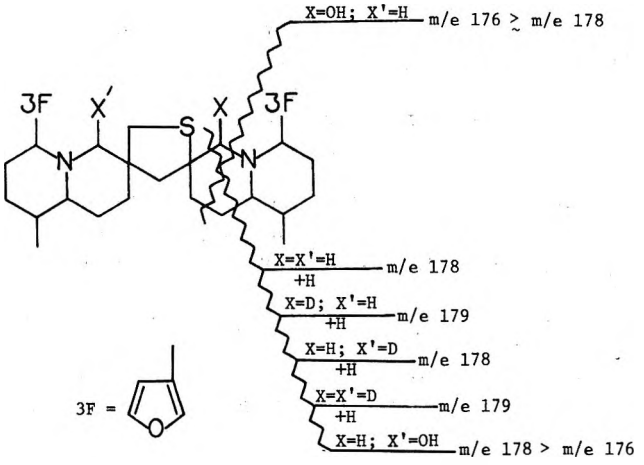


Figure 1. Mass spectral fragmentations of a thiaspirane nuphar alkaloid: the origin of *m/e* 178 and the possible origin of *m/e* 176.

of *m/e* 178 and 176 appears to be from the AB quinolizidine system, the one directly attached to sulfur, rather than the A′B′ quinolizidine ring. That this is the case in the fully reduced thiobinupharidine is evident from the observation that *m/e* 178 is shifted to *m/e* 179 by more than 90% in the mass spectrum of thiobinupharidine-6-d_1,[11] but the same shift occurs to only 9% in the mass spectrum of thiobinupharidine-6′-d_1. These results illustrate the potential usefulness of deuteride reduction and the determination of the *m/e* 178 to 179 shift in distinguishing a C-6 from a C-6′ hemiaminal. This procedure has been used, as described in another section below, in distinguishing C-6 from C-6′ hemiaminals in the thionuphlutine B series.

The uv of 6′-hydroxythiobinupharidine exhibited end absorption in neutral ethanol. However, the addition of perchloric acid resulted in the emergence of a new peak at 279 nm (ε 830) appearing on the long-wavelength slope of the end absorption. In comparison, 6-hydroxythiobinupharidine in acid solution exhibited absorption at 292 nm (ε 3,200).[5] The CD of 6′-hydroxythiobinupharidine in neutral solution exhibited a weak positive band at 250 nm and a moderate negative band at 228 nm. However, as shown in Figure 2, acidification of the solution generated a new positive band at 280 nm and an even stronger positive band at 241 nm. Clearly, a comparison of the curves (Figure 2) of 6,6′-dihydroxythiobinupharidine, 6-hydroxythiobinupharidine, and 6′-hydroxythiobinupharidine, all in acid solution, reveals that both C-6 and C-6′ thiobinupharidine hemiaminals give positive CD bands, but that the C-6 monohemiaminals absorb at longer wavelengths than the C-6′ monohemiaminals.

6-Hydroxythionuphlutine B (8). A 2-mg sample of this alkaloid also was isolated from *N. luteum*. There was insufficient material for a combustion analysis. However, the high-resolution mass spectrum indicated that the molecular formula was $C_{30}H_{42}N_2O_3S$. The ir exhibited hydroxyl and Bohlmann band absorption. The nmr (Table I) showed one C-6 hemiaminal proton at δ 4.08 and one C-6 equatorial proton α to nitrogen at δ 2.88. In the mass spectrum *m/e* 176 and 178 were of nearly the same intensity, an observation which suggested that the hemiaminal hydroxyl was at C-6, not C-6′.

Reduction of 6-hydroxythionuphlutine B with sodium borohydride gave thionuphlutine B (**9**), whose tlc properties agreed with those of an authentic sample but differed from those of thiobinupharidine (**6**) and neothiobinupharidine (**10**). Reduction of the monohemiaminal with sodium borodeuteride gave a singly labeled thionuphlutine B. Significantly *m/e* 178 was shifted to *m/e* 179 by more than 90%. This result, coupled with the previously described mass spectral studies of singly labeled thiobinupharidines, meant that the hemiaminal hydroxyl of 6-hydroxythionuphlutine B could be attached to C-6. The CD (Figure 3) confirmed this choice. In acidic ethanol solution, 6-hydroxythionuphlutine B showed a negative CD band at 298 nm. This observation agrees with the negative CD band in the same region exhibited by 6,6′-dihydroxythionuphlutine B (Figure 3) and the fact that the immonium perchlorate derived from 7α-methylthiodeoxynupharidin-6β-ol also gives a negative band in the same region.[8]

The negative CD band exhibited by 7-hydroxythionuphlutine B also confirms that this monohemiminal cannot belong to the stereoisomeric thiobinupharidine series or to a fourth, still unknown, stereoisomeric series represented by structure **12**,[12] since both of the latter two would show positive CD bands in the 300-nm region. While the appearance of the negative CD band at 298 nm does not distinguish 6-hydroxythionuphlutine B from still unknown 6-hydroxyneothiobinupharidine (**13**), the above-mentioned tlc properties of the fully reduced thiaspiranes do. Therefore the structure **8** is assigned to the newly isolated 6-hydroxythionuphlutine B.

6′-Hydroxythionuphlutine B (14). Careful reduction of 6,6′-dihydroxythionuphlutine B (**2**) with sodium borohydride gave a mixture of products of which the major component had tlc properties different from those of the starting bishemiaminal, 6-hydroxythionuphlutine B, and fully reduced thionuphlutine B. There was insufficient material for combustion analysis but the high-resolution mass spectrum indicated that the molecular formula was $C_{30}H_{42}N_2O_3S$. The ir exhibited hydroxyl and Bohlmann band absorption. The mass spectrum showed a strong peak at *m/e* 178 but a weak one at *m/e* 176 and thus indicated that the hemiaminal hydroxyl was located at C-6′. The nmr (Table I) showed one C-6 hemiaminal proton at δ 3.94 and one C-6 equatorial proton α to nitrogen at δ 2.70.

Reduction of this monohemiaminal with sodium borodeuteride gave thionuphlutine B-6′-d_1 (**15**) whose tlc properties were identical with those of an unlabeled sample of thionuphlutine B. The mass spectral study showed that *m/e* was shifted to *m/e* 179 by only 10% and indicated

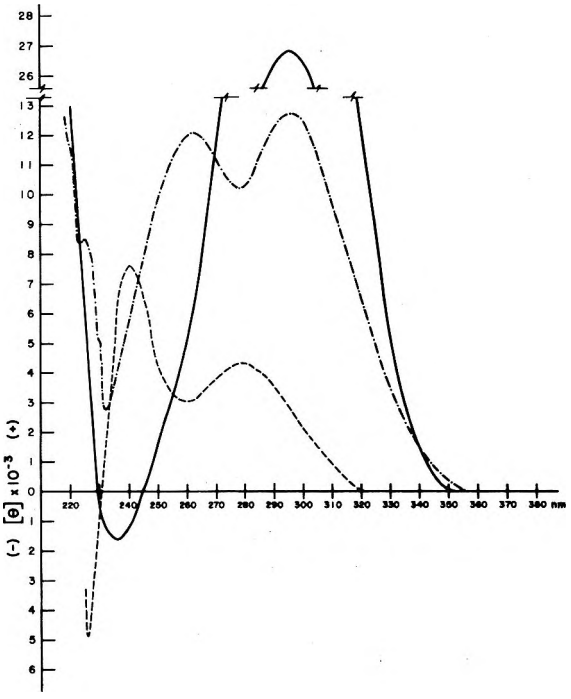


Figure 2. The circular dichroism of 6-hydroxythiobinupharidine (**1**) (——), 6′-hydroxythiobinupharidine (**4**) (– – –), and 6,6′-dihydroxythiobinupharidine (**3**) (— · —) in EtOH with added $HClO_4$.

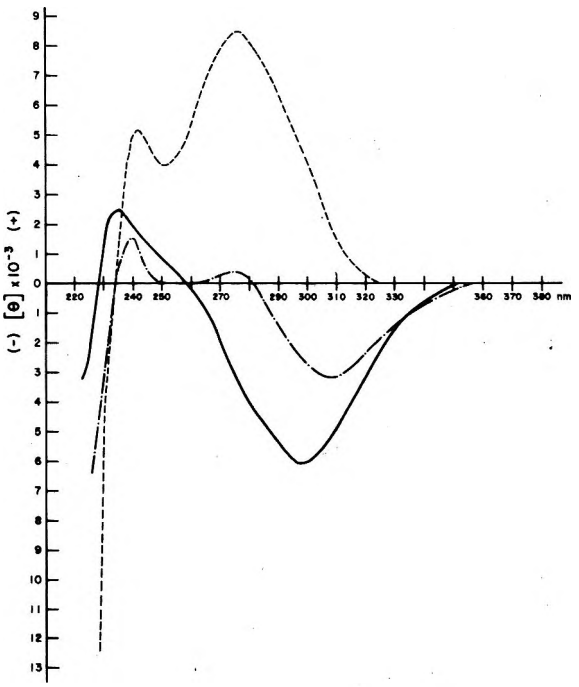
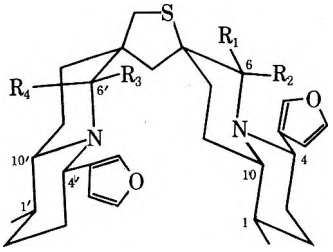
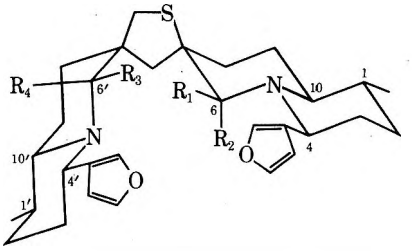


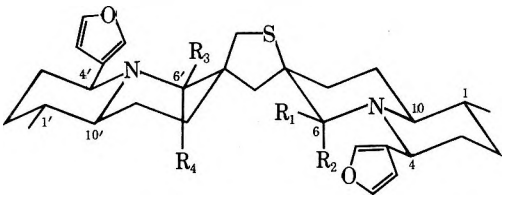
Figure 3. The circular dichroism of 6-hydroxythionuphlutine B (**8**) (——), 6′-hydroxythionuphlutine B (**14**) (- - -), and 6,6′-dihydroxythionuphlutine B (**2**) (— · —) in EtOH with added $HClO_4$.



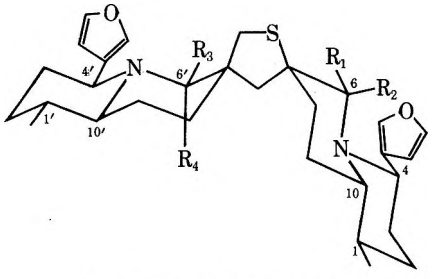
1, R_1+R_2 = OH + H; R_3+R_4 = OH + H
3, R_1+R_2 = OH + H; $R_3 = R_4$ = H
4, $R_1 = R_2$ = H; R_3+R_4 = OH + H
5, R_1+R_2 = OH + H; R_3 = H; R_4 = D
6, $R_1 = R_2 = R_3 = R_4$ = H
7, $R_1 = R_2 = R_3$ = H; R_4 = D



2, R_1+R_2 = OH + H; R_3+R_4 = OH + H
8, R_1+R_2 = OH + H; $R_3 = R_4$ = H
9, $R_1 = R_2 = R_3 = R_4$ = H
11, $R_1 = R_3 = R_4$; R_2 = D
14, $R_1 = R_2$ = H; R_3+R_4 = OH + H
15, $R_1 = R_2 = R_3$ = H; R_4 = D



10, $R_1 = R_2 = R_3 = R_4$ = H
13, R_1+R_2 = OH + H; $R_3 = R_4$ = H



12, $R_1 = R_2 = R_3 = R_4$ = H

thereby that the deuterium label was located at C-6′ and that the hydroxyl group in the precursor hydroxythionuphlutine B was at the same position.

The uv of 6′-hydroxythionuphlutine B was similar to that of 6′-hydroxythiobinupharidine. In neutral solution the former exhibited only strong end absorbtion, but in acidic solution it showed an absorption maximum at 274 nm (ε 940). The CD of 6′-hydroxythionuphlutine B determined in neutral solution showed a negative CD band at 249 nm but in acidic solution positive bands at 275 and 241 nm emerged (Figure 3). These CD results correspond to those observed in the case of 6′-hydroxythiobinupharidine and agree completely with the structure assigned to 6′-hydroxythionuphlutine B (**14**).

Experimental Section

Spectra were obtained as follows: nmr in solution as indicated, 2% TMS (δ 0.0), on Varian A-60, HA-100, and XL-100 Fourier transform spectrometers, symbols br, d, q, and m refer to broad, doublet, quartet, and multiplet, respectively; ir in KBr and in solution as indicated; mass spectra on a Hitachi Perkin-Elmer RMU6E using a direct inlet probe and other conditions as indicated; high-resolution mass spectra were determined at the High Resolution Mass Spectrometry Laboratory, Battelle's Columbus Laboratories, Columbus, Ohio, AEI MS-9 using a direct inlet probe and other conditions as indicated. Melting points were determined on a Köfler micro hot stage and a Mel-Temp apparatus and are uncorrected. Optical rotations were determined in solution as indicated on a Perkin-Elmer 141 polarimeter. The circular dichroism (CD) was determined on a Jasco Model 5 spectropolarimeter in solution at the concentrations indicated. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Thin layer chromatography was carried out on microscope slides uniformly coated with alumina HF_{254} and using the solvent indicated. The sodium borodeuteride was purchased from Merck, Sharp and Dohme and contained a minimum of 98% deuterium.

Isolation of 6′-Hydroxythiobinupharidine (4). As described earlier,[4] elution of a *Nuphar luteum* extract from alumina, using first hexane and then C_6H_6, gave fractions (A1–A7) yielding thiobinupharidine and neothiobinupharidine. Continued elution with 100 ml of 20% CH_2Cl_2–C_6H_6 gave fraction A8; two 300-ml portions of 50% CH_2Cl_2–C_6H_6 gave fractions A9 and A10; three 200-ml portions of CH_2Cl_2 gave fractions A11–A13; and finally 400 ml of MeOH gave fraction A14. Fraction A11 (136 mg) was chromatographed on a column of neutral alumina (activity 2.5) using C_6H_5N–EtOEt–hexane (3:10:37). Sixty-one (B1–B61), 5-drop fractions were taken after the first Dragendorff active substance was detected in the effluent. Continued elution with two 15-ml portions and then one 30-ml portion of the same solvent gave B62, 63, and 64, respectively. Finally the column was eluted with 50 ml of MeOH, which gave 32.8 mg of brown oil. Combined B62–63 gave 57 mg of **4**: tlc (C_5H_5N–EtOEt–hexane, 6:20:74) R_f 0.36; $[\alpha]^{25}D$ + 34° (*c* 10 mg/ml, 95% EtOH); uv (neutral 95% EtOH) λ_{max} 204 nm (ε 35,000); uv (acidic 95% EtOH) $\lambda_{max\,1}$ 204 nm (ε 29,000), $\lambda_{max\,2}$ 279 (830); ir (CCl_4) 2.75 (w, OH), 3.59 (m, Bohlmann bands), 11.45 μ (s, 3-furyl); nmr (60 MHz, $CDCl_3$) δ 0.92 (d, *J* = 3 Hz, 6 H, C-1 CH_3), 2.46 (absent when D_2O is added, d, *J* = 4 Hz, 1 H, OH), 2.16, 2.36, 2.69, 2.90 (AB q centered at δ 2.53, *J* = 11.5 Hz, CH_2S), 2.83 (d of d, *J* = 11 and 1.5 Hz, 1 H, C-6 H_{eq}), 2.94 (br t, 1 H, C-4 H_{ax}), 3.62 (t, 1 H, C-4′ H_{ax}), 4.25 (br d but br s on addition of D_2O, 1 H, HOC-6 H), 6.36 (br s, 2 H, β-furyl H), 7.35 (m, 4 H, α-furyl H); mass spectrum (70 eV, 120°) *m/e* (rel intensity) 510 (7.7) (M^+), 509 (1.5) ($M^+ - H$), 508 (1.5) ($M^+ - H_2$), 492 (60) ($M^+ - H_2O$), 262 (15), 230 (69), 178 (100), 176 (13), 136 (8), 107 (40), 94 (26), 81 (18); high-resolution mass spectrum (70 eV, 200°) obsd/calcd mass (formula), 492.2782/492.2810 ($C_{30}H_{40}N_2O_2S$); CD (*c* 0.3 mg/ml, neutral 95% EtOH *l* = 0.1 dm) $[\theta]_{270}$ ±0°, $[\theta]_{258}$ + 530°, $[\theta]_{250}$ +850°, $[\theta]_{244}$ 530°, $[\theta]_{240}$ ±0°, $[\theta]_{232}$ −2650°, $[\theta]_{288}$ −5900°, $[\theta]_{225}$ 5100°; CD (c 0.3 mg/ml, acidic 95% EtOH, *l* = 0.1 dm) $[\theta]_{320}$ ±0°, $[\theta]_{300}$ +2110°, $[\theta]_{288}$ +3810°, $[\theta]_{380}$ +4350°, $[\theta]_{266}$ +3400°, $[\theta]_{260}$ +3070°, $[\theta]_{250}$ +4250°, $[\theta]_{248}$ +5300°, $[\theta]_{241}$ +7650°, $[\theta]_{234}$ +4040°, $[\theta]_{230}$ −960°, $[\theta]_{266}$ −4900°, $[\theta]_{225}$ −3200°.

A 10-mg sample of **4** was treated with 0.2 ml of *M* aqueous $HClO_4$ (2 equiv) and sufficient acetone to obtain a homogeneous solution. The solvent was evaporated and the residue was recrystallized from MeOH, giving the immonium ammonium diperchlorate: mp 216–220°; ir (KBr) Bohlmann bands absent, 6.02 μ (m, > C=N⁺<).

Anal. Calcd for $C_{30}H_{42}N_2O_{10}SCl_2$: C, 51.93; H, 6.11; N, 4.04; S, 4.62. Found: C, 51.77; H, 6.06; N, 4.06; S, 4.56.

Thiobinupharidine-6′-d_1 (7) from 6′-Hydroxythiobinupharidine (4). To a solution of 8 mg of **4** in methanol at 0° was added 20 mg of $NaBD_4$. After 10 min the solvent was vacuum evaporated and the residue was mixed with 1 ml of H_2O and 1 ml of CH_2Cl_2. The H_2O layer was extracted repeatedly with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and the solvent was vacuum evaporated to afford 6 mg of colorless residue which was taken up in 20 ml of C_6H_6. The resulting solution was passed through 6 g of neutral alumina. Vacuum evaporation of the C_6H_6 gave 5.3 mg of colorless, oily **7** which in time became crystalline: mp 130–132.5°; $[\alpha]D$ +6.5 (*c* 4.8 mg/ml, 95% EtOH); ir (CCl_4) 3.60 (s, Bohlmann bands), 4.92 μ (w, CD); nmr (100 MHz, C_6D_6) same as that of thiobinupharidine except δ 3.16 (br s, 1.82 H including δ 3.10, C-6′ H_{eq}), 3.10 (d of d, 1.82 H including δ 3.16, C-6 H_{eq}), 1.41

(d, C-6′ H_{ax} absent); mass spectrum *m/e* (rel intensity) 495 (45) (M^+, 11% d_0, 83% d_1, 6% d_2), 360 (15), 231 (24), 230 (57), 179 (23), 178 (100), 136 (9), 107 (22), 94 (14), 81 (10), 79 (8).

Thiobinupharidine-6′-d_1 (7) from 6,6′-Dihydroxythiobinupharidine (1). One or two particles of $NaBD_4$ were added at one time to a solution of 18 mg of **1** in 5 ml of MeOH. Addition of $NaBD_4$ (five particles) was continued until the presence of thiobinupharidine was detected by tlc (20 drops of *t*-BuOH in 10 ml of C_6H_6). At this point, tlc showed the presence of three components, 6,6′-dihydroxythiobinupharidine (R_f 0.36), 6-hydroxythiobinupharidine (R_f 0.56), the major component, and thiobinupharidine (R_f 0.85). Processing the reaction mixture in the usual manner[13] gave 16 mg of residue, which was separated on a column of 6 g of neutral alumina (activity 2.5). The column was eluted with 20 ml of C_6H_6, giving fraction 1; 29 ml of C_6H_6 which contained 5 drops of *t*-BuOH–10 ml of C_6H_6, giving fraction 2; the latter solvent collected in 13 3-drop fractions, giving fractions 3–15; and 15 ml of the same solvent, giving fraction 16. Fractions 1 and 16 consisted of 4 mg of thiobinupharidine-6,6′-d_2 and 0.7 mg of dihydroxythiobinupharidine, respectively. Combined fractions 3–15 yielded 8 mg of **5**: ir (CH_2Cl_2) 2.80 (OH), 2.43–2.52 (CH), 2.61 (Bohlmann bands), 4.90 (CD), and 11.45 μ (3-furyl); uv (acidic, MeOH) 292 nm (ϵ 3400); nmr (60 MHz, $CDCl_3$) δ 2.95 (br d, 1 H, C-6 H_{eq}), 1.4 (d, J = 11 Hz) absent; mass spectrum *m/e* (rel intensity) 511 (11) (M^+, 6% d_0, 87% d_1, 7% d_2), 493 (100), 231 (67), 230 (65), 229 (53), 228 (92), 179 (17), 178 (16), 177 (24), 176 (96), 136 (15), 107 (40), 94 (40), 81 (25), 79 (30).

The above-described sample of **4** in 1 ml of MeOH was treated with 20 mg of $NaBH_4$ and the resulting mixture was stored under N_2 at 25° for 2 days. Thereafter tlc (20 drops of *t*-BuOH–10 ml of C_6H_6) showed only thiobinupharidine (R_f 0.85). Processing the reaction mixture in the usual manner[13] gave 11 mg of residue, which was chromatographed on 5 g of neutral alumina (activity 2). Elution of the column with 30 ml of C_6H_6 gave 8 mg of colorless, oily thiobinupharidine-6′-d_1 which in time became crystalline: mp 131–132.5°; admixture with a sample from $NaBD_4$ reduction of 6′-hydroxythiobinupharidine, mp 130–132.5°; ir (CCl_4) and nmr (100 MHz C_6D_6) identical with spectra of a sample from $NaBD_4$ reduction of 6′-hydroxythiobinupharidine; mass spectrum *m/e* (rel intensity) 495 (30) (M^+, 9% d_0, 89% d_1, and 2% d_2), 360 ((13), 231 (22), 230 (47), 179 (25), 178 (100), 136 (10), 107 (23), 94 (15), 81 (11), 79 (11).

6′-Hydroxythionuphlutine B (14) from 6,6′-Dihydroxythionuphlutine B (2). A solution of 15 mg of **2**[2] in 5 ml of MeOH was treated with particles of $NaBH_4$ at −77° until **2** was no longer observed in the tlc [20% acetone–hexane, R_f 0.36 (6′-hydroxythionuphlutine B), 0.46 (6-hydroxythionuphlutine B), 0.71 (thionuphlutine B)]. Processing the reaction mixture in the normal manner[13] gave 12.5 mg of oily residue which was chromatographed on 7 g of neutral alumina (activity 3). Elution with 20 ml of C_6H_6 gave 6.2 mg of thionuphlutine B.[2] Continued elution with 20% acetone–hexane gave 7.9 mg of impure **14** which was applied, in a minimum amount of C_6H_6, to a column of 10 g of neutral alumina (activity 2). Elution with 10% acetone–hexane continued until the effluent was Dragendorff active; thereafter, 32 10-drop fractions were taken. Fractions 16–32 were combined to give 4.5 mg of pure **14**: tlc (20% acetone–hexane) R_f 0.5; ir (CH_2Cl_2) 2.75, 2.60 (m, Bohlmann band), 11.45 μ (3-furyl); uv (neutral 95% EtOH) end absorption; uv (acidic 95% EtOH) λ_{max} 205 nm (ϵ 24,400), $\lambda_{max\,2}$ 274 (940); nmr (100 MHz, $CDCl_3$) δ 0.89 (d, J = 6 Hz, 6 H), 2.31, 2.45, 2.63, 2.75 (AB q centered at δ 2.53, J = 12 Hz, 2 H, CH_2S), 2.70 (d of d, J = 11 and 2 Hz, 1 H, C-6 H_{eq}), 2.95 (m, 1 H, C-4H), 3.50 (m, 1 H, C-4′ H), 3.94 (d, J = 4 Hz, 1 H, C-6′ H), 6.20 (m, 1 H, β-furyl H), 6.43 (m, 1 H, β-furyl H), 7.30 (m, 4 H, α-furyl H); mass spectrum (70 eV, 110°) *m/e* (rel intensity) 510 (0.5) (M^+), 509 (0.5) ($M^+ - H$), 508 (0.5) $M^+ - H_2$), 492 (100) ($M^+ - H_2O$), 262 (14), 230 (60), 228 (22), 178 (74), 176 (13), 136 (5), 107 (37), 94 (30), 81 (18); high-resolution mass spectrum (70 eV, 150°) obsd/calcd mass (formula), 510.2846/510.2916 ($C_{30}H_{42}N_2O_3S$), 509.2656/509.2838 ($C_{30}H_{41}N_2O_3S$), 508.2710/508.2759 ($C_{30}H_{40}N_2O_3S$), 492.2756/492.2810 ($C_{30}H_{40}N_2O_2S$); CD (*c* 0.28 mg/ml, neutral 95% EtOH, *l* = 0.1 dm) $[\theta]_{288}$ ±0°, $[\theta]_{276}$ −450°, $[\theta]_{266}$ −810°, $[\theta]_{257}$ −2520°, $[\theta]_{249}$ $[\theta]_{243}$ −2780°, $[\theta]_{238}$ −990°, $[\theta]_{236}$ 990°, $[\theta]_{231}$ 3680°, $[\theta]_{228}$ 7360°, $[\theta]_{227}$ 4850°; CD (*c* 0.28 mg/ml, acidic 95% EtOH, *l* = 0.1 dm), $[\theta]_{325}$ ±0°, $[\theta]_{313}$ +900°, $[\theta]_{298}$ +4500°, $[\theta]_{288}$ +6750°, $[\theta]_{277}$ +8450°, $[\theta]_{274}$ +8450°, $[\theta]_{263}$ +6460°, $[\theta]_{257}$ +4670°, $[\theta]_{250}$ +3960°, $[\theta]_{241}$ +5210°, $[\theta]_{238}$ +4140°, $[\theta]_{234}$ ±0°, $[\theta]_{230}$ −4120°, $[\theta]_{228}$ −12,500°, $[\theta]_{225}$ −18,000°.

Thionuphlutine B-6′-d_1 (15) from 6′-Hydroxythionuphlutine B (14). A solution of 0.5 mg of **14** in MeOH at 25° was treated with 5 mg of $NaBD_4$ until tlc (15% acetone–hexane) showed no remaining **14**. Processing the reaction mixture in the normal manner[13] gave 0.1 mg of residue which was chromatographed on 1 g of neutral alumina (activity 3). Elution with 25 ml of C_6H_6 afforded 0.1 mg of **15**: tlc (10% EtOEt–hexane) R_f 0.50, (40% isooctane–CH_2Cl_2) R_f 0.35, (10% CH_2Cl_2–C_6H_6) R_f 0.52, (C_6H_6) R_f 0.35, which in each case was the same as that for an authentic sample of thionuphlutine B; mass spectrum *m/e* (rel intensity) 495 (31) (M^+, 11% d_0, 89% d_1), 360 (13), 231 (26), 230 (52), 179 (26), 178 (100), 136 (11), 107 (24), 94 (15), 81 (4).

6-Hydroxythionuphlutine B (8). Fraction A66 (53 mg), obtained in the same elution chromatography from which 6-hydroxythiobinupharidine was obtained,[5] was eluted from a column of 20 g of neutral alumina (activity 2) with 30 ml of hexane, to give fraction E1, and then with 5% acetone in hexane, which contained 60 drops of *t*-BuOH per 100 ml of solvent. Fractions E2–33, each containing 20 drops of the latter solvent, were taken. Fractions E19–25 were combined to obtain 2 mg of **8**: tlc (10% acetone–hexane and 60 drops of *t*-BuOH/100 ml) R_f 0.32; ir (CCl_4) 2.66 (OH), 3.55 (Bohlmann band), 6.65 and 11.51 μ (3-furyl); nmr (100 MHz, $CDCl_3$) δ 0.88 (d, J = 5 Hz, 6 H, C-1 and C-1′ CH_3), 2.32 (AB q, J = 12 Hz, 2 H, CH_2S), 2.88 (2, H, C-6′$_{eq}$ and C-4′ H), 3.55 (1 H, C-4 H), 4.08 (1 H, >NCHOH), 6.22 and 6.41 (2 H, β-furyl H), 7.27 (4 H, α-furyl H); mass spectrum *m/e* (rel intensity) 510 (2), 493 (10), 492 (21), 477 (1.5), 461 (2), 359 (5.5), 230 (100), 228 (15), 178 (45), 176 (30), 136 (7), 107 (18), 94 (14), 81 (13); high-resolution mass spectrum (70 eV, 160°) obsd/calcd mass (formula) 510.2883/510.2916 ($C_{30}H_{42}N_2O_3S$), 509.2827/509.2828 ($C_{30}H_{41}N_2O_3S$), 508.2745/508.2759 ($C_{30}H_{40}N_2O_3S$), 493.2830/493.2889 ($C_{30}H_{41}N_2O_2S$), 492.2750/492.2810 ($C_{30}H_{40}N_2O_2S$); CD (*c* 1.0 mg/ml, 95% EtOH + 3 drops of aqueous 1 *N* HCl) $[\theta]_{350}$ ±0°, $[\theta]_{330}$ −1430°, $[\theta]_{314}$ −4100°, $[\theta]_{298}$ −6010°, $[\theta]_{280}$ +4100°, $[\theta]_{270}$ +1840°, $[\theta]_{258}$ ±0°, $[\theta]_{245}$ +1530°, $[\theta]_{235}$ +2550°, $[\theta]_{230}$ +1530°, $[\theta]_{228}$ ±0°, $[\theta]_{222}$ −3260°, $[\theta]_{220}$ −1530°.

By similar, repeated elution chromatography of fractions A63–65[5] an additional 2-mg sample of **8** was obtained.

Thionuphlutine B (9) from 6-Hydroxythionuphlutine B (8). A solution of 0.5 mg of **8** in MeOH at 25° was treated with 5 mg of $NaBH_4$ for 30 min. Thereafter the MeOH was vacuum evaporated and the residue was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated for studies of tlc properties: tlc (10% EtOEt–hexane) R_f 0.50, (40% isooctane–CH_2Cl_2) R_f 0.35, (CH_2Cl_2–C_6H_6) R_f 0.52, (C_6H_6) R_f 0.35, which in each case was the same as that for an authentic sample of thionuphlutine B obtained from reduction of 6,6′-dihydroxythionuphlutine B[2] but different from that of thiobinupharidine [tlc (10% EtOEt–hexane) R_f 0.61, (40% isooctane–CH_2Cl_2) R_f 0.56, (10% CH_2Cl_2–C_6H_6) R_f 0.70, (C_6H_6) R_f 0.50] and different from that of neothiobinupharidine [tlc (10% EtOEt–hexane) R_f 0.2, (40% isooctane–CH_2Cl_2) R_f 0.12, (10% CH_2Cl_2–C_6H_6) R_f 0.18, (C_6H_6) R_f 0.16]; mass spectrum *m/e* (rel intensity) 494 (26), 359 (11), 231 (15), 230 (47), 179 (14), 178 (100), 136 (11), 107 (22), 94 (27), 81 (14).

Thionuphlutine B-6-d_1 (11) from 6-Hydroxythionuphlutine B (8). A solution of 2 mg of **8** in 5 ml of methanol was treated with 10 mg of $NaBD_4$, the reaction mixture was processed in the usual manner,[13] and the crude **11** was purified on a column of alumina (activity 2) using 10% EtOEt–hexane as the eluting solvent to obtain pure **11**: ir (CCl_4) 3.56 (Bohlmann bands), 4.9 (CD), 6.17 and 11.47 μ (3-furyl); mass spectrum *m/e* (rel intensity) 495 (25) (M^+), 462 (3), 448 (4), 360 (13), 231 (34), 179 (100), 136 (12), 107 (26), 94 (17), 81 (12), 79 (13).

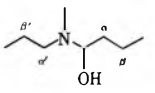
Registry No.—**1**, 30343-70-5; **2**, 30343-71-6; **3**, 50478-55-2; **4**, 52002-85-4; **4** immonium ammonium perchlorate, 52002-88-7; **5**, 52002-89-8; **7**, 52079-26-2; **8**, 52002-90-1; **9**, 30343-74-9; **11**, 52079-24-0; **14**, 52002-84-3; **15**, 52079-25-1.

References and Notes

(1) Support of this work by the National Institutes of Health, U. S. Public Health Service (Grant No. AI10188), is gratefully acknowledged.
(2) R. T. LaLonde, C. F. Wong, and W. P. Cullen, *Tetrahedron Lett.*, 4477 (1970).
(3) 6,6′-Dihydroxythiobinupharidine had originally been named 6,6′-dihydroxythionuphlutine A (ref 2) but the latter name was dropped when it was discovered (ref 4) that thionuphlutine A and thiobinupharidine were identical.
(4) R. T. LaLonde and C. F. Wong, *Phytochemistry*, **11**, 3305 (1972).
(5) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Amer. Chem. Soc.*, **95**, 6342 (1973).
(6) T. I. Martin, D. B. MacLean, J. T. Wróbel, A. Iwanow and W. Starzec [*Can. J. Chem.*, **52**, 2705 (1974)] have recently reported the structure

of this same monohemiaminal which they refer to as thionupharoline. We wish to thank Professor MacLean for communicating his results to us prior to publication.

(7) We erroneously referred to α-thiohemiaminals as β-thiohemiaminals in an earlier paper (ref 5). The α and β positions of a hemiaminal are designated as follows. The α and β positions of the corresponding immonium ion are similarly designated.



(8) R. T. LaLonde and C. F. Wong, *J. Org. Chem.*, **38**, 3225 (1973).
(9) (a) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); (b) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962); (c) M. W. Wiewioroski and J. Skolick, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **10**, 1 (1962).
(10) R. T. LaLonde and C. F. Wong, unpublished observations.
(11) R. T. LaLonde, C. F. Wong, J. T. Woolever, E. Auer, K. C. Das, and A. I-m. Tsai, *Org. Mass Sppectom.*, in press.
(12) Conceivably an A'B' quinolizidine moiety belonging to the same absolute configurational series as (−)-deoxynupharidine combined with an AB hemiaminal belonging to the enantiomeric deoxynupharidine series could also give a C_{30} thiaspirane possessing a negative CD band in the 300-nm region. However, (+)-deoxynupharidine has never been reported nor has its incorporation in any of the Nuphar alkaloids been observed. Therefore we assume that all quinolizidine moieties of the thiaspiranes belong to the same enantiomeric series as (−)-deoxynupharidine.
(13) The work-up procedure is the same as that described above in the conversion 6'-hydroxythiobinupharidine to thiobinupharidine-6'-d_1.

Reaction of Phosgene with *N*-Methyleneaniline Derivatives

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The reaction of *N,N'*-diphenylmethylenediamine (**1**) and 1,3,5-triphenylhexahydro-*s*-triazine (**2**) with phosgene is accompanied by cleavage of a carbon–nitrogen bond to give *N*-chloromethyl-*N*-phenylcarbamoyl chloride (**5**) and 1,3,5-trisaza-1,3,5-triphenyl-1,5-bis(chloroformyl)pentane (**7**), respectively. 4-Aminobenzylaniline upon reaction with phosgene produces *N*-phenyl-*N*-4-isocyanatobenzylcarbamoyl chloride in high yield, which on reaction with hydrogen chloride undergoes a carbon–nitrogen bond cleavage to give phenyl isocyanate and 4-isocyanatobenzyl chloride.

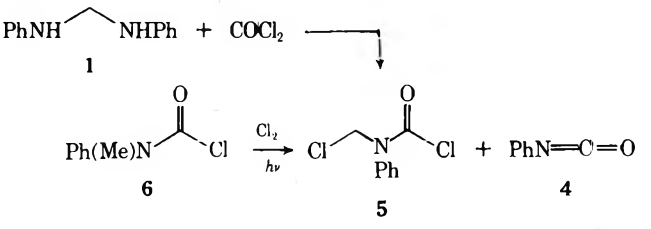
The reaction of aniline with aqueous formaldehyde in the presence of mineral acids to give diphenylmethane derivatives proceeds in two steps. Initially, phenyl-*N,N*-acetals of formaldehyde are formed, which rapidly rearrange in the presence of the acid catalyst to give benzylamines and finally diphenylmethane derivatives.[1] These di- and oligomeric amines are the precursors of commercially important di- and polyisocyanates. It is of interest to study the reaction of the intermediate products with phosgene, because small amounts could be present in the polyamine mixture.

Reaction of aniline with aqueous formaldehyde in the absence of acid produces a mixture of phenyl-*N,N*-acetals (aminals) in which *N,N'*-diphenylmethylenediamine (**1**) and 1,3,5-triphenylhexahydrotriazine (**2**) could be detected by nmr spectroscopy. Using a ratio of aniline–formaldehyde of 10:1 only one methylene signal at δ 4.45 (attributed to **1**) was present, while a solution prepared from a ratio of aniline–formaldehyde of 2:1 showed two methylene signals at δ 4.4 and 4.75 ppm (attributed to **1** and **2**; ratio approximately 1:1).

In order to investigate the reaction of *N*-methyleneanilines with phosgene, model compounds **1** and **2** were synthesized independently.[2] The model compound selected for the benzylamine intermediates, *p*-aminobenzylaniline (**3**), was prepared by reduction of the Schiff base[3] derived from *p*-nitrobenzaldehyde and aniline (Scheme III). The literature procedure,[4] using 4-nitrobenzyl chloride and aniline, followed by reduction did not produce **3** in our hands.

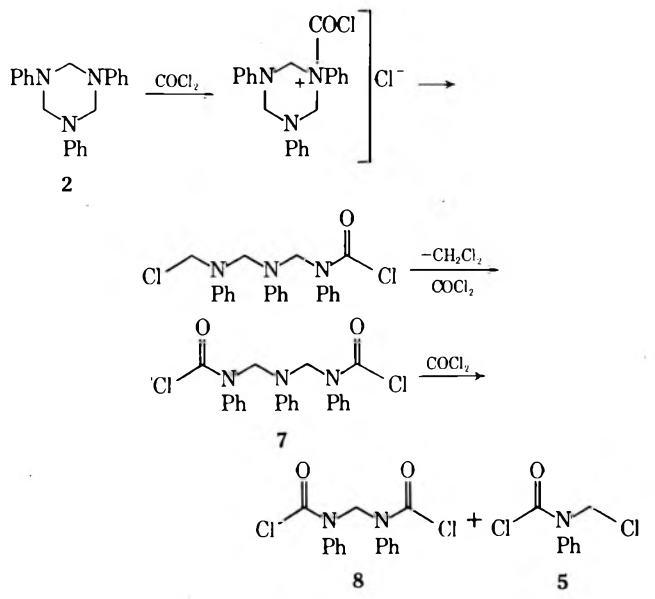
The model compounds with the exception of **2** are secondary amines, and formation of disubstituted carbamoyl chlorides is expected in their reaction with phosgene.[5] However, complications could arise due to the lability of the carbon–nitrogen bonds in phenyl-*N,N*-acetals of formaldehyde, and to a lesser degree in benzylamines. When **1** was treated with excess phosgene, a mixture of products was obtained which contained phenyl isocyanate (**4**) and the novel *N*-chloromethyl-*N*-phenylcarbamoyl chloride (**5**). The latter compound was synthesized independently in 80% yield by monochlorination of *N*-methyl-*N*-phenylcarbamoyl chloride (**6**) (Scheme I). Initial attack of phosgene on one of the nitrogens of **1** leads to the formation of hydrogen chloride, which cleaves the other carbon–nitrogen bond. This pathway explains both of the observed reaction products.

Scheme I



The reaction of **2** with phosgene gave **5**, the novel biscarbamoyl chloride **7** and a third unknown product of intermediate molecular weight as observed by gel permeation chromatography. Since the center nitrogen atom in **7** is the most likely site of attack of phosgene, the unknown compound could have the biscarbamoyl chloride structure **8** (see Scheme II), based on comparative gel permeation chromatography with **5** and **7**. The nmr spectrum of the biscarbamoyl chloride **7** shows, as expected, only one signal for the methylene protons at δ 4.85 ppm; the mass spectrum of the compound shows, due to its thermal lability, only fragments (HCl, $PhNCH_2$, PhNCO, PhN, etc.) and no molecular ion peak.

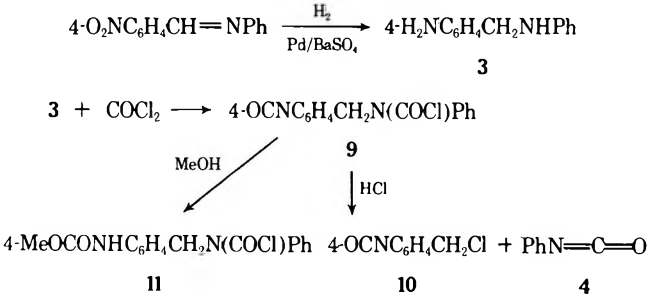
Scheme II



The initial reaction of the hexahydro-*s*-triazine **2** with phosgene occurs at one of the nitrogen atoms, giving rise to the formation of a polar complex which rearranges to a linear carbamoyl chloride. This reaction is reminiscent of the reaction of tertiary alkylamines with phosgene, in which a secondary carbamoyl chloride and an alkyl halide is produced.[5] Subsequent reaction of the linear carbamoyl chloride with phosgene leads to the formation of **7** and methylene chloride by the same reaction sequence. Reaction of **7** with phosgene finally produces **5** and **8**. However, both products **5** and **8** could also arise from the initially formed linear carbamoyl chloride.

The reaction of **3** with excess phosgene under mild conditions produces the expected previously unreported *N*-phenyl-*N*-4-isocyanatobenzylcarbamoyl chloride (**9**) in 90% yield; however, variable amounts of phenyl isocyanate (**4**) and 4-chloromethylphenyl isocyanate (**10**) were obtained as lower boiling by-products. The structure of **9** was verified by conversion to the crystalline carbamate derivative **11** (Scheme III).

Scheme III



In order to elucidate the pathway of formation of the lower boiling isocyanate by-products **4** and **10**, the carbamoyl chloride **9** was treated under the reaction conditions (refluxing chlorobenzene) with phosgene and hydrogen chloride, respectively. While no reaction was observed with phosgene, complete conversion of **9** to **4** and **10** occurs in the presence of dry hydrogen chloride. The formation of isocyanates from secondary carbamoyl chlorides has only been shown to occur when *N*-*tert*-butyl-*N*-alkylcarbamoyl chlorides were thermolyzed in polar solvents with or without an added catalyst ($FeCl_3$).[6] The facile reaction of *N*-phenyl-*N*-4-isocyanatobenzylcarbamoyl chloride (**9**) with hydrogen chloride constitutes a new synthesis of isocyanates from secondary arylbenzyl carbamoyl chlorides.

This reaction apparently proceeds by initial protonation of the nitrogen, followed by elimination of the benzyl chloride **10**.

The cleavage of the carbon–nitrogen bond in carbamoyl chlorides derived from the aminals of formaldehyde **1** and **2** is even more pronounced as evidenced by the formation of fragmentation products **5** and **8**.

Experimental Section[7]

Preparation of Starting Materials. *N*,*N*′-Diphenylmethylenediamine (**1**) and 1,3,5-triphenylhexahydro-*s*-triazine (**2**) were prepared according to the literature.[2]

4-Aminobenzylaniline (3). A solution of 5.66 g (0.25 mol) of nitrobenzylideneaniline in 100 ml of diethyl ether was purged with nitrogen and hydrogenated in the presence of 0.56 g of 5% palladium on barium sulfate. The theoretical uptake of 8.66 p.s.i. of hydrogen was observed within 0.5 hr. Filtration and evaporation of the solvent under vacuum gave 4.7 g (95%) of crude **3**, which crystallized to a white granular solid. Recrystallization from 10 ml of diethyl ether gave 3.7 g (75%), mp 47.5–48° (lit.[4] mp 49°). The thin layer chromatogram of the total mixture showed one spot: nmr ($CDCl_3$) δ 3.53 (s, 3, NH), 4.1 (s, 2, $-CH_2-$), 6.45–6.8, 7.0–7.3 (m, 9, aromatic).

Reaction of *N*,*N*′-Diphenylmethylenediamine (1) with Phosgene. A solution of 50 g (0.25 mol) of **1** in 200 ml of chlorobenzene was added to a solution of 150 g (1.5 mol) of phosgene in 300 ml of chlorobenzene at 12°. After slowly heating to 90° (3.2 hr) excess phosgene was removed with nitrogen, and the solvent was evaporated to give a liquid residue which contained phenyl isocyanate (**4**), ir 2220 cm^{-1} (N=C=O), and chloromethylphenylcarbamoyl chloride (**5**), ir 1735 cm^{-1}; nmr δ 5.48 (s, 2, CH_2). Attempted vacuum distillation gave 19.5 g of a fraction, bp 86–89° (0.05 mm), consisting of a mixture of **4** and **5**; however a major portion of the mixture underwent thermal degradation.

***N*-Chloromethyl-*N*-phenylcarbamoyl Chloride (5).** Into a solution of 17.0 g of *N*-methyl-*N*-phenylcarbamoyl chloride (**6**) in 200 ml of carbon tetrachloride was introduced 7.0 g of chlorine, and the resulting solution was irradiated with a 110-W medium pressure uv lamp. A Dry Ice condenser attached to the reaction flask prevented loss of chlorine and solvent during the exothermic reaction. The progress of the chlorination was followed by nmr (disappearance of $N-CH_3$, appearance of $N-CH_2Cl$ signal). Toward the end of the reaction it often became necessary to add more chlorine in small increments in order to complete the chlorination. To avoid overchlorination, the reaction was terminated with trace amounts of starting material left unchanged. Solvent removal under vacuum left a syrupy crude material which crystallized on standing. Recrystallization from boiling hexane gave 16.2 g (80%) of **5**: mp 45–46°; ir (CCl_4) 1735 cm^{-1} (C=O); nmr δ 5.4 (s, 2, CH_2). *Anal.* Calcd for $C_8H_7Cl_2NO$: C, 47.09; H, 3.45; N, 6.87; Cl, 34.75. Found: C, 47.15; H, 3.47; N, 6.71; Cl, 34.85.

Reaction of 1,3,5-Triphenylhexahydro-*s*-triazine (2) with Phosgene. A solution of 15.0 g of phosgene in 25 ml of benzene was added at once to 9.45 g of **2**, dissolved in 50 ml of warm (40–50°) benzene. The reaction mixture was kept for 30 min at ambient temperature. On concentrating the solution under vacuum, a colorless crystalline precipitate was separated, which was filtered off, washed with a small amount of cold benzene, and dried under vacuum; 2.0-g yield (15%) of 1,3,5-trisaza-1,3,5-triphenyl-1,5-bis(chloroformyl)pentane (**7**): mp 120° dec (from chloroform); ir (KBr) 1720 cm^{-1} (C=O). The colorless needles turn rapidly yellow and orange if exposed to air.

Anal. Calcd for $C_{22}H_{19}Cl_2N_3O_2$: C, 61.69; H, 4.47; N, 9.81. Found: C, 61.51; H, 4.33; N, 10.03.

The filtrate was evaporated to dryness, leaving a yellow-orange syrup, which on exposure to air turned deep red and became highly viscous. The gel permeation analysis of a freshly prepared sample showed the presence of 11.4% of phenyl isocyanate, 56% of *N*-phenyl-*N*-chloromethyl carbamoyl chloride (**5**), 24.2% of an unknown (possibly **8**), and 4.6% of **7** besides trace amounts (3.8%) of benzene.[8]

***N*-Phenyl-*N*-4-isocyanatobenzylcarbamoyl Chloride (9).** A solution of 9.9 g (0.05 mol) of 4-aminobenzylaniline (**3**) in 100 ml of dry chlorobenzene was added dropwise to a stirred solution of 19.8

g (0.2 mol) of phosgene in 100 ml of dry chlorobenzene. After completion of addition the reaction mixture was slowly heated to 50°, and after stirring for 90 min the solvent was removed by distillation. Vacuum distillation of the residue gave 13 g (91%) of a slightly impure *N*-phenyl-*N*-4-isocyanatobenzylcarbamoyl chloride (**9**), containing small amounts of phenyl (**4**) and 4-chloromethylphenyl isocyanate (**11**), as indicated by glc. Repeated fractional distillation produced pure **9**: bp 166° (0.25 mm); ir ($CHCl_3$) 2247 cm^{-1} (N=C=O), 1739 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.85 (s, 2, CH_2). *Anal.* Calcd for $C_{15}H_{11}N_2O_2Cl$: C, 62.84; H, 3.87; N, 9.77. Found: C, 62.96; H, 3.97; N, 10.05.

In a larger scale experiment (0.15 mol) phenyl isocyanate (**4**), [bp 39° (0.005 mm)] and 4-chloromethylphenyl isocyanate (**10**) [bp 68° (0.005 mm), mp 31–33° (lit.[9] mp 34°)] were isolated by fractional distillation.

Reaction with Methanol. A solution of 2.86 g (0.01 mol) of **9** in 10 ml of methanol was allowed to stand at room temperature overnight. Concentration of this solution gave 2.91 g (92%) of the methyl carbamate **11**, mp 108–109° after recrystallization from methanol. *Anal.* Calcd for $C_{16}H_{15}N_2O_3Cl$: C, 60.28; H, 4.74; N, 8.79. Found: C, 60.10; H, 4.95; N, 8.77.

Reaction with Hydrogen Chloride. A slow stream of dry hydrogen chloride was added to a refluxing solution of 1.5 g of **9** in 15 ml of dry chlorobenzene. After refluxing for 4 hr, complete conversion to **4** and **10** was observed as indicated by monitoring of the reaction mixture by nmr spectroscopy and glc.

Acknowledgment. We are indebted to F. P. Recchia and E. Goerland, who conducted part of the experimental investigation.

Registry No.—**1**, 622-14-0; **2**, 91-78-1; **3**, 24007-66-7; **4**, 103-71-9; **5**, 52123-54-3; **6**, 4285-42-1; **7**, 52123-55-4; **9**, 52123-56-5; **11**, 52123-57-6; phosgene, 75-44-5; nitrobenzylideneaniline, 785-80-8; methanol, 67-56-1; hydrogen chloride, 7647-01-0.

References and Notes

(1) P. Cohn, *Z. Angew. Chem.*, **14**, 313 (1901).
(2) M. Wakae and K. Konishi, *Osaka Furitsu Kogyo-Shoreikan Hokoku*, **29**, 47 (1963); *Chem. Abstr.*, **59**, 6280 (1963).
(3) O. Fischer, *Ber.*, **14**, 2525 (1881).
(4) C. Paal and O. Sprenger, *Ber.*, **30**, 69 (1897).
(5) H. Babad and A. G. Zeiler, *Chem. Rev.*, **73**, 75 (1973).
(6) J. N. Tilley and A. A. R. Sayigh, *J. Org. Chem.*, **28**, 2076 (1963).
(7) Melting and boiling points are uncorrected. Analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ir spectra were determined using a Beckman IR-8 spectrophotometer. Nmr spectra were obtained from samples in $CDCl_3$ solutions with a Varian T-60 instrument using tetramethylsilane as the internal standard. Gas chromatography was carried out on a Model 810 F & M gas chromatograph; 5% silicon grease columns were used. Gel permeation chromatography was conducted on a Waters 200 chromatograph.
(8) The indicated per cent values are by area ratio.
(9) British Patent 752,931 (1956); Farbenfabriken Bayer A.-G.; *Chem. Abstr.*, **51**, 7420 (1957).

Carbon-13 Magnetic Resonance Spectral Study of Some Phosphorinanes and Their 1-Sulfides[1]

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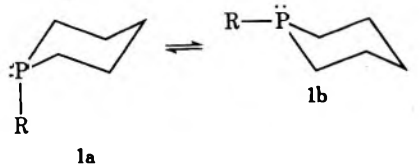
The ^{13}C nmr spectra of a group of five 1-substituted phosphorinanes (**1**) and of their corresponding sulfides (**4**) were obtained. Chemical shift trends within each group can be interpreted in terms of the familiar α,β,γ effects. The known axial predominance in **1** of *P*-methyl, -ethyl, and -phenyl is manifested in their ^{13}C spectra by slightly higher field $C_{3,5}$ signals than seen for the *tert*-butyl and isopropyl compounds, and also by the small value for the sterically sensitive $^2J_{PC_{3,5}}$ in the former (3.0–3.5 Hz) relative to the latter compounds (6–7 Hz). In the sulfides, all compounds appear to have a predominance of the conformer with equatorial carbon substituent, as judged from shift effects at $C_{2,6}$ and $C_{3,5}$. Of value in reaching this conclusion was a comparison of the spectra of the conformationally biased 1,4-disubstituted 4-phosphorinanols with their sulfides. The greater shielding exerted at $C_{3,5}$ by axial sulfur rather than by axial methyl was especially useful in this study. The ^{31}P nmr signal was the more upfield for that isomer where the steric compression was the greatest.

Carbon-13 nmr spectroscopy has been employed with much success in the determination of structural and stereochemical features of several types of six-membered heterocyclic compounds.[2d] Little is known, however, about the ^{13}C properties of the ring where phosphorus is the heteroatom; only 4-hydroxy derivatives of this system have been studied so far.[3,4] This phosphorinane system is of special interest because of the remarkably small value for $\Delta H°$ in the equilibrium of **1a** and **1b** (−0.68 kcal/mol for R = CH_3).[5] Indeed, entropy effects cause the equilibrium position at 27° to rest on the side of the axial conformer when R is methyl (K = 0.56),[5] ethyl (K = 0.65),[6] or phenyl (K = 0.72).[6] We have now obtained the ^{13}C nmr spectra of these and other 1-substituted phosphorinanes and have established relations between chemical shifts and structural and conformational properties of this system.



1a **1b**

Carbon spectra of phosphorus compounds contain more information than just chemical shift values; the ^{31}P atom couples with carbon to produce doublets of easily measured magnitude through two and sometimes three bonds. The size of two-bond coupling for trivalent phosphorus is subject to steric control[3,7,8] and consequently is of value in conformational analysis.

We have included in our study a consideration of the consequences of adding a fourth group to phosphorus. We have used the sulfides of the phosphorinanes for this purpose, since they are easily prepared, nonhygroscopic crystalline solids. While a proton nmr conformational study of the sulfide of phosphorinane itself (**1**, R = H) has been reported,[9] no attention has been given previously to the stereochemical consequences of placing both sulfur and an alkyl group on phosphorus.

Phosphorinanes. Carbon-13 nmr data for five 1-substituted phosphorinanes are recorded in Table I. Assignments were made as follows. (1) Relative to a carbon substituent, the phosphino group shields the attached carbons, presumably because of weak inductive electron displacement to carbon. This causes the carbon of the PCH_3 group (mostly axial[5]) to absorb about 5 ppm upfield from CH_3 when axial

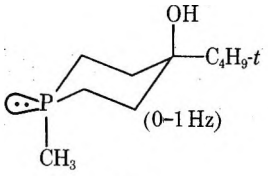
Table I
^{13}C Nmr Spectra of Phosphorinanes[a]

Registry no.	1, R =	δ $C_{2,6}$	δ $C_{3,5}$	δ C_4	δ P–C	δ P–C–C
39763-50-3	CH_3	165.8 (13)	169.1 (3)	164.2 (2)	181.6 (19)	
52032-39-0	CH_3CH_2	167.6 (14)	168.8 (4)	164.1 (3)	172.4 (14)	182.8 (16)
52032-40-3	$(CH_3)_2CH$	168.4 (12)	168.6 (6)	164.2 (2)	166.1 (12)	173.5 (17)
52032-41-4	$(CH_3)_3C$	171.1 (18)	167.5 (7)	164.1 (3)	169.1 (28)	165.8 (14)
3302-83-8	C_6H_5	167.9 (14)	169.1 (4)	164.6 (2)		

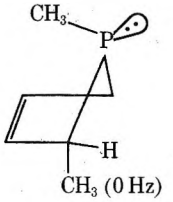
[a] See ref 25 for experimental details. Chemical shifts were determined on neat samples from internal TMS and are calculated from CS_2 as standard. ^{31}P–^{13}C coupling constants (in hertz) are given in parentheses.

on the cyclohexane ring.[10] Its signal is easily recognized. (2) The coupling of trivalent phosphorus with adjacent carbon is generally about 12–15 Hz, also assisting in the recognition of the exocyclic carbon, as well as of $C_{2,6}$ of the ring. (3) C_4 is least affected by the presence of phosphorus; of the ring carbons it gives the most downfield peak, which is of half the intensity of the ring carbon signals. (4) The chemical shift and phosphorus coupling of $C_{3,5}$ are influenced by conformational effects to be discussed subsequently. Generally, the coupling at $C_{3,5}$ was much smaller than at $C_{2,6}$, and this was an aid in the assignments.

Within the family, certain trends are clearly discernible for the ring carbons. (1) As methyls replace hydrogen on the exocyclic carbon attached to phosphorus, the chemical shift of $C_{2,6}$ progresses to higher field. This is explainable on the basis of the well-known[2b] γ effect, in this case operating through P in the fragment C_γ–C_β–P_α–$C_{2,6}$ and increasing with the number of γ carbons. Coupling of $C_{2,6}$ to ^{31}P is consistently 11.5–13.5 Hz except for the *tert*-butyl case, where it rises to 17.5 Hz. Similarly, the exocyclic C–P coupling in the *tert*-butyl derivative is considerably larger than in the other compounds. This effect has been observed elsewhere for acyclic *tert*-butyl phosphines[11] and is believed to be the result of increased bond angles about the phosphorus atom in this more crowded system. (2) $C_{3,5}$ are susceptible to a γ effect from the exocyclic P substituent ($C_\gamma P_\beta C_\alpha C_{3,5}$). If the substituent is axially oriented, the effect will be maximal, since $C_{3,5}$ are then gauche related to this substituent. As the size of the P substituent increases, the conformational equilibrium should shift so that the equatorial conformer concentration is increased. Low-temperature ^{31}P nmr measurements have indicated this to be the case.[5,6] The data in Table I show that δ $C_{3,5}$ for the various phosphorinanes does vary in accord with the conformational effect; δ $C_{3,5}$ moves to lower field as the substituent size increases. However, relative differences in the γ effect of various P substituents could also influence δ $C_{3,5}$. The magnitude of the two-bond phosphorus coupling to $C_{3,5}$ is more specifically related to the position of conformational equilibrium. In freely rotating acyclic phosphines $^2J_{PC}$ is about 12–15 Hz,[11,12] but in cyclic phosphines the value can vary from 0 to 32 Hz.[7,8] The large values seem to occur in systems where the dihedral angle relating the phosphorus lone-pair orbital to the coupled carbon is small,[7] as for the 2-methyl of *cis*-1,2-dimethyl-3-phospholene[8] (shown as conformation **2a**). Negligible coupling occurs in the trans isomer **2b**, and for $C_{3,5}$ of the ring in *trans*-1-methyl-4-*tert*-butyl-4-phosphorinanol[3] (**3a**); in

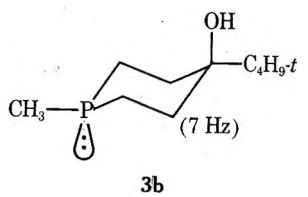


2a



2b

3a



3b

both the pertinent dihedral angle is large. Coupling is small but significant (7 Hz) for the cis isomer of the 4-phosphorinanol (**3b**) where $C_{3,5}$ and the lone pair are in closer proximity than the trans isomer.[3] It is obvious that $^2J_{PC}$ is very much dependent on steric relations, and with definite dihedral angle values a useful stereochemical tool would be at hand;[13] for the present the relation must remain qualitative. Nevertheless, the limits appear defined for the phosphorinane ring by **3a** and **3b** with axial and equatorial substituents. The $^2J_{PC}$ values for $C_{3,5}$ of the 1-substituted phosphorinanes of Table I may then be compared to these limits. The largest value (7 Hz) is seen for the 1-*tert*-butyl compound; since this value is the same as for compound **3b**, the implication is clear that the *tert*-butyl group on phosphorus is predominantly equatorial. This is supported by the low-temperature ^{31}P studies.[6] The isopropyl group is also suggested from its value of 6 Hz to be largely equatorial. The smaller values (about 3 Hz) for the remaining compounds are in keeping with a conformational equilibrium mixture having a considerable concentration of the axial conformer, as found also from the ^{31}P studies.[5,6] (3) The chemical shift of C_4 is remarkably constant for the series (164.1–164.6), and is consistently downfield from the range for comparable alkylcyclohexanes (166.2–166.7 ppm).[2a] This is quite in keeping with the trend established among noncyclic phosphines; in the structure $XCH_2CH_2CH_2CH_3$, the γ carbon is farther downfield by about 2 ppm when X is a tertiary phosphine group than when X is methyl.[12] The reverse trend is seen for nitrogen; in both piperidines[2e] and noncyclic amines,[14] the γ carbon is upfield of that in the cyclohexanes and alkanes, respectively.

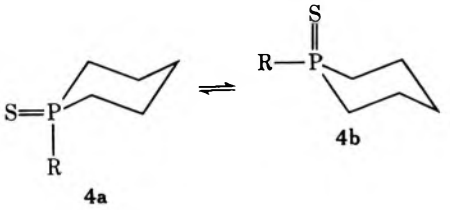
Phosphorinane Sulfides. Spectral data for the sulfides (4) of the five phosphorinanes are given in Table II. Assignments of carbons attached directly to phosphorus were easily made because of the large coupling constants, typically 45–50 Hz. Relative to the phosphines, the sulfides have chemical shifts for attached carbons that are several parts per million downfield. This effect has also been observed for acyclic sulfides.[2c] In the ring, coupling was substantial (5–8 Hz) at both $C_{3,5}$ and C_4; the latter signal was readily recognized from its intensity relation. Unlike for the phosphine, $^1J_{PC}$ for 1-*tert*-butylphosphorinane sulfide did not differ from the range seen for the other members of the series.

Table II
^{13}C Nmr Spectra of Phosphorinane Sulfides[a]

Registry no.	4, R =	δ $C_{2,6}$	δ $C_{3,5}$	δ C_4	δ P–C	δ P–C–C
1661-16-1	CH_3	159.8 (49)	170.1 (6)	166.3 (8)	174.0 (53)	
52032-42-5	CH_3CH_2	162.2 (48)	170.6 (8)	166.1 (6)	168.5 (50)	186.7 (5)
52032-43-6	$(CH_3)_2CH$	163.7 (48)	171.3 (8)	166.0 (7)	164.3 (50)	177.4 (0)
52032-44-7	$(CH_3)_3C$	167.9 (47)	171.7 (7)	165.6 (7)	159.8 (50)	168.2 (0)
4963-94-4	C_6H_5	160.6 (50)	170.7 (6)	165.9 (8)		

[a] See ref 25 for experimental details. Chemical shifts were determined from internal TMS and are calculated from CS_2 = 0; ^{31}P–^{13}C coupling constants (hertz) are given in parentheses. Samples were run in chloroform.

Several trends are apparent in the family. (1) At $C_{2,6}$ a steady upfield progression of the ^{13}C shift occurs as the protons of the PCH_3 group are replaced by methyl. This γ effect is the same as observed in the phosphine family. (2) At $C_{3,5}$ the chemical shift moves upfield with an increase in the size of the *P*-alkyl substituent and hence with its degree of equatorial character. This is the reverse of the trend seen in the phosphines, but is easily accounted for from an observation made in previous work[4] and discussed further in the next section: in the 4-phosphorinanol sulfides, greater shielding at $C_{3,5}$ is found for axial sulfur than for axial methyl. Although proton nmr studies[9] have suggested that the sulfur prefers the equatorial position when a proton is on phosphorus in **4**, the conformational equilibrium for the phosphorinane sulfides may be presumed to shift to the right when the proton is replaced by an alkyl substituent, the shift increasing with the size of the alkyl group. There



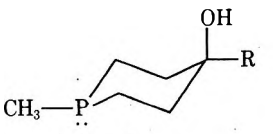
4a **4b**

is consequently increased shielding at $C_{3,5}$ since the contribution of the conformer with axial sulfur is greater. The chemical shift of $C_{3,5}$ is therefore intimately associated with the position of the conformational equilibrium. It is very likely that the *P*-*tert*-butyl group is largely equatorial, as usual, and that the *P*-methyl group has considerably more axial character. (3) C_4 shows the same chemical shift constancy within the series as observed for the phosphines. The range covered (165.6–166.3 ppm) is slightly to higher field than that of the phosphines (164.1–164.6 ppm), and is similar to the range for some alkylcyclohexanes (166.2–166.7 ppm).[2a] A steady progression of δ C_4 to lower field does occur for the sulfides as the size of the alkyl group increases, but the effect is small.

The position of the conformational equilibrium in the phosphorinane sulfides should be controlled by the relative magnitude of the nonbonded interactions of alkyl *vs.* sulfur with the axial protons at $C_{3,5}$. It might be anticipated that these interactions would be more severe with the alkyl group, and molecular parameters as determined by X-ray analysis support this position.[4] The interactions would of course increase with the size of the alkyl group. Two pieces of evidence suggest that even in 1-methylphosphorinane sulfide the conformer with equatorial methyl is dominant in the equilibrium. (1) As will be discussed further in the next section, the placement of sulfur on the axial site in a 1,4-dimethyl-4-phosphorinanol (conformationally biased) causes an *upfield* shift (2.5 ppm) at $C_{3,5}$, but placement on the equatorial site causes a *downfield* shift (1.8 ppm). These changes can then serve as a basis for a similar consideration of the sulfurization of 1-methylphosphorinane. Here it must be assumed that a new equilibrium position will be attained after the addition of sulfur, to reflect the relative preferences of methyl and sulfur. The fact that *shielding* at $C_{3,5}$ (by 1.0 ppm) accompanies the sulfurization strongly suggests that the sulfur is largely in the axial position, for if methyl remained in the axial position that it prefers in the phosphorinane, then a downfield shift at $C_{3,5}$ would have taken place and deshielding, rather than the observed shielding, would occur at $C_{3,5}$. (2) At $C_{2,6}$, there is deshielding by 6.0 ppm when 1-methylphosphorinane is sulfurized. When the phosphorinanol isomer with axial methyl is sulfurized, the deshielding is 8.7 ppm, while only 5.2 ppm is realized when the equatorial form is sulfurized. It is therefore again implied that sulfurization of the axial form of 1-methylphosphorinane is followed by a shift in the position of equilibrium to the side with equatorial methyl. In future work, we expect to determine the conformation adopted by 1-methylphosphorinane sulfide in the solid state by X-ray analysis.

An important effect also occurs at an exocyclic carbon β to phosphorus on conversion of a phosphine to its sulfide. In 1-ethylphosphorinane, the methyl of the substituent is shifted 3.9 ppm upfield on addition of sulfur. If the sulfur atom is considered as an added β substituent to the methyl, the upfield shift becomes understandable. The same effect is seen for the methyls of the isopropyl (3.9 ppm) and *tert*-butyl (2.4 ppm) substituents.

The 4-Phosphorinanol Series. Some of the effects observed in the phosphorinanes on sulfurization are clearly evident in 4-hydroxy derivatives as well, for which spectral data have been presented previously.[3,4] This system has the desirable feature that, when a 4-alkyl (or phenyl) substituent is also present, the resulting cis–trans isomers each have conformational equilibria strongly biased towards the conformer with equatorial orientation of this substituent (**5** and **6**, respectively). On sulfurization, compounds with



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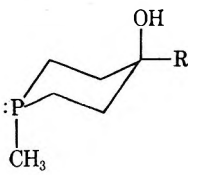


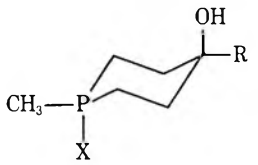
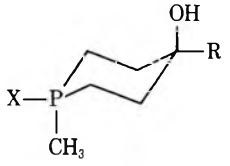
6

known orientation of the P substituents result, since this reaction is stereospecific (retention[15]).

Considering first the placement of axial sulfur on the ring (**5** → **7**), deshielding by the β effect is noticed at $C_{2,6}$, while γ shielding is noted at $C_{3,5}$ (Table IIIA). At C_4, the shielding effect on sulfurization discussed previously for the phosphorinanes is noticeable.

Placement of equatorial sulfur (Table IIIB) causes great-

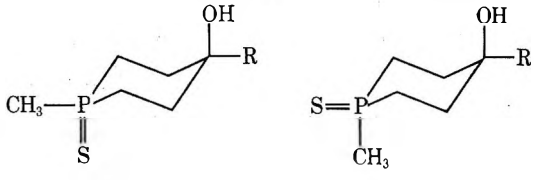
Table III
Changes[a] of ^{13}C Shifts on Converting 4-Phosphorinanols to Their Sulfides[b]

R	Δδ $C_{2,6}$	Δδ $C_{3,5}$	Δδ C_4
A. 			5, X = lone pair 7, X = S
CH_3	−5.2	+2.5	+1.1
t-C_4H_9	−3.1	+3.9	+0.5
C_6H_5	−3.1	+3.7	+0.8
B. 			6, X = lone pair 8, X = S
CH_3	−8.7	−1.8	+1.2
t-C_4H_9	−10.0	−4.2	+1.3
C_6H_5	−9.7	−3.9	+2.9

[a] Negative sign means deshielding accompanies the conversion to the sulfide; positive sign means shielding occurs. [b] Spectral data for the 4-phosphorinanols are given in ref 3, and for the sulfides in ref 4.

er deshielding at $C_{2,6}$ than accompanies axial placement, and deshielding occurs at $C_{3,5}$ as well. The effect at $C_{3,5}$ possibly due to the bond angle changes at phosphorus; these angles are increased in the sulfide owing to the greater s character, and this might tend to lessen the steric crowding of axial methyl with the axial 3,5 protons, thus causing a downfield shift relative to the phosphine. Geometric deformations are known to modify the size of the γ effect for gauche interactions of carbon atoms in carbocyclic systems.[16]

That the $C_{3,5}$ signals for the axial sulfur series (7) are more upfield than those for the axial methyl series (6) is



7 8

a, R = CH_3
b, R = t-C_4H_9
c, R = C_6H_5

the point mentioned earlier in this paper that led to the suggestion[4] of greater γ shielding by sulfur than methyl. This rather surprising result should not be taken to mean that the "size" of sulfur is greater than that of methyl; data from cyclohexanes are available to show that the magnitude of the γ-shielding effect of heteroatom substituents depends on other factors than size of the substituent alone. Thus, axial OH and axial F both exert a greater shielding effect on $C_{3,5}$ than does axial CH_3.[17] Another manifestation of this effect may be seen on N-oxidation (presumably axial) of N-methylpiperidine; $C_{3,5}$ are shielded by 5.1 ppm,[2e] a strikingly large amount for an atom the size of oxygen.[18] Also, an axial oxygen on sulfur of a 1,3,2-dioxathiane causes shielding at $C_{4,6}$ of 9 ppm relative to the equatorial isomer.[20]

Finally, we can derive evidence from ^{31}P spectra that the steric compression is greater for the compound with the axial methyl substituent. We have pointed out elsewhere[21] that in acyclic phosphorus compounds, both tri- and tetrasubstituted, the ^{31}P atom is deshielded by carbons located β to it and shielded by γ carbons, just as is true for ^{13}C shifts. It follows that in cyclic compounds steric effects influencing carbon shifts should also influence phosphorus shifts. Therefore, steric compression should shield phosphorus in the phosphorinane ring as it does carbon in the ring of crowded cyclohexanes.[2b] In Table V are given ^{31}P nmr data for the isomeric 4-phosphorinanol sulfides, and in every case the most upfield signal is associated with the isomer with axial methyl, as expected. This relation appears to hold in other series as well, and constitutes a useful tool for isomer assignment. For example, in the 1,3,2-dioxaphosphorinane oxides[22] and sulfides,[23] an axial $-OCH_3$ or $-N(CH_3)_2$ group causes the ^{31}P shift to occur several parts per million upfield of the value for the equatorial isomer. The useful parallel to the steric compression effect of ^{13}C nmr spectroscopy was not drawn in these studies, although more recently the operation of this effect in some trivalent phosphorus cycles has been recognized.[24]

Experimental Section[25]

Synthesis of 1-Substituted Phosphorinanes (1). The procedure employed was essentially that of Grüttner and Wiernik.[26] The di-Grignard reagent was prepared from 1,5-dibromopentane by treating 1 mol of magnesium with 0.44 mol of the dibromide in 500 ml of tetrahydrofuran (THF, dried over calcium hydride). After the exothermic reaction had subsided, the mixture was stirred at room temperature for 3 hr. A solution of 0.5 mol of the appropriate phosphonous dichloride in 300 ml of THF was added dropwise while the reaction was controlled with cooling. The dark color of the Grignard solution lightened and a white solid precipitated. The mixture was stirred overnight (24 hr for the less reactive *tert*-butyl), and then hydrolyzed with 600 ml of saturated NH_4Cl solution, added slowly with cooling. After all solid had been dissolved, the layers were separated. The aqueous layer was extracted with three 200-ml portions of ether; the original organic layer was combined with the other extracts, and drying was performed with $MgSO_4$. Solvent was then stripped off and the residue was distilled. The products with lower molecular weight were pyrophoric and required special care in handling. New phosphines were further characterized by conversion to their sulfides. Data for the compounds prepared are given in Table IV.

Synthesis of Phosphorinane Sulfides (4). Following a reported procedure,[27] the phosphorinane (5 mmol) in 50 ml of benzene was treated with 0.2 g of sulfur, and the mixture was refluxed for 2–3 hr. Unreacted sulfur was removed by filtration of the hot solution. The benzene was evaporated and the residue was recrystallized from petroleum ether or cyclohexane. Sulfides so obtained are listed in Table IV.

***r*-1,*t*-4-Dimethyl-*c*-4-phosphorinanol Sulfide (7a) and *r*-1,*c*-4-Dimethyl-*t*-4-phosphorinanol Sulfide (8a).** 1-Methyl-4-phosphorinanone[28] (3.9 g, 0.03 mol) in 20 ml of THF was added slowly to a solution of 52.2 ml of 2.3 M methyllithium in ether and 20 ml of THF. The mixture was refluxed for 24 hr and then cooled (ice bath). Cold water (20 ml) was added cautiously, and the mixture was stirred for 30 min. It was then extracted with ether, and the extract was dried ($MgSO_4$) and distilled. Product (2.5 g, 57%) was collected at 59.5–60.5° (0.6 mm); it consisted of a 2:3 mixture (determined[29] by ^1H and ^{31}P nmr differences) of phosphines **5** and **6**, R = CH_3. The product was placed in 50 ml of benzene and converted to the sulfide as for **2**. The isomeric sulfides were separated by repeated fractional crystallization from benzene. Isomer **8a** was the less soluble. Properties are given in Table V.

***r*-1-Methyl-*t*-4-*tert*-butyl-*c*-4-phosphorinanol Sulfide (7b) and *r*-1-Methyl-4-*c*-*tert*-butyl-*t*-4-phosphorinanol Sulfide (8b).** A cis–trans (2:3) mixture of 1-methyl-4-*tert*-butyl-4-phosphorinanol[29] was converted to the isomeric sulfides by the same procedure as used for **2**. Repeated fractional crystallization from benzene gave the less soluble **8b** in isomerically pure condition; **7b** could not be obtained in pure form, and a 1:1 isomer mixture was used for the spectral study. Properties are given in Table V.

Table IV
Properties of Phosphorinanes and Their Sulfides

A. Phosphorinanes (1)

R	Yield, %[a]	Bp, °C (mm)	Lit. bp, °C (mm)
C_6H_5	32	68–72 (0.2)	119(3.0)[b]
CH_3	38	144–147 (760)	
C_2H_5	20	65–69 (19)	170(760)[b]
i-C_3H_7	24	79–84 (19)	
t-C_4H_9	45	95–99 (20)	

B. Phosphorinane Sulfides (4)

R	Mp, °C	Lit. mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
C_6H_5	71–73[c]	83,[d] 86[b]	$C_{11}H_{15}PS$	62.83	7.19	14.73	62.61	6.97	14.59
CH_3	49–50	51–52[e]							
C_2H_5	68.5–69.5	67[d]							
i-C_3H_7	147–148.5		$C_8H_{17}PS$	54.51	9.72	17.57	54.39	9.93	17.43
t-C_4H_9	145–147		$C_9H_{19}PS$	56.81	10.06	16.28	57.04	10.30	16.05

[a] General procedure is described in the Experimental Section. [b] K. Issleib and S. Häusler, *Chem. Ber.*, **94**, 113 (1961). [c] This value was obtained on a sample crystallized from petroleum ether[b,d] and also on a sublimed sample. The analysis was satisfactory; the discrepancy with the literature melting point values is unresolved. [d] Reference 27. [e] L. Maier, *Helv. Chim. Acta*, **48**, 133 (1965).

Table V
Properties of 4-Phosphorinanol Sulfides

Registry no.	Compd	Mp, °C	δ PCH_3	J_{PCH}, Hz[a]	δ ^{31}P[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
52032-45-8	7a	103–105	2.37	13.5	−31.1	$C_7H_{15}OPS$	47.17	8.48	17.38	47.30	8.52	17.37
52032-46-9	8a	168–170	2.32	13.0	−28.8	$C_7H_{15}OPS$	47.17	8.48	17.38	47.08	8.55	17.62
52032-47-0	7b	*c*	1.79	14.0	−31.9							
52032-48-1	8b	146–148	1.75	13.5	−29.4	$C_{10}H_{21}OPS$	54.52	9.61	14.06	54.43	9.78	14.38
52109-47-4	7c	190–192	1.79	13.5	−32.0	$C_{12}H_{17}OPS$	59.98	7.13	12.89	59.83	7.10	12.76
52109-48-5	8c	182–184	1.82	13.0	−29.1	$C_{12}H_{17}OPS$	59.98	7.13	12.89	59.91	7.25	12.69

[a] In $CDCl_3$ with internal TMS except for **7a** and **8a** (external TMS). [b] Obtained on $CHCl_3$ solutions, except for **7c** and **8c** (methanol). Values were obtained for isomerically pure specimens, except for **7a** and **7b**. [c] Obtained only in admixture with **8b**.

***r*-1-Methyl-*t*-4-phenyl-*c*-4-phosphorinanol Sulfide (7c) and *r*-1-Methyl-*c*-4-phenyl-*t*-4-phosphorinanol Sulfide (8c).** 1-Methyl-4-phenyl-4-phosphorinanol (58% cis, 42% trans)[28] was treated with sulfur as in the synthesis of **2**. Fractional crystallization from benzene gave the less soluble **8c** in pure form. To obtain pure **7c**, the mixture was separated by high-pressure liquid chromatography using a 1:9 v/v mixture of acetonitrile and chloroform on a column of Porasil A. Properties are given in Table V.

The sulfides were also obtained by adding phenylmagnesium bromide [made from 0.8 g (0.03 mol) of magnesium and 4.7 g (0.03 mol) of bromobenzene in 100 ml of THF] to 2.4 g (0.015 mol) of 1-methyl-4-phosphorinanone sulfide[30] in 50 ml of THF. The mixture was refluxed for 4.5 hr, and then hydrolyzed (ice bath) with 10 ml of cold water and 40 ml of 25% NH_4Cl. After standing overnight, the mixture was extracted with chloroform; the extract was dried ($MgSO_4$) and evaporated to leave a crystalline mass. The crystals were washed with a small amount of methanol; the yield was 3.6 g (50%) with the approximate composition 50% **7c** and 50% **8c**.

Registry No.—**5a**, 42565-01-5; **5b**, 33835-61-9; **5c**, 16327-56-3; **6a**, 42565-02-6; **6b**, 33835-62-0; **6c**, 16327-57-4.

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(18) We observe the same effect on addition of oxygen to 1-ethylphosphorinane: the oxide in $CHCl_3$ with internal TMS has δ $C_{2,6}$ = 166.0 ($^1J_{PC}$ = 62 Hz), δ $C_{3,5}$ = 170.0 (5 Hz), δ C_4 = 166.0 (7 Hz); CH_2 in the ethyl substituent has δ 172.3 (66 Hz) and CH_3 has δ 187.5 (5 Hz). The upfield shift relative to the phosphine (Table I) of 1.2 ppm at $C_{3,5}$ suggests a shielding effect for oxygen, which is presumably largely axial. Also, the spectrum of 1-phenylphosphorinane 1-oxide has been reported by others,[19] and the same effect is seen at $C_{3,5}$; on the TMS scale, 22.54 is reported, while our value for the corresponding phosphine on this scale is 23.4.
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Proton Magnetic Resonance and ^{31}P Nuclear Magnetic Resonance Studies of Substituted Phospholan-3-one 1-Oxides[1]

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A study of the pmr and ^{31}P nmr spectra of a series of 3-phospholanone 1-oxides is reported. Both types of nmr spectra and infrared analysis indicate that an enol–keto tautomerism exists in the solid state and in F_3CCO_2H solution. The following 1-oxides were investigated: 1-benzyl-2-phenylphospholan-3-one, 1-benzyl-2-phenyl-4-methylphospholan-3-one, 1-benzyl-2-phenyl-5-methylphospholan-3-one, 1-benzyl-2-phenyl-4,5-dimethylphospholan-3-one, 1-benzyl-2,5-diphenylphospholan-3-one, and also 4-oxo-2-benzyl-2-phosphabicyclo[3.3.0]octane 2-oxide. Comparison of chemical shifts and coupling constants for HH and $H^{31}P$ with model systems indicates that substituents at C-5 of the phospholan-3-one ring are cis with respect to the P→O group. For substituents at both C-5 and C-4 the relationship with the P→O group is tentatively given as cis and trans, respectively. Methylation of several of these phospholan-3-one 1-oxides gave the corresponding *O*-methyl ethers except for 1-benzyl-2-phenyl-4-methylphospholan-3-one 1-oxide, which afforded 1-benzyl-2-phenyl-2,4-dimethylphospholan-3-one 1-oxide.

As part of a continuing study of the chemistry of saturated, polycyclic carbon–phosphorus heterocycles,[3,4] we have examined the pmr and ^{31}P nmr spectra of several substituted phospholan-3-one 1-oxides.[5] To our knowledge, no systematic spectral analysis of the molecular geometry of these systems has been published. Although our primary objective was to determine the stereochemistry of these products, it was noted that the condensation of dibenzylphosphine oxide with α,β-unsaturated esters in the presence of NaH in THF was dependent upon the concentration of NaH with respect to the yield of the corresponding cyclic 1-oxides **1**–**7** (Chart I), an observation not recorded in the pioneering work in this area.[5a] As will be noted in Table I, this dependence on concentration of NaH may be of a steric nature, since differences in yield were not observed until the α,β-unsaturated ester was ethyl tiglate, ethyl cinnamate, or carbethoxycyclopentene. The presence of a bulky substituent (R′) of **9** may hinder the conversion of **9** to **10** as proposed originally (Scheme I).[5a] This situation could necessitate the addition of a second equivalent of NaH to convert **9** or **10** to the dianion **11**, which may then cyclize to the desired phospholan-3-one 1-oxide. Although the conditions of the reaction were generally not meticulously optimized for each compound, it is likely with careful manipulation that excellent conversions can be expected with 2 equiv of NaH. Whether or not a dianion such as **11** participates cannot be answered unequivocally, since **12** appears to exist heavily in the enol form even in the

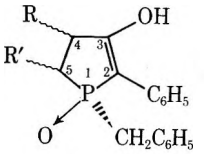
Table I
Yields and Physical Data for the Substituted Phospholan-3-one 1-Oxides

Compd	% yield of 1-oxide: 1 equiv NaH	2 equiv NaH	Mp, °C	Molecular formula	Anal., % (P)	
1[a,b]	49	59	207–208	$C_{17}H_{17}O_2P$	Calcd	10.89
					Found	10.54
2[a]	76	62	216–218	$C_{18}H_{19}O_2P$	Calcd	10.38
					Found	10.19
3	54	49	221.5–223	$C_{18}H_{19}O_2P$	Calcd	10.38
					Found	10.12
4	81	75	181–183	$C_{19}H_{21}O_2P$	Calcd	9.92
					Found	9.74
5[a]	45	89	217–219	$C_{23}H_{21}O_2P$	Calcd	8.59
					Found	8.31
6[a]	67	83	225–226	$C_{20}H_{21}O_2P$	Calcd	9.55
					Found	9.21
7		6[c]	225–226	$C_{23}H_{21}O_2P$	Calcd	8.59
					Found	8.57

[a] These compounds were previously reported in ref 5a. [b] Registry no., 40203-63-2. [c] A yield of 73% of the open-chain compound $(C_6H_5CH_2)_2P(O)CH(C_6H_5)CH(CO_2C_2H_5)_2$ was also obtained. *Anal.* Calcd for $C_{28}H_{31}O_5P$: P, 6.47. Found: P, 6.43. Compound **7** is believed to be the 3 isomer **12b**.

Chart I

$(C_6H_5CH_2)_2P(O)H + NaH \xrightarrow[2.\ R'CH{=}C(R){-}CO_2C_2H_5]{1.\ THF,\ \Delta,\ 15\ min} \xrightarrow{3.\ H_3O^+}$

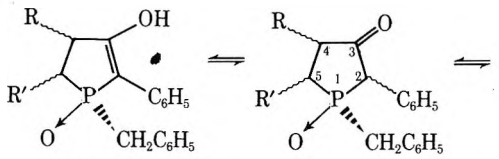


1-7

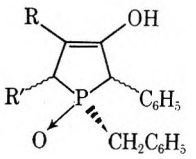
Compd	R	R′
1	H	H
2	CH_3	H
3	H	CH_3
4	CH_3	CH_3
5	H	C_6H_5
6	$-(CH_2)_3-$	
7[a]	H	C_6H_5

[a] Minor product from the above reaction utilizing diethyl benzalmalonate as the α,β-unsaturated ester, with the double bond between C-3 and C-4.

solid state. Although the double bond may be formed between C-2 and C-3 (**12a**) or C-3 and C-4 (**12b**), enolization



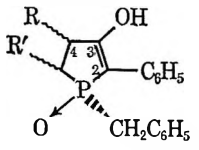
12a **12**



12b

between C-2 and C-3 would probably be favored owing to conjugation with the 2-phenyl substituent and the phosphoryl group. Table II lists the major infrared absorption maxima for the phospholan-3-one 1-oxides. The predominance of the enol form is quite apparent with the appearance of a broad OH absorption between 2445 and 2532 cm^{-1} and the olefinic absorption between 1595 and 1615 cm^{-1}.[6,7]

Table II
Major Infrared Absorption Maxima of the Substituted Phospholan-3-one 1-Oxides[a]



Compd	R	R′	OH	-C=C-	P→O
			← cm⁻¹ →		
1	H	H	2500	1608	1101
2	CH_3	H	2445	1600	1087
3	H	CH_3	2505	1615	1099
4	CH_3	CH_3	2489	1603	1105
5	H	C_6H_5	2532	1613	1130
6	$-(CH_2)_3-$		2483	1595	1106
7[b]	H	C_6H_5	2469	1607	1098

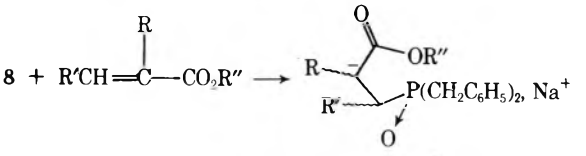
[a] The spectra were obtained on samples (4 mg) with KBr (400 mg) pellets. [b] This structure is suggested to have the double bond located between positions 3 and 4.

Assuming that **9** or **11** are the logical precursors of **12a**, it is quite reasonable that epimerization at position **4** could occur, since that carbon atom holds a negative charge and would expectedly assume the most stable configuration with respect to adjacent groups. Consequently, one isomer could well be envisioned as a final product. Deduction of the stereochemistry at positions 1, 4, and 5 for this isomer has heretofore been unreported, although it is crucial for not only understanding the mechanism of ring closure but also for making the method of further synthetic utility.

Scheme I

$(C_6H_5CH_2)_2P(O)H + NaH \xrightarrow[\Delta]{THF} (C_6H_5CH_2)_2P(O)^-Na^+ + H_2$

8



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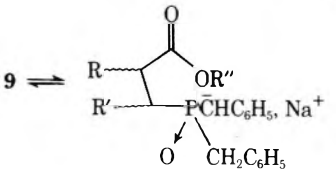

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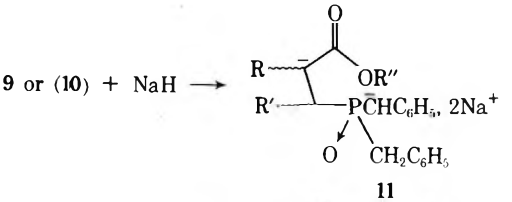

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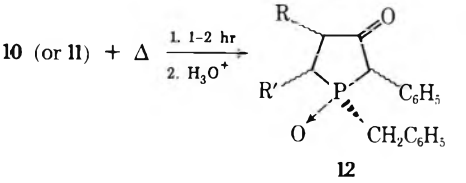
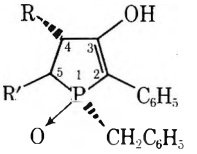


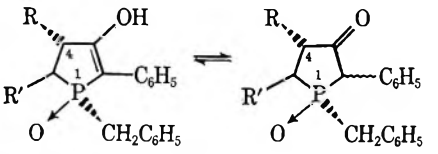
12

Structural models constructed from several sets of molecular models (including Courtauld models) strongly suggest a cis arrangement for P→O *vs.* R′ (C-5) and a trans arrangement for R′ *vs.* R (at C-5 *vs.* C-4) on the basis of molecular crowding in either the keto or enol form. Since



solubilities in all organic solvents tested was negligible (a few of these oxides were reported[5a] soluble in CH_3OH but we could not reproduce this observation to the extent that a signal could be detected by nmr analysis at 100 MHz), 2–3 drops of F_3CCO_2H was always added to a suspension of the compound in $DCCl_3$. Solution occurred rapidly but, of course, this process would expectedly favor enol formation. Enolization at C-2 to give a conjugated system (**12a**) involving the 2-phenyl substituent and the phosphoryl groups is preferred. This preference is supported by the observations that with varying acid concentrations, signals for

Table III
^{31}P Resonances of Enol–Keto Equilibria Relative to H_3PO_4[a]



Compd	Enol, ppm	Rel abundance, %	Registry no.	Keto, ppm	Rel abundance, %	Registry no.
1	−77.2	98	52050-76-7	−59.8	2	40203-59-6
2[b]	−74.4	34.2	52050-77-8	−55.5	11.5	52080-01-0
	−70.0	45		−53.3	9.3	
3	−77.6	91.7	52050-78-9	−62.9	8.3	52050-82-5
4[b]	−70.4	67.8	52050-79-0	−57.7	12.3	52050-83-6
	−68.4	10.2		−51.6	9.7	
5	−71.4	92.9	52050-80-3	−59.0	7.1	52080-02-1
6	−72.3	92.5	52050-81-4	−56.8	7.5	52080-03-2

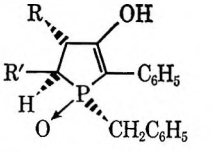
[a] The spectra were obtained on samples (1.5 g) in $DCCl_3$ (4 ml) with 4–5 drops of CF_3CO_2H added, which would favor the enol form. [b] Resonances believed to be due to cis–trans isomers involving the methyl group at C-4 with respect to the phosphoryl group in each tautomer.

the protons at C-4 (as in **1**) were not removed nor was the doublet observed for a methyl substituent at C-4 (as in **2**) converted to a singlet. These changes would be expected if enolization at the third bond in oxides **1–6** to form **12b** were to occur. Consequently, we feel that the stereochemistry at C-4 relative to that at positions 1 and 5 is unchanged.

^{31}P nmr analysis of compounds **1–6** confirmed this enol–keto equilibrium (Table III). At least two signals were observed in each case for these relatively concentrated solutions.[8] The resonance signal furthest downfield with respect to 85% H_3PO_4 was assigned the enol form in agreement with the infrared data (Table II), pmr spectra (Table IV), and the reported ^{31}P assignments for the enol–keto forms of 1-methylphospholan-3-one 1-oxide of −60.5 and −51.0 ppm, respectively.[6] The observation of four signals for **2** is considered to result from epimerization at C-4 during the course of the cyclization involving intermediates **9** or **11**. Thus, the possibility of cis–trans isomers at C-4 with respect to the phosphoryl group exists which would yield signals for two enol forms and for two keto forms.[9] Although a similar situation might be anticipated for the dimethyl derivative **4**, epimerization in this case may be hindered by the presence of the methyl at C-5, and the initial trans relationship of the two methyls of ethyl tiglate may be expected to be retained. This hypothesis is substantiated by the observation that 9% (by glc analysis) ethyl angelate was initially present in the commercial ethyl tiglate and could contribute to the signal at −68.4 ppm observed in only 10% relative abundance (proposed to be the *cis*-dimethyl derivative). Since none of these compounds other than **7** indicated the presence of a proton resonance for C-2 in the pmr spectra, the possibility of cis–trans isomers at C-2 in order to explain the two keto signals of **2** and **4** is not considered tenable.

Resolution of the pmr spectra was best with the substituted oxides **2, 3, 4,** and **5** (Table IV). The benzylic protons ($PCH_2C_6H_5$) are at nearly identical δ values and the J_{PCH} values are quite comparable (18 Hz). The possibility of cis–trans isomers for the methyl at C-4 of **2** discussed earlier is substantiated by the presence of two doublets, δ 0.71 and 1.25 ppm (J_{HCCH} = 7.0 Hz for both doublets), of nearly equivalent intensity. Focusing on δ positions for the methyl protons at C-5 in **3** (Figure 1) and **4**, there is very similar shielding (δ 1.19 and 1.22 ppm) and coupling (J_{PCCH_3} = 16.5 *vs.* 17 Hz and J_{HCCH} = 7.0 *vs.* 7.0 Hz) in **3** and **4**, respectively. The proton at C-5 of **3** and **4** experiences a slightly different shielding environment (δ 2.44 and 1.89 ppm); however, the couplings are comparable (J_{HCCH} = 7.0 *vs.* 7.0 Hz and J_{PCH} = 7 *vs.* 7 Hz) for **3** and **4**, respectively. Extensive homonuclear and heteronuclear decoupling (^1H and ^{31}P) confirmed these assignments. Although decoupling experiments on **5** were not as definitive as desired because of overlap of signals for the proton at C-5 and the benzylic doublet, an approximate J_{PCH} = 7 Hz was observed for the C-5 proton.

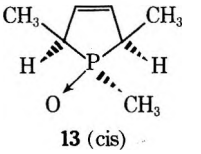
Table IV
Pmr Data for the Substituted Phospholan-3-one 1-Oxides[a]



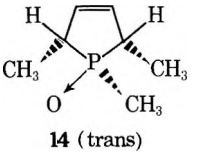
	δ, ppm					
		C-4		C-5		
Compd	$PCH_2C_6H_5$[b]	CH	CH_3	CH	CH_3	C_6H_5
1	3.43 (18.0)	2.34		2.34		7.25
2	3.49 (18.0)	1.87	0.71[c]	2.48		7.25
			1.25			
3	3.46 (17.5)	2.44		2.44[d]	1.19[e]	7.22
4	3.44 (18.0)	2.61[f]	0.91[g]	1.89[h]	1.22[i]	7.20
5	3.57 (18.0)	2.95		3.57		7.33
6[j]	3.51 (18.0)	2.80		2.80		7.25
7	3.17 (18.0)	6.51		3.67		7.20

[a] Spectra obtained on $DCCl_3$ solutions of each compound with 2–3 drops of CF_3CO_2H added. [b] Resonances were doublets due to ^{31}P coupling with $J_{PCH_2C_6H_5}$ (Hz) in parentheses. [c] Two doublets, J_{HCCH} = 7.0 Hz for each; possibility of cis–trans isomers about C-4 with respect to P→O. [d] Multiplet, J_{HCCH} = 7.0, J_{PCH} = 7 Hz. [e] Doublet of doublets, J_{HCCH} = 7.0, J_{PCCH_3} = 16.5 Hz. [f] Multiplet, J_{HCCH} = 7 Hz. [g] Doublet, J_{HCCH} = 7 Hz. [h] Multiplet, J_{HCCH} = 7, J_{PCH} = 7 Hz. [i] Multiplet, J_{HCCH} = 7, J_{PCCH_3} = 17.0 Hz. [j] $-(CH_2)_3-$ resonance at 1.80 ppm.

Model systems are rare for a comparison of J_{PCH} couplings when the P→O group is cis or trans to the C–H bond on an α carbon atom of phospholane 1-oxides. However, others[10] have found a J_{PCH} = 6.50 Hz for cis (**13**) and J_{PCH}



13 (cis)



14 (trans)

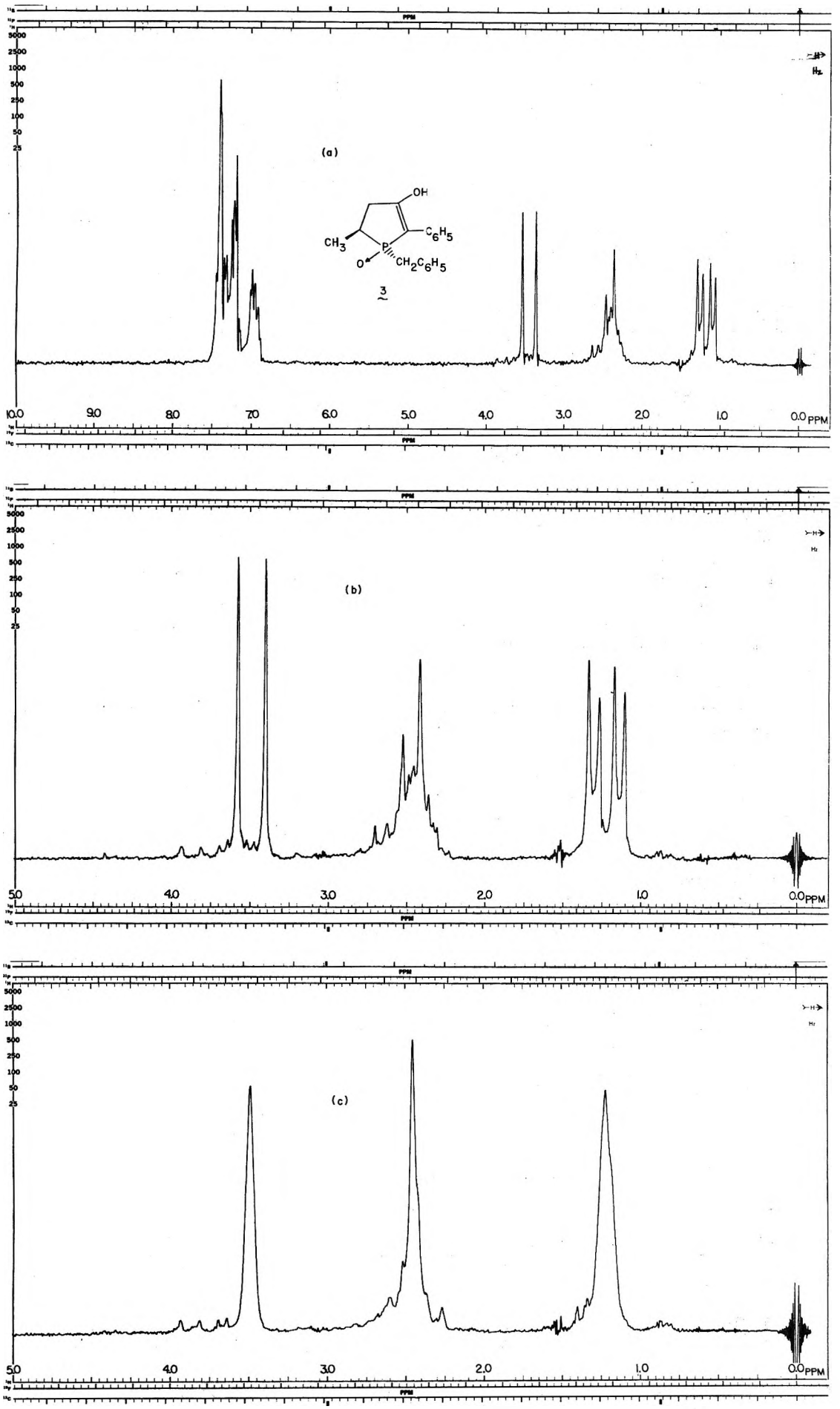
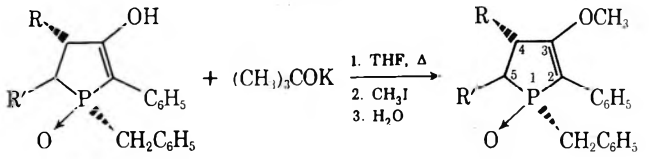


Figure 1. (a) Pmr spectrum of **3** ($DCCl_3$/3 drops of F_3CCO_2H) obtained at 100 MHz; (b) spectrum of the area 0–5.0 ppm of (a) expanded at 100 MHz; (c) ^1H spectrum for the 0–5.0 ppm area (b above) while irradiating ^{31}P (40.548 MHz). TMS is the internal standard.

Chart II



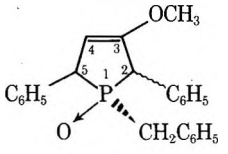
15-17

Compd	R	R′	% yield of O-methylated oxide
15	H	CH_3	86
16	H	C_6H_5	79
17	$-(CH_2)_3-$		82

= 13.5 Hz for trans (**14**) in $DCCl_3$. Thus, in the cis isomer **13** the P→O and C–H bonds are trans. Our values of J_{PCH} = 7.0 Hz for the C-5 proton for **3**, **4**, and **5** strongly suggest a similar stereochemistry as in **13**. Additional support is available on this point from ^{13}C–^{31}P couplings in the *P*-phenyl analogs of **13** and **14** as well as in the *P*-methyl compounds **13** and **14**.[10b] From the ^{13}C spectra, it was concluded that with a trans relationship of the P→O group *vs.* the CCH_3 group (at the α carbon), the methyl group was more deshielded.[10b] These conclusions were based in part on similar observations with the corresponding phosphines and on the assumption that the stereochemistry is preserved in oxidation to the phosphine oxides, which is reasonable and well known in the literature.[11]

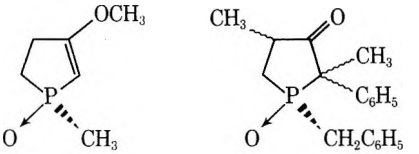
The J_{HCCH_3} = 7 Hz coupling in **3** and **4** is normal and the J_{HCCH} = 7 Hz is likewise defensible. Models imply the system may not deviate much from planarity. On this reasonable assumption, the *J* value for HCCH vicinal coupling is defensible for a trans arrangement.[12] In the case of **4**, this situation may also be defended on steric considerations in the anion **9** in that proton addition to the enolate ion will occur in such a manner that the methyl at C-4 is positioned trans to the methyl group at C-5. However, without a substituent at C-5 as in **2**, inversion may occur at C-4 prior to hydrogen exchange to give **10** or prior to closure of **11** to give, after neutralization, **12**. Epimerization may also occur with **12**, since the reaction mixture is basic ($C_2H_5O^-$ is displaced) prior to work-up. This would explain the observed signals for the protons on the cis or trans methyl group at C-4 of **2**.

Methylation of **3**, **5**, and **6** in THF with $(CH_3)_3COK$ and CH_3I at room temperature or 40° gave the corresponding *O*-methyl ethers (**15–17**, Chart II) in high yield. In the case of **7** (with the alkene linkage of the enol between C-3 and C-4), methylation under identical conditions yielded (87%) the corresponding *O*-methyl ether **18**. Infrared and pmr



18

analysis of these O-methylated phospholan-3-one 1-oxides indicated that the alkylation occurred at the enolic oxygen atom. The evidence is the olefinic absorption in the ir spectrum (1575–1592 cm^{-1}) (Table V) and the presence of a sharp singlet for the *O*-methyl resonance in the pmr spectra (δ 3.58–3.74 ppm) (Table VI). This would indicate that the environment around the *O*-methyl groups was very much alike and similar to that observed (δ 3.78 ppm) for the *O*-methyl ether **19**.[6] The relationship of the C-5 substit-



19 **20**

uents with respect to the phosphoryl group of these *O*-methyl ethers also has not changed, since the C-5 methyl of **15** (R = H; R′ = CH_3) (Figure 2) appears as a doublet of doublets, δ 1.23 ppm (J_{HCCH} = 7.0 and J_{PCCH_3} = 15 Hz) compared to a doublet of doublets, δ 1.19 ppm (J_{HCCH} = 7.0 and J_{PCCH_3} = 16.5 Hz) for the starting compound **3**.

An exception to the observed methylations to afford the *O*-methyl ethers was noted in the case of 1-benzyl-2-phenyl-4-methylphospholan-3-one 1-oxides (**2**). The major product isolated in a 67% yield was the C-2 methylated derivative 1-benzyl-2-phenyl-2,4-dimethylphospholan-3-one 1-oxide (**20**). The infrared spectrum displayed a strong band for the C=O at 1725 cm^{-1} and a shift in the P→O vibration to 1179 cm^{-1} (Table V).[13] Pmr analysis did not afford a singlet indicative of the other *O*-methyl derivatives (**15–18**) but instead a doublet appeared (δ 1.76 ppm, J_{PCCH_3} = 12 Hz) in addition to the doublet for the methyl at C-4 (δ 1.34 ppm, J_{HCCH} = 7.0 Hz).[14] Interestingly, the

Table V
Major Infrared Absorption Maxima of the *O*-Methyl Phospholan-3-one 1-Oxides[a]

Compd	Registry no.	ν, cm^{-1} –C=C–	ν, cm^{-1} P→O
15	52050-84-7	1592	1173
16	52050-85-8	1575	1159
17	52050-86-9	1583	1167
18	52050-49-4	1583	1172
20	52050-50-7	(1725)[b]	1179

[a] The spectra were obtained on samples (4 mg) with KBr (400 mg) pellets. [b] Absorption of the C=O of the C-methylated product.

Table VI
Pmr Data for the *O*-Methyl Phospholan-3-one 1-Oxides[a]

Compd	$PCH_2C_6H_5$[b]	OCH_3[c]	δ values C-4 CH	C-4 CH_3	C-5 CH	C-5 CH_3	C-2 CH	C_6H_5
15	3.27 (17.5)	3.60	2.25		2.25	1.23[d]		7.41
16	3.22 (18.0)	3.65	2.87		3.22			7.24
17[e]	3.27 (18.0)	3.58	2.20		2.20			7.43
18	3.02 (16.0)	3.74	6.53[f]		2.42		2.42	7.35
20[g]	2.58		2.58	1.34[h]	2.58		(1.76)[i]	7.24

[a] Spectra obtained on $DCCl_3$ solutions of each compound with TMS as internal standard. [b] Resonances were doublets due to ^{31}P coupling with $J_{PCH_2C_6H_5}$ (Hz) in parentheses. [c] Resonances were intense singlets in all cases except **20**. [d] Doublet of doublets, J_{HCCH} = 7.0, J_{PCCH_3} = 15 Hz. [e] Resonances for $-(CH_2)_3-$ also appear as a broad multiplet at 2.20 ppm [f] Vinylic resonance due to –C=C– between C-3 and C-4. [g] Possible C-methylation at C-2 rather than O-methylation. [h] Doublet, J_{HCCH} = 7.0 Hz. [i] Resonance for methyl group at C-2 appearing as a doublet, J_{PCCH_3} = 12 Hz.

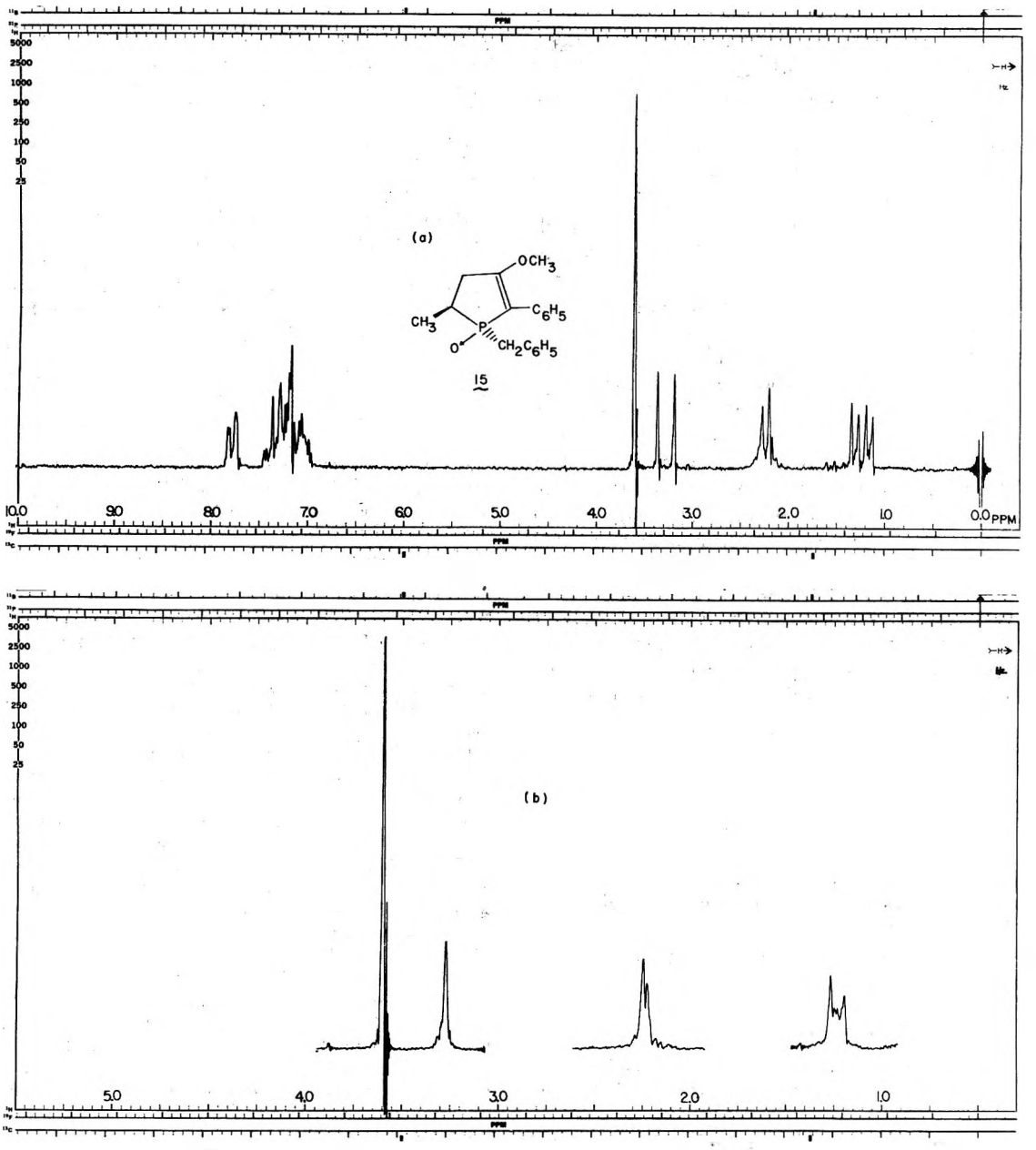


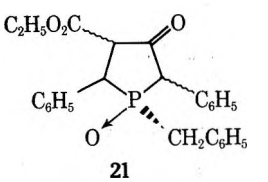
Figure 2. (a) Pmr spectrum of **15** ($DCCl_3$) obtained at 100 MHz; (b) ^1H spectrum for the 0–5.0 ppm area of (a) while irradiating ^{31}P (40.548 MHz). TMS is the internal standard.

two doublets observed for the isomers (cis–trans C-4 methyl group) of **2** (Table IV) afforded only the one doublet (Table VI) in the methylated product indicating a possible interconversion of one to the other. Also it was noted that the benzylic protons are no longer equivalent, appearing as two doublets (J_{HCH} = 7.0 and $J_{PCH_2C_6H_5}$ = 16.0 Hz). Extensive homonuclear and heteronuclear decoupling (^1H and ^{31}P) supported these assignments. The mass spectral and elemental analysis supported the hypothesis that methylation had occurred (Table VII).[15]

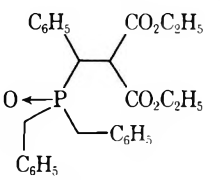
Table VII
Physical Properties for Products from Methylations of Phospholan-3-one 1-Oxides

Compd	Mp, °C	Molecular formula	Anal., % (P)	
15	150–151	$C_{19}H_{21}O_2P$	Calcd	9.92
			Found	9.89
16	177–179	$C_{24}H_{23}O_2P$	Calcd	8.27
			Found	8.27
17	148.5–150	$C_{21}H_{23}O_2P$	Calcd	9.15
			Found	9.19
18	142–144	$C_{24}H_{23}O_2P$	Calcd	8.27
			Found	8.14
20	154–155.5	$C_{19}H_{21}O_2P$	Calcd	9.92
			Found	9.97

In attempting to extend the condensation of dibenzylphosphine oxide with α,β-unsaturated esters (eq 1) to α,β-unsaturated diesters, such as diethyl benzalmalonate, the reaction did not afford 1-benzyl-2,5-diphenyl-4-carbethoxyphospholan-3-one 1-oxide (**21**), even with 2 equiv of NaH in THF and 18 hr at reflux. Instead, **22** was isolated (73%)



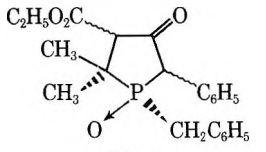
21



22

along with **7** (6%). The structure of **22** is based upon ir, pmr, mass spectral, and elemental analysis. The formation of **7**, which is believed to be isomeric with **5**, with the dou-

ble bond between C-3 and C-4 rather than C-2 and C-3, may arise from very slow cleavage of the residual ester group of **21** (perhaps during work-up) to give a carboxyl group β to the keto group. Decarboxylation could then occur to give the oxide **7** with the enol in the observed position. This assignment is based on the observed differences in infrared absorption [2469 (OH), 1607 (-C=C-), and 1098 cm^{-1} (P→O) for **7** *vs.* 2532 (OH), 1613 (-C=C-), and 1130 cm^{-1} (P→O) for **5**] and the presence of a vinylic multiplet (δ 6.51 ppm) for the C-4 proton of **7** and broad doublets for the protons at C-2 and C-5 (δ 3.67 ppm) in the pmr spectrum. The mass spectral[15] and elemental analysis (Table I) also support this structure. Methylation of **7** gave a product with the alkene linkage retained between C-3 and C-4 and was designated as the *O*-methyl ether **18** [ir 1583 (-C=C-) and 1172 cm^{-1} (P→O) for **18** *vs.* 1575 (-C=C-) and 1159 cm^{-1} (P→O) for **16** (R = H; R′ = C_6H_5) derived from **5** (Table V)]. The vinylic signal for the C-4 proton is also retained in the pmr spectrum of **18** (Table VI). The mass spectral and elemental analysis support an *O*-methyl structure for **18** and isomerism with **16** (Table VII). The inability to undergo cyclization observed for the diester diethyl benzalmalonate does not appear to be general, since utilizing diethyl isopropylidenemalonate and 3 equiv of NaH in the condensation with dibenzylphosphine oxide afforded 1-benzyl-2-phenyl-5,5-dimethyl-4-carbethoxyphospholan-3-one 1-oxide (**23**) as the major product.



23

Infrared, pmr, mass spectral, and elemental analysis again argue for the structure assigned. An extension of this synthetic procedure to other α,β-unsaturated systems is currently under study.

Experimental Section

General Procedure. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A unit as KBr pellets. Pmr and ^{31}P nmr spectra were obtained with a XL-100 (15) Varian spectrometer in $DCCl_3$ with 3–4 drops of CF_3CO_2H added in the case of the substituted phospholan-3-one 1-oxides. Mass spectral analysis was performed on a CEC Model 21 HR unit. Anhydrous THF was obtained fresh for each run by distillation from NaH immediately before use.

Starting Materials. Dibenzylphosphine oxide was prepared by a literature procedure.[16] Carbethoxycyclopentene was also prepared by a published route[17] with the modification that reduction of 2-carbethoxycyclopentanone to 2-carbethoxycyclopentanol was achieved with $NaBH_4$. All other esters were either commercially available or were prepared in routine fashion from esterification of commercial acids.

Although the preparation of some of these oxides was reported while our work was in progress[5a] (except for ethyl crotonate, ethyl tiglate, diethyl benzalmalonate, and diethyl isopropylidenemalonate), experimental details were not included. Therefore, our general procedure will be described. Standard apparatus used was a 500-ml, three-necked, round-bottomed flask equipped with mechanical stirrer, additional funnel, condenser, and N_2 inlet. The preparation of 1-benzyl-2,5-diphenylphospholan-3-one 1-oxide (**5**) will be described using 1 and 2 equiv of NaH.

1-Benzyl-2,5-diphenylphospholan-3-one 1-Oxide (5). A. From 1 Equiv of NaH. A slurry of 1.7 g (55.6% in mineral oil, 0.04 mol) of NaH in 50 ml of anhydrous THF at room temperature was treated with 9.2 g (0.04 mol) of dibenzylphosphine oxide in 50 ml of THF. The resulting mixture was heated at reflux for 15 min with vigorous evolution of a gas (presumed H_2) and with formation of a clear, pale-yellow solution. This solution heated to reflux was treated (dropwise) with a solution of 7.05 g (0.04 mol) of ethyl cinnamate in 75 ml of THF. After addition, the dark yellow mixture was boiled (2 hr), cooled to room temperature, and hydrolyzed (25 ml of 1.6 *N* ammonium chloride solution). Two layers separated upon saturation (NaCl) and the aqueous layer was extracted (2 × 100 ml) with THF. The dried ($MgSO_4$) organic extracts were evaporated *in vacuo* to give a pale yellow powder. Recrystallization of this powder from C_2H_5OH–H_2O (1:1) afforded 6.5 g (45%) of a white solid, mp 217–219° (lit.[5] mp 217–219°). Infrared, nmr, and analytical data are found in Tables I–IV.

B. From 2 Equiv of NaH. A slurry of 1.3 g (55.6% dispersion in mineral oil, 0.03 mol) of NaH in 50 ml of anhydrous THF at room temperature was treated with 6.9 g (0.03 mol) of dibenzylphosphine oxide in 50 ml of THF. Again the mixture was boiled for 15 min with much evolution of a gas and with formation of a clear, pale-yellow solution. While boiling, the solution was treated with 5.3 g (0.03 mol) of ethyl cinnamate in 75 ml of THF. When addition was complete, the mixture was boiled for 2 hr and treated with another slurry of 1.3 g (0.03 mol) of NaH in 50 ml of THF. After another 2 hr at reflux (much gas evolved), the solution was cooled to room temperature and hydrolyzed with 30 ml of 2 *N* acetic acid. Two layers resulted upon saturation (NaCl) and the aqueous layer was extracted (2 × 100 ml) with THF. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to leave a white powder. Recrystallization (C_2H_5OH–H_2O) gave 9.6 g (89%) of the desired phospholan-3-one 1-oxide, mp 217–219°. Infrared, nmr, and analytical data for the other substituted phospholan-3-one 1-oxides prepared by the above procedures are given in Tables I–IV.

***O*-Methyl Derivative of 1-Benzyl-2,5-diphenylphospholan-3-one 1-Oxide (16).** A mixture of 1.0 g (2.7 mmol) of the oxide **5** in 25 ml of anhydrous THF was treated with 0.34 g (3 mmol) of $(CH_3)_3COK$ in 25 ml of THF at room temperature. After 1 hr the yellow solution was treated with 0.5 g (3.5 mmol) of CH_3I in 25 ml of THF. After complete addition, the orange mixture was stirred for 1 hr at room temperature and hydrolyzed (25 ml H_2O), and the resulting mixture was extracted (1 × 50 ml of THF). The organic extracts were dried ($MgSO_4$) and the THF was removed by evaporation to afford a yellow powder. Two recrystallizations (C_6H_6–C_6H_{12}) gave 0.8 g (79%) of the *O*-methyl ether **16**, mp 177–179°, mass spectrum (70 eV) *m/e* 374 (M^+). Infrared and nmr data are given in Tables V and VI.

Anal. Calcd for $C_{24}H_{23}O_2P$: C, 76.99; H, 6.19; P, 8.27. Found: C, 77.16; H, 6.20; P, 8.27.

Physical data for other O-methylated phospholan-3-one 1-oxides prepared by a similar procedure are listed in Table VII.

1-Benzyl-2-phenyl-2,4-dimethylphospholan-3-one 1-Oxide (20). A mixture of 2.0 g (6.7 mmol) of the oxide **2** in 25 ml of anhydrous THF was treated with 1.0 g (8.9 mmol) of $(CH_3)_3COK$ in 25 ml of THF at room temperature. After 1 hr, the yellow solution was treated with 10.0 g (7 mmol) of CH_3I in 25 ml of THF. After complete addition, the orange mixture was stirred for 1 hr at room temperature and hydrolyzed (15 ml H_2O), and the resulting mixture was extracted [2 × 75 ml of $(C_2H_5)_2O$]. The organic extracts were dried ($MgSO_4$) and the solvent was removed by evaporation to afford a yellow powder. Two recrystallizations from cyclohexane–chloroform (4:1) gave 1.4 g (67%) of **20**, mp 154–155.5°. Infrared, nmr, and analytical data are given in Tables V–VII.

Anal. Calcd for $C_{19}H_{21}O_2P$: P, 9.92. Found: P, 9.97.

Dibenzylphosphine Oxide with Diethyl Benzalmalonate. A slurry of 1.3 g (55.6% dispersion in mineral oil, 0.03 mol) of NaH in 50 ml of anhydrous THF at room temperature was treated with 6.9 g (0.03 mol) of dibenzylphosphine oxide in 50 ml of THF. The resulting mixture was heated at reflux for 15 min with vigorous evolution of gas (presumed H_2) and with formation of a clear, pale-yellow solution. This solution heated to reflux was treated (dropwise) with a solution of 7.5 g (0.03 mol) of diethyl benzalmalonate[18] in 100 ml of THF. When addition was complete, the mixture was boiled for 2 hr with the appearance of a white precipitate and then treated with another slurry of 1.3 g (0.03 mol) of NaH in 50 ml of THF. After an additional 3 hr at reflux (gas evolved), the now dark-orange mixture was cooled to room temperature and hydrolyzed (30 ml of 2 *N* acetic acid). Two layers resulted upon saturation (NaCl) and the aqueous layer was extracted (2 × 150 ml) with THF. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to leave a yellow oil. Titration of this oil with boiling cyclohexane followed by a hot filtration yielded a yellow, insoluble powder. Recrystallization of this powder from ethyl acetate–ethanol gave 0.65 g (6%) of 1-benzyl-2,5-diphenylphospholan-3-one 1-oxide (**7**), mp 225–226°. Infrared, nmr, and analytical data are given in Tables I, II, and IV.

After standing for 2 days at room temperature, the cyclohexane filtrate gave a white powder. Recrystallization (hexane) of this powder afforded 7.0 g (73%) of ethyl 2-carbethoxy-3-dibenzylphosphoryl-3-phenylpropionate (**22**): mp 85–86°; ir (KBr pellet) ν 1715 (C=O), 1228 (C–O), 1153 cm^{-1} (P→O); pmr ($DCCl_3$) δ 0.90 (t, CH_3, 3 H), 1.30 (t, CH_3, 3 H), 2.60 (m, HCCH, 2 H), 3.24 (d, $^{31}PCH_2C_6H_5$, 2 H), 3.88 (quartet, CH_2, 2 H), 4.30 (m, $^{31}PCH_2C_6H_5$ and CH_2, 4 H), 7.20 (m, 3 C_6H_5, 15 H); mass spectrum (70 eV) *m/e* (rel intensity) 433 ($M^+ - C_2H_5O\cdot$, 9.0), 388 (71.0), 387 (75.6), 313 (13.2), 230 (63.8), 203 (25.3), 176 (13.2), 139 (78.2), 131 (100.0), 103 (37.9), 92 (29.5), 91 (75.2), 77 (21.1), 65 (27.7), 45 (15.6).

Anal. Calcd for $C_{28}H_{31}O_5P$: P, 6.47. Found: P, 6.43.

1-Benzyl-2-phenyl-4-carbethoxy-5,5-dimethylphospholan-3-one 1-Oxide (23). A slurry of 1.3 g (55.6% in mineral oil, 0.03 mol) of NaH in 50 ml of anhydrous THF at room temperature was treated with 6.9 g (0.03 mol) of dibenzylphosphine oxide in 50 ml of THF. The resulting mixture was heated at reflux for 15 min with vigorous evolution of a gas (presumed H_2) and with formation of a clear, pale-yellow solution. This solution heated to reflux was treated (dropwise) with a solution of 6.0 g (0.03 mol) of diethyl isopropylidenemalonate[19] in 75 ml of THF. After addition, the mixture was boiled for 2 hr and then treated with a slurry of 2.6 g (0.06 mol) of NaH in 50 ml of THF.

After an additional 3 hr at reflux (much gas evolved), the solution was cooled to room temperature and hydrolyzed (45 ml of 2 *N* acetic acid). The solution was concentrated to ~50 ml volume and extracted (3 × 75 ml) with $HCCl_3$. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to a thick yellow oil. Dissolution of this oil in boiling diethyl ether and standing for 2 days at room temperature deposited a white powder. Recrystallization of this powder from cyclohexane–chloroform (5:1) yielded 6.5 g (56.4%) of **23**: mp 171–173°; ir (KBr) ν 2540 (OH), 1717 (C=O), 1608 (–C=C–), 1107 cm^{-1} (P→O); pmr ($DCCl_3$) δ 1.28 (m, CH_3, 9 H), 2.16 (m, CH, 1 H), 3.22 (m, $^{31}PCH_2C_6H_5$, OH, 3 H), 4.20 (m, CH_2, 2 H), 7.24 (m, 2 C_6H_5, 10 H); mass spectrum (70 eV) *m/e* (rel intensity) 384 (M^+, 18.0), 312 (19.9), 221 (20.9), 155 (22.3), 118 (28.1), 91 (100.0), 90 (18.0), 89 (14.4), 83 (32.4), 65 (14.4), 31 (16.2).

Anal. Calcd for $C_{22}H_{25}O_4P$: P, 8.06. Found: P, 8.21.

Registry No.—22, 52050-51-8; **23,** 52050-52-9; dibenzylphosphine oxide, 13238-16-9; ethyl cinnamate, 103-36-6; diethyl benzalmalonate, 5292-53-5; diethyl isopropylidenemalonate, 6802-75-1.

References and Notes

(1) We gratefully acknowledge partial support of this work by the Public Health Service, National Cancer Institute, Grant CA 11967-10. We also acknowledge the National Science Foundation Institution grant to purchase the XL-100 nmr unit, Grant NSF GP-17641.
(2) Research Associate, 1973–1975.
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(8) Solutions of concentrations on the order of 500 mg or less of sample in 4 ml of $DCCl_3$ did not afford the signals assigned the keto tautomer.
(9) In the present case, the existence of cis–trans isomers for a methyl function situated *β on the ring to a phosphoryl group* in phospholane 1-oxides is not considered unique. The presence of cis–trans isomers for a methyl function at C-3 of 1,3-dimethylphospholane 1-oxide and 1-phenyl-3-methylphospholane 1-oxide has been noted for but not reported from the same reaction mixture; K. L. Marsi, *Chem. Commun.*, 846 (1968); K. L. Marsi, F. B. Burns, and R. T. Clark, *J. Org. Chem.*, **37**, 238 (1972).
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(13) This value is in good agreement with that band at 1730–1740 cm^{-1} observed for the carbonyl of 1-methylphospholan-3-one 1-oxide depending upon the medium (solution or a KBr pellet); see ref 6.
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(18) C. F. H. Allen and F. W. Spangler, "Organic Syntheses," Collect. Vol. III, New York, N. Y., 1967, p 377.
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Purine *N*-Oxides. LVII. 9-Hydroxyhypoxanthine, Xanthine, and Guanine[1]

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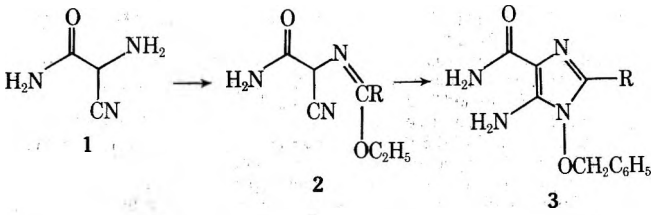
By direct application of the Shaw synthesis 8-methyl-9-hydroxypurines were successfully synthesized *via* the condensation of benzyloxyamine with the acetimidate from aminocyanoacetamide and triethyl orthoacetate. This condensation failed with triethyl orthoformate. In a modified sequence of reactions, the cyclization of the condensation product of *N*-benzyloxyformimidate and aminocyanoacetate to the imidazole was found to be catalyzed by HCl. The use of benzyloxyamine hydrochloride and the formimidate from aminocyanoacetamide also yielded the requisite imidazole. From the imidazole the title 9-hydroxypurines were obtained.

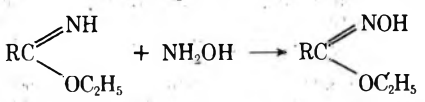
A recent synthesis of 9-hydroxy-8-methylpurines[2] involved an application of the Shaw route to 9-alkylpurines.[3] In the initial steps the condensation of triethyl orthoacetate with 2-amino-2-cyanoacetamide (1) to yield **2**, R = CH_3, was followed by condensation with benzyloxyamine to yield 5-amino-1-benzyloxy-2-methylimidazole-4-carbox-



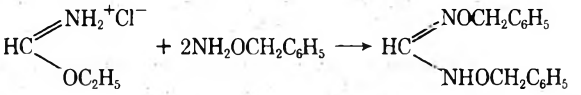
1 2 3

amide (3, R = CH_3). Attempts to extend this synthesis to 9-hydroxypurines with no substituent at position 8 failed because benzyloxyamine displaced the imino group rather than the ethoxy group from the derivative from triethyl orthoformate (2, R = H).

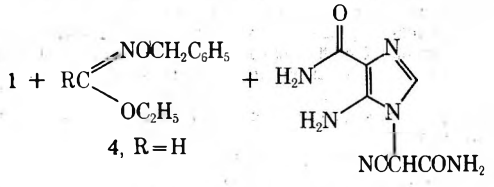
Pinner first discovered[4] that the imino group of imidiates was readily replaced by the oximino group, and Houben, *et al.*,[5] has demonstrated that good yields of hydroxamic esters could be obtained when hydroxylamine in aqueous solution was shaken with ethereal solutions of imidates. There was also a report[6] that both the imino and the



ether groups of ethyl formimidate hydrochloride were replaced by the interaction with benzyloxyamine.



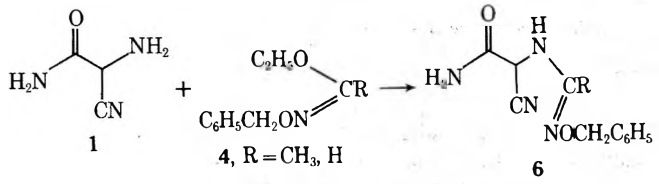
Upon further study of the reaction mixture of 2, R = H, with benzyloxyamine three products were identified, 2-amino-2-cyanoacetamide (1), ethyl *N*-benzyloxyformimidate (4, R = H), and 5-amino-1-[2-(2-cyanoacetamido)]-imidazole-4-carboxamide] (5). There are two pathways by



4, R=H 5

which the amino intermediate 1 can be regenerated, either by benzyloxyamine replacement of the imino group, giving 4, or by the direct decomposition of 2.[3] 1 then reacts with unchanged 2 to yield 5. It is evident that this reaction of benzyloxyamine is the type observed by Houben.[5]

Cook, *et al.*,[7] and Miller, *et al.*,[8] have shown that in some instances the ethoxy group of free imino ethers could react with 1 to yield imidazoles. A modification of the Shaw[3] route to 9-substituted purines was therefore explored, first to the known 5-amino-1-benzyloxy-2-methylimidazole-4-carboxamide (3, R = CH_3). The condensation of 2-amino-2-cyanoacetamide (1) with ethyl *N*-benzyloxyacetimidate (4, R = CH_3) was studied. The latter was prepared by



1 4, R=CH_3, H 6

treating the free amine with triethyl orthoacetate. The preparation of 3, R = CH_3, was carried out in two steps in refluxing methanol. After several hours tlc indicated the presence of a new non-uv-absorbing spot and after 24 hr ~1 equiv of concentrated HCl was added, thus adding a minimum amount of water. The solution was again refluxed for 18 hr or until tlc showed the disappearance of the non-uv-absorbing material, presumably 6, R = CH_3, and the appearance of a new uv-absorbing spot which had the same R_f value and uv spectrum as authentic 3, R = CH_3.[2] It therefore seemed possible that this procedure, with triethyl orthoformate, would yield the required imidazole with R = H. In the preparation of ethyl *N*-benzyloxyformimidate, also from the free amine and triethyl orthoformate, two products were recognized by glc of the reaction mixture. They were also separated by preparative tlc, and identified as the syn and anti isomers of 4, R = H, through their nmr spectra. It was also possible to separate these on a larger scale by column chromatography. Only the one assigned the anti configuration could be condensed with 1, under the conditions used for 4, R = CH_3. The imidazole 3, R = H, was obtained in a prohibitively low yield (~ 2%) by this route, but the results do show that 1 equiv of HCl facilitates the ring closure of 6 to 3, with R = CH_3 or H.

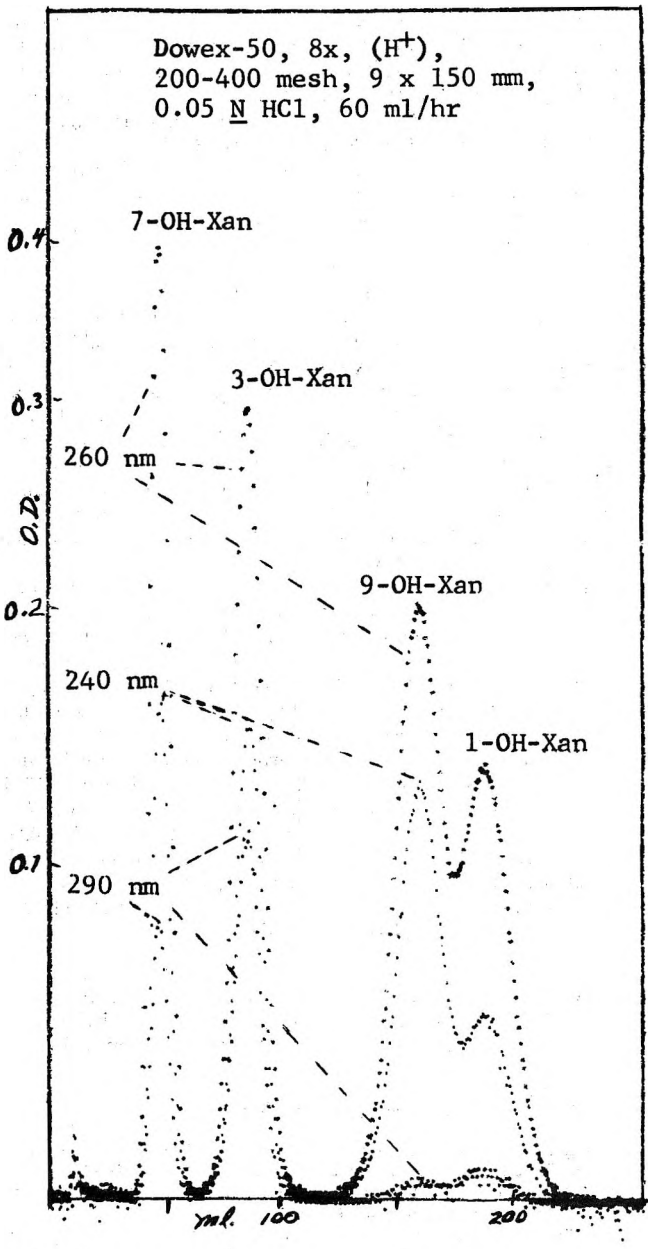
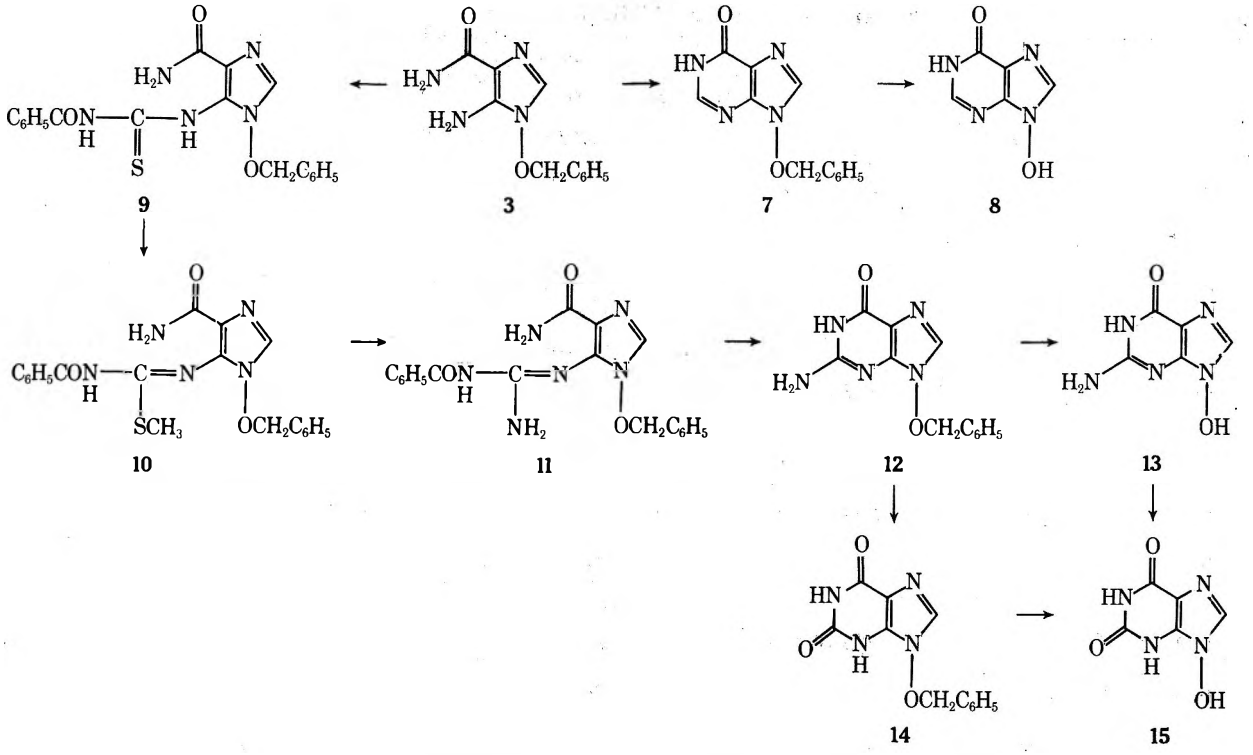


Figure 1.

The replacement of the ethoxy group of 2, R = H, with benzyloxyamine was then reinvestigated. When the hydrochloride of the latter was stirred with 2 at room temperature in ether–methanol, the proposed intermediate 6, R = H, was obtained. Upon removing the ether followed by prolonged refluxing in the methanol, the ring closure to the de-

Scheme I



sired 5-amino-1-benzyloxyimidazole-4-carboxamide (**3**, R = H) was brought about in an acceptable yield. No HCl other than that originally added as the benzyloxyamine hydrochloride was needed. From **3**, R = H, the desired 9-hydroxyhypoxanthine (**8**), guanine (**13**), and xanthine (**15**) were obtained by the general methods previously applied[2] to the 8-methyl derivatives. 9-Hydroxyhypoxanthine (**8**) was prepared by ring closure with ethyl formate in the presence of excess NaOEt to give 9-benzyloxyhypoxanthine (**7**), and the latter was debenzylated to **8** with HBr.

The cyclization of 5-amino-1-benzyloxyimidazole-4-carboxamide (**3**) to a 9-hydroxyguanine derivative involved refluxing with benzoyl isothiocyanate in acetone to give 5-(*N'*-benzoylthiocarbamoyl)amino-1-benzyloxyimidazole-4-carboxamide (**9**), which with methyl iodide in dilute sodium hydroxide at room temperature yielded 5-(*N'*-benzoylmethylmercaptocarbamoyl)amino-1-benzyloxyimidazole-4-carboxamide (**10**) (Scheme I). When the methyl mercaptoimidazole derivative, **10**, was heated at 100° with 2% NH_3 in ethanol, no displacement of the methylmercapto group by the amino group was observed, probably because of the insolubility of **10**. With Me_2NCHO as the solvent[9] 5-*N'*-benzoylguanidino-1-benzyloxyimidazole-4-carboxamide (**11**) was obtained, and this was refluxed for 3 hr in 1 *N* NaOH to give a mixture of 9-benzyloxyguanine (**12**) and benzoic acid. After neutralizing with acetic acid the benzoic acid was removed by ether extraction and the 9-benzyloxyguanine was purified by recrystallization from methanol. Debenzylation yielded 9-hydroxyguanine (**13**).

Ring closure of **3**, R = H, with diethyl carbonate, as used previously for the 8-methyl derivative, did not yield 9-benzyloxyxanthine (**14**). However, by application of the nitrosation procedure[10] used to convert 1-hydroxyguanine to 1-hydroxyxanthine,[11] **12** or **13** were converted to 9-benzyloxyxanthine (**14**) and to 9-hydroxyxanthine (**15**), respectively.

This now makes available all of the possible isomeric *N*-hydroxyxanthines. A chromatogram of the four on a Dowex-50 (H^+) column is shown in Figure 1. Parallel assays *in vivo* are now being conducted to establish further the relationships between oncogenicity, structure, and chemical reactivities.

Certain reactivities of 9-hydroxyxanthine were compared with those known for the other isomers. Like the 3[12,13] and 7 isomers,[14] the 9 isomer yields uric acid in hot acetic anhydride. It reacts very slowly because of its insolubility, but does react readily in trifluoroacetic anhydride. The 1 isomer forms a stable 1-acetoxy derivative under these conditions.[13]

The acetoxy derivatives of the 3- and 7-hydroxyxanthines have been isolated. They react in neutral aqueous solution at room temperature to yield uric acid.[12,14] The reaction of 3-acetoxyxanthine in water has been characterized as the "3-acyloxypurine 8-substitution reaction" [15,16] which results in substitution at C-8 by many nucleophiles. In parallel, some reduction to the parent purine occurs and an insoluble blue product is also produced. The rapid reaction in water is associated with the ionization of the imidazole proton of 3-acetoxyxanthine, which can facilitate the departure of the acetoxy group from the 3 position.[16] The 7-acetoxyxanthine yields the same array of products under the same mild conditions, and a similar mechanism involving ionization of the proton at N-3 and departure of the acetoxy group from N-7 was proposed.[14] Most purine *N*-oxide derivatives are rapidly esterified by acetic anhydride in buffered aqueous solutions,[17] and the ester then reacts with any nucleophile present. Direct comparisons were made of the 3-, 7-, and 9-hydroxyxanthines under identical conditions, followed by chromatographic analyses in which uric acid, the acetoxyxanthine, 8-methylmercaptoxanthine, xanthine, and the parent *N*-hydroxyxanthine could be detected.[17] From the 3 and 7 isomers all of those products could be detected, but 9-hydroxyxanthine remained unchanged, with no evidence of any formation of an acetoxy derivative, or uric acid. Presumably a 9-acetoxy derivative is formed only under vigorous conditions, under which it yields uric acid immediately.

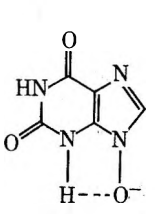
The lack of reactivity of 9-hydroxyxanthine suggests that it should not be an oncogen. Reasons for the marked contrast between the difficulty of acetylation of the 9 and the

Table I
Spectral Data and pK Values for 9-Hydroxypurines

pH	Species	λ_{max}, nm ($\epsilon \times 10^{-3}$)			pK_a
		9-Hydroxyhypoxanthine			
−1	+		252 (9.1)		
					0.91 ± 0.05
3.3	0	245 sh (9.1)	250 (9.6)		
					5.18 ± 0.02[a]
7.98	−		235 (24.4)		
					10.61 ± 0.06
13	−2		228 (18.5)	257 (7.5)	
			277 sh (4.2)		
		9-Hydroxyguanine			
0	+	252 (10.2)	278 (6.6)		
					2.12 ± 0.04
4.18	0	207 sh (17.0)	238 (9.2)	253 (9.5)	
		270 (7.4)			
					5.91 ± 0.04
8.0	−1	234 (24.2)	274 (6.8)		
					10.70 ± 0.04
13.0	−2	228 (14.9)	272 (8.6)		
		9-Hydroxyxanthine			
2.3	0	235 (6.7)	262 (9.8)		
					5.06 ± 0.04
6.8	−1	219 (18.4)	269 (10.9)		
					8.41 ± 0.07
11.0	−2	224 (24.9)	273 (8.1)		

[a] Potentiometric titration; others spectrophotometrically by methods described.[18,19]

ease of acetylation of the 7 isomer are not obvious. By analogy to previous interpretations,[20] the monoanion of 9-hydroxyxanthine shows unusually broad absorption maxima, and an incomplete expression of the strong absorption at 219–224 nm attributable to the nitrone anion (Table I). These observations are both compatible with the monoanion being a mixture of two species. Ionization of either the H of the 9-hydroxy group or of the 3-H would lead to a species which is capable of hydrogen bonding between the 3-H and the 9-N–O$^-$. If such hydrogen bonding be intermolecular, the resulting dimer could also explain the extreme insolubility in water of the 9 as compared to the 7 or 3 isomers.



Experimental Section

Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were obtained with a Mel-Temp apparatus and are uncorrected. For thin layer chromatography (tlc) Eastman chromagram sheets with a silica gel layer containing a fluorescent indicator were used. The uv spectra were determined with a Unicam SP800A recording spectrophotometer, and nmr spectra with a Varian A-60 with $(CH_3)_2SO$-d_6, as solvent and $(CH_3)_4Si$ as the internal standard. Silica gel grade 923, 100–200 mesh, was used for column chromatography. The gas–liquid chromatography (glc) was carried out with an Aereograph Model A-90-P.

Ethyl N-Benzyloxyacetimidate (4, R = CH_3). Benzyloxyamine (6 g, 0.05 mol) and 80 ml of triethyl orthoacetate were warmed on a steam bath for ~2 hr, when tlc and glc of the reaction mixture indicated the absence of benzyloxyamine and the appearance of a new uv-absorbing material. The solvent was removed *in vacuo* and the pale yellow oil was chromatographed on silica gel with a 1:1 mixture of petroleum ether–ether. Traces of triethyl orthoacetate were eluted first, followed by ethyl N-benzyloxyacetimidate, which was obtained as a colorless oil upon evaporation (7.5 g, 80%): nmr δ 7.38 (s, 5, $C_6H_5CH_2$), 5.07 (s, 2, $OCH_2C_6H_5$), 4.00 (q, 2, OCH_2CH_3), 1.94 (s, 3, CH_3), 1.21 (t, 3, CH_2CH_3).

5-Amino-1-benzyloxy-2-methylimidazole-4-carboxamide (3, R = CH_3). 2-Amino-2-cyanoacetamide (2.5 g, 0.025 mol) and ethyl N-benzyloxyacetimidate (4.75 g, 0.025 mol) in methanol were refluxed with stirring for 24 hr. Tlc in 9:1 chloroform–ethanol showed a new spot when the plate was developed with iodine. An equivalent of concentrated HCl was added and the reaction mixture was refluxed for 18 hr until the tlc indicated the presence of both starting materials and the imidazole, and the absence of the non-uv-absorbing material, in that sequence. The solvent was removed *in vacuo*, leaving a dark red semisolid which was chromatographed over silica gel. Elution with chloroform gave ethyl N-benzyloxyacetimidate as an oil, and chloroform–ethanol (9:1) then gave **3**, R = CH_3, as white plates (816 mg, 13%), mp 208–209° dec (from ethanol). The uv, ir, and nmr were identical with those of an authentic specimen.[2]

Ethyl N-Benzyloxyformimidate (4, R = H). Benzyloxyamine (12 g, 0.1 mol) and 150 ml of triethyl orthoformate were warmed on a steam bath and the reaction was monitored as in **4**, R = CH_3. In this experiment two new uv-absorbing spots were present. The solvent was removed *in vacuo* to leave a pale yellow oil. The two major products were separated by chromatographing the oil on silica gel with petroleum ether–ether (1:1). These were identified from their nmr spectra. The first, a colorless oil (7.19 g), was assigned the anti ethyl N-benzyloxyformimidate structure, and the second, also a colorless oil (4.73 g), was assigned the syn structure, from their nmr: anti nmr δ 8.60 (s, 1, N=CH), 7.34 (s, 5, $CH_2C_6H_5$), 4.89 (s, 2, $OCH_2C_6H_5$), 4.00 (q, 2, OCH_2CH_3), 1.22 (t, 3, CH_2CH_3); syn nmr δ 7.34 (s, 5, $CH_2C_6H_5$), 6.83 (s, 1, N=CH), 4.90 (s, 2, $OCH_2C_6H_5$), 4.01 (q, 2, OCH_2CH_3), 1.20 (t, 3, CH_2CH_3).

Ethyl N-(Carbamoylcyano)methylformimidate (2, R = H). 2-Amino-2-cyanoacetamide (9.9 g, 0.1 mol) and 150 ml of triethyl orthoformate were stirred at 90° for ~ 3 hr, by which time tlc (chloroform–ethanol, 19:1) showed the absence of **1**, the presence of the imino ether **2**, R = H, and a uv-absorbing spot at the origin. The reaction mixture was cooled, 600 ml of petroleum ether was added, and it was kept at −10° until the precipitation was completed. The solid was collected and washed with petroleum ether. Chromatography over silica gel with chloroform–ethanol (19:1) gave the imino ether **2**, R = H, as fine crystals (6.85 g, 44%): mp 86–87° (lit.[3] mp 86–87°); nmr δ 7.99 (s, 1, N=CH), 7.61 (d, 2, $CONH_2$), 5.28 (s, 1, CH), 4.23 (q, 2, OCH_2CH_3), 1.25 (t, 3, CH_2CH_3).

5-Amino-1-benzyloxyimidazole-4-carboxamide (3, R = H).

A. Either the syn or anti **4**, R = H, isomer (4.48 g, 0.025 mol) from the foregoing and 2-amino-2-cyanoacetamide (2.5 g, 0.025 mol) in methanol were refluxed with stirring for 24 hr and the mixtures were treated as described for **3**, R = CH_3. The imidazole was formed only from the anti iomer, as indicated by tlc. The red oily residue obtained was chromatographed over silica gel with chloroform to yield some unreacted **4**, R = H. Elution with chloroform–ethanol (19:1) then gave 5-amino-1-benzyloxyimidazole-4-carboxamide (**3**, R = H), as white plates (113 mg, 2%), mp 168–169°.

B. The formimidate **2** (7.9 g, 0.05 mol) and benzyloxyamine hydrochloride (8 g, 0.05 mol) were stirred in ether–methanol (400 ml, 3:1) at room temperature for 24 hr. The white precipitate was collected and washed with 40 ml of reaction solvent to yield 4 g of 5-amino-1-[2-(2-cyanoacetamido)]imidazole-4-carboxamide, mp 212–216° (lit.[3] mp 212–216°). A tlc of the filtrate showed that it contained four products: ethyl *N*-benzyloxyformimidate (**4**), the intermediate **6**, 2-amino-2-cyanoacetamide (**1**), and traces of **5**. The ether was removed by distillation and the methanol solution was refluxed for ~18 hr or until tlc indicated complete loss of the intermediate and the formation of the required imidazole. The solvent was removed *in vacuo* to give a dark red, gum-like product which was chromatographed over silica gel with chloroform to give **4**. Elution with chloroform–ethanol (19:1) gave the imidazole. Removal of solvent and recrystallization from acetone–petroleum ether afforded white needles (1.63 g, 15%): mp 168–169°; uv λ_{max} (EtOH) 263 nm (ϵ 11.8 × 10^3); nmr δ 7.43 (s, 5, $CH_2C_6H_5$), 7.17 (s, 1, 2-CH), 6.71 (s, 2, $CONH_2$), 5.87 (s, 2, CNH_2), 5.16 (s, 2, $OCH_2C_6H_5$).

Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.71; H, 5.28; N, 24.06.

9-Benzyloxyhypoxanthine (7). 5-Amino-1-benzyloxyimidazole-4-carboxamide (**3**, 464 mg, 0.002 mol) and ethyl formate (1.2 ml, 0.02 mol) were refluxed for 4 hr with sodium (460 mg, 0.02 mol) in 40 ml of ethanol. Water (40 ml) was added to the cooled reaction mixture to dissolve the precipitate. When acidified with acetic acid, the 9-benzyloxyhypoxanthine precipitated and was collected and washed with water. Recrystallization from ethanol–water gave the product, **7**, as white plates (358 mg, 74%): mp 222–223°; uv λ_{max} (pH 1) 254 nm (ϵ 12.1 × 10^3), λ_{max} (pH 13) 246 nm (ϵ 11.1 × 10^3), 249 (11.8 × 10^3); nmr δ 8.20 (s, 2, 2-CH, 8-CH), 7.50 (s, 5, $CH_2C_6H_5$), 5.46 (s, 2, $OCH_2C_6H_5$), 12.5 (br, 1, 1-NH).

Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.70; H, 4.30; N, 23.21.

9-Hydoxyhypoxanthine (8). 9-Benzyloxyhypoxanthine (**7**, 242 mg, 0.001 mol) was warmed on a steam bath in 4 ml of 32% HBr in glacial acetic acid for 3.5 hr. The reaction mixture was cooled and the HBr salt was removed by filtration and washed with several portions of ether. The product was dissolved in hot water containing a few drops of concentrated ammonia, treated with charcoal, and precipitated with acetic acid. The 9-hydroxyhypoxanthine was collected, washed with water, ethanol, and ether, and dried at 78° over P_2O_5 (118 mg, 79%); for uv data see Table I.

Anal. Calcd for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.83. Found: , 39.57; H, 2.64; N, 36.86.

5-(*N'*-Benzoylthiocarbamoyl)amino-1-benzyloxyimidazole 4-carboxamide (9). The imidazole **3** (1.16 g, 0.005 mol) was dissolved in hot acetone (200 ml) and 100 ml of acetone solution containing 1.1 equiv of benzoyl isothiocyanate was added. The mixture was refluxed for ~6 hr, when tlc in ethyl acetate indicated the absence of **3**. The acetone was removed *in vacuo* and the yellow oil was chromatographed on silica gel. Eluting with chloroform removed the excess benzoyl isothiocyanate. The thioureidoimidazole **9** was then eluted with chloroform–ethanol (19:1). Upon removing the solvent a yellow, gum-like product was obtained that could not be crystallized. Tlc on silica gel showed that it was chromatographically homogeneous and its nmr indicated that it was the requisite compound. This was used directly in the next step: nmr δ 8.09 (m, 2, COC_6H_5), 7.94 (s, 1, 2-CH), 7.66 (m, 3, COC_6H_5), 7.42 (s, 5, $-CH_2C_6H_5$), 5.38 (s, 2, $OCH_2C_6H_5$), 7.25 (br s, 2, $CONH_2$), 11.99 (d, 2, –NHCSNH–).

5-(*N'*-Benzoyl-*S*-methylthiocarbamoyl)amino-1-benzyloxyimidazole-4-carboxamide (10). The thioureidoimidazole **9** was dissolved in 0.1 *N* NaOH (100 ml) and treated with 0.5 ml of methyl iodide at room temperature. The mixture was stirred for 6 hr and the solution was then adjusted to pH 5 with glacial acetic acid and extracted several times with chloroform (100 ml). The combined chloroform extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was triturated with ethanol and collected. Recrystallization from $CHCl_3$–EtOH produced white needles of **10**: yield 623 mg (61%) based on **3**; mp 193–195°; nmr δ 7.68 (m, 5, COC_6H_5, 2, $CONH_2$), 7.45 (s, 1, 2-CH), 7.35 (s, 5, $CH_2C_6H_5$), 5.29 (s, 2, $OCH_2C_6H_5$), 2.51 (s, 3, SCH_3), 11.88 (s, 1, =CNH).

Anal. Calcd for $C_{20}H_{19}N_5O_3S$: C, 58.67; H, 4.68; N, 11.72; S, 7.83. Found: C, 58.61; H, 4.70; N, 11.75; S, 7.78.

5-*N'*-Benzoylguanidino-1-benzyloxyimidazole-4-carboxamide (11). **10** (402 mg, 0.001 mol) was treated with 50 ml of 2% NH_3 in $(CH_3)_2NCHO$ at 120° in a steel bomb for 6 hr, when the odor of methyl mercaptan could be recognized. The solvent was removed *in vacuo* to yield **11**. Tlc (chloroform as a solvent) showed the residue to be chromatographically pure and it was used for the preparation of **12**.

9-Benzyloxyguanine (12). To the glass-like residue of **11** was added 30 ml of 1 *N* NaOH and the solution was warmed on a steam bath for 3 hr. The reaction mixture was cooled and acidified to pH 5 with concentrated HCl. The white precipitate was collected and benzoic acid was removed by several extractions, or by continuous extraction, with hot ether. The solid residue was dissolved in methanol, after charcoal treatment, affording 9-benzyloxyguanine (**12**) as white plates: yield 170 mg (67%) based on **10**; uv λ_{max} (pH 1) 255 nm (ϵ 12.4 × 10^3), 275 (8.2 × 10^3); λ_{max} (pH 13) 259 sh nm (ϵ 10.8 × 10^3), 268 (11.6 × 10^3); nmr δ 7.61 (s, 1, 8-CH), 7.39 (s, 5, $CH_2C_6H_5$), 6.62 (br, s, 2, NH_2), 5.30 (s, 2, $OCH_2C_6H_5$), 11.66 (s, 1, 1-NH).

Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.02; H, 4.31; N, 27.22. Found: C, 55.85; H, 4.31; N, 27.13.

9-Hydroxyguanine (13). The debenzylation of **12** (129 mg, 0.0005 mol) was carried out as above. The free base was obtained from the HBr salt by dissolving in hot dilute ammonia, treatment with charcoal, and precipitation by glacial acetic acid. The white crystals of **13** were collected, washed with water, ethanol, and ether, and dried *in vacuo* over P_2O_5 at 78°: yield 65 mg (74%); uv data, see Table I.

Anal. Calcd for $C_5H_5N_5O_2 \cdot \frac{1}{2}H_2O$: C, 34.10; H, 3.43; N, 39.76. Found: C, 34.14; H, 3.32; N, 39.83.

9-Benzyloxyxanthine (14). A suspension of 9-benzyloxyguanine (**12**, 257 mg, 0.001 mol) in 50 ml of 2 *N* HCl was stirred at room temperature, and a solution of 2 *M* $NaNO_2$ was added dropwise for 30 min. After stirring overnight the reaction mixture was evaporated to dryness *in vacuo*, and the solid residue was dissolved in methanol–water and chromatographed on Dowex 50 (H^+). A trace of 9-hydroxyxanthine was eluted with 1 *N* HCl. Further elution with 2 *N* HCl gave 9-benzyloxyxanthine as a white solid. Recrystallization from acetone afforded white crystals of **14**: 155 mg (52%); uv λ_{max} (pH 1) 238 nm (ϵ 8.1 × 10^3), 261 (10.6 × 10^3); λ_{max} (pH 13) 249 nm (ϵ 10.1 × 10^3), 276 (9.9 × 10^3); nmr δ 7.70 (s, 1, 8-CH), 7.47 (s, 5, $CH_2C_6H_5$), 5.27 (s, 2, $OCH_2C_6H_5$), 10.81 (br s, 1, 1-NH), 12.20 (br s, 1, 3-NH).

Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.69. Found: C, 55.62; H, 4.13; N, 21.79.

9-Hydroxyxanthine (15). The debenzylation of **14** (129 mg, 0.0005 mol) was carried out. The free base, **15**, was obtained from the HBr salt by dissolving in hot dilute ammonia, treatment with charcoal, and precipitation by glacial acetic acid. The white crystals were collected, washed with water, ethanol, and ether, and dried *in vacuo* over P_2O_5 at 78°: yield 66 mg (73%); uv data, see Table I.

Anal. Calcd for $C_5H_4N_4O_3$: C, 35.72; H, 2.40; N, 33.32. Found: C, 35.54; H, 2.52; N, 33.38.

Reaction of 9-Hydroxyxanthine with Acid Anhydrides. 15 (10 mg) was refluxed in 5 ml of trifluoroacetic anhydride for 8 hr. After evaporation and dissolving in a few drops of NaOH, the reaction mixture was then chromatographed on Dowex 50 (H^+). Elution with water gave uric acid as the major product. A few micrograms of **15** in a few drops of acetic anhydride was heated to near dryness and the presence of some uric acid was shown on an analytical chromatogram.

The reactivities of the 3, 7, and 9 isomers were compared in an esterification in buffered aqueous solutions, which contained methionine, followed by analysis of the products on a standardized Dowex 50 column eluted with 0.05 *N* HCl.[17] At short reaction times, 2–3 min, the 3 and 7 isomers showed evidence of the formation of acetoxy derivatives, and after 1–16 hr showed maximal formation of 8-methylmercaptoxanthine.[21] Under both conditions 9-hydroxyxanthine remained unchanged.

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Registry No.—**1**, 6719-21-7; **2** (R = H), 37842-62-9; **3** (R = CH_3), 34407-36-8; **3** (R = H), 51932-94-6; **4** (R = CH_3), 16115-53-0; *anti*-**4** (R = H), 52019-90-6; *syn*-**4** (R = H), 52019-91-7; **7**, 51932-95-7; **8**, 51932-96-8; **9**, 51932-97-9; **10**, 51932-98-0; **11**, 51932-99-1; **12**, 51933-00-7; **13**, 51933-01-8; **14**, 51933-02-9; **15**, 51933-03-0; benzyloxyamine, 622-33-3; triethyl orthoacetate, 78-39-7; triethyl orthoformate, 122-51-0; benzyloxyamine hydrochloride, 2687-43-6; ethyl formate, 109-94-4; benzoyl isothiocyanate, 532-55-8.

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(21) Although they are eluted close together from the column, the low absorption of 9-hydroxyxanthine and the very high absorption of 8-methylmercaptoxanthine at 290 nm permit a recognition of as little as 1% of the latter.

1,3-Bridged Aromatic Systems. XI. Stereochemistry of Reactions of Heterocyclic *N*-Oxides with Acetic Anhydride, Acetyl Chloride, and *p*-Toluenesulfonyl Chloride[1,2]

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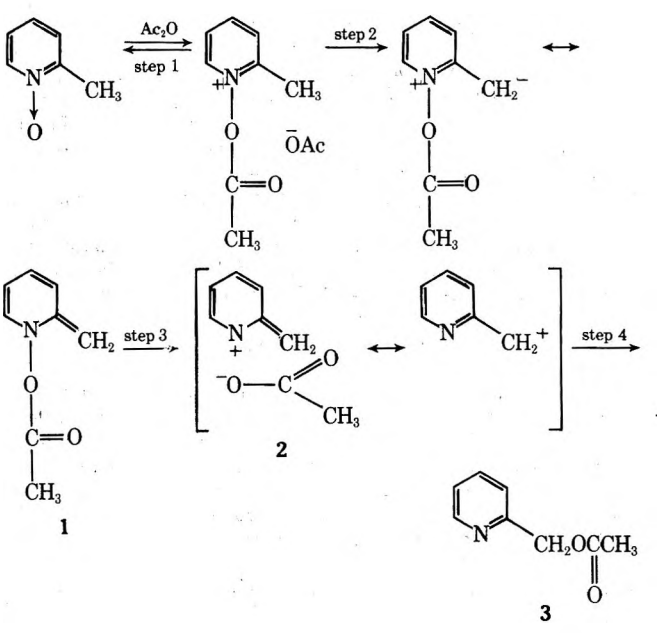
Reaction of the deuterium-labeled *N*-oxide **4** with acetic anhydride and acetyl chloride is highly stereospecific in that abstraction of syn deuterium leads to syn acetate **5**, while abstraction of anti hydrogen leads to anti acetate **6**; anhydro base **8**, in which the acetate function can rotate about the N–O axis, cannot, therefore, be an intermediate in these reactions. In reactions with acetyl chloride a bimolecular component of reaction diverts significant quantities of intermediate normally leading to anti acetate **6** to anti chloride **10**; the latter retains 95% of syn-deuterium label. Reaction of the unlabeled *N*-oxide of **4** with acetic anhydride-^{18}O shows that both syn and anti acetates are formed both by intramolecular transfer of *N*-acetate to the benzylic carbon atom (78.8 and 73.9%, respectively) and by a process involving return of external acetate (21.2 and 26.1%, respectively). Distribution of ^{18}O label in both the CO and C=O functions of derived acetates has been determined.

The mechanism of reaction of alkylpyridine *N*-oxides with acid anhydrides (Scheme I) and acid halides has been studied in great detail, and reviewed.[3] In reactions leading to substitution at the α-carbon atom it is generally thought that (1) step 1 is reversible,[4] (2) step 2 is generally rate determining,[4] (3) anhydro base (**1**) is an intermediate,[5] (4) step 3 involves heterolytic cleavage of the N–O bond (**2**),[6] and (5) step 4 is intramolecular in that it does not involve capture of external acetate.[4b,c,7]

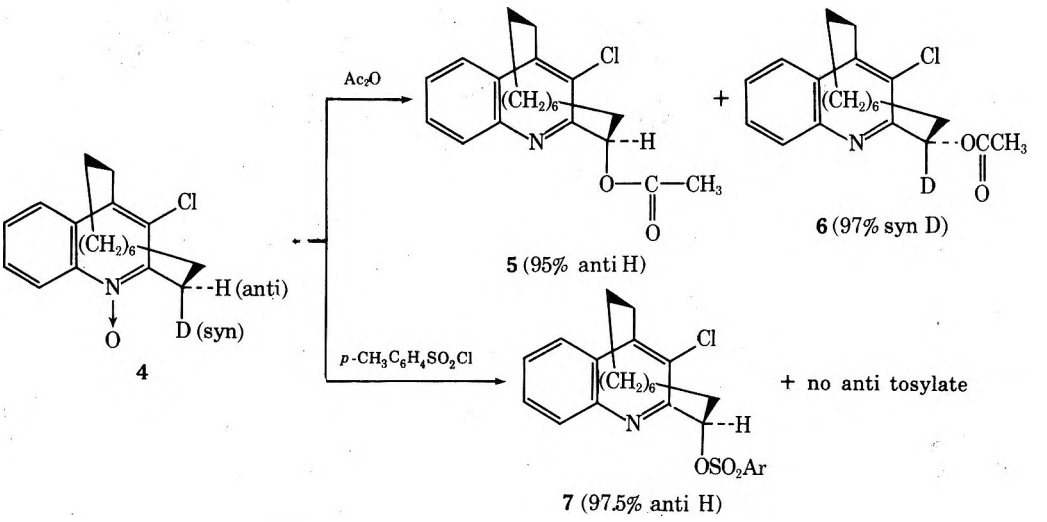
The recent availability of syn-deuterium labeled **4**[2] has provided an opportunity to consider the stereochemical aspects of such reaction for the first time. The reaction of **4** with acetic anhydride is summarized in Scheme II.

Reaction of **4** with acetic anhydride gives syn and anti-acetates **5** and **6** in the ratio of 1:4 as compared to a ratio of 1:1.1 when unlabeled[8] **4** is employed. This isotope effect is consistent with previous observations that proton removal (step 2, Scheme I) is rate determining.[4] What was not anticipated was the stereospecificity observed; syn acetate **5** was formed almost exclusively (95%) by removal of deuterium, while anti acetate **6** was formed almost exclusively by removal of anti hydrogen (97%). Reaction of **4** with *p*-toluenesulfonyl chloride led exclusively to syn tosylate, as pre-

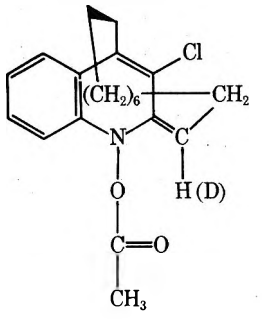
Scheme I



Scheme II



viously reported,[9] and the product was formed almost exclusively (97.5%) by removal of syn deuterium. These results clearly preclude a common intermediate in these reactions such as the anhydro base 8 in which the acetate function can rotate about the N–O bond.



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Results of our study of the reaction of 4[2] with acetyl chloride are summarized in Scheme III. Since syn and anti acetates 5 and 6 are not converted to chlorides by prolonged treatment with hot acetyl chloride,[10] formation of chlorides 9 and 10 established an intermolecular component of reaction in collapse of intermediates (type 1 and/or 2) to products.

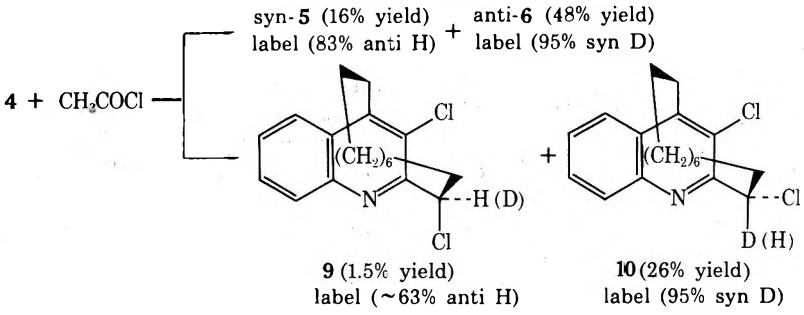
When reaction of unlabeled 4 was carried out in acetic anhydride saturated with tetramethylammonium chloride, no syn or anti chlorides (9 and 10) were formed. It was concluded, therefore, that the intermolecular component of reaction probably occurs rapidly from intermediates derived from the ion pair 11 without appreciable intervention by external nucleophile.

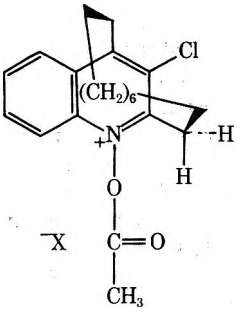
The results summarized in Scheme III are consistent with those observed with acetic anhydride in that syn acetate 6 is formed largely by removal of syn deuterium while anti acetate 7 is formed almost exclusively by removal of anti hydrogen. The total amounts of syn products (5 + 9) and anti products (6 + 10) are comparable with those formed with acetic anhydride; however, it is apparent that the intermediate(s) leading to labeled anti acetate is significantly diverted to anti chloride 10.

Examination of the reaction of unlabeled 4 with symmetrically labeled acetic anhydride-^{18}O (95.5% ^{18}O) furnished additional information[7] relative to this reaction. The products are summarized in Scheme IV. The syn and anti acetates were separated by liquid chromatography; the ^{18}O label was determined by mass spectrometry. Distribution of label in products was simplified since, in addition to the parent ion (which gave total ^{18}O label), these acetates fragmented as illustrated in Scheme V (ketene formation is common for aromatic acetates[11]), which permitted definition of label in the alcohol oxygen as well as the carbonyl oxygen.

Two conclusions are apparent from the ^{18}O-labeling

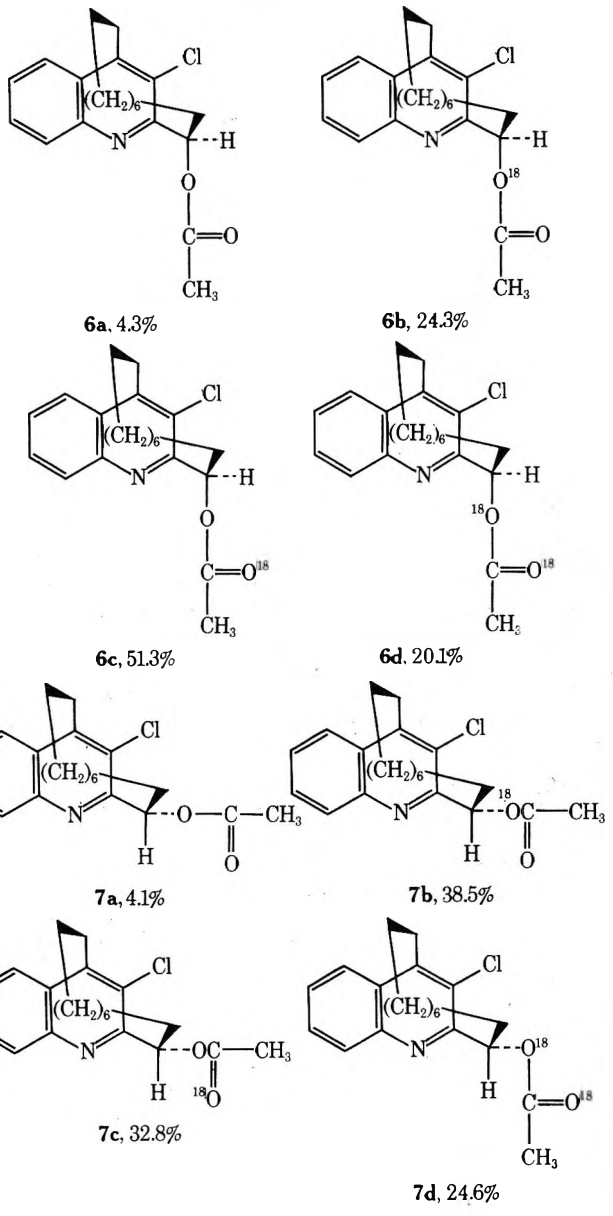
Scheme III



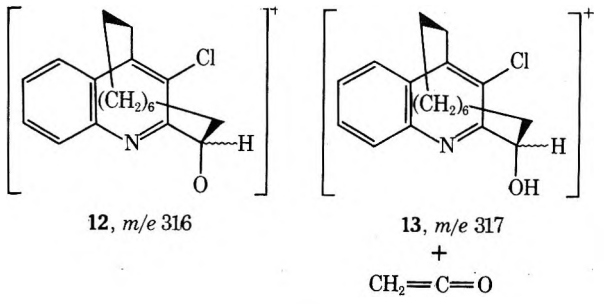


11

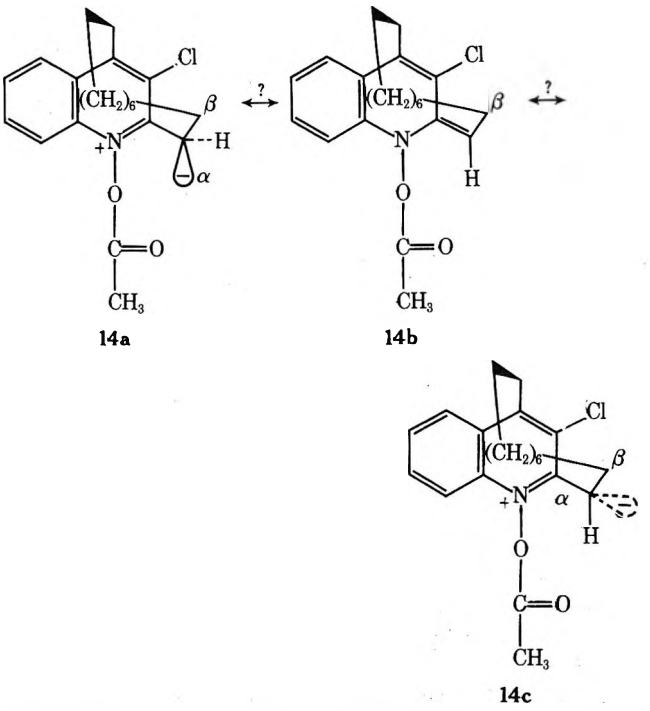
Scheme IV



Scheme V



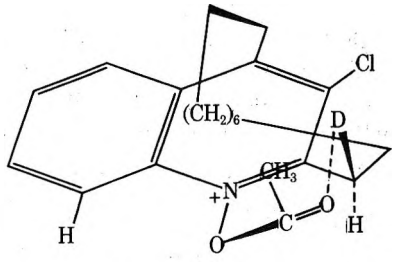
studies: (1) Unlike reaction of 2-picoline *N*-oxide with labeled acetic anhydride which involves only intramolecular transfer[7] of acetate (from **1**), formation of **6d** and **7d** implies that the reaction of **4** with acetic anhydride involves only ~78.8% intramolecular transfer in formation of the syn acetate **6** and ~73.9 intramolecular transfer[12] in formation of anti acetate **7** from intermediates such as **14a** and **14c.** In addition there is a competing reaction leading to acetates (21.2 and 26.1%, respectively) which involves return of ^{18}O doubly labeled acetate.[12,13] When a sample of a mixture of unlabeled **5a** and **6a** was heated (7.5 hr) with symmetrically labeled acetic anhydride-^{18}O, there was no



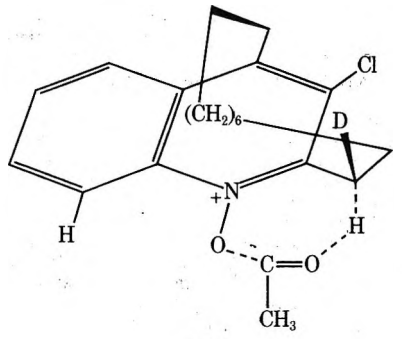
incorporation of ^{18}O in recovered **5a** or **6a.** Thus, it would appear that dilabeled acetates **6d** and **7d** are primary reaction products, which supports the intermolecular return of external acetate (~25%) with acetic anhydride. This result is consistent with the intermolecular component with acetyl chloride leading to halides.[14]

The second observation is that in the intramolecular transfer of acetate leading to syn acetate **6,** the oxygen atom attached to the original *N*-oxide becomes preferentially attached to the benzylic carbon atom in product (ratio of **6c/6b** 2.1). In the intramolecular transfer reaction leading to anti acetate **7** there is more nearly complete scrambling of the oxygen atoms (ratio of **7b/6c** 1.1). The distribution of ^{18}O label in anti acetate is nearly identical with that observed by Oae[7b] for reaction of quinaldine *N*-oxide with labeled aceetic anhydride. By similar studies of ^{18}O-label distribution in products derived from 2-picoline *N*-oxide and 2,6-lutidine *N*-oxide, Oae[4c] has provided strong support for the importance of conformational preference of rotation about the N–O bond in the intermediate **1** (Scheme I) on distribution of ^{18}O label in products.

While we are not able at this time to conclusively explain these results, we have no reason to question intermediates of type **14a** and **14c** and the conclusion that such intermediates collapse to products with retention of configuration at the α-carbon atom. Whether there is any contribution from an anhydro base structure (**14b**) may, in fact, be irrelevant to the stereochemistry of products. Inspection of models (Stuart–Briebgleb) shows that there may be two conformational isomers, **14a** (acetate up relative to the aromatic ring) and **14c** (acetate down relative to the aromatic ring), which are derived from two conformational stereomers of the assumed salts **15u** and **15d.** Presumably **15u** and **15d** could interconvert chemically by reversibility to *N*-oxide and CH_3COX. Inspection of such models show, however, that **15u** and **15d** probably cannot eequilibrate by simple rotation about the N–O bond. Furthermore, if the β-carbon atom (labeled β in **14** and **15**) is conformationally as near to coplanarity as possible with the aromatic ring (a requisite for maximum interaction of the type **14a** ↔ **14b**), these models show that the syn proton in **15u** can be in close proximity to the *N*-oxide carbonyl function while in **15d** the *N*-oxide carbonyl group has access to the anti proton. Anchimeric assistance by the *N*-acetate group during



15u



15d

proton abstraction may, therefore, provide rational for the observation that removal of syn proton leads to syn acetate while removal of anti proton leads to anti acetate. The observation that reaction of unlabeled **4** with acetic anhydride saturated with sodium acetate causes no change in the ratio of syn to anti acetate is consistent with such anchimeric assistance. The importance of *N*-acetate conformational isomers and their effect on label product distribution has already been noted.[4b,c,7b]

In this model the zwitterion intermediate corresponding to **14a** (whether ultimately going to cationic, radical, or anhydro base intermediates) leading to syn acetate has the *N*-acetate function (and presumably the acetic acid being formed) up relative to the α carbon. Preferential migration of ^{16}O to carbon would be indicative of steric constraint of the migrating acetyl group, caused by bridge methylene, which prevents the two oxygen atoms from being totally equivalent during the rapid collapse to products. Similarly, the intermediate zwitterion **14c** may have the nucleophile(s) down relative to the α-carbon atom, and thus lead to anti products. Lack of preference for migration of N oxygen to the benzylic carbon leading to anti acetate suggests that, in this case, the oxygen atoms of the mmigrating *N*-acetate group are less constrained by the bridge methylene groups. This is consistent with Oae's[7b] interpretation for results with quinaldine *N*-oxide which is a limiting case since there is no bridge for interaction. In this regard, attention should also be called to the work of Koenig[8] who has suggested a two-electron transfer process for decomposition of the zwitterion through σ overlap of the α and 3-carbon atoms; symmetry considerations make it clear that a planar transition state for the heterocyclic cleavage of the N–OAc bond is unlikely. Our stereochemical results are not inconsistent with this interpretation.

Attempts to confirm the presence of two salts of type **15d** and **15u** by isolation of isomeric acetyl perchlorates, acetyl fluoroborates, and/or acetyl picrates were unsuccessful. Reaction of unlabeled **4** under conditions which readily give such salts[4a,d,e] with 2-picoline lead only to the corresponding protonated salts of unlabeled *N*-oxide **4**.

Experimental Section

Reaction of 4 with Acetic Anhydride. A. Unlabeled 4. A mixture of unlabeled *N*-oxide **4**[9] (500 mg, 1.57 mmol) and acetic anhydride was heated (100°) for 11 hr. Excess acetic anhydride was destroyed by treatment with water; the cooled mixture was extracted with chloroform which was subsequently washed with aqueous bicarbonate. The oil (690 mg) obtained from the chloroform gave a single spot by tlc[15] composed of syn and anti acetate.

The acetates were separated analytically by high pressure liquid chromatography [8 ft × 2.2 mm i.d., Porasil A, eluted with chloroform–petroleum ether[16] (1:1) at 0.75 ml/min; retention time of syn andd anti acetates are 16 min and 22.5 min, respectively], or preparatively [on ⅜ in. × 8 ft (or ¼ in. × 8 ft) columns at 3-ml/min flow rate].

Syn acetate **5**: mp 116–118° from petroleum ether;[17] pmr ($CDCl_3$) δ 8.3–7.3 (m, 4, aromatic H), 6.55 [q (X portion of ABX, $J_{AX} + J_{BX}$ = 14 Hz), 1, $CHOCOCH_3$], 3.80–3.00 (m, 2, benzylic CH_2), 2.7 to −0.3 (m, 16, CH_2), 2.10 (s, 3, CH_3CO_2).

Anal. Calcd for $C_{21}H_{26}ClNO_2$: C, 70.11; H, 7.23; N, 3.88. Found: C, 69.88; H, 7.36; N, 3.82.

Anti acetate **6** (unlabeled): mp 149–150° from petroleum ether[17]–chloroform; pmr ($CDCl_3$) δ 8.2–7.4 (m, 4, aromatic H), 6.08 [q (X portion of ABX, $J_{AX} + J_{BX}$ = 16 Hz, 1, $CHOCOCH_3$)], 3.8–3.3 (m, 2, benzylic CH), 2.7 to −0.3 (m, 16, CH_2), 2.08 (s, 3, CH_3CO_2).

Anal. Calcd for $C_{21}H_{26}ClNO_2$: C, 70.11; H, 7.23; N, 3.88. Found: C, 70.02; H, 7.22; N, 3.88.

The ratio of syn acetate to anti acetate was 1:1.1 as determined by the CH_3CO_2 pmr resonances and by hydrolysis and isolation of the corresponding syn and anti alcohols.[9]

B. Labeled 4.[2] This compound was treated as described above. The ratio of syn acetate to anti acetate was 1:4 (pmr resonances at δ 2.10 and 2.08). Deuterium analyses were concluded on the separated pure syn and anti alcohol obtained[9] from the mixed acetates by hydrolysis.

Syn alcohol: mass spectral analysis[18] showed 94.3% unlabeled alcohol and 5.7% d_1 species; the pmr spectrum ($CDCl_3$) integrated for 0.95 protons at δ 5.35[9] *vs.* 4 aromatic protons at 8.11–7.46 (sample was shaken with D_2O to eliminate hydroxyl proton which overlaps the methine absorption).

Anti alcohol: mass spectral analysis[18] showed 2.6% unlabeled species and 97.4% monodeuterated speciees; the pmr spectrum ($CDCl_3$) showed no methine resonance at δ 5.05.[9]

Reaction of Unlabeled 4 with Acetic Anhydride-^{18}O. The reaction of unlabeled **4** (75.1 mg) with acetic anhydride-^{18}O (250 mg, 95.52% ^{18}O, from Miles Laboratory, Elkhart, Ind.) was carried out (100°, 7.5 hr) essentially as described in A, above; however, labeled solvent (203.3 mg) was recovered by distillation. The mixture of syn and anti acetates (**6** and **7**) were separated by high pressure liquid chromatography to give pure syn acetate **6** (mp and mmp 115–117°) and pure anti acetate **7** (mp and mmp 152–153°).

The ^{18}O label in the syn and anti acetates **6** and **7** was determined by mass spectral analysis:[18] the molecular ion region (M^+ 359) gave mono- and dilabeled ^{18}O acetate abundances; the molecular ion minus acetyl (**12**, *m/e* 316) and molecular ion minus ketene (**13**, *m/e* 317) gave alcohol oxygen ^{18}O abundances. Possible ^{18}O isotope effects leading to **12** and **13** was assumed to be negligible at high (70 eV) ionization voltages. The calculations were performed by the method of Biemann[18] and the results are shown in Scheme IV.

Reaction of 4 with Acetyl Chloride. A. With Unlabeled 4. Unlabeled *N*-oxide **4** (300 mg, 0.944 mmol) was heated (60°) with excess acetyl chloride (16 hr); the mixture was cooled; and excess acetyl chloride was destroyed by additions of water. The mixture was extracted with chloroform which was subsequently washed with water and dilute aqueous bicarbonate. The oil obtained from the dried chloroform extract was subjected to preparative tlc[19] to give the following listed in order of increasing R_f.

1. A mixture of pure syn and anti acetates **5** and **6** unlabeled: 220 mg, 65% yield; ratio of syn:anti 1:1.5 by pmr integration of resonance at δ 6.55 (methine H) and 6.08 (methine H) and a ratio of 1:1.45 by integration of resonances at 2.10 and 2.08, respectively, for CH_3CO_2).

2. Anti chloride (unlabeled **10**): 70 mg, 22% yield; mp 140–140.5° from chloroform–petroleum ether;[17] pmr ($CDCl_3$) δ 8.25–7.55 (m, 4, aromatic H), 5.18 [q (X portion of ABX system, $J_{AX} + J_{BX}$ = 16 Hz), 1, methine H], 3.86–3.08 (m, 3, benzylic CH_2 plus 1 bridge proton), 2.55 to −0.16 (m, 15, CH_2); mass spectrum *m/e* (rel intensity), M^+ 335 (36), 300 (100), 265 (8.7), 241 (8.9) and 239 (13) (M^+ consistent for two chlorine atoms).

Anal. Calcd for $C_{19}H_{23}Cl_2N$: C, 67.92; H, 6.90; N, 4.17. Found: C, 67.66; H, 6.73; N, 4.20.

Confirmation of the anti configuration was made by noting the pmr shift (1.79 ppm) in methine resonance in going from the free base to the *N*-oxide by a procedure previously described.[10]

3. Syn chloride (unlabeled **9**): 30 mg, 9.5% yield; mp and mmp[10] 144–145°.

B. With Labeled 4.[2] The reaction was carried out as described in A, above, to give the following.

1. A mixture of pure syn and anti acetates **5** and **6**: 64.3% yield; ratio of syn:anti 1:3.3.

2. Pure anti chloride **10** (25.9% yield): the pmr spectrum showed no methine at δ 5.18 (anti chloride) which confirmed deuterium at the methine carbon; mass spectral analysis showed 95.2% monodeuterated species and 4.8% unlabeled species.

3. Pure syn chloride (1.5% yield): mass spectral analysis showed 63.2% nondeuterated, 32.7% monodeuterated, and 4.1% dideuterated species; the pmr spectrum (using a computer of average transients) gave an apparent triplet centered at δ 5.97 for anti H (**9**) which integrated for ~0.5H *vs.* aromatic H.

Analysis of the label in acetates **5** and **6** was conducted on the pure alcohols obtained by hydrolysis.[9] The syn alcohol (mp and mmp 158–159°)[9] showed by mass spectral analysis 82.7% unlabeled and 17.3% monodeuterated species; the pmr spectrum ($CDCl_3$) showed, subsequent to treatment of a sample with D_2O to eliminate overlapping signals due to OH, a quartet at δ 5.33 (methine H) which integrated to 0.85 H *vs.* the aromatic H. The anti alcohol (mp and mmp 205–206°)[9] showed by mass spectral analysis[18] 97.4% d_1 and 2.6% d_2 species; pmr showed no observable methine resonance.

Reaction of 4 with *p*-toluenesulfonyl chloride was carried out as previously described[10] to give only syn tosylate (m 122–123° from ether);[20] no anti tosylate[10] was detected. The mass spectrum of this product showed 97.5% d_1 and 2.5% d_2 species; pmr ($CDCl_3$) showed one proton (methine H) at δ 6.35.[9]

Registry No.—**4** (unlabeled), 25907-81-7; **4** (labeled), 51820-05-4; *syn*-**5** acetate, 51933-62-1; *syn*-**5** alcohol, 25866-36-8; *anti*-**6** acetate (unlabeled), 52078-88-3; *anti*-**6** acetate (labeled), 52151-91-4; *anti*-**6** alcohol (labeled), 52079-43-3; *syn*-**7** tosylate, 37781-25-2; *syn*-**9**, 37781-27-4; *anti*-**10** (unlabeled), 52019-95-1; *anti*-**10** (labeled), 52078-89-4; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5; *p*-toluenesulfonyl chloride, 98-59-9.

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(1) Supported in part by the National Science Foundation Grant No. GP 35429.
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(10) W. E. Parham, K. B. Sloan, K. R. Reddy, and P. E. Olson, *J. Org. Chem.*, **38**, 927 (1973).
(11) No chlorides were detected on prolonged (138.5 hr) treatment of syn and anti acetates with refluxing acetyl chloride.
(12) D. Rosenthal, private communication.
(13) Calculations were performed by modified method of S. Oae and coworkers; *cf.* ref 7.
(14) Return of an acetate ion pair associated with the activated complex may be analogous to results obtained with acetyl chloride.
(15) Silica gel, petroleum ether[16]–ether (3:2) as eluent.
(16) Bp 30–60°.
(17) Bp 60–90°.
(18) K. Biemann, "Mass Spectrometry; Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, pp 204–250.
(19) Silica gel developed with petroleum ether[16]–ether (85:15).
(20) The syn tosylate melts at 104–107° when crystallized from chloroform–petroleum ether[16] and is analytically pure. When the material is crystallized from ether, the mp is 122–123°.

Hydrolysis of 2-Methoxyfuran[1]

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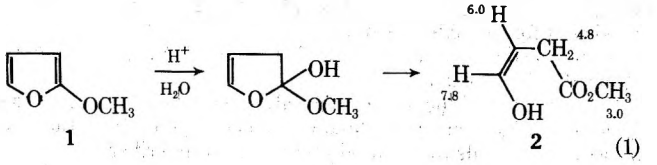
The acid-catalyzed hydrolysis of 2-methoxyfuran in aqueous dimethyl sulfoxide results in the formation of crotonolactone (**4**, 55–65%), methyl succinate semialdehyde (**5**, 16–23%), and methyl *cis*-4-hydroxycrotonate (**6**, 16%), as determined by nmr spectroscopy. These findings are not in agreement with an earlier report[2] and require revision of the proposed mechanism of hydrolysis of 2-methoxyfuran.

The acid-catalyzed hydrolysis of 2-methoxyfuran (**1**) has been reported[2] to yield the enol **2** of the methyl ester of succinic acid semialdehyde, presumably arising *via* a tetrahedral addition intermediate[3] (eq 1). The proposed intermediate is similar in structure to those believed to be formed in many acyl transfer reactions,[4] and in particular to those of ester hydrolysis[5] and formation.[6] It seemed of special interest to determine whether the direction of decomposition of the addition intermediate would be pH dependent, as had been found with the closely related intermediates generated during the lactonization of coumarinic acids,[6] and if so, to measure the partitioning ratio of the different ionic species of the intermediate. While attempting to obtain this information, we have found that the hy-



1 2 (1)

Table I
Hydrolysis of 2-Methoxyfuran

[HCl], M[a]	$k_{obsd} \times 10^3$, sec^{-1}	[DCl], M[b]	$k_{obsd} \times 10^3$, sec^{-1}	
0.001	1.64, 1.68	0.01	0.28[c]	0.24[d]
0.003	4.70, 5.46	0.08	2.8[c]	2.4[d]
0.005	8.05, 8.20, 8.38	0.25	11.2, 12.5[c]	7.8, 9.6[d]
	$k_H = 1.66\ M^{-1}$ sec^{-1}		$k_D = 0.033\ M^{-1}$ sec^{-1}	

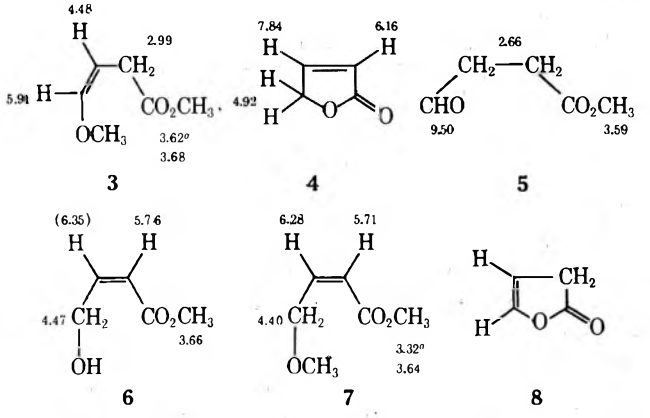
[a] At 25°, 0.8% CH_3CN–H_2O, μ = 0.1. [b] At 32.5°, 41 mol % dimethyl sulfoxide-d_6–deuterium oxide. [c] Disappearance of 2-methoxyfuran. [d] Appearance of 4.

drolysis of 2-methoxyfuran is appreciably more complex than hitherto reported.[2]

Results and Discussion

The identification[2] of the enol **2** as the product of hydrolysis of 2-methoxyfuran was based on the interpretation of the nmr spectrum of the reaction product (in 50 mol % dimethyl sulfoxide) as shown in eq 1. That the assigned structure **2** is probably incorrect is revealed by the published[7a] nmr spectrum (in CCl_4) of the corresponding enolic methyl ether **3** (Chart I). On the other hand, the measured chemical shifts and coupling constants assigned[2] to structure **2** correspond closely to those determined in this laboratory for 4-hydroxycrotonic acid lactone (**4**) in 50 mol % dimethyl sulfoxide–water.[8] In the same solvent, the methyl group of methanol had a chemical shift of 3.23 ppm relative to tetramethylsilane.

Chart I



[a] Individual values of the chemical shifts of the two methyl groups in **3** and **7** (ref 7a) were not assigned.

Kinetic Studies. The disappearance of 2-methoxyfuran in 0.8% acetonitrile–water (μ = 0.1, NaCl) at 25°, followed by the decrease in ultraviolet absorbance at 230 nm, was found to obey the rate law $k_{obsd} = k_H[H^+]$, with k_H = 1.66 M^{-1} sec^{-1} (Table I). This constant agrees very well with the reported[2] value of 1.68 M^{-1} sec^{-1} in water (25°), measured by gas chromatography.

The rate of hydrolysis of 2-methoxyfuran was also determined in 41 mol % dimethyl sulfoxide-d_6–deuterium oxide solvent (at 32.5 ± 1.0°), using nmr spectroscopy. Measurements were made at 0.01, 0.08, and 0.25 M DCl concentration, and the ionic strength was equal to the concentration of added acid. The resulting rate constants were considerably less precise than those determined in dilute solution by uv spectroscopy, especially at the highest acidity, but were approximately linearly dependent on D^+ concentration and gave k_D = 0.033 M^{-1} sec^{-1} (Table I). The protons at C_3 and C_5[9] were found to disappear at the same rate, in agreement with the previous report,[2] thus ruling out rapid, preequilibrium hydrogen exchange at C_5, such as was found in the hydrolysis of 2-methylfuran.[10] In addition, the appearance of the C_4 and the (single) C_5 protons of the crotonolactone **4** also followed first-order kinetics at a rate equal to that of the disappearance of 2-methoxyfuran (Table I), suggesting that no significant concentration of any intermediates accumulated prior to the formation of **4**.

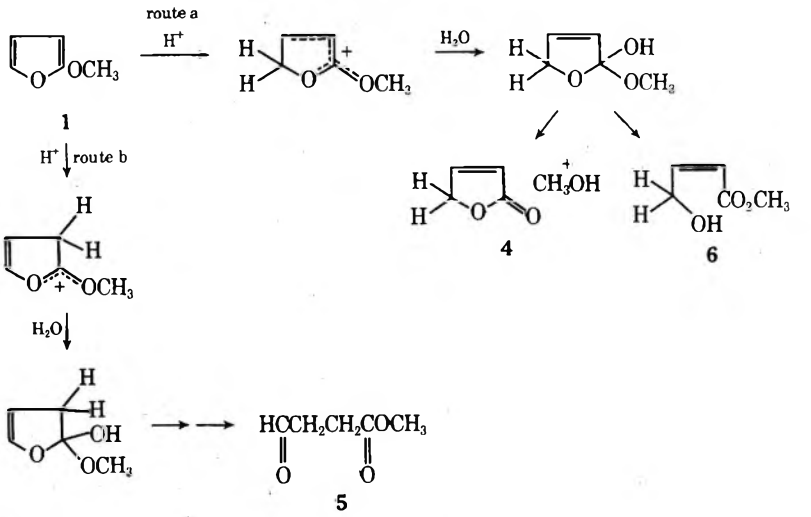
The reaction rate was also measured by the nmr technique in 47 mol % CD_3CN–D_2O at a single acid concentration (0.08 M DCl), yielding k_D = 0.07 M^{-1} sec^{-1}.

Reaction Products. Nmr spectra of reactions carried out in 41 mol % dimethyl sulfoxide-d_6–deuterium oxide were obtained after complete disappearance of 2-methoxyfuran (at least 8 half-lives) over the range of 0.001–0.93 M DCl. These spectra showed that the reaction product was an unexpectedly complex mixture of components. The predominant product (55–65% yield) exhibited chemical shifts, spin–spin multiplicity, and coupling constants identical with those measured in this solvent for the crotonolactone **4** (Chart I) and similar to those reported for $CDCl_3$.[8] The integrated signals showed that the protons at δ 4.92, 6.16, and 7.84 were present in the ratio of 1:1:1 when hydrolysis was performed in solvents containing deuterium oxide (the integration of the signal at δ 6.16 was invariably 10–15% greater than that of the signal at δ 7.84; see below). The splitting pattern for each of the C_3 and C_4 protons changed from a doublet of doublets for the D_2O reaction to a doublet of triplets when hydrolysis was carried out in H_2O. The splitting patterns, integrated areas, and the broadening of the signal at δ 4.92 are consistent with the conclusion that the crotonolactone **4** produced in the presence of deuterium oxide contains a single deuterium atom incorporated at the C_5 positions.

Comparison to authentic material allowed the identification of the second reaction product (16–23% yield) as the methyl ester of succinic acid semialdehyde (**5**) (singlets for the aldehydic proton[11] at δ 9.50 and for the methoxyl group at δ 3.59, Chart I). The weak and broad signal (at least two deuterium atoms are expected to be incorporated in the $-CH_2CH_2-$ group; see below) anticipated at δ 2.66 for the methylene groups of **5** is masked by protonic impurities in dimethyl sulfoxide-d_6.

A third product formed in significant quantities (about 16%) is tentatively identified as *cis*-4-hydroxycrotonic acid methyl ester (**6**) (Chart I). Although this substance does not seem to have been described, the corresponding methyl ether **7** is well known[7a,c] and its nmr spectrum[7a] (Chart I) is consistent with the assignments made here for **6**. The large coupling constant ($J_{2,3}$ = 11.7 Hz)[7a] for the olefinic protons of **7** is reflected in the well-separated doublet of doublets centered at δ 5.76 and assigned to C_2 in **6**. The C_3 proton of **6** (centered approximately at δ 6.35) appears partially masked by the more prominent C_3 proton of the crotono-

Chart II



lactone. This overlap is presumably responsible for the consistent observation mentioned above that the integral of the C_3 proton of **4** was always slightly higher than that of the C_4 proton. For reactions in D_2O, the signal at δ 4.47 (C_4 of **6**) is expected to correspond to one proton only, although precise integration of these weak signals is difficult. The most convincing indication of the existence of **6** is, of course, the presence of the sharp methoxy singlet slightly downfield from the methoxy signal of the aldehyde ester **5**.

The lactone **4** and the two acyclic products **5** and **6** account for about 90–95% of the reaction products. Particular attention was directed at the possibility that the enol lactone **8** might be a reaction product. Although the preparations[12] of **8** and of its tautomer 2-hydroxyfuran[13] have been claimed, the existence of these compounds is in doubt.[14,15] In any event, a signal at *ca.* δ 6.75 would be expected for the C_5 proton of **8** (based on the reported[17] nmr spectrum of the 3-methyl derivative of **8**). The absence of any significant resonance in this area of the reaction product spectrum serves to rule out the possibility that the enol lactone **8** is a stable product of the hydrolysis of 2-methoxyfuran.

No systematic variation in the yield of the crotonolactone **4** was noted in the acidity range of [DCl] = 0.001–0.9 *M*. In 0.04 *M* DCl, the crotonolactone undergoes neither hydrolysis nor hydrogen exchange over a period of 6 days. Similarly, the yield of the aldehyde **5** appears approximately constant over the same range of acidity, as judged from the intensity of the methyl signal at δ 3.59. It is noteworthy that the aldehydic proton signal is not a reliable indication of aldehyde yield in these experiments. The sharp singlet observed at δ 9.50 in 50 mol % dimethyl sulfoxide-d_6–D_2O is appreciably broadened in 0.04 *M* DCl and is essentially undetectable in 0.93 *M* DCl. This behavior is most likely the result of the increasing rate of the (acid-catalyzed) chemical exchange reaction between the aldehyde and its hydrate. In the absence of acid, the nmr spectrum of the aldehyde exhibits a weak triplet at δ 4.84,[18] presumably the signal of the spin-coupled proton of the hydrated aldehyde, whose intensity suggests that about 25% of the total aldehyde exists as the hydrate.[19] That exchange between the aldehyde and its hydrate would become significant on the nmr time scale in this range of acid concentrations is supported by the report[20] of line broadening in the ^{17}O nmr spectrum of acetaldehyde and its hydrate in 0.1–1 *M* HCl and the measured rates of the acid-catalyzed hydration of simple aliphatic aldehydes.[19b,c,21]

The yield of methyl *cis*-4-hydroxycrotonate (**6**) is constant in solutions where [DCl] = 0.001–0.08 *M*, is reduced by half in 0.25 *M* DCl, and falls to nearly zero at higher acidities. It is not certain whether the acyclic alcohol was not formed at high acidity, or underwent rapid subsequent reaction. Under conditions where an appreciable amount of **6** is formed (*e.g.*, 16% in 0.04 *M* DCl after 1.5 hr), the methyl signal associated with **6** had almost completely disappeared after 14 hr, while that of the aldehyde **5** was largely unchanged. Possibly, the 4-hydroxy ester **6** undergoes acid-catalyzed lactonization to the crotonolactone **4**.[22] However, the relative stability of **6** after short reaction times rules out the possibility that lactonization of initially produced **6** constitutes the main pathway for the formation of the crotonolactone **4**.

Reaction Mechanism. For the hydrolysis of 2-methoxyfuran in 41 mol % dimethyl sulfoxide–water, a reaction mechanism consistent with the observations made in this study is outlined in Chart II. According to this proposal, 2-methoxyfuran suffers rate-determining protonation either at the 5 position (route a) or the 3 position (route b). The former pathway, resulting (formally) in 1,4-addition across the dienic system, occurs four times as fast as the competing 1,2-addition of route b. For route a, the allylic oxocarbonium ion is suggested to yield a tetrahedral addition intermediate (of unspecified ionic state) which breaks down mainly by expulsion of methanol but also undergoes significant ring opening to the allylic alcohol **6**. The incorporation of one atom of deuterium at C_5 of the crotonolactone is in accord with the proposed pathway.

In route b, the protonation which occurs at C_3 yields eventually a tetrahedral intermediate which appears to break down solely by ring cleavage, presumably to the enolic form of **5**; rapid tautomerization then gives the observed aldehyde.

The pattern of deuterium incorporation in the crotonolactone **4** (one atom of deuterium at C_5) rules out a mechanism wherein the predominant hydrolytic pathway is that of route b, yielding mainly the (possibly unstable) enol lactone **8**, which undergoes double-bond migration to the crotonolactone **4**. Such a mechanism would necessarily require the presence of a deuterium atom at C_3 of the crotonolactone.

The mechanism of hydrolysis of 2-methoxyfuran thus appears to differ from those proposed for the acid-catalyzed hydrolysis of furan[23] and its alkyl-substituted derivatives,[10,23,24] for which it has been suggested that the major reaction pathway consists of rate-determining β-protonation (*i.e.*, at C_3 of the furan ring).

The identity of the products of hydrolysis of 2-methoxyfuran in dilute aqueous solution is not known. If both hydrolytic pathways also occur in predominantly aqueous medium, the observed[2] solvent deuterium isotope effect and general acid catalysis may contain contributions from both reaction pathways and are thus not amenable to interpretation at this time.

Experimental Section[25]

2-Methoxyfuran (1) (Aldrich Chemical Co.) had bp 103–105° (lit.[26] bp 108–109°) and was kept in the dark in sealed ampoules at −10°. Prior to use, the purity of the compound was routinely checked by nmr spectroscopy and compared to the nmr spectrum of a freshly distilled sample.

1: Uv (CH_3CN) λ_{max} 222 nm (ϵ 6750);[27] nmr ($CDCl_3$)[28] δ 3.73 (s, 3 H, OCH_3), 5.05 (m, 1 H, C_3), 6.14 (m, 1 H, C_4), 6.75 (m, 1 H, C_5); nmr (50 mol % DMSO-d_6–D_2O:) δ 3.79, 5.30, 6.34, 7.00.

4-Hydroxycrotonic acid γ-lactone (4), bp 107–109° (24 mm) [lit.[29] bp 107–109° (24 mm)], was prepared using the procedure of Price and Judge.[29] The nmr spectrum in $CDCl_3$ agreed with the reported values.[8] Nmr (50 mol % DMSO-d_6–D_2O): δ 4.92 (t, 2 H, CH_2), 6.16 (m, 1 H, C_3), 7.84 (m, 1 H, C_4).

Succinic Acid Semialdehyde Methyl Ester (5). Methyl hydrogen succinate[30] was converted to the acid chloride.[31] Rosenmund reduction[32] of the latter gave the aldehyde: bp 68–71° (11 mm) [lit.[32] bp 69–70° (14 mm)]; nmr ($CDCl_3$) δ 2.66 (m, 4 H, CH_2CH_2), 3.62 (s, 3 H, OCH_3), 9.67 (s, 1 H, CHO); nmr (50 mol % DMSO-d_6–D_2O) δ 2.33–2.90 (m, 4 H, CH_2CH_2), 3.59 (s, 3 H, OCH_3), 4.84 [t, 0.25 H, $HC(OD)_2C$], 9.50 (s, 0.75 H, CHO).

Deuterium oxide, concentrated aqueous DCl, CD_3CN, and dimethyl sulfoxide-d_6 were obtained from Merck Sharpe and Dohme of Canada.

Kinetic Measurements. The rate of hydrolysis of 2-methoxyfuran in dilute aqueous HCl solution (25°, μ = 0.1, NaCl) was determined by following the decrease in absorbance at 230 nm, using a Cary 15 spectrophotometer. Reaction was initiated by addition of 25 μl of a stock solution of 2-methoxyfuran in acetonitrile to 3 ml of aqueous HCl solution previously equilibrated in the thermostated cell compartment of the spectrophotometer. The final concentration of substrate was about 3×10^{-4} M, and the absorbance change was 0.8–0.9 units.

The following procedure was used for rate measurements in 41 mol % DMSO-d_6–D_2O. A mixture of 0.5 g of DMSO-d_6 and 0.13 g of D_2O was added to 0.05 g of 2-methoxyfuran in an nmr tube. The sample was allowed to equilibrate to the temperature of the probe (32.5 ± 1.0°), and the nmr spectrum was recorded to check the purity of the reactant. Hydrolysis was initiated by the addition of 50 μl of standard aqueous DCl solution, and the nmr tube was rapidly shaken and immediately reinserted into the probe. The rate of disappearance of 2-methoxyfuran was followed by the decrease in the integrated signal of the protons at C_3 and C_5, while the signals at C_4 and C_5 of the crotonolactone 4 were used to monitor the formation of product. First-order rate constants were calculated by means of the integrated first-order rate equation.

Product Analysis. Nmr spectra of reaction mixtures were recorded after 10–20 half-lives of reaction. The yield of crotonolactone 4 was calculated by comparison of the area of the signal for the C_4 proton to that of an authentic sample of 4. The total concentration of methyl esters 5 and 6 was determined from the combined areas of the methoxy signals at about δ 3.6 and the relative amounts of 5 and 6 were estimated from the relative heights of the signals at δ 3.59 and 3.66.

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Registry No.—2-Methoxyfuran, 25414-22-6.

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Notes

Nucleophilic Additions to Diethyl Cyclopropylmethylidenemalonate

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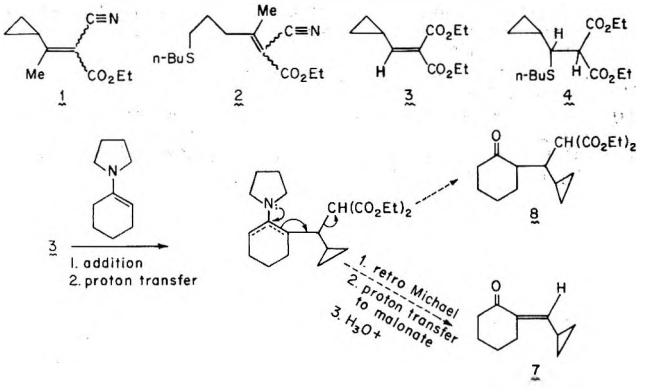
The reaction of *n*-butyl mercaptan with ethyl α-cyano-β-cyclopropylcrotonate (1 cis and trans mixture) has been reported to give ethyl 2-cyano-3-methyl-6-*n*-butylmercaptohex-2-enoate (**2**, cis and trans mixture).[1] In the light of the greater receptivity of α,β-unsaturated carbonyl systems toward 1,4-addition relative to equivalently activated cyclopropanes,[2] it appeared that the generality of this type of terminal attack merited further examination. The particular substrate which we chose for study was the cyclopropylmethylidenemalonate, **3**. This compound was easily prepared (78%) by the Knoevenagel condensation of cyclopropanecarboxaldehyde[3] with diethyl malonate under the influence of ammonium acetate.

The condensation of **3** with *n*-butyl mercaptan was studied under neutral as well as base-catalyzed conditions. In both cases the only product obtained (71 and 75% yields, respectively) was the simple 1,4 adduct, **4**. We could find no evidence for the presence of ring-opened products similar to those obtained in the case of **1**. Apparently, in the latter case, the β,β disubstitution hinders simple Michael addition. Whether the ring-opened product, **2**, results from *bona fide* nucleophilic attack in a "homo" extended conjugate sense or is the result of a free-radical pathway[4] is not known. Such a free-radical mechanism has been implicated[5] in the ring-opened products arising from the reaction of 1,1-dicarbethoxy-2-vinylcyclopropane (**5**) with *n*-butyl mercaptan.

Since the thermal reaction of **5** with enamines occurs *via* overall terminal attack,[6,7] it was of interest to investigate the corresponding reaction for the case of **3**. Accordingly, compound **3** was heated in toluene with a twofold excess of 1-*N*-pyrrolodinocyclohexene (**6**). After acidic hydrolysis, the reaction residue was separated by fractional distillation. The products obtained in ascending order of boiling points were (1) a mixture of cyclohexanone and diethyl malonate, the latter in *ca.* 40% yield; (2) 2-cyclopropylmethylidenecyclohexanone (**7**) in 40–45% yield; and (3) 2-carbethoxy-3-cyclopropyl-3-(cyclohexan-2-on-1-yl) propionate (**8**) in 15% yield. An attractive sequence which accounts for these results is set forth below. The key step leading to **7** is formulated as a reverse Michael reaction, with malonate as the leaving group, coupled at some stage to a proton transfer. It will be seen that this scheme invokes the tetrasubstituted enamine isomer on the pathway to the major product. In the case of pyrrolidine enamines, the trisubstituted isomer is expected to predominate.[8] However, under the vigorous reaction conditions, equilibration between the tri- and tetrasubstituted tautomers could well be anticipated.



The generality of synthesizing α-alkylidenecycloalkanones *via* a Michael–retro-Michael combination between the corresponding enamines and alkylidenemalonates remains to be explored. In the case at hand, the trans configuration is tentatively assigned to compound **7** on the basis of the 2 Hz allylic coupling constant of its vinylic proton.

Recently, Grieco[9] reported exclusive 1,4-addition of lithium dimethylcopper to **3**. It would thus appear to be safe to generalize that, for the case of this substrate, extension of conjugation by the cyclopropane ring is not manifested at the chemical level.[10]

Experimental Section[11]

Preparation of Cyclopropylmethylidenemalonate (3). A solution of 9.96 g (0.056 mol) of diethyl malonate, 5.0 g (0.071 mol) of cyclopropanecarboxaldehyde,[3] 0.727 g (0.012 mol) of acetic acid, and 0.463 g (0.006 mol) of ammonium acetate in 10 ml of dry benzene was heated under reflux, with the condensate collected in a Dean-Stark trap. After 4 hr, 1.1 ml of water was collected.

The solution was poured into ether and extracted with water. After being dried, the organic fraction was concentrated *in vacuo*. The residue was distilled to give **3**: 9.3 g (0.044 mol, 78%); bp 74–75° (0.025 mm); λ_{max} (CCl_4) 320, 5.80, 6.11 μ; nmr (CCl_4) τ 3.70 (d, J = 11 Hz, 1 H), 5.76 (q, J = 7 Hz, 2 H), 5.84 (q, J = 7 Hz, 2 H), 7.8–8.4 (m, 1 H), and 8.5 ppm (m, 10 H, containing t at 8.77, J = 7 Hz); *m/e* 212 (parent), 110 (base).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%. Found: C, 62.15; H, 7.65%.

Reactions of 3 with *n*-Butyl Mercaptan. Formation of Mercapto Diester 4. Method A. To a 100-ml glass pressure flask was added 3.0 g (0.0141 mol) of **3** and 7.08 g (0.078 mol) of *n*-butyl mercaptan. The solution was purged with nitrogen, sealed, and heated at 110° for 48 hr. Excess mercaptan was removed under reduced pressure and the residue was distilled *in vacuo* to give 0.05 g (16%) of recovered **3** as forerun and 3.03 g (71%) of diester sulfide **4**, bp 110 ° (0.1 mm).

Method B. To a suspension of 41 mg (1.7 mmol) of sodium hydride in 10 ml of dry dimethoxyethane was added 1.53 g (17 mmol) of *n*-butyl mercaptan and 3.0 g (14.1 mmol) of **3**. The solution was heated under reflux for 4 hr. The solution was concentrated *in vacuo*, diluted with ether, and extracted with water. The organic layer was dried ($CaCl_2$) and then concentrated at reduced pressure. Vacuum distillation of the residue afforded, after removal of a forefraction, 3.2 g (75%) of **4**: bp 116–118° (0.2 mm); λ_{max} (CCl_4) 3.21, 5.70 sh, 5.77, 9.58, 9.79, and 10.48 μ; nmr τ 5.88 (q, J = 7 Hz, 4 H), 6.45 (d, J = 9 Hz, 1 H), 7.15–7.60 (m, 3 H), 8.2–9.8 ppm (m, 18 H containing t, J = Hz, at 8.78 ppm); *m/e* 302 (parent), 67 (base peak).

Anal. Calcd for $C_{15}H_{26}O_4S$: C, 59.60; H, 8.60; S, 10.60. Found: C, 59.44; H, 8.46; S, 10.39.

Reaction of 3 with 1-Pyrrolodinocyclohexene.[9] Formation of 7 and 8. A solution of 3.5 g (23.2 mol) of the enamine[8] and 2.5 g (11.8 mmol) of **4** in 10 ml of toluene was heated under reflux for 5 days. The solution was diluted with ether and extracted with 3 ml of dilute HCl. The ether fraction was dried ($CaCl_2$) and concentrated *in vacuo* and the residue was submitted to fractional distillation. A fraction distilling at 100–110° (25 mm) was shown by nmr integration to consist of *ca.* 3:2 diethyl malonate (41% yield):cyclohexanone. A second fraction (1.15 g) distilling at 68–70° (0.025 mm), was chiefly (*ca.* 85% pure) **7** (41% yield). The highest boiling

fraction [118–120° (0.025 mm)] was chiefly (85% pure) 8 (15% yield). Further purification of 7 and 8 was effected by distillation at 55 (0.005 mm) and 116° (0.005 mm), respectively.

For 7: λ_{max} (CCl_4) 3.19, 3.29, 5.83, 5.93, and 6.12 μ; nmr (CCl_4) τ 4.24 (d, J = 10.5 Hz, of t, J = 2 Hz, 1 H), 7.25–9.3 ppm (m, 13 H); m/e 150 (parent), 122 (base peak).

For 8: λ_{max} (CCl_4) 5.70 sh, 5.7, 9.41 sh, 9.67 μ; nmr (CCl_4) τ 5.88 (q, J = 7 Hz, 4 H), 6.3 (d, J = 7 Hz, 1 H), 6.8 (m, 1 H), 7.1–9.9 ppm (m, 20 H, containing t, J = 7 Hz, at 8.77 ppm); m/e 310 (parent), 264 (base peak).

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Registry No.—3, 39000-53-8; 4, 51933-04-1; 7, 51933-05-2; 8, 51933-06-3; diethyl malonate, 105-53-3; cyclopropanecarboxaldehydes, 1489-69-6; *n*-butyl mercaptan, 109-79-5; 1-pyrrolidinocyclohexene, 1125-99-1.

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Preparation and Reactions of a Tris Annelating Agent

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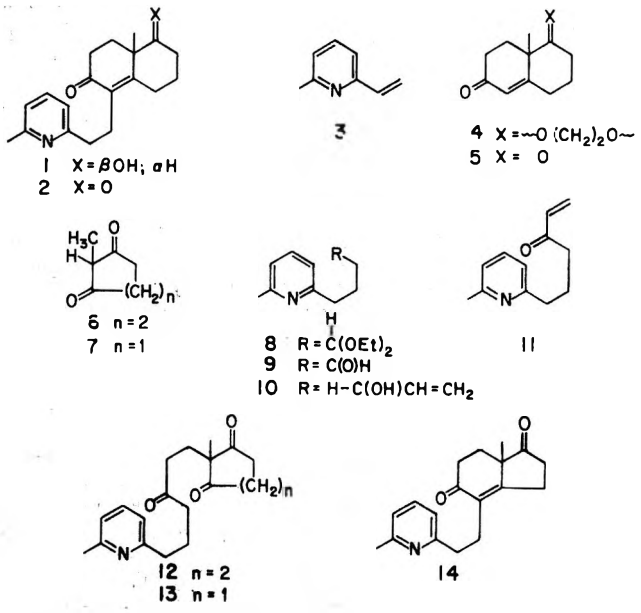
Recently we reported the synthesis of *dl*-D-homoestrone *via* the picolylethylated octalone derivative **1**.[1] This intermediate was assembled by the Michael reaction of ketalenone **4** with bis annelating agent[2] **3**. Precursor **4** is the monoketalization product[3,4] of the Wieland–Miescher ketone **5**, itself the Robinson annelation product of diketone **6** with methyl vinyl ketone.[5,6] The vinylpicoline **3**[7] is obtained in low yield[7] *via* hydroxymethylation of 2,6-lutidine.

A major simplification in the lutidine route to 19-norsteroids could be contemplated by the utilization of the tris annelating agent **11**. Were this compound to be easily available, its merger with diketones (*e.g.*, **6**) to produce, directly, products such as **2** could be envisioned as a means of eliminating the lowest yield facets of the synthetic approach described above. Below we set forth a convenient and efficient synthesis of **11**. Its high-yield condensations with **6** and **7** are also described.

Treatment of 2,6-lutidine with phenyllithium followed by alkylation of the resultant anion with 3-chloropropionaldehyde diethyl acetal[8] gives **8**, which is converted, without purification, to aldehyde **9** (70% overall). Addition of



vinylmagnesium chloride to **9** gives (89%) alcohol **10** which undergoes oxidation by manganese dioxide to afford (88%) the desired **11**.

Some indication of the potential applications of this compound can be seen from the following experiments. Under the influence of sodium hydride, enone **11** couples smoothly with **6** to give **12**. Cyclization of **12** under the influence of 3-aminopropionic acid[9] affords (75%) **2**, which is converted to its crystalline dihydro derivative **1**.

Condensation of **7** with **11** can be conducted in one step in aqueous acid to give enedione **14** in 92% yield. Alternatively **7** and **11** can be coupled through the action of triethylamine in ethyl acetate[10] to give trione **13**, which can be cyclized, in a separate step, *via* 3-aminopropionic acid[9] to give **14**.

The advantages[9] of passing through symmetrical intermediates such as **12** and **13** on the way to compounds such as **2** and **14** will be set forth in future publications.

Experimental Section[11]

Preparation of Picolylbutyraldehyde 9. To a stirred solution containing 16.2 g (0.15 mol) of 2,6-lutidine in 250 ml of dry THF (freshly distilled from CaH_2) under a nitrogen atmosphere was slowly added 65 ml (0.15 mol) of 2.4 *M* PhLi in 70:30 benzene–ether. The resulting solution was stirred at room temperature for 20 min. After cooling to 0°, 10.6 g (0.10 mol) of 3-chloropropionaldehyde diethyl acetal was slowly added. After stirring for 30 min at 0°, the solution was refluxed for 12 hr. The solution was then cooled to room temperature, 150 ml of aqueous 10% HCl was slowly added, and the resulting solution was stirred for 5 hr. The solution was then neutralized with $NaHCO_3$ and extracted with 5 × 100 ml CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4. After evaporation of the solvents, distillation afforded 10.84 g (70%) of **9** as an oil: bp 64–65° (0.05 mm); ir ($CHCl_3$) 2810, 2710, 1715, 1590, 1575 cm^{-1}; nmr (CCl_4) δ 1.8–2.4 (m, 4 H), 2.48 (s, 3 H), 2.68 (t, 2 H), 6.90 (d, 2 H), 7.38 (t, 1 H); m/e 163.

Although this material was judged to be pure by nmr, two combustion analyses[11] gave results not in accord with prediction.

Preparation of Allylic Alcohol 10. To a stirred solution containing 8.2 g (0.05 mol) of aldehyde **9** in 150 ml of dry THF (freshly distilled from CaH_2) under a nitrogen atmosphere and at −78° was slowly added 26.4 ml (0.075 mol) of 2.84 *M* vinylmagnesium chloride in THF. The resulting solution was stirred for 0.5 hr at −78° and then at room temperature for 1.5 hr. The solution was then poured into 50 ml of H_2O and acidified with 10% HCl. After neutralization with $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted with 4 × 50 ml of CH_2Cl_2. Evaporation of the solvent and filtration of the residue through 150 g of silica gel using 3:1 hexane–ethyl acetate as the eluent afforded 8.5 g (89%) of the desired allylic alcohol **10** as a pale yellow oil: ir

($CHCl_3$) 3600, 3450, 1590, 1575, 990, 925 cm^{-1}; nmr ($CDCl_3$) δ 1.5–2.1 (m, 4 H), 2.59 (s, 3 H), 2.80 (t, 2 H), 4.18 (q, 1 H), 4.39 (s, 1 H), 4.9–5.4 (m, 2 H), 5.65–6.2 (m, 1 H), 6.90 (d, 2 H), 7.38 (t, 1 H); *m/e* 191.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.95; H, 8.66; N, 7.21.

Preparation of Pyridine Enone 11. A solution containing 12.0 g (0.063 mol) of allylic alcohol **10** and 120 g of activated MnO_2[12] in 300 ml of CH_2Cl_2 was refluxed for 5 hr. The mixture was filtered, the precipitate was thoroughly washed with $CHCl_3$, and the combined washings were concentrated. Filtration of the concentrate through 200 g of silica gel using 3:1 hexane–ethyl acetate as the eluent afforded 10.5 g (88%) of the desired vinyl ketone **11** as a pale yellow oil: ir ($CHCl_3$) 1670, 1610, 1590, 1575 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (m, 2 H), 2.47 (s, 3 H), 2.55–3.0 (m, 4 H), 5.66 (d of d, 1 H), 6.21 (m, 2 H), 6.90 (d, 2 H), 7.38 (m, 1 H); *m/e* 189.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 4.65. Found: C, 76.15; H, 7.65; N, 4.50.

Coupling of Diketone 6 with Vinyl Ketone 11. Formation of Adduct 12. To a solution containing 1.5 g (0.0118 mol) of 2-methyl-1,3-cyclohexanedione in 50 ml of dry DME (freshly distilled from CaH_2) under a nitrogen atmosphere was added 10 mg of NaH. After stirring for 10 min at room temperature, 2.0 g (0.0106 mol) of vinyl ketone **11** in 10 ml of dry DME was slowly added. The resulting solution was heated under reflux for 0.5 hr and cooled to room temperature, and 25 ml of H_2O was added. The mixture was extracted with 3 × 25 ml of CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvents, the residue was chromatographed on 100 g of silica gel. Elution with $CHCl_3$ afforded 3.18 g (95%) of trione **12** as an oil: ir ($CHCl_3$) 1710, 1690, 1590, 1575 cm^{-1}; nmr ($CDCl_3$) δ 1.27 (s, 3 H), 1.8–2.9 (m, 19 H), 6.90 (d, 2 H), 7.38 (t, 1 H); *m/e* 315.

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.50; H, 8.15; N, 4.50.

Cyclodehydration of Trione 12. Formation of Octalindione 2. A solution containing 1.0 g (3.18 mmol) of trione **12**, 565 mg (6.36 mmol) of 3-aminopropionic acid, and 2.5 ml of 1 *N* $HClO_4$ in 25 ml of CH_3CN was heated under reflux for 55 hr. The solution was cooled to room temperature, 25 ml of H_2O was added, and the mixture was neutralized with $NaHCO_3$. This mixture was extracted with 4 × 25 ml of CH_2Cl_2, the combined organic extracts were dried, the solvents were evaporated, and the residue was chromatographed on 50 g of silica gel. Elution with $CHCl_3$ afforded 711 mg (75%) of 2 as an oil: ir ($CHCl_3$) 1705, 1665, 1590, 1575 cm^{-1}; nmr ($CDCl_3$) δ 1.38 (s, 3 H), 1.8–3.0 (m, 17 H), 6.90 (t, 2 H), 7.38 (t, 1 H); *m/e* 297.

Reduction of Picolylethylated Octalindione. Preparation of Hydroxyoctalone 1. To a solution containing 750 mg (2.5 mmol) of enedione **2** in 25 ml of absolute ethanol under an atmosphere of nitrogen at 0° was added 47.5 mg (1.25 mmol) of $NaBH_4$. The solution was stirred at 0° for 0.5 hr and then at room temperature for 1.5 hr. To the resulting solution was then added 10 ml of saturated KCl solution and the mixture was extracted with 4 × 25 ml of $CHCl_3$. The combined organic extracts were dried over anhydrous Na_2SO_4 and, after evaporation of the solvents, the residue was chromatographed on 50 g of silica gel. Elution with $CHCl_3$ afforded 682 mg (91%) of hydroxyenone **1** as white crystals, which were recrystallized from ethyl acetate–hexane: mp 103–104°;[1] ir ($CHCl_3$) 3600, 3400, 1660 1590, 1575 cm^{-1}; nmr ($CDCl_3$) δ 1.07 (s, 3 H), 1.5–2.9 (m, 17 H), 3.24 (t, 1 H), 3.31 (s, 1 H), 6.90 (t, 2 H), 7.38 (t, 1 H); *m/e* 299.

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.14, H, 8.37; N, 4.52.

One-Step Condensation of Vinyl Ketone 11 with Diketone 7. Formation of Enedione 14. A solution containing 50 g (0.0264 mol) of vinyl ketone **11** and 3.88 g (0.0345 mol) of 2-methyl-1,3-cyclopentanedione (**7**) in 100 ml of aqueous 10% H_2SO_4 was heated under reflux for 20 hr. The solution was then cooled to room temperature, neutralized with $NaHCO_3$, and extracted with 3 × 25 ml of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and, after evaporation of the solvent, the residue was chromatographed on 250 g of silica gel. Elution with $CHCl_3$ afforded 6.9 g (29%) of **14** as a pale yellow oil:[13] ir ($CHCl_3$) 1740, 1660, 1590, 1575 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (s, 3 H), 1.9–3.0 (m, 15 H), 6.92 (t, 2 H), 7.41 (t, 1 H); *m/e* 283.

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.21; H, 7.38; N, 4.80.

Coupling of Diketone 7 with Vinyl Ketone 11. Formation of Adduct 13. To a solution containing 5.0 g (0.0264 mol) of vinyl ketone **11** and 3.8 g (0.034 mol) of 2-methyl-1,3-cyclopentanedione in 20 ml of ethyl acetate was added 10 ml of 20% Et_3N in ethyl acetate. After stirring at room temperature for 36 hr the resulting solution was added to 15 ml of H_2O. The mixture was extracted with 3 × 20 ml of $CHCl_3$ and the combined extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 7.88 g of crude trione **13**. Examination of the "crude" material by tlc (4:4:1 hexane–ethyl acetate–methanol) showed one spot, R_f 0.43, and the absence of **11**, R_f 0.56. A small spot at the origin appeared to be the only contamination. Trione **13** showed ir ($CHCl_3$) 1785 (shoulder), 1721, 1590, 1575 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (s, 3 H), 1.6–2.2 (m, 4 H), 2.3–2.9 (m, 13 H), 6.90 (d, 2 H), 7.38 (t, 1 H); *m/e* 301.

Preparation of Enedione 14 from Trione 13. A solution containing 7.88 g (0.028 mol) of crude trione **13**, 4.45 g (0.050 mol) of 3-aminopropionic acid, and 10.5 ml of 1 *N* $HClO_4$ in 105 ml of CH_3CN was heated under reflux for 55 hr. The resulting solution was cooled to room temperature, 50 ml of H_2O was added, and the solution was neutralized with $NaHCO_3$. The solution was then extracted with 4 × 50 ml of CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvents and chromatography on 500 g of silica gel afforded 7.04 g (7) of the enedione **14** after elution with $CHCl_3$.

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Registry No.—**1**, 51965-91-4; **2**, 51965-92-5; **6**, 1193-55-1; **7**, 765-69-5; **9**, 46119-04-4; **10**, 51965-93-6; **11**, 51965-94-7; **12**, 51965-95-8; **13**, 51965-96-9; **14**, 51965-97-0; 2,6-lutidine, 108-48-5; 3-chloropropionaldehyde diethyl acetal, 35573-93-4; 3-aminopropionic acid, 107-95-9.

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(10) G. Baudin, H. Christol, and Y. Pietrasante, *Bull. Soc. Chim. Fr.*, 359 (1973).
(11) Melting points and boiling points are uncorrected. Nmr spectra were measured on Varian T-60 or A-60D spectrometers using tetramethylsilane as an internal standard. Mass spectra were obtained on an L.K.B.-9000 system *via* direct insertion. Combustion analysis were performed by Galbraith Laboratories, Knoxville, Tenn. Phenyllithium and vinylmagnesium chloride were obtained from Alpha Inorganics.
(12) H. B. Henbest, E. R. H. Jones, and T. C. Owen, *J. Chem. Soc.*, 4909 (1957).
(13) It is interesting to note that the corresponding reaction, vinyl ketone **11** with β-diketone **6**, failed for reasons not understood.

Phenylation of Perchlorocyclobutenone

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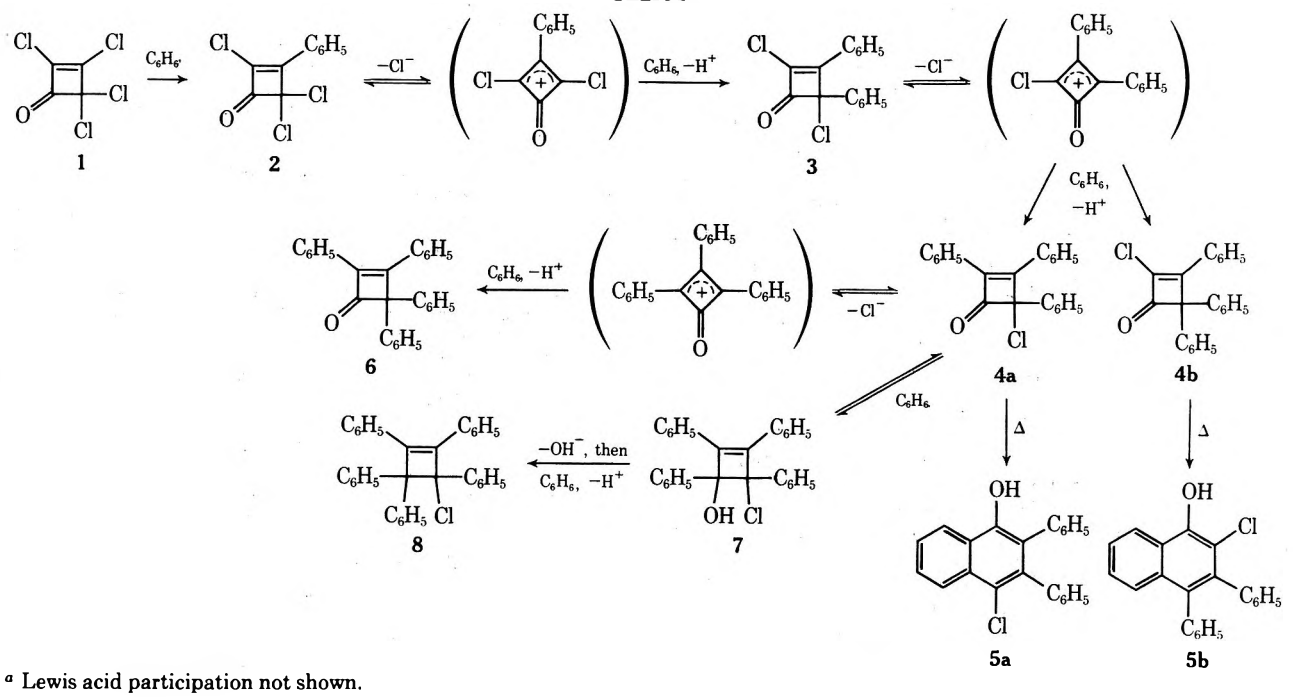
The interaction of perchlorocyclobutenone (1,2,3,3-tetrachlorocyclobutene-4-one, **1**) with benzene under Friedel–Crafts conditions was first studied by De Selms, *et al.*,[1] who observed no phenylation in the presence of 1 molar equiv of aluminum chloride. Subsequently, Ried and Lantzsch,[2] employing 3 molar equiv of the same Lewis acid, obtained the two polyphenylated cyclobutene derivatives, 1,2,3,3-tetraphenylcyclobuten-4-one (**6**) and 3-chloro-1,2,3,4,4-pentaphenylcyclobutene (**8**), in respective yields of 25 and 50%.

Chart I[a]



[a] Lewis acid participation not shown.

As a study of the arylation of squaryl dichloride in this laboratory[3,4] required the independent synthesis of ketone **6**, we modified Ried's procedure, treating **1** in benzene solution with 4 mol of $AlCl_3$ at 6° (24 hr). Both **6** and **8** were formed, although in different yields (54 and 18%, respectively), under the conditions of our experiment. In addition to the two major products, separation by chromatography furnished in 0.5% yield a chlorodiphenylnaphthol melting at 149–152°, which proved identical with the 1-naphthol derivative obtained in previous work[4] from squaryl dichloride and benzene and assigned[4] one of the two isomeric structures **5** (Chart I). The compound most likely resulted from thermal electrocyclic ring opening of the corresponding chloro ketone precursor **4** and recyclization of the intermediary vinylketene.[5] On a tentative basis, we ascribe structure **4a** to the postulated precursor ketone and, correspondingly, structure **5a** to the separated naphthol with mp 149–152°. This decision is based on the isolation, in a separate, short-time experiment (1 hr at 10°, same reactant ratio), of a chloro ketone **4** (0.6%), for which we consider **4b** the most reasonable assignment on the basis of the 100-MHz nmr [acetone-d_6; three multiplets centered at δ 7.9 (2 H, ortho protons, phenyl group at C-2), 7.55 (3 H, meta and para protons, same group),[6] and 7.37 ppm (10 H, all other protons)], electronic [λ_{max} (EtOH) 310 nm[7]], and mass [*m/e* 330 (P^+), correct isotopic distribution for one Cl atom] spectra. On thermal treatment (0.5 hr at 130°), the chloro ketone readily converted to a chlorodiphenylnaphthol (mp 145–148°), for which the mode of formation[5] then suggests structure **5b**. Since this compound, although similar in melting and spectral behavior, clearly proved nonidentical with the naphthol (mp 149–152°) obtained in the main experiment, we are left with the assignment of **5a** for the latter compound (and, hence, of **4a** for its hypothetical, nonintercepted chloro ketone precursor), no isomer structures other than **a** and **b** being conceivable in the present reaction scheme. Support for this reasoning is found in the observed indifference of the presumed **4b** toward further phenylation; upon treatment with excess $AlCl_3$ in benzene solution (24 hr at 6°), the chloro ketone was recovered almost quantitatively, and no traces of **6** or **8** were detected in that experiment.[9] Such behavior accords with the chemical inertness of the vinylic Cl atom at C-1, whereas with Cl at C-3, as in **4a**, fast Lewis acid assisted dissociation of Cl^- and subsequent electrophilic attack on benzene (to give **6**), as well as (slower) benzene addition and following substitution at C-4 (to furnish **8** *via* **7**),[10] would be the expected consequence. In fact, the last-named two sequences are almost certainly the paths of formation of both **6** and **8** in the main experiment, although the unavailability of **4a** has so far prevented an experimental verification.

The formation of intermediates **4** may proceed *via* chlorides **2** and **3**. A likely pathway, involving the 1,3-dichloro-4-oxo-2-phenylcyclobutenyl and 1-chloro-4-oxo-2,3-diphenylcyclobutenyl cations, is suggested in Chart I.[11] We were able to isolate the key compound **2** (3%) in the aforementioned short-time experiment. The structure of **2** derives from the 60-MHz nmr [acetone-d_6: two signals centered at δ 7.8 (2 H, ortho phenyl protons) and 7.5 ppm (3 H, remaining phenyl protons)[6]] and electronic [λ_{max} (EtOH) 301 nm, in accord with 2-chloro-1-phenylenone chromophore[12]] spectra and is corroborated by mass spectral evidence [*m/e* 246 (P^+), correct isotopic distribution for 3 Cl atoms]. The unique lability of the vinylogous chloro group at C-2 in **1**, demonstrated for such related systems as squaryl dichloride,[1,3,4,14] 2-chloro-1-phenylcyclobutene-3,4-dione,[8a] and 2-chloro-1-phenylcyclobuten-4-ones,[13] leaves no doubt as to the primary formation of **2** in the acylation of benzene with **1**. The early-stage interception of the compound and its elusiveness in the 24-hr experiment both lend support to this inference.

The isolation of **4b**, but not of **4a**, in initial stages and the collection of **5a**, but not of **5b**, in final stages of the reaction require discussion. Ionization of **4a** and formation of **6** is probably a fast reaction because of expected high stability of the oxotriphenylcyclobutenyl cation intermediate. Electrocyclic ring opening and cycloaddition to the naphthol **5a** likewise is a low activation energy process, as manifested in the formation of **5a** even at the low reaction temperature (6°) employed. Both factors combine to keep the instantaneous concentration of **4a** below a convenient isolation threshold, even though the compound is probably generated from the precursor cation appreciably faster[15] than is **4b**. Isomer **4b**, on the other hand, cannot readily ionize to a highly stabilized cation, nor is its conversion to **5b**, requiring either fusion (130°) or heating in benzene so-

lution (24 hr at 77°, no isomerization observed after 24 hr at 20°), a rapid process. Its instantaneous concentration, hence, will be higher than that of **4a**, permitting preparative separation. The ease of isomerization of **4a** to **5a** most likely results from relief of steric strain on ring opening in the 1,2-diphenyl derivative; no such (kinetic and thermodynamic) driving force exists for the conversion of **4b** to **5b**. A parallel situation can be found with the two ketones **6** and 1-hydroxy-2,3,3-triphenylcyclobuten-4-one.[3] While the former converts with great ease[5] to the corresponding triphenylnaphthol in boiling benzene, we have been unable to achieve (kinetically and energetically disfavored) naphthol formation from the strongly chelated[3] 1-hydroxy derivative under the same conditions.

Experimental Section

Friedel–Crafts Reaction of Perchlorocyclobuten-4-one with Benzene. A. 24 Hr at 6°. The solution of 0.51 g (2.5 mmol) of **1**[1,16] in benzene (5 ml, predried and distilled from Na) was stirred with 1.35 g (10 mmol) of freshly sublimed $AlCl_3$ for 24 hr at 6° under dry N_2. The reaction mixture was shaken with ice-cold 0.1 *M* aqueous hydrochloric acid (25 ml) and benzene (25 ml), and the organic phase was thoroughly washed with water and dried (Na_2SO_4). Solvent removal under reduced pressure and chromatography of the residue (silica gel, Merck 7734, fractionation monitored by tlc) produced three fractions (eluents in parentheses), which, after a single recrystallization from hexane, gave crude product yields as stated.

Fraction I (hexane): 3-chloro-1,2,3,4,4-pentaphenylcyclobutene (**8**), 0.21 g (17.9%). Three times recrystallized from hexane, the compound melted at 153–153.5° (lit.[2] mp 161°), undepressed on admixture of authentic[2] **8**.

Fraction II (1:1 hexane–benzene): 4-chloro-2,3-diphenyl-1-naphthol (**5a**), 0.004 g (0.48%), mp 149–152° (no further recrystallization attempted), undepressed on admixture of naphthol derivative (mp 150–153°) from previous work,[4] ir (KBr) 3503 (s), 3480 cm^{-1} (m) (ν_{OH}).

Fraction III (benzene): 1,2,3,3-tetraphenylcyclobuten-4-one (**6**), 0.50 g (53.7%). Twice recrystallized from hexane, the compound had mp 128–129° (lit. mp 139,[2] 129–130° [3]), undepressed on admixture of authentic[3] **6**.

B. 1 Hr at 10°. An experiment was set up as under A, but was conducted for 1 hr at 10°. Chromatographic work-up as before yielded four slightly overlapping bands; these were rechromatographed, and corresponding fractions were combined and once recrystallized from hexane to give the product yields stated.

Fraction I (hexane): **8**, 0.003 g (0.26%).

Fraction II (hexane): 1,3,3-trichloro-2-phenylcyclobuten-4-one (**2**), 0.018 g (2.9%). The faintly yellow crystals, once more recrystallized from hexane, had mp 125–126°. *Anal.* Calcd for $C_{10}H_5Cl_3O$ (247.5): C, 48.52; H, 2.04. Found: C, 48.45; H, 1.91. Electronic spectrum λ_{max} (EtOH) 301 nm (ϵ 30,000); ir (KBr) 1798 cm^{-1} (s) ($\nu_{C=O}$); mass spectrum *m/e* 246 (P^+ for ^{35}Cl).

Fraction III (1:1 hexane–benzene): 1-chloro-2,3,3-triphenylcyclobuten-4-one (**4b**), 0.005 g (0.6%), mp 129.5–130.5° (twice recrystallized from hexane). *Anal.* Calcd for $C_{22}H_{15}ClO$ (330.8): C, 79.87; H, 4.58. Found: C, 80.00; H, 4.70. Electronic spectrum λ_{max} (EtOH) 310 nm (ϵ 21,000); ir (KBr) 1777, 1773 cm^{-1} (s) ($\nu_{C=O}$); mass spectrum *m/e* 330 (P^+ for ^{35}Cl).

Fraction IV (benzene): **6**, 0.075 g (8.1%).

Isomerization of 4b. A sample (0.002 g) of **4b** recovered from spectroscopic analysis was fused for 0.5 hr at 130° in a capillary tube, and the solidified product, 2-chloro-3,4-diphenyl-1-naphthol (**5b**), was once recrystallized from hexane: mp 145–148° (purity not optimized), depressed on admixture of **5a**; ir (KBr) 3470 cm^{-1} (s) (ν_{OH}), remaining details similar to, but not identical with, those in spectrum of **5a**; mass spectrum *m/e* 330 (P^+ for ^{35}Cl).

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Registry No.—**1**, 3200-96-2; **2**, 51965-98-1; **4b**, 51965-99-2; **5a**, 51966-00-8; **5b**, 51966-01-9; benzene, 71-43-2.

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(5) An almost quantitative yield of 2,3,4-triphenyl-1-naphthol can be obtained by electrocyclic ring opening of 1,2,3,3-tetraphenylcyclobuten-4-one. This reaction is brought about by heating the ketone in the melt or in benzene solution.
(6) We find (acetone-d_6, 60 MHz) the analogous multiplets for ortho and meta plus para protons, respectively, at δ 8.0 and 7.55 ppm in 1-phenylcyclobutene-3,4-dione[8a,d] and at 8.0 and 7.5 ppm in 1-hydroxy-2-phenylcyclobutene-3,4-dione[8a,c] (samples of both compounds kindly supplied by Professor Ried). A similar pattern has been reported[8d] for 1-hydroxy-2-phenyl-3-alkylcyclobuten-4-ones.
(7) The related 1-chloro-2-phenylcyclobutene-3,4-dione absorbs at 296 and 306 nm (isooctane),[8a] and maxima at 295 and 304 nm are found in the spectrum of 1-chloro-2,3-diphenylcyclobuten-4-one (J. D. Roberts, private communicatons). In contrast, a red shift by 10–15 nm would be expected for the 1,2-diphenylenone chromophore in **4a**. For example, both 1,2-diphenylcyclobutene-3,4-dione[8b] and **6**[2] show λ_{max} (EtOH) at 322 nm.
(8) (a) E. J. Smutny, M. C. Caserio, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 1793 (1960); (b) A. T. Blomquist and F. A. LaLancette, *ibid.*, **83**, 1387 (1961); (c) W. Ried, W. Kunkel, and G. Isenbruck, *Chem. Ber.*, **102**, 2688 (1969); (d) W. Ried and H. Kohl, *ibid.*, **104**, 2896 (1971).
(9) The observed stability of **4b** suggests that the compound should have been among the products of the main experiment. The similarity of the R_f values of **4b** and **6** possibly caused the chloro ketone to be "buried" in the large quantities of **6** present in that experiment (54% as against 8% in the 1-hr run) and so simply prevented its detection and isolation.
(10) One might argue that **4b**, although indifferent to phenylation at C-1, could react in an analogous fashion through benzene addition and subsequent substitution at C-4, giving first 1-chloro-4-hydroxy-2,3,3,4-tetraphenylcyclobutene and then 1-chloro-2,3,3,4,4-pentaphenylcyciobutene. We were unable, however, to detect either product in these reactions. It appears that *gem*-diphenyl substitution at C-3 provides sufficient steric hindrance for successful approach of a benzene molecule. The same situation holds for **6** and, going one step farther, for **8**: neither in previous work[2-5] nor in the present investigation were even traces of hexaphenylcyclobutene detected, which would have resulted from further Lewis acid catalyzed reaction with benzene.
(11) Sequences providing alternative pathways to **6** and **8** from **2** and **4a**, almost certainly of higher activation energy, have for reasons of clarity been omitted from Chart I.
(12) The closely related 1,3-dichloro-2-phenylcyclobuten-4-one shows λ_{max} (cyclohexane) at 298 nm.[13] (See also ref 7.) For the alternative isomer structure, 1,2,3-trichloro-3-phenylcyclobuten-4-one, on the other hand, absorption at wavelengths below 250 nm can be predicted. Thus, we find **1** to absorb at 234 nm.
(13) M. C. Caserio, H. E. Simmons, Jr., A. E. Johnson, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 3102 (1960).
(14) (a) W. Ried and F. Batz, *Justus Liebigs Ann. Chem.*, **755**, 32 (1972); (b) E. Neuse and B. Green, *ibid.*, 619 (1973); (c) E. W. Neuse and B. R. Green, *Polymer*, **15**, 339 (1974).
(15) Preferred attack of the precursor cation at benzene is expected to proceed through the C atom bearing the (Lewis acid complexed) Cl substituent.
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Enol Ethers and Monoketals of Biacetyl

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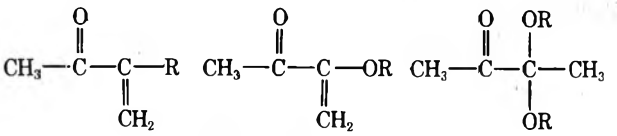
In extension of recent studies[1] on the photochemistry of various α-methylene ketones (**1**) we were interested in examining the photochemical behavior of the formally related compounds bearing oxygen directly on the olefinic double bond. These substances (**2**) are alkyl enol ethers of biacetyl, and we were somewhat surprised to learn that such compounds have never been described. The photochemical behavior of these systems ultimately proved disappointing, but we report below an indirect procedure permitting

transformation of biacetyl into these rather unstable enol ethers (2) by way of the related simple and mixed monoketals 3 and 4.



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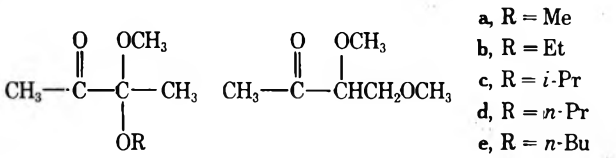


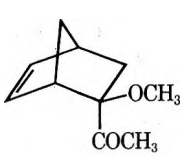
4 5

a, R = Me
b, R = Et
c, R = *i*-Pr
d, R = *n*-Pr
e, R = *n*-Bu
f, R = *sec*-Bu

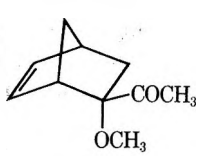
The dimethyl ketal **3a** is readily available from direct ketalization of biacetyl with methanol, although the method is essentially useless for higher members of the series.[2] We found that under carefully defined acidic conditions methanol could be eliminated from **3a** to furnish **2a** in 65% yield. Our best procedure involved dropwise addition of **3a** to a stirred melt of *o*-nitrobenzoic acid maintained at 170° and 80 Torr, with continuous distillation of the product from the reaction mixture. Final purification of the distillate by preparative vapor phase chromatography (vpc) furnished analytically pure **2a**. Although this enol ether is reasonably stable as a dilute solution in inert solvent, even highly purified neat samples undergo noticeable polymerization when stored overnight at −20°.

Exposure of **2a** to aqueous acid gave biacetyl, while reaction with dry acidic methanol led to efficient reversion to **3a** with no detectable formation of the isomeric 3,4-dimethoxy-2-butanone (**5**) through competing Michael addition to the double bond. These results suggested that simple acid-catalyzed interchange of the methoxyl groups of **3a** with other alcohols might well proceed without complication and provide access to other ketals. This proved to be correct. Treatment of readily available **3a** with a variety of alcohols in the presence of dry hydrogen chloride led to good yields of simple and mixed monoketals **3** and **4**.[3] The exact product composition varied somewhat with the alcohol used and with the reaction time. These products were readily purified by preparative vapor phase chromatography and fully characterized; in this way were prepared the 3,3-dialkoxy-2-butanones **3b–f** and the 3-alkoxy-3-methoxy-2-butanones **4c–f**. Use of these ketals in the acid-catalyzed elimination reaction now provided a route to other enol ethers **2**. Since methanol appeared to be preferentially eliminated from the mixed ketals **4**, the elimination reaction could be carried out to advantage on the crude mixture of **3** and **4** obtained by alcohol interchange. In this fashion the isopropyl and propyl enol ethers **2c** and **2d** were prepared.

The methyl enol ether **2a** was further characterized by its Diels–Alder reaction with cyclopentadiene. As anticipated on electronic,[4] and probably to some extent steric,[5] grounds, **2a** is a considerably less reactive dienophile than methyl vinyl ketone. At 120° it furnished a modest yield of adducts **6** and **7** in the ratio 63:37. The stereochemistry of these norbornenes could be assigned from their nmr spectra on the basis of the known chemical shift differences of endo and exo substituents in related systems.[5–7]



6



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Experimental Section

Materials and Equipment. Previous descriptions and comments[1] apply with the following changes. Vpc columns used were A, 30% SE-30, 10 ft; B, 25% Carbowax 20M, 10 ft. Nmr spectra were obtained on a Varian HR-220 (220 MHz) or a Bruker HX-90 (90 MHz) spectrometer.

General Procedure for Alcohol Exchange with 3,3-Dimethoxy-2-butanone (3a). A 10-g sample of **3a**[2] was added to 500 ml of dry alcohol through which hydrogen chloride had been bubbled for 30 sec. In some cases 3A or 4A molecular sieves were added as a water scavenger. The resulting solution was stirred for 48 hr at room temperature. Solid Na_2CO_3 (3 g) was then added and stirring was continued for 24 hr; the solution was filtered and worked up by distillation. The resulting mixture contained **3** and **4** which were separated and purified by vpc on column A. Yields were >90% for primary and ~75% for secondary alcohols. Characterization data for each product are given below.

3,3-Diethoxy-2-butanone (**3b**): ir 3010, 1730, 1345, 1115, 1035, and 940 cm^{-1}; nmr δ 1.18 (t, J = 7 Hz, 6 H), 1.23 (s, 3 H), 2.11 (s, 3 H), 3.40 (q, J = 7 Hz, 2 H), and 3.43 (q, J = 7 Hz, 2H).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.83; H, 10.07.

3,3-Diisopropoxy-2-butanone (**3c**): ir 3000, 1730, 1370, 1100, 1075, and 940 cm^{-1}; nmr δ 1.02 (d, J = 6 Hz, 6 H), 1.04 (d, J = 6 Hz, 6 H), 1.33 (s, 3 H), 2.13 (s, 3 H), 4.91 (septet, J = 6 Hz, 2 H).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.97; H, 10.82.

3-Isopropoxy-3-methoxy-2-butanone (**4c**): ir 3000, 1730, 1375, 1360, 1345, 1110, 1040, and 995 cm^{-1}; nmr δ 1.24 (d, J = 6.5 Hz, 6 H), 1.26 (s, 3 H), 2.11 (s, 3 H), 3.17 (s, 3 H), 3.83 (septet, J = 6.5 Hz, 1 H).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.83; H, 10.04.

3,3-Dipropoxy-2-butanone (**3d**): ir 3000, 2960, 2900, 1730, 1345, 1110, 1060, 1040, and 980 cm^{-1}; nmr δ 0.94 (t, J = 7 Hz, 6 H), 1.27 (s, 3 H), 1.55 (m, 4 H), 2.11 (s, 3 H), 4.20 (t, J = 7 Hz, 2 H), 4.22 (t J = 7 Hz, 2 H).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 64.02; H, 10.81.

3-Methoxy-3-propoxy-2-butanone (**4d**): 3000, 2960, 1730, 1360, 1340, 1110, 1060, and 985 cm^{-1}; nmr δ 0.94 (t, J = 7 Hz, 3 H), 1.25 (s, 3 H), 1.55 (m, 2 H), 2.09 (s, 3 H), 3.15 (s, 3 H), 3.27 (m, J = 7 Hz, 2 H).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.12; H, 10.12.

3,3-Dibutoxy-2-butanone (**3e**): ir 3000, 2970, 2910, 1735, 1120, and 1060 cm^{-1}; nmr δ 0.98 (t, J = 6 Hz, 6 H), 1.28 (s, 3 H), 1.48 (m, 8 H), 2.10 (s, 3 H), 3.34 (t, J = 6 Hz, 4 H).

Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.77; H, 11.21.

3-Butoxy-3-methoxy-2-butanone (**4e**): ir 2995, 2960, 2900, 1735, 1370, 1350, 1120, and 1040 cm^{-1}; nmr δ 0.96 (m, 3 H), 1.32 (s, 3 H), 1.50 (m, 4 H), 2.15 (s, 3 H), 3.22 (s, 3 H), 3.38 (m, J = 6 Hz, 2 H).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.18; H, 10.54.

3,3-Di-*sec*-butoxy-2-butanone (**3f**): ir 3010, 2970, 1730, 1375, 1105, and 980 cm^{-1}; nmr δ 0.89 (m, 6 H), 1.04 (q, J = 3 Hz, 3 H), 1.12 (q, J = 3 Hz, 3 H), 1.33 (m, 3 H), 1.43 (m, 4 H), 2.11 (s, 3 H), 3.68 (m, 2 H). No attempt was made to separate the diastereomers of **3f**.

Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.54; H, 11.12.

3-*sec*-Butoxy-3-methoxy-2-butanone (**4f**): ir 3010, 2970, 1730, 1370, 1340, 1110, 1040, 1020, and 980 cm^{-1}; nmr δ 0.89 (m, 3 H), 1.08 (t, J = 6 Hz, 3 H), 1.24 (s, 3 H), 1.43 (m, 2 H), 2.10 (s, 3 H), 3.10 and 3.14 (2 s, 3 H), 3.63 (m, 1 H). No attempt was made to separate the diastereomers of **4f**.

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.20; H, 10.51.

3-Methoxy-3-buten-2-one (2a). A stirred melt of 1 g of *o*-nitrobenzoic acid was maintained at 170° and 80 Torr in a flask fitted with a dropping funnel and arranged for continuous distillation. To this was added dropwise 10 g of **3a**. The distillate, a mixture of **2a** and **3a**, was collected at −78° and could be stored over 4A molecular sieves at this temperature without change. **2a** was conveniently purified on column B: yield 65% (by calibrated vpc and based on unrecovered **3a**); ir 3000, 2950, 2840, 1710, 1620,

1365, 1350, 1299, 1145, 1045, and 835 cm^{-1}; nmr δ 2.23 (s, 3 H), 3.63 (s, 3 H), 4.20 (d, J = 2 Hz, 1 H), 5.05 (d, J = 2 Hz, 1 H); mass spectrum m/e 100.0523 (M^+, calcd for $C_5H_8O_2$, 100.0523).

3-Isopropoxy-3-buten-2-one (2c). In the way just described for **2a**, **2c** was prepared in 50% yield from a mixture of **3c** and **4c** (2:3): ir 3000, 1720, 1610, 1355, 1280, 1140, and 1105 cm^{-1}; nmr δ 1.27 (d, J = 6 Hz, 6 H), 2.15 (s, 3 H), 4.15 (d, J = 2 Hz, 1 H), 4.20 (septet, J = 6 Hz, 1 H), 5.06 (d, J = 2 Hz, 1 H); mass spectrum m/e 128.0843 (M^+, calcd for $C_7H_{12}O_2$, 128.0837).

3-Propoxy-3-buten-2-one (2d). In the way just described for **2a**, **2d** was prepared from a mixture of **3d** and **4d:** ir 3000, 2970, 1715, 1615, 1370, 1355, 1300, 1150, and 840 cm^{-1}; nmr δ 1.04 (t, J = 6 Hz, 3 H), 1.77 (dt, $J = J_2$ = 6 Hz, 2 H), 2.20 (s, 3 H), 3.68 (t, J = 6 Hz, 2 H), 4.23 (d, J = 2 Hz, 1 H), 5.05 (d, J = 2 Hz, 1 H); mass spectrum m/e 128.0860 (M^+, calcd for $C_7H_{12}O_2$, 128.0837).

Hydrolysis of Enol Ethers to Biacetyl. A solution of **2a** (150 mg) in ether (15 ml) was treated with 10% aqueous HCl (0.5 ml) at room temperature for 12 hr. Then 2 g of Na_2CO_3 was added and the ethereal layer was filtered and dried over 4A molecular sieves. Solvent was removed by distillation, and biacetyl was isolated as the only product by vpc on column B. The same results were obtained with **2c**.

Reaction of 2a with Methanol. Treatment of **2a** with methanolic hydrogen chloride following essentially the procedure described above for alcohol interchange gave **3a** as the only isolated product.

***endo*- and *exo*-2-Methoxy-5-norbornen-2-yl Methyl Ketone (6 and 7).** A solution of 500 mg of **2a**, 450 mg of cyclopentadiene, and 10 mg of hydroquinone in 5 ml of benzene was heated in a sealed tube at 120° for 48 hr. Solvent was removed, and bulb-to-bulb distillation of the residue gave 465 mg (56%) of a mixture of **6** and **7** (63:37 by nmr). These were separated and purified on column B. Major isomer **6** showed the following properties: ir 3010, 2960, 1715, 1340, 1240, 1090, 1075, 1060, and 700 cm^{-1}; nmr δ 1.50 (d, J = 13 Hz, 1 H), 1.54 (d, J = 13 Hz, 1 H), 1.78 (m, 2 H), 2.09 (s, 3 H), 2.18 (d, J = 6 Hz, 1 H), 2.86 (d, J = 6 Hz, 1 H), 3.02 (s, 3 H), 5.80 (dd, J_1 = 3, J_2 = 6 Hz, 1 H), 6.08 (dd, J_1 = 3, J_2 = 6 Hz, 1 H); mass spectrum m/e 166.0989 (M^+, calcd for $C_{10}H_{14}O_2$, 166.0993). Minor isomer **7** showed the following properties: ir 3010, 1715, 1345, 1120, 1080, 1070, and 705 cm^{-1}; nmr δ 1.07 (dd, J_1 = 4, J_2 = 12 Hz, 1 H), 1.27 (m, 2 H), 1.43 (m, 1 H), 1.95 (dd, J_1 = 4, J_2 = 12 Hz, 1 H), 2.14 (s, 3 H), 2.72 (m, 1 H), 2.98 (s, 3 H), 5.93 (dd, J_1 = 4, J_2 = 5.5 Hz, 1 H), 6.23 (dd, J_1 = 4, J_2 = 5.5 Hz, 1 H); mass spectrum m/e 166.0947 (M^+, calcd for $C_{10}H_{14}O_2$, 166.0993).

Registry No.—**2a**, 51933-10-9; **2c**, 51933-11-0; **2d**, 51933-12-1; **3a**, 21983-72-2; **3b**, 51933-13-2; **3c**, 51933-14-3; **3d**, 51933-15-4; **3e**, 51933-16-5; **3f**, 51933-17-6; **4c**, 51933-18-7; **4d**, 51933-19-8; **4e**, 51933-20-1; **4f** isomer A, 51933-21-2; **4f** isomer B, 51933-22-3; **6**, 51933-23-4; **7**, 51933-24-5.

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(7) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Structure and Stereochemistry of Simmondsin

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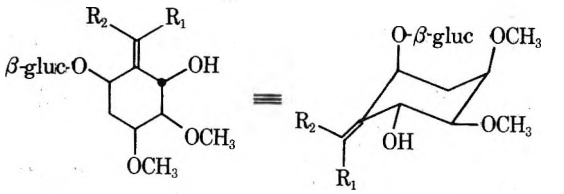
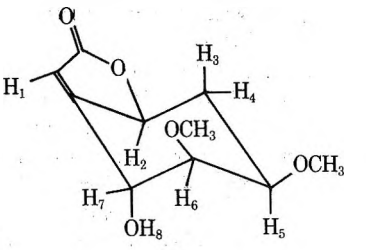
We recently[1] reported the isolation of a naturally occurring toxicant from *Simmondsia californica* and tentatively characterized its structure as **1a**. We now wish to report the definite establishment of structure **1b** in which the configuration of the cyano group is syn to the axial β-glucosyl substituent.



1a, R_1 = CN; R_2 = H
b, R_1 = H; R_2 = CN

Acid hydrolysis of the parent glucoside in boiling 1 *N* HCl for 1.5 hr produces, in addition to the previously reported phenolic derivatives, an α,β-unsaturated lactone, mp 138–140°, whose structure (**2**) is very closely related to



2

the starting glucoside. Satisfactory elemental analysis was obtained, and its infrared absorptions at 1665 and 1755 cm^{-1} are consistent with the proposed structure.[2] The nmr spectrum (Table I) permits unequivocal assignment of

Table I
Nmr Spectrum of 2 [$(CD_3)_2CO$]

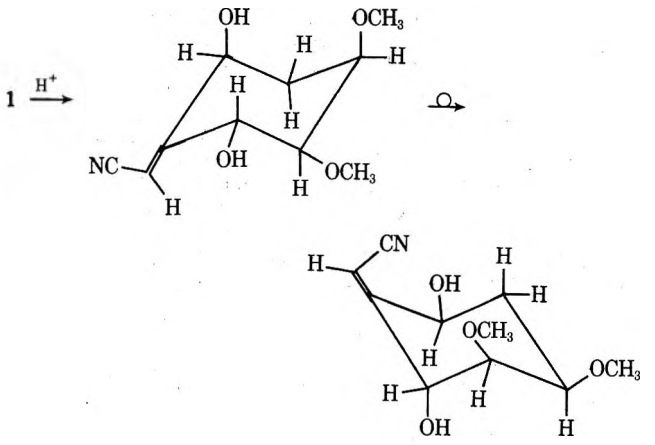
H_1 δ 5.98, d, $J_{1,2}$ = 2 Hz
H_2 δ 5.12, 8 lines, $J_{1,2}$ = 2, $J_{2,3}$ = 11, $J_{2,4}$ = 6.5 Hz
H_3 δ 1.58, q, $J_{2,3} = J_{3,4} = J_{3,5}$ = 11 Hz
H_4 δ 2.52, complex, $J_{3,4}$ = 11, $J_{2,4}$ = 6, $J_{4,5}$ = 4 Hz
H_5 δ 3.90 (d), d, d (upfield half concealed by H_6), $J_{4,5}$ = 4, $J_{5,6}$ = 2 Hz
H_6 δ 3.83, complex (partially obscured by upfield half of H_5), $J_{5,6}$ = 3, $J_{6,7}$ = 3 Hz
H_7 δ 4.90, t, $J_{6,7} = J_{7,8}$ = 3, $J_{1,7}$ = 0 Hz
H_8 δ 5.03, d, $J_{7,8}$ = 3 Hz (31°)
$-OCH_3$'s (6 H) δ 3.40, 3.44

stereochemistry (spin-decoupling techniques were used for proton assignment). Protons H_{2-5} neatly reveal their orientation by the quartet exhibited by H_3 in which coupling of the adjacent axial hydrogens as well as the geminal coupling constant is 11 Hz. The observation that H_1 and H_2 possess a coupling of 2 Hz while that of H_1 and H_7 is zero is consistent with approximate 90° orientation of the C–H_2 bond with respect to the plane of the lactone ring. The orientation of H_7 nearly within the same plane would result in minimal coupling to H_1, as is found.[3] Hydrogens 6 and 7 are equatorially located.

The formation of lactone **2** must occur *via* initial hydrolysis of the glucosyl residue as in Scheme I followed by ring inversion to place the now equatorial hydroxyl group extremely close to the nitrile function. Under acid catalysis ring closure may occur easily to give lactone from the initially formed imino ester.

The proximity of the nitrile function to any adjacently located equatorial substituent no doubt is the cause of the rather unusual stereochemistry in simmondsin (**1b**) itself. To minimize the interaction of the glucosyl portion of the molecule with the cyano group, the glycosidic linkage assumes axial geometry even though this introduces 1,3-diax-

Scheme I



ial strain between the glucose and the methoxyl in this conformation. Such interaction in the vicinity of a double bond has been termed allylic 1,3 strain [$A^{(1,3)}$] by Johnson,[4] and he has pointed out that this can be of higher energy than 1,3-diaxial interaction in a cyclohexane system, even when the groups involved are of moderate size. The observed conformation of simmondsin is consistent with this theory.

Experimental Section

Melting points were measured on a Thomas-Hoover capillary apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 257 instrument. Nmr spectra were measured on a Varian A-60 instrument or on a HA-100 spectrometer. Spin-decoupled spectra were obtained on the latter machine in the frequency mode. Elemental analyses were performed in this laboratory.

Treatment of Simmondsin with Acid. Simmondsin (4.40 g) dissolved in 1 *N* hydrochloric acid (50 ml) was refluxed for 1.5 hr. After cooling to room temperature, the mixture was concentrated under reduced pressure to a semisolid paste which was triturated with four 25-ml portions of ethyl acetate. Evaporation gave an oil (2.19 g) which was applied in ethyl acetate to a column (25 × 1000 mm) prepared with 190 g of silica gel (Mallinckrodt SilicAR CC-7, special) in chloroform. Elution was carried out at 60 ml/hr in a linear gradient from 100% chloroform to 20% methanol–chloroform (2 l.). Three major fractions were obtained: (i) between 370 and 580 ml (0.16 g), (ii) between 860 and 740 ml (0.33 g), and (iii) between 1040 and 1160 ml (1.31 g). Fraction iii was dissolved in ethyl acetate (40 ml) and extracted with 5% sodium hydrogen carbonate solution (3 × 30 ml). The organic layer was dried over magnesium sulfate and evaporated to give 0.32 g of crude lactone 2, which was crystallized from benzene to give 0.17 g of material, mp 138–140°. *Anal.* Calcd for $C_{10}H_{14}O_5$: C, 59.34; H, 5.53. Found: C, 59.6; H, 5.57. The infrared spectrum, ν_{max} ($CHCl_3$), showed absorptions at 1665 (conjugated double bond in C-5 ring) and 1755 cm^{-1} (α,β-unsaturated, five-ring lactone). The nmr spectrum in deuterioacetone is shown in Table I.

Acidification of the aqueous extract from iii followed by extraction with ethyl acetate provided 2-hydroxy-5-methoxyphenylacetic acid (0.40 g). Fractions i and ii were shown to be respectively the lactone of the above phenolic acid and the corresponding methyl ester (formed during chromatography).[1]

Acknowledgments. We wish to thank Mrs. Mabry Benson for obtaining the 100-MHz nmr spectra and Miss G. E. Secor for elemental analysis.

Registry No.—**1b**, 51771-52-9; **2**, 52032-66-3.

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Studies on Vitamin D and Its Analogs. I. Synthesis of 1α-Hydroxycholest-5-ene

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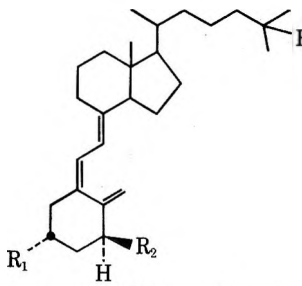
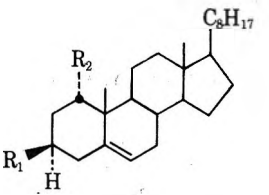
Vitamin D_3 (**1a**),[2] a steroidal hormone intimately associated with calcium transport, must be successively hydroxylated in the liver[3] and then in the kidney to produce the metabolite 1α,25-dihydroxyvitamin D_3 (**1b**)[4] before eliciting its physiological action. Recent investigations have led to the suggestion that the 1α-hydroxyl contained in the carbon framework represented by structure **1** may be the critical functionality necessary for vitamin D activity.[5] If this is the case, an attractive substance for study is the analog **1c**, which lacks both the seemingly unnecessary 3β- and 25-hydroxyl groups of the natural system **1b**. Our ongoing studies directed toward synthesizing **1c** and related analogs required the availability of the hitherto unknown cholesterol isomer 1α-hydroxycholest-5-ene (**2a**). It is the purpose of this note to provide the details for its preparation.

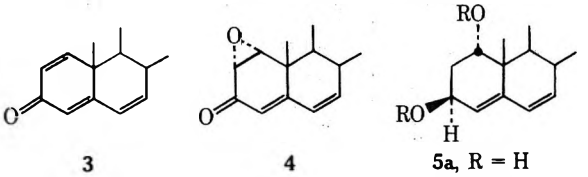


1a, $R_1 = OH$; $R_2 = R_3 = H$
b, $R_1 = R_2 = R_3 = OH$
c, $R_2 = OH$; $R_1 = R_3 = H$



2a, $R_1 = H$; $R_2 = OH$
b, $R_1 = OH$; $R_2 = H$
c, $R_1 = H$; $R_2 = OAc$
d, $R_1 = R_2 = OH$
e, $R_1 = OTs$; $R_2 = OH$

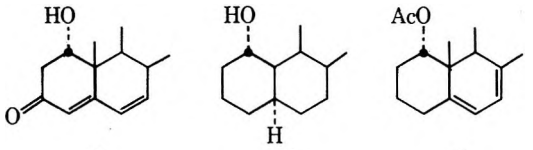
The title compound **2a** has been prepared by two different routes. Cholesterol was converted as described previously to the epoxydienone **4** by successive treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[6] and alkaline hydrogen peroxide.[7] In the first route, **4** was reduced with lithium aluminum hydride yielding **5a** (62%), which upon subsequent reduction with lithium–ammonia pro-



3 **4**

5a, R = H
b, R = Ac

duced the title compound **2a** (60%).[8] The structures of **5a** and its diacetate **5b** were evident from their spectral data and chemical behavior. Besides exhibiting nmr and ir spectral data appropriate for their assigned structures, **5a** and **5b** revealed uv bands at 232, 240, and 248 nm characteristic of other cholesta-4,6-dienes.[9] The orientation of the 3 substituent in **5a** and **5b** is presumably mainly β. A similar reduction of 4-cholesten-3-one gave mainly the 3β alcohol.[10] The dienediol **5a**, on selective oxidation at C-3 with DDQ, afforded **6** (92%). The latter revealed appropriate nmr, ir, and uv spectra and was convertible to **3** by isopropenyl acetate–acid treatment. Spectral data for **2a** and the monoacetate **2c** were also in accord with their assigned structures. The structure of **2a** was confirmed by its hydrogenation to the known alcohol **7**,[11] and furthermore, the acetate **2c** could be converted to 1α-acetoxycholesta-5,7-diene (**8**, 11%).[12]



6 **7** **8**

In the second route, the epoxydienone **4** was first converted to **2d** (49%) according to Barton, *et al.*, by lithium–ammonia reduction.[5d] The treatment of the latter with excess *p*-toluenesulfonyl chloride–pyridine afforded the monotosylate **2e** in almost quantitative yield. Lithium aluminum hydride reduction of **2e** afforded **2a** (72% based on **2d**) identical in every respect with the material prepared from **5a**.

The pathway through which **5a** proceeds to **2a** can be considered to arise by initial cleavage of **5a** to a pentadienyl anion. It can then be presumed that the latter is protonated regioselectively to give 1α-hydroxy-4,6-cholestadiene, which upon further reduction gives **2a**. The reductive cleavage of the allylic hydroxyl is analogous to the known lithium reduction of 4-cholesten-3β-ol to 4-cholestene[10a] and the conversion of dienes to monoenes with lithium is well precedented.[8b,17]

Experimental Section

General. Infrared (ir) spectra (Nujol) were obtained with a Perkin-Elmer Model 137 or 621 spectrophotometer and ultraviolet (uv) spectra (95% ethanol) with a Beckman DB or Cary Model 14 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded with a Varian 60-MHz spectrometer with deuteriochloroform as solvent and tetramethylsilane (TMS, τ 10.00) as the internal standard. In most cases, C_{19} and C_{18} angular methyl singlets are expressed in hertz downfield from TMS.[11b] Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6D spectrometer. Microanalyses were performed by C. F. Geiger, Ontario, Calif. Melting points (Thomas-Hoover capillary melting point apparatus) are uncorrected. Low-boiling petroleum ether (30–60°) was used.

1,4,6-Cholestatrien-3-one (3). A known procedure,[6] DDQ (40 g) oxidation of cholesterol (20 g) in dry dioxane (500 ml) followed by purification by chromatography and then crystallization, afforded pure **3**: 11.0 g, 56%; mp 84–85° (lit.[13] mp 82–83°).

1α,2α-Oxido-4,6-cholestadien-3-one (4). A known procedure,[7] aqueous 30% hydrogen peroxide (25 ml)–aqueous 15% w/v sodium hydroxide (2 ml) treatment of **3** (11.0 g) in methanol (450 ml) followed by purification by crystallization, afforded pure **4**: 8.2 g, 72%; mp 106–107° (lit.[7b] mp 105–107°).

4,6-Cholestadiene-1α,3β-diol (5a). A solution of **4** (5.0 g, 0.013 mol) in dry ether (200 ml) was refluxed with lithium aluminum hydride (2.5 g, 0.066 mol) under anhydrous conditions for 4–5 hr. The mixture was ice cooled and then water (2.5 ml), aqueous sodium hydroxide (2.5 ml, 15% w/v), and water (7.5 ml) were added successively and cautiously to the well-stirred mixture. The precipitated aluminum salts were removed by filtration. The combined filtrate and washings were concentrated under vacuum to dryness. The residue was chromatographed over alumina (Woelm neutral III, 150 g). The product (3.8 g), which was eluted with benzene–ether (2:1), was crystallized from acetone–methanol to afford **5a** as stout needles (3.25 g, 62%): mp 120–121°; uv λ_{max} 248 nm (ϵ 15,400), 240 (23,800), and 232 (21,700); nmr τ 3.97 and 4.31 ($H_{6,7}$, AB q, $J_{AB} \simeq$ 10 Hz), 4.39 (H_1, d, $J \simeq$ 4 Hz), 5.71 and 6.06 ($H_{1\beta,3\alpha}$ br peaks), 9.09 (C_{21} CH_3, d, $J \simeq$ 6 Hz), 9.11 (C_{19} CH_3, s), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \simeq$ 5.5 Hz), and 9.27 (C_{18} CH_3, s); ir ν_{max} 3400 cm^{-1} (OH).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.81; H, 11.21.

1α,3β-Diacetoxy-4,6-cholestadiene (5b). A mixture of **5a** (2 g, 0.005 mol), acetic anhydride (10 ml), and pyridine (10 ml) was heated on a steam bath for 3 hr. The cooled mixture was quenched with ice-cold water and then worked up in the usual way. The dark crystalline residue (2.3 g) thus obtained was purified by chromatography over alumina (Woelm neutral III) to afford 1.6 g (67%) of diacetate. Crystallization of this material from methanol afforded glistening needles: mp 178–179°; uv λ_{max} 232 nm (ϵ 23,100), 240 (25,600), and 248 (17,500); nmr τ 3.94 and 4.24 ($H_{6,7}$, AB q, $J_{AB} \simeq$ 10 Hz), 4.36–4.73 ($H_{3\alpha,4}$, m), 5.04 ($H_{1\beta}$, pseudo-t, $J \simeq$ 2.5 Hz), 7.94 ($AcCH_3$, s), 7.99 ($AcCH_3$, s), 9.02 (C_{19} CH_3, s), 9.07 (C_{21} CH_3, d, $J \simeq$ 5 Hz), 9.12 ($C_{26,27}$ 2 CH_3, d, $J \simeq$ 6 Hz), and 9.27 (C_{18} CH_3, s); ir ν_{max} 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{31}H_{48}O_4$: C, 76.81; H, 9.98. Found: C, 76.93; H, 9.71.

1α-Hydroxy-4,6-cholestadien-3-one (6). An anhydrous mixture of dienediol **5a** (1.0 g, 0.0025 mol) and DDQ (0.90 g, 0.0040 mol) in purified dioxane (30 ml) was allowed to stand at ambient temperatures for 24 hr. The mixture was diluted with ether and then washed successively with 1 *M* aqueous sodium hydroxide and water. After drying (sodium sulfate) and filtration, concentration left a residue which on crystallization (aqueous acetone) afforded **6** (920 mg, 92%) as shiny flakes: mp 177°; uv λ_{max} 286 nm (ϵ 26,600);[14] ir ν_{max} 3470 (OH) and 1668 cm^{-1} (C=O); nmr τ 3.81 ($H_{6,7}$, br s, $W \simeq$ 2 Hz), 4.22 (H_4, br s, $W \simeq$ 2 Hz), 5.82 ($H_{1\beta}$, br m, $W \simeq$ 7 Hz), 7.14–7.44 ($H_{2\alpha,\beta}$, br m), 9.07 (C_{21} CH_3, d, $J \simeq$ 5 Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \simeq$ 6 Hz) [C_{19} CH_3, 67.0 Hz (calcd, 69.0); C_{18} CH_3, 45.5 Hz (calcd, 45.5)].[11b]

Anal. Calcd for $C_{27}H_{42}O_2$: C,81.35; H, 10.62. Found: C, 81.13; H, 10.36.

A mixture of **6** (100 mg), isopropenyl acetate (2 ml), and *p*-toluenesulfonic acid (10 mg) in benzene was refluxed for 4 hr. After sodium bicarbonate treatment to neutralize the acid, the mixture was worked up in the usual way with water and ether. The residue obtained after drying and concentrating the organic extract was chromatographed and then recrystallized to afford pure **3** with mp 83–84°.

1α-Hydroxy-5-cholestene (2a) from 5a. A three-necked standard taper round-bottom flask equipped with a mechanical stirrer, a Dry Ice condenser, a nitrogen inlet, and an ammonia inlet was thoroughly dried and flushed with nitrogen. A solution of lithium metal (0.4 g, 0.06 mol) in ammonia (60 ml) was prepared under nitrogen in the usual manner. A solution of **5a** (0.518 g, 0.00129 mol) in dry, freshly distilled tetrahydrofuran (60 ml) was added to the Dry Ice–acetone cooled solution and then the mixture was stirred for 3 hrs after the cooling bath had been removed. Solid ammonium chloride (~0.5 g) was added and after the solution was stirred for 1 hr, saturated aqueous ammonium chloride was added. The ammonia was allowed to evaporate, water was added to dissolve the precipitated salts, and then the mixture was thoroughly extracted with ether. The ethereal extract was washed with water, dried (sodium sulfate), and then concentrated under vacuum to afford 0.509 g of a white solid. Silica gel column chromatography (petroleum ether–ether mixtures) gave 0.3 g (60%) of enol **2a**. Further purification by preparative tlc (silica gel H) and crystallization (95% ethanol) yielded very pure **2a**: mp 102–103°; nmr τ 4.34 (H_6, br, $W \simeq$ 10 Hz), 6.26 ($H_{1\beta}$, br, $W \simeq$ 8 Hz), 9.08 (C_{21} CH_3, d, $J \simeq$ 5 Hz), 9.14 ($C_{26,27}$ 2 CH_3, d, $J \simeq$ 6 Hz) [C_{19} CH_3, 60.5 Hz (calcd, 61.5) and C_{18} CH_3, 41.0 Hz (calcd, 42.0)];[11b] ir ν_{max} 3400 cm^{-1} (OH).

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.71; H, 12.34.

1α-Acetoxy-5-cholestene (2c). The enol **2a** (1.5 g, 0.0039 mol) was treated with acetic anhydride (5 ml), pyridine (5 ml), and 4-dimethylaminopyridine (1.0 g)[5d] at room temperature and allowed to stand overnight. The mixture was treated with cold water and extracted with ether. The ethereal extract was washed successively with cold dilute hydrochloric acid, water, and aqueous sodium bicarbonate and finally dried over sodium sulfate. After filtration

and removal of the solvent under vacuum, the resulting dark red residue was passed through a column of silica gel with benzene as eluent. This gave 1.62 g of crude acetate which upon crystallization (95% ethanol) afforded **2c** as stout needles (1.40 g, 85%): mp 69–70°; nmr τ 4.69 (H_6, br, $W \simeq 10$ Hz), 5.13 ($H_{1\beta}$, br, $W \simeq 5.5$ Hz), 8.01 ($AcCH_3$, s), 9.11 (C_{21} CH_3, d, $J \simeq 5$ Hz), 9.16 ($C_{26,27}$ 2 CH_3, d, $J \simeq 6$ Hz) [C_{19} CH_3, 61.5 Hz (calcd, 63.5), C_{18} CH_3, 39.0 Hz (calcd, 40.5)];[11b] ir ν_{max} 1770 cm^{-1} (C=O).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.51; H, 11.20.

Hydrogenation of 2a. 1α-Hydroxy-5α-cholestane (7). A solution of **2a** (68 mg) in absolute ethanol containing a catalytic quantity of 10% palladium on carbon was hydrogenated at room temperature and pressure. After work-up, the product (mp 102–103°, lit.[11a] mp 103–105°) revealed an nmr spectrum[11b] identical with that published elsewhere.

1α-Acetoxy-5,7-cholestadiene (8). To a refluxing, magnetically stirred solution of **2c** (415 mg, 0.0097 mol) in a 1:1 mixture of benzene–hexane (90 ml) under anhydrous conditions was added 1,3-dibromo-5,5-dimethylhydantoin (145 mg, 0.00051 mol) at once. The mixture turned yellow and then finally colorless during the 15-min reflux period after adding the brominating agent. The mixture was ice cooled and filtered to remove the precipitated 5,5-dimethylhydantoin and the solid was rinsed thoroughly with cold petroleum ether. The combined filtrates were concentrated to dryness at room temperature on a rotary evaporator under vacuum. The yellow residual syrup in xylene (50 ml) was added dropwise under nitrogen to a refluxing, magnetically stirred solution of trimethyl phosphite (1.5 ml) in xylene (25 ml). After the addition (0.5 hr), the mixture was maintained at reflux for 1.0 hr. The cooled mixture was concentrated to dryness at water pump vacuum and then under high vacuum.

The residue dissolved in a small volume of petroleum ether was chromatographed (10% silver nitrate impregnated silica gel, 15 g; 1-cm diameter column, prepared with petroleum ether; 14-ml fractions) using ether–petroleum ether mixtures (0%, 200 ml; 2%, 350 ml; 4%, 500 ml; 10%, 100 ml) and the fractions were analyzed by examination of their uv spectra. Fractions 34–51 showed absorptions expected for the $\Delta^{4,6}$-diene and were not examined further. Fractions 52–75 contained mainly the $\Delta^{5,7}$-diene and these fractions were pooled and the solvent removed under vacuum. The residue (55 mg) was rechromatographed (silica gel, 8 g; 1-cm column prepared with petroleum ether; 30-ml fractions) using ether–petroleum ether mixtures (0%, 60 ml; 2%, 90 ml; 6%, 30 ml). Fraction 4 contained the desired provitamin acetate 8 (45 mg, 11%; mp 105–106°) uncontaminated by material with λ_{max} 311 nm which was not removed by the first chromatography.

In another experiment, further purification by preparative tlc followed by crystallization (ethanol) afforded 8 as colorless needles: mp 108–109°; nmr τ 4.32 and 4.61 ($H_{6,7}$, AB q, $J_{AB} \simeq 6$ Hz), 5.08 ($H_{1\beta}$, br, $W \simeq 6$ Hz), 7.92 ($AcCH_3$, s), 9.07 (C_{21} CH_3, d, $J \simeq 5$ Hz), 9.12 ($C_{26,27}$ 2 CH_3, d, $J \simeq 6$ Hz) [C_{19} CH_3, 59.0 Hz (calcd, 58.0); C_{18} CH_3, 37.5 Hz (calcd, 36.5)];[11b] uv λ_{max} 252 nm sh (ϵ 2700), 262 sh (6800), 271 (10,300), 281 (11,600), 293 (6800);[15] mass spectrum (80 eV) selected *m/e* (rel intensity) 428 (0.4), 427 (1.6), 426 (5) (parent), 366 (50), 253 (20), 226 (27), 211 (100 base), 199 (43), 183 (28), 168 (30), 158 (45), 143 (40), 131 (35), 43 (89).

1α-Hydroxycholesterol (2d).[5d,16] The epoxide **4** (3.0 g, 0.0076 mol) in tetrahydrofuran (100 ml) was treated with lithium (4.0 g, 0.58 mole) in ammonia (100 ml) for 3 hr as described above for the reduction of **5a**. Solid ammonium chloride (25 g) was added, the mixture was stirred for 1 hr, and then saturated aqueous ammonium chloride was added cautiously with vigorous stirring. The ammonia was allowed to evaporate and water was added to dissolve the precipitated salts. After extraction with ether, the combined ethereal extracts were washed with water, dried over sodium sulfate, filtered, and then concentrated under vacuum. The residue (3.05 g) was chromatographed over alumina (Woelm neutral III; 50% ethyl acetate–ethanol) to afford 1α-hydroxycholesterol (**2d**, 2.07 g). Crystallization (acetone) afforded 1.5 g (49%) of pure material: mp 156–157° (lit.[5d] mp 162–163°); $[\alpha]^{24}D$ −35° (*c* 8.72 mg/ml, $CHCl_3$); nmr τ 4.39 (H_6, br, $W \simeq 8$ Hz), 6.0 ($H_{3\alpha}$, very br, $W \gg 10$ Hz), 6.13 ($H_{1\beta}$, br, $W \simeq 7$ Hz), 9.07 (C_{21} CH_3, d, $J \simeq 5.5$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \simeq 6$ Hz) [C_{19} CH_3, 61.5 Hz (calcd, 62.0); C_{18} CH_3, 41.5 Hz (calcd, 42.0)].[11b]

The diacetate of this material was a liquid, but subsequent bromination–dehydrobromination according to the procedure described above for preparing 8 afforded the known crystalline 1α,3β-diacetoxy-5,7-cholestadiene (mp 113–114°, lit.[5d] mp 118–119°).

1α-Hydroxycholesteryl Tosylate (2e). The diol **2d** (1.0 g, 0.0025 mol) and *p*-toluenesulfonyl chloride (1.0 g, 0.0052 mol) dissolved in dry pyridine (5 ml) were allowed to stand overnight in the freezer (<0°). After addition of a small volume of cold water to the reaction mixture and then addition of ether, the ethereal phase was washed with cold water, dried (sodium sulfate), and concentrated to afford a crystalline residue (1.35 g). This material, which was mainly **2e**, was used in the next step without further purification. In another experiment, crystallization (acetone–petroleum ether) afforded a sample: mp 147° dec; nmr τ 2.18 and 2.65 (4 H, aryl ring, AB q, $J_{AB} \simeq 8$ Hz), 4.45 (H_6, br, $W \simeq 10$ Hz), 5.2 ($H_{3\alpha}$, very br, $W \gg 10$ Hz), 6.18 ($H_{1\beta}$, br, $W \simeq 8$ Hz), 7.54 ($ArCH_3$, s), 9.02 (C_{19} CH_3, s), 9.07 (C_{21} CH_3, d, $J \simeq 5$ Hz), 9.12 ($C_{26,27}$ 2 CH_3, d, $J \simeq 6$ Hz), and 9.33 (C_{18} CH_3, s).

Anal. Calcd for $C_{34}H_{52}O_4S$: C, 73.33; H, 9.41. Found: C, 73.02; H, 9.48.

1α-Hydroxy-5-cholestene (2a) from 2e. The crude **2e** (1.35 g) from the immediately preceding step in ether (80 ml) was treated in the usual way with lithium aluminum hydride (908 mg, 0.0239 mol). The reaction mixture was worked up as described above and then the ensuing crude alcohol was purified by chromatography (silica gel, 25 g, petroleum ether–benzene mixtures as eluent to afford **2a** (mp 99–100°, 705 mg, 72% based on **2d**), which proved homogeneous by tlc. Further purification by crystallization (95% ethanol) afforded stout needles mp 102–103°. This material was identical (nmr, melting point, tlc) with **2a** prepared in the different manner described above.[17]

Registry No.—**2a**, 52032-61-8; **2c**, 52932-62-9; **2d**, 26358-75-8; **2e**, 52032-63-0; **3**, 3464-60-6; **4**, 28893-44-9; **5a**, 51525-89-4; **5b**, 52032-64-1; **6**, 52032-65-2; **8**, 52109-45-2; DDQ, 84-58-2.

References and Notes

(1) (a) Department of Biochemistry. (b) Supported by U. S. Public Health Service grants AM-09012 and AM-14,750 to A. W. N. (c) Recipient of USPHS Career Development Award 1-KD-AM-13,654. (d) Department of Chemistry. (e) Supported by an Intramural Research Fund Grant, University of California, Riverside, and by a grant from the U. S. Public Health Service (AM-16595).

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(14) See ref 9; 4,6-dien-3-ones show λ_{max} 281–284 nm (ϵ 25,000–30,000).

(15) This spectrum is characteristic of provitamin D. See ref 2, p 93, as well as ref 9.

(16) For other reported preparations of **2d**, see (a) B. Pelc and E. Kodicek, *J. Chem. Soc.*, 1624 (1970); (b) E. J. Semmler, M. F. Holick, H. K. Schnoes, and H. F. DeLuca, *Tetrahedron Lett.*, 4147 (1972); (c) C. Kaneko, S. Yamada, A. Sugimoto, and M. Ishikawa, *ibid.*, 2339 (1973); (d) M. Morisaki, K. Bannai, and N. Ikekawa, *Chem. Pharm. Bull.*, **21**, 1853 (1973); (e) A. Fürst, L. Labler, W. Meier, and K.-H. Pfoertner, *Helv. Chim. Acta*, **56**, 1708 (1973).

(17) Since the submission of this manuscript, 3-deoxy-1α-hydroxyvitamin D_3 (**1c**) has been found to be highly biologically active in stimulating intestinal calcium transport in vitamin D deficient chicks.

Kinetics of Deuteration of 1,2,4-Triazole

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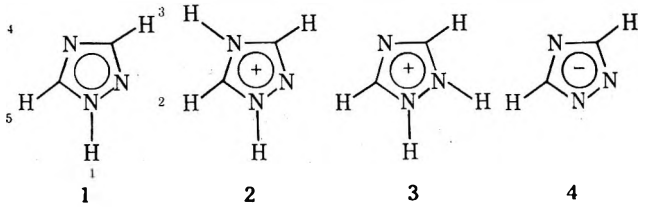
1,2,4-Triazole (1) can gain a proton or lose one with about equal ease to form cations 2 or 3 or an anion 4. From



1 2 3 4

literature values[1] of pK_b and pK_a for 1, the concentrations of cations and anion in a 1 *M* solution of 1 at pH 7 are calculated to be 2×10^{-5} and 5×10^{-4} *M*, respectively. In earlier work, the 4 position in pyrazole[2a] was found to undergo deuteration *via* parallel electropholic attacks of the anion and the free molecule to form σ intermediates. However, the 3(5) position in pyrazole[2a] and the 2 and 4(5) positions in imidazole[2b] were deuterated *via* proton abstraction from the cation by OD^- to form ylide intermediates; for pD > 10, deuteration of the imidazole 4(5) position involved parallel proton abstractions from both cation and molecule. Since neutral molecules, cations, and anions are all present in kinetically significant concentrations in aqueous solutions of 1,2,4-triazole, it is of interest to determine which of these forms are involved in the deuteration of the compound. In addition, it is of interest to compare the rates of deuteration of sites in 1,2,4-triazole with sites in other five-membered heterocycles.

Rates of deuteration of the 3(5) position in 1,2,4-triazole were measured as functions of pD, ammonia buffer concentration, temperature, and ionic strength. The ionic strength was held at 1.0 *M* in all runs except those in which the rate was studied as a function of ionic strength. The effect of pD upon the pseudo-first-order rate constant is shown in Figure 1. pD rate profiles qualitatively similar to this one have been observed for imidazole,[2a] substituted imidazoles,[3] and thiazole.[4] The rate constant decreases abruptly as pD decreases in the region of substrate self-buffering. When pD equals the pK_a value of the conjugate acid 2 (or 3), the rate of deuteration is halved. Thus, at pD = pK_a = 2.8, k_1^{obsd} is half that for pD values larger than 5. In ammonia buffered runs, the buffer ratio $[ND_3]/[ND_4^+]$ was fixed at 3.2 (pD 10.4). In seven such runs at 65°, in which $[ND_3]$ ranged from a low of 5×10^{-4} *M* to 1.73 *M*, k_1^{obsd} remained constant at $9.7 \times 10^{-5} \pm 0.5 \times 10^{-5}$ sec^{-1}. It is evident from this result that the deuteration reaction is not catalyzed by either the base or acid component of the buffer.

Activation parameters were determined from runs made at 55, 65, 70, and 75°; k_1^{obsd} values were 3.1×10^{-5}, 9.8×10^{-5}, 15.8×10^{-5}, and 23.7×10^{-5} sec^{-1}, respectively. The experimental activation energy was 23 ± 2 kcal and the log *A* value 13 ± 1. pD was 6.6 in these runs, while substrate concentration was 1.0 *M*.

To determine the effect of ionic strength μ upon the observed rate constant, the concentration of NaCl was varied from zero ($\mu \sim 0$) to 5 *M*. The results are shown in Table I. At low salt concentrations, no effect is discernible. The dependence of the rate constant upon μ is small even at high salt concentrations.

The pD–rate profile exhibited in Figure 1 is consistent with rate-determining ylide 6 formation (Scheme I). Alternatively, 1,2,4-triazolium-*1,2-d*$_2$ (7) could replace 1,2,4-triazolium-*1,4-d*$_2$ (5) in this scheme, leading to the corresponding ylide 8. However, ylide 8 with its adjacent lone pairs is likely to be far less stable than ylide 6, in which the lone pairs are separated. CNDO/2 calculations carried out in this laboratory and others reported in the literature[5] suggest that 5 is slightly more stable than 7, and that 6 is markedly more stable than 8. Similarly, EHT calculations by Adam, Grimison, and Hoffmann[6] on six-membered heteroaromatic carbanions showed that carbanions with adjacent lone pairs are less stable than those with separated lone pairs. Accordingly, deuteration *via* 7 is likely to be negligible compared to deuteration *via* 5.

Table I
Effect of Ionic Strength upon the Rate Constant

μ	$k_1^{obsd} \times 10^5$, sec^{-1}
0.000	11.77
0.025	11.54
0.050	12.05
0.100	11.69
1.00	9.94[a]
2.50	9.78
5.00	8.17

[a] pD > 5, [substrate] = 1.0 *M*, average of 15 runs. In other runs, pD = 6.6, [substrate] = 0.5 *M*.

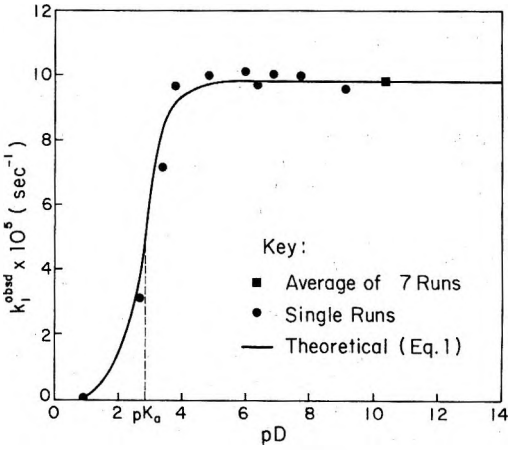
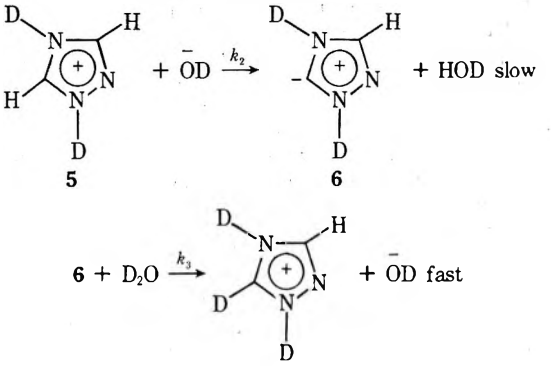


Figure 1. Dependence of the rate of deuteration of 1,2,4-triazole upon pD at 65°.

Scheme I



5 6

7 8

For deuterations conforming to Scheme I, the following equation has been derived.[2b,3b,4]

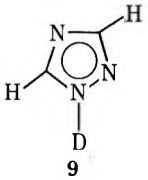
$$k_1^{obsd} = k_2 K_w/(K_a + [D^+]) \quad (1)$$

Here, K_w[7] $[D^+][OD^-] = 2.9 \times 10^{-15}$, and $K_a = 1.6 \times 10^{-3}$ is the acid dissociation constant for cationic substrate **5** (see Experimental Section). Equation 1 provides a good fit of the data if k_2 is set equal to 8×10^7 sec^{-1} M^{-1} (solid curve in Figure 1). For $[D^+] \ll K_a$, eq 1 reduces to

$$k_1^{obsd} = k_2 K_w/K_a \quad (2)$$

which is applicable for pD values larger than 5.

The effect of ionic strength upon k_1^{obsd} can be predicted by first applying the Brønsted–Bjerrum equation[8] to the slow bimolecular formation of **6**, then replacing the concentration of **5** in the differential rate equation by the concentration of 1,2,4-triazole-*1*-d_1 (**9**). Thus, we find



9

$$\text{rate} = -\frac{d}{dt}[\mathbf{9}] = k_2^\circ(\gamma^{(4)}\gamma_{OD}/\gamma^\ddagger)[\mathbf{4}][OD^-]$$

$$[\mathbf{4}] = \frac{1}{K_a^\circ}(\gamma_{D^+}\gamma^{(9)}/\gamma^{(4)})[\mathbf{9}][D^+]$$

Here the superscript ° indicates infinite dilution and γ the activity coefficient. Substituting the second equation into the first,

$$\text{rate} = \frac{k^{\circ(2)}}{K_a^\circ} K_w^\circ \frac{\gamma^{(9)}}{\gamma^\ddagger}[\mathbf{9}] = k_1^{obsd}[\mathbf{9}]$$

$$k_1^{obsd} = \frac{k_2^\circ}{K_a^\circ} K_w^\circ \frac{\gamma^{(9)}}{\gamma^\ddagger} \quad (3)$$

where $K_w^\circ = \gamma_{D^+}\gamma_{OD^-}[D^+][OD^-]$. Since both **9** and the transition state leading to the ylide intermediate (**6**) have zero charge, $\gamma^{(9)}$ and $\gamma^\ddagger$ are each unity for low salt concentrations (Debye–Hückel region). Therefore, eq 3 predicts the observed independence of k_1^{obsd} upon ionic strength for low ionic strength. This agreement at low ionic strength provides additional support for Scheme I. Outside the Debye–Hückel region, eq 3 cannot predict the dependence of k_1^{obsd} upon ionic strength, because estimates of the magnitudes of activity coefficients of uncharged solutes in media of high ionic strength cannot be reliably made.[9]

Most of the rate data on hydrogen exchange in five-membered heterocyclic cations reported in the literature[4,10-12] were taken at 31 and 33°. The k_2 value for 1,2,4-triazolium cation calculated for 33° using the Arrhenius equation is 1.5×10^6 sec^{-1} M^{-1}. Carrying out similar reductions of k_2 from higher temperatures to 33° for positions in imidazolium and pyrazolium cations, the following comparison with literature values was obtained.

1,4-diethyltetrazolium (5 position)[10]	$\sim 10^{9.5}$
3,4-dimethyloxazolium (2)[12]	$\sim 10^5$
1,2,4-triazolium (5), thiazolium (2)[4] 3,4-dimethylthiazolium (2)[12]	$\sim 10^{3.5}$
imidazolium (2)[2b] 1,3-dimethylimidazolium (2)[10] 1,3,4-trimethylimidazolium (2)[12]	$\sim 10^0$
imidazolium [4(5)][2b]	$\sim 10^{-5}$
pyrazolium [3(5)][2a] 1,2-dimethylpyrazolium (3,5)	$\sim 10^{-5}$–10^{-7}

No distinction was made in this reactivity order between unsubstituted and *N*- or *C*-alkyl substituted cations, since these substituents have relatively small effect upon the exchange reactivity.[2b] As expected, the exchange reactivity of 1,2,4-triazolium lies between the reactivities of imidazolium and tetrazolium cations.

For discussing relative reactivities of cationic substrates undergoing hydrogen exchange according to Scheme I, the ylide intermediate is probably a reasonable model for the transition state.[2-5,10-12] Factors that stabilize the intermediate would tend to stabilize the transition state. If a β C–H group in imidazolium cation is replaced by a pyridine-type nitrogen atom, yielding 1,2,4-triazolium ion, the rate constant for hydrogen exchange is enhanced by a factor of $10^{3.5}$; this enhancement is the same as that observed by Olofson, *et al.*,[11] when an extra β nitrogen was added to the thiazole molecule yielding 1,3,4-thiadiazole. A second pyridine-type nitrogen atom added to imidazolium, yielding tetrazolium, produces an additional increase in rate constant of 10^6. It is evident that the second nitrogen heteroatom provides significantly greater stabilization in the ylide intermediate than does the first one. Further, a vicinal pair of nitrogen heteroatoms, as in 1,2,4-triazolium cation, stabilizes the five-membered ylide to about the same extent as a single sulfur heteroatom, as in thiazolium.

Experimental Section

Materials. 1,2,4-Triazole from Aldrich Chemical Co. was recrystallized three times from a benzene–ethanol solution (4:1 by volume), mp 120°. The nmr spectrum of 1,2,4-triazole exhibited two singlets (δ 4.8 and 8.5 relative to TMS) attributed to hydroxyl protons and protons in equivalent 3 and 5 positions, respectively. It is clear that nitrogen protons exchange rapidly with deuterons in heavy aqueous solution.

Kinetic Runs. The details of the kinetic procedures are given elsewhere.[2] The ionic strength of solutions was adjusted by measured addition of heavy aqueous NaCl. All deuterations were carried out in 100-ml round-bottom flasks held at constant temperature in a water bath. Aliquots of 2 ml each were removed periodically, then thermally quenched (0°). Proton peak areas for substrate exchange sites were determined for each aliquot using the Varian A-60A spectrometer.[2] Pseudo-first-order rate constants ($k_1^{obsd} = k_2[D_2O]$) were obtained from [−slope of ln (peak area)] *vs.* time plots.

pD values were measured at room temperature with the Beckman Zeromatic pH meter, corrected by the formula of Glaskoe and Long (pD = meter reading + 0.4).[13] The pK_a value for 1,2,4-triazolium cation was determined in heavy water solutions at ionic strength of 1.0 *M* and at buffer ratios [triazole]/[triazolium] of 1:1 and 1:3. The value pK_a = 2.8 ± 0.1 is the average of two measurements.

Temperatures were reproducible to within ±0.1° and rate constants to within ±10%. Uncertainties in concentrations arising from thermal changes in volume are discussed elsewhere.[2]

Registry No.—1,2,4-Triazole, 288-88-0.

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Electrogenerated Chemiluminescence. XIX. Preparation and Chemiluminescence of 5,12-Dibromo-5,12-dihydro-5,6,11,12-tetraphenylnaphthacene[1]

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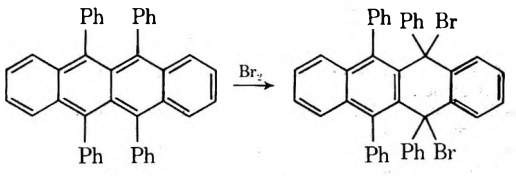
In recent years considerable interest has been centered on reactions that convert chemical energy directly to light, with the discovery of new chemiluminescor compounds comprising an important segment of the work. Two general types of electrogenerated chemiluminescence (ecl) have been investigated. The most widely studied is ecl occurring when reduced (A^-) and oxidized (D^+) species (frequently radical ions) generated at an electrode undergo an electron transfer reaction producing an electronically excited state (eq 1).[2] A second form of ecl involves the reduction of cer-

$$A^- + D^+ \longrightarrow D + A^*(\longrightarrow A + h\nu) \quad (1)$$

tain halogenated hydrocarbons [*e.g.*, 9,10-dichloro-9,10-dihydro-9,10-diphenylanthracene ($DPACl_2$)] at an electrode without the electrogeneration of an oxidant;[3,4] chemical reduction of these same compounds, *e.g.*, $DPACl_2$, by naphthalene or 9,10-diphenylanthracene (DPA) radical anions was shown to produce light in earlier studies.[5] The ecl studies of Siegel and Mark[3,4] demonstrated that the electrode potential must be such that reduction of the $DPACl_2$ and the generation of a radical anion occurs for emission to be observed. Thus reduction of $DPACl_2$ and 5,6,11,12-tetraphenylnaphthacene (rubrene) (I) produces emission characteristic of rubrene fluorescence[3,4] while reduction of $DPACl_2$ and $\alpha,\beta,\gamma,\delta$-tetraphenylporphin (TPP) produces emission from excited TPP.[6] We report here the preparation of 5,12-dibromo-5,12-dihydro-5,6,11,12-tetraphenylnaphthacene (RBr_2) (II) and the luminescence produced on its electroreduction. The preparation and chemiluminescent properties of this molecule have not previously been reported.

Results

When rubrene in dry dichloromethane solution is treated with bromine at room temperature, RBr_2 is produced (eq 2)



(2)

I II

with the quantitative uptake of 1 mol of Br_2/mol of rubrene, without further bromination even in the presence of excess bromine. The solid RBr_2 decomposes at atmospheric pressure at temperatures above 120° to produce rubrene (identified by its fluorescent spectrum) and bromine; thermogravimetric studies of RBr_2 confirm the liberation of 1 mol of Br_2/mol of RBr_2 with the production of pure rubrene.[7] Uv irradiation of solutions of RBr_2 also causes decomposition with the production of rubrene. RBr_2 itself

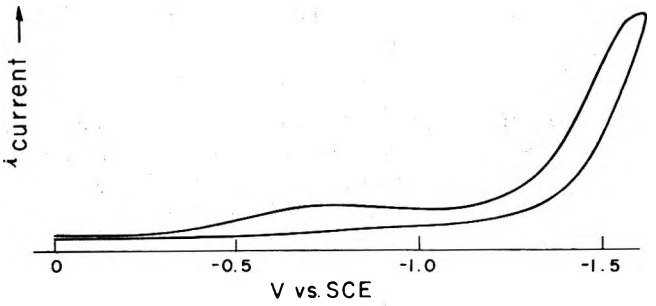


Figure 1. Cyclic voltammogram of a dichloromethane solution containing 1 m*M* RBr_2 and 0.1 *M* TBAP at a platinum electrode; the solvent background reduction occurs shortly beyond the span shown.

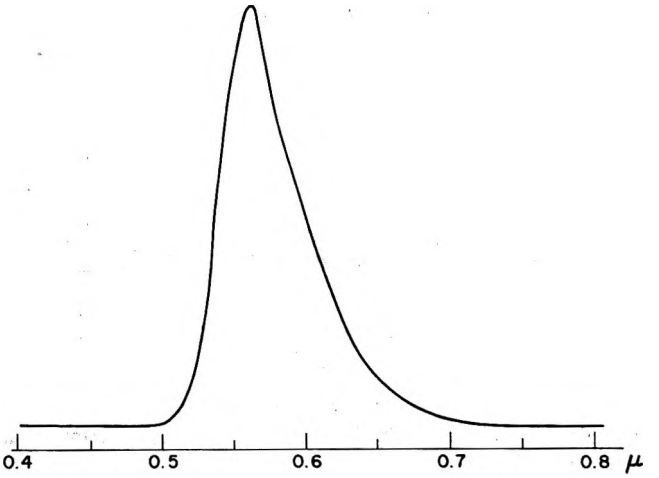


Figure 2. Electrogenerated chemiluminescence observed in the solution of Figure 1 upon application of a steady potential corresponding to the reduction peak.

shows weak fluorescence emission (λ_{max} 402 nm) and an excitation maximum at 320 nm; these results are consistent with absorption and emission from a molecule containing a conjugated diphenylnaphthalene chromophore.

A cyclic voltammogram for the reduction of RBr_2 in dichloromethane containing 0.1 *M* tetra-*n*-butylammonium perchlorate (TBAP) at a platinum electrode, shown in Figure 1, shows an irreversible reduction wave at about −1.5 V *vs.* sce. Since the reduction of rubrene (R) to its radical anion ($R\cdot^-$) occurs with an $E_{1/2}$ value of −1.39 V *vs.* sce, any rubrene produced in the reduction of RBr_2 is immediately reduced further. The electroreduction is accompanied by the emission of radiation characteristic of rubrene fluorescence (λ_{max} 560 nm) (Figure 2). Although a detailed mechanistic study of the mechanism of electroreduction of RBr_2 has not been carried out, the reaction probably follows a sequence of electron transfers and loss of bromide ions (an ecec reaction) leading to rubrene, as observed in the electrochemistry of other organic halides.[8] The overall electrode reaction is thus

$$RBr_2 + 3e \longrightarrow R\cdot^- + 2Br^- \quad (3)$$

By analogy with previous systems of this type,[3-5] the production of excited state rubrene probably results from reaction of a strong oxidant intermediate (formed by reduction of the RBr_2 diffusing toward the electrode by $R\cdot^-$ diffusing away from it) with another molecule of $R\cdot^-$, for example

$$RBr_2 + R\cdot^- \longrightarrow RBr\cdot + Br^- + R \quad (4)$$

$$RBr\cdot + R\cdot^- \longrightarrow R + Br^- + R^* \quad (5)$$

It is possible that reaction 4 produces an excited state, although it is unlikely that the free energy of this reaction is sufficient to produce excited rubrene directly. Following Siegel and Mark's[4] suggestion, there is also the possibility of dissociation of RBr· to $R\cdot^+$ and Br^- followed by the familiar ecl reaction of $R\cdot^+$ and $R\cdot^-$ to produce an excited state.

Experimental Section

Rubrene, $C_{42}H_{28}$, puriss., mp >300°, from Aldrich Chemical Co., was recrystallized twice from a mixture of dichloromethane and hexane (both solvents are spectroscopic grade). A number of preparations of II were carried out under slightly different conditions, indicating that bromination proceeds readily and quantitatively. In a typical preparation, 50 mg of I was dissolved in 30 ml of dried dichloromethane under subdued light to reduce formation of rubrene photoperoxide, followed by stepwise addition of bromine until a 50% excess was present. The reaction between I and Br_2 is immediate at room temperature, and pure II was recovered by evaporation of solvent and excess bromine in a stream of purified nitrogen. The product II was recrystallized by dissolving it in dichloromethane, followed by addition of hexane to the solution which causes pale yellow crystals of II to separate out. *Anal.* Calcd for $C_{42}H_{28}Br_2$: C, 72.85; H, 4.08; Br, 23.08. Found: C, 72.70; H, 3.89; Br, 23.20. In separate experiments the quantitative uptake of 1 mol of Br_2/mol of I was verified by carrying out the initial preparation under gravimetric conditions, without transferring the product II prior to weighing.

The compound II does not exhibit a well-defined melting point; decomposition by the liberation of bromine gas commences above 100°, and continues past 150°, even at moderate heating rates. We have maintained room temperature conditions throughout our preparations; the possibility of additional bromination under strenuous conditions and a large excess of bromine cannot be ruled out. Moureu and Dufraisse[9] mention that in chloroform solutions under unspecified conditions rubrene adds four bromine atoms to yield products with exceptionally high melting points.

The ecl experiments generally followed previous practice.[2] Necessary precautions that have been adopted in this field over the years include the exclusion of air and moisture, hence the glassware housing the test solution and electrodes was evacuable and could be removed from the vacuum line in a hermetically sealed condition. In preparing the ecl solutions the solid supporting electrolyte, TBAP, was first dried in the ecl cell at 100° using a hot water bath, and the solute was added only subsequently with brief drying under reduced pressure at room temperature to remove any traces of solvent from the recrystallization procedure. Dried, freeze–pump–thawed CH_2Cl_2 is subsequently transferred under a temperature gradient into the ecl cell containing II and TBAP, followed by freeze–pump–thawing. The experimental procedure for generating and recording the ecl emission, as well as the cyclic voltammetric studies, were according to established methods.[10] Because of possible interference by oxygen, fluorescence studies were also conducted in a sealed cell containing freeze–pump–thawed CH_2Cl_2–II solutions. Fluorescence and ecl spectra were obtained with an Aminco-Bowman spectrophotofluorometer and are uncorrected for photomultiplier response (Hamamatsu TV Corp., R456, having uv improved S-20 characteristics).

Registry No.—I, 517-51-1; II, 51932-53-7; Br_2, 7726-95-6.

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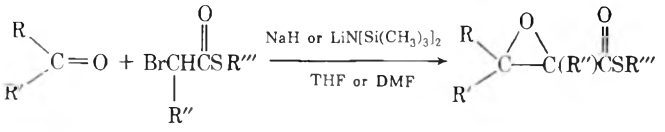
The Darzens Synthesis of Glycidic Thiol Esters[1]

Summary: Using select conditions including polar, aprotic solvents, and nonnucleophilic bases, glycidic thiol esters have been prepared in high yield with the Darzens method when α-bromo thiol esters are used in place of α-chloro thiol esters.

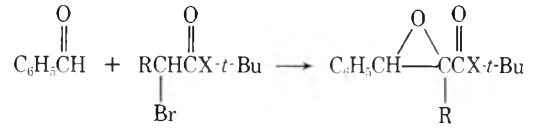
Sir: Despite the involvement of the thiol ester functional group in many metabolic transformations it has received much less attention in the literature than many other functional groups with little or no biological importance. There has been relatively little interest in the preparation of polyfunctional compounds containing the thiol ester group.[2] In connection with our interest in glycidic thiol esters,[3] we have developed the first Darzens synthesis of these compounds.[4] Interestingly the Darzens synthesis of glycidic thiol esters requires a nonnucleophilic base {NaH or LiN[$Si(CH_3)_3]_2$} and a polar, aprotic solvent (DMF or THF).[5] It is also important to use α-bromo thiol esters rather than α-chloro thiol esters. Chloro derivatives have been used in preference to bromo derivatives or iodo derivatives in the Darzens synthesis of epoxides substituted with all other types of electron-withdrawing groups reported to date.[6] Presumably the greater effectiveness of α-bromo thiol esters in the Darzens synthesis of glycidic thiol esters is due to an intramolecular nucleophilic acyl substitution reaction involving attack of the intermediate halohydrin oxyanion at the thiol ester group. This process may be expected to compete effectively with epoxide formation when the leaving group ability of the halogen is reduced.



To benzaldehyde (0.010 mol) and *tert*-butyl 2-bromothiolacetate[8] (**1a**, 0.010 mol) in dry THF (10 ml) at 0° under a nitrogen atmosphere was added $LiN[Si(CH_3)_3]_2$ (0.010 mol) in THF (12 mml) at a rate of 1 ml/min. The reaction was stirred at 0° for an additional 30 min and at room temperature for 30 min. Work-up followed by column chromatography on silica gel (Baker 60–200 mesh) eluting with petroleum ether followed by benzene–petroleum ether (1:1) gave a 9:1 mixture of trans and cis thiolglycidates (**2a**) in 59% yield. The pure trans isomer was obtained after preparative thin layer chromatography on silica gel (Merck GF254) developing five times with benzene–*n*-hexane (3:7). Recrystallization (*n*-hexane) gave *S-tert*-butyl (*E*)-3-phenyloxiranecarbothioate (**2a**) as colorless plates: mp 43–44°; nmr[9] (CCl_4, TMS) δ 7.20 (s, 5 H), 3.90 (d, 1 H, J = 1.5 Hz), 3.33 (d, 1 H, J = 1.5 Hz), 1.45 (s, 9 H); ir (KBr) 1660, 1690 cm^{-1} (sh). *Anal.* Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82; S, 13.57. Found: C, 65.91; H, 6.99; S, 13.34.

The cis isomer, *S-tert*-butyl (*Z*)-3-phenyloxiranecarbothioate (**2a**), was the major product (70% *Z*, 30% *E*) when benzaldehyde and *tert*-butyl 2-bromothiolacetate (**1a**) were allowed to react with NaH in DMF solvent. The cis isomer was obtained as a colorless oil after short-path distillation [bath temperature 130–135° (1.0 mm)] of the mixture followed by thin layer chromatography on silica gel: nmr[9] (CCl_4, TMS) δ 7.25 (s, 5 H), 4.13 (d, 1 H, J = 4.5 Hz), 3.72 (d, 1 H, J = 4.5 Hz), 1.20 (s, 9 H); ir (thin film) 1665, 1695 cm^{-1}. Also of interest is the reaction of benzaldehyde with *tert*-butyl 2-bromothiolpropionate[10] (**1b**). A 57% sodium hydride dispersion in mineral oil (0.013 mol) was washed with *n*-hexane, and dry DMF (20 ml) was added at 0° under a nitrogen atmosphere. Benzaldehyde (0.010 mol) and *tert*-butyl 2-bromothiolpropionate (**1b**, 0.010 mol) in dry DMF (10 ml) were added dropwise over a period of 10–15 min. The reaction was stirred for an additional 30 min at 0° and then at room temperature for 30 min. Column chromatography on silica gel gave a 58% yield of a 9:1 mixture of trans and cis thiolglycidates (**2b**). The product was subjected to short-path distillation [125–130° bath temperature (0.15 mm)] to give pure *S-tert*-butyl (*E*)-2-methyl-3-phenyloxiranecarbothioate as a colorless oil: $n^{26}D$ 1.5287; nmr (CCl_4, TMS) δ 7.25 (s, 5 H), 4.05 (s, 1 H), 1.46 (s, 9 H), 1.20 (s, 3 H); ir (thin film) 1670 cm^{-1}. *Anal.* Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25; S, 12.81. Found: C, 67.29; H, 7.15; S, 12.68.

The stereochemistry of this product was unequivocally established by independent synthesis using an exotic Schotten–Baumann procedure. Sodium (*E*)-2-methyl-3-phenyloxiranecarboxylate[11] (0.010 mol) was suspended in dry THF (25 ml) under a nitrogen atmosphere and the mixture was cooled to 0°. Pyridine (3–5 drops) was added followed by the dropwise addition over a period of 1 hr of freshly distilled oxalyl chloride (0.016 mol) in dry THF (5 ml) and the reaction mixture was stirred for an addditional 30 min at 0°. The THF was removed (below 15°) and DMF (40 ml) was added at 0° followed by immediate, separate, and simultaneous addition over a period of 20 min of *tert*-butyl mercaptan (0.010 mol) in DMF (5 ml) and Dabco (0.010 mol) in DMF (5 ml). The reaction was stirred at 0° for 4 hr and then at room temperature for an additional 2 hr before work-up. Column chromatography gave *S-tert*-butyl (*E*)-2-methyl-3-phenyloxiranecarbothioate (2b, 37%, $n^{26}D$ 1.5282). This compound had the same nmr and ir spectrum as the thiolglycidate prepared using the Darzens method.



1 2

No.	X	R	1 Base	Solvent	2 % cis	2 % trans	% yield
a	S	H	$LiN[Si(CH_3)_3]_2$	THF	10	90	59
			NaH	DMF	70	30	67
b	S	CH_3	NaH	DMF	10	90	58[12]
c	O	CH_3	NaH	DMF	55	45	61

Bachelor and Bansal[13] have found that the per cent of cis isomer increases as the size of the ester alkyl group is increased in the reaction of benzaldehyde with alkyl 2-chloroacetates using KO-*t*-Bu in *t*-BuOH. This has also been our experience with the α-halopropionate oxygen esters. The cis isomer predominated in the reaction of benzaldehyde with *tert*-butyl 2-chloropropionate or *tert*-butyl 2-bromopropionate (**1c**) using either the KO-*t*-Bu–*t*-BuOH conditions (~75% cis) described by Bachelor and Bansal[13] or our NaH–DMF conditions (~55% cis). In contrast, in the

reaction of benzaldehyde with *tert*-butyl 2-bromothiolpropionate (**1b**) using the NaH–DMF conditions, the trans isomer predominated, although the cis thiolglycidate was favored in the reaction of *tert*-butyl 2-bromothiolacetate (**1a**) with benzaldehyde under the same conditions. Although the explanation for this result is not immediately apparent, the high percentage of the trans isomer obtained in the less polar THF solvent in the reaction of benzaldehyde with *tert*-butyl 2-bromothiolacetate (**1a**) could be explained on the basis of steric considerations assuming that the last, intramolecular substitution step in the reaction is rate limiting.[7] We are continuing our studies with glycidic thiol esters in an attempt to determine the origin of these unusual stereochemical results.

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(1) Presented in part at the 6th Central Regional Meeting of the American Chemical Society, Detroit, Mich., April 21–24, 1974.
(2) For reviews of thiol ester chemistry, see T. C. Bruice in "The Chemistry of Organic Sulfur Compounds," Vol. 1, Pergamon Press, Oxford, 1961, p 421; M. J. Janssen in "The Chemistry of Functional Groups—The Chemistry of Carboxylic Acids and Esters," Interscience, London, 1969, p 724.
(3) J. Wemple, *J. Amer. Chem. Soc.*, **92**, 6694 (1970).
(4) An unsuccessful attempt has been reported: L. Field and C. G. Carlile, *J. Org. Chem.*, **26**, 3170 (1961).
(5) Protic solvents (alcohols) and nucleophilic (NaOEt) bases have been generally used in the Darzens reaction in the synthesis of epoxides substituted with a wide variety of electron-withdrawing groups. For example, aqueous methanolic NaOH has been used recently in the Darzens condensation of 1-chloro-3-diazopropanone with benzaldehyde: N. F. Woolsey and M. H. Khalil, *J. Org. Chem.*, **38**, 4216 (1973).
(6) M. S. Newman and B. J. Magerlein, *Org. React.*, **5**, 417 (1949). However, α-bromo esters have recently been shown to be preferred to α-chloro esters in the synthesis of glycidic esters from low molecular weight aldehydes such as acetaldehyde.[7]
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(8) *tert*-Butyl 2-bromothiolacetate was obtained from bromoacetyl bromide, *tert*-butyl mercaptan, and pyridine as a colorless oil: n^{26}D 1.5077; nmr (CCl_4, TMS) δ 3.88 (s, 2 H), 1.48 (s, 9 H); ir (thin film) 1690 cm^{-1}.
(9) The epoxide proton coupling constants are in agreement with the trans (1.5 Hz) and cis (4.5 Hz) stereochemical assignments: R. L. Williamson, C. A. Lanford, and C. R. Nicholson, *J. Amer. Chem. Soc.*, **80**, 6389 (1958).
(10) n^{26}D 1.4965; nmr (CCl_4, TMS) δ 4.31 (q, 1 H, J = 7.0 Hz), 1.77 (d, 3 H, J = 7.0 Hz), 1.48 (s, 9 H); ir (thin film) 1690 cm^{-1}.
(11) Ethyl (*E*)-2-methyl-3-phenyloxiranecarboxylate was prepared according to the method of V. R. Valente and J. L. Wolfhagen, *J. Org. Chem.*, **31**, 2509 (1966). It was hydrolyzed with NaOH in ethanol to give the corresponding sodium salt.
(12) The trans isomer also predominated (90% trans, 10% cis) in the reaction of benzaldehyde and *tert*-butyl 2-bromothiolbutyrate with NaH in DMF. It is interesting to note that in both cases the small amount of cis isomer was easily removed by short-path distillation at ~130°.
(13) See F. W. Bachelor and R. K. Bansal, *J. Org. Chem.*, **34**, 3600 (1969), and references cited therein.

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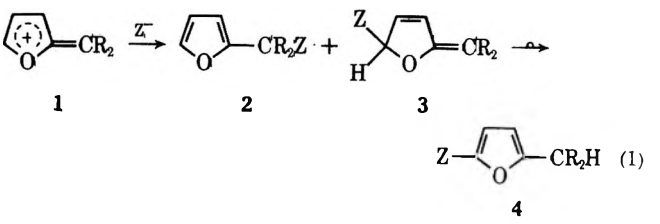
Furfuryl Cationic Capture Processes. 5-Substituted $\Delta^{3,4}$-2,5-Dihydro-2-methylenefurans and Their Rearrangement to Furfuryl Derivatives

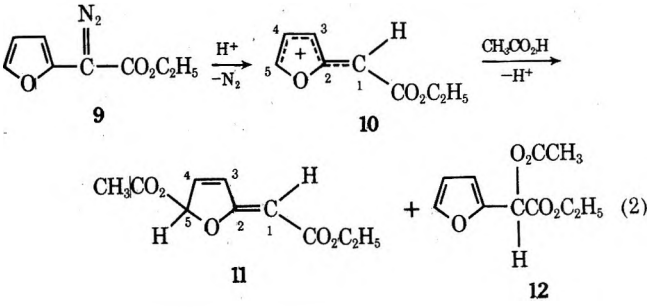
Summary: Decomposition of ethyl (2-furyl)diazoacetate (**9**) occurs carbenically to **17** and cationically by 1,1 and 1,5 solvent incorporation to derivatives of **2** and **3**; ring closures of **17** by hydroxylic solvents as catalyzed by silver(I) yield furans **3** which isomerize anionotropically to **2**.

Sir: Furfuryl cations (**1**) usually undergo nucleophilic conversion to furfuryl analogs (**2**, eq 1).[1a] Such cations (**1**) might also be expected to react at their 5 positions to give $\Delta^{3,4}$-2-alkylidene-2,5-dihydrofurans (**3**, eq 1) which tautomerize to 5-substituted 2-alkylfurans (**4**, eq 1).[1b-d,2] As yet, however, products analogous to **3** have been detected only in reaction of 2-furyldiphenylcarbinol (**5**) with methanolic hydrochloric acid to give $\Delta^{3,4}$-2-diphenylmethylidene-5-methoxy-2,5-dihydrofuran (**6**) and methyl 2-furyldiphenylcarbinyl ether (**7**).[3] Methanolic hydrochloric acid then effects prototropic rearrangement of **7** to 2-diphenylmethyl-5-methoxyfuran (**8**).[3]



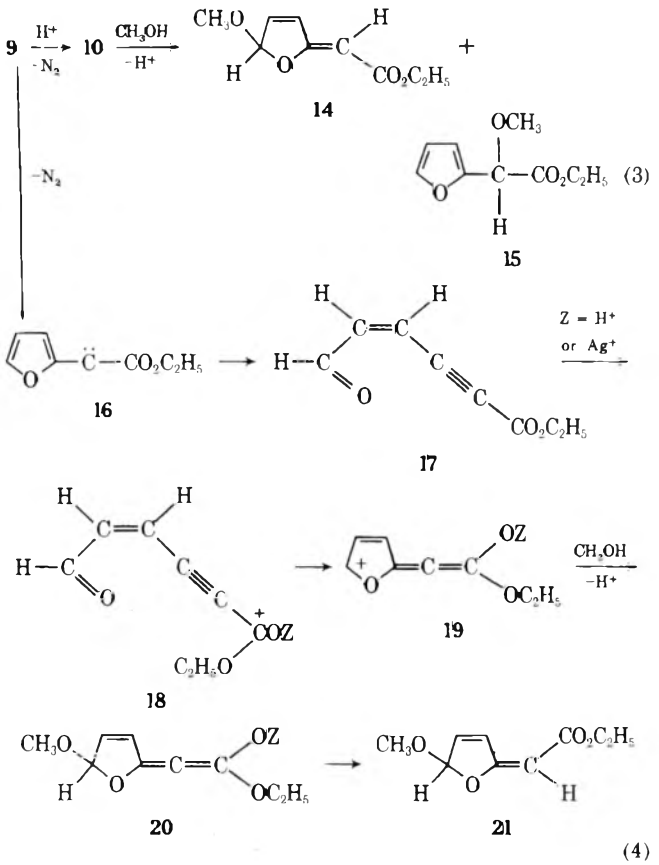
We now report a series of cationic reactions of ethyl (2-furyl)diazoacetate (**9**) in which nucleophiles are incorporated at the 5-furano position (as **3** in eq 1); these products may then undergo anionotropic isomerization to ethyl α-substituted α-(2-furyl)acetates (**2**, eq 1) rather than tautomerization to ethyl (5-substituted 2-furyl)acetates (**4**, eq 1). Of further significance are that cationic conversion of **9** by nucleophiles may be directed to **2** or **3** by appropriate catalysts and that carbenic decomposition of **9** (eq 3) and subsequent reaction with hydroxylic solvents (eq 4) serves as a new method for synthesis of derivatives such as **3**.

Diazo ester **9**, prepared from ethyl (2-furyl)glyoxylate *p*-tosylhydrazone and tetramethylguanidine, reacts with acetic acid (eq 2) at 25° to give (*Z*)-$\Delta^{3,4}$-5-acetoxy-2-carboethoxymethylidene-2,5-dihydrofuran (**11**, 55%) and ethyl α-acetoxy-α-(2-furyl)acetate (**12**, 45%).[4] Esters **11** and **12** are apparently produced by reactions of acetic acid with α-carboethoxyfurfuryl carbenium ion **10** at its 5-furano and its furfuryl positions, respectively. It is not clear whether reaction to give **11** and **12** occurs by protonation of **9** or/and its subsequent carbene (**16**). The stereochemistry of **11** is assigned on the basis that it is not isomerized when heated and the supposition that the steric bulk about furano oxygen is less than that at C-3 H.



Isomerization of **11** occurs in acetic acid at 85° to give **12**; prototropic rearrangement of **11** to ethyl α-(5-acetoxy-2-furyl)acetate (**13**) does not take place. Reaction of **9** with acetic acid thus reveals that 1,5-cationic addition to give **11** is the major kinetic process, whereas **12**, formally the product of 1,1-cationic addition of acetic acid to **9**, may result from thermodynamic or kinetic circumstances. The present observations raise the possibility that solvolysis of furfuryl derivatives to furfuryl analogs (eq 1) may be more complex than has been apparent.

A study has also been made of reactions of **9** with alcohols. Thus **9** decomposes in methanol with nitrogen evolution to (*Z*)-$\Delta^{3,4}$-2-carboethoxymethylidene-5-methoxy-2,5-dihydrofuran[4] (**14**, 29%, eq 3) and ethyl α-methoxy-α-(2-furyl)acetate[4] (**15**, 17%, eq 3) along with ethyl 5-formyl-*cis*-



(4)

4-penten-2-ynoate[4] (**17**, 34%, eq 4) and (E-$\Delta^{3,4}$-2-carboethoxymethylidene-5-methoxy-2,5-dihydrofuran[4] (**21**, 21%, eq 4). Esters **14** and **15** are presumably formed by attack of methanol on **10** (Eq 3). Aldehydo ester **17** is a product of carbenic reaction[5] of **9** (eq 4) even though the environment is protic. Indeed decomposition of **9** in methylene chloride results in evolution of nitrogen and stereospecific conversion to **17** (100%, eq 4).[5] The conclusion that **9** undergoes competitive carbenic decomposition in methanol is consistent with the observation that upon addition of *p*-toluenesulfonic acid (0.5 equiv) the conversions to **14** (44%) and **15** (16%) are increased.

Of particular note is that **17** reacts with methanol as catalyzed by protonic acids or much faster and more efficiently (100%) by silver nitrate to give **21**, the E isomer of **14**. Conversion of **17** to **21** is a new synthesis of $\Delta^{3,4}$-2-alkylidene-2,5-dihydrofurans and may be the source of **21** obtained from **9** and methanol *via* a mechanistic sequence as in eq 4. The stereochemistry of **21** is presumed on the basis that protic attack is favored kinetically from the furano oxygen direction in **20** and in particular that **21** is converted by heat or by uv irradiation to its less strained isomer **14**.

Silver nitrate in methanol converts **9** rapidly to **14** (25%), **15** (11%), and **21** (65%), presumably by processes analogous to those of eq 3 and 4. Of interest is that cupric acetate reacts rapidly with **9** and methanol exclusively by 1,1 addition (100%) to give **15**. The present example of 1,1 rather than 1,5 addition of methanol to **9** with loss of nitrogen emphasizes further the specificity possibly derived from reactions of diazo compounds as catalyzed by copper ions.[6]

Acknowledgment. We gratefully acknowledge the National Science Foundation and the National Institutes of Health for support of this research.

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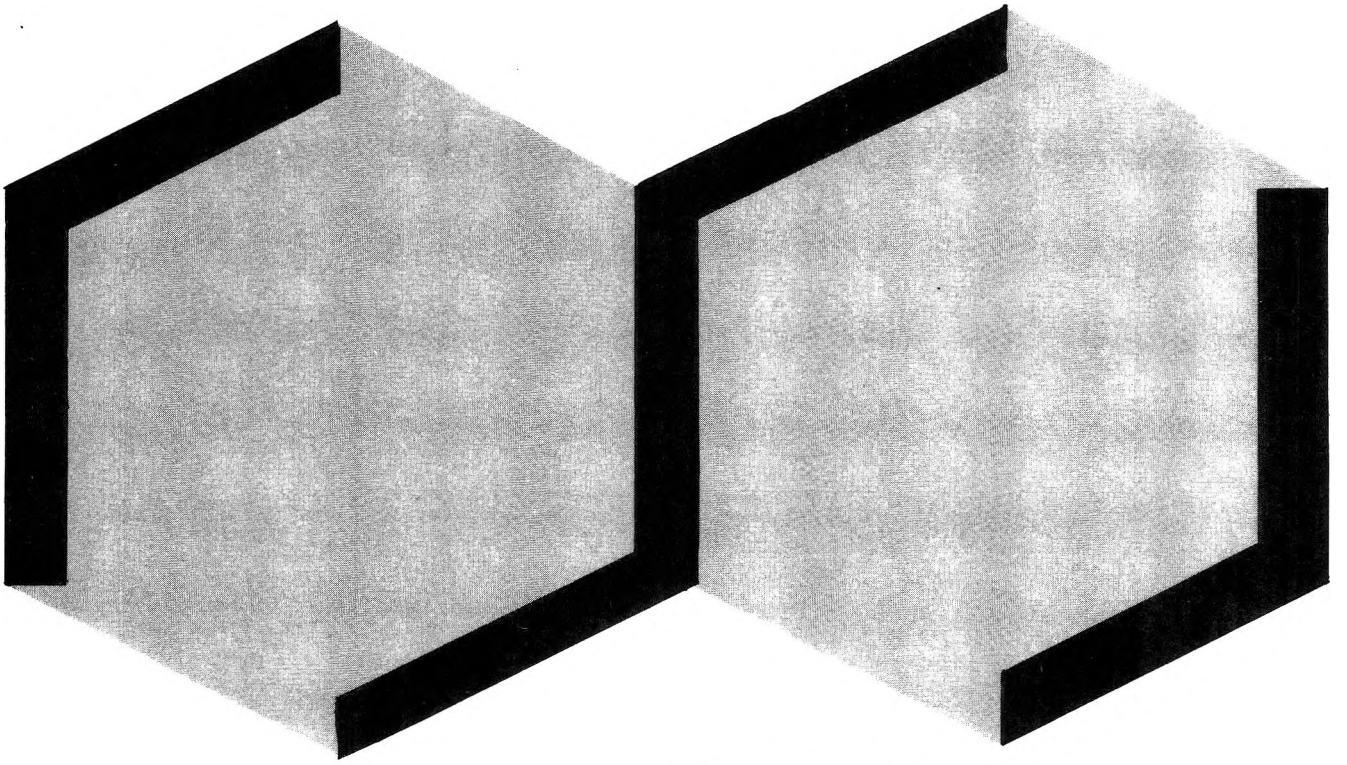

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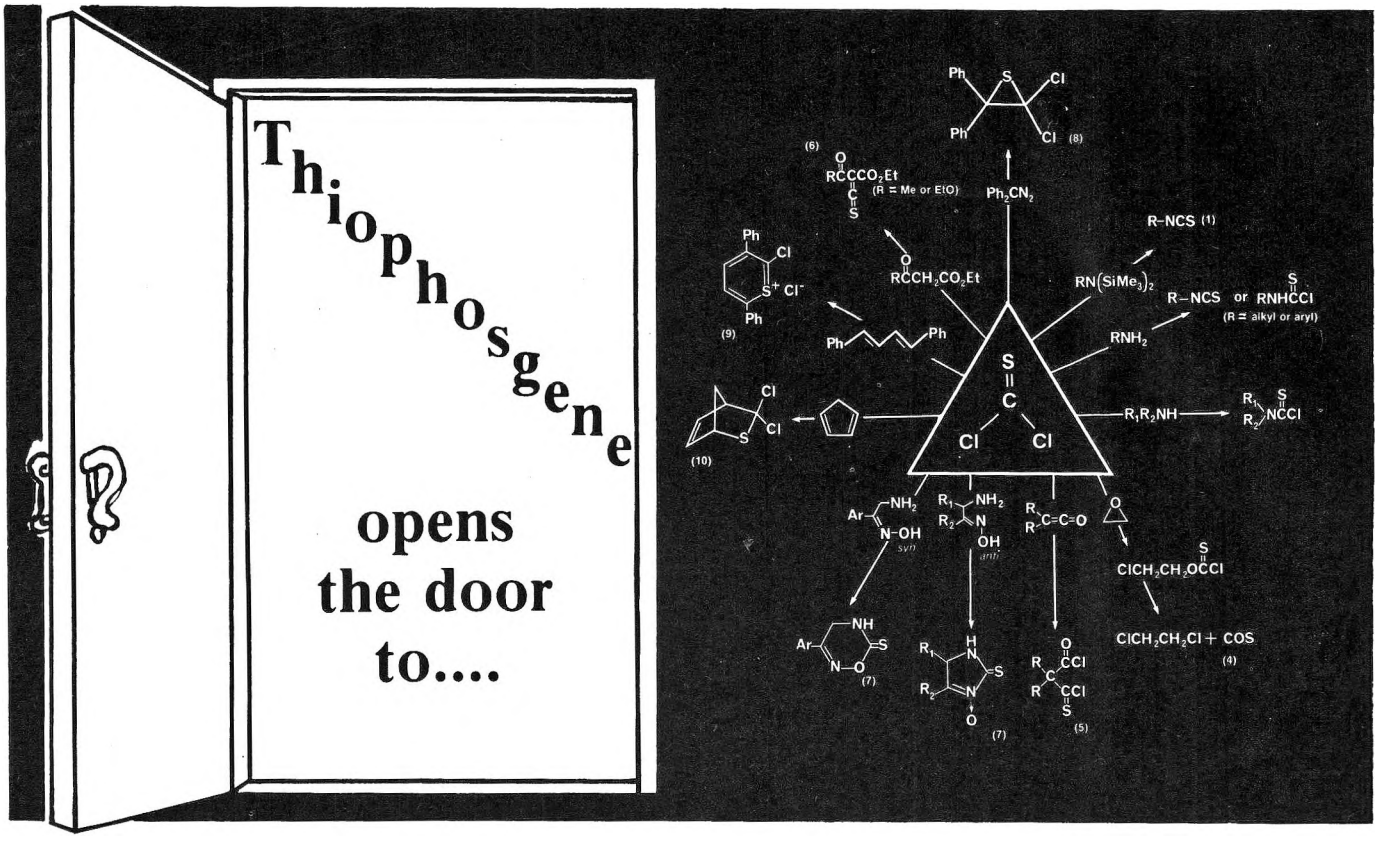

THIOPHOSGENE reacts with alcohols, phenols, mercaptans, thiophenols, and various amines giving products that vary depending on the reaction conditions and the starting materials. For instance, **aromatic amines** give the thiocarbamoyl chlorides in anhydrous ether, but afford the isothiocyanates and/or the thioureas in an aqueous medium or upon heating the reaction mixture. **Primary aliphatic amines** give isothiocyanates with great ease, whereas **secondary aliphatic amines** lead to thiocarbamoyl chlorides. Other amines, such as silylated amines,[1] hydrazines, hydrazides and semicarbazides behave similarly.

Thiophosgene reacts with **aromatic diazoketones** to produce various interesting products including some heterocycles.[2,3] It also reacts with **epoxides**,[4] **ketenes**[5] and **activated methylenes**.[6] A Friedel-Crafts reaction on benzene produces thiobenzophenone.[6]

Thiophosgene leads to a great variety of heterocycles, especially with substrates containing either two amino, hydroxyl or mercapto groups, or any combination thereof at 1,2- or 1,3-positions.[7] Reactions with **diazo compounds**[8] and Diels-Alder condensations with 1,3-dienes afford sulfur-containing heterocycles.[9,10]

For additional reactions involving **thiophosgene**, please send for data sheet.

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