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NOTES

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There is no supplementary material for this issue.

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

AUTHOR INDEX

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Cyclopropane Ring Opening by Photolytically Generated Bromine Atoms

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Bromine atoms, generated by irradiation by a mercury lamp bearing a filter to assure that only wavelengths >310 nm passed, were permitted to react with a series of 1,2-diarylcyclopropanes in carbon tetrachloride solution. The major product in all cases (>80%) was the 1,3-dibromo-1,3-diarylpropane. Kinetic data at approximately 10^{-3} *M* gave a rate expression $dBr_2/dt = -k(\text{cyclopropane})(\text{bromine})^{1/2}$. A Hammett treatment of the data gave $\rho = -0.5$ for both the cis series and the trans series. Synthesis of several possible minor products and their comparison with the reaction mixture by TLC is reported. Possible reactions such as induced isomerization are thus eliminated from consideration.

The addition of halogens to cyclopropanes to give ring opening products is generally accepted as one of the unusual properties of the three-membered ring. In studies of the 1,2-diphenylcyclopropanes and phenylcyclopropane with bromine, LaLonde[2] delineated three reaction modes: type A, photocatalyzed, nonpolar solvents, free-radical-like ring opening; type B, electrophilic ring opening; and type C, aromatic substitution. This paper addresses itself to type A reactions in the 1,2-diarylcyclopropane series.

Results

It is important to assure that the reactions which we have studied were the same as those that LaLonde observed. Our work was aimed at determining something about the reaction's sensitivity to electron density of the cyclopropane ring and, hence, used a number of compounds not used in LaLonde's work. We shall return to examine those that do overlap after considering the general character of our study.

We synthesized a series of 1,2-diarylcyclopropanes by standard methods[3,4] and characterized them by elemental analysis, molecular weights, and spectral examinations (cf. Table I).

Carbon tetrachloride solutions of these compounds were subject to irradiation from a medium-pressure mercury arc (GE-AH-4) equipped with a Corning no. 5031 filter. This filter was effective below 310 nm as seen by the failure of this assembly to expose any malachite green leucocyanide after 1 hr of irradiation.

Irradiation of the carbon tetrachloride solutions of the cyclopropanes in the absence of bromine gave no rearrangement or ring opening products after several hours with this system. Mixtures of the cyclopropane solutions with equimolar bromine under dark conditions showed no detectable reaction after 48 hr. For reference, the photochemical studies were 90% complete on the order of 120 min.

The reaction was shown to utilize 1 mol of bromine per mole of cyclopropane and to produce no HBr, except in the cases of the *p*-methyl and *p*-dimethylamino compounds which were not included in the kinetic study as a result.

Major products were isolated by chromatography and characterized by spectral means. In two cases, *p*-chloro and unsubstituted, the 1,3-diaryl-1,3-dibromopropanes were synthesized and the compounds compared with the isolated material and with the TLC and GLC of the reaction mixtures. Several minor product candidates, 1,2-diphenyl-1,3-dibromopropane, 1,3-diphenyl-1,2-dibromopropane, and 1,3-diphenylpropene, were synthesized and found to be absent from the appropriate crude product mixture. The minor products remain unknown as their molecular weight and elemental analyses were quite variable and their mobility and volatility in chromatography were very low. Polymers or polyhalogenated by-products are likely.

Is the reaction we have studied the same as that of LaLonde?

We believe that it is for several reasons. The 1,2-diphenylcyclopropane cases studied by us at room temperature have nearly identical yields of 1,3 products [90% (isolated) vs. 100% "crude"] and the meso/*dl* ratios measured in the NMR are similar (trans, 52:48 vs. 62:38; cis, 57:43 vs. 41:59) but our reaction times were much shorter and activated species of higher concentration. All of the conditions of reaction and the rest of the data collected are essentially the same within experimental error.

Our comparative kinetic studies were made on a total of 42 runs (plus some used to establish the best instrumental parameters, etc.). Concentration dependence studies were run on the 1,2-diphenylcyclopropanes using GLC to check the spectrophotometric results in a few cases in order to

Table I
Physical Properties of the Substituted Cyclopropanes

Compd	Bp, °C (Torr)	$n^{25}D$	Uv λ_{max} nm	Uv ϵ_{max}	NMR, ppm	Ref	Registry no.
trans-1,2-Diphenylcyclopropane	115–118 (1)	1.5987			2.10 (m), 1.28 (m), 7.05 (m)	10, 3a, 6	1138-47-2
cis-1,2-Diphenylcyclopropane	73 (0.25)	1.5925	220	1.6×10^4	2.38 (m), 1.34 (m), 6.96 (m)	3a, 6, 9	1138-48-3
trans-1-*p*-Methylphenyl-2-phenylcyclopropane	142–146 (0.6)[c]	1.5895	(EtOH) 234	2.19×10^4	1.28 (m), 2.05 (m), 7.00 (m), 2.28 (s)	*a*	56363-35-0
cis-1-*p*-Methylphenyl-2-phenylcyclopropane	94–95 (0.1)	1.5808	223	1.78×10^4	1.22 (m), 2.22 (m), 6.82 (m), 2.05 (s) (2:2:9:3)	*a*	56363-36-1
trans-1-*p*-Chlorophenyl-2-phenylcyclopropane		1.6066	(EtOH) 236	2.58×10^4	1.30 (m), 2.11 (m) 7.09 (m) (2:2:9)	*a*	56363-37-2
cis-1-*p*-Chlorophenyl-2-phenylcyclopropane		1.5951	225	1.55×10^4	1.30 (m), 2.32 (m), 6.95 (m) (2:2:9)	*a*	2001-61-8
trans-1-*m*-Chlorophenyl-2-phenylcyclopropane		1.6062	233	2.28×10^4	1.28 (m), 2.00 (m), 7.08 (m) (2:2:9)	*a*	56363-38-3
cis-1-*m*-Chlorophenyl-2-phenylcyclopropane	96–98 (0.5)	1.5925	(EtOH) 216	1.94×10^4	1.37 (m), 2.40 (m), 6.92 (m) (2:2:9)	*a*	56363-39-4
trans-1-*p*-Fluorophenyl-2-phenylcyclopropane	130 (1.3)	1.5779	(EtOH) 230	1.73×10^4	1.30 (m), 2.00 (m) 7.00 (m) (2:2:9) 118.4 (m) ($CFCl_3$)	8	1611-89-8
cis-1-*p*-Fluorophenyl-2-phenylcyclopropane	125 (1.3)	1.5655	(EtOH) 220	1.46×10^4	1.30 (m), 2.31 (m), 6.90 (m) (2:2:9) 117.9 (m) ($CFCl_3$)	*a*	1611-88-7
trans-1-*p*-Methoxyphenyl-2-phenylcyclopropane	mp 78.5–79.5		(EtOH) 232	1.98×10^4	1.32 (m), 2.10 (m), 7.0 (m), 3.75 (s) (2:2:9:3)	*a*, *c*	34221-26-6
cis-1-*p*-Methoxyphenyl-2-phenylcyclopropane	141 (0.45)	1.5885	229	1.14×10^4	1.28 (m), 2.31 (m), 6.78 (m), 3.45 (s) (2:2:9:3)	*a*	53400-00-3
trans- + *cis*-1-(*p*-dimethylaminophenyl)-2-phenylcyclopropane	145–147° (0.2)	1.6140			1.28 (m), 2.03 (m), 7.10 (m), 2.76 (s) and 1.30 (m), 2.30 (m), 6.55 (m), 2.69 (m)	*a* *b*	56363-40-7 56363-41-8

[a] Elemental analysis agreed within less than 0.08 in carbon, 0.09 in hydrogen, and (as appropriate) 0.19 in chlorine and 0.19 in fluorine. [b] Cis about 15% of the mixture. [c] Mol wt 223.

guarantee that the cyclopropane was being used up at the same rate as the bromine. Each of the runs was found to fit the appropriate three-halves order expression. Further support for this comes from plotting the appropriate functions for the integrals of the three-halves order. Invariably the plot was linear and gave excellent integral fit regardless of the relative concentration relationship. The correlation coefficient from a linear regression analysis (R) obtained for each run ranged from 0.999993 to 0.992670 with an average of 0.9981 for plots of the appropriate arctangent and ln terms when the concentrations were not equimolar.

Our studies of relative rates for use in the Hammett treatment varied enough from run to run to make the slope of the resultant curves at best approximate ($\rho = -0.5 \pm 0.1$ for both cis and trans).

Approximate data on the effect of the intensity of the light was obtained by assuming normal radial dependence and changing the path length to the reaction cells. The rate was found to be proportional to the light intensity to a fractional power (0.4–0.7), a range that seems to agree fairly well with the theoretically half-order value for two bromine atom chain carriers.

Quantum yields using a cinnamic acid–bromine actinometer were obtained. Unfortunately, the value for the actinometer seems to be in dispute[5] but, as an order of magnitude, the value for the cyclopropane reaction appears to be about 100.

Experimental Section

Preparation of 1,2-Phenyl-Substituted Cyclopropanes. All of the cyclopropanes used in this study were prepared by the pyrolysis of the corresponding 1- or 2-pyrazoline. Only the *p*-chlorophenyl compound offered any difficulty with respect to the stability of the intermediate heterocycle but all of these compounds were used as soon as possible after isolation as they formed intractable tars on standing. In the *p*-chlorophenyl case the 1-pyrazoline failed to give the desired cyclopropane but the 2-pyrazoline did so if the pyrolysis reaction was not delayed after isolation of the nitrogen compound.

The preparation of the 1-pyrazoline was carried out by the treatment of styrene with the appropriately substituted phenyldiazomethane.[3] Pyrolysis gave trans cyclopropanes.

The 2-pyrazolines were prepared from the corresponding chalcones (1,3-diphenylpropenones) and hydrazine.[4] Pyrolysis gave mixtures of cis and trans cyclopropanes (Table I). Isomers were separated by distillation through a 20-plate spinning band column.

Preparation of the 1,3-Diphenylpropenes. 1,3-Diphenyl-2-propanol was prepared by the $LiAlH_4$ reduction of dibenzyl ketone. After work-up, the crude alcohol was distilled (2 Torr) through an 18-in. alumina column maintained at 330°C by a furnace. The resulting distillate was fractionated to give a 78% yield of olefin. Fractions were identified as cis or trans by GLC on Carbowax 20M at 250°C where the mixed olefin was found resolvable.

Products were characterized by boiling point, refractive index, uv, ir, and NMR spectra, and elemental analysis.

Preparation of 1,2-Dibromo-1,3-diphenylpropane. To a solution of 1.0 g (0.005 mol) of *trans*-1,3-diphenylpropene in 10 ml of CCl_4 was added 0.05 mol of Br_2 until the color persisted for 30 min. No HBr was noted.

Separation of the product and recrystallization from benzene gave mp 105–107°C (lit.[11] 111–112°C); ir 2915, 2838, 590, 560, 510 cm^{-1}; NMR multiplets centered at 3.18, 3.83, 4.59, 5.00 ppm and an unsymmetric doublet centered at 7.23 ppm.

Preparation of 1,3-Dibromo-1,3-diphenylpropane. 1,3-Diphenyl-1,3-propanediol was prepared as reported by Zimmerman.[12]

The product recrystallized from benzene melted at 129–130°C (lit.[12] 128–130°C) and showed broad OH absorption at 3350 cm^{-1}.

To 2.7 g (0.012 mol) of 1,3-diphenyl-1,3-propanediol in 25 ml of heptane was added 12 g of PBr_3. The system was warmed gently until a single phase was formed. After standing for 1 hr a syrupy phase appeared from which the heptane layer was decanted. After about half of the heptane had been evaporated, the solution was streaked on two 20 × 20 cm, 1 mm thick silica gel H plates and developed with a 2:1 benzene–heptane solvent. The edges of the plate were developed with formaldehyde and sulfuric acid. The untreated portion between the colored spots that appeared was shaved off and washed with ethyl ether, and the ether was evaporated. A nearly colorless viscous oil remained which had the following physical constants: ir 2910, 2840, 1260, 695 (doublet), 600 cm^{-1}; NMR multiplets at 2.90, 4.80, 5.12 ppm and a singlet at 7.26 ppm.

Anal. Calcd for $C_{15}H_{14}Br_2$: C, 50.88; H, 3.98; Br, 45.14. Found: C, 50.97; H, 3.78; Br, 45.09.

Preparation of 1-*p*-(Chlorophenyl)-3-phenyl-1,3-dibromopropane. By the analogous route to that used for the unsubstituted compound, the title compound was prepared and isolated.

Its physical properties were: oil, ir 2920, 2860, 725, 695, and 645 cm^{-1}. The compound was quite unstable and both the NMR and elemental analysis indicated that some decomposition had occurred during shipping.

Anal. Calcd for $C_{15}H_{13}ClBr_2$: C, 46.37; H, 3.37; Br, 41.13. Found: C, 51.53; H, 3.82; Br, 35.73.

Preparation of 1,2-Diphenyl-1,3-propanediol. The basic carbon structure was established by a Reformatsky reaction between ethyl 2-bromo-2-phenylethanoate and benzaldehyde.[13] The alcohol was prepared by the lithium aluminum hydride reduction of the keto ester. This compound was a thick, viscous gum which could not be induced to crystallize: lit.[13] mp 112°C (erythro), 115–118°C (threo). Other properties were ir 3350, 3080, 3060, 3030, 2940, 2870, 1620, 1510, 1475, 1200, 1030, 1010, 910, 850, 730, 690 cm^{-1}.

Comparison of Dibromides with the Photolysis Product. Treatment of 1,2-diphenylpropane-1,3-diol with PBr_3 in ether solution gave a dibromide which was resolvable from 1,3-diphenyl-1,3-dibromopropane when compared on 0.25-mm silica gel H thin layer chromatograms with 25% $HCCl_3$ in CCl_4 as the eluting solvent mixture.

When the photolysis products and the two dibromides were compared under these conditions with 2% formaldehyde–sulfuric acid as the developing reagent, no indication of the 1,2-diphenyl compound was found in the photolysis mixture. The two synthetic halides developed to different colors, had slightly different R_f values when separate (0.60 for the 1,3 vs. 0.55 for the 1,2), and could be seen in the presence of each other at 5% of the 1,2 in the presence of the 1,3.

Isolation of the Major Product from the Bromination Reaction. For both the cis and the trans of the cyclopropanes indicated, the following sequence was used.

The reaction was permitted to go to completion in the presence of excess bromine under room illumination. In all cases the bromine used up was found to correspond with the number of moles of cyclopropane present.

The solutions resulting from such treatment and those resulting from kinetic runs were subjected to TLC analysis.

Development of silica gel H plates with 2:1 to 3:1 benzene–heptane mixtures followed by development with 2% formaldehyde and sulfuric acid showed the disappearance of the spot characteristic of the cyclopropane and the appearance of three spots in each case. If the plates were heated slightly to aid the initial application of the solutions, other spots appeared in addition.

The major product was isolated either by column chromatography or by streaking a TLC plate (as above).

***cis*- and *trans*-1,2-Diphenylcyclopropane.** The major band amounted to 84.2% of the recovered product and was identical with 1,3-dibromo-1,3-diphenylpropane as described above in ir, NMR, and elemental analysis.

***cis*- and *trans*-1-(*p*-Chlorophenyl)-2-phenylcyclopropane.** The product from this reaction contained 89% of the 1,3-dibromo product which was identical with that prepared above in ir.

Anal. Calcd for $C_{15}H_{13}ClBr_2$: C, 46.37; H, 3.37. C, 47.91; H, 3.63.

***cis*- and *trans*-1-(*p*-Fluorophenyl)-2-phenylcyclopropane.** The products were the same and separation of the major products showed 95% of the 1,3-dibromo compound as seen by ir 2950, 2910, 2850, 590, 570 cm^{-1}; NMR multiplets at 2.90, 4.96, and 7.20 ppm.

Anal. Calcd for $C_{15}H_{13}Br_2F$: C, 48.51; H, 3.52; Br, 42.95. Found: C, 48.10; H, 3.44; Br, 43.19.

***cis*- and *trans*-1-(*p*-Methoxyphenyl)-2-phenylcyclopropane.** The products from this set of reactions contained 88% of a major product which had essentially identical ir spectra with the earlier 1,3 products with the addition of bands at 1628 and 590–570 (doublet) cm^{-1}; mol wt (by vapor pressure osmometer) 379 vs. 384 calculated; NMR showed mixture present. Attempts to countersynthesize the expected product gave a nearly identical mixture which could not be separated.

***cis*- and *trans*-1-(*m*-Chlorophenyl)-2-phenylcyclopropane.** The major product was 81% of the recovered material. Its properties were: mol wt (vapor pressure osmometer) 390, 380 calculated; ir 2970–2950 (doublet), 2900, 2850, 593, and 550 cm^{-1}; NMR multiplets centered at 2.90, 4.90, and 7.25 ppm.

Anal. Calcd for $C_{15}H_{13}Br_2Cl$: C, 46.37; H, 3.37; Br, 41.14. Found: C, 46.01; H, 3.38; Br, 41.17.

Kinetic Studies. The kinetic studies were of two types: studies carried out to measure the general form of the rate equation and studies to obtain relative rate data.

In the first type the rate data were obtained by use of a flow system in which the mixed solution was circulated before a Corning no. 5031 filter-equipped GE-AH-4 Hg lamp and through a DK-1A set at 5800 Å to permit the measurement of the rate of disappearance of Br_2. Except at these two points the system was in total darkness during irradiation because of a black felt blanket placed over the assembly.

The system was filled with the starting solution and circulated without irradiation. In no case was any indication of a change in the bromine concentration noted over a period of 30 min, the time characteristic of the reaction of the irradiated solutions. A series of runs with various of the substituted cyclopropanes was made in the concentration ranges of 0.5 to 0.003 *M* cyclopropane and 0.1 to 0.003 *M* in bromine. In all cases the flow system had a path length of 0.5 mm for the irradiating light.

The second type involved a comparative method in which 1-cm cuvettes were placed close together on the arc of a circle of radius 30.5 cm with the mercury lamp at the center. Periodically during irradiation, the mercury lamp was shuttered and the bromine concentration measured with a DU spectrometer set at 500 nm. The six cuvettes which were used contained initially the same bromine concentration and as nearly as possible the same concentrations of the various substituted cyclopropanes. During each run the cuvettes were rotated through the various sites to eliminate any bias from that source.

On duplicate runs, the variously substituted cyclopropanes were rotated through the various cuvettes to assure strictly comparable irradiation. Larger circles (radii of 35.5, 50.8, and 161 cm) were prepared in the same way and used to obtain qualitative data on the intensity dependence. All manipulations for these studies were carried out in total darkness aided by only a pen light except during actual irradiation.

The results obtained from these studies are summarized in Tables II and III.

Qualitative data about the quantum yield was obtained by the following experiments.

Five cuvettes containing the solution of interest were set into a slot cut in a short section of 2 × 4. The entire assembly was placed

Table II
Relative Rate Constants[a]

Substituent	Cis	Trans
H	1.00	1.00
p-Cl	0.81 ± 0.03	0.80 ± 0.04
m-Cl	0.75 ± 0.09	0.64 ± 0.03
p-F	0.93 ± 0.03	0.90 ± 0.04
p-OCH_3	1.5 ± 0.2	1.4 ± 0.2

[a] $k \cong 2.9 \times 10^{-4}$ l.$^{1/2}$ mol$^{-1/2}$ sec^{-1} for the unsubstituted case under the described experimental conditions (cf. Experimental Section).

under a small light-tight box equipped with an entrance opening of 1 × 6 cm which was lined up with the lamp and the cuvettes to provide a straight line as seen through a small hole at the back of the box. All interior surfaces were painted black.

In the first experiment all of the cuvettes were filled with an actinometer solution that was 0.05 *M* in bromine. The solution was the cinnamic acid–bromine system.[5]

Periodically the lamp was shuttered and the Br_2 concentration of each of the cuvettes measured with the DU spectrometer. All five cuvettes showed reaction occurring from the very beginning with the effect of the reduced intensity obvious.

In a like manner the first cuvette was filled with the substituted cyclopropane system at 0.05 *M* in both bromine and cyclopropane and the remaining cuvettes were filled with the cinnamic acid actinometer. The quantum yield calculated from comparison of the first and second cuvettes in each case indicated that the two reactions had similar quantum yields of about 10^2. Since the quantum yield of the actinometer seems, at best, to be approximately defined, an order of magnitude is all that one may hope to obtain. The use of uranyl oxalate in the wavelength region that is used for this reaction required such long irradiation times relative to those of the reaction under study that it is doubtful that such things as lamp variations would permit meaningful measurements to be made.

Charge Transfer Spectra. After LaLonde's report[2] of the charge transfer complex between Br_2 and phenylcyclopropane, which we confirmed, we examined some of the diarylcyclopropanes for similar complexes.

Scans were run from 310 to 420 nm for two conditions of relative concentration: 1:1 at ca. 5×10^{-4} *M* in both the cyclopropane and Br_2, and at 5×10^{-4} *M* in bromine and ca. 10^{-2} *M* in the cyclopropane. The value of the absorbance at 420 nm was used to generate the appropriate absorbance for bromine at other wavelengths. When the synthetic spectrum thus generated was subtracted from the measured spectrum the residue was taken as produced by the interaction of the cyclopropane and the bromine. Spectra run with the cyclopropane omitted and with the bromine omitted showed that the new absorption was not due to impurities, etc., in solvent or reactants. The region studied was limited by consideration of the effective range of the filter used in the kinetic studies.

The *cis*-diphenylcyclopropane initially showed a broad new absorption between 310 and 340 nm. Over 4–5 min in the dark this absorption increased and then died away. No reaction of the bromine was observed as measured by changes in its absorbance during this period. LaLonde's observations with the phenylcyclopropane case showed direct relation to bromine decline. Neither *trans*-diphenyl nor *trans*-*p*-methoxydiphenyl showed any absorbance in the scanned region.

Discussion

From our kinetic studies, it is clear that for these aryl cyclopropanes the rate expression in the concentration range of 3×10^{-3} to 5×10^{-2} *M* is first order in cyclopropane and half order in bromine.

Our data seem to fit a classical radical chain reaction best where product is 1,3-dibromo-1,3-diarylpropane.

$$Br_2 \xrightarrow[k_1]{h\nu} 2Br \quad (1)$$

$$Br + \text{cyclopropane} \xrightarrow{k_2} \text{radical} \quad (2)$$

$$\text{radical} + Br_2 \xrightarrow{k_3} \text{product} + Br \quad (3)$$

$$2Br \xrightarrow{k_4} Br_2 \quad (4)$$

$$\text{radical} + Br \xrightarrow{k_5} \text{product} \quad (5)$$

$$2\,\text{radical} \xrightarrow{k_6} \text{dimer} \quad (6)$$

If one assumes a nearly photosteady state with step 4 as the only significant termination step for the 10^{-3} *M* range, the rate expression fits the experimentally determined one.

Such a classical radical mechanism leads to prediction of certain properties for the reaction which a reading of the literature finds wanting or unusual.

The first question is the lack of significant competition from hydrogen abstraction rather than ring opening. The available literature on chlorine reactions under similar conditions shows that the abstraction process does compete when the energetically more favorable HCl is formed rather than HBr.[14,15]

Table III
Runs Representative of the Extremes in the Kinetic Runs (from a Total of 42 Runs)[a]

Substituent	Cyclopropane, mol/l. × 10^3	Bromine, mol/l. × 10^3	Slope y × 10^3	Correlation coefficient	Grouping
cis-*m*-Cl	3.32	3.17	6.12	0.9926(7)	Poorest correlation
trans-*p*-CH_3O	3.04	3.13	5.86	0.9931(7)	
trans-*p*-H	4.06	4.18	5.23	0.9938(9)	
cis-*p*-Cl	3.26	3.15	6.43	0.9999(9)	Best correlation
cis-*m*-Cl	3.42	3.17	5.14	0.9999(7)	
trans-*p*-F	3.02	2.84	4.77	0.9999(3)	
cis-*p*-CH_3O	2.68	3.18	1.56	0.9997(2)	Cases where one reactant
trans-*p*-F	3.34	3.03	6.95	0.9997(2)	is over 10% more con-
trans-*m*-Cl	3.19	2.84	3.35	0.9984(2)	centrated than the other
trans-*p*-Cl	3.19	2.84	4.04	0.9996(4)	
trans-*p*-H	3.59	3.17	7.92	0.0995(5)	
cis-*p*-CH_3O	3.73	3.17	10.89	0.9986(4)	
cis-*p*-CH_3O	3.73	3.17	10.29	0.9993(0)	
trans-*p*-H	3.59	3.17	7.61	0.9995(6)	

[a] Runs with the cyclopropane at 10 times the bromine concentration were made. Because the analysis required work-up before GC analysis of intermediate reaction samples and only the peaks of the starting materials were cleanly resolvable, the values obtained are, at best, rough. They did, nevertheless, give 0.995 for a correlation coefficient for the ½ order equation. These were not included in the 42 runs of this table.

One of these studies is on unsubstituted cyclopropane.[15] The photolysis was carried out in CCl_4 at 0 and at 68°C. As seen with the bromine (cf. below), the lower temperature favored the ring opening but substitution was a major process. Use of *tert*-butyl hypochlorite gave only substitution on cyclopropane itself. Rather than ring substitution, however, these workers found that methylcyclopropane gave little ring opening and a good deal of methyl substitution.

The second case is bicyclopentane,[14] where one must tread with care. Nevertheless, the two processes competed about equally at moderate temperature under irradiation. Ring opening was favored by lower temperature and both processes favored by peroxide addition.

The competition between substitution and ring opening when bromine is the halogen and the substituents are alkyl groups may not be only radical competition as the use of more polar solvents leaves doubts.[16,17] Nevertheless, when the temperature was held at −78°C and photolysis performed, rapid ring opening was the nearly exclusive result for an entire series of alkyl-substituted cyclopropanes.[16] The reaction of 1,2,3-trimethylcyclopropane gave some substitution of the product but no substitution that could be shown to be solely a reaction of the starting material.[17]

Only competition between aromatic substitution and ring opening occurs at low temperature in the dark for phenylcyclopropane with Br_2. Cyclopropane ring substitution products are not seen.[2,18]

In itself, it does not seem surprising that there should be a balance between these competing reactions for the radical processes and, as such, merely tells us that the E_a for ring opening is less than that for C–H bond breaking.

The effects of inhibitors and initiators in the aromatic systems is more of a problem for the proposed mechanism. For the 1,2-diaryl cases the literature records the following.

Levina[18] tried to brominate the diphenyl case using *N*-bromosuccinimide at 80° in carbon tetrachloride. Use of irradiation in conjunction with or separate from benzoyl peroxide or AIBN had no effect on the reaction. No product was formed. He also reported this to be true for phenylcyclopropane. LaLonde[2] has confirmed his results.

When studying the ionic reaction of the 1,2-diphenyl compound LaLonde[2] added isoamyl nitrite to the reaction carried out in chloroform. The rate of the trans isomer dropped by about a third but that of the cis isomer increased by about the same factor.

Studies with phenylcyclopropane as the substrate offers further signs of unusual lack of dependence on general radical conditions. The presence of trinitrobenzene had no effect on the photolytic halogenation.

Attempts to get other radical reactions to occur were equally unsuccessful as conditions that led to rapid addition of thiolacetic acid to olefins gave no reaction with the phenylcyclopropane substrate. Attempts to add bromotrichloromethane to the ring under irradiation and with benzoyl peroxide gave only the 1,3-dibromo-1,3-diphenylpropane in low yield after 48 hr. The tetrahalide had decomposed to give bromine.

On the other hand, addition of hydrolyic solvents and amines to these 1,2-diarylcyclopropanes under photolytic conditions has been reported.[19] The author suggests that the process involves a reaction of the cyclopropane excited state.

In the face of such conflicting data the radical nature of the process is in doubt, although the conditions otherwise are certainly strongly suggestive of such a mechanism. The LaLonde[2] proposal that a charge transfer absorption for a complex of the halogen molecule and the cyclopropane is implicated, coupled with his observation of such absorptions, seemed to circumvent this problem. Our rate equation and the failure to find significant charge transfer bands in the region open to our filter system seems to place this solution to the inhibitor–initiator insensitivity in doubt also.

Our mechanism is not far from that proposed by Shea and Skell[16] except that they propose a "solvated" bromine atom associated with the aromatic ring as a step between 1 and 2. Their proposal then explains the ring opening as controlled by transfer of the bromine atom to the benzyl carbon.

In analogy with other ring opening studies, reduction for example, one might note that the association is with the most highly conjugated bond of the cyclopropane ring as noted by Norin and Dauben.[20] Perhaps the association can be visualized as an edge complex such as proposed by Ketley[21] and Irwin.[22]

There is not sufficient definition in the data on stereochemical relationships to permit comment on these proposals. Although our *dl* vs. meso ratios for the dibromides from the cis and trans symmetrical cyclopropanes are different from 50:50 and from LaLonde's, it is not clear that the separation technique has not modified them. We found that the separated 1,3-dibromides from the *p*-F, *m*-Cl, and *p*-methoxy series were also resolvable into *dl* and meso in the NMR and were essentially 50:50 in all cases.

Our Hammett treatment, at best rather qualitative, could certainly be accommodated by either approach of the bromine atom in search of electron density.

It can be said that it does not appear that the reaction of cyclopropane with bromine atoms in nonpolar solvents is fully understood.

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Registry No.—1,2-Dibromo-1,3-diphenylpropane, 56363-42-9; *trans*-1,3-diphenylpropene, 3412-44-0; 1,3-dibromo-1,3-diphenylpropane, 17714-40-8; 1,3-diphenyl-1,3-propanediol, 5471-97-6; 1-*p*-(chlorophenyl)-3-phenyl-1,3-dibromopropane, 56363-43-0; 1-(*p*-chlorophenyl)-2-phenyl-1,3-dibromopropane, 56363-44-1; 1-(*p*-fluorophenyl)-2-phenyl-1,3-dibromopropane, 56363-45-2; 1-(*m*-chlorophenyl)-2-phenyl-1,3-dibromopropane, 56363-46-3.

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Reactions of Diaryliodonium Salts with Sodium Alkoxides‡

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The reaction of a diaryliodonium salt with a metal alkoxide to give an alkyl aryl ether plus an aryl iodide is considered to be of synthetic utility. We have found, however, that an aromatic hydrocarbon, an aryl iodide, and an aldol resin (or a ketone if the alkoxide is derived from a secondary alcohol) are frequently the major products. We now present evidence that the latter products arise by a radical chain reaction, while the former products are the result of an aromatic nucleophilic displacement reaction. Furthermore, the yields of alkyl aryl ether plus aryl iodide can be increased markedly by the addition of a radical trap to the reaction mixture to inhibit the undesired, competing process. Some important solvent effects and differences with triarylsulfonium alkoxide reactions are also discussed.

Several widely used textbooks of organic chemistry depict the reaction of a diphenyliodonium cation with an alkoxide anion (or other base) to produce a phenyl alkyl ether plus iodobenzene as an example of an aromatic SN reaction and as a potentially useful synthetic procedure. One of the major purposes of this article is to point out that, under ordinary conditions of reaction, the alkyl aryl ether is frequently a minor product, the major products being benzene, iodobenzene, and an aldol resin (or a ketone, depending on the structure of the alkoxide ion). However, with the use of a suitable additive, such as 1,1-diphenylethylene, the alkyl aryl ether becomes the major product in all cases.

Diaryliodonium salts are known to be versatile arylating agents.[1-3] Whereas the early mechanistic studies provided indications that the reactions of diaryliodonium cations with bases were of the aromatic SN type,[4-6] later investigations provided convincing evidence that radical reactions could also take place.[7-11] That aromatic SN reactions of diaryliodonium cations with aromatic amines can take place with prior formation of a hypervalent iodine intermediate was demonstrated by Reutov and his coworkers,[12-15] who also showed that the corresponding reactions with aliphatic amines have an important radical component.[16-19]

We have recently demonstrated that radical chain reactions compete with aromatic SN reactions when diaryliodonium salts are treated with sodium alkoxides.[20] The same combination of mechanistic pathways has been shown to occur in the reactions of triarylsulfonium salts with sodium alkoxides,[21] and furthermore, it has been demonstrated that the balance between these routes is a delicate one, being influenced strongly by various factors, such as the presence of radical inhibitors, the polarity of the solvent, and the structure of both the triarylsulfonium cation and the alkoxide anion.[22] We now wish to report in detail on the factors which influence the ratio of the competing modes of reaction of diaryliodonium cations with alkoxide anions.

The most striking demonstration of the occurrence of competing aromatic SN and radical chain reactions in the reaction of a diaryliodonium salt with a sodium alkoxide is the effect of the addition of a radical inhibitor, such as 1,1-diphenylethylene. For example, the reaction of 5.0×10^{-4} mol of phenyl-*p*-tolyliodonium fluoroborate with 7.0×10^{-4} mol of sodium ethoxide in 2.0 ml of ethanol solution at 71° for 90 min was found to give phenetole (9.5% yield), *p*-methylphenetole (2.6%), benzene (34%), toluene (36%), iodobenzene (56%), *p*-iodotoluene (47%), and a mixture of biaryls (0.01%). When the same reaction was carried out in the presence of 5.0×10^{-4} mol of 1,1-diphenylethylene, however, there was obtained phenetole (55%), *p*-methylphenetole (22%), benzene (5.2%), toluene (4.8%), iodobenzene (31%), and *p*-iodotoluene (62%). These and additional data are shown in Tables I–IV. Clearly, 1,1-diphenylethylene is functioning as an inhibitor of a radical reaction which produces benzene and toluene; however, the presence of 1,1-diphenylethylene does not affect the rate of production of phenetole and *p*-methylphenetole, which arise by conventional aromatic SN reactions. It is evident from the data presented in Tables I–IV that the presence of a relatively small amount of diphenylpicrylhydrazyl in the reaction solution also results in the inhibition of the radical chain reactions.

As previously suggested,[20] and in analogy with the chain mechanism indicated for the decomposition of triarylsulfonium alkoxides,[21,22] a possible radical chain process for the conversion of diphenyliodonium isoproxide, for example, to a mixture of benzene, iodobenzene, and acetone is shown below.

1. Initiation

$$Ph_2I^+ + Me_2CHO^- \rightleftharpoons Ph_2I{-}O{-}CHMe_2 \rightleftharpoons (Ph_2I\cdot, \cdot O{-}CHMe_2)^{o} \rightleftharpoons Ph_2I\cdot + \cdot O{-}CHMe_2 \rightleftharpoons Ph\cdot + PhI$$

[1] Contribution from (a) Universidad Simon Bolivar, (b) Johnson State College, (c) Instituto Venezolano de Investigaciones Cientificas, (d) The University of Massachusetts.

Table I
Reactions of $Ph_2I^+X^-$ with NaOR at 71°C[a,b]

Mol X^-	Mol RO^-	Time, min	Additive	% yield products: Acetone	Benzene	PhOR	PhI	Ph–Ph
0.0007	0.0014							
BF_4^-	CH_3O^-	15 hr			7	79	91	0.3
BF_4^-	CH_3O^-	15 hr	DPE[c]		Tr	80	91	0.0
0.005	0.0007							
Cl^-	*i*-PrO^-	90		74	80	49	69	0.1
0.0005								
BF_4^-	*i*-PrO^-	90		68	73	51	72	0.2
BF_4^-	*i*-PrO^-	90	DPPH[d]	37	51	20	100	Tr
BF_4^-	*i*-PrO^-	90	G[e]	38	46	16	100	Tr
BF_4^-	*i*-PrO^-	90	DPE[f]	33	32	69	100	0.0
BF_4^-	*i*-PrO^-	90	TP[g]	34	62	0.0	100	Tr
BF_4^-	*i*-PrO^-	90	BT[h]	45	90	0.0	71	0.1
0.00035								
BF_4^-	*i*-PrO^-	90		72	74	53	73	0.1
No salt[i]	*i*-PrO^-	90		0.0	0.0	0.0	100	

[a] Two milliliters of the alcohol corresponding to the alkoxide ion used as solvent. Argon atmosphere employed. [b] Diphenyliodonium iodide is insoluble in alcohol. Any iodide ion produced in the reaction mixture containing unreacted Ph_2I^+ causes a precipitate of the iodide to form; 9% was obtained in the fourth experiment and 5% in the tenth. [c] 0.007 mol of 1,1-diphenylethylene added, of which not less than 90% recovered unchanged. [d] 0.0002 mol of diphenylpicrylhydrazyl. [e] 0.0002 mol of galvinoxyl. [f] 0.0005 mol of 1,1-diphenylethylene added, of which not less than 90% recovered unchanged. [g] 0.0007 mol of thiophenol added. Ph_2S obtained in 36% yield. [h] 0.0007 mol of 1-butanethiol added. PhSBu obtained in 21% yield. [i] Control experiment with 0.00055 mol of PhI.

2. Propagation (Scheme I)

$$Ph_2I—O—CHMe_2 + Ph\cdot \longrightarrow PhH + Ph_2I—O—\dot{C}Me_2$$

$$Ph_2I—O—\dot{C}Me_2 \longrightarrow Ph_2I\cdot + CH_3COCH_3$$

$$Ph_2I\cdot \longrightarrow Ph\cdot + PhI$$

3. Termination

$$2Ph\cdot \longrightarrow Ph—Ph$$

$$Ph\cdot + Me_2CH—O\cdot \longrightarrow Ph—O—CHMe_2$$

[a] $(Ph\cdot, Ph—\dot{I}—O—CHMe_2)$ may be formed at this point.

In addition to the inhibition data cited above, there are several additional facts which support the concept that a radical chain reaction is competing with an aromatic SN reaction. (1) The use of a phenyl-*p*-tolyliodonium salt leads to the formation of nearly equal amounts of benzene and toluene; this lack of discrimination in the formation of aryl radicals has been observed in other radical reactions of diaryliodonium salts.[7] (2) The apparent rates of the radical processes vary with the alkoxide ion used in the order *i*-$PrO^- > EtO^- > MeO^-$. The order of carbinyl C–H bond dissociation energies for the corresponding alcohols is $H–CH_2OH > H–CH(CH_3)OH > H–C(CH_3)_2OH$,[23] and therefore the apparent rate sequence cited above is that expected in consideration of the respective propagation steps. (3) Small amounts of biaryls, the products of chain termination reactions, are found in the reaction mixtures. (4) The fact that about three times as much phenetole as *p*-methylphenetole is produced in the reaction of phenyl-*p*-tolyliodonium fluoroborate with sodium ethoxide constitutes valid additional evidence for the aromatic nucleophilic substitution process.[21,22] Whether the displacement takes place on the cation or on the adduct of the cation with ethoxide ion, p-$CH_3C_6H_4(OC_2H_5)C_6H_5I$, as suggested by Reutov and his coworkers[12,13] for related systems, is unknown at present.

All of the points covered above represent parallels in the behavior of diaryliodonium and triarylsulfonium salts toward sodium alkoxides. However, there are also some important differences, the major ones having to do with (1) the addition of nonpolar cosolvents to the alcohol reaction mixtures; (2) the reactions of the salts with benzoyl peroxide in alcohol solution; and (3) the effects of oxygen on the reactions.

Table II
Reactions of $Ph_2I^+BF_4^-$ with Sodium Ethoxide in the Atmosphere and under Argon[a]

	% yield products: No additive	1 equiv DPE	0.05 equiv DPPH
	Air		
PhH	66	6.2	53
PhOEt	14	77	26
PhI	92	98	92
Ph–Ph	0.32	0.26	0.26
% additive recovered		95	
	Argon		
PhH	68	6.0	50
PhOEt	14	80	28
PhI	92	100	99
Ph–Ph	0.42	0.29	0.17
% additive recovered		88	

[a] All reactions were carried out with 0.0005 mol of $Ph_2I^+BF_4^-$ and 0.0007 mol of sodium ethoxide in 2 ml of ethanol solution at 71° for 90 min. For the additives, 1.0 equiv = 0.0005 mol; 0.05 equiv = 0.000025 mol.

Let us first consider the anticipated effect when the polarity of the solvent is decreased by the addition of a hydrocarbon cosolvent in, for example, the reaction of diphenyliodonium fluoroborate with sodium ethoxide in ethanol. Since the coming together of two ions with unlike charges is always a fast process,[24] the initial step of the initiation process of the radical chain reaction of the type depicted above is almost certainly faster than the subsequent steps, those that give rise to radicals. Therefore, since there would be no marked effects of changes of solvent polarity on the rates of the radical processes, the change from 100% ethanol to an ethanol–toluene or ethanol–hexane mixed solvent system would exert no major influence on the rate of for-

Table III
Reactions of PhI^+PhMe-*p* BF_4^- with Sodium Ethoxide under Argon[a]

Additive	% additive recovered	% yield products					
		p-MePhOEt	PhOEt	*p*-Me-Ph-I	PhI	$PhCH_3$	PhH
None[b]		2.6	9.5	47	56	36	34
1 equiv *cis*-stilbene	100[c]	15	49	65	32	17	15
0.14 equiv *trans*-stilbene		8.7	29	57	34	24	24
1 equiv DPE	87	22	55	62	31	4.8	5.2
5 equiv DPE	87	16	59	59	20	1.9	3.5
0.05 equiv DPPH		11	39	60	37	21	18
1.0 equiv DPPH		2.9	12	45	29	9.4	13

[a] All reactions were carried out with 0.0005 mol of *p*-$MePhI^+PhBF_4^-$ and 0.0007 mol of sodium ethoxide in 2 ml of ethanol solution at 71° for 90 min. For the additives, 1.0 equiv = 0.0005 mol; 0.05 equiv = 0.000025 mol; and 5.0 equiv = 0.0025 mol. [b] Trace amounts of biaryls were detected in the first and fifth experiments. [c] Since *cis*-stilbene is converted to the trans isomer at the injection port, it was analyzed in the latter form.

Table IV
Reactions of PhI^+PhMe-*p*-BF_4^- with Sodium Ethoxide in the Atmosphere[a]

Additive	% additive recovered	% yield products					
		p-MePhOEt	PhOEt	*p*-Me-Ph-I	PhI	PhMe	PhH
None[b]		1.7	7.2	45	55	37	33
1 equiv *cis*-stilbene	100[c]	16	50	68	28	16	14
0.13 equiv *trans*-stilbene[d]		9.4	28	58	35	23	24
1 equiv DPE	89	25	51	60	31	4.3	4.8
5 equiv DPE	92	14	58	59	19	2.5	4.3
0.05 equiv DPPH		8.7	42	62	34	21	19
1.0 equiv DPPH		2.0	10	46	31	12	15

[a] All conditions are parallel to those given in Table III, with the exception that the reactions were carried out in the atmosphere. [b] Trace amounts of biaryls were detected in the first and sixth experiments. [c] Converted to *trans*-stilbene at the injection port. [d] Solubility limit.

mation of benzene. However, since the aromatic nucleophilic substitution reaction involves dissipation of charges as the transition state is formed, the change from a more polar to a less polar solvent would cause acceleration of this reaction. It therefore follows that, with a decrease of the polarity of the solvent, the ratio of nucleophilic aromatic substitution product (phenetole) to the radical products (benzene and acetaldehyde, which subsequently forms an aldol resin in the strongly basic medium) would increase. This was the result we found in the reaction of triphenylsulfonium bromide with sodium ethoxide, and, as shown by the data presented in Table V, it also appears to be the result in the reaction of diphenyliodonium fluoroborate with sodium ethoxide. However, inasmuch as aromatic hydrocarbons are known to inhibit other radical chain reactions,[25-27] it was deemed necessary to evaluate the possible role of toluene (and *n*-hexane) as a specific inhibitor of the radical chain reaction as against its effect as a relatively nonpolar component of the solvent system. Unlike the situation with triphenylsulfonium ethoxide, where no specific effect was found,[22] it is obvious from the data shown in Table VI that the cosolvent toluene (or *n*-hexane) functions as a specific inhibitor in the case of the diphenyliodonium ethoxide decomposition, as well as exerting the nonpolar solvent effect. *n*-Dodecane and 1-phenylhexane were detected in the reaction mixtures by the "mixture VPC test" when *n*-hexane was used as the cosolvent, and the presence of several additional peaks having similar retention times indicated the presence of isomeric dodecanes and phenylhexanes. No bibenzyl was detected in the reaction mixtures when toluene was used as the cosolvent, and this suggests that the specific inhibition caused by the presence of this aromatic hydrocarbon is the result of complexation between one or more of the radical chain carriers and toluene, of the type described by Russell.[28-31]

A possible explanation of this contrasting behavior can be gleaned from the reactions of triarylsulfonium salts[22] with benzoyl peroxide in alcohol as against those of diaryliodonium salts.[32] No more than trace amounts of toluene and bis(*p*-tolyl) sulfide are formed by treatment of tris(*p*-tolyl)sulfonium bromide with benzoyl peroxide in isopropyl alcohol solution,[22] but, as reported previously[32] (and also shown in Table VII), high yields of benzene and iodobenzene (plus a small amount of biphenyl) are obtained by treatment of diphenyliodonium salts with benzoyl peroxide in isopropyl alcohol. Thus, another sequence of propagation steps is available for the conversion of the diphenyliodonium cation to benzene plus iodobenzene, as shown below.

1. Propagation (Scheme II)

$$Ph\cdot + Me_2CHOH \longrightarrow PhH + Me_2\dot{C}{-}OH$$

$$(Ph)_2I^+ + Me_2\dot{C}{-}OH \longrightarrow (Ph)_2\overset{+\cdot}{I}{-}\overset{OH}{\overset{|}{C}}Me_2$$

$$(Ph)_2\overset{+\cdot}{I}{-}\overset{OH}{\overset{|}{C}}Me_2 \longrightarrow Ph\cdot + Ph{-}\overset{+}{I}{-}\overset{OH}{\overset{|}{C}}Me_2$$

2. Termination

$$2Ph\cdot \longrightarrow Ph{-}Ph$$

$$Ph\cdot + Me_2\dot{C}{-}OH \longrightarrow Me_2\overset{OH}{\overset{|}{C}}{-}Ph$$

3. Subsequent Reaction

$$Ph{-}\overset{+}{I}{-}\overset{OH}{\overset{|}{C}}{-}Me_2 \longrightarrow PhI + Me{-}\overset{O}{\overset{\|}{C}}{-}Me + H^+$$

Obviously, the same or closely related[33] types of propagation steps could be operative in the reactions of diarylio-

Table V
Effects of Toluene or *n*-Hexane as Cosolvents on the Reactions of Diphenyliodonium Fluoroborate with NaOEt[a]

Solvent		% yield products			
% EtOH	% additive	PhH	PhOEt	PhI	Ph–Ph
100		62	15	86	0.21
90	10 (*n*-hexane)[b]	35	50	97	0.13
60	40 (*n*-hexane)	32	54	98	0.12
50	50 (*n*-hexane)	26	60	96	0.12
90	10 (toluene)[c]	49	34	90	0.19
80	20 (toluene)[c]	35	50	91	0.21
70	30 (toluene)[c]	29	57	100	0.30
60	40 (toluene)[c]	23	62	98	0.26
50	50 (toluene)[c]	20	66	100	0.26

[a] 5.0×10^{-4} mol of $Ph_2I^+BF_4^-$ treated with 7.0×10^{-4} mol of NaOEt in 2 ml of specified solvent at 71° for 90 min (argon atmosphere). [b] *n*-Dodecane and 1-phenylhexane were detected by GLC, comparison being made with known samples. Additional peaks indicated presence of isomeric dodecanes and phenylhexanes. [c] No bibenzyl detected in product.

Table VI
Effects of Small Amounts of Toluene, Benzene, and *n*-Hexane on the Reactions of Diphenyliodonium Fluoroborate with NaOEt[a]

Additive	% yield products			
	PhH	PhOEt	PhI	Ph–Ph
0.7 equiv *n*-hexane	50	28	89	0.09
1.5 equiv *n*-hexane	39	42	92	0.10
1.0 equiv toluene[b]	51	32	99	0.28
0.25 equiv toluene[b]	67	19	95	0.22
1.0 equiv benzene	60[c]	23	90	0.35
0.25 equiv benzene	65	19	95	0.25

[a] Concentrations of reagents and conditions the same as specified in Table V; solvent, absolute EtOH. [b] Specific inhibition of the chain reaction without formation of bibenzyl suggests that a molecular complex of one or more of the radical chain carriers with toluene is being formed.[28-31] [c] 100% recovery of additive assumed.

donium salts with sodium alkoxides. Since the chain carriers in the diaryliodonium salt reactions differ from those in the triarylsulfonium salt reactions in their behavior toward a number of reagents (toluene, *n*-hexane, oxygen of the air), it appears likely that at least some of the chain carriers in the two sets of reactions have fundamentally different structures. Furthermore, since the types of propagation steps shown in Scheme II do not occur to any major extent with triarylsulfonium salts,[22] it appears likely that the triarylsulfonium salts undergo mainly the Scheme I propagation steps. This line of reasoning thus leads to the conclusion that the diaryliodonium salts undergo mainly the Scheme II propagation sequence. It should be mentioned that this conclusion does not change in any way the argument about the effect of a change in solvent polarity on the relative rates of the competing aromatic SN reactions and the radical chain reactions. That diaryliodonium ions have a greater tendency than triarylsulfonium ions to undergo the Scheme II sequence of propagation reactions is probably attributable in part to the known fact that hypervalent molecules (or intermediates) are more likely to exist the larger the donor atom, the lower the group in the periodic table, and the higher the electronegativity of the ligand.[34,35] An important steric factor could also be operative.

Table VII
Reactions of $Ph_2I^+BF_4^-$ with Benzoyl Peroxide[a]

Concn benzoyl peroxide, *m*	Alcohol	% yield products						
		Acetone	Benzene	Ether	Iodobenzene	Biphenyl	H^+, mm	H^+, % yield
0.00025	EtOH		81	Tr	78	2.1	0.84	84
0.00025	*i*-PrOH	107	89	Tr	90	2.1	0.96	96
0.00010	*i*-PrOH	84	73	Tr	73	1.2	0.76	76

[a] All reaction solutions contained 0.0005 mol of $Ph_2I^+BF_4^-$ and were carried out at 71°C for 90 min. [b] Percent yield based on formation of 2 mm of H^+/mm of iodonium salt.

As shown by the data in Tables II–IV, reactions of diaryliodonium salts with sodium alkoxides carried out both under argon and in the air give identical yields of products. This is in marked contrast to the behavior of triarylsulfonium salts.[22] As mentioned above, this reinforces the argument that there must be a fundamental difference in the structures of some of the chain carriers involved in the respective major sequences of the propagation reactions.

In the reactions of diphenyliodonium fluoroborate with sodium isopropoxide in isopropyl alcohol solution, iodobenzene is formed in quantitative yield when 1,1-diphenylethylene, diphenylpicrylhydrazyl, or galvinoxyl is present as an additive, but the yield drops to 72% (with a corresponding increase in the combined yield of benzene and phenyl isopropyl ether) in the absence of these radical scavengers (Table I). It is obvious from the control experiment, in which no iodobenzene is consumed when it is treated with sodium isopropoxide in isopropyl alcohol under the same conditions as used for the diphenyliodonium salt reactions, that isopropoxide ion does not enter into an aromatic SN reaction with iodobenzene. Thus, the loss of iodobenzene in the simple diphenyliodonium isopropoxide reaction must be the result of a radical chain process, one which has already been discussed in detail by Bunnett and Wamser.[36,37] The radical scavengers mentioned above inhibit this radical chain reaction and therefore permit the iodobenzene to be isolated in 100% yield. Bunnett and Wamser[37] have provided examples of similar inhibition by other well-known radical traps.

The effects of thiophenol and 1-butanethiol, respectively, on the reaction of diphenyliodonium fluoroborate with sodium isopropoxide warrant comment. As shown by the data in Table I, addition of thiophenol causes the yields of acetone, benzene, and phenyl isopropyl ether to drop markedly as against the results when no additive is present. However, iodobenzene is produced in 100% yield when thiophenol is present, but in only 72% yield when it is absent. On the other hand, with 1-butanethiol as an additive, the yields of acetone and ether drop as against the results when no additive is present, but the yield of benzene increases sharply. Moreover, destruction of iodobenzene takes place, as the yield is but 71%. Thiols are known to be efficient hydrogen transfer agents in radical processes, and aromatic thiyl radicals are less reactive than aliphatic thiyl radicals, presumably owing in large part to resonance stabilization in the former.[38-41] Being better electron transfer agents than alkoxide ions, the anions derived from thiophenol and 1-butanethiol would be expected to initiate radical processes. However, whereas the more reactive 1-butanethiyl radical would readily function as a chain carrier, leading to an increase in the yield of benzene from the diphenyliodonium salt and to destruction of iodobenzene, the more stable benzenethiyl radical inhibits such processes. Of course, both the 1-butanethiolate and benzenethiolate an-

ions are strong nucleophiles toward carbon, and aromatic SN reactions with the diphenyliodonium cation account for the formation of *n*-butyl phenyl sulfide and diphenyl sulfide, respectively (Table I).

From the data given in Tables III and IV, it is evident that 1,1-diphenylethylene is more efficient than *cis*-stilbene as an inhibitor of the radical chain reaction leading to aromatic hydrocarbons as products. This parallels the data on "methyl affinities" compiled by Szwarc and his coworkers,[42-48] which, in turn, parallels the relative rates of addition of phenyl radicals to the unsaturated systems.[49]

We have demonstrated previously[50] that 4-methylbenzyne (generated from the appropriate diazonium carboxylate) adds an alcohol to give a mixture of 3-alkoxytoluene and 4-alkoxytoluene. Since 4-alkoxytoluenes only are found in the alkyl tolyl ether fractions from the reactions of phenyl-*p*-tolyliodonium salts with sodium alkoxides, it is clear that a benzyne type of intermediate is not involved in the formation of the ethers.

Experimental Section

Melting points and boiling points are uncorrected. Gas chromatography was performed on an F & M 609 flame ionization gas chromatograph equipped with a 6-ft 10% SE-30, 100/100 Anakrom column or a 5-ft Carbowax 20M column.

Infrared spectra were obtained by use of a Beckman IR-10 spectrophotometer, and a Varian A-60 NMR spectrophotometer was used for all NMR determinations. Ultraviolet spectra were obtained by use of the Cary 14 spectrophotometer.

Diphenyliodonium Bromide. This salt, mp 211–213° dec, was prepared by the method of Beringer et al.[51,52]

Diphenyliodonium Fluoroborate. Material of mp 134–136° was obtained as described in the literature.[52]

Diphenyliodonium Chloride. This salt, mp 228–229° dec, was obtained as described in the literature.[51,52]

Phenyl-*p*-tolyliodonium Fluoroborate. This salt, mp 121–123°, was prepared by the method of Neilands.[53]

Phenyl-*p*-tolyliodonium Iodide. This compound was obtained in quantitative yield by addition of a saturated solution of sodium iodide to an aqueous solution of phenyl-*p*-tolyliodonium fluoroborate. After recrystallization from chloroform–absolute ether, its mp was 155–157°.

Anal.[54] Calcd for $C_{13}H_{12}I_2$: C, 37.00; H, 2.86; I, 60.14. Found: C, 36.88; H, 2.97; I, 60.20.

Reactions of Diaryliodonium Salts with Sodium Alkoxides. All reactions, not specified otherwise, were carried out under an argon atmosphere. For these reactions, 50 ml of the respective alcohol solvents was deoxygenated and caused to react with sodium under argon. Appropriate volumes, as specified in the tables, were used for each reaction. The reaction tube, which had been flushed with argon after addition of the iodonium salt, was again flushed after addition of the alkoxide solution, the tube then being sealed under argon. For the reactions carried out in isopropyl alcohol, the temperature of the alcohol solution was maintained just below its boiling point during its reaction with sodium in order to accelerate the reaction and prevent the precipitation of sodium isopropoxide.

The sealed tubes were placed in an oil bath for the duration of the reaction time. After completion of the reaction, the tubes were opened, neutralized with 85% phosphoric acid (usually requiring only 2 drops from a micropipet), and immediately analyzed on a F & M 609 flame ionization gas chromatograph equipped with either a 6-ft 10% SE-30, 100/110 Anakrom or a 5-ft Carbowax 20M column.

To assure maximum reproducibility, the reactions were carried out in batches of four to eight at a time. Each batch contained the same alkoxide solution, and all reaction mixtures were deoxygenated in the same manner. The yields of the reaction products were determined by calculating the areas of the peaks observed in the vapor phase chromatogram. Approximate peak areas were obtained by multiplying the peak height by the peak width at half-height. Three standard solutions, having compositions near the approximate value obtained from the reaction mixture, were then prepared for each component and subjected to VPC analysis; the approximate areas were obtained and plotted graphically vs. composition. The actual product compositions were then obtained directly from the graphs.

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Registry No.—Diphenyliodonium bromide, 1483-73-4; diphenyliodonium fluoroborate, 313-39-3; diphenyliodonium chloride, 1483-72-3; phenyl-*p*-tolyliodonium fluoroborate, 2665-59-0; phenyl-*p*-tolyliodonium iodode, 56391-18-5; sodium iodide, 7681-82-5; sodium methoxide, 124-41-4; sodium isopropoxide, 683-60-3; sodium ethoxide, 141-52-6; benzoyl peroxide, 94-36-0.

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$$Ph—\overset{+}{I}—Ph + Me_2\dot{C}OH \longrightarrow Ph—I—Ph + Me_2\overset{+}{C}OH$$
$$Ph—I—Ph \longrightarrow PhI + Ph\cdot$$
$$Ph\cdot + Me_2CHOH \longrightarrow PhH + Me_2\dot{C}OH$$

This would imply that Ph_3S^+ is not able to accept an electron from $Me_2\dot{C}OH$ as readily as Ph–I^+–Ph, whereas $Ph_2C{=}CH_2$ can do so more readily.
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Reaction of Polyarylated Carbinols. V. Mechanism of the Reaction of Sodium Amide with 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol

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The kinetics of the reaction of 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (**1**) with <1 molar equiv of sodium amide in isoamyl ether (IAE) at 173° has been investigated. These reactions are observed to be first order in the disappearance of dienol **1** to produce the unconjugated ketone 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**2**) and the conjugated ketone 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**3**). The rate constant (k) obtained for the conversion of **1** to **2** with 10% sodium amide was found to be 5.27×10^{-5} sec^{-1} and 1.24×10^{-4} sec^{-1} for the conversion of **2** to **3**, while with 20% sodium amide the rate constants (k) obtained were 5.58×10^{-3} sec^{-1} and 5.31×10^{-4} sec^{-1}, respectively. The results obtained indicate that dienol **1** is not a quenching agent in the reaction, that the conversion of **2** to **3** is base catalyzed, and that **2** is a mandatory intermediate for the formation of **3**. These results lead to a simple proposed mechanism.

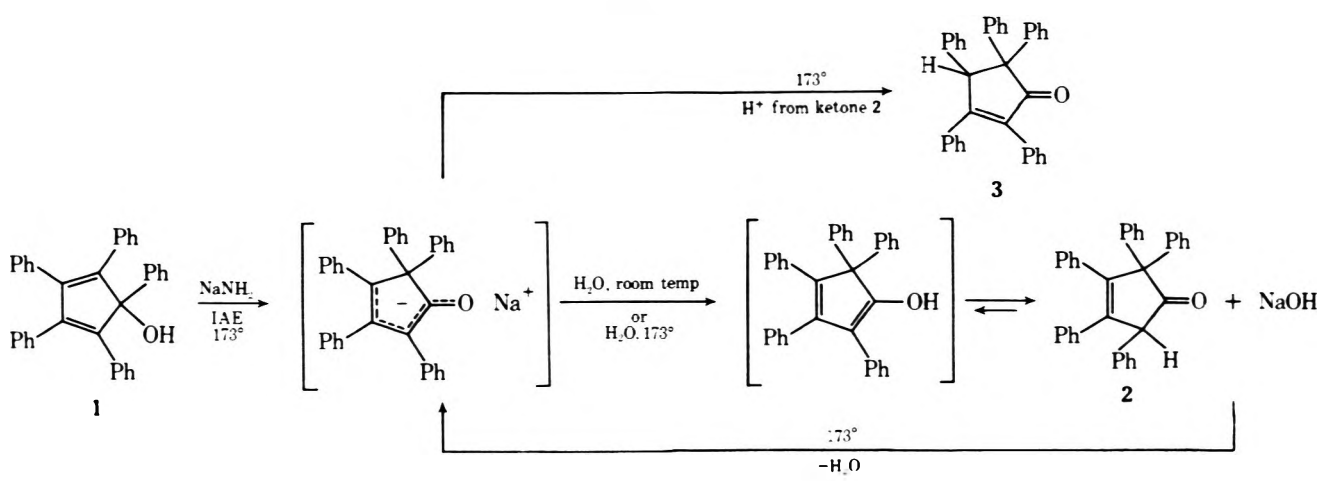
We have previously reported[1,2] that 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-one (**1**) undergoes a thermally induced suprafacial [1,5]-sigmatropic phenyl shift to produce 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**2**). We have also previously reported[3] that treatment of dienol **1**, ketone **2**, or 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**3**) at 173° in isoamyl ether (IAE) with 1 molar equiv of sodium amide, followed by cooling of the anion solution to room temperature and quenching with water, produced exclusively ketone **2**. However, if the anion solution prepared in the same manner from either dienol **1**, ketone **2**, or ketone **3** is quenched at 173° with water, ketone **3** was produced exclusively. These results led to the previously reported[3] mechanism shown in Scheme I.

With this mechanism established for the reaction of dienol **1**, unconjugated ketone **2**, or conjugated ketone **3** with equimolar amounts of sodium amide, it became of interest to investigate the mechanism of the reaction of dienol **1** with less than 1 molar equiv of sodium amide. This reaction appeared interesting, because unlike the previously studied reaction of dienol **1**, ketone **2**, or ketone **3** with 1 molar equiv of sodium amide, where the only quenching agent was the water externally added, in this reaction of the dienol **1** with <1 molar equiv of sodium amide, extensive high-temperature internal quenching by more than one source, the unreacted dienol **1** or the thermally formed ketone **2**, is possible. It thus became of interest to establish to what extent this internal quenching by dienol **1** or thermally formed ketone **2** was important to the production of products from this reaction. Moreover, a study of the reaction of dienol **1** with other bases[4] had already established that ketone **2** was a required intermediate in the conversion of dienol **1** to ketone **3** and it became of importance to establish mechanistically if ketone **2** was also a required intermediate for the production of ketone **3** in the reaction of dienol **1** with <1 molar equiv of sodium amide.

Results

The evaluation of the kinetic data was complicated by the lack of reliable values for the initial concentration of either the dienol **1** or the added sodium amide base. This was true because as can be seen from Scheme I, the conjugate base of ketone **2** and ketone **3** is a catalyst in this reaction which upon quenching affords ketone **2**. However, ketone **2**

Scheme I



is also formed directly from dienol 1 via an uncatalyzed thermal [1,5]-sigmatropic phenyl rearrangement. Therefore, the amount of ketone 2 formed from the enolate upon quenching must be subtracted from the observed total of ketone 2. Another complication was caused by the fact that the kinetically important amount of dienol 1 began at less than 100% because an amount of dienol 1 equal to the concentration of the sodium amide was converted immediately to the enolate ion at time zero.

With these limitations in mind we proceeded to evaluate the kinetic data. Since the concentration–time curves for the reaction resembled a consecutive first-order reaction sequence (eq 1), plots of the logarithm of the starting di-

$$\text{dienol 1} \xrightarrow{k_1} \text{unconjugated ketone 2} \xrightarrow{k_2} \text{conjugated ketone 3} \quad (1)$$

enol 1 vs. time were made to establish the first-order character of the disappearance of the dienol 1. These plots for the 10 and 20% sodium amide reactions were both linear. A linear least-squares computer program was used to evaluate the rate constant, k_1, and the initial concentration of the dienol 1. Evaluation of these data for the nominal 10% sodium amide reaction by use of the linear least-squares program afforded a $k_1 = 5.27 \times 10^{-5}$ sec^{-1} and an initial concentration of dienol 1 of 100 ± 2%, while in the nominal 20% sodium amide reaction this evaluation afforded a $k_1 = 5.58 \times 10^{-3}$ sec^{-1} and an initial concentration of dienol 1 of 81.3 ± 2%. With this information in hand, a nonlinear least-squares computer program was used to calculate the best value of k_2 based upon the exact solutions of the kinetic expression for calculating ketone 2 and ketone 3

$$\text{ketone 2} = \frac{k_1\,[\text{dienol 1}]_0}{k_2 - k_1}\,(e^{-k_1 t} - e^{-k_2 t})$$

$$\text{ketone 3} = [\text{dienol 1}]_0 \left[1 - \frac{(k_2 e^{-k_1 t} - k_1 e^{-k_2 t})}{k_2 - k_1}\right]$$

where $[\text{dienol 1}]_0$, the best value for the initial concentration of dienol 1, and the rate constant, k_1, were both determined from the linear least-squares computer program discussed above. The values required as input for this nonlinear least-squares program were k_1 and the true concentration of ketone 3 at the time specified. These values of ketone 3 were obtained by dividing the observed concentration of ketone 3, at the specified times, by the percentage of dienol 1 actually present at the start of the reaction (time zero); for 10% sodium amide, 95%, and for 20% sodium amide, 81.3%.

Using this nonlinear least-squares program and the input described above and allowing for numerous iterations until convergence and minimization was obtained afforded the best value of the rate constant, k_2, the corresponding calculated concentrations of unconjugated ketone 2 and conjugated ketone 3/$[\text{dienol 1}]_0$, and the initial concentration of dienol 1 of approximately 95 and 81.3% based upon the best calculated values of the k_2's for the 10 and 20% sodium amide reactions, respectively. Table I shows the data and the calculated concentrations, and also that the agreement of the observed and calculated values of unconjugated ketone 2 and conjugated ketone 3/$[\text{dienol 1}]_0$ are well within the uncertainty expected. The rate constants obtained for the two molar ratios of sodium amide used are $k_1 = 5.27 \times 10^{-5}$ sec^{-1} and $k_2 = 1.24 \times 10^{-4}$ sec^{-1} for the nominal 10% molar ratio sodium amide reaction, and $k_1 = 5.58 \times 10^{-3}$ sec^{-1} and $k_2 = 5.31 \times 10^{-4}$ sec^{-1} for the nominal 20% molar ratio sodium amide reaction.

Discussion

The addition of sodium amide to the dienol 1 is assumed to form the conjugate base of the alcohol immediately. The anion formed rearranges rapidly at the temperature of the reaction, 173°.

The reactions which can take place at this point are (1) thermal conversion[1,2] of the dienol 1 to unconjugated ketone 2, (2) quenching of the rearranged anion produced from the dienol 1 to yield either unconjugated ketone 2 or conjugated ketone 3, and (3) quenching of the rearranged anion produced by unconjugated ketone 2 to produce conjugated ketone 3.

Since quenching of the rearranged anion by either dienol 1 or unconjugated ketone 2 produces rearranged anion as a product, this process is catalytic and the amount of catalyst (rearranged anion) should remain constant.

The k_1 value for the thermal rate[2] (0% sodium amide) is 4.6×10^{-5} sec^{-1} and for the nominal 10 and 20% sodium amide reactions the k_1 values are 5.27×10^{-5} and 5.58×10^{-3} sec^{-1}, respectively. The upward trend of these values may be attributed to the differences in boiling point elevation produced by the differing concentrations of salt. Temperature increases in the boiling point of the IAE solvent of 1 and 2° have been observed in the solution containing the sodium amide over the temperature observed when the reaction is run with 0% sodium amide, and these increases in the boiling point of the solutions easily account for the slight upward trend of the rate constant k_1. Viewed together these results indicate that the rate of disappearance of the dienol 1 shows no significant dependence upon the concentration of the base. This observation rules out the possibility that the rearranged dienol 1 is quenched initially by the starting dienol 1 to yield either unconjugated ketone 2 or conjugated ketone 3. Therefore, the first step in this reaction must be the thermal rearrangement of the starting dienol 1 to unconjugated ketone 2.

The values of k_2 are 1.24×10^{-4} sec^{-1} (10% sodium amide reaction) and 5.31×10^{-4} sec^{-1} (20% sodium amide reaction). These pseudo-first-order rate constants become second-order rate constants when divided by the base concentration. The average concentration of catalyst in the 10% sodium amide reaction is 2.2×10^{-3} M (5.1%). Inspection of Table I shows that this computer calculated value of the catalyst concentration together with the computer calculated values of k_1 and k_2 gives a very accurate reproduction of the amount of conjugated ketone 3 produced as a function of time over the entire course of the reaction. In the 20% sodium amide reaction, extrapolation of the logarithm of the concentration of starting dienol 1 vs. time plot to the initial concentration of dienol 1 yields a concentration of 81.3% and, therefore, 18.7% (8.1×10^{-3} M) as the effective catalyst concentration. This value is exactly the same as that obtained from the linear least-squares computer program for the effective catalyst concentration. The mean concentration of catalyst as calculated from the difference between the measured and calculated amounts of unconjugated ketone 2 for all points is 17.4%; the average of the last four data points is 19%, in good agreement with the extrapolated value and the computer generated value of 18.7%.

If the conversion of unconjugated ketone 2 to conjugated ketone 3 is essentially base catalyzed, then the ratio $k_2(20\%)/k_2(10\%)$ should equal the ratio of the catalyst concentrations for the two reactions. The ratio of catalyst concentrations 19/5 = 3.8 can be compared with $5.31 \times 10^{-4}/1.24 \times 10^{-4} = 4.2$. The agreement between these ratios confirms the base catalysis quantitatively. In view of the medium effect previously noted for the k_1 values, it is reason-

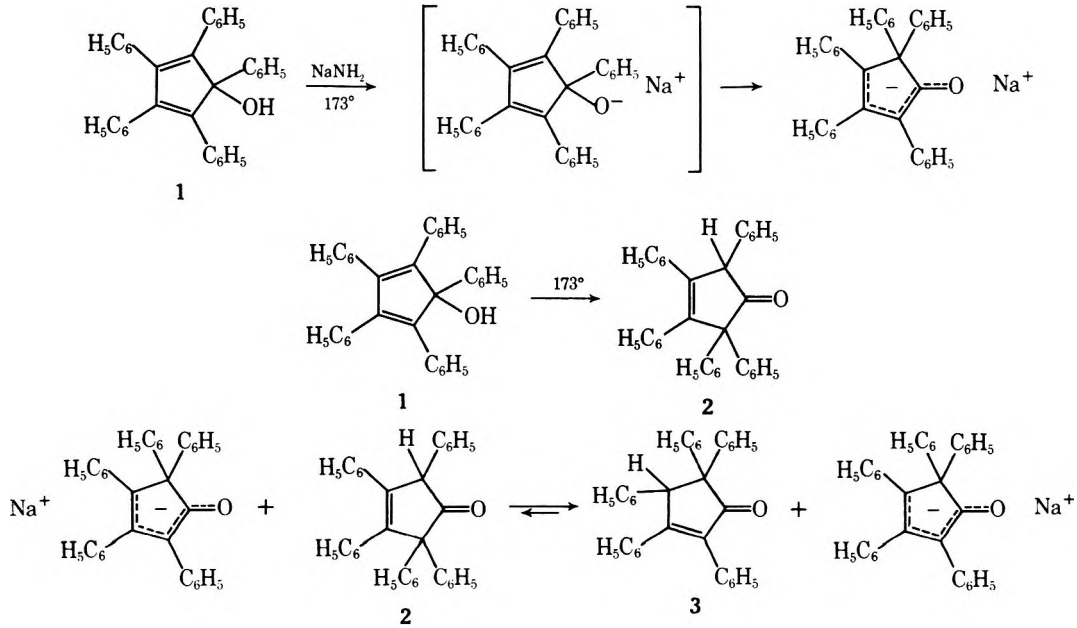
able to suppose that a portion of the variation between the two ratios obtained for the k_2's is due to a small difference in the temperature of the boiling IAE solution.

Although chemical experiments previously published[3,4] indicate that the conversion of unconjugated ketone **2** to conjugated ketone **3** is reversible, the data reported here indicate that the equilibrium constant for this conversion must be greater than 20 and, in these runs, indeterminable.

The possibility that the conversion of the conjugated base of dienol **1** (initial anion) to the rearranged anion was important was tested by taking a sample at relatively long times and quenching it at the reaction temperature (173°) followed by analysis. Such high-temperature quenches had previously[3] been shown to favor the formation of conjugated ketone **3** over unconjugated ketone **2**. Results of this quench established that conjugated ketone **3** was increased and unconjugated ketone **2** was decreased over their concentrations in a sample treated normally under the same conditions, but the remaining dienol **1** was unaffected and therefore no conjugate base of the dienol **1** was present under either analytical conditions at long times. The rearrangement reaction of the anion appears to be quite rapid at these temperatures and thus the catalyst is not the added sodium amide but is indeed the rearranged anion.

The kinetic data rule out the possibility of unconjugated ketone **2** or conjugated ketone **3** being obtained via the quench of the rearranged anion catalyst by the starting dienol **1**. The formation of conjugated ketone **3** results from the quenching of the rearranged anion catalyst by the intermediate unconjugated ketone **2** and indeed requires that the conversion of dienol **1** to conjugated ketone **3** take place via the intermediate unconjugated ketone **2**.

These results give rise to the following mechanism for the reaction of isoamyl ether (IAE) solutions of dienol **1** with sodium amide, which is simpler and slightly different from the mechanism previously proposed.[3]



Experimental Section

General. The gas–liquid partition chromatographic (GLC) analysis of samples was performed on a Bendix Model 2600 (flame) gas chromatograph and a Bendix Model 1200 recorder. The GLC was equipped with a 3 ft × 0.25 in. column packed with 3% QF-1 on Chromosorb W (H.P., mesh 100/120) support. Operating conditions were as follows: temperature of inlet 210°, detector 255°, injector 255°, column 210°, and He carrier gas flow rate of 80 ml/min. The retention times and relative molar response to a flame ionization detector, based on 100 for dienol **1**, for the materials involved were as follows: dienol **1**, 6 min 15 sec, 100; unconjugated ketone **2**, 13 min 45 sec, 80; conjugated ketone **3**, 15 min 45 sec, 86. The temperature of the reaction mixture was maintained at the temperature reported ±1° by means of a thermostatically controlled oil bath. Extreme care was exercised to remove impurities, especially water, from the IAE solvent used. The solvent was distilled, under nitrogen, from lithium aluminum hydride ($LiAlH_4$), chromatographed under nitrogen, on alumina and redistilled, under nitrogen, from $LiAlH_4$ directly into the reaction flask, which was oven baked, flamed, and cooled under nitrogen. The reaction flask containing the IAE was then continuously swept with nitrogen. Although ultrahigh-purity nitrogen was used, it was pased through a BTS catalyst (pelleted form of finely divided copper on an inert support). The nitrogen was passed successively through a column of molecular sieves, a column of BTS catalyst heated by means of a heating tape, and finally through another column of molecular sieves. The output gas had an oxygen and water content each below 1 ppm. These precautions were utilized because in several initial experiments where these precautions were not taken the results obtained were found to be irreproducible. This irreprodicibility was not observed when the above described precautions were taken. To ensure against premature hydrolysis of the sodium amide used, vials containing preweighed base were prepared in a drybox and were opened immediately before introduction to the IAE solution.

Kinetic Runs. Reaction of 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol (1) with 10% (Molar Ratio) of Sodium Amide. Into a 100-ml, three-necked, round-bottomed flask equipped with a reflux condenser, a serum cap, a magnetic stirrer, and a nitrogen inlet tube was placed 50 ml of purified isoamyl ether (IAE), which was then heated to 173° under nitrogen. At this point 1.0 g (2.16 mmol) of the dienol **1** was added as a solid all at once. After solution occurred (almost instantaneously), 8.0 mg (0.2 mmol) of preweighed sodium amide was added all at once. At this point a vigorous reaction occurred but the reaction mixture was contained by the confines of the flask. While the mixture was refluxing, samples of 1 ml each were taken at various times (Table I) by inserting a hypodermic syringe through the serum cap. The samples thus removed were placed in a flask containing twice the volume of water and well shaken. To this mixture was added 1 ml of benzene, the solution was shaken, and the organic layer was removed. The remaining water solution was extracted a second time with another 1 ml of benzene, the benzene solutions were combined, and then dried over anhydrous magnesium sulfate. All samples removed were treated as described above. After all the required samples were collected, GLC analysis was carried out using the instrument and conditions described above. For each kinetic run the peak areas of the three peaks corresponding to the dienol **1**, the unconjugated ketone **2**, and the conjugated ketone **3** were determined by triangulation[5] and the percent concentrations represented by these peak areas, corrected for the flame response ratios, were then calculated (Table I) and plotted on the same graph vs. time (Figure 1). Using analytical GLC on all kinetic samples and from previous-

Table I
Isomerization Reaction of 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol in Isoamyl Ether at 173° with Various Molar Ratios of Sodium Amide

Reaction time, min	Ratio, %[b]			[Ketone 3/(dienol 1)$_0$][c]	[Ketone 3/(dienol 1)$_0$]$_{calcd}$[d]	[Ketone 2]$_{calcd}$[d]
	Dienol 1	Ketone 2	Ketone 3			
30[a]	89.0	11.0	Trace	0.0	0.9	8.0
60	82.5	15.2	2.3	2.4	3.4	13.8
90	74.2	18.4	7.4	7.7	7.0	17.7
120	66.2	20.6	13.2	13.8	11.3	20.2
150	61.7	22.8	15.5	16.3	16.0	21.7
180	59.3	22.7	18.0	18.9	20.9	22.3
210	51.0	22.6	26.4	27.7	26.0	22.4
240	48.8	21.9	29.3	30.8	31.0	22.1
300	39.6	20.2	40.4	42.5	40.6	20.5
360	32.9	19.8	47.3	49.7	49.4	18.5
420	28.0	20.0	52.0	54.7	57.2	16.2
480	22.9	17.5	59.6	62.7	64.0	14.0
540	17.7	14.9	67.4	70.9	69.8	11.9
660	11.8	13.0	75.2	79.1	79.0	8.5
750	9.3	11.2	79.5	83.6	84.0	6.5
30[e]	75.6	18.4	5.0	6.1	3.4	6.0
60	66.8	21.8	11.3	13.8	10.3	7.8
90	57.6	27.7	15.8	19.4	18.0	7.9
150	49.5	27.3	22.8	28.0	32.5	6.9
210	40.8	23.3	35.9	44.1	44.7	5.7
270	33.2	22.0	44.9	55.2	54.7	4.7
270[f]	37.0	12.8	50.3			

[a] 10% sodium amide; results reported are for three kinetic runs which were reproducible to within 1% of each other. [b] Amounts reported are corrected for flame response ratios. [c] Concentration of ketone 3 used in nonlinear least-squares computer program to obtain rate constant k_2. [d] Computer generated values. [e] 20% sodium amide; results reported are for three kinetic runs which were reproducible to within 1% of each other. [f] Sample of kinetic solution quenched at 173° with water.

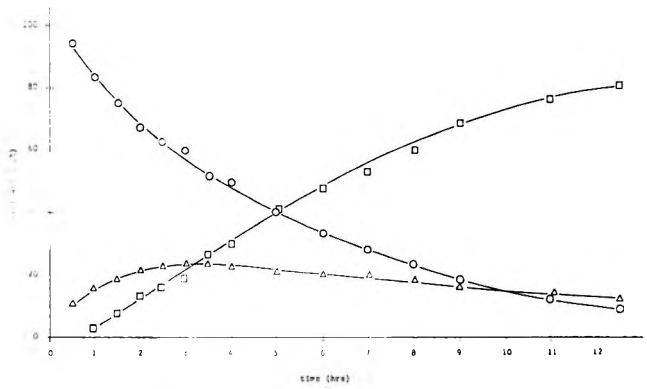


Figure 1. Variation with time of concentration of dienol **1**, unconjugated ketone **2**, and conjugated ketone **3** at 173° in isoamyl ether with 10% (molar ratio) sodium amide: O, dienol **1**; △, unconjugated ketone **2**; □, conjugated ketone **3**.

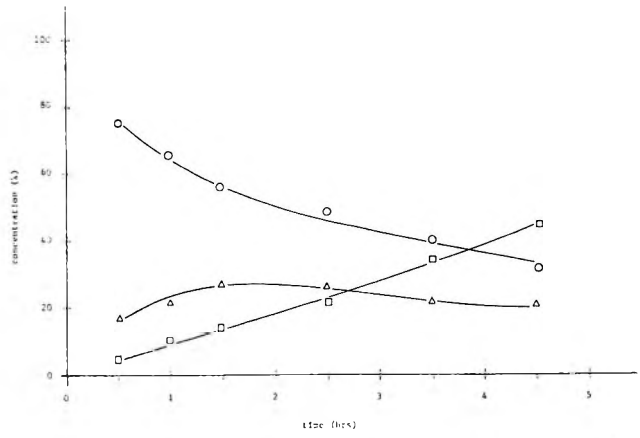


Figure 2. Variation with time of concentration of dienol **1**, unconjugated ketone **2**, and conjugated ketone **3** at 173° in isoamyl ether with 20% (molar ratio) sodium amide: O, dienol **1**; △, unconjugated ketone **2**; □, conjugated ketone **3**.

ly reported[3,4] synthetic experiments the results indicate that only three species are present in each kinetic sample, dienol **1**, unconjugated ketone **2**, and conjugated ketone **3**. This information established a mass balance for each kinetic sample and for the overall reaction of approximately 100%.

Reaction of 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol (1) with 20% (Molar Ratio) of Sodium Amide. This experiment was performed exactly as described above except that 16 mg (0.4 mmol) of sodium amide was used. After all the required samples were removed from the kinetic run and were treated as described above, water was added dropwise to the refluxing reaction mixture remaining in the flask so that a quench at 173° could be performed. After this high-temperature quench was completed, the mixture was cooled to room temperature, extracted with benzene, the organic layer was separated, dried over anhydrous magnesium sulfate, and analyzed on the GLC using the same instrument and conditions previously described for the kinetic samples. The results of this kinetic run and the high-temperature quench are reported in Table I and Figure 2.

Registry No.—**1**, 2137-74-8; **2**, 34759-47-2; **3**, 34759-48-3; sodium amide, 7782-92-5.

References and Notes

(1) A. K. Youssef and M. A. Ogliaruso, *J. Org. Chem.*, **37**, 2601 (1972).
(2) A. K. Youssef and M. A. Ogliaruso, *J. Org. Chem.*, **38**, 487 (1973).
(3) A. K. Youssef and M. A. Ogliaruso, *J. Org. Chem.*, **38**, 3998 (1973).
(4) A. K. Youssef and M. A. Ogliaruso, *J. Org. Chem.*, **38**, 2023 (1973).
(5) As described in H. M. McNair and E. J. Bonelli, "Basic Gas Chromatography", Varian Associates, Palo Alto, Calif., 1969, p 154.

Mechanism of Thermolysis of α-Chloro Ethers in Aprotic Solvents

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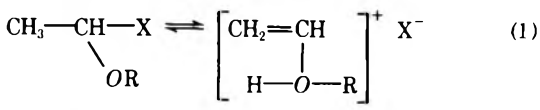
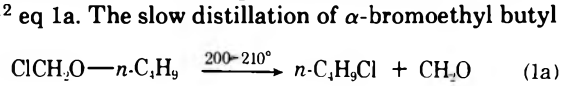
The thermolysis of α-chloroalkyl ethers, even those which are capable of β-hydrogen elimination, is found to give in aprotic solvent media only aldehyde and alkyl halide products, in contradistinction to the gas phase thermolysis process which is reported to yield only the products of HCl elimination. A series of para-substituted α-chlorobenzyl methyl ethers exhibit reaction rates which are correlated by Hammett σ^+ relationships, characterized by large, negative ρ values in a variety of aprotic solvents. Where the alkyl moiety is *sec*-butyl or neopentyl, reaction occurs somewhat more slowly but yielding, nonetheless, alkyl halide products stemming from cationic intermediates in the aprotic medium. The optically active *sec*-octyl substrate gives rise to *sec*-octyl chloride with ~85% inversion. Thermolysis in a series of seven nonnucleophilic solvents, varying in their E_T values from 32–46, show rate variations of 2×10^5 (fastest for the better cation solvators), encompassing an activation energy range of over 23 kcal mol^{-1}. These results are interpreted to support Ingold's classical concept of the ionization process in solvolytic reactions with a solvated ion-pair transition state. They are in clear contradiction with widely held views to the contrary based on data in hydroxylic solvents and tested with non-general-reaction circumstances. The general mechanism of thermolysis of α-chloroalkyl ethers seems to be in best accord with formation of a series of ion pair intermediates (8 → 11) of similar energies. The major transition state may shift from the initial heterolysis of the C-Cl bond when steric difficulties arise in the structuring of a subsequently formed alkyl cation.

The general mechanism of solvolysis of α-chloro ethers has been summarized by Ingold.[1] Current thinking of the reaction of $ROCH_2Cl$ in hydroxylic solvent, involving slow ionization to the stabilized alkoxymethyl cation followed rapidly by nucleophilic bonding to solvent and ultimate formation of the alcohol and aldehydic products, has been developed by the work of Boehme,[2] Salomaa,[3,4] and Cocker[5] and their coworkers. A somewhat differing view which conceived of α-halo ethers as occurring as tautomeric vinyl–oxonium ion pair species (eq 1), advanced by Shostakovskii,[6-9] has been reconsidered in the light of evidence presented[10,11] somewhat later by workers of the Russian school.



(1)

Far less is known about the thermal decomposition of α-halo ethers than about their often competing solvolysis reactions. Presently two different thermal decomposition pathways have been identified in the literature. (a) The elimination of RX on heating α-halo ethers has been reported,[12] eq 1a. The slow distillation of α-bromoethyl butyl



(1a)

ether has been shown[13] to yield 97.1% butyl bromide, significant amounts of water, and traces of acetaldehyde. Aromatic α-halo ethers, PhCHXOR, do not show this reaction course, however. (b) The gas phase thermolysis of α-halo ethers, which has received much attention, appears to follow an entirely different course. The thermolysis reactions of α-chloroethyl methyl ether[14] and α-chloroethyl ethyl ether[15] have been studied kinetically. Both investigations report that the reaction is a unimolecular, reversible elimination of HCl to form a vinyl ether. The equilibrium was reached from either direction and the condensed products were reintroduced into the reaction vessel with duplication of the kinetics. Maccoll, in his discussion of gas-phase elimination reactions,[16] cites the increased rate of HX elimination from α-halo ethers vs. alkyl halides as one piece of evidence indicating an ionic mechanism for the elimination. He concluded that the role of the methoxyl group was essentially the same as in solvolytic reactions, promoting ionization of the C–Cl bond.[1]

These results engender a possible contradiction. On the one hand, the thermolysis of α-halo ethers in an apparently low ionizing power, nonnucleophilic medium affords products which are entirely different from the aldehyde and alcohol products resulting from the ionic, solvolytic pathway to be observed in hydroxylic media. On the other hand, when conducted in the gas phase where it is conventionally assumed that the ionizing power of the medium is either nonexistent, or attributable to the intervention of a wall-reaction process, the thermolysis of α-chloro ethers is reported to result in the very same elimination products expected on the basis of the ionic mechanism of solvolysis which invoked the disproven vinyl–oxonium tautomer, eq 1. The program of studies designed for the purpose of resolving this contradiction is discussed in the ensuing report.

Experimental Section

NMR spectra were recorded on a Varian A-60 or a Perkin-Elmer R12B spectrometer. All samples used carbon tetrachloride as solvent and tetramethylsilane as internal standard. Ir spectra were taken of neat liquid films between sodium chloride plates on a Perkin-Elmer 137 spectrophotometer.

Optical rotation measurements were performed on an ETL-NPL automatic polarimeter Type 142A equipped with a 0.1-dm cell. Chloride analyses were conducted using a modified Volhard method. The α-chloro ethers were treated with methanolic sodium methoxide prior to acidification and titration with Ag^+. This formed sodium chloride and an acetal rather than an aldehyde which would interfere with the titration.

Preparation of Reaction Substrates. Acetals. All acetals were synthesized according to the procedure developed by Lorette and Howard.[17] Ir spectra showed the characteristic acetal absorptions in the 1200–1040-cm^{-1} region:[18] bp 42° (2 mm) [lit.[19] bp 196° (760 mm)]; NMR (CCl_4) δ 7.55–7.09 (m, 5 H, phenyl), 5.34 (s, 1 H, CH), 3.22 (s, 6 H, 2 OCH_3).

***p*-Toluenealdehyde Dimethyl Acetal:** bp 57° (0.5 mm) [lit.[20] bp 113.5–114° (35 mm)]; NMR (CCl_4) δ 7.18 (m, 4 H, phenyl), 5.31 (s, 1 H, CH), 3.22 (s, 6 H, 2 OCH_3), 2.28 (s, 3 H, CH_3).

***p*-Chlorobenzaldehyde Dimethyl Acetal:** bp 56–59° (0.5 mm) [lit.[21] bp 114–115° (19 mm)]; NMR (CCl_4) δ 7.34 (s, 4 H, phenyl), 5.33 (s 1 H, CH), 3.23 (s, 6 H, 2 OCH_3).

***p*-Nitrobenzaldehyde Dimethyl Acetal:** no melting point was obtained as the compound remained an oil (lit.[22] mp 28°); NMR (CCl_4) δ 8.22 and 8.63 (m, J = 9 Hz, 4 H, phenyl), 5.45 (s, 1 H, CH), 3.31 (s, 6 H, 2 OCH_3).

***p*-Fluorobenzaldehyde Dimethyl Acetal:** bp 75° (10 mm) [lit.[23] bp 84° (16 mm)]; NMR (CCl_4) δ 7.73–6.98 (m, 4 H, phenyl), 5.47 (s 1 H, CH), 3.28 (s, 6 H, 2 OCH_3).

Benzaldehyde Di-*sec*-butyl Acetal: bp 76° (0.7 mm); NMR

(CCl_4) δ 7.60–7.05 (m, 5 H, phenyl), 5.52 (s, 1 H, CH), 3.70 (m, 2 H, 2 OCH), 1.80–0.60 (complex m, 16 H, aliphatic H).

(−)-Benzaldehyde Di-2(*R*)-octyl Acetal: bp 88° (21 mm) [lit.[24] bp 80° (11 mm)]; $[\alpha]^{24}D$ −9.9° (C_2H_5OH) (lit.[24] $[\alpha]^{20}D$ −9.84°); bp 120° (8 mm); $[\alpha]^{24}D$ −19° (C_2H_5OH); NMR (CCl_4) δ 7.50–7.10 (m, 5 H, phenyl), 5.41 (s, 1 H, CH), 3.64 (m, 2 H, 2 OCH), 1.70–0.62 (complex m, 32 H, aliphatic H).

Benzaldehyde Dineopentyl Acetal: bp 75° (0.8 mm); NMR (CCl_4) δ 7.27 (m, 5 H, phenyl), 5.48 (s, 1 H, CH), 3.10 (s, 4 H, 2 OCH_2), 0.95 (s, 18 H, 6 CH_3).

Isobutyraldehyde Dimethyl Acetal: bp 100–110° (760 mm) [lit.[25] bp 104° (760 mm)]; NMR (CCl_4) δ 3.81 (d, J = 6.6 Hz, 1 H, CH), 3.21 (s, 6 H, 2 OCH_3), 1.78 (m, 1 H, CH), 0.85 (d, J = 6.6 Hz, 6 H, 2 CH_3).

Butyraldehyde Dimethyl Acetal: bp 113–117° (760 mm) [lit.[25] bp 114° (760 mm)]; NMR (CCl_4) δ 4.28 (t, 1 H, CH), 3.20 (s, 6 H, 2 OCH_3), 1.60–0.70 (complex m, 7 H, aliphatic H).

α-Chloro Ethers. The α-chloro ethers were synthesized by the reaction of the corresponding acetals with CH_3COCl + $SOCl_2$, according to the procedure by Straus and Heinze.[26] The α-chloro ethers were isolated by fractional distillation.

α-Chlorobenzyl Methyl Ether: bp 50° (1.1 mm) [lit.[25] bp 71–72° (0.1 mm)]; NMR (CCl_4) δ 7.57–7.06 (m, 5 H, phenyl), 6.33 (s, 1 H, OCHCl), 3.52 (s, 3 H, OCH_3). Anal. Calcd: Cl, 22.64. Found: Cl, 22.1.

α-Chloro-*p*-methylbenzyl Methyl Ether: bp 75° (0.3 mm) [lit.[21] bp 70° (0.15 mm)]; NMR (CCl_4) δ 7.48–6.93 (m, 4 H, phenyl), 6.34 (s, 1 H, OCHCl), 3.52 (s, 3 H, OCH_3), 2.25 (s, 3 H, CH_3). Anal. Calcd: Cl, 20.78. Found: Cl, 21.17.

α-*p*-Dichlorobenzyl Methyl Ether: bp 80° (0.1 mm) [lit.[21] bp 80–82° (0.15 mm)]; NMR (CCl_4) δ 7.39 (m, 4 H, phenyl), 6.38 (s, 1 H, OCHCl), 3.65 (s, 3 H, OCH_3). Anal. Calcd: Cl, 18.56. Found: Cl, 18.27.

α-Chloro-*p*-nitrobenzyl Methyl Ether: NMR (CCl_4) δ 8.30 and 7.73 (m, J = 9 Hz, 4 H, phenyl), 6.57 (s, 1 H, OCHCl), 3.77 (s, 3 H, OCH_3). Anal. Calcd: Cl, 17.58. Found: Cl, 17.22.

α-Chloro-*p*-fluorobenzyl Methyl Ether: bp 80–85° (20 mm); NMR (CCl_4) δ 7.70–6.80 (m, 4 H, phenyl), 6.38 (s, 1 H, OCHCl), 3.64 (s, 3 H, OCH_3). Anal. Calcd: Cl, 20.31. Found: Cl, 19.66.

α-Chlorobenzyl *sec*-Butyl Ether: bp 80–85° (1 mm); NMR (CCl_4) δ 7.30 (m, 5 H, phenyl), 6.67 (s, 1 H, OCHCl), 4.05 (m, J = 6 Hz, 1 H, OCH), 2.00–0.70 (complex m, 8 H, aliphatic H). Anal. Calcd: Cl, 17.85. Found: Cl, 17.47.

(−)-α-Chlorobenzyl 2(*R*)-Octyl Ether: bp 112–115° (2 mm); $[\alpha]^{24}D$ −36.8° (CCl_4); NMR (CCl_4) δ 7.39 (m, 5 H, phenyl), 6.58 (s, 1 H, OCHCl), 4.05 (m, 1 H, OCH), 1.90–0.60 (complex m, 16 H, aliphatic H). Anal. Calcd: Cl, 13.92. Found: Cl, 13.39.

α-Chlorobenzyl Neopentyl Ether: bp 61° (0.8 mm); NMR (CCl_4) δ 7.35 (m, 5 H, phenyl), 6.42 (s, 1 H, OCHCl), 3.80 and 3.20 (2 d, J = 9 Hz, 2 H, OCH_2), 0.98 (s, 9 H, 3 CH_3). Anal. Calcd: Cl, 16.68. Found: Cl, 16.79.

α-Chloroisobutyl Methyl Ether: bp 57–60° (130 mm) [lit.[27] bp 77–78° (260 mm)]; NMR (CCl_4) δ 5.26 (d, J = 4 Hz, 1 H, OCHCl), 3.46 (s, 3 H, OCH_3), 2.00 (m, 1 H, CH), 1.00 (d, J = 6.7 Hz, 6 H, 2 CH_3). Anal. Calcd: Cl, 28.92. Found: Cl, 29.58.

Kinetics

Procedure. Solutions of α-chloro ethers used in kinetic runs were 20% by volume. All samples were used soon after fractional distillation as their shelf life was limited. Solvents were those commercially available and were purified according to procedures found in Weissberger and Proskauer.[28]

All kinetic runs were carried out in sealed NMR tubes which were thoroughly rinsed with organic solvents and annealed overnight in an oven prior to use. An oil bath equipped with a Hallikainen Instruments Thermotrol provided constant temperatures controlled to within ±0.05°. Temperatures were monitored with calibrated thermometers provided by the National Bureau of Standards. Time intervals were measured by a Time-It from Precision Scientific Co.

Kinetic measurements were made on a Varian A-60 or a Perkin-Elmer R-12-B spectrometer equipped with an electronic digital voltmeter. Calculations were based on the disappearance of the ether vs. the appearance of the aldehyde peaks with passage of time. For the reactions of $C_6H_5CH(Cl)OCH(CH_3)C_2H_5$ and $C_6H_5CH(Cl)OCH_2C(CH_3)_3$ in chlorobenzene, the rate of disappearance of the chloromethine proton was followed.

Table I
NMR Absorptions for the Reaction *p*-X-$C_6H_4CHClOR$ → *p*-X-C_6H_4CHO + RCl

α-Chloro ether	NMR absorptions observed, δ: Disappearance	Appearance
1, X = H; R = CH_3	3.52 (OCH_3)	9.83 (CHO)
1a, X = CH_3; R = CH_3	3.52 (OCH_3)	9.88 (CHO)
1b, X = Cl; R = CH_3	3.65 (OCH_3)	9.85 (CHO)
1c, X = NO_2; R = CH_3	3.77 (OCH_3)	9.90 (CHO)
1d, X = F; R = CH_3	3.64 (OCH_3)	9.85 (CHO)
2, X = H; R = *sec*-butyl	6.67 (benzyl H)	9.83 (CHO)
3, X = H; R = neopentyl	6.42 (benzyl H)	9.83 (CHO)

Hammett ρ Values. Hammett ρ values were calculated from the equation

$$\log \frac{k_X}{k_H} = \rho\sigma^+$$

where k_X = rate constant for the decomposition of *p*-X-$C_6H_5CH(Cl)OCH_3$, k_H = rate constant for $C_6H_5CH(Cl)OCH_3$, and σ^+ = the substituent parameter.[29] Least-squares analysis of the plot of log k_X/k_H vs. σ^+ gave the ρ values.

Results

The thermal decomposition of α-chlorobenzyl alkyl ethers to yield aldehyde and alkyl chloride (eq 2) products

$$p\text{-X—}C_6H_4\underset{\underset{\text{Cl}}{|}}{\text{CHOR}} \xrightarrow{\Delta} p\text{-X—}C_6H_4\text{CHO} + \text{RCl} \qquad (2)$$

1

was found to follow first-order kinetics. The reaction constant in each case was independent of chloro ether concentration, but was highly influenced by the nature of the solvent ion-solvating power and temperature. Infinity runs showed the reaction to be irreversible.

The kinetics for the decomposition were conveniently followed in the NMR by monitoring the disappearance of a suitable α-chloro ether proton vs. the appearance of an aldehyde proton with time. The appropriate NMR absorptions applied for each chloro ether are summarized in Table I.

Thermolysis of α-Chlorobenzyl Methyl Ether. α-Chlorobenzyl methyl ether (1) was thermally decomposed in a series of seven aprotic solvents. In all cases the sole products were benzaldehyde and methyl chloride. The results are summarized in Table II.

Thermolysis of Para-Substituted α-Chlorobenzyl Methyl Ethers. A series of para-substituted α-chlorobenzyl methyl ethers (**1a–d**) were thermolyzed with formation of the corresponding para-substituted benzaldehyde and methyl chloride. These results are summarized in Table III.

Thermolysis of α-Chlorobenzyl Alkyl Ethers. Both α-chlorobenzyl *sec*-butyl ether (2) and α-chlorobenzyl neopentyl ether (3) were thermolyzed in chlorobenzene to produce benzaldehyde and the corresponding alkyl chloride. However, the reaction of 3 did not proceed as cleanly as the others in that here several extraneous peaks developed in the NMR (δ 5.16, 4.38, 4.30, and the aliphatic region) indicating that other products were being formed alongside of the aldehyde and unrearranged neopentyl chloride. A sample of 3, thermolyzed for 40 hr at 170° in chlorobenzene,

Table II
Thermolysis of α-Chlorobenzyl Methyl Ether

Solvent	E_T value, kcal mol^{-1}	Temp range, °C	$k_{298\,K}$, sec^{-1}	E_a, kcal mol^{-1}	$\Delta S^{\ddagger}$ 298 K, kcal mol^{-1}	$\Delta G^{\ddagger}_{298\,K}$, eu	$\Delta G^{\ddagger}_{298\,K}$, kcal mol^{-1}	A (frequency factor), sec^{-1}
CH_3CN	46.0	60–90	2.88×10^{-5}	6.3 ± 0.0	5.7 ± 0.0	−60.1 ± 0.1	23.6	1.16 ± 0.22
Sulfolane	44.0	60–90	4.30×10^{-6}	16.5 ± 0.1	15.9 ± 0.1	−29.6 ± 0.8	24.8	$5.67 \pm 0.14 \times 10^{6}$
$C_6H_5NO_2$	42.0	70–110	3.78×10^{-6}	18.8 ± 0.4	18.1 ± 0.4	−26.9 ± 1.0	26.2	$2.17 \pm 0.07 \times 10^{7}$
$CHCl_3$	39.1	90–130	1.29×10^{-7}	19.6 ± 0.2	19.0 ± 0.2	−26.1 ± 0.9	26.8	$3.14 \pm 0.08 \times 10^{7}$
C_6H_5Cl	37.5	100–130	6.31×10^{-9}	23.4 ± 0.7	22.8 ± 0.7	−19.5 ± 3.5	28.6	$9.07 \pm 0.78 \times 10^{8}$
$C_6H_5CH_3$	33.9	100–140	9.79×10^{-10}	25.8 ± 0.2	25.3 ± 0.2	−15.0 ± 1.0	29.7	$8.59 \pm 0.09 \times 10^{9}$
CCl_4	32.5	110–150	1.73×10^{-10}	29.1 ± 0.2	28.5 ± 0.2	−7.5 ± 1.2	30.8	$3.77 \pm 0.08 \times 10^{11}$

[a] For comparison the E_T value for water = 63.1, ethanol = 51.9, acetone = 42.4, and dioxane = 36.0.

Table III
Thermolysis of Para-Substituted α-Chlorobenzyl Methyl Ethers

Substrate	Para subst	Solvent	Temp range, °C	k_{298K}, sec^{-1}	E_a, kcal mol^{-1}	$\Delta H^{\ddagger}$ 298K, kcal mol^{-1}	$\Delta S^{\ddagger}$ 298K, eu	$\Delta G^{\ddagger}$ 298K, kcal mol^{-1}	A (frequency factor), sec^{-1}
1a	CH_3	Sulfolane	60–90	1.53×10^{-5}	14.7 ± 0.3	14.1 ± 0.3	−33.2 ± 1.6	24.0	$9.19 \pm 0.55 \times 10^{5}$
	CH_3	C_6H_5Cl	100–130	2.39×10^{-7}	18.3 ± 0.2	17.8 ± 0.2	−29.1 ± 0.8	26.4	$5.26 \pm 0.14 \times 10^{6}$
	CH_3	CCl_4	100–140	1.57×10^{-9}	27.4 ± 0.4	26.8 ± 0.4	−8.9 ± 2.3	29.5	$1.93 \pm 0.09 \times 10^{11}$
1b	Cl	Sulfolane	60–100	8.94×10^{-7}	20.1 ± 0.4	19.5 ± 0.4	−20.7 ± 2.4	25.7	$4.91 \pm 0.30 \times 10^{8}$
	Cl	C_6H_5Cl	110–150	3.62×10^{-9}	21.8 ± 0.2	21.2 ± 0.2	26.0 ± 1.0	28.9	$3.48 \pm 0.10 \times 10^{7}$
	Cl	CCl_4	135–155	5.62×10^{-11}	28.1 ± 0.6	27.5 ± 0.6	−13.3 ± 2.7	31.4	$2.10 \pm 0.12 \times 10^{10}$
1d	F	C_6H_5Cl	130–160	1.74×10^{-8}	20.8 ± 0.1	20.2 ± 0.1	−26.2 ± 0.4	28.0	$3.09 \pm 0.04 \times 10^{7}$
	F	CCl_4	150–180	5.68×10^{-11}	28.9 ± 0.3	28.3 ± 0.3	−10.4 ± 1.5	30.7	$9.10 \pm 0.28 \times 10^{10}$
1c	NO_2	Sulfolane	100–130	4.81×10^{-8}	20.8 ± 0.2	20.2 ± 0.2	−24.3 ± 1.1	27.4	$8.17 \pm 0.25 \times 10^{7}$

Table IV
Thermolysis of α-Chlorobenzyl Alkyl Ethers in Chlorobenzene

Substrate	Alkyl group	Temp range, °C	k_{298K}, sec^{-1}	E_a, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$ 298K, kcal mol^{-1}	A (frequency factor), sec^{-1}
1	Methyl	100–130	6.31×10^{-9}	23.4 ± 0.7	22.8 ± 0.7	−19.5 ± 3.5	28.6	$9.07 \pm 0.78 \times 10^{8}$
2	*sec*-Butyl	110–140	3.14×10^{-9}	26.0 ± 0.5	25.2 ± 0.5	−12.0 ± 2.5	30.0	$3.71 \pm 0.19 \times 10^{10}$
3	Neopentyl	160–190	3.13×10^{-11}	26.8 ± 0.8	25.9 ± 0.8	−18.6 ± 3.4	34.2	$1.33 \pm 0.11 \times 10^{9}$

was distilled and the fraction boiling below chlorobenzene submitted to preparative gas chromatography. Three major peaks were noted in the GLC trace and collected in NMR tubes. Peak 2 (~50%) was identified as neopentyl chloride by comparison of the NMR spectrum with that of an authentic sample (δ 3.31 and 1.00 in chlorobenzene) as well as sharp peak enhancement in the GLC trace when an authentic sample was added to the reaction mixture. A very similar product composition was obtained on heating 3 in chlorobenzene for 4 hr at 180°. The complex product, moreover, does not seem to be a consequence of neopentyl chloride decomposition. An authentic sample of the latter, when heated at 170° for 20 hr in chlorobenzene, remained unchanged. The kinetics parameters determined for these reactions are presented in Table IV.

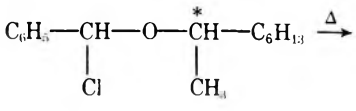
Thermolysis of (−)-α-Chlorobenzyl 2(*R*)-Octyl Ether. A preliminary thermolysis of (−)-α-chlorobenzyl 2(*R*)-octyl ether (4) in sulfolane in which only low-boiling products were collected gave 2-octene: NMR δ 5.40 (m, 2 H, -CHCH-), 2.30–0.70 (m, aliphatic H). (An excellent comparison with Sadtler spectrum no. 3439 was used as the means of identification.) When the reaction system was evacuated to distil the total product composition, 2-octene, benzaldehyde, 2-octyl chloride, and sulfolane (solvent) were collected and identified by GLC and NMR criteria: NMR δ 9.90 (s, 1 H, -CHO), 7.65 (m, 5 H, phenyl), 5.35 (m, 2 H, -CH=CH-), 3.88 (m, 1 H, CHCl), 2.40–0.70 (several m's, aliphatic H). The 2-octyl chloride component, 23 and 27% in two different quantitative runs, was subjected to optical rotation measurements whose results are listed in Table V.

Table V
Optical Rotation Measurements of 2-Octyl Chloride from (−)-α-Chlorobenzyl 2(*R*)-Octyl Ether Thermolysis

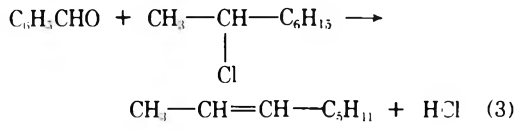
Total wt of distillate, g	Wt of 2-octyl chloride, g	Solvent	$[\alpha]^{24}D$ [a]	% inversion
0.2466	0.0708	CCl_4	+22.9°	82
0.1773	0.0509	EtOH	+26.7°	87

[a] Lit.[30] $[\alpha]^{20}D$ +33.7° and lit.[33] $[\alpha]^{5}D$ +31.0°; using these two values to calculate the thermal coefficient of rotation *Z*, the theoretical $[\alpha]^{24}D$ is obtained from the expression $[\alpha]^{t}D = [\alpha]^{20}D + Z(t - 20)$.

Since the optically active ether was synthesized from (−)-2(*R*)-octanol without rupture of the C–O bond, it too has the *R* configuration. Dextrorotatory 2-octyl chloride is known to have the same configuration as (+)-2(*S*)-octanol.[31–33] Therefore, inversion of the configuration during the course of the reaction expressed by eq 3 at the 2-octyl carbon had occurred to the extent of ca. 85%.



4-(*R*)



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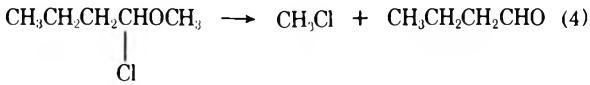
Thermolysis of α-Chlorobutyl Methyl Ether. An attempt to follow the thermal decomposition of α-chlorobutyl methyl ether (**5**) in chlorobenzene kinetically failed owing to formation of an immiscible liquid, presumed to be water, at approximately 15% disappearance of **5** at 120°. The formation of water in the case of an α-chloro ether with a β-H would be consistent with the findings of Shostakovskii and Bogdanova,[13] as previously discussed.

In an attempt to further elucidate the source of the water and to determine the nature of the products formed, a sample of **5** was thermolyzed in chloroform at 160° and the progress of the reaction was followed in the NMR. After 2500 sec, water was visible in the tube accompanying the disappearance of **5**. A singlet at δ 2.90 indicated the formation of methyl chloride. A small triplet at δ 6.38, a singlet at δ 9.30, and a new aliphatic multiplet centered at δ 2.25 also appeared. The singlet at δ 9.30 was not due to CHO from butyraldehyde, as an authentic sample showed CHO at δ 9.70.

After 10 hr, **5** was completely consumed and the NMR appeared as follows: δ 9.70 (s), 9.30 (s), 6.38 (t), 2.90 (s), 2.60–1.95 and 1.72–0.70 (aliphatic multiplets). The peaks at δ 9.70 and 2.90 can be accounted for by formation of butyraldehyde and methyl chloride, eq 4. The ratio of the singlet at δ 9.30 and the triplet at δ 6.38 was 1:1, suggesting that butyraldehyde had undergone an aldol condensation producing 2-ethyl-2-hexenal and water. To test this hypothesis, a sample of butyraldehyde was thermolyzed under the same conditions. After 18 hr, a singlet at δ 9.30 and a triplet at δ 6.38 had appeared and water was visible in the tube. The ratios of the triplet to singlet and singlet to CHO from butyraldehyde were 1:1 and 6:1, respectively (25% reaction). An interesting point to note is that the condensation, eq 5, was so much faster in the presence of **5** than when



(4)

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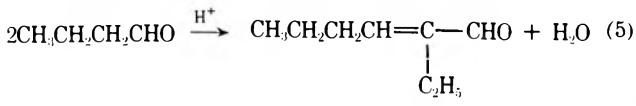
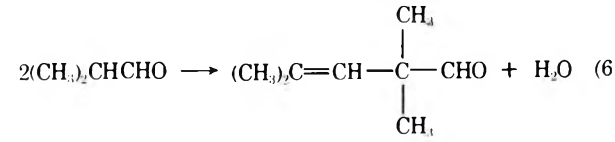


(5)

butyraldehyde was thermolyzed alone. This can be explained by acid catalysis. As soon as any water formed, hydrolysis of **5** occurred and produced HCl, which then catalyzed the condensation reaction.

Thermolysis of α-Chloroisobutyl Methyl Ether. It seemed reasonable to assume that an aliphatic α-chloro ether producing an aldehyde which would not readily undergo aldol condensation could be thermolyzed and the kinetics followed at least for a portion of the reaction. The condensation of isobutyraldehyde, eq 6, proved to be a good example.

The precursor α-chloroisobutyl methyl ether (**6**) was thermolyzed in chloroform at 160°. Water did not become visible until nearly 50% disappearance of **6** and the assumption was made that the reaction could be pursued without the competing side reaction for a significant fraction of the first half-life when subjected to thermolysis in chlorobenzene between 160 and 190°. Clean first-order kinetics were obtained during observation of the first 27% of disappearance of **6**. The appearance in the NMR of singlets at δ 9.55 (CHO) and 2.93 (CH_3X) afforded the desired measure of the formation of isobutyraldehyde and methyl chloride.



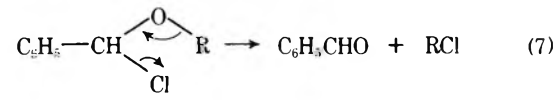
(6)

The activation parameters determined in this fashion ($k_{25°} = 1.75 \times 10^{-11}$ sec^{-1}, $E_a = 24.9$, and $\Delta S^{\ddagger}_{25°} = -26.2$) are to be compared to the corresponding values for the aromatic substrate α-chlorobenzyl methyl ether thermolyzed in chlorobenzene (Table II). Thus, the substitution of alkyl for phenyl has reduced the reaction rate in an almost totally nonpolar solvent by a factor of 360 at 25°, as a result of an increase in activation enthalpy of ca. 1.5 kcal and an addition of −7 eu to the entropy term.

Discussion

Several possible routes by which α-chlorobenzyl alkyl ethers can decompose to benzaldehyde and alkyl chloride clearly must be considered.

(1) A cyclic concerted, one-step mechanism: a one-step elimination of alkyl chloride, eq 7.



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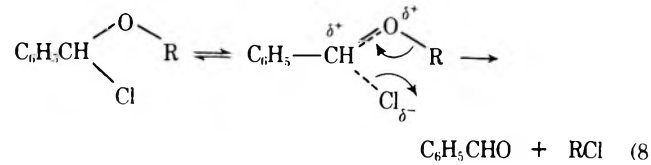
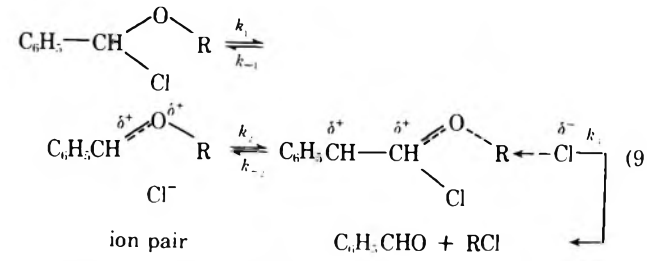
(2) A cyclic concerted, two-step mechanism: an ionization of the C–Cl bond, followed by elimination of alkyl chloride through a four-membered transition state, similar to an SNi mechanism,[32] eq 8.



(8)

(3) Carbonium ion or ion pair mechanism: an ionization of the C–Cl bond to form an ion pair, followed by a nonconcerted nucleophilic attack by Cl^- at R. This would be analogous to the mechanism proposed by Lewis and Boozer[34] to explain the inversion of configuration observed when *sec*-alkyl chlorosulfites are decomposed in toluene. Shielding of the front side by the departing SO_2 accounts for inversion. For the case of α-chlorobenzyl alkyl ethers, the mechanism can be represented by eq 9.



(9)

(4) A free-radical mechanism of chain character.

The Substituent Effect on α-Chloro Ether Thermolysis. The slope ρ of the plot of log k_X/k_H vs. σ^+ is a linear function of the intensity of the charge development in the transition state if the reaction series is isoentropic. The ρ

Table VI
Hammett Data for the Thermolysis of Para-Substituted α-Chlorobenzyl Methyl Ethers

Para subst	Log k_X/k_H (25)	σ^{+} [a]	ρ [b]	r [c]
		In Sulfolane		
CH_3	0.5512	−0.311	−2.33 ± 0.19	0.990
H	0.0	0.0		
Cl	−0.6820	+0.114		
NO_2	−1.9510	+0.779		
		In Chlorobenzene		
CH_3	1.5783	−0.311	−3.90 ± 0.5	0.928
H	0.0	0.0		
F	0.4405	+0.07		
Cl	−0.2413	+0.114		
		In Carbon Tetrachloride		
CH_3	0.9589	−0.311	−3.49 ± 0.24	0.993
H	0.0	0.0		
F	−0.4837	+0.07		
Cl	−0.4881	+0.114		

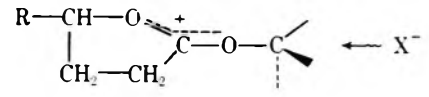
[a] Reference 29. [b] Calculated by the method of least squares. [c] Correlation coefficient.

value will underestimate the degree of charge development to the extent that solvation will tend to disperse the charge. Table VI lists the data for such Hammett plots and summarizes the results computed therefrom.

The large negative ρ values indicate extensive positive charge development on the benzyl carbon in the transition state of the thermolysis reaction. Apparently, the higher ρ value in CCl_4 correlates with the increased value of $\Delta S^{\ddagger}$ in this solvent, and consequently the reduced extent of positive charge dispersion from the reaction centers and through the solvent structure encasing the cation. Examples of ρ values of the same sign and comparable magnitude are (1) solvolysis of α,α-dimethylbenzyl chlorides in 90% aqueous acetone at 25° (SN1), $\rho = -4.52$;[29] (2) solvolysis in 40% EtOH and 60% Et_2O at 0° (SN1), $\rho = -2.35$.[35] However, without an estimate of the $\Delta S^{\ddagger}$ in each of these cases, it is not possible to realize a direct comparison of ρ values with those of the α-chloro ethers under consideration.

Effect of Changing the Alkyl Group and the Configuration at the Carbon Seat of Reaction. A cyclic four-membered transition state would be expected to produce an alkyl chloride of retained configuration. The attack of Cl^- on the same face as the departing oxygen would require this SNi mechanism. If solvent separated ions intervened a racemic mixture would result through attack by Cl^- on both faces of a planar carbonium ion. The formation of 2-octyl chloride ~85% inverted when (−)-α-chlorobenzyl 2(*R*)-octyl ether was thermolyzed in the highly polar aprotic solvent sulfolane eliminates both a cyclic concerted process and a mechanism involving solvent-separated, carbonium ion pair formation. Only one other possibility, namely, ion pair formation with subsequent nucleophilic attack at the back side of the alkyl group, seems to merit further consideration.

This is entirely analogous to the Lewis and Boozer[34] mechanism for chlorosulfite decomposition in which the front side of the carbonium ion intermediate is shielded from attack by the departing group. It bears as well analogy to the mechanism of thermolysis of γ-halo esters in nonnucleophilic solvents, for which pure ionic character is demanded on the basis of results obtained by Kwart and Waroblak.[36] Weinstock[37] has also proposed a path involving ion pair formation, followed by rearward attack by halide ion at the ester alkyl group in the intermediate, 7, on

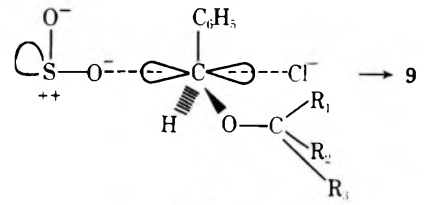


7

the basis of studies with optically active substrates in which he found complete inversion of configuration at the carbon seat of bond breaking in the neat, low-dielectric, aprotic medium employed.

Taking into full consideration these earlier results, the following may be suggested as an attractive picture of the stereochemical course of thermolysis of α-chloro ethers.

(1) In the sulfolane medium the initially formed, solvated ion pair intermediate can be represented by



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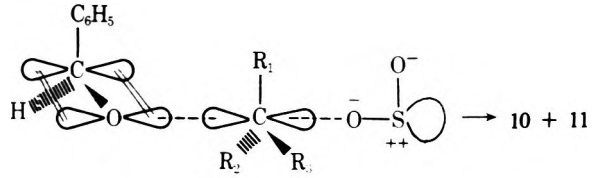
(2) The aldehyde product is then released from this intermediate only after the formation of a second ion pair intermediate, **9**.



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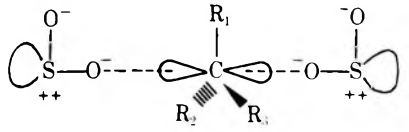
(3) The ion pair **9** has two available courses of product formation: (a) the benzaldehyde solvating the front lobe of the carbonium ion reaction center can be displaced by sulfolane to form the symmetrically solvated structure, **10**, or (b) the chloride ion, which is actually very close to the rear of the carbonium ion reaction center in **9**, can displace the sulfolane solvation at this nearby lobe to form the unsymmetrically solvated ion pair, **11**.



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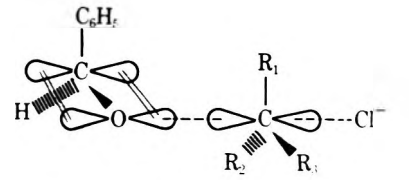

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The formation of intermediate **11** would seem to be favored over **10** since 85% inversion of the product composition is observed. This degree of preference for forming **11** may be due to the propinquity of chloride to the rear lobe of the initial carbonium ion intermediate in **8** at the instant of its formation.

Firm support for these mechanistic conceptions is to be found in the rate and product composition results which are realized through variation of the alkyl group in the α-chlorobenzyl alkyl ether substrates. In a (pure) solvolysis

reaction the rate-determining step is the conversion of the C–Cl bond to an ion pair. If these circumstances also prevail in the thermolysis of α-chlorobenzyl alkyl ethers in nonnucleophilic solvents, changing the alkyl group should have little rate effect. Comparison of the rates of the methyl (k_{rel} = 1), sec-butyl ($k_{rel} \simeq 0.5$), and neopentyl ($k_{rel} \simeq 0.005$) ethers discloses that this expectation is not completely fulfilled in the temperature range 100–200°. The significant differences between methyl and neopentyl are reminiscent of rate effects in direct solvolytic processes.[38] They must also be considered in conjunction with the occurrence here of substantial carbonium ion mediated rearrangement products[38,39] in the case of the neopentyl substrate. The conclusion then to be drawn for the neopentyl is that the formation of its intermediate **9**, and subsequently its **11**, is attended by steric difficulties in achieving the required planar structure. Therefore, the energy requirement for its formation is equivalent to or even slightly greater than is required for formation of 8 from **3**. In the case of methyl (1) and sec-butyl (2), on the other hand, the transition state for formation of 8 constitutes the highest barrier to the reaction.

An analogy for these observations and conclusions is to be found in the reaction of alcohols with triphenylphosphine dichloride, by which even neopentyl chloride is formed in excellent yields.[40] The product-forming step is claimed to involve a similar attack by chloride on an ion pair intermediate with inversion of configuration at the carbon seat of reaction.[41,42] In a series of alcohols undergoing this reaction methyl is (again) twice as fast as *sec*-butyl. However, neopentyl is very much slower; $k_{rel} = 10^{-5}$ compared to 5×10^{-3} in the α-chloro ether reaction. In all likelihood, this is because the neopentyl carbon center has even greater steric difficulties attaining the planar arrangements of carbonium ion structures like **9**, **10**, and **11**, where these intermediates possess the bulkier triphenylphosphorane moiety.

Thermolysis of Aliphatic α-Chloro Ethers. The thermal decomposition of α-chloro ethers with β hydrogen in the gas phase has been reported[14,15] to form vinyl ether products by the β-elimination of HX via a postulated gas phase ionization mechanism proceeding through a quasi-ion pair intermediate. This has been drawn[16] as an analogy to the simple E_i elimination process occurring with alkyl halides in nonnucleophilic solvents, originally elucidated by Hughes and Ingold and their coworkers.[40,41]

The results of thermolysis of α-chlorobutyl and α-chloroisobutyl methyl ethers in nonnucleophilic solvents, however, can account for the products only by a reaction which follows the identical course of the α-chlorobenzyl ether reaction, i.e., the formation of an aldehyde and an alkyl halide rather than the olefin + HX elimination reaction products. Moreover, the greater reactivity of the α-chlorobenzyl by a rate factor of ca. 360 vs. the β-hydrogen containing α-chloroisobutyl ether, while forming exclusively products of identical type, affords further support by analogy for the similarity in ionic nature of their thermolysis mechanisms. Similar results have been obtained earlier by Shostakovskii and Bogdanova[13], when α-bromoethyl butyl ether was allowed to react in a nonnucleophilic solvent containing allyl bromide to trap any HBr evolved. Thus, the fact that only elimination products are formed in the gas phase reaction, apparently to the total exclusion of the aldehyde and alkyl halide products of the ionic, thermolysis pathway identified here for the reaction in nonnucleophilic solvents, allows for a simple interpretation. The gas phase thermolysis of α-chloro ethers with β hydrogen conducted under the circumstances of the earlier[14,15] studies may proceed either via a free radical, dissociation mechanism, or a four-membered cyclic concerted activated complex unattended by charge or free radical development.

Effect of Solvent on Rates and Activation Parameters in α-Chloro Ether Thermolysis. The classical view of solvolysis reactions with charged transition states, as proposed by Ingold et al., makes the following assumptions: (1) solvation will increase with the magnitude of the charge, (2) solvation will decrease with increasing dispersal of a given charge, and (3) the decrease of solvation due to the dispersal of charge will be less than that due to its destruction. For a process in which uncharged reactants pass through a charged transition state, this theory predicts that, in changing from a less polar to a more polar solvent, the heat of activation will decrease and the rate of ionization will increase. This can be accounted for by the fact that the energy of ionizing a covalent bond is compensated by the energy released in solvating the transition state; the greater the degree of solvation (solvation energy released), the greater the decrease in activation energy producing acceleration of reaction. The theory also makes the qualitative assumption that this enthalpy change is greater than the resulting decrease in activation entropy accompanying the solvation process, which has the opposite effect of resisting ionization. Therefore, the energy change dominates the free energy change. This theory was verified by the rate data for solvolysis reactions, both SN1 and SN2, observed by the Hughes and Ingold school in protic solvents.[42]

The more recent literature, however, although further verifying the solvent–rate relationship, does not support the qualitative assumption concerning the entropy change. Whereas the classical view predicts a decrease in entropy ($\Delta S^{\ddagger}$ becomes more negative) with an increase in the solvating power of the solvent, the current concept claims that just the opposite effect is to be expected.[43]

The relative rates and activation energies of thermolysis are shown in Table II. The solvents are listed in decreasing order of solvating power as measured by the E_T values.[49] Two observations should be emphasized in regard to the range of solvents listed: (1) the rate varies by a factor of almost 2×10^5, being faster in the better cation-solvating solvents, and (2) the activation energy varies by over 23 kcal mol^{-1}, being smaller in the better cation-solvating solvents. These trends are consistent with both the classical and nonclassical concepts of ionizing processes and are strong evidence for an ionic transition state. It is on this basis that a free-radical mechanism can be discarded as a possibility; free radicals, generally do not exhibit such marked solvent effects paralleling E_T,[49] the measure of ion-solvating property.

These trends are continuous for the series of para-substituted α-chlorobenzyl methyl ethers studied, as seen in Table III, as well as in Table II. Two clear inferences should be emphasized: (1) the entropies are all negative, showing a higher degree of solvent organization in the transition state than in the ground state, and (2) the entropy decrease is greatest for solvents having higher E_T values. The degree of ground state organization of the solvent structure is considerably smaller than in the case with protic solvents. However, very extensive organization of aprotic solvent molecules around ion-paired transition state structures apparently can be realized in cases of the better ion solvators among the list in Tables II and III. The greatest decrease in entropy of activation is to be correlated with the aprotic solvents of highest ion-solvating abilities as characterized by their E_T values.

It might be argued that the large negative $\Delta S^{\ddagger}$ is indicative of a cyclic four-membered, concerted transition state

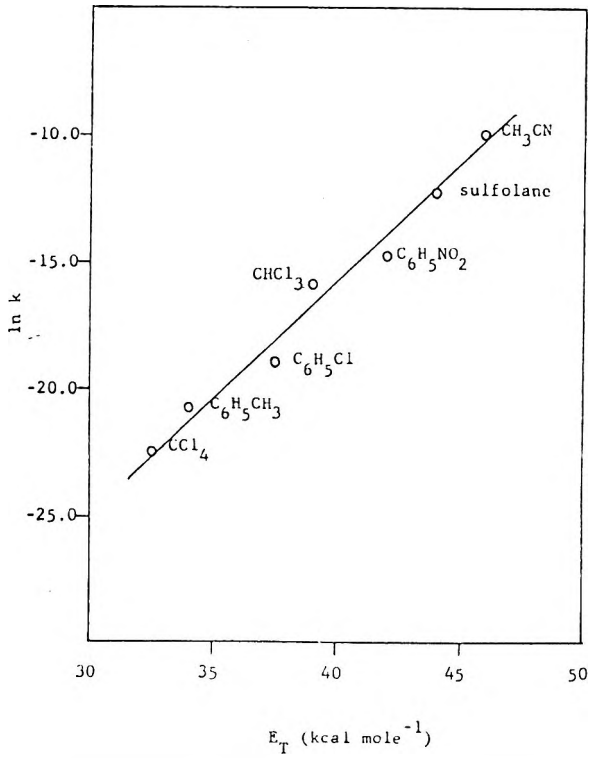

Figure 1. Plot of ln k vs. E_T for α-chlorobenzyl methyl ether thermolysis in aprotic solvents.

of alkyl halide elimination shown by eq 8. However, if the cyclic transition state were not largely ionic in character and therefore nonconcerted, the rate data discussed above and the correlation of $\Delta S^{\ddagger}$ with solvent ionizing power would lack a plausible explanation.

Correlation of the Rate and Activation Parameters with an Empirical Solvent Parameter, E_T. The influence of solvent on the position, intensity, and shape of peaks in the absorption spectra of a substance has long been known.[50] Dimroth et al.[51] calculated transition energies (E_T values) using pyridinium N-phenol betaines as their test substances. Their list of E_T values is probably the most comprehensive solvent scale to date[52] and exhibits good linear correlation with other empirical parameters and kinetic data.[49]

As a test of this last claim, a plot of ln k for the thermolysis of α-chlorobenzyl methyl ether vs. E_T values for the seven solvents studied was made (Figure 1). From the value of the correlation coefficient (r = 0.992) and the standard deviation (less than ±5%), the linear relationship between rate and E_T appears to merit confidence. Thus, E_T values seem to provide a scale of relative solvating power useful in predicting reaction rate.

The free energy of activation, as might be expected, also correlates well with E_T (r = 0.989, and standard deviation ±7%), decreasing with increasing E_T. On the other hand, the plots of E_a and $\Delta S^{\ddagger}$ vs. E_T (respectively), although not a perfect fit, also show clearly a general trend; both E_a and $\Delta S^{\ddagger}$ decrease with increasing E_T. Since $G^{\ddagger}$ and E_a follow the same trend, it must be assumed that the free energy change is dominated by the activation energy in agreement with Ingold's classical picture of the ionization processes in solvolytic reactions.

This effect is rationalized by referring to the relative ground state organization of polar vs. nonpolar solvents. The molecules of a polar solvent in their ground state will have a higher degree of organization than those of a nonpolar solvent. Therefore, the *change* in organization in solvating an ionic transition state will be greater for a nonpolar solvent. Support for this rather widely held view is found in a wealth of information in the literature of two types: (1) the reaction of uncharged species to form ions,[44,45] and (2) first-order solvolysis data in hydroxylic solvents.[46] As an example of the relationship of entropy and solvent polarity, the work of Cox[44] is often cited, wherein the $\Delta S^{\ddagger}$ increases from −56 to −39 to −28 eu in the series of solvents benzene, acetone, ethanol, for the reaction of aniline with phenacyl bromide. This type of reaction is a poor choice to cite, however. In general, ion-forming reactions show a higher activation energy in more polar solvents in contrast to both the classical and nonclassical concepts;[45] e.g., for the above reaction, the E_a is 8.1 kcal mol^{-1} in benzene and 13.9 kcal mol^{-1} in ethanol. What is not taken into account is the ground state solvation of the amine, especially by ethanol and acetone, in which the oxygen atom can hydrogen bond to the protons. Energy must be supplied to strip solvent molecules from the amine to allow bond formation to occur in the transition state. The activation energy will then be greater for solvents which can more efficiently solvate the amine. If the liberated solvent is less organized in the transition state vs. the ground state, then the relationship of energy and entropy can be explained.[47]

Leffler[47] has pointed out that there is considerable danger in making generalized statements concerning the relationship of energy and entropy of ionic processes when comparing hydroxylic and nonhydroxylic solvents. This was apparent in correlating E_a vs. ln A data for the decomposition of triethylsulfonium bromide. A plot of E_a vs. ln A gave two different lines for hydroxylic and nonhydroxylic solvents. This discontinuity is not completely unexpected considering the different solvating characteristics of protic and aprotic solvents. Protic solvents solvate both cations and anions through ion–dipole interactions. In addition, solvation of the anion is intensified by strong hydrogen bonding. Aprotic solvents, on the other hand, are much more efficient solvators of cations than anions because of their inability to form hydrogen bonds.[48] This difference accounts for the greater solvation energy and greater degree of orientation of protic solvents relative to aprotic solvents in ionic transition states. Thus, Gould's rationale[43] concerning relative ground state vs. transition state organization of the solvent may well hold true within a series of protic solvents, but, until more data for unimolecular ionizations in aprotic solvents become available, their inclusion within the scope of this argument must be regarded with some skepticism.

Registry No.—**1**, 35364-99-9; **1a**, 56377-70-9; **1b**, 56377-71-0; **1c**, 56377-72-1; **1d**, 56377-73-2; **2**, 56377-74-3; **3**, 56377-75-4; **4**, 56377-76-5; **5**, 5760-37-2; **6**, 5760-38-3; *p*-toluenealdehyde dimethyl acetal, 3395-83-3; *p*-chlorobenzaldehyde dimethyl acetal, 3395-81-1; *p*-nitrobenzaldehyde dimethyl acetal, 881-67-4; *p*-fluorobenzaldehyde dimethyl acetal, 32691-93-3; (−)-benzaldehyde di-2(*R*)-octyl acetal, 56377-77-6; benzaldehyde dineopentyl acetal, 56377-78-7; isobutyraldehyde dimethyl acetal, 41632-89-7; butyraldehyde dimethyl acetal, 4461-87-4; CH_3COCl, 75-36-5; 2-octyl chloride, 16844-08-9.

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Cleavage of Carboxylic Acid Esters to Acid Chlorides with Dichlorotriphenylphosphorane[1]

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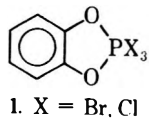
The scope and mechanism of the cleavage of carboxylic acid esters RCOOR′ to RCOCl and R′Cl with Ph_3PCl_2 (2) was investigated. The reaction was rapid in refluxing CH_3CN with the methyl esters of halogenated acids, such as CF_3COOH, but was retarded considerably by steric hindrance in the alkoxy fragment. Esters of nonhalogenated acids were more effectively cleaved with $Ph_3PCl^+BF_3Cl^-$ (3). A mechanism involving initial nucleophilic cleavage of the alkyl–oxygen bond with Cl^- is proposed for halogenated esters (CF_3COOR), whereas an initial electrophilic attack by Ph_3PCl^+ on the carbonyl oxygen is proposed for the cleavage of nonhalogenated esters (CH_3COOR).

The direct conversion of an ester to an acid halide has the obvious advantage that the otherwise necessary steps of hydrolysis and isolation of the acid are obviated. An aqueous hydrolysis may indeed be precluded because of sensitivity of other functionalities in the molecule to water or acids and bases. A one-step regeneration of an active acid derivative from an ester, initially generated for the purpose of masking an acid halide or carboxyl group, would also be of value in a multistep synthesis.

Ester cleavage to an acid halide has previously been observed with reagents such as BCl_3,[2] $COCl_2$,[3] PCl_5,[4] $CHCl_2OCH_3$,[5] and catechylphosphotrihalides[6] 1.



1. X = Br, Cl

We have observed ester cleavage with Ph_3PCl_2[7] 2 and have investigated the scope and mechanism of this reaction.[8]

$$RCOOR' + Ph_3PCl_2 \longrightarrow RCOCl + R'Cl + Ph_3PO$$

Results and Discussion

Scope. Preliminary experiments showed that esters of halogenated acids were cleaved more readily than those of nonhalogenated acids. The cleavage of trifluoroacetic acid esters (CF_3COOR) with Ph_3PCl_2 or Ph_3PBr_2 in refluxing CH_3CN was very sensitive to the steric requirements of R; the methyl ester cleaved very rapidly (90% consumption after 2 hr of reflux) whereas secondary alkyl esters reacted sluggishly (cf. Table I). Cleavage was also suppressed by substitution of electron-withdrawing groups in R (Table II), a result not unexpected if in the cleavage process a nucleophilic attack by halide ion occurs at the alkoxy carbon.[9]

The effect of electron withdrawal in the acyl fragment of an ester is evident from the results presented in Table II. The successive substitution of the α hydrogens in the acyl portion of ethyl acetate with halogens results in an increasing susceptibility of the ester to cleavage. The lack of electron-withdrawing substituents in the acyl fragment necessitates the use of vigorous conditions to effect cleavage. Phthalide, for example, was only cleaved to the extent of 11% after 39-hr reflux with 2 in CH_3CN. When the reaction

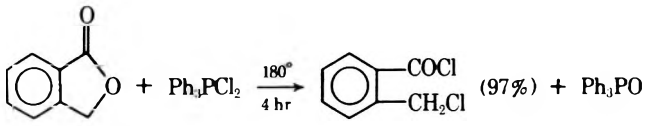
Table I
Effect of Steric Hindrance in the Alkoxy Fragment

$$CF_3COOR + Ph_3PX_2 \xrightarrow[\text{reflux}]{CH_3CN} CF_3COX + RX + Ph_3PO$$

R	X	Reflux, hr	CF_3COX,[a] %	RX,[a] %
CH_3[b]	Cl	9	79	
n-C_4H_9[c]	Cl	72	78	68
i-C_3H_7[d]	Cl	97	16	17
$CH_3(C_6H_{13})CH$[e]	Cl	132	10[f]	44
CH_3[g]	Br	14	93	
n-C_4H_9	Br	95		87
i-C_3H_7	Br	95	11	11
$CH_3(C_6H_{13})CH$	Br	336	15[g]	38

[a] Yields are based on the amount of ester initially present and were obtained by GLC analysis. The acid halide was determined as its derivative butyl ester or by titration of its aqueous hydrolysis products. [b] Registry no., 431-47-0. [c] Registry no., 367-64-6. [d] Registry no., 3974-99-0. [e] Registry no., 332-83-2. [f] The ratio of phosphorane to ester was 1.5:1.0 in this experiment. [g] The derivative ester (CF_3COOBu-n) of the acid halide was subject to losses by evaporation during long reaction periods.

was repeated in the absence of solvent and at an elevated temperature, an almost quantitative conversion to acid chloride resulted.



$$+ Ph_3PCl_2 \xrightarrow[4\text{ hr}]{180^\circ} \text{(97\%)} + Ph_3PO$$

It was found that nonhalogenated esters were more effectively cleaved by a modification of **2** involving its complexation with a Lewis acid. When a heterogeneous solution of **2** in CH_2Cl_2 was treated with BF_3, a homogeneous solution resulted which gave a nearly quantitative yield of $Ph_3PCl^+BF_3Cl^-$ **3** when the solvent and excess BF_3 were removed under vacuum. A comparison of the reactivities of **2** and **3** with those of a few nonhalogenated esters showed that **3** was a much more active cleavage agent[10] (Table III).

$$RCOOR' + Ph_3PCl^+BF_3Cl^- \longrightarrow RCOCl + R'Cl + Ph_3PO \cdot BF_3$$

3 also displayed the advantage of being less reactive toward acid chlorides. Thus, when **2** was heated with $ClCH_2COCl$ in CH_3CN for 4 hr at 150°, an 80% consumption of the acid chloride resulted. Under the same conditions, $ClCH_2COCl$ was recovered in 97% yield after being heated with **3**.

Mechanism. Halogenated Esters. Experiments were carried out to ascertain the role of chloride ion in the cleavage of halogenated esters, since **2** is dissociated appreciably in organic solvents such as CH_3CN.[11]

$$Ph_3PCl_2 \rightleftharpoons Ph_3PCl^+ + Cl^-$$

It was found that $(n\text{-}Bu)_4N^+Cl^-$ was indeed a more effective cleavage agent than **2** with halogenated esters. When CF_3COOBu-n was heated in separate ampoules with **2** and $(n\text{-}Bu)_4N^+Cl^-$ in CH_3CN at 150° for 3 hr, a 100% consumption of ester was obtained in the ammonium salt ampoule, while an 87% consumption was found in the phosphorane ampoule. These results suggest that an SN2 displacement of carboxylate ion by chloride ion is occurring at the alkoxy carbon as a first step in the phosphorane cleavage of halogenated esters.

The carbonyl carbon offers an obvious alternate site of attack by Cl^-.

Table II
Effect of Electron Withdrawal in the Acyl and Alkoxy Fragments

$$RCOOR' + PhPCl_2 \xrightarrow[-Ph_3PO]{CH_3CN} RCOCl + R'Cl$$

R	R'	Time, hr	Temp, °C	RCOCl,[b] %	R'Cl,[b] %
CH_2Cl	CH_2CH_3	4	150	8.5	28
$CHCl_2$	CH_2CH_3	4	150		70
CHF_2	CH_2CH_3	4	150		58
CF_3	CH_2CH_3	48	80	69	17[c]
CF_3	CH_2CF_3	48	80	12	14

[a] Registry numbers are, respectively, 105-39-5, 535-15-9, 454-31-9, 383-63-1, 407-38-5. [b] Yields are based on the amount of ester initially present and were obtained with NMR or GLC analysis by comparison to an internal standard. [c] The volatile EtCl was at times inefficiently trapped in systems at atmospheric pressure, as opposed to ampoule reactions where the measurement of EtCl is considered to be quite reliable.

$$RCOOR' + Cl^- \rightleftharpoons RCOCl + OR'^-$$

Evidence for this type of reaction was obtained when extensive transesterification was observed between CF_3COOEt (10.0 mmol) and $CF_2ClCOOMe$ (10.0 mmol) after 1.5 hr of reflux in CH_3CN in the presence of $(n\text{-}Bu)_4N^+Cl^-$. GLC analysis indicated the following solution composition.[12]

$$\underset{1.8\text{ mmol}}{CF_2ClCOOMe} + \underset{7.4\text{ mmol}}{CF_3COOEt} \xrightarrow[CH_3CN]{(n\text{-}Bu)_4N^+Cl^-} \underset{4.5\text{ mmol}}{CF_2ClCOOEt} + \underset{2.2\text{ mmol}}{CF_3COOMe}$$

The silyl ether, Me_3SiOEt, was detected in solution when $CF_2ClCOOEt$ was heated in CH_2Cl_2 with $(n\text{-}Bu)_4N^+Cl^-$ and Me_3SiCl.

Nonhalogenated Esters. In the case of nonhalogenated esters $(n\text{-}Bu)_4N^+Cl^-$ was found to be unreactive under conditions where cleavage was obtained with **2**. The nonhalogenated esters also exhibited markedly different behavior with **2** and **3** as compared to the halogenated esters. When equal amounts of each type of ester were heated with **2** in CH_2Cl_2, the halogenated ester was consumed almost exclusively, whereas the opposite result was obtained with **3**.

The cleavage behavior of nonhalogenated esters was further compared to that of halogenated esters with respect to steric effects. Equimolar amounts of the ethyl and butyl esters of acetic acid and of **2** were heated in CH_2Cl_2 in an ampoule. Measurement of the amounts of unreacted esters after ca. 35% reaction showed the relative reactivity of the ethyl to butyl ester to be 0.92. In a similar experiment with the ethyl and butyl esters of chlorodifluoroacetic acid competing for **2**, a reactivity ratio of 1.24 (Et/Bu) was found.

$$\underset{71\%}{CF_3COOBu\text{-}n} + \underset{0.6\%}{CH_3COOBu\text{-}n} + Ph_3PCl^+Cl^- \xrightarrow[CH_2Cl_2]{100^\circ,\ 8\text{ hr}} n\text{-BuCl}$$

$$\underset{0\%}{CF_3COOBu\text{-}n} + \underset{18\%}{CH_3COOBu\text{-}n} + Ph_3PCl^+BF_3Cl^- \xrightarrow[CH_2Cl_2]{100^\circ,\ 8\text{ hr}} n\text{-BuCl}$$

In further investigation of the mechanism of nonhalogenated ester cleavage, the possible intermediacy of an α,α-dichloro ether was considered.

Table III
Cleavage of Esters with Ph_3PCl_2 and with $Ph_3PCl^+BF_3Cl^-$

Ester	Reagent	Time, hr	Temp, °C	Ester consumed, %[a]	Acid chloride, %[a,b]	Ethyl chloride, %[c]
(*E*)-PhCH=CHCOOEt[d]	Ph_3PCl_2	8	150	77	69	20
(*E*)-PhCH=CHCOOEt	$Ph_3PCl^+BF_3Cl^-$	0.8	150	90	77	78
(*E*)-PhC(CF_3)=CHCOOEt[e]	Ph_3PCl_2	12	180	73	42	75
(*E*)-PhC(CF_3)=CHCOOEt	$Ph_3PCl^+BF_3Cl^-$	5	150	~100	97[f]	54
(*E*)-PhC(CF_3)=CHCOOEt	$Ph_3PCl^+BF_3Cl^-$	1.5	150	89	92	67

[a] The measurements of the amounts of acid chloride and ester were made by NMR analysis, following their removal from the reaction flask by distillation. [b] No isomerization of the double bond was noted. [c] The efficiency of trapping the volatile EtCl (bp 12°) was variable. [d] Registry no., 4192-77-2. [e] Registry no., 56210-74-3. [f] The *Z* acid chloride was formed in ca. 3% yield.

$$RCOOR' + Ph_3PCl^+Cl^- \longrightarrow RCCl_2OR' + Ph_3PO$$

$$RCCl_2OR' \longrightarrow RCOCl + R'Cl$$

This replacement of the carbonyl oxygen with two chlorine atoms was observed by Gross in the reaction of **1** (X = Cl) with alkyl formates.[13] This type of reaction occurred with **2** and HCOOBu-*n*.

$$Ph_3PCl^+Cl^- + HCOOBu\text{-}n \xrightarrow{115^\circ,\ 20\ hr} HCCl_2OBu\text{-}n\ (11\%) + n\text{-}BuCl\ (30\%)$$

In an attempt to extend evidence of ether formation to acetate esters, it was found that $ClCH_2CCl_2OEt$ could not be detected in the cleavage of $ClCH_2COOEt$ with **2** under a variety of reaction conditions. It was demonstrated that the α,α-dichloro ether expected from $ClCH_2COOEt$ would decompose to yield acid chloride in high yield.

$$ClCH_2CCl_2OEt \xrightarrow[CH_3CN]{150^\circ,\ 4\ hr} ClCH_2COCl\ (93\%) + EtCl\ (98\%)$$

Modes of Cleavage. The results obtained from the mechanistic experiments suggest that different modes of cleavage are operative for halogenated (CF_3COOR) and nonhalogenated (CH_3COOR) esters. In the case of halogenated esters a mechanism involving an initial nucleophilic attack on the ester seems most reasonable (Scheme I),

Scheme I
Halogenated Esters

$$CF_3COOR + Ph_3PCl^+Cl^- \xrightarrow{-RCl} CF_3COO^- + Ph_3PCl^+ \longrightarrow CF_3COCl + Ph_3PO \quad (1)$$

$$CF_3COOR + Ph_3PCl^+Cl^- \rightleftharpoons CF_3C(O^-)(Cl)-OR + Ph_3PCl^+ \rightleftharpoons CF_3COCl + OR^- + Ph_3PCl^+ \quad (2)$$

$$Ph_3PCl^+ + OR^- \longrightarrow RCl + Ph_3PO$$

whereas in the case of nonhalogenated esters an initial electrophilic attack appears most consistent with the data (Scheme II).

An initial BAL2[14] cleavage with chloride ion seems to be the main pathway toward acid chloride formation in the case of halogenated esters. This mode of cleavage would be consistent with the steric sensitivity observed for these reactions. The formation of a carboxylate anion is also consistent with an instance of decarboxylation observed with a

Scheme II
Nonhalogenated Esters

$$CH_3COOR + Ph_3PCl^+Cl^- \rightleftharpoons CH_3-C(Cl)(OPPh_3^+)-OR\ Cl^- \quad (\mathbf{4})$$

$$\mathbf{4} \rightleftharpoons CH_3C(Cl)(OPPh_3^+)-OR \quad (\mathbf{5})$$

$$\mathbf{4} \xrightarrow{-RCl} CH_3C(=O)-OPPh_3^+\ Cl^- \longrightarrow CH_3COCl + Ph_3PO$$

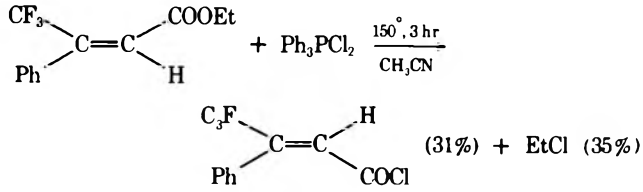
alternatively, $\mathbf{5} \xrightarrow{-Ph_3PO} CH_3CCl_2OR \longrightarrow CH_3COCl + RCl$

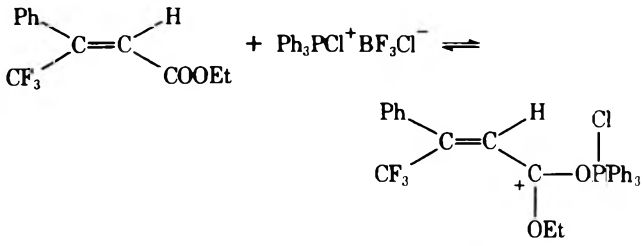
halogenated ester. Reaction of **2** with CCl_3COOCH_3 for 0.8 hr at 150° resulted in a 23% yield of CO_2.

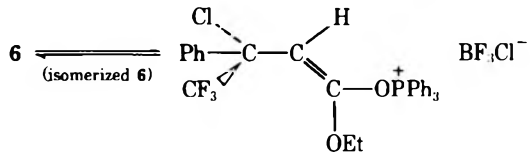
The equilibrium exchange of chloride and alkoxide at the carbonyl carbon (mechanism 2) is considered as a possible cleavage mechanism based on the extensive Cl^--catalyzed transesterification observed between CF_3COOEt and $CF_2ClCOOMe$. This type of reaction has rarely been documented in the literature. Halide ions are normally considered insufficiently nucleophilic to attack the carbonyl carbon of esters,[15] and this type of equilibrium would be expected to lie far to the left. Even a small production of alkoxide ions by this equilibrium would be sufficient, however, to cause efficient transesterification because these ions are regenerated in the transesterification reaction. In the phosphorane ester cleavage reactions a slow exchange of Cl^- for OR^- would be insufficient to achieve an appreciable rate of cleavage, since a chain reaction would not be operative. The exchange mechanism is thus considered to be a minor pathway of halogenated ester cleavage.

Cleavage of nonhalogenated esters with **2** is proposed to proceed by an initial electrophilic attack by Ph_3PCl^+ at the carbonyl oxygen to give species **4**. Consistent with this observation is the fact that the reactivity of **2** is increased by complexing it with a Lewis acid (BF_3), presumably because the availability of the Ph_3PCl^+ cation is thereby increased. A comparison of the results obtained from the cleavage of (*Z*)-CF_3PhC=CHCOOEt with **2** and **3** gives support to this mechanism. Reagent **2** produced only isomerized acid chloride, and 14% of the unreacted ester was isomerized to the

E isomer. Reagent **3** similarly produced only isomerized acid chloride, but the isomerization of unreacted ester increased to 85%. The extensive isomerization of the unreacted ester with **3** is suggested to occur via the ion pair formed from the ester and the phosphonium cation.[16] The fact that



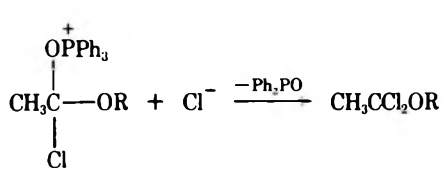




less isomerization of unreacted ester is observed with **2** is in agreement with the lower concentration of an ion pair of type **6** expected for this less electrophilic reagent. Production of only the *E* isomer of the acid chloride from the reaction of *Z* ester with **2** or **3** is apparently due to the isomerization of cation **6** being faster than its decomposition to acid chloride and ethyl chloride.

An electrophilic attack on the carbonyl oxygen by a phosphonium cation was also proposed by Green and Thorp in the cleavage of esters with PCl_5.[17] They found that esters labeled with oxygen-18 in the alkoxy fragment gave acid chlorides containing labeled oxygen.

The equilibration of **4** and **5** may be nonproductive, or it may lead to cleavage products by ionization of the P–Cl bond in **5** with subsequent formation of an α,α-dichloro ether.



The question of the possible intermediacy of α,α-dichloro ethers has not been resolved by the results of this work. It is possible that formate esters are unique in the formation of these ethers,[18] or it is possible that the ethers are formed in the phosphorane cleavage of other esters but the conditions necessary for their formation result in their immediate decomposition to acid chloride and alkyl chloride.

Summary

The data obtained in this study of the cleavage of carboxylic esters with **2** show that this reaction proceeds most readily when the ester contains electron-withdrawing substituents on the α carbon of the acyl fragment, whereas the presence of these groups on the β carbon of the alkoxy fragment retards cleavage. The effect of steric hindrance in the alkoxy fragment of the esters of halogenated acids is significant; secondary alkyl esters cleave very slowly. The esters of nonhalogenated acids are most effectively cleaved with **3**. The cleavage of both types of esters is favored by the use of polar solvents such as CH_3CN or PhCN.

The mechanism of cleavage is dependent on the effects of electron withdrawal in the acyl fragment of the ester. Esters derived from halogenated acids appear to cleave by an initial nucleophilic displacement of carboxylate by halide ion. In the absence of these electron-withdrawing substituents, an initial electrophilic attack by Ph_3PCl^+ occurs at the carbonyl oxygen to form a species which then is converted to cleavage products by reaction with halide ion.

Experimental Section[19]

Materials. Ph_3P was obtained from Cincinnati Milacron. Unless otherwise indicated, the esters used in this work were either prepared by standard procedures from the acid and alcohol or were obtained from commercial sources and distilled before use. $(n\text{-}Bu)_4N^+Cl^-$ (Eastman) was dried at 50° in vacuo. CH_2Cl_2 and CH_3CN were dried by distillation from P_2O_5 and stored over molecular sieves.

Procedures. Reactions which involved the use of moisture-sensitive materials such as dihalophosphoranes, α,α-dichloro ethers, hygroscopic salts, etc., were carried out under a N_2 atmosphere. The reaction apparatus was oven dried, assembled while hot, and flushed with N_2 prior to introduction of the solvent and reagents. The dry solvents were transferred by syringe or pipet, and the reagents were handled by syringe or were transferred in a N_2-filled glovebag.

Phosphorane Reagents. Ph_3PCl_2 (**2**) or Ph_3PBr_2 were prepared by adding an equimolar amount of the halogen to a solution of the phosphine in CH_2Cl_2 or CH_3CN at 0°. The solvent was then removed under reduced pressure if the reaction was to be carried out neat. Stock solutions of **2** were prepared in CH_3CN or CH_2Cl_2 in concentrations of ca. 0.8 and 0.4 *M*, respectively.[20,21] The solutions were conveniently dispensed by syringe and assayed for phosphorane content by base titration of the HCl released upon hydrolysis of aliquots of the solutions in H_2O. Solutions of **2** in CH_3CN (0.758 *M*) and CH_2Cl_2 (0.423 *M*) exhibited single absorptions at − 47.4 and −57.4 ppm, respectively, in their phosphorus NMR spectra.

$Ph_3PCl^+BF_3Cl^-$ (3). BF_3 (16.5 g, 0.244 mol) was bubbled into a magnetically stirred slurry of 0.210 mol of **2** in 100 ml of CH_2Cl_2 while a positive pressure of N_2 was maintained in the system by means of a bubbler. The solution became homogeneous after the addition of 12.9 g of BF_3. With the further addition of 3.6 g of BF_3, fumes appeared at the bubbler and the addition was stopped. The flask was heated and the solvent and excess BF_3 were removed under reduced pressure (maximum bath temperature of 90°, minimum pressure of 7 mm) to give 84.4 g (97%) of **3**, mp 89.4–91.0°.

A ^{31}P NMR of a 1.15 *M* solution[22] of **3** in CH_2Cl_2 showed one absorption only, at −59.7 ppm. The ^{19}F NMR showed absorptions at ϕ^* 105 (q, J_{B-F} = 51 Hz), 126 (broad peak), 144 (s), and 151 ppm (broad peak). At −30° the peak at 126 ppm became a quartet with J_{B-F} = 24 Hz, and the broad peak at 151 ppm sharpened markedly. The peaks at 105, 126, and 151 ppm correspond to the $BF_2Cl_2^-$, BF_3Cl^-, and BF_4^- absorptions expected for a mixture resulting from disproportionation of the BF_3Cl^- ion in solution.[23] The absorption at 144 ppm (small area) is due to $Ph_3PO{\cdot}BF_3$, apparently resulting from exposure of **3** to traces of moisture.[24]

$PhCF_3C{=}CHCOOEt$.[25] Trifluoroacetophenone[26] (43.5 g, 0.250 mol) was added dropwise (0.3 hr) to a refluxing solution (mechanically stirred) of 87.0 g (0.250 mol) of $Ph_3P{=}CHCOOEt$[27] in 300 ml of dry benzene under a N_2 atmosphere. The solution was refluxed overnight. The resultant heterogeneous solution was subjected to reduced pressure (aspirator) on a rotary evaporator. The residual slurry was suction filtered, and the white solid was washed with hexane to give 59.6 g (86%) of Ph_3PO (mp 158–158.5°, lit.[28] mp 156.5–157.0°). The solution of combined filtrates was distilled through an 11-cm Vigreux column to give two fractions of $PhCF_3C{=}CHCOOEt$: (1) 45.4 g (bp 88–92°, 27 mm) of 96.4% *E* and 3.6% *Z*; (2) 4.8 g (bp 92–100°, 27 mm) of 41.0% *E* and 59.0% *Z*, for total yields of 75% *E* and 7% *Z*. The pure isomers were obtained by a spinning band distillation (63-cm Nester-Faust column) at 18 mm.

The pure *E* isomer had the following properties: n^{20}D 1.4646; micro bp 220° (747 mm); ir (film) 1715 (C=O) and 1645 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 7.30 (m, 5, C_6H_5), 6.54 (q, 1, $J_{CF_3,H}$ = 1.33 Hz, vinyl H), 3.94 (q, 2, J = 7.2 Hz, CH_2CH_3), and 1.00 ppm (t, 3, J = 7.2 Hz, CH_2CH_3); ^{19}F NMR (CCl_4) ϕ^* 68.02 ppm (d, $J_{CF_3,H}$ = 1.29 Hz, CF_3); uv max (95% EtOH) 244 nm (ϵ 3160).

Anal. Calcd for $C_{12}H_{11}F_3O_2$: C, 59.01; H, 4.54. Found: C, 59.26; H, 4.92.

Isomer *Z* contained 2.5% isomer *E* by GLC analysis and had the following properties: n^{20}D 1.4769; micro bp 243.5° (740 mm); ir (film) 1736 (C=O) and 1650 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 7.35 (m, 5, C_6H_5), 6.24 (s, 1, vinyl H), 4.22 (q, 2, J = 7.2 Hz, CH_2CH_3), and 1.31 ppm (t, 3, J = 7.2 Hz, CH_2CH_3); ^{19}F NMR (CCl_4) ϕ^* 60.82 ppm (s, CF_3); uv max (95% EtOH) 247 nm (ϵ 7540).

Anal. Calcd for $C_{12}H_{11}F_3O_2$: C, 59.01; H, 4.54. Found: C, 59.26, H, 4.82.

Cleavage of CF_3COOR in Refluxing CH_3CN. The cleavage of CF_3COOMe will be described as an example of the procedure used for trifluoroacetate esters.

A homogeneous solution of 9.66 g (75.4 mmol) of CF_3COOMe and 75.4 mmol of **2** in 100 ml of CH_3CN was prepared under N_2 in a flask equipped with a magnetic stirring bar, septum-covered inlet, and reflux condenser. The volatile CF_3COCl generated during the reaction was carried by a slow flow of N_2, passing through a glass "T" set atop the condenser, into a gas bubbling apparatus containing 100 ml of H_2O[29] followed by a cold trap. Rapid bubbling ensued in the water trap as the reaction solution was brought to reflux temperature. GLC analysis indicated that the reaction was 90% complete after 2 hr of reflux. After 9 hr of reflux 98% of the ester was consumed. The solution was diluted to 250 ml. Hydrolysis of a 25-ml aliquot of this solution in a mixture of 130 ml of H_2O and 100 ml of benzene, followed by the addition of excess $AgNO_3$ to the aqueous layer, gave 0.20 g (±0.00) of AgCl for two trials, indicating a 91% consumption of **2**. Titration of the water trap for CF_3COOH and HCl with standardized base indicated that a 79% yield of CF_3COCl was obtained.

The same procedure was used in the reactions with Ph_3PBr_2 in place of **2**. The dibromophosphorane is less soluble than **2** in CH_3CN, however, and its reactions were performed in heterogeneous solution.

$ClCH_2COOEt$ and 2. A 5-ml ampoule containing 0.2497 g (2.04 mmol) of $ClCH_2COOEt$ and 2.8 ml (2.1 mmol) of 0.758 *M* solution of **2** in CH_3CN was sealed and heated in a 150° oil bath for 4 hr. An internal standard ($HCCl_2CCl_2H$) was added, and the solution was analyzed by NMR to reveal a 36% consumption of ester together with an 8.5% yield of $ClCH_2COCl$ and a 28% yield of EtCl.

The $HCCl_2COOEt$ and $CF_2HCOOEt$ cleavage reactions (Table II) were carried out in the same manner.

Phthalide and 2. A flask containing 105 mmol of **2** and 13.4 g (100 mmol) of phthalide was heated in a 180° oil bath for 4 hr. The contents of the flask formed a homogeneous, black solution which was magnetically stirred. Analysis of two aliquots of a CH_3CN solution (100 ml) of the flask contents with NMR by comparison to an internal standard (dioxane) indicated a 97.4% (±1.8) yield of *o*-chloromethylbenzoyl chloride[30] and a 11.1% (±0.8) recovery of phthalide.

A sample of the acid chloride was obtained by distillation and had the following properties: ir (film) 1770 cm^{-1} (C=O); NMR (CCl_4) δ 8.4–7.3 (m, 4, C_6H_4) and 4.85 ppm (s, 2, CH_2Cl); mass spectrum (70 eV) *m/e* (rel intensity) 188 (28, M^+), 153 (100), 125 (76), 118 (36), and 105 (74).

(*E*)-$PhCF_3C$=CHCOOEt and 2. A flask containing 60.0 mmol of **2** was charged with 11.8 g (48.4 mmol) of (*E*)-$PhCF_3C$=CHCOOEt and heated in an oil at 180° for 12 hr. These reagents were slow to form a homogeneous melt. At the end of the heating period there were still small particles of solid present in the black solution. Volatile materials were removed from the flask under reduced pressure (maximum bath temperature of 195°, minimum pressure of 0.25 mm) and collected in a Dry Ice cooled receiver to give 9.4 g of a pale-green distillate. A vapor trap attached to the flask during the heating period contained 2.3 g (75%) of EtCl.

A 10% solution of the distillate in CCl_4 showed the vinyl hydrogen quartets at δ 6.79 and 6.54 expected for the *E* acid chloride and *E* ester, respectively. The downfield quartet disappeared with the addition of EtOH, while the intensity of the upfield quartet increased. The ^{19}F spectrum showed the CF_3 group of the acid chloride as a doublet (J_{H,CF_3} = 1.4 Hz) which was slightly upfield of, but overlapping with, the CF_3 doublet (J_{H,CF_3} = 1.3 Hz) of the ester. These overlapping absorptions were centered at ϕ^* 68. The distillate composition as indicated by the proton spectrum was 1.5 g of CH_2Cl_2,[31] 3.2 g of unreacted ester (27% recovery), and 4.7 g (42%) of (*E*)-$PhCF_3C$=CHCOCl.

(*E*)-PhHC=CHCOOEt and 3. A flask containing 56.0 mmol of **3** and 9.0 g (51.1 mmol) of (*E*)-PhHC=CHCOOEt was heated in a 150° oil bath for 0.8 hr. The flask contents formed a homogeneous solution which frothed during the first 0.3 hr, while condensate collected rapidly in a vapor trap attached to the flask. The solution became black and viscous, and the bubbling ceased during the last 0.3 hr. The material in the flask cooled to a red solid which was broken up in 20 ml of dry Et_2O. The resultant mixture was pressure filtered with N_2 through a sintered glass funnel. The solid was washed with three 10-ml portions of Et_2O, and the filtrates (red solution) were combined. The air-dried, white solid (mp 213–229°) weighed 19.3 g, representing a 100% yield of crude Ph_3PO-BF_3. A sample was recrystallized from $CHCl_3$ to give material with mp 235–239° (lit.[32] mp 239°). The Et_2O was removed from the combined filtrates, and the residue was distilled at reduced pressure (maximum bath temperature of 120°, minimum pressure of 0.25 mm) to give 7.5 g of a clear distillate and 0.2 g of solid residue. The vapor trap contained 2.6 g (78%) of EtCl and 0.5 g of CH_2Cl_2.[33]

Analysis of a sample of the distillate dissolved in CCl_4 by NMR showed the vinyl hydrogen absorptions of unreacted ester and of acid chloride. The vinyl hydrogen doublets of the acid chloride appeared at δ 7.70 (J = 15.6 Hz) and 6.51 (J = 15.4 Hz). Addition of EtOH resulted in the disappearance of these doublets together with a corresponding increase in the absorptions of the ester. Three aliquots were withdrawn from the distillate and an internal standard (dioxane) was added to each. Analysis of these samples by NMR showed a 9.6% (±1.8) recovery of ester and a 77.0% (±3.4) yield of (*E*)-PhHC=CHCOCl.

The reactions of (*E*)-PhHC=CHCOOEt with **2** and (*E*)-$PhCF_3C$=CHCOOEt with **3** were carried out as described for the above two experiments (Table III).

$ClCH_2COCl$ and 2. A 5-ml ampoule was charged with 0.2202 g (1.95 mmol) of $ClCH_2COCl$ and 2.8 ml (2.1 mmol) of a 0.758 *M* solution of **2** in CH_3CN. The ampoule was sealed and heated in a 150° oil bath for 4 hr. The black solution was analyzed with NMR by comparison to an internal standard ($HCCl_2CCl_2H$) to reveal an 80% consumption of $ClCH_2COCl$.

In a similar experiment with $ClCH_2COCl$ and **3**, the acid chloride was recovered in 97% yield.

CF_3COOBu-*n* and 2. A 5-ml ampoule containing 0.3473 g (2.04 mmol) of CF_3COOBu-*n* and 2.8 ml (2.1 mmol) of a 0.758 *M* solution of **2** in CH_3CN was sealed and heated in a 150° oil bath for 3 hr. The dark-brown solution was analyzed by GLC with the use of an internal standard (benzene) to reveal an 87% consumption of ester and an 87% yield of *n*-BuCl.

CF_3COOBu-*n* and $(n\text{-}Bu)_4N^+Cl^-$. A 5-ml ampoule containing 0.5664 g (2.04 mmol) of $(n\text{-}Bu)_4N^+Cl^-$, 0.3264 g (1.92 mmol) of CF_3COOBu-*n*, and 2.8 ml of CH_3CN was sealed and heated in a 150° oil bath for 3 hr. The dark-brown solution effervesced when the ampoule was opened, indicating that some decarboxylation had occurred. Analysis by GLC showed no trace of unreacted ester.[34]

$CF_2ClCOOEt$, $CF_2ClCOOBu$-*n*, and 2. A 10-ml ampoule containing 0.4881 g (2.62) mmol of $CF_2ClCOOBu$-*n*, 0.4145 g (2.62 mmol) of $CF_2ClCOOEt$, 0.1740 g of cyclohexane (internal standard), and 6.4 ml (2.71 mmol) of a 0.423 *M* solution of **2** in CH_2Cl_2 was sealed and heated in a 100° oil bath for 4 hr. The colorless solution was analyzed by GLC[35] to reveal a 63.0% (±0.0) consumption of the ethyl ester and a 51.0% (±0.6) consumption of the butyl ester, for a consumption ratio (Et/Bu) of 1.24 (±0.02).

$CF_2ClCOOMe$, CF_3COOEt, and $(n\text{-}Bu)_4N^+Cl^-$. A 30-ml, one-necked flask equipped with a septum inlet was charged with 1.202 g (4.32 mmol) of $(n\text{-}Bu)_4N^+Cl^-$ under N_2 (glovebag) and fitted with a reflux condenser, which was connected to a vapor trap. A solution which contained 1.455 g (10.0 mmol) of $CF_2ClCOOMe$, 1.422 g (10.0 mmol) of CF_3COOEt, 0.7655 g of *n*-hexane (internal standard), and 10 ml of CH_3CN was syringed into the flask. The flask was heated in a 85° oil bath for 6 hr. Analysis by GLC after 1.5 hr showed (mmol) CF_3COOMe (2.2), CF_3COOEt (7.4), $CF_2ClCOOMe$ (1.8), and $CF_2ClCOOEt$ (4.5). At the conclusion of the 6-hr reflux period the flask and condenser walls were washed down with solvent to correct for possible errors in analysis caused by fractionation of the solution components. The resultant solution showed only traces of the methyl esters together with CF_3COOEt (6.2 mmol) and $CF_2ClCOOEt$ (3.8 mmol). The vapor trap contained 0.5 g (99%)[36] of CH_3Cl.

$CF_2ClCOOEt$, $(n\text{-}Bu)_4N^+Cl^-$, and Me_3SiCl. A 10-ml ampoule containing 0.6174 g (2.22 mmol) of $(n\text{-}Bu)_4N^+Cl^-$, 0.3431 g (2.16

mmol) of $CF_2ClCOOEt$, 0.3324 g (3.06 mmol) of Me_3SiCl, and 5 ml of CH_2Cl_2 was sealed and heated in an 80° oil bath for 3.5 hr. An internal standard (toluene) was added and the solution was analyzed by GLC to reveal 1.92 mmol (89% recovery) of $CF_2ClCOOEt$ and 0.10 mmol (5% yield) of Me_3SiOEt.

CF_3COOBu-*n*, CH_3COOBu-*n*, and 2. A 10-ml ampoule containing 0.3058 g (2.63 mmol) of CH_3COOBu-*n*, 0.4478 g (2.63 mmol) of CF_3COOBu-*n*, and 6.4 ml (2.71 mmol) of a 0.423 *M* solution of **2** in CH_2Cl_2 was sealed and heated in a 100° oil bath for 8 hr. GLC analysis (toluene internal standard) showed a 71% consumption of CF_3COOBu-*n* and a 0.6% consumption of CH_3COOBu-*n*.

CF_3COOBu-*n*, CH_3COOBu-*n*, and 3. A 10-ml ampoule containing 0.3022 g (2.60 mmol) of CH_3COOBu-*n*, 0.4434 (2.61 mmol) of CF_3COOBu-*n*, 4.0 ml of CH_2Cl_2, and 2.3 ml (2.64 mmol) of a 1.15 *M* solution of **3** in CH_2Cl_2 was sealed and heated in a 100° oil bath for 8 hr. GLC analysis (toluene internal standard) showed a 0% consumption of CF_3COOBu-*n* and an 18% consumption of CH_3COOBu-*n*.

CH_3COOEt, CH_3COOBu-*n*, and 2. A 10-ml ampoule containing 0.2344 g (2.66 mmol) of CH_3COOEt, 0.3044 g (2.62 mmol) of CH_3COOBu-*n*, and 6.4 ml (2.71 mmol) of a 0.423 *M* solution of **2** in CH_2Cl_2 was sealed and heated in a 120° oil bath for 40 hr. GLC analysis[32] (cyclohexane internal standard) showed a 34.8% (±0.2) consumption of the ethyl ester and a 37.6 (±1.0) consumption of the butyl ester, for a consumption ratio (Et/Bu) of 0.92 (±0.02).

CH_3COOEt, CH_3COOBu-*n*, and $(n\text{-}Bu)_4N^+Cl^-$. A 10-ml ampoule containing 0.2326 g (2.65 mmol) of CH_3COOEt, 0.3040 g (2.62 mmol) of CH_3COOBu-*n*, 0.7685 g (2.76 mmol) of $(n\text{-}Bu)_4N^+Cl^-$, and 6.4 ml of CH_2Cl_2 was sealed and heated in a 100° oil bath for 30 hr. GLC analysis (toluene internal standard) showed a 98.5% recovery of the butyl ester and a 105% recovery of the ethyl ester.[37] There was no EtCl detected by GLC.

In comparison to the above results, **2** cleaved the same mixture of esters to the extent of ca. 10% for each ester under the same conditions.

HCOOBu-*n* and 2. A heterogeneous mixture of 105 mmol of **2** and 10.2 g (100 mmol) of HCOOBu-*n* was magnetically stirred and heated in a 115° oil bath for 20 hr. The volatile materials were removed from the flask under reduced pressure (maximum bath temperature of 125°, minimum pressure of 0.5 mm) and collected in a Dry Ice cooled receiver to give 16.7 g of distillate. The presence of $HCCl_2OBu$-*n* was indicated by the fact that spiking of the distillate with an authentic sample[38] resulted in enhancement of the singlet at δ 7.35 (CCl_2H) and triplet at δ 3.94 ($-OCH_2Pr$). The addition of water to the distillate resulted in the disappearance of these signals and enhancement of the ester absorptions, as expected for hydrolysis of the dichloro ether to the corresponding ester. The mole percent composition of the distillate, obtained from its NMR spectrum, showed that *n*-BuCl and $HCCl_2OBu$-*n* were produced in 30 and 11% yields, respectively. A 66% recovery of HCOOBu-*n* was also indicated.

$ClCH_2COOEt$ and 2. Equimolar amounts of $ClCH_2COOEt$ and **2** (0.758 *M* solution) were heated together in CH_3CN at 80° for 4.5 hr and 4 days, and at 150° for 4 hr in an attempt to detect the presence of $ClCH_2CCl_2OEt$ in the cleavage of this ester. Spiking of these solutions with an authentic sample[39] of the ether demonstrated that it could be detected in low concentration by NMR analysis. The ester and **2** were also heated together neat at 110° for 30 hr. None of these attempts were successful in detecting any trace of the α,α-dichloro ether.

$ClCH_2CCl_2OEt$ and Heat. A solution of 0.3470 g (1.96 mmol) of $ClCH_2CCl_2OEt$ in 2.8 ml of CH_3CN was heated in a sealed, 5-ml ampoule at 150° for 4 hr. Analysis of the black solution by NMR, following the addition of an internal standard ($HCCl_2CCl_2H$), showed a 96% consumption of the ether together with 98 and 93% yields of EtCl and $ClCH_2COCl$, respectively.

CCl_3COOMe and 2. A mixture of **2** (197 mmol) and CCl_3COOMe (181 mmol) was heated in a flask at 150° for 0.8 hr. A $Ba(OH)_2$ bubbler connected to the flask collected 8.29 g of $BaCO_3$, representing a 23% yield of CO_2.

(*Z*)-$PhCF_3C$=CHCOOEt and 2. A solution of 0.3100 g (1.27 mmol) of (*Z*)-$PhCF_3C$=CHCOOEt and 2.0 ml (1.5 mmol) of a 0.758 *M* solution of **2** in CH_3CN was heated at 150° for 3 hr in a 5-ml, sealed ampoule. GLC analysis showed the consumption of unreacted ester to be 86% *Z* isomer and 14% *E* isomer. Analysis with NMR by comparison to an internal standard (CH_2Cl_2) showed 0.823 mmol of both ester isomers (65% recovery) and 0.442 mmol of EtCl (35% yield). Comparison of the areas of the vinyl hydrogen absorptions of the esters and acid chloride indicated a 31% yield of (*E*)-$PhCF_3C$=CHCOCl. The *Z* isomer of the acid chloride was not detected by NMR or GLC analyses.

(*Z*)-$PhCF_3C$=CHCOOEt and 3. A 5-ml ampoule containing 2.4 ml (1.5 mmol) of a 0.657 *M* solution of **3** in CH_3CN and 0.3203 g (1.31 mmol) of $PhCF_3C$=CHCOOEt, composed of 97.6% *Z* isomer and 2.4% *E* isomer, was sealed and heated in a 150° oil bath for 3 hr. GLC analysis showed the composition of unreacted ester to be 12.9% *Z* isomer and 87.1% *E* isomer. Comparison of the areas of the vinyl hydrogen absorptions of the esters and acid chloride indicated a 52% yield of (*E*)-$PhCF_3C$=CHCOCl. The *Z* isomer of the acid chloride was not detected by NMR or GLC analyses.

(*Z*)-$PhCF_3C$=CHCOOEt and $(n\text{-}Bu)_4N^+Cl^-$. A 5-ml ampoule containing 0.3037 g (1.09 mmol) of $(n\text{-}Bu)_4N^+Cl^-$, 1.5 ml of CH_3CN, and 0.2371 g (0.971 mmol) of $PhCF_3C$=CHCOOEt, composed of 95% *Z* isomer and 5% *E* isomer, was sealed and heated in a 150° oil bath for 3 hr. Analysis with NMR by comparison to an internal standard (CH_2Cl_2) showed a 97% recovery of ester having a composition of 91% *Z* isomer and 9% *E* isomer.

Registry No.—**2**, 2526-64-9; **3**, 42957-71-1; $(n\text{-}Bu)_4N^+Cl^-$, 1112-67-0; $CF_2ClCOOEt$, 383-62-0; $CF_2ClCOOBu$-*n*, 56210-76-5; $CF_2ClCOOMe$, 1514-87-0; Me_3SiCl, 75-77-4; CH_3COOBu-*n*, 123-86-4; CH_3COOEt, 141-78-6; $HCOOBu$-*n*, 592-84-7; $ClCH_2CCl_2OEt$, 56210-77-6; CCl_3COOMe, 598-99-2; Ph_3PBr_2, 1034-39-5; trifluoroacetophenone, 434-45-7; (*Z*)-$PhCF_3C$=CHCOOEt, 56210-75-4; PH_3P=CHCOOEt, 1099-45-2; phthalide, 87-41-2; o-chloromethylbenzoyl chloride, 42908-86-1; $ClCH_2COCl$, 79-04-9.

References and Notes

(1) (a) This paper is based on the Ph.D. Thesis of W.M.K., University of Iowa, 1972. Partial support for this work was obtained from Public Health Grant GM11809. (b) A preliminary account of this work has appeared: D. J. Burton and W. M. Koppes, *J. Chem. Soc., Chem. Commun.*, 425 (1973).
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(10) Preliminary experiments have indicated that **3** is also a more effective reagent for ether cleavage than **2**. Ether cleavage by Ph_3PBr_2 has also been enhanced by its complexation with BF_3. Other salts such as $Ph_3PCl^+SbCl_6^-$ would presumably also represent more reactive "phosphorane" reagents in many types of reactions, and other complexed phosphoranes will be tried in future work.
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(12) After 6 hr of reflux the methyl esters were completely cleaved to CH_3Cl (99% yield in vapor trap) and carboxylate anions, while the ethyl group was completely retained in solution as CF_3COOEt and $CF_2ClCOOEt$.
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(14) This type of alkyl–oxygen bond fission was denoted as $B_{AL}2$ by Ingold to symbolize a mode of ester hydrolysis: C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed, Cornell University Press, Ithaca, N.Y. 1969, p 1131.
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(18) The unique chemical properties of formate esters do not qualify them to be representative of carboxylic esters as a class. For a review of the properties of formate esters see H. W. Gibson, *Chem. Rev.*, **69**, 673 (1969).
(19) GLC analyses were performed on a Hewlett-Packard Model 5750B chromatograph. Melting points were determined on a Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded with a Perkin-Elmer Model 21 instrument and calibrated with a polystyrene film. Ultraviolet spectra were obtained with a Cary 14 instrument. NMR spectra were determined with Varian A-60 and H-100 instruments using Me_4Si and CCl_3F as internal standards or 85% H_3PO_4 as an external standard. Elemental analyses were performed in the analytical laboratory of the Chemistry Department at The University of Iowa.

(20) Cl_2 was first condensed into a tared cold trap from which it was revaporized and condensed into the phosphine solution via a Dry Ice condenser. Alternatively, the Cl_2 was delivered as a solution in CH_3CN the concentration of which was determined by iodometric titration.
(21) These concentrations represent the approximate limit of solubility of **2** in these solvents.
(22) Solutions of **3** were prepared in a volumetric flask with solid **3** and CH_2Cl_2; in situ preparation of a solution was not feasible because of difficulty in removal of any excess BF_3. A 1.15 *M* solution of **3** in CH_2Cl_2 was assayed by hydrolysis in 0.1 *M* NaOH (~0.75 equiv) followed by titration of this aqueous solution with dilute NaOH to a phenolphthalein endpoint. Two trials gave a molarity of 1.16 *M* (±0.00), based on the release of 5 mol of acid per mole of **3**.
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(33) Residual solvent from the preparation of **3**.
(34) The amount of *n*-BuCl in the solution was not calculated because of the interference from decomposition of the ammonium salts in the gas chromatograph, which also produces *n*-BuCl.
(35) The average of two to three analyses is given followed by, in parentheses, the average deviation.
(36) This yield is based on the amount of $CF_2ClCOOMe$ initially present. It indicates that decarboxylation of CF_2ClCOO^- occurred with the release of Cl^-, since the amount of $(n\text{-}Bu)_4N^+Cl^-$ present is insufficient to account for all of the CH_3Cl formed.
(37) The butyl chloride peak due to decomposition of the ammonium salts in the gas chromatograph tailed slightly into the ethyl ester peak.
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Stereochemistry and Mechanism of Ionic Cyclopropane Ring Cleavage by Arenesulfenyl Chloride Addenda in Quadricyclene Systems

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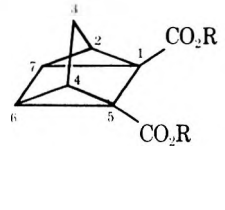
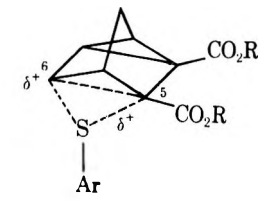
Addition of benzenesulfenyl chloride to quadricyclenedicarboxylic acid (**1a**) and to the corresponding dimethyl ester (**1b**) gave adducts [*exo*-5-chloro-*endo*-3-phenylthiotricyclo[2.2.1.$0^{2,6}$]heptane-2,*exo*-3-dicarboxylic acid (**3a**) and the C-3 epimer (**4a**) from **1a** and the corresponding dimethyl esters from **1b**, **3b**:**4b**, ca. 1:1]; these are the result of electrophilic cleavage of a cyclopropane ring in this system by retention and inversion processes (in nearly equal amounts). The addition of toluenesulfenyl chloride to **1b** gives analogous results. All such results demonstrate the lack of bridged sulfonium ions (e.g., **2**) as the sole product precursors and indicate that corner-attached electrophilic addition intermediates, relative to the corresponding edge-attached species, may have a far greater importance than previously suspected. The stereochemistry of the adducts was confirmed by spectral (largely proton magnetic resonance) and chemical (lactone formation) studies.

Although the ionic cleavage of cyclopropanes has been the subject of a large amount of research,[1] the stereochemical role of the electrophile has not been totally established. The vast majority of studies show that cyclopropane ring cleavages by nucleophile have occurred by inversion,[1,2] whereas electrophilic ring cleavage stereochemistry has been reported to involve each of retention,[1,3,4] inversion, and mixed retention–inversion processes.[1,5,6] Completion of our work[5] on the ionic cleavage of a cyclopropane in quadricyclenedicarboxylic acid with hydrogen chloride implied that the stereochemistry of new proton position in our final adduct was not a result of *direct* cyclopropane ring cleavage. We thus decided to investigate the arenesulfenyl chloride cyclopropane ring cleavage of quadricyclenedicarboxylic acid (**1a**, tetracyclo[3.2.0.$0^{2,7}$.$0^{4,6}$]heptane-1,5-dicarboxylic acid) and ultimately its dimethyl ester (**1b**). This combination seemed ideal because of the known propensity for C_5–C_6 (C_1–C_7) bond cleavage in this system[5,7] and the great driving force for sulfenyl halides to add via a bridged sulfonium ion.[8] We felt that the possibility of the latter would enhance the chances of direct electrophilic attack on the carbon atoms of the cyclopropane ring skeleton, perhaps to the exclusive formation of ion **2**, which should result in the exclusive formation of **3**.[9] The work described below shows that such an exclusive pathway is *not* the case, but that one, in all cases, obtains quantities of **4** essentially equivalent to the amount of **3** formed. This implies, as far as comparisons can be made between theoretical considerations of protonated cyclopropanes and cyclopropane cleavage intermediates involving other electrophiles, that the balance may lie much more heavily toward corner-attached species (as opposed to edge-attached species) than previously suspected.[1,10,11]



1a, R = H
b, R = CH_3



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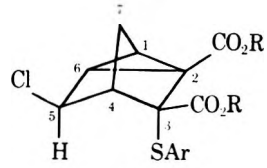

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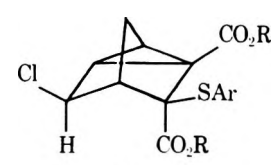

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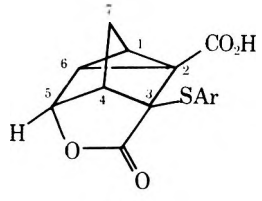
2–**4a**, R = H; Ar = C_6H_5
b, R = CH_3; Ar = C_6H_5
c, R = H; Ar = *p*-$CH_3C_6H_4$
d, R = CH_3; Ar = *p*-$CH_3C_6H_4$

The preparation of the quadricyclene diacid (**1a**) was carried out as has been described earlier.[5,12] Treatment of diacid **1a** (in dioxane at room temperature) with benzenesulfenyl chloride[13] resulted in quantitative yields of ad-

ducts (**3a–4a**) after 5 min. The sample quantitatively analyzed (see Experimental Section) for a 1:1 adduct and displayed an NMR spectrum characteristic of a nortricyclene skeleton. The NMR spectrum showed two signals in the region consistent for protons α to chlorine (δ 4.1, 0.5 H; 4.9, 0.5 H) implicating the existence of (at least) two adduct isomers.[5] Previous studies[5,9] imply that the isomer pair would be the C-3 epimers: *exo*-5-chloro-*endo*-3-phenylthiotricyclo[2.2.1.$0^{2,6}$]-heptane-2,*exo*-3-dicarboxylic acid (**3a**), and the *exo*-3-thiophenyl-*endo*-3-carboxyl isomer (**4a**). Arguments have been outlined earlier[5] that speak against the other two epimers (endo chlorine) possible. The chemical and spectral evidence described below confirm the structures and rule out other regioisomers.[9]

The diacid adduct (**3a–4a**) mixture (from above) was treated under conditions expected to give rise to lactone.[5] The resulting solids led to a characterizable product (mp 189–190°), the infrared of which showed a band at 5.5 μm (1818 cm^{-1}) consistent with lactone formation (**5a**).[5,7]



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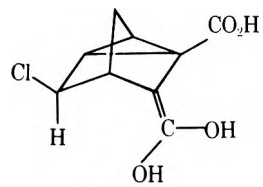

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5a. Ar = C_6H_5; **c**, Ar = *p*-$CH_3C_6H_4$

The NMR spectrum of the isolated sample is very similar to that of the diacid precursors (**3a–4a**) except that the δ 4.10 signal had disappeared and the signal at δ 4.85 integrated for one proton. This implies a **5a–3a** mixture with superimposition of the 5-H signal of **5a** upon the 5-H signal of **3a**. Quantitative elemental analysis is consistent with a **5a–3a** mixture (see Experimental Section). Formation of lactone **5a** confirms the identity of adduct **4a**[5,7] and the NMR spectra of the mixtures and known general ring opening routes[1] argue for concurrent formation of adduct **3a**.

In view of the known mechanism for hydrogen chloride opening of **1a**,[5] a possible mechanism for the benzenesulfenyl chloride ring opening of **1a** was (a) formation of hydrogen chloride from the reaction of benzenesulfenyl chloride with the dicarboxylic acid followed by (b) cleavage of **1a** with hydrogen chloride to form enediol **6**; the nearly equally available faces of the C=C unit in **6** would predict that (c) the addition to **6** of benzenesulfenyl chloride,[8] followed by deprotonation, should give a nearly 50:50 ratio of **3a–4a**. Thus further addition reactions were carried out on quadricyclene diacid dimethyl ester (**1b**) to preclude such possibilities.

Although the preparation of quadricyclenedicarboxylic acid dimethyl ester (**1b**) has been reported,[12] we have prepared our diester by a different method.[14] Thus treatment of diacid **1a** with an acetone solution of dimethyl sulfate and potassium carbonate resulted in **1b**.

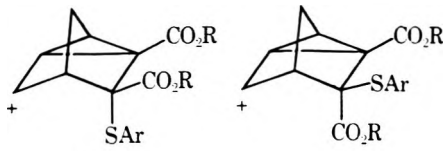
Treatment of diester **1b** with benzenesulfenyl chloride[13] in methylene chloride at room temperature for 2 days results in formation of adduct (**3b + 4b**, see below); after isolation by dry column chromatography,[16] an 82% yield of adduct (**3b–4b**, see below) was realized. The NMR spectrum ($CDCl_3$) of the product mixture was very similar to that we had observed (above) for the (diacid) adducts from **1** (**3a–4a**); the observation of signals at δ 3.91 and 4.95, each integrating for ca. 0.5 H, was especially significant and strongly implied a 50:50 mixture of **3b** and **4b**. The nortricyclene skeleton was confirmed by observation of a near-infrared band[17] at 1.663 μm. Repeated dry column chromatography[16] lead to separation of the two adducts (**3b–4b**); this separation was confirmed by NMR since one sample displayed a δ 3.91 signal[5] and the other a δ 4.95 signal (1 H).[18] Saponification of the **3b** and **4b** samples (individually and mixed) gave rise to diacids **3a** and lactone **5a**; the ester sample with the NMR signal ($CDCl_3$) at δ 3.91 (1 H) gave rise to lactone **5a**; the ester sample with the signal at δ 4.95 gave rise to diacid with the signal at δ 4.95. Lactone characterization procedures are well described[5,7] (ir shows high-energy C=O stretch; see Experimental Section). It has been clearly established that such lactone formation requires exo (C-5) chlorine and endo (C-3) carboxyl groups[19] and thus the δ 4.00 diacid sample is **4a**, the δ 3.91 diester sample is **4b**, the δ 4.95 diacid sample is **3a**, and the δ 4.95 diester sample is **3b**. In view of the known[20] deshielding effect of CO_2R groups (R = alkyl) when endo at C-3 (or C-5) upon endo protons at C-5 (or C-3), the preceding assignment was surprising. We can only speculate that the phenylthio group imposes an unusual conformational orientation upon the geminal carbomethoxy or carboxyl group such that the proton α to chlorine is thrust into the shielding cone of the endo carbonyl group of **4a** and **4b**.

In view of the varied stereochemical results that predictably depend upon the nature of the sulfenyl halide addendum,[8,21] we felt that the addition of *p*-toluenesulfenyl chloride to **1b** offered a better possibility for reaction solely via bridged ion **2d** (and thus production of product **3d** only). That this is not the case is shown in the Experimental Section and discussed here. Addition of *p*-toluenesulfenyl chloride to **1b** proceeded smoothly, in substantial yield, to give adduct which was identified as a mixture of **3d–4d** (ca. 1:1) by the same investigational procedure described above for the **3b–4b** mixture. Briefly, **3d–4d** displayed an NMR spectrum (generally similar to the spectrum of the **3b–4b** mixture) with chemical shifts at δ 3.87 (0.5 H) and at δ 4.96 (0.5 H), assigned (based on arguments above and evidence below) to the proton α to Cl in **4d** and **3d**, respectively. These isomers were separable by fractional crystallization; saponification of the separated esters lead to diacid **3c** (from **3d**) and lactone **5c** (from **4d**). Saponification of these isomers also showed that the ester with the more downfield NMR signal for the proton α to chlorine (**3d**) corresponded to the acid (**3c**) with the more downfield NMR signal for the proton α to chlorine; acid **4c** was never isolated. Kinetic control is supported since the adducts (**4d** and **3d**), when treated under addition reaction conditions, did not interconvert. Thus ionic cleavage of the cyclopropane ring with *p*-toluenesulfenyl chloride, as well as with benzenesulfenyl chloride, resulted in electrophilic cleavage of the ring with retention (**3** type products) and inversion (**4** type products) processes[1] and with nearly equal amounts of the two processes occurring in each of the two addition reactions.

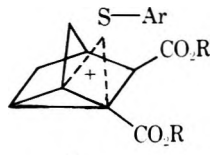
The results observed here can be interpreted in the light of previous discussions.[1,2] In view of the two highly electron-withdrawing carbomethoxy (or carboxyl) groups, the substantially stabilized carbocation apparently necessary[1-3] for nucleophilic cleavage retention product (endo C-5-chlorine) is not available; previous nucleophile cleavage studies on the same carbon skeleton experimentally support this idea.[5] Cleavage of the 5–6 (or 1–7) bond in **1** (**a** or **b**) is not surprising in view of the approximately 40 kcal/mol in stability gained by loss of ring strain.[22]

The approximately 1:1 (**3**:**4**) product ratios clearly preclude **2** type precursors as the sole stereochemistry-determining intermediates; this was somewhat surprising in view of the known excellent bridging ability of vicinal sul-

fur.[8,20,21,23] The reaction has shunned the edge-attached (2 intermediate) pathway for a pathway that likely involves corner-attached species such as 7 and 8 (formed in nearly



7 8



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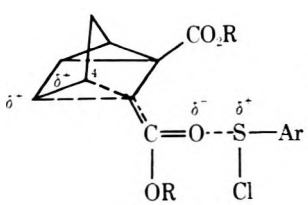
equal amounts). These intermediates likely are an order of magnitude[23] more stable than previously anticipated.[1,10,11] Based upon experimental results, we cannot rule out edge-attached species (2 and 9) as transition states leading to the corner-attached intermediates (7 and 8, respectively), but there does not seem to be any clear reason to retain both types. Finally, we should also consider polarized interactions (e.g., 10) analogous to the proposed[5] precursors to the enediol intermediates (e.g., 6). Such interaction would be consistent[5] with the nucleophile cleavage process (inversion) reported herein but the requisite analog to the enediol (6)[5] intermediate, 11, seems very unlikely. Thus, our results are most easily interpreted in terms of intermediates such as 7 or 8 (or 10).[5,24]



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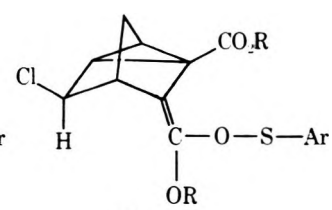

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Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 257 instrument. Proton magnetic resonance (^{1}H NMR) spectra were obtained on a Perkin-Elmer R-20 (60 MHz) instrument. Chemical shifts are expressed as parts per million relative to Me_4Si (δ 0.00). Mass spectra were obtained from a Perkin-Elmer RMU-6E instrument. Microanalyses were done by Baron Consulting Orange, Conn. NMR notations: s, singlet; d, doublet; t, triplet; brs, broadened singlet.

The preparations of diacid **1a** and diester **1b** are modifications of known procedures.[12,25]

Preparation of the Dimethyl Ester of Quadricyclenedicarboxylic Acid (1b). The methyl sulfate (dimethyl sulfate) to be used in this preparation should be carefully purified by both of the procedures described by Vogel.[26] A solution of 4.0 g (0.020 mol) of quadricyclenedicarboxylic acid (**1a**) and 8.4 g (0.060 mol) of anhydrous potassium carbonate, suspended in 180 ml of anhydrous acetone, was prepared. To this stirred mixture was added 4.8 ml (0.050 mol) of the purified dimethyl sulfate. This solution was allowed to reflux for 14 hr. To this warm solution was added 0.4 ml (0.010 mol) of concentrated ammonium hydroxide and the reflux procedure was continued for an additional 10 min. The solution was evaporated to dryness (rotary evaporator) and the resulting materials were dissolved in 25 ml of water. This aqueous solution was extracted with 8 × 75 ml of chloroform. Any solids that resulted from this work-up were filtered off and washed with chloroform and the chloroform washings were added to the chloroform extracts. The combined chloroform solutions were extracted with 2 × 250 ml of saturated sodium chloride and once with water (250 ml) and dried over magnesium sulfate. Filtration and solvent removal (rotary evaporator) resulted in a yellow oil. Distillation at 110–115° (0.45 Torr) resulted in pure (79% yield) quadricyclene diester (**1b**); the pot temperature must *not* be allowed to exceed 135°. Use of a Rinco Kugelrohr (horizontal) distillation apparatus allows vacuum distillation that does not require severe pot temperatures. Multiple distillations often lead to samples that spontaneously crystallize (various melting points in the area of 52–58°, some ranges as narrow as 3°). Liquid samples resulted in accurate quantitative elemental (C, H) analyses (C, 63.18; H, 5.98; calcd C, 63.45; H, 5.81) and were used for spectral analyses: ir (thin liquid film) 3080, 2990, 2950, 2860 (C–H stretch), 1715 (C=O stretch), 1440 ($\delta_{as}CH_3$), 1383 (δ_sCH_3), 1300 (ring skeleton C–H bend), 1230 [C(CO)–O "C–O" stretch], 1108 cm^{-1} (O–CH_3 stretch); NMR ($CDCl_3$) m, δ 2.2–2.55 (6 H, ring skeleton); s, δ 3.68 (6 H, CO_2CH_3); n^{23}D 1.4995 (lit.[12] n^{20}D 1.5022, n^{25}D 1.5022).

Addition of Benzenesulfenyl Chloride to Dimethyl Ester of Quadricyclenedicarboxylic Acid (1b). To a solution of 1.11 g (5.3 mmol) of the dimethyl ester of quadricyclenedicarboxylic acid (**1b**) in 40 ml of dry methylene chloride at room temperature, the freshly distilled benzenesulfenyl chloride[13] (0.763 g, 5.3 mmol) was added dropwise. The first and second drops of red benzenesulfenyl chloride added to the reaction flask were decolorized immediately. The red color of the reagent upon mixing changed to yellow during the remaining addition. By the end of the addition, the reaction temperature had risen from 29° to 45°. The mixture was stirred for another 8 hr at room temperature, resulting in a slightly yellow solution. The solvent was then removed (rotary evaporator) to yield a pale, yellow, viscous liquid (mixture of isomers **3b, 4b**), 1.8 g (100% crude yield). NMR data (solvent $CDCl_3$): m, δ 1.4–2.8, 5 H, nortricyclene skeleton protons; s, δ 3.64, 3 H, CO_2CH_3; s, δ 3.70, 3 H, CO_2CH_3; brs, δ 3.91, 0.5 H, H α to Cl in **4b**; brs, δ 4.95, 0.5 H, α to Cl in **3b**; m, δ 7.2–7.8, 5 H, aromatic protons.

The reaction product was fractionated (see below) by dry column chromatography[16] (silica gel) to yield 1.53 g (82%) of two liquid isomers, **3b** and **4b**, in the ratio of 50:50 as demonstrated by NMR. One (isomer **3b**) is a colorless, viscous liquid, n^{25}D 1.5617, while the other (isomer **4b**) crystallized spontaneously (mp 110–113°). The ester adducts (**3b, 4b**) gave a negative test for chlorine upon reaction with alcoholic silver nitrate while a positive chlorine test was obtained from a sodium fusion test.

Anal. Calcd for $C_{17}H_{17}O_4SCl$: C, 57.86; H, 4.85; O, 18.13; Cl, 10.05; S, 9.08. Found: C, 57.58; H, 4.57; O, 18.9; Cl, 10.15; S, 8.80.

NMR data of solid isomer (**4b**) (solvent $CDCl_3$): m, δ 2.1–2.8, 5 H, nortricyclene skeleton protons; s, δ 3.64, 3 H, CO_2CH_3; s, δ 3.7, 3 H, CO_2CH_3; brs δ 3.92, 1 H, H α to Cl; m, δ 7.2–7.8, 5 H, aromatic protons.

NMR data of liquid isomer (**3b**) (solvent $CDCl_3$): m, δ 1.6–2.4, 5 H, nortricyclene skeleton protons; s, δ 3.64, 3 H, CO_2CH_3; s, δ 3.7, 3 H, CO_2CH_3; brs, δ 4.95, 1 H, H α to Cl; m, δ 7.2–7.8, 5 H, aromatic protons.

Near-infrared of each isomer (**3b, 4b**) (solvent CCl_4), instrument Beckman DK-2A, tungsten lamp, 0.5 *M*) each showed a peak at 1.663 μm indicative of a nortricyclene structure.[17]

A mass spectrum of a **3c–4c** (1:1) mixture showed a molecular ion (*m/e* 352) of intensity 49% (base peak, *m/e* 211, 100%). Defining the molecular ion as 100% results in *m/e* 353 (M + 1) and 354 (M + 2) peaks of, respectively, 20.9 and 40.4% (calcd for $C_{17}H_{17}O_4SCl$: M + 1, 19.8; M + 2, 39.6).

Separation of the Isomeric *exo*-5-chloro-*exo*- (4b) and *endo*- (3b) -3-phenylthio-2,3-*exo*- (and *endo*-) dicarbomethoxytricyclo[2.2.1.0^{2,6}]heptanes by Dry Column Chromatography.[16] A nylon dry column with 2-in. diameter and 16-in. length was used for the mixture of 2.3 g of isomers **3b** and **4b**. The column was sealed and packed with silica gel.[16] The liquid mixture of ester adducts **3b** and **4b** was dissolved in 20 ml of anhydrous ether and 11.5 g of silica gel (five times the weight of the mixture) was added to the solution. The solvent was then removed (rotary evaporator) at 30–40°. The dry compound–silica gel mixture was deposited on the top of the column which then was covered with a layer (0.5 in.) of sand. A mixture of 20% ether and 80% petroleum ether (determined by TLC as a suitable developing solvent) was allowed to drop from a separatory funnel to the column under a constant liquid head of 5.0 cm. When the solvent reached the bottom of the column, the only band (located by ultraviolet light) present on the column was sliced into five segments. Each segment was extracted with anhydrous ether. The first three segments (top site) yielded 1.195 g of the colorless liquid (isomer **3b**), the fourth segment gave 0.895 g of the mixture of two isomers, whereas 0.387 g of isomer **4b** was obtained from the last segment (total yield was 84%).

Saponification of Diester 3b. To a solution of 0.376 (1 mmol) of liquid ester adduct **3b** in 20 ml of 100% ethanol, 1.8 g of 85% potassium hydroxide in water was added. The mixture was stirred at

room temperature for 2.5 days. An orange solution with a white precipitate was obtained at the end of this period. To this mixture, 200 ml of water was added which dissolved the precipitate. The solution was acidified (Congo Red indicator paper) with 5% hydrochloric acid and was left at room temperature for 1 day (a light brown solid precipitated). The crude product was recrystallized from anhydrous ether and decolorized with charcoal to give 0.121 g of white, solid, diacid product (**3a**). In addition, 0.210 g of white solid was obtained from extraction of the aqueous solution with anhydrous ether, decolorization with charcoal, and drying over magnesium sulfate, followed by evaporation of solvent (rotary evaporator) (95% total yield). This solid melted (with foaming) at 234–238° and stopped foaming and turned brown at 241°. NMR data (solvent, polysol-*d*): m, δ 1.1–2.4, 5 H, nortricyclene skeleton protons; s, δ 4.87, 1 H, H α to Cl; m, δ 7.2–7.8, 5 H, aromatic protons; s, δ 10.0, 2 H, COOH. Ir (Nujol): 5.82 and 6.15 μm (1718 and 1626 cm^{-1}) (C=O stretch). Anal. Calcd for $C_{15}H_{13}O_4ClS$: C, 55.46; H, 4.03; O, 19.70; Cl, 10.91; S, 9.87. Found: C, 55.65; H, 4.15; O, 19.87; Cl, 10.67; S, 9.66.

Attempted Lactonization of *exo*-5-Chloro-*endo*-3-phenylthiotricyclo[2.2.1.$0^{2,6}$]heptane-2,*exo*-3-Dicarboxylic Acid (3a). This is a modification of the procedure of Cristol and LaLonde.[12] A suspension of 0.20 g of acid adduct **3a** in 200 ml of water was allowed to reflux for 2 hr. During this time the solid dissolved. The water was then removed (rotary evaporator) and the resulting solid was vacuum dried to give 0.20 g (100% yield) of starting material (**3a**). The melting point, infrared, and NMR (including proton α to Cl at δ 4.95, polysol-*d* solvent) spectra of the resulting solid were exactly the same as of the acid adduct **3a**. There was no lactone absorption[12] in the infrared spectrum.

Saponification of *exo*-5-Chloro-*exo*-3-phenylthiotricyclo-[2.2.1.$0^{2,6}$]heptane-2,*endo*-3-dicarboxylic Acid Dimethyl Ester (4b). To a solution of 1.54 g (4 mmol) of solid ester adduct **4b** in 50 ml of 100% ethanol, 4.4 g of 85% potassium hydroxide in water was added. The mixture was stirred at room temperature for 2.5 days. At the end of this period, the orange solution with a white precipitate was obtained. To this saponification mixture, 250 ml of water was added to dissolve the precipitate. The solution was acidified (Congo Red indicator paper) with 5% hydrochloric acid and was left at room temperature for 1 day. A 0.285-g precipitate of mixed dark brown and white solids formed. The crude precipitate was recrystallized from water (reflux) and decolorized with charcoal to give 0.18 g of white solid of the lactone **5a**, mp 198–200°. An additional 0.677 g of white solid was obtained from extraction of the aqueous layer with ether, decolorization with charcoal, drying over magnesium sulfate, evaporation of solvent, and recrystallization in water (76% total yield). The NMR spectra taken before and after purification were the same.

NMR (solvent polysol-*d*): m, δ 1.7–2.7, 5 H, nortricyclene skeleton protons; brs, δ 4.87, 1 H, HCO of lactone; m, δ 7.2–7.7, 5 H, aromatic proton; brs, δ 8.85, 1 H, COOH. Ir (Nujol): 5.62 μm (1779 cm^{-1}) (C=O stretch of lactone),[7] 5.92 μm (1689 cm^{-1}) (C=O stretch of COOH group).

Anal. Calcd for $C_{15}H_{12}O_4S$: C, 62.48; H, 4.20; O, 27.20; S, 11.12. Found: C, 62.30; H, 4.34; O, 22.44; S, 10.92.

Preparation of *p*-Toluenesulfenyl Chloride. To a three-necked flask, equipped with a condenser (topped by a $CaCl_2$ drying tube), a thermometer, and a magnetic stirrer, was added 3.46 g (1.54 mmol) of *p*-tolyl disulfide (Aldrich). The solid disulfide was dissolved in 9.0 ml of methylene chloride (freshly distilled from calcium chloride); to this stirred, aluminum foil jacketed, yellow-green solution was added 1.14 ml (1.40 mmol) of freshly distilled (bp 69–70°) sulfuryl chloride (Eastman). Stirring this solution for 2 days at room temperature resulted in an orange solution; solvent removal (rotary evaporator) yielded a reddish-yellow solid and a red liquid. The red liquid was decanted and passed through a glass sintered funnel into a vacuum distillation apparatus. Red liquid fractions (combined yield 44%) boiling at ca. 55° (0.45 Torr) were stored (refrigerator) and used for analysis and preparative purposes. NMR ($CDCl_3$): δ 2.36, s, 3 H, CH_3; δ 7.20, apparent doublet, 2 H; δ 7.60, apparent doublet, 2 H, aromatic AA'BB' system; ir (thin film) 3000 (aromatic C–H stretch), 2895, 2830 (aliphatic C–H stretch); 1582, 1478 (aromatic C=C stretch); 1388, 1366 (methyl C–H bend); 791 (aromatic C–H bend); 640 (C–S stretch); 500 cm^{-1} (S–Cl stretch). The methyl group (NMR) of the disulfide precursor (δ 2.29, $CDCl_3$) was undetected in these samples.

Addition of *p*-Toluenesulfenyl Chloride to Diester 1b. A solution of 4.80 g (0.023 mol) of diester **1b** in 80 ml of methylene chloride was placed in the same type of apparatus as used in the preceding experiment. To this pale yellow solution, 3.64 g (0.023 mol) of *p*-toluenesulfenyl chloride was added dropwise over a period of 5 min. This red-orange solution was stirred at room temperature for 3 hr, whereupon the color had returned to pale yellow. Stirring was continued for 48 hr (room temperature); solvent removal (rotary evaporator) resulted in 8.5 g (ca. 100% crude yield) of an amorphous substance. The NMR spectrum of this substance indicated that it was primarily **4d** and **3d** (in nearly equal amounts). Treatment of the amorphous material with several small (ca. 2 ml) portions of anhydrous ether resulted in a fine, powdery, white precipitate (**4d**, mp 122.5–127.5°) which was removed with a glass-sintered filter; the remaining solution yielded a rigid, brown powder (**3d**, mp 53–62°) upon solvent removal. Compound **4d** could be recrystallized from ether: mp 130–133°; ir (KBr pellet) 3070 (cyclopropane C–H stretch); 3010, 2990 (aromatic C–H stretch): 2945, 2908 (aliphatic C–H stretch); 1712 (broad) (C=O stretch); 1593 (C=C stretch); 1484, δ CH_2; 1428, δ_{as} CH_3; 1367, δ_s CH_3; multiple complex bands 1260–1150 (C–O "alcohol" stretch of esters); 1127, 1105 (C(C=O)O stretch of esters); 797 ("nortricyclene" band);[27] 840, 777 (out-of-plane, aromatic C–H bend); 690 cm^{-1} (C–Cl and/or C–S stretch). Ir of **3d** (KBr pellet): 3067 (cyclopropane C–H stretch), 3008 (aromatic C–H stretch); 2950, 2930, 2880, 2860 (aliphatic C–H stretch); 1491, δ CH_2; 1438, δ_{as} CH_3; 1374, δ_s CH_3; multiple, complex bands 1260–1150 (C–O "alcohol" stretch of ester); 1163, 1130, 1112 (C(C=O)O stretch); 842, 809, 750 (out-of-plane, aromatic C–H bend); 772 ("nortricyclene" band);[30] 705, 692 cm^{-1} (C–Cl and C–S stretch). NMR spectrum of **4d** ($CDCl_3$): δ 2.03–2.79, m, 5 H, nortricyclene ring skeleton; δ 2.34, s, 3 H, $ArCH_3$; δ 3.67, s, 3 H, CO_2CH_3; δ 3.73, s, 3 H, CO_2CH_3; δ 3.89, brs, 1 H, CHCl; δ 7.07–7.37, apparent doublet, 2 H, benzenoid, ortho to CH_3 group; δ 7.37–7.59, apparent doublet, 2 H, benzenoid, ortho to SR group. NMR spectrum of **3d** ($CDCl_3$): δ 1.83–2.57, m, 5 H, nortricyclene ring skeleton; δ 2.33, s, 3 H, $ArCH_3$; δ 3.66. s, 3 H, CO_2CH_3; δ 3.71, s, 3 H, CO_2CH_3; δ 4.96, brs, 1 H, CHCl; δ 7.00–7.36, distorted apparent doublet, 2 H, benzenoid, ortho to CH_3 group, apparent doublet, 2 H, benzenoid, ortho to SR group. The NMR spectrum of this sample of **3d** showed a trace amount of the CHCl signal of **4d**, indicating a small amount of contamination by **4d**.

Saponification of Diester Adduct 4d (Leading to Lactone 5c). A charge of 5.6 g of reagent grade (Baker) potassium hydroxide was added (with magnetic stirring) to a solution of 1.6 g of adduct **4d** in 50 ml of (Fisher reagent) methanol; this procedure was carried out in the 500-ml round-bottom flask portion of a standard reflux apparatus. Continual stirring for 2 days (room temperature) did not result in a homogeneous solution; homogenization was effected by reflux for 15 min. Since color formation implied substantial reaction, the solution was acidified (to litmus) with aqueous hydrogen chloride. This solution was allowed to reflux for 2 days; methanol removal (rotary evaporator) afforded 0.15 g of a tan powder (presumably lactone **5c**) which precipitated from the aqueous system. Acetone was added to effect dissolution resulting in precipitation of a new white solid (assumedly potassium chloride); after removal of the solid, the solution was extracted with 4 × 150 ml of ether. Solvent removal gave 0.90 g of yellow powder (combined, crude yield 1.05 g, 85%). The combined solids were recrystallized from ether to give 0.80 g of lactone **5c**, mp 213–215°, 68.5% yield; ir (KBr pellet) 3650–2400 (max at 3422) (O–H stretch of CO_2H), 1787 (C=O stretch of lactone),[5] 1693 cm^{-1} (C=O stretch of CO_2H); NMR (dimethyl sulfoxide-d_6) δ 1.89–2.76, ca. 5 H, m, ring skeleton protons plus CD_3SOCD_2H; δ 2.30, s, 3 H, $ArCH_3$; δ 4.60, brs, 1 H, CO_2H (and/or water); δ 4.93, 1 H, brs, CHO– of lactone moiety;[5] δ 7.06–7.56, 4 H, pair of apparent doublets, aromatic protons, AA'BB'; system.

Saponification of Diester Adduct 3d (Leading to Diacid Formation). Exactly the same procedure was used here as for the isomer **4d** above, up to the point of ether solvent removal; this afforded a tan powder (0.70 g, 56% yield, mp 203.5–207°). This tan powder was spectrally consistent with one of the two half-esters of **3d**; ir spectrum (KBr pellet) 3600–2300 (O–H stretch of CO_2H), 1739 cm^{-1} [C=O stretch of ester group, overlaps with 1712 (C=O stretch of carboxylic acid group)]; NMR spectrum (dimethyl sulfoxide-d_6) δ 1.25–2.60, ca. 7 H, m, ring skeleton protons plus CD_3SOCD_2H; δ 3.66, s, 3 H, CO_2CH_3; δ 4.96, 1 H, brs, CHCl; δ 7.10–7.72, 4 H. pair of apparent doublets, aromatic protons, AA'BB' system.

Virtually all of this sample of tan powder was placed under the same type of experimental conditions as above, except that it was subjected to 0.50 g (2.84 mmol, 2 equiv) of potassium hydroxide; this solution was stirred for 1.5 weeks (room temperature). The solution was then heated (steam bath) to reflux for 0.5 hr. Neutral-

ization (as above) was followed by solvent removal (rotary evaporator). The resulting tan precipitate was filtered off and dissolved in ether and the new solution was dried (magnesium sulfate). Solvent removal (rotary evaporator) afforded a semiamorphous, tan powder (0.43 g, 31% crude yield). The NMR spectrum (dimethyl sulfoxide-d_6) showed no signal at δ 3.66 and was consistent with diacid **3c**: δ 1.54–2.68, m, ca. 5 H, ring skeleton protons plus solvent impurities, δ 2.33, 3 H, s, $ArCH_3$; δ 4.88, brs, 1 H, CHCl; δ 7.10–7.71, 4 H, pair of apparent doublets, aromatic protons, AA'BB' system.

This sample (presumably diacid adduct **3c**) was allowed to reflux in water for 8 hr. Ether extraction (3 × 100 ml) and solvent removal (rotary evaporator) afforded 100% yield of a semiamorphous, brown solid that had NMR ($CDCl_3$) and infrared signals attributable to diacid **3c** only.

Kinetic Control Determinations on Diester Adducts 4d and 3d. A solution of 0.15 g (0.41 mmol) of adduct **4d** and 0.060 g of *p*-toluenesulfenyl chloride in 15 ml of methylene chloride was allowed to stir for 4 days in a system protected from light (aluminum foil on outer surface of flask) and from water (calcium chloride drying tube). NMR analysis ($CDCl_3$) of the sample (obtained upon solvent removal did not reveal the presence of **3d** (no signal near δ 4.90); only signals attributable to the reagents and/or *p*-toluene disulfide were observed. An experiment that was nearly identical with the preceding (except that 3.69 mmol of each of **3d** and the arenesulfenyl halide were combined in 25 ml of methylene chloride for 2.5 days) was carried out. Solvent removal afforded a sample which demonstrated (NMR, $CDCl_3$) that no change (within experimental error estimated at ±10%) had occurred in the minor proportion (ca. 20%) of isomer **4d** (δ 3.90 signal) in this sample of adduct **3d** (δ 4.98 signal).

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Registry No.—**1a**, 30715-39-0; **1b**, 714-53-4; **3a**, 55925-35-0; **3b**, 56084-09-4; **3c**, 55975-75-2; **3d**, 55925-66-1; **4b**, 55925-67-2; **4d**, 55954-93-3; **5a**, 55925-68-3; **5c**, 55925-69-4; benzenesulfonyl chloride, 931-59-9; *p*-toluenesulfonyl chloride, 933-00-6.

References and Notes

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(10) G. Klopman, *J. Am. Chem. Soc.*, **91**, 89 (1969).
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(13) Arenesulfenyl halides were prepared by the method of W. M. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, **90**, 2080 (1968).
(14) The dimethyl ester **1b** has been reportedly[12] synthesized by diazomethane treatment of **1a**. In our hands, the procedure resulted in a sample of refractive index ($n^{23}D$ 1.4800) quite different from that reported earlier;[12] this sample showed two (or more) NMR signals in the CH_3O region (δ 3.5–4.0) and three gas chromatographic peaks.
(15) Our methylation procedure is an adaptation of the procedure used by Mirrington to methylate phenols. The procedure is especially useful for acid-sensitive substrates: R. N. Mirrington and G. I. Feutrill, *Tetrahedron Lett.*, 1327 (1970). We used acetone, rather than *N,N*-dimethylformamide, as a solvent. In view of the sensitivity of the rings in **1a** to acid and base cleavage our results demonstrate the utility of this procedure under such demands.
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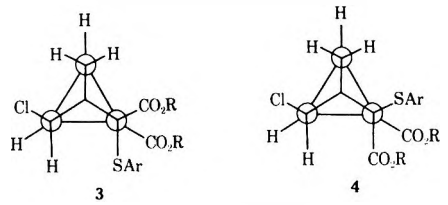
(17) It has been shown that the nortricyclene, quadricyclene, and corresponding olefinic isomers all give unique near-infrared bands: P. G. Gassman and W. M. Hooker, *J. Am. Chem. Soc.*, **87**, 1079 (1965).
(18) This separation[16] is impressive in view of the fact that diastereoisomers **3b** and **4b** have very subtle structure differences (replacement of Cl by



H in **3b** and **4b** gives rise to enantiomers) and thus they would be expected to have minute dipolar differences. The signals of δ 3.91 and 4.18 are assumed to be due to protons on carbon bearing chlorine.
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(21) (a) S. J. Cristol, et al., *J. Am. Chem. Soc.*, **79**, 6035 (1957); (b) T. C. Morrill and N. D. Saraceno, "The Addition of 2,4-Dinitrobenzenesulfenyl Chloride to Norbornadiene: The Absence of Results Directed by a Bridged Sulfonium Ion", Abstract 259, XXIII IUPAC Meeting, Boston, Mass., July 25–30, 1971. These works suggest that the methyl group on the aryl group should provide greater positive charge stabilization, thus enhancing bridging.
(22) The strain energy of nortricyclene has recently been reestimated to be 38.8 kcal/mol and that of quadricyclene to be 78.7 kcal/mol: H. K. Hall, Jr., et al., *J. Am. Chem. Soc.*, **95**, 3197 (1973).
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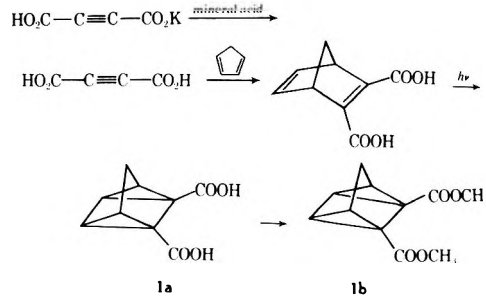
(24) The second site of positive charge (delocalization to C-4) in **10** is possible in view of earlier studies;[5] there is no evidence, however, of the (highly strained) product that would arise as a result of nucleophilic attack at that position.
(25) The sequence



has been described.[7] We have not included our preparation descriptions, in order to preserve space, but it should be pointed out that we have improved upon the procedure in all steps and the procedure used earlier[12] to prepare **1b** was likely not completely successful.[14]
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(27) G. T. Youngblood et al., *J. Org. Chem.*, **23**, 684 (1958); also note the discussion in ref 17.

Oxidations By Thionyl Chloride. VI. Mechanism of the Reaction with Cinnamic Acids[1,2]

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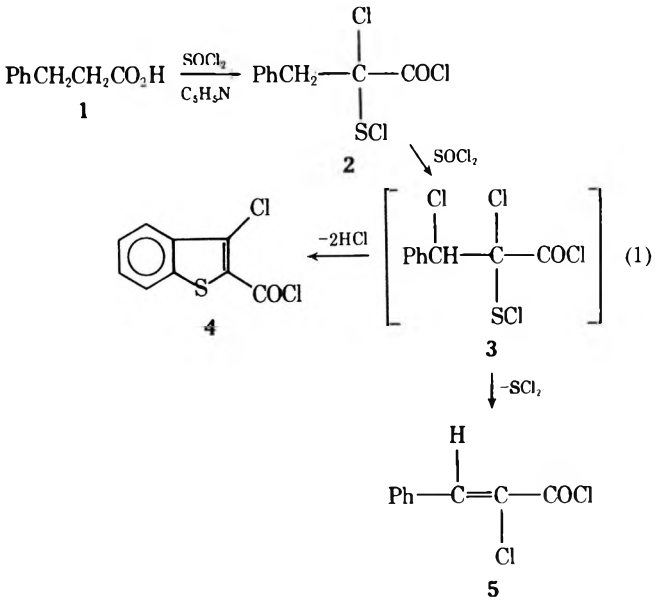
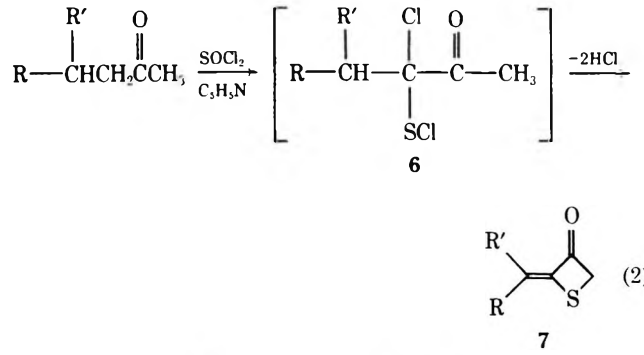
Thionyl chloride, in the presence of catalytic amounts of pyridine, apparently adds across the double bonds of α,β-unsaturated carboxylic acids to form β-chloro-α-chlorosulfinyl acid chloride intermediates which are converted to α,β-dichloro-α-chlorosulfenyl acid chlorides which can be isolated. Thus, *trans*-crotonic acid (**11**) gave 2-chlorosulfenyl-2,3-dichlorobutanoyl chloride (**12**, 55%) which upon heating decomposed to *trans*-2-chloro-2-butenoyl chloride (**13**) and sulfur dichloride. *trans*-Cinnamic acid (**9**) furnished 3-chloro-2-chlorocarbonylbenzo[*b*]thiophene (**4**, 69%) and *trans*-2-chloro-3-phenylpropenoyl chloride (**5**, 23%) as a result of further transformation of the sulfenyl chloride **3** which could be isolated in 19% yield. Mechanism of the cyclization of **3** to **4** was studied by product analyses in the reaction with *m*-nitrocinnamic acid (**20**), *m*-methoxycinnamic acid (**26**), *p*-nitrostilbene (**31**), 3-(3-methoxyphenyl)propanoic acid (**36**), and 3-(3-formylphenyl)propanoic acid (**45**). Both electrophilic and nucleophilic cyclizations were rejected by successful isolation of the benzo[*b*]thiophenes **21** and **22** from **20** and of **27**, **28**, **29**, and **30** from **26**. Isolation of only benzo[*b*]thiophene **34** from the reaction of **31** eliminated episulfide **33** as an intermediate. Formation of 3-unchlorinated benzo[*b*]thiophenes **37**, **38**, and **39** furnished evidence for a concerted elimination–cyclization (CEC) mechanism. The reaction of **45** did not give the expected 3-unchlorinated benzo[*b*]thiophenes, but the benzo[*b*]thiophenes **50**. Formation of **50** could be rationalized in terms of the stereochemical consequence of the CEC mechanism in the transition state. The CEC mechanism appeared to be the most reasonable explanation for the formation of the minor products, **22** and **51**.

In the presence of a catalytic amount of a tertiary amine, thionyl chloride generally oxidizes carboxylic acids and ketones at α carbon atoms to form α-chloro-α-chlorosulfenyl derivatives and their subsequent reaction products. Thus, 3-phenylpropanoic acid (**1**), for example, when treated with an excess of thionyl chloride and a small amount of pyridine, can be converted to sulfenyl chloride **2**, which then undergoes further reaction to form benzo[*b*]thiophene **4** and α-chlorocinnamoyl chloride (**5**) via intermediate **3** (eq 1).[3] Another example is the conversion of methyl ketones to



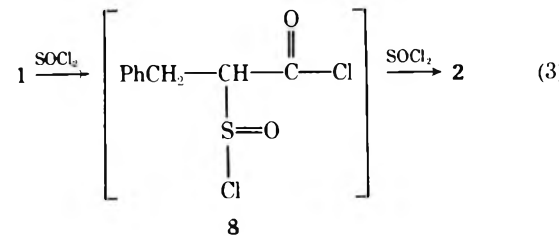
(1)

3-thietanones **7** presumably through intermediates **6**, that offered a one-step synthesis of the four-membered heterocycles (eq 2).[4]

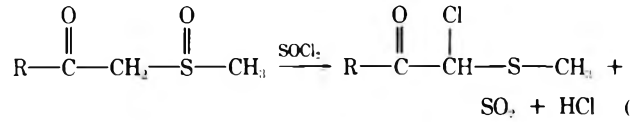


(2)

The proposed mechanism[3] for the formation of **2** from **1**, that involved Hell–Volhard–Zelinsky type reaction of **1** with thionyl chloride to form sulfinyl chloride **8** and subsequent Pummerer-type rearrangement of **8** to **2** (eq 3), was



(3)



(4)

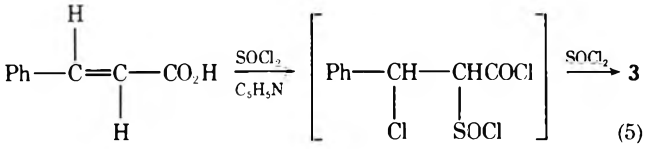
supported by detection[3] of the sulfinyl chloride analogous to **8** from the reaction of 2-methyl-3-phenylpropanoic acid with thionyl chloride–pyridine reagent and by the thionyl chloride induced rearrangement of β-keto sulfoxides[5] (eq 4), the latter being essentially the same sequence as **8** to **2**.

We have shown that β-chlorination,[6] such as the transformation of **2** to **3**, is also a general reaction and that **3** but not **2** undergoes cyclization under the reaction conditions. Like its saturated analog, cinnamic acid **9** can also react with thionyl chloride to form **4** and **5** *via* the sulfenyl chloride **3**. In this paper we describe the mechanism of the reaction of thionyl chloride with cinnamic acids.

Results and Discussion

Treatment of **9** with 4 equiv of thionyl chloride and 0.12 equiv of pyridine at 120–125° for 3 hr furnished **4** and **5** in 69 and 23% yield, respectively. Under milder conditions (bath temperature 88°, 24 hr) sulfenyl chloride **3** could be isolated in 19% yield. Sulfenyl chloride **3**, a yellow, viscous oil, showed in the infrared spectrum characteristic[3,7] multiple bands (5.55, 5.65, and 5.70 μm) in the carbony. region and NMR absorption at τ 2.54 (aromatic) and 4.21 (methine proton).

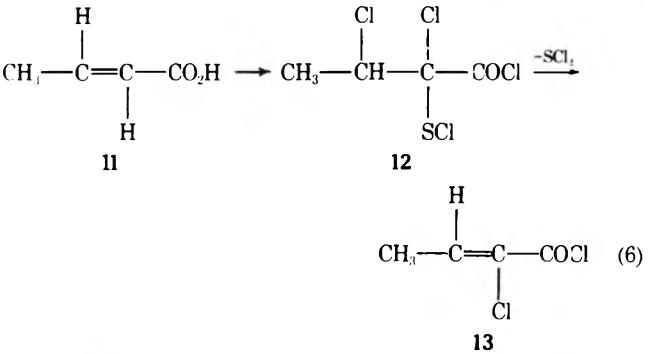
The initial step of the reaction of thionyl chloride with cinnamic acid is no doubt an electrophilic addition of thionyl chloride across the double bond of cinnamoyl chloride to form sulfinyl chloride **10** which is then converted to **3** by the Pummerer reaction (eq 5). Such additions of



(5)

9 **10**

thionyl chloride to carbon–carbon multiple bonds have been reported for at least three different types of compounds: enol ethers,[8] 1,1-diarylethylenes,[9] and acetylenedicarboxylic acid.[10] The addition is particularly facile in the former two types of compounds; for example, the addition to an enol ether to form a sulfoxide is effected at 0° in the absence of catalyst. In contrast to such electron-rich double bonds, the double bonds of α,β-unsaturated carboxylic acids such as **9** do not allow the addition of thionyl chloride in the absence of a catalyst. *trans*-Crotonic acid (**11**), for example, when treated with an excess of thionyl chloride at reflux for 48 hr, gave no addition products but only crotonyl chloride, while the treatment of **11** with 7 equiv of thionyl chloride and 0.12 equiv of pyridine[11] at moderate reflux for 3 hr afforded a mixture which showed virtually no trace of either **11** or crotonyl chloride, as revealed by NMR spectroscopy. Fractional distillation of the mixture furnished sulfenyl chloride **12** and 2-chloro-2-butenoyl chloride (**13**) in 55 and 10% yield, respectively. The latter was identified by converting it to the known[13] *trans*-2-chloro-2-butenamide. Sulfenyl chloride **12**, an approximately 1:1 mixture of diastereomers, revealed infrared absorption at 5.56 and 5.67 μm and NMR signals at τ 5.10 (q, 1 H, J = 6.5 Hz), 8.20 and 8.27 (two sets of d, 3 H, J = 6.5 Hz). Sulfenyl chloride **12** apparently eliminates sulfur dichloride when treated with pyridine hydrochloride and thionyl chloride at reflux, furnishing **13**.

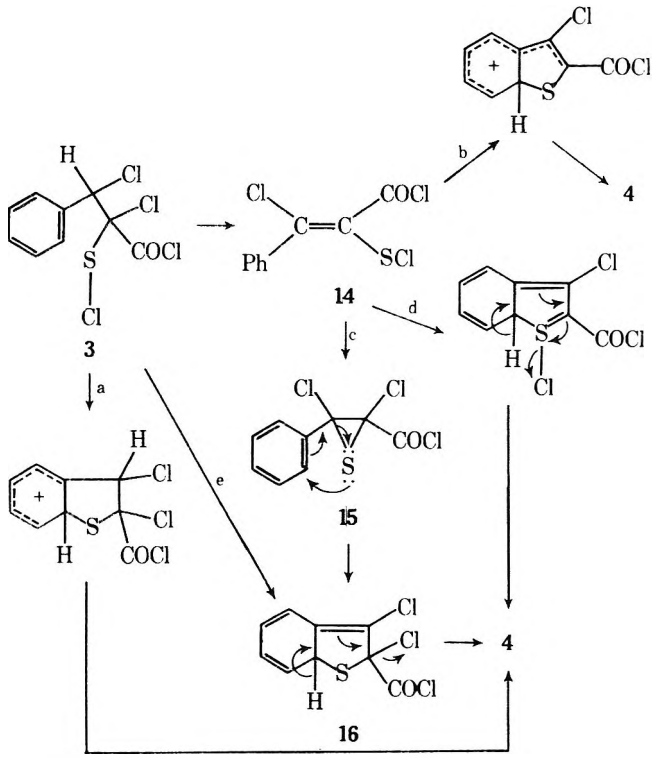


(6)

11 **12** **13**

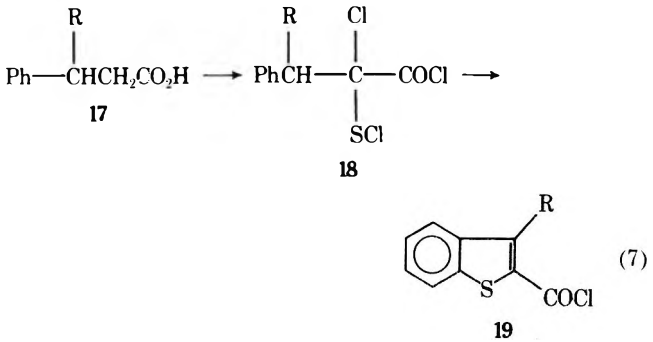
Treatment of **3** with a catalytic amount of pyridine hydrochloride at 130° for 5 hr afforded a mixture of **3** (32%), **4** (38%), and **5** (30%) as revealed by NMR spectroscopy. Fractional crystallization of the mixture from carbon tetrachloride afforded benzo[*b*]thiophene **4** in 36% yield. To account for the cyclization of **3** to **4** we proposed five possible

Scheme I



mechanisms: (a) direct electrophilic substitution; (b) electrophilic substitution of the intermediate **14** which could be formed by 1,2 elimination of hydrogen chloride; (c) rearrangement of **14** to episulfide **15** which could then be transformed into **4** by either nucleophilic attack by sulfur or by a concerted process via **16**; (d) concerted transformation of **14** which can be regarded as a 6-π-electron system; (e) concerted elimination–cyclization of **3** via **16** (see Scheme I). We evaluated each of those mechanisms by means of product analyses and abandoned all but path e.

Electrophilic Cyclization. Treatment of sulfenyl chloride **2** with pyridine hydrochloride under the conditions in which **3** underwent cyclization gave only intractable tar. The anticipated benzo[*b*]thiophene-2-carbonyl chloride could not be isolated.[14] Furthermore, 3,3-diphenylpropanoic acid (**17a**), when treated with thionyl chloride and pyridine, furnished benzo[*b*]thiophene **19a** in 65% yield; however 3-phenylbutanoic acid (**17b**) produced **19b** in 16% yield[15] even though **17b** is converted completely to sulfenyl chloride **18b** under the conditions. Thus, sulfenyl chlorides



(7)

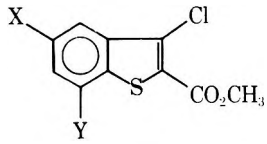
17 **18** **19**

a, R = Ph
b, R = Me

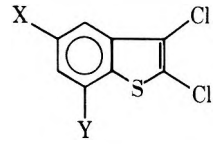
3 and **18a** undergo smooth cyclization, while **2** and **18b** are difficult to cyclize. Comparison of these two groups of sulfenyl chlorides suggested that a direct electrophilic substitution reaction (path a) was unlikely, and that the success of ring closure seemed to be related to the acidity of the

benzylic hydrogens of the sulfenyl chlorides. Therefore the ring closure may be related to the ease of hydrogen chloride elimination from **3** to form **14**.

We next examined the reaction of *m*-nitrocinnamic acid (**20**). Acid **20** was treated with 3.5 equiv of thionyl chloride and 0.12 equiv of pyridine at 135° for 1.5 hr. The product mixture was treated with methanol and separated on an alumina column to furnish four benzo[*b*]thiophenes, **21a**, **21b** (23.4%), **22a** (1.2%), and **22b** (1.8%). Although **21a** was



21

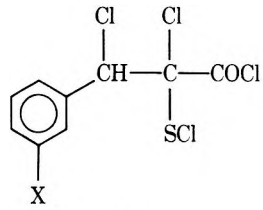


22

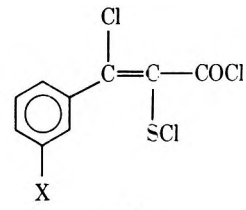
a. X = NO_2; Y = H
b. X = H; Y = NO_2

a major product, only a small amount of it was isolated owing to its difficult separation from **21b**. The structures of those products were assigned by spectroscopic data and elemental analyses. The benzo[*b*]thiophenes **21** were distinguished by NMR spectroscopy,[16] i.e., splitting patterns of the aromatic protons. Both minor products, **22**, showed no carbonyl absorptions in their infrared spectra. Their mass spectra showed molecular ions of *m/e* 247 (base), 249 (68–70%), and 251 (14.5%), indicating the presence of two chlorine atoms. The positions of the nitro groups in **22a** and **22b** were assigned by correlating their ir absorption patterns in the 5–6-μm region[17] with those of 3-chloro-6-nitrobenzo[*b*]thiophene[15] (for **22a**) and 3-chloro-7-nitrobenzo[*b*]thiophene (for **22b**), prepared by saponification and decarboxylation of **21b**.

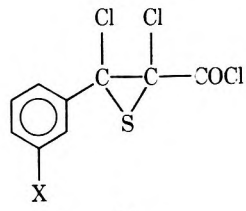
Since a *m*-nitro group deactivates an aromatic ring to electrophilic substitution, the ease of benzo[*b*]thiophene formation from **20** indicated that the ring closure involved neither path a from **23a** nor path b from **24a**, but it rather suggested a nucleophilic process of episulfide **25a**, path c (see Scheme I).



23



24

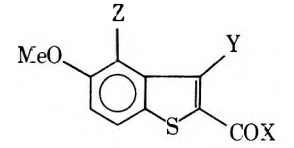


25

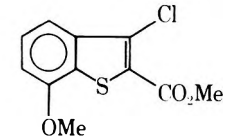
a. X = NO_2
b. X = OCH_3

Episulfide Mechanism. In view of a number of reported instances[18] for rearrangement (and related transformations) of α-halo episulfides to benzo[*b*]thiophenes the episulfide mechanism (path c) was particularly attractive. The behavior of **20** appeared to be consistent with this mechanism. We tested this mechanism by the reactions of thionyl chloride with *m*-methoxycinnamic acid (**26**) and with *p*-nitrostilbene (**31**).

The reaction of **26** afforded four benzo[*b*]thiophenes, **27–30**, under two sets of conditions. In the first set **26** was



27a. X = OMe; Y = Cl; Z = H
27b. X = Y = Cl; Z = H
28. X = OMe; Y = Z = Cl
29. X = OMe; Y = H; Z = Cl



30

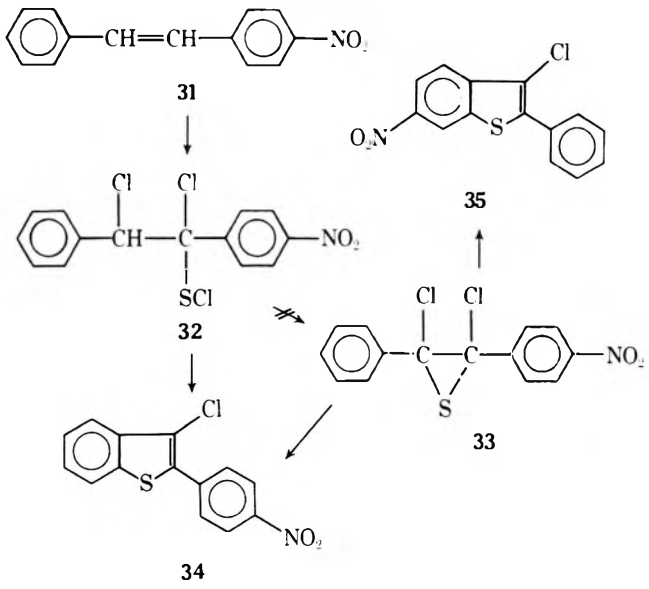
treated with 3.5 equiv of thionyl chloride and 0.12 equiv of pyridine at 140° for 70 min, and the product mixture was treated with methanol and chromatographed on an alumina column to furnish **27a** (26.4%), **28** (1.4%), and **29** (0.8%). In the second set **26** was allowed to react with 7 equiv of thionyl chloride and 0.12 equiv of pyridine at reflux (bath temperature 105°) for 48 hr to yield, after esterification with methanol and separation in the same manner, **27a** (54.4%), **28** (6%), and **30** (2%). Thirdly **26** was treated with an excess of thionyl chloride and a catalytic amount of pyridine at reflux (bath temperature 95–98°) for 21 hr, similar conditions that permitted isolation of sulfenyl chloride **3**. Recrystallization of the product mixture from hexane furnished **27b** in 41.5% yield. The acid chloride of **26** was recovered in 41.3% yield by distillation of the mother liquor.

The structures of benzo[*b*]thiophenes **27–30** were determined by elemental and spectroscopic analyses. The mass spectra of all the compounds showed molecular ions as the base peaks and fragment ions corresponding to the loss of CH_3, OCH_3, $COCH_3$, CO_2CH_3, and $CH_3 + CO_2CH_3$. Each of the peaks was accompanied by isotope peaks of appropriate intensities due to ^{37}Cl and ^{34}S. NMR spectra[16] easily distinguished **27a** from **30**. Compound **28** was also obtained by independent treatment of **27b** with thionyl chloride followed by methanolysis. In the NMR spectrum of **29**, the long-range coupling[16] between the C_3-H and C_7-H aromatic protons permitted the assignment of the structure.

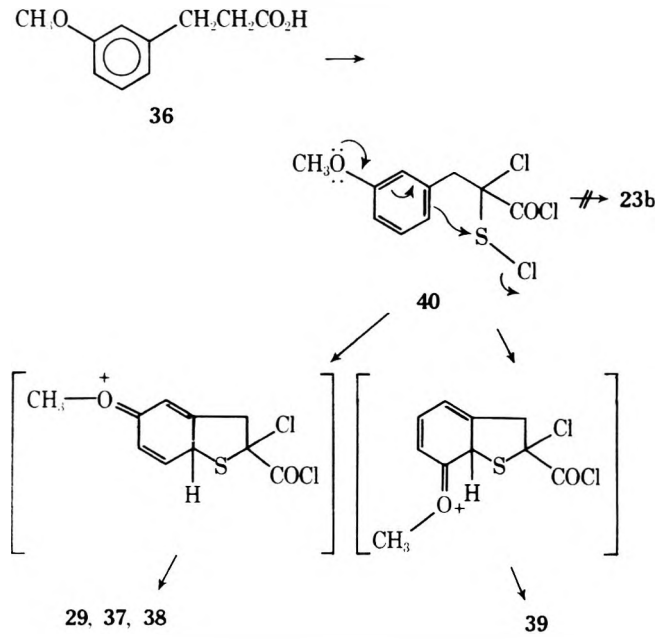
These results with **26** revealed that sulfenyl chloride **23b** undergoes ring closure more readily than sulfenyl chloride **3**. Thus, a *m*-methoxy group, which should effectively suppress a nucleophilic substitution reaction, instead promotes the thiophene ring formation. Furthermore, the formation of **29** cannot be explained by a path involving episulfide **25b** as an intermediate. Therefore, neither a nucleophilic nor a concerted process through an episulfide was a likely mechanism for benzo[*b*]thiophene formation.

Further evidence against the episulfide mechanism was provided by the reaction of *p*-nitrostilbene (**31**). With its strongly electron-withdrawing group at one end of the double bond, **31** is expected to react with thionyl chloride in the same fashion[19] as cinnamic acids. Thus, **31** was treated with an excess of thionyl chloride and a catalytic amount of pyridine at reflux for 48 hr. The product mixture was chromatographed on an alumina column, affording benzo[*b*]thiophene **34** (15.2%), a small amount of **31**, and two other compounds, mp 204–205 and 208–210°, which appeared to be isomeric as shown by their nearly identical infrared spectra. One (mp 204–205°) of the isomers showed a molecular ion at *m/e* 514, which corresponds to formula $C_{28}H_{13}ClN_2O_4S$, a dimeric structure of stilbene **31** linked by sulfur and bearing a chlorine atom. Such products presumably result by addition of sulfenyl chloride **32** to **31** and subsequent elimination of 2 mol of hydrogen chloride. We have not yet determined the structures of these products. The structure of **34** was determined by elemental and spectroscopic analyses, i.e., the mass spectrum revealed molecular ions at *m/e* 289 and 291 and the base peak at *m/e* 208 [M − (NO_2 + Cl)]; the NMR spectrum showed an AA'BB' pattern at τ 1.60 and 1.94 (J = 9.0 Hz) for protons ortho

Scheme II



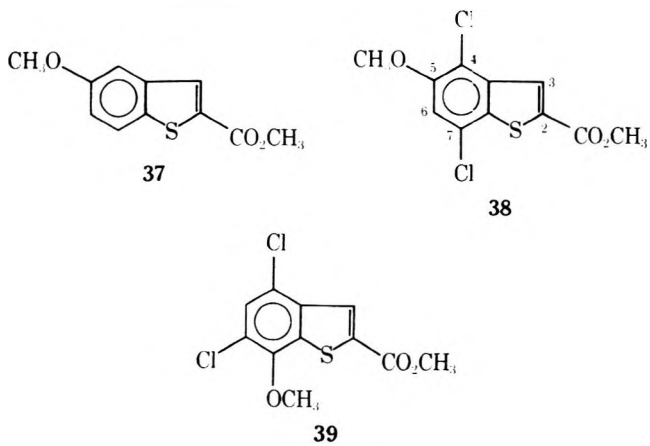
Scheme III



and meta to the nitro group, and a complex at τ 1.91–2.52 which was closely analogous to the spectra of other 2,3-disubstituted benzo[*b*]thiophenes, e.g., 3-chloro-2-methoxycarbonylbenzo[*b*]thiophene. Thus the spectrum unambiguously distinguished **34** from its isomer **35.** Should espisulfide **33** be involved in the process, there is anticipated the formation of an equal amount of **35** which we did not observe (see Scheme II). We therefore conclude that episulfides are not intermediates in the ring closure of sulfenyl chlorides to form benzo[*b*]thiophenes.

Concerted Mechanisms. The concerted cyclization (path d in Scheme I) should be a thermally allowed process, for intermediate **14** can be regarded as a 6-π-electron system. The crucial step in this process appears to be 1,2 elimination of hydrogen chloride from **3** to form **14.** In the concerted elimination–cyclization mechanism (CEC, path e in Scheme I), loss of hydrogen from the benzylic carbon and chlorine atom from the sulfur simultaneously closes the ring to form **16** which then expels another molecule of hydrogen chloride by a 1,4-elimination process to give rise to **4.** For both mechanisms acidity of the benzylic hydrogen is important to the success of the cyclization, as discussed earlier.[2] We examined the operation of these mechanisms by the following reactions.

Treatment of 3-(3-methoxyphenyl)propanoic acid (**36**) with 3.3 equiv of thionyl chloride and a catalytic amount of pyridine at 135° for 2 hr afforded, after esterification with methanol and separation on an alumina column, the known[16b] benzo[*b*]thiophene **37** in 15.5% yield. When **36** reacted with 6.7 equiv of thionyl chloride in the presence of a small amount of pyridine at reflux for 46 hr, it furnished, after similar treatment, benzo[*b*]thiophenes **29, 38,** and **39** in 56, 1.3, and 3% yield, respectively. The structures of the minor products **38** and **39** were determined by elemental and spectroscopic analyses. NMR spectra of both compounds revealed two singlets in the aromatic region, which indicated that one proton was at the C_3 and the other at either C_4, C_5, or C_6 but not at the C_7 position.[16] The spectrum of **38** was compared to that of **29,** while **39** was compared to **30** to establish their structures as indicated. As shown earlier in the formation of **28,** the chlorine substituents in **29, 38,** and **39** are results of further reaction of thionyl chloride on the methoxybenzo[*b*]thiophenes formed. The positions of the chlorine substituents in these compounds are coincident with activated positions under the attack of electrophilic reagents (e.g., thionyl chloride).

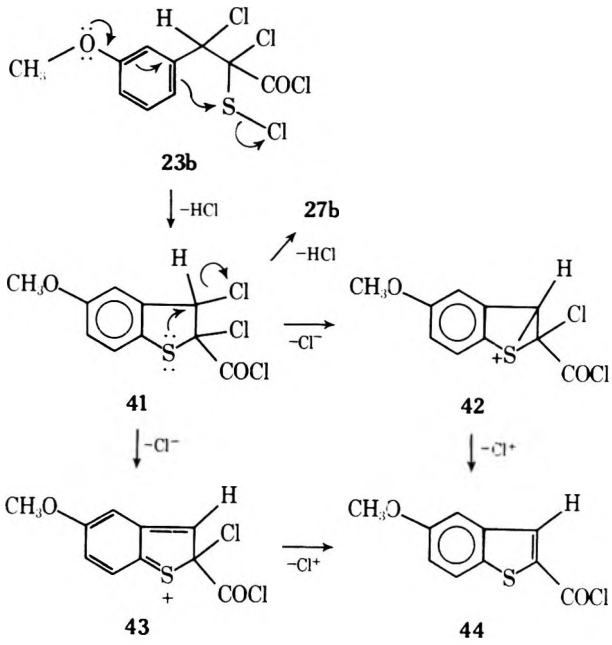


None of the benzo[*b*]thiophenes here has chlorine substituents at the C_3 position. This indicates that sulfenyl chloride **40** undergoes rapid ring closure prior to transformation into **23b** by β-chlorination, while the analogous sulfenyl chloride **2** undergoes cyclization only after its β-chlorination. Apparently the success of ring closure in **40** is assisted by donation of a pair of electrons on the methoxy oxygen (see Scheme III). Although the process can technically be regarded as an electrophilic aromatic substitution reaction, the result also suggests that the cyclization of sulfenyl chlorides such as **3** (in which a lone pair of electrons is not available) proceeds through the generation of a pair of electrons upon loss of an acidic hydrogen (i.e., CEC mechanism).

A possible route for the formation of **29** from the reaction of **26** then might be as follows. Sulfenyl chloride **23b** undergoes cyclization to form intermediate **41** which, by loss of hydrogen chloride, would furnish the major product **27b.** A fraction of **41,** however, might eliminate chlorine molecule to form **44** via cation **42** or **43.** The intermediate **44** would then be chlorinated by thionyl chloride at the C_4 position and esterified in the next step to furnish **29** (see Scheme IV).

For further evidence of the CEC mechanism, we investigated the reaction of 3-(3-formylphenyl)propanoic acid (**45**) with thionyl chloride in the presence of pyridine. Since benzaldehyde is known[20] to form benzal chloride when treated with thionyl chloride, **45** would first be converted to **46** and then to sulfenyl chloride **47.** The hydrogen of the

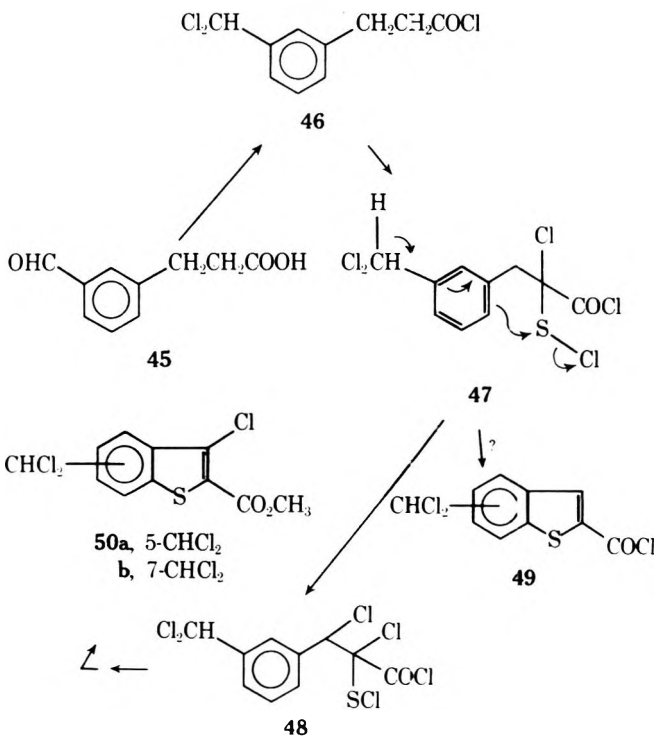
Scheme IV



dichloromethyl group of **47** would be at least equally or more acidic than the benzylic hydrogen of **3**. Thus we expected that **47** would cyclize prior to its conversion to **48** and would furnish benzo[*b*]thiophenes (**49**) which bear no chlorine atoms at their C_3 positions.

We treated **45**[21] with 4 equiv of thionyl chloride and a catalytic amount of pyridine at 140° for 105 min. The reaction mixture was then treated with methanol and separated by column chromatography, furnishing benzo[*b*]thiophenes **50a** and **50b** in 8 and 15% yield, respectively. The rest of the material was a mixture consisting mainly of the methyl ester of **46**. Both **50a** and **50b** showed molecular ions at *m/e* 308 which were accompanied by M + 2 (equal intensity) and M + 4 (ca. 35% of M^+) peaks, indicating the presence of three chlorine atoms. The two benzo[*b*]thiophenes were easily differentiated by their NMR spectra (see Experimental Section). The structural assignments, particularly the chlorine substituents at the C_3 positions, were confirmed by isolating the same products, **50a** (13.5%) and **50b** (32.3%), from the reaction of *m*-formylcinnamic acid.

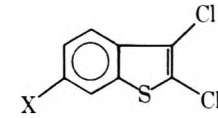
Scheme V



The result reveals that sulfenyl chloride **47** undergoes ring closure only after its conversion into **48**. This is in accord with the concerted cyclization mechanism through a 6-π-electron system such as **14** (path d in Scheme I). Another interpretation which is in line with the CEC mechanism is that the ring closure of **47** is sterically prohibited. The transition state of this cyclization requires two chlorine atoms of the dichloromethyl group to approach from the bottom (or top) of the phenyl ring to the plane of the ring as the hydrogen is leaving from the top (or bottom) of the plane. This process also results in the shortening of the bond lengths of one carbon–carbon and two carbon–chlorine bonds (so as to form $Cl_2C{=}C$).

The cyclization of **47** to this intermediate by a CEC mechanism would be in a direction that creates two sites of new nonbonded interactions among the two large chlorine and two perihedral hydrogen atoms.[22] Thus the process would be slower than the conversion of **47** into **48**.

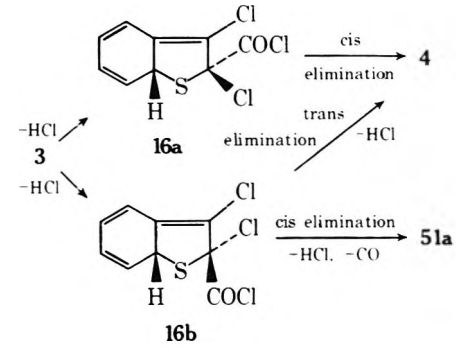
Additional evidence for the CEC mechanism comes from the rationale for the formation of minor products, 2,3-dichlorobenzo[*b*]thiophenes, e.g., **22**. In addition to **22**, we obtained similar products **51a** (1.6%) and **51b** (0.7%) from the



51a, X = H
b, X = OCH_3

reactions of thionyl chloride with **9** and with *p*-methoxycinnamic acid,[15] respectively. The formation of these products can best be rationalized in terms of the stereochemical consequence of the CEC mechanism. The ring closure of **3**, which is presumably a mixture of diastereomers,[24] by the CEC mechanism should give rise to the diastereomeric intermediates **16a** and **16b**. If cis 1,4 elimination is much faster[25] than trans, the elimination of hydrogen chloride from **16a** could afford exclusively the major product **4**. On the other hand, if the loss of hydrogen chloride from **16b** is an unfavorable trans 1,4 elimination, a part of **16b** might lead to the cleavage of the chlorocarbonyl group by cis 1,4 elimination to form the observed minor product (see Scheme VI). A higher yield (10%) of **51b** from the reaction of methyl cinnamate provides further evidence for the proposed mechanism.[26]

Scheme VI



Experimental Section

Thionyl chloride (Matheson Coleman and Bell) was distilled from triphenyl phosphite by a recommended[27] procedure; the fraction boiling over the range 75.5–76.5° was used. Alumina used for chromatographic columns was Woelm neutral unless otherwise

specified. Infrared spectra were recorded with a Perkin-Elmer Model 137 spectrophotometer with a sodium chloride prism; solid samples were taken as potassium bromide pellets and liquid samples were taken as neat films. Mass spectra were processed by Mr. C. R. Weissenberger with an AE1 MS-9 mass spectrometer[28] at 70 eV. The nuclear magnetic resonance spectra were taken on a Varian Model A-60 spectrometer, using tetramethylsilane as the internal reference and carbon tetrachloride as solvent unless otherwise specified. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.; Crobaugh Laboratories, Cleveland, Ohio; and Galbraith Laboratories, Knoxville, Tenn.

Reaction of Thionyl Chloride with *trans*-Cinnamic Acid (9). A. To a mixture of **9** (7.41 g, 0.05 mol) and 0.5 ml (0.006 mol) of pyridine was added approximately ¼ of 24 g (0.2 mol) of thionyl chloride. The mixture was heated to 120–125° (bath 130–140°), and the rest of the thionyl chloride was added dropwise over a period of 2 hr. The mixture was stirred at this temperature for an additional 1 hr, cooled, and dissolved in 300 ml of hexane. The solution was decanted from pyridine hydrochloride and from it was crystallized 3.85 g of the benzo[*b*]thiophene **4**, mp 113.5–115° (lit.[3] mp 114.4–115.1°). Four more crystallizations from the mother liquor gave a total of 4.14 g of **4**, mp 111–114.5°; total yield of **4** was 7.99 g (69%). The liquid product was distilled to yield 2.32 g (23%) of the acid chloride **5**, bp 83–92° (0.18 mm). The infrared spectrum of this product was identical with that of an authentic sample.

B. A mixture of 14.82 g (0.1 mol) of **9**, 2 ml of pyridine, and 84 g (0.7 mol) of thionyl chloride was heated at 65–80° (bath temperature) for 24 hr. The infrared spectrum of the sample showed that it was nearly identical with a spectrum of an authentic sample of cinnamoyl chloride. The mixture was then heated at 88° for 24 hr. After removing excess thionyl chloride by rotary evaporation the product was dissolved in 100 ml of hexane, and the mixture was filtered to remove pyridine hydrochloride. The solution was concentrated and fractionally distilled to yield 7.4 g of cinnamoyl chloride, bp 77–90° (0.2 mm); 0.8 g of an intermediate fraction, bp 100–110° (0.12 mm); and 5.8 g (19%) of sulfenyl chloride **3**, bp 110–112° (0.12 mm). Redistillation of the latter compound furnished 96% pure (by NMR) **3**: bp 107° (0.08 mm); ir 5.55, 5.67, 5.70, 6.88, 9.44, 9.70, 9.92, 13.25, and 14.35 μm; NMR τ 2.54 (m, 5 H) and 4.21 (s, 1 H); mass spectrum *m/e* 234, 232, 230, 197, 195, 169, 167, 134, 132, 125, 123 (seemingly **4**); and 204, 202, 200, 167, 165, 139, 137, 102, and 101 (seemingly **5**).

Anal. Calcd for $C_9H_6Cl_4OS$: C, 35.56; H, 1.99; Cl, 46.65; S, 10.55. Found: C, 36.43; H, 2.08; Cl, 46.39; S, 10.39.

Reaction of Thionyl Chloride with *trans*-Crotonic Acid (11). A. To a mixture of 4.30 g (0.05 mol) of **11** (mp 71–72°) and 0.5 ml (0.006 mol) of pyridine was added 42 g (0.35 mol) of thionyl chloride. The mixture was heated at reflux (bath temperature 95°) for 3 hr. Excess thionyl chloride was removed under vacuum (25 mm) in a Dry Ice-2-propanol trap. The NMR spectrum of the product mixture showed the compounds **12** and **13** in 88 and 12% yield, respectively. The mixture was dissolved in dry ether, pyridine hydrochloride was filtered, ether was removed, and the residue was distilled to yield 0.70 g (10%) of α-chlorocrotonyl chloride [bp 23–30° (0.25 mm); ir 5.70, 6.17, 8.66, 9.27, and 13.20 μm; NMR (neat) τ 2.30 (q, 1 H, *J* = 7 Hz) and 7.88 (d, 3 H, *J* = 7 Hz)] and 6.66 g (55%) of sulfenyl chloride **12**, bp 55–61° (0.18 mm). Redistillation of the latter compound gave a fraction with bp 46–48° (0.7 mm): ir 5.56, 5.67, 6.92, 7.22, 9.00, 9.06, 9.46, 9.76, 10.05, 12.15, 12.92, 13.40, 13.97, 14.55, and 14.86 μm; NMR τ 5.10 (q, 1 H, *J* = 6.5 Hz) and 8.20 and 8.27 (two sets of doublets, 3 H, *J* = 6.5 Hz). An analytical sample, bp 56–56.5° (0.45 mm), was obtained by four more fractionations.

Anal. Calcd for $C_4H_4Cl_4OS$: C, 19.86; H, 1.66; Cl, 58.61; S, 13.25. Found: C, 20.55; H, 1.83; Cl, 58.59; S, 13.60.

B. A mixture of 4.30 g (0.05 mol) of **11** and 42 g (0.35 mol) of thionyl chloride was heated at reflux for 48 hr. Infrared and NMR spectra were recorded after 1, 19, and 48 hr. These spectra showed no change over the reaction period, and the product was identified as *trans*-crotonyl chloride: ir 5.72, 6.18, 7.01, 8.83, 9.24, 9.60, 10.45, and 13.13 μm; NMR ($SOCl_2$) τ 2.79 (quadrupled doublet, 1 H, *J* = 15.5, 7 Hz), 3.96 (quadrupled doublet, 1 H, *J* = 15.5, 1.6 Hz), and 8.05 (quadrupled doublet, 3 H, *J* = 7, 1.6 Hz).

2-Chloro-2-butenoyl Amide. Acid chloride **13** (300 mg, 0.002 mol) was added dropwise to 4 ml of concentrated ammonium hydroxide solution. The product was extracted with ether (2 × 25 ml), dried, and evaporated to yield 150 mg of a yellow solid. The solid was recrystallized from ligroin to give white, fine needles, mp 107–112°, which were again recrystallized from water to give white prisms, mp 112–113.5° (lit.[13] mp 112°).

Decomposition of 2,3-Dichloro-2-chlorosulfenyl-3-phenylpropanoyl Chloride (3). Pyridine hydrochloride was prepared by adding several drops of thionyl chloride to a mixture of 0.04 ml of pyridine and 2 drops of methanol and removing excess thionyl chloride under vacuum. Sulfenyl chloride **3** (1.36 g, 0.0044 mol) was added to the pyridine hydrochloride and heated at 130° for 5 hr. The reaction mixture which solidified on cooling was taken up in dry carbon tetrachloride (4 ml). The NMR spectrum of this solution showed a singlet at τ 1.85 due to **5**, a complex in the aromatic region (τ 1.95–2.73), and a singlet at τ 4.33 due to **3**. The ratio of these peaks gave relative yields of the compounds **3**, **4**, and **5** at 32, 38, and 30%, respectively. Furthermore, crystallization from the carbon tetrachloride solution afforded 380 mg (36%) of **4**, mp 114–115°.

Reaction of Thionyl Chloride with *m*-Nitrocinnamic Acid (20). To a mixture of 3.86 g (0.02 mol) of **20** and 0.2 ml of pyridine was added at 135° over a period of 1 hr, 8.4 g (0.07 mol) of thionyl chloride. The mixture was heated at the same temperature for an additional 30 min, cooled, and added to 75 ml of absolute methanol. The mixture was heated at reflux for 30 min, excess methanol was removed, and the residue was chromatographed on alumina (activity grade III, 150 g). The column was eluted with benzene into 20 fractions: 50 ml each for fractions 1–3, 100 ml each for 4–7, and 200 ml each for 8–20. Fractions 1–2 gave 0.11 g of a mixture of **22a** and **22b**. Each of the fractions 3–9 (2.94 g) was a mixture of **21a** and **21b**. Fractions 10–20 (0.99 g) were of a single component which recrystallized from ethanol and ethyl acetate to furnish 0.80 g of **21b**, mp 194–196°. More **21b** (0.47 g) was obtained by fractional crystallization of fractions 5–9; total yield of **21b** was 1.27 g(23.4%). One more recrystallization from the same solvents afforded an analytical sample of **21b** as yellow needles: mp 196.5–197°; NMR ($CDCl_3$) ca. τ 1.45 (dd, H^6, *J* = 8.0, 1.5 Hz), 1.68 (dd, H^4, *J* = 8.0, 1.5 Hz), 2.33 (t, H^5, *J* = 8.0 Hz), and 5.99 (s, OCH_3); ir 5.76, 6.56, 7.58, and 8.02 μm; mass spectrum *m/e* 273, 271 (M^+), 241 (−NO), 242, 240 (base, $-OCH_3$), 196, 194 ($-NO_2$, $-OCH_3$), and 166 ($-NO_2$, $-CO_2CH_3$).

Anal. Calcd for $C_{10}H_6ClNO_4S$: C, 44.21; H, 2.23; Cl, 13.05; N, 5.16; S, 11.80. Found: C, 44.31; H, 2.14; Cl, 13.36; N, 4.87; S, 12.09.

Further chromatography of a mixture (1.21 g) of **21a** and **21b** (fractions 5–7) was attempted on activity grade III alumina (50 g) with benzene–petroleum ether (1:2). All fractions (11 × 50 ml) still showed two carbonyl absorptions, indicating no separation of **21a** and **21b**. Fractional crystallization of these fractions from ethyl acetate furnished, besides 0.105 g of **21b**, 5 mg of **21a**: mp 186–190°; ir 5.89, 6.60, 7.41, and 7.74 μm; mass spectrum *m/e* 273, 271 (base, M^+), 241 (−NO), 242, 240 ($-OCH_3$), 210 (−NO, $-OCH_3$), 196, 194 ($-NO_2$, $-OCH_3$), and 166 ($-NO_2$, $-CO_2CH_3$). Compound **21a** (5.89) was unambigously distinguished from **21b** (5.76 μm) by the carbonyl absorption.

Separation of **22a** and **22b** was achieved on an activity grade I alumina (107 g) column by eluting with petroleum ether into five (200 ml each) fractions and petroleum ether–ether (10:1) into 15 fractions (200 ml each).

Fraction 7 afforded 50 mg of **22b**, recrystallization of which from ligroin gave yellow flakes: mp 140–141°; ir 6.56, 6.64, 7.47, 7.60, 10.19, and 13.56 μm; mass spectrum *m/e* 251 (M + 4, 14.3%), 249 (M + 2, 70%), 247 (M^+, 100%), 219, 217 (−NO), 203, 201 ($-NO_2$), 168 and 166 ($-NO_2$, −Cl).

Fraction 8 (34 mg) was recrystallized from ligroin to yield **22a** as pale yellow flakes: mp 182–183.5°; ir 6.66, 7.45, 7.54, and 13.49 μm; mass spectrum *m/e* 251 (M + 4, 14.5%), 249 (M + 2, 68.5%), 247 (M^+, 100%), 219, 217 (−NO), 203, 201 ($-NO_2$), 168 and 166 ($-NO_2$, −Cl).

3-Chloro-7-nitrobenzo[*b*]thiophene. The ester **22b** (1.086 g, 4 mmol) was saponified by heating it at reflux with 50 ml of 1 *N* sodium hydroxide and 100 ml of ethanol for 1 hr. After most of the ethanol was removed the aqueous solution was acidified with 60 ml of 1 *N* hydrochloric acid. The precipitate was filtered to furnish 950 mg (92%) of carboxylic acid as a yellow powder, mp 309–310° dec.

The acid (873 mg, 3.4 mmol) was decarboxylated by treatment[29] with copper chromite (100 mg) and quinoline (5 ml) to yield 700 mg (98%) of crude product, treatment of which with charcoal and recrystallization from ethanol gave 530 mg of 3-chloro-7-nitrobenzo[*b*]thiophene as yellow needles: mp 146–147.5°; ir 6.64, 7.46, 7.62, 9.82, and 13.55 μm; NMR ($CDCl_3$) ca. τ 1.59 (dd, H^6, *J* = 8.0, 1.5 Hz), 1.87 (dd, H^4, *J* = 8.0, 1.5 Hz), 2.42 (t, H^5, *J* = 8.0 Hz), and 2.51 (s, H^2); mass spectrum *m/e* 215, 213 (M^+, base), 185, 183

(−NO), 169, 167 (−NO_2), 157, 155 (−NO, −CO), 132 (−NO_2, −Cl), 125, and 123 (−NO_2, −CS).

Reaction of Thionyl Chloride with *m*-Methoxycinnamic Acid (26). A. To a mixture of 3.56 g (0.02 mol) of **26** (mp 118–119°) and 0.2 ml of pyridine was added approximately ⅓ of 8.4 g (0.07 mol) of thionyl chloride. The mixture was heated to 140°, and the rest of the thionyl chloride was added at a rate such as not to drop the temperature below 135° (40 min). The mixture was then heated at 140–145° for an additional 30 min, dissolved in benzene (30 ml), poured into a flask containing 30 ml of absolute methanol, and heated at reflux for 30 min. After benzene and excess methanol were removed, the mixture was chromatographed on alumina (activity grade II, 100 g). The column was eluted with petroleum ether–benzene (1:1) to furnish 17 fractions (50 ml each).

Recrystallization of fractions 3–6 (total 2.865 g) from methanol afforded 1.355 g (26.4%) of **27a**, mp 115–116°. One more recrystallization from the same solvent furnished an analytical sample: mp 116°; ir 5.79 (C=O), 6.63, and 8.14 and 8.25 μm (C–O); NMR ($CDCl_3$) ca. τ 2.47 (dd, H^7, J = 8.5, 0.7 Hz), 2.81 (dd, H^4, J = 2.5, 0.7 Hz), 2.95 (dd, H^6, J = 8.5, 2.5 Hz), and 6.09 and 6.14 (2 s, 2 OCH_3); mass spectrum *m/e* 258, 256 (M^+, base), 241 (−CH_3), 227, 225 (−OCH_3), 197 (−CO_2CH_3), 182 (−CH_3, −CO_2CH_3), and 119 (C_7H_3S).

Anal. Calcd for $C_{11}H_9ClO_3S$: C, 51.47; H, 3.53; Cl, 13.81; S, 12.49. Found: C, 51.47; H, 3.34; Cl, 14.00; S, 12.30.

Recrystallization of fractions 7–15 from methanol afforded 86 mg (1.4%) of **28**, mp 160–172°. Further recrystallization from the same solvent gave rise to **28** as pale yellow needles: mp 172.0–172.8°; ir 5.79 (C=O), 6.68, 7.78, 8.06, and 8.16 and 8.22 μm (C–O); NMR ($CDCl_3$) τ 2.36 (d, H^7, J = 8.5 Hz), 2.78 (d, H^6, J = 8.5 Hz), and 6.04 (s, 2 OCH_3); mass spectrum *m/e* 294, 292, 290 (M^+, base), 277, 275, (−CH_3), 261, 259 (−OCH_3), 249, 247 (−CO, −CH_3), 233, 231 (−CO_2CH_3), 218, and 216 (−CH_3, −CO_2CH_3).

Anal. Calcd for $C_{11}H_8Cl_2O_3S$: C, 45.38; H, 2.77; Cl, 24.35; S, 11.01. Found: C, 45.44; H, 2.36; Cl, 24.38; S, 10.98.

The residues (1.60 g) after crystallization of **27a** and **28** were combined and chromatographed again on alumina (activity grade III, 40 g) with petroleum ether (13 fractions, 50 ml each) and benzene (one fraction, 200 ml).

Each of the fractions 1–13 was still a mixture. Two recrystallizations of fraction 14 (160 mg) from methanol afforded 40 mg of **29** as white needles: mp 159–160°; ir 5.82 (C=O), 6.57, and 8.03 μm (C–O); NMR ($CDCl_3$) τ 1.85 (d, H^3, J = 0.7 Hz), 2.32 (dd, H^7, J = 8.5, 0.75 Hz), 2.82 (d, H^6, J = 8.5 Hz), and 6.03 (s, 2 OCH_3); mass spectrum *m/e* 258, 256 (M^+, base), 243, 241 (−CH_3), 227, 225 (−OCH_3), 215, 213 (−CH_3, −CO), 199, 197 (−CO_2CH_3), 184, and 182 (−CH_3, −CO_2CH_3).

B. A mixture of 7.12 g (0.04 mol) of **26**, 0.4 ml of pyridine, and 33.6 g (0.28 mole) of thionyl chloride was heated at reflux for 21 hr. The oil bath temperature was kept at 95–98°. After excess thionyl chloride was removed, the reaction mixture was taken up in 500 ml of dry hexane, heated to ensure dissolution, and decanted from pyridine hydrochloride. Two crystallizations from the solution furnished 4.34 g (41.5%) of acid chloride **27b**: mp 147.3–148.3°; ir 5.66 (C=O), 6.73, 8.18 (C–O), and 8.57 μm. Further crystallization from the mother liquor gave 0.93 g of a mixture of solids, mp 117–128°. Treatment of **27b** with methanol in ether gave **27a**, mp 116°.

The red liquid left after separation of the solids was distilled to yield 3.25 g (41.3%) of *m*-methoxycinnamoyl chloride, bp 107–112° (0.26 mm), and a small amount of residue. The acid chloride (1.90 g) was hydrolyzed with aqueous acetone to afford 1.45 g of acid **26**, mp 117–119°; mixture melting point with an authentic sample of **26** showed no depression, and the infrared spectra were identical.

C. A mixture of 2.67 g (0.015 mol) of **26**, 0.15 ml of pyridine, and 12.0 g (0.1 mol) of thionyl chloride was heated at reflux (bath temperature 105°) for 48 hr. The product mixture, which solidified upon cooling, was dissolved in 70 ml of benzene and 20 ml of absolute methanol and heated at reflux for 1 hr. After benzene and excess methanol were removed, the residue was separated on an alumina (activity grade III, 150 g) column by eluting with petroleum ether–benzene (10:3) (33 fractions of 50 ml each).

Recrystallization of fraction 7 (145 mg) from methanol afforded 75 mg (2%) of the benzo[*b*]thiophene **30** as white, fine needles: ir 5.80 (C=O), 6.58, 7.64, 7.89, and 8.60 μm; NMR ca. τ 2.49 (dd, H^4, J = 7.7, 1.7 Hz), 2.67 (t, H^5, J = 7.9 Hz), 3.18 (dd, H^6, J = 7.0, 1.7 Hz), and 6.00 and 6.05 (2 s, 2 OCH_3); mass spectrum *m/e* 258, 256 (H^+, base), 243, 241 (−CH_3), 227, 225 (−OCH_3), 215, 213 (−CH_3, −CO), 197 (−CO_2CH_3), 184, 182 (−CO_2CH_3, −CH_3), and 119 ($C_7H_3S^+$); mol wt (mass spectrum) for $C_{11}H_9ClO_3S$ 255.99572 (calcd, 255.99609).

Recrystallization of fractions 9–16 (total 2.75 g) from methanol gave rise to 2.095 g (54.4%) of benzo[*b*]thiophene **27a**, mp 113–115°.

Recrystallization of fractions 19–25 (total 0.28 g) afforded 0.26 g (6%) of **28** as light yellow needles, mp 171–172°.

Formation of 3,4-Dichloro-5-methoxy-2-methoxycarbonylbenzo[*b*]thiophene (28) from 3-Chloro-2-chlorocarbonyl-5-methoxybenzo[*b*]thiophene (27b). A mixture of 1.044 g (4 mmol) of **27b** (mp 147.3–148.3°) and 5 ml of thionyl chloride was heated at reflux (bath temperature 95°) for 24 hr. Excess thionyl chloride was removed, and the product was treated with 50 ml of absolute methanol at reflux for 10 min, concentrated, and separated on an alumina (activity grade II, 40 g) column by eluting with benzene (seven fractions of 25 ml each). Recrystallization of fractions 1 and 2 (total 585 mg) gave rise to 345 mg (30%) of **28** as pale yellow needles, mp 170–171.5°; the infrared spectrum was identical with that of **28** previously obtained. The remaining fractions were mixtures.

Reaction of Thionyl Chloride with *trans*-*p*-Nitrostilbene (31). *trans*-*p*-Nitrostilbene, mp 156–157° (lit.[30] mp 150–153°), was prepared by condensation of *p*-nitrophenylacetic acid (27.15 g) with benzaldehyde (17.50 g) in the presence of piperidine (7.5 ml) according to the method of Jambotkar and Ketcham.[30] A mixture of 2.14 g (9.5 mmol) of **31**, 0.1 ml of pyridine, and 7.2 g (0.06 mol) of thionyl chloride was heated at reflux (bath temperature 100°) for 48 hr. More thionyl chloride (2.4 g) was added after 24 hr. After excess thionyl chloride was removed, the residue was dissolved in 100 ml of benzene, decanted from pyridine hydrochloride, concentrated, and chromatographed on alumina (activity grade II, 100 g). The column was successively eluted with petroleum ether–benzene (2:1) (ten fractions of 30 ml each), benzene (ten fractions of 300 ml each), and ether (four fractions of 100 ml each).

Recrystallization of fractions 3–6 (total 550 mg) from 95% ethanol afforded 420 mg (15.2%) of benzo[*b*]thiophene 34 as yellow, fine crystals, mp 154–155°. One more recrystallization from the same solvent furnished an analytical sample: mp 155–156°; ir 6.27, 6.61, 7.48, 7.52, 11.69, 11.81, 13.05, and 13.34 μm; NMR ($CDCl_3$) τ 1.60 (d, two hydrogens ortho to nitro group, J = 9.0 Hz), 1.94 (d, two hydrogens meta to nitro group, J = 9.0 Hz), and 1.91–2.52 (complex, four aromatic hydrogens); mass spectrum *m/e* 291, 289 (M^+), 261, 259 (−NO), 245, 243 (−NO_2), 233, 231 (−NO, −CO), 208 (−Cl, −NO_2, base), 203, 201, 199 (−NO, −CO, −S), 164 (−NO_2, −CS, −Cl), 163 (−NO_2, −HCl, −CS), and 104.

Anal. Calcd for $C_{14}H_8ClNO_2S$: C, 58.03; H, 2.78; Cl, 12.23; N, 4.83; S, 11.07. Found: C, 58.07; H, 2.57; Cl, 11.90; N, 4.98; S, 10.98.

Recrystallization of fractions 7–9 (total 155 mg) from 95% ethanol afforded 65 mg of the starting material, mp 151–153°; mixture melting point with authentic sample showed no depression; the infrared spectrum was identical with that of stilbene **31**.

Fractional recrystallization of fractions 15–24 (total 1.13 g) from 95% ethanol gave rise to 530 mg of yellow crystals, mp 204–205°, ir 6.64 and 7.48 μm, mass spectrum *m/e* 514 (M^+), and 60 mg of another yellow, crystalline solid, mp 208–210°, ir 6.65 and 7.48 μm. The infrared spectra of these two products were very similar, but mixture melting point showed depression. The structures of these products have not been determined.

3-(3-Methoxyphenyl)propanoic Acid (36). *m*-Methoxycinnamic acid (7.13 g) in 150 ml of 95% ethanol was hydrogenated at atmospheric pressure over 10% palladium on carbon (0.4 g). The uptake ceased after 997 ml of hydrogen at 25° (750 mm) was introduced. After the catalyst and the solvent were removed, the residue was washed with petroleum ether to yield 7.00 g (97.1%) of **36**, mp 44–45°.

Reaction of Thionyl Chloride with 3-(3-Methoxyphenyl)-propanoic Acid. A. To a mixture of 3.60 g (0.02 mol) of **36** and 0.2 ml of pyridine was added approximately ⅓ of 8.0 g (0.067 mol) of thionyl chloride. The mixture was heated to 135° (bath temperature 140–145°), the rest of the thionyl chloride was added over a 1-hr period, and the mixture was stirred at this temperature for an additional 1 hr. The mixture was then treated with benzene (50 ml) and absolute methanol (25 ml) at reflux for 30 min. After excess methanol and benzene were removed the tarry residue was separated on a column containing 150 g of neutral alumina (activity grade III) by eluting with petroleum ether–benzene (2:1) (ten 50-ml fractions). Recrystallization of fractions 2–6 from 95% ethanol gave rise to 0.71 g (15.5%) of known[16b] benzo[*b*]thiophene **37**, mp 100.5–102°. One more recrystallization from the same solvent afforded white needles: mp 102.5–103.5°; ir 5.84 (C=O), 7.74 and 8.18 (C–O), and 8.66 μm; NMR ($CDCl_3$) ca. τ 2.06 (d, H^3, J = 0.7 Hz), 2.31 (tripled doublet, H^7, J = 8.6, 0.7 Hz), 2.75 (m, H^4), 2.92 (dd, H^6, J = 8.6, 2.5 Hz), and 6.07 and 6.16 (2 s, 2 OCH_3); mass

spectrum *m/e* 224, 222 (M^+, base), 207 ($-CH_3$), 191 ($-OCH_3$), 179 ($-CH_3$, $-CO$), 163 ($-OCH_3$, $-CO$), and 148 ($-CH_3$, $-CO_2CH_3$).

B. A mixture of 2.70 g (0.015 mol) of acid **36**, 0.15 ml of pyridine, and 12.0 g (0.1 mol) of thionyl chloride was heated at reflux (bath temperature 100°) for 46 hr. Excess thionyl chloride was destroyed by careful addition of methanol. The mixture was dissolved in 70 ml of dry benzene and 30 ml of absolute methanol, heated under reflux for 30 min, filtered to remove a small amount of insoluble material (sulfur), and evaporated to remove solvent and excess methanol to yield 4.48 g of a mixture of solid products. The mixture was placed on an alumina (activity grade III, 150 g) column and eluted with petroleum ether–benzene (2:1) to afford 32 fractions (50 ml each for fractions 1–22 and 100 ml each for 23–32).

Fractions 1 and 2 gave 85 mg of sulfur. Each of the fractions 4 (105 mg) and 5 (160 mg) was recrystallized from 95% ethanol to yield a total of 130 mg (3%) of benzo[*b*]thiophene **39** as white, fine crystals: mp 138–138.5°; ir 5.83 (C=O), 6.68, 7.71 (C–O), and 9.32 μm; NMR ($CDCl_3$) τ 1.88 (s, H^3), 2.56 (s, H^5), and 5.93 and 6.01 (2 s, 2 OCH_3); mass spectrum *m/e* 292, 290 (M^+, base), 277, 275 ($-CH_3$), 261, 259 ($-OCH_3$), 249, 247 ($-CH_3$, $-CO$), 218, and 216 ($-CH_3$, $-CO_2CH_3$).

Anal. Calcd for $C_{11}H_8Cl_2O_3S$: C, 45.38; H, 2.77; Cl, 24.35; S, 11.01. Found: C, 45.30; H, 2.60; Cl, 24.62; S, 10.73.

Recrystallization of fraction 6 (275 mg) from 95% ethanol afforded 55 mg (1.3%) of compound **38** as pale yellow needles: mp 174–174.5°; ir 5.80 (C=O), 6.56, 7.94, and 8.15 μm (C–O); NMR ($CDCl_3$) τ 1.85 (s, H^3), 2.80 (s, H^6), and 6.01 (s, 2 OCH_3); mass spectrum *m/e* 292, 290 (M^+, base), 277, 275 ($-CH_3$), 261, 259 ($-OCH_3$), 249, 247 ($-CH_3$, $-CO$), 233, 231 ($-CO_2CH_3$), 218, and 216 ($-CH_3$, $-CO_2CH_3$).

Anal. Calcd for $C_{11}H_8Cl_2O_3S$: C, 45.38; H, 2.77; Cl, 24.35; S, 11.01. Found: C, 45.51; H, 2.55; Cl, 24.34; S, 10.78.

Recrystallization of fractions 8–29 (total 2.61 g) from 95% ethanol yielded 2.16 g (56%) of benzo[*b*]thiophene **29** as white needles, mp 160–162°; both infrared and NMR spectra were identical with those of **29** obtained by the reaction of the acid **26**.

Anal. Calcd for $C_{11}H_9ClO_3S$: C, 51.45; H, 3.53; Cl, 13.81; S, 12.49. Found: C, 51.51; H, 3.32; Cl, 13.67; S, 12.64.

Isophthaloyl Dichloride. A mixture of 50 g (0.3 mol) of isophthalic acid and 120 g (1 mol) of thionyl chloride was stirred at reflux. The evolution of hydrogen chloride was very slow until 2 ml of pyridine was added. The mixture was heated under reflux for 5 hr. After excess thionyl chloride was removed the product was dissolved in 300 ml of hot hexanes, filtered to remove pyridine hydrochloride, and concentrated to 150 ml. Crystallization afforded 60.0 g (98.5%) of isophthaloyl dichloride, mp 44°.

Isophthalaldehyde was prepared by Rosenmund reduction of isophthaloyl dichloride by the method of Hershberg and Cason.[31] Thus 40.6 g (0.2 mol) of isophthaloyl dichloride was allowed to react with atmospheric hydrogen over 5.5 g of 5% palladium on barium sulfate and 0.5 ml of catalyst poison solution[31] in 150 ml of dry xylene at reflux over a period of 4 hr. After the catalyst and xylene were removed the crude product was steam distilled, yielding 17.43 g (65%) isophthalaldehyde, mp 87–89° (lit.[32] mp 89°).

***m*-Formylcinnamic Acid.** A mixture of 17.43 g (0.13 mol) of isophthalaldehyde, 14.79 g (0.14 mol) of malonic acid, 35 ml of pyridine, and 35 ml of 95% ethanol was heated under reflux over a period of 9 hr. The mixture was cooled and 90 ml of 6 *N* hydrochloric acid was added. The precipitate was filtered, washed with 500 ml of water, and dried under vacuum at 80° overnight to yield 18.50 g of a mixture. The mixture was separated by extraction with chloroform in a Soxhlet extractor to yield 12.66 g (55.3%) of *m*-formylcinnamic acid (monoacid), mp 189–191°, and 3.62 g (12.8%) of 1,3-bis(2-carboxyethenyl)benzene, mp 285–288° (lit.[33] mp 277°) which remained in the thimble. An analytical sample of the monoacid, mp 190–192°, was obtained by recrystallization from chloroform.

Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 67.89; H, 4.73.

Ethyl *m*-Diethoxymethylcinnamate. In a 500-ml round-bottomed flask equipped with a condenser, Dean-Stark trap, and a drying tube was placed 11.40 g (0.064 mol) of *m*-formylcinnamic acid, 130 ml of absolute ethanol, and 0.5 ml of concentrated sulfuric acid. The mixture was heated at reflux for 10 hr, 100 ml of dry benzene was added, the azeotropic mixture was distilled, and more ethanol (100 ml) was added. The process of reflux, addition of benzene, and azeotropic distillation was repeated. To the final reaction mixture in 100 ml of dry benzene was added 30 ml of 2 *N* sodium hydroxide solution with stirring at the freezing point of benzene. The layers were separated, and the benzene layer was washed with saturated sodium bicarbonate solution, concentrated, and separated on an alumina (basic, activity grade I, 100 g) column by eluting with 500 ml of petroleum ether–ether (10;3) to yield 6.89 g (38%) of ethyl *m*-diethoxymethylcinnamate: bp 126–130° (0.04 mm); ir (neat) 3.34 (C–H), 5.86 (C=O), 6.11 (C=C), and 7.72, 7.98, and 8.55–8.70 μm (C–O); NMR ($CDCl_3$) τ 2.24 and 3.49 (2 d, two vinyl hydrogens, *J* = 16 Hz), 2.27–2.52 (m, four aromatic hydrogens), 4.45 (s, one methine hydrogen), 5.70 (q, CH_2, *J* = 7.0 Hz), 6.30 (q, 2 CH_2, *J* = 7.0 Hz), 8.66 (t, CH_3, *J* = 7.0 Hz), and 8.74 (t, 2 CH_3, *J* = 7.0 Hz).

Ethyl 3-(3-Diethoxymethylphenyl)propanoate. The unsaturated ester (4.41 g) was reduced with atmospheric hydrogen over 0.5 g of Raney nickel (W-2) in 25 ml of absolute ethanol. After the catalyst was removed by filtration, the ethanolic solution was concentrated to yield 4.37 of crude ester. The crude product was distilled to afford 4.075 g (91%) of pure ethyl 3-(3-diethoxymethylphenyl)propanoate as a colorless oil: bp 105–108° (0.06 mm); ir (neat) 3.32 (C–H), 5.75 (C=O), 8.65 (C–O), and 9.52 μm; NMR τ 2.71–2.92 (m, four aromatic), 4.54 (s, one methine), 5.91 and 6.48 (2 q, 3 OCH_2, *J* = 7.0 Hz), 6.90–7.52 (m, 2 CH_2), and 8.77 (t, 3 CH_3, *J* = 7.0 Hz).

3-(3-Formylphenyl)propanoic Acid (45). Ethyl 3-(3-diethoxymethylphenyl)propanoate (4.00 g) was heated with 20 ml of 1 *N* sodium hydroxide solution and 25 ml of methanol on a steam bath. After most of the methanol was evaporated, the aqueous solution was cooled, extracted with ether, and acidified with 1 *N* hydrochloric acid (25 ml). The resulting emulsion was heated to form a clear solution, cooled, and extracted with ethyl acetate, dried ($MgSO_4$), and concentrated to yield 2.79 g of the crude acid. The crude product was distilled to afford 1.93 g (76%) of the acid **45**: bp 147–148° (0.06 mm); NMR ($CDCl_3$) τ −1.63 (s, COOH), −0.03 (s, CHO), 2.20–2.53 (m, aromatic), and 6.73–7.40 (m, 2 CH_2).

Reaction of Thionyl Chloride with (3-(3-Formylphenyl)-propanoic Acid (45). To a mixture of 1.82 g (0.0102 mol) of **45** and 0.1 ml of pyridine was added approximately half of 5.0 g (0.041 mol) of thionyl chloride. The mixture was heated to 140° (bath temperature), and the rest of the thionyl chloride was added at 140–145° over a period of 45 min. The mixture was heated at this temperature for an additional 1 hr. After cooling 5 ml of absolute methanol was added, and the mixture was heated at reflux for 15 min. The precipitate (60 mg of sulfur, mp 117–118°) was removed by filtration, and excess methanol was evaporated. The residue was chromatographed on an alumina (activity grade III, 100 g) column by eluting with petroleum ether–benzene (5:1) (ten 50-ml fractions) and with a 1:1 mixture (five 250-ml fractions).

Fraction 1 was 40 mg of sulfur. Each of the fractions 2–6 (total 2.32 g) was shown to be a mixture of the benzo[*b*]thiophenes **50a** and **50b** and the methyl ester of **46** by NMR spectroscopy. Fractions 7 and 8 (total 105 mg) consisted mainly of the ester of **46**. The rest of the fractions gave only small amounts of tarry material.

Fractional crystallization of fractions 2–6 from ligroin afforded 460 mg (15%) of **50b**, mp 135–138°, and 250 mg (8%) of **50a**, mp 100–105°. Recrystallization of **50b** from carbon tetrachloride afforded colorless prisms: mp 138.5–139°; ir 5.90 (C=O), 7.64 and 7.76 (C–O), and 13.64 μm; NMR ($CDCl_3$) ca. τ 1.94 (dd, H^4, *J* = 7.7, 1.7 Hz), 2.20 (dd, H^6, *J* = 7.3, 1.7 Hz), 2.47 (t, H^5, *J* = 7.7 Hz), 2.96 (s, $CHCl_2$), and 5.97 (s, OCH_3); mass spectrum *m/e* 312, 310, 308 (M^+), 277, 275, 273 (−Cl, base), 242 (−Cl, $-OCH_3$), 216, 214 (−Cl, $-CO_2CH_3$), 181, 179 (−2 Cl, $-CO_2CH_3$), 144 (−3 Cl, $-CO_2CH_3$), 122, and 121.

Anal. Calcd for $C_{11}H_7Cl_3O_2S$: C, 42.68; H, 2.28; Cl, 34.35; S, 10.36. Found: C, 42. 61; H, 2.34; Cl, 34.11; S, 10.19.

Compound **50a** was recrystallized from ligroin, affording colorless plates: mp 104.5–105.5°; ir 5.80 (C=O), 6.62, 8.02, and 8.11 (C–O), 9.48, and 13.54 μm; NMR ($CDCl_3$) τ 1.88 (finely divided singlet, H^4), 2.12 (finely divided singlet, H^6 and H^7), 3.08 (s, $CHCl_2$), 5.98 (s, OCH_3); mass spectrum *m/e* 312, 310, 308 (M^+), 277, 275, 273 (−Cl, base), 242 (−Cl, $-OCH_3$), 216, 214 (−Cl, $-CO_2CH_3$), 181, 179 (−2 Cl, $-CO_2CH_3$), 144 (−3 Cl, $-CO_2CH_3$), 122, and 121.

Anal. Calcd for $C_{11}H_7Cl_3O_2S$: C, 42. 68; H, 2.28; Cl, 34.35; S, 10.36. Found: C, 42.80; H, 2.06; Cl, 34.17; S, 10.10.

Reaction of Thionyl Chloride with *m*-Formylcinnamic Acid. A mixture of 3.52 g (0.02 mol) of *m*-formylcinnamic acid, 0.2 ml of pyridine, and 19.2 g (0.16 mol) of thionyl chloride was heated at reflux (bath temperature 98–100°) for 48 hr. After excess thionyl chloride was removed the residue was stirred with 15 ml of absolute methanol at room temperature for 30 min. The methanolic solution was poured into a flask containing 100 ml of dry carbon tetrachloride, filtered to remove pyridine hydrochloride, and concentrated to furnish a mixture of products. The mixture was fraction-

ally crystallized from ligroin to afford 2.00 g (32.3%) of **50b**, mp 130–135°; recrystallization from chloroform gave prisms, mp 137.5–138.5°. The infrared spectrum was identical with that of **50b** obtained from the reaction of **45**.

Crystallization from the mother liquor after separation of **50b** furnished 0.84 g (13.5%) of **50a**, mp 104–106°; mixture melting point with **50a** previously obtained showed no depression.

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Registry No.—**3**, 39252-24-9; **4**, 21815-91-8; **5**, 56030-35-4; **9**, 140-10-3; **11**, 107-93-7; **12**, 51656-69-0; **13**, 56030-36-5; **20**, 1772-76-5; **21a**, 34674-00-5; **21b**, 41280-78-8; **22a**, 41280-79-9; **22b**, 41280-80-2; **26**, 17570-26-2; **27a**, 41280-81-3; **27b**, 56030-16-1; **28**, 41280-82-4; **29**, 41280-83-5; **30**, 41280-84-6; **31**, 1694-20-8; **34**, 41280-85-7; **36**, 10516-71-9; **37**, 19492-99-0; **38**, 56030-17-2; **39**, 56030-18-3; **45**, 56030-19-4; **50a**, 56030-20-7; **50b**, 56030-21-8; thionyl chloride, 7719-09-7; cinnamoyl chloride, 17082-09-6; *trans*-crotonyl chloride, 625-35-4; *trans*-2-chloro-2-butenoyl amide, 56030-37-6; 3-chloro-7-nitrobenzo[*b*]thiophene, 56030-22-9; *trans*-*m*-methoxycinnamoyl chloride, 56030-38-7; *trans*-*m*-methoxycinnamic acid, 17570-26-2; isophthaloyl chloride, 99-63-8; isophthalic acid, 121-91-5; isophthalaldehyde, 626-19-7; *m*-formylcinnamic acid, 56030-23-0; malonic acid, 141-82-2; ethyl *m*-diethoxymethylcinnamate, 56030-24-1; ethyl 3-(3-diethoxymethylphenyl)propanoate, 56030-19-4.

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(14) Our initially proposed mechanism[3] for the formation of **4** from **1** involved an electrophilic substitution reaction of **2** to form benzo[*b*]thiophene-2-carbonyl chloride, which was then chlorinated at the C-3 position to yield **4**. Treatment of benzo[*b*]thiophene-2-carboxylic acid, prepared by an unambiguous method,[15] with thionyl chloride in the presence of pyridine for 6 hr at 135–140° and for an additional 10 hr at reflux furnished **4** in 21% yield. The rest was unchanged starting material. On the other hand, treatment of **1** with thionyl chloride and pyridine at 130–140° for 4.5 hr afforded **4** in 56.2% yield. The slow reaction rate and the diminished yield of **4** in the former experiment revealed that our initial mechanism was incorrect.
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(16) For NMR spectra of substituted benzo[*b*]thiophenes, see (a) B. Caddy, M. Martin-Smith, R. K. Norris, S. T. Reid, and S. Sternhell, *Aust. J. Chem.*, **21** 1853 (1968); (b) N. B. Chapman, D. F. Ewing, R. M. Scrowston, and R. Westwood, *J. Chem. Soc. C*, 764 (1968).
(17) As described in most textbooks of infrared spectroscopy, substituted benzenoid components show definite absorption patterns in the 5–6-μm region depending on the number and relative positions of substituents. Since **22a** and 3-chloro-6-nitrobenzo[*b*]thiophene can be regarded as 1,2,4-trisubstituted benzenes and **22b** and 3-chloro-7-nitrobenzo[*b*]thiophene as 1,2,3-trisubstituted benzenes, their spectra were compared and showed good correlation.
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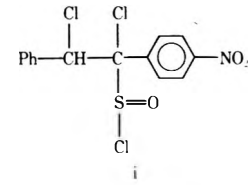

i

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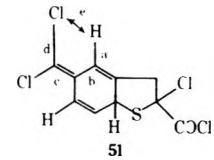
(21) Acid **45** was prepared as follows. Rosenmund reduction of isophthaloyl dichloride gave isophthaldehyde, which was treated with 1 equiv of malonic acid in pyridine to yield *m*-formylcinnamic acid. The latter was converted to ethyl *m*-diethoxymethylcinnamate upon treatment with absolute ethanol in the presence of concentrated sulfuric acid. Reduction of the acetal ester with Raney nickel followed by saponification and then acid hydrolysis gave acid **45**.
(22) The distance between chlorine and the perihedral hydrogen atom in **51** is measured as 2.53 Å by drawing the structure in which bond angles of 120° and bond lengths[23] as indicated are assumed. This distance is 0.47 Å shorter than the sum of the Van der Waals radii of chlorine (1.80 Å) and hydrogen (1.20 Å).



	Bond lengths, Å
a	1.083
b	1.466
c	1.337
d	1.72
e	2.53

51

(23) Taken from "Interatomic Distances Supplement", *Chem. Soc., Spec. Publ.*, **No. 18** (1965).
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The Photochemical Reactions of 1-Thiacycloheptan-4-one Derivatives. An Approach to Pantothiolactone[1]

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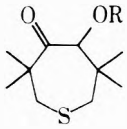
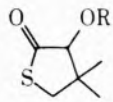
The photochemical reactions of 3,3,6,6-tetramethyl-5-acetoxy-1-thiacycloheptan-4-one (1) and several related keto sulfides including 3,3,6,6-tetramethyl-5-hydroxy-1-thiacycloheptan-4-one (11), its 2,2,2-trichloroethoxycarbonate derivative 12, and 3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (14) have been studied. The major photoproducts, which were isolated in 50–60% yields from the photolyses of 1, 12, and 14 but not ketol 11, were identified as 3,3-dimethyl-γ-butyrothiolactone derivatives (pantothiolactones). These products were believed to result from electron transfer quenching processes. Minor products were also isolated and characterized by alternate synthesis. Most of the minor products were postulated to have resulted from type I processes. Type II processes were shown to be unimportant in these systems. Some reactions of 2-acetoxy-3,3-dimethyl-γ-butyrothiolactone (2) were also studied.

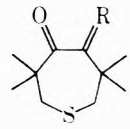
Our interests in the syntheses and reactions of alicyclic ketones and α-diones,[2] particularly those molecules capable of undergoing ground state[3] or excited state[4] transannular reactions, has led us to study the photochemical reactions of 3,3,6,6-tetramethyl-1-thiacycloheptan-5-acetoxy-4-one (1)[5] and related systems as routes to 2-acetoxy-3,3-dimethyl-γ-butyrothiolactone (2) and 2-hydroxy-3,3-dimethyl-γ-butyrothiolactone (pantothiolactone, 3).



1. R = Ac
11. R = H
12. R = TrOC

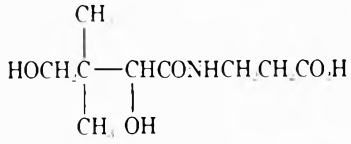


2. R = Ac
3. R = H
13. R = TrOC



6. R = O
14. R = H,H

Thiolactone 3 would be a key intermediate in a study of sulfur analogs of pantothenic acid (4),[6] pantetheine (5), and ultimately coenzyme A.



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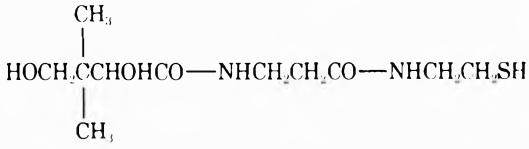

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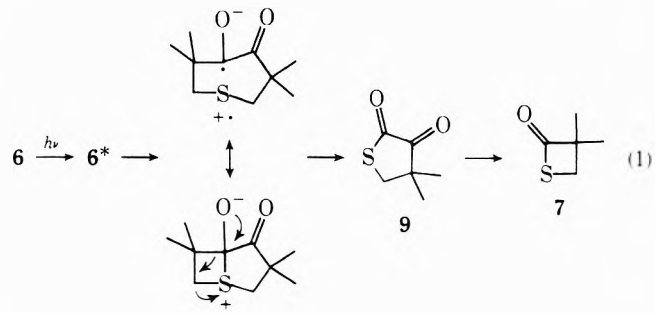
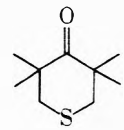
Historical. In an earlier study involving the photochemical reactions of 3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-dione (6),[4a] we showed that the major product resulting from irradiation of 6 in alcoholic solvents was β-thiolactone 7. While minor products isolated in those studies, mainly olefinic aldehydes, were believed to have resulted from type I and type II cleavages, we postulated that 7 resulted from electron transfer quenching processes (i.e., 6* → 8) to give an intermediate thiolactone 9 which we believed would be expected to further react under the photolysis conditions (eq 1).

Shortly after our original report, a second study on the photolysis of 6 was reported by Wynberg and Kellogg.[7] Arguing that they felt a reactive ground state intermediate such as 8 was too strained to be of importance,[8] they postulated a more traditional diradical mechanism for the formation of 7. They also felt that certain relationships (at least at shorter wavelengths) between the photolysis of keto sulfide 10, which cannot undergo type II processes,



(1)

8



10

and dione 6 ruled out the likelihood that type II processes were important in the photolysis of 6.

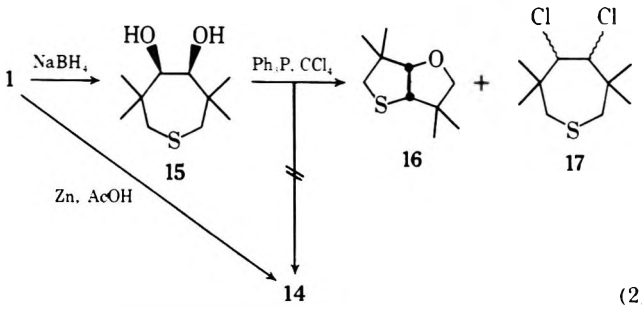
Our continued interest in the photochemistry of 6 has caused us to study the photochemistry of related systems which we believe add some insight into the reactions of 6. Turro,[9] after a careful study on the quenching of biacetyl by excitation transfer, hydrogen abstraction, and electron transfer processes, concluded that the photochemistry of biacetyl may be expected to parallel the known behavior of the n,π* states of monoketones. The mechanism he envisioned for electron transfer quenching of diones by amines is similar to that proposed for the quenching of ketones by either amines[10] or sulfides.[11]

This being the case, we felt that the photolysis of keto acetate 1 or ketol 11 might be expected to parallel that of dione 6 and lead to photostable analogs of 9 such as 2 and 3.

Results

Ketol 11 and its acetate 1 were synthesized in high yield by established procedures.[12] A second acyl derivative of 11, 2,2,2-trichloroethoxycarbonate 12, which was synthesized in 82% yield by reaction of 2,2,2-trichloroethoxycarbonyl chloride (TrOC)[13] and ketol 11, was also irradiated as part of these studies. It was hoped that irradiation of 12 might lead to the protected thiolactone 13. Reaction of 12 with zinc in acetic acid for 2 hr at 25° allowed recovery of acyloin 11 in 91% yield, indicating that the TrOC moiety was a

viable protecting group for these sulfur-containing molecules. Ketone **14** was synthesized in 5% yield by treating acetate **1** with zinc in refluxing acetic acid. Ketol **11** was also isolated in low yield from this reaction. Attempts to make ketone **14** in better yield by treating cis diol **15**[14] with triphenylphosphine in CCl_4 according to a procedure of Applequist[15] did not yield **14** but rather gave an interesting rearranged isomer **16**[16] in 44% yield along with some dichloride, **17**, of unknown stereochemistry (eq 2). Ketone **14**

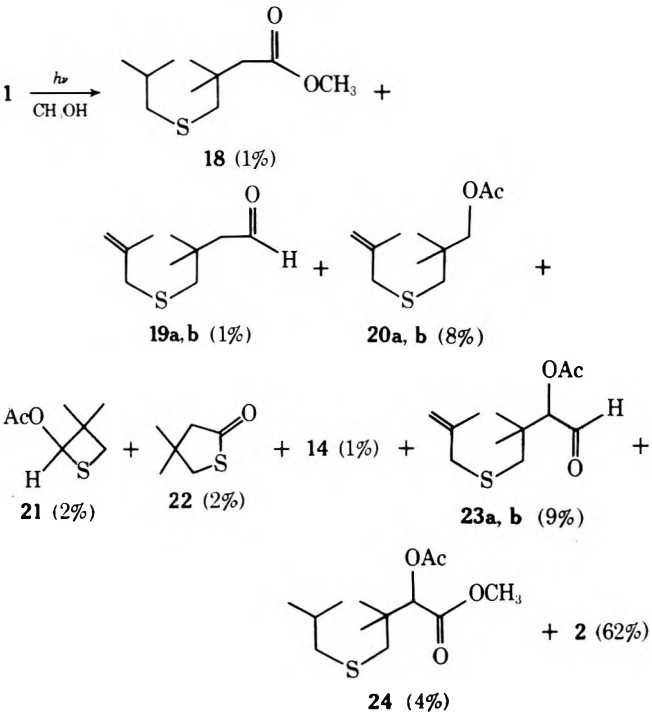


(2)

could also be synthesized from dione **6** by the two-step procedure of Wynberg.[12]

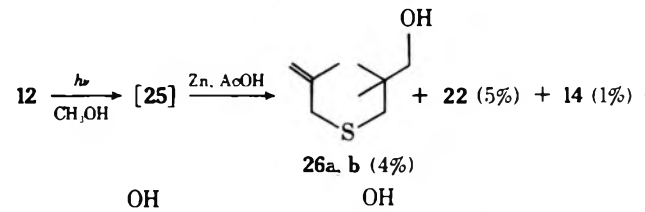
Photolysis[17] of ketol **11** in degassed methanol for 14 hr resulted in no observable (TLC, GLC) products. Unreacted **11** was recovered in 69% yield in this case. In contrast, photolysis of acetate **1** in degassed methanol led to the formation of one major product, thiolactone **2**, and several minor products shown in Scheme I listed in their order of elution

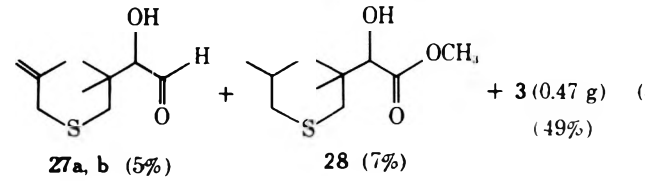
Scheme I



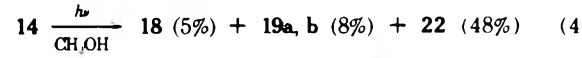
from a silicic acid column (hexane–ether elution; see Table I, run I, for conditions). Results obtained from the photolysis of **1** under other conditions are given in Table I (runs II → VI). Photolysis of **12** in degassed methanol for 9 hr (the photolysis mixture was analyzed after removal of the TrOC group with zinc in acetic acid) gave the products shown in Scheme II, eq 3, listed in their order of elution from a silicic acid column (hexane–ether elution). Analysis of ^1H NMR spectra taken of mixture **25** (in retrospect) showed that it was composed primarily of a 2:1 mixture of **13** and **3**, indicating that the TrOC protecting group is not particularly photostable. Photolysis of ketone **14** for 10 hr in degassed

Scheme II





(3)

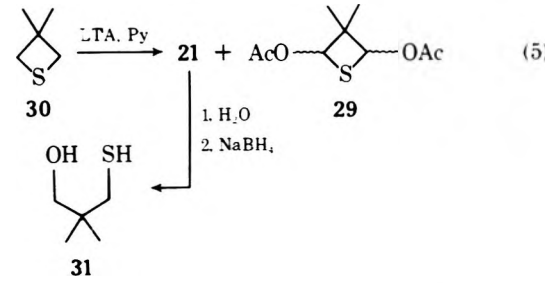


(4)

methanol gave thiolactone **22** as the major product as well as several minor products as shown in Scheme II, eq 4.

Products obtained from the photolysis of **1**, **12**, and **14** were identified by alternate synthesis, interconversion, and spectral analysis.

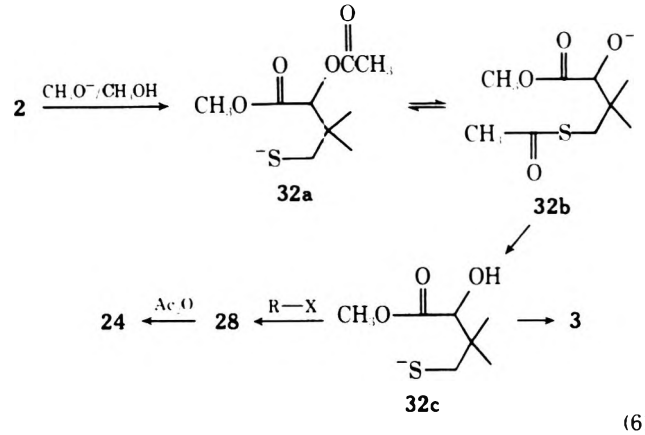
Thietane **21** was synthesized in 30% yield along with some 2,4-diacetate **29** of unknown stereochemistry by treating 3,3-dimethylthietane (**30**) with lead tetraacetate (LTA) in pyridine for 2 hr at 25° (eq 5). The yield of this



(5)

reaction was much higher when determined by GLC, indicating that severe losses were taken in the work-up of this labile molecule. Mild hydrolysis of **21** followed by reduction of the crude product with excess $NaBH_4$ gave the known mercaptan **31**.[18] By contrast, it is interesting to note that reaction of sulfur containing ketol **11** with LTA in pyridine at 25° results only in formation of dione **6**[12,19] with no evidence of oxidation at or α to sulfur.

Ester acetate **24** was synthesized from thiolactone **2** in moderate yield in two steps. Treatment of **2** with several equivalents of 1-chloro-2-methylpropane in refluxing methanol containing 1 equiv of sodium gave alcohol **28** in 30% yield (eq 6). It is interesting to note that thiolactone **3** was also isolated in nearly 30% yield from this reaction



(6)

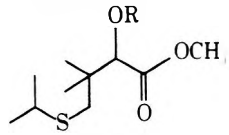
Table I
Photolyses[17] of Acetate 1

Run	g	Solvent (ml)	Time, hr	Products, yield[a] (yield),[b] %
I	2.019	MeOH (250)	11	18 (1), 19 (1), 20, 7 (8), 21 (2), 22 (2), 14 (1), 23, 7.7 (9), 24 2.9 (4), 2, 0.981 g, 62
II[c]	3.910	MeOH (250)	12	23, 7.9, 24, 3.2, 1.57 g, 52
III	1.977	*t*-BuOH (250)	11	20 (7), 21 (4), 22 (4), 23, 8 (9), 24,[e] (2), 2, 0.911 g, 61
IV	0.109	Freon 113[f] (25)	15	20 (6), 21 (2), SM[g] (10), 23, 8 2, 21, polymer
V	0.111	Cyclohexane (25)	18	20 (9), 21 (2), SM (7), 23 (2), 2, 19
VI[d]	1.501	MeOH (250)	9	22 (1), 14 (1), SM (1), 24 (1), 2, 0.520 g, 45

[a] Isolated yield. [b] GLC yields based on isolated 2 as a standard. [c] This reaction was run for synthetic purposes. No effort was made to isolate all minor products. [d] This solution was not degassed with N_2 before irradiation. [e] Isolated as the *tert*-butyl ester (40) and not a methyl ester; see Experimental Section. [f] 1,1,2-Trichloro-2,2,1-trifluoroethane. [g] Starting material.

since earlier attempts to synthesize **3** by partial hydrolysis of **2** had resulted in failure. In fact, it was those failures that led us to synthesize and photolyze **12** as an alternate route to **3**.

Alcohol **28** was found to air oxidize; however, fresh samples gave spectra which were identical with those obtained for photoproduct **28**. The mass spectrum of **28** showed a new ion developing at *m/e* $M^+ - 2$ after being allowed to stand for several hours in the presence of air. (Acetate **24** displayed similar properties). In contrast, a model system, **33**, synthesized as shown in eq 6 (RX = isopropyl bromide), was stable to air oxidation indicating that the hydrogen attached to the tertiary carbon of the isobutyl group of **28** (and **24**) is responsible for the rapid oxidation of those molecules and not other potential sites. The fact that alcohols and not acetates were obtained from these reactions (eq 6), even under the relatively mild conditions used in the attempted synthesis of **33b**, tends to suggest that an equilibrium between O-Ac **32a** and S-Ac **32b**, which would be expected to be more readily transesterified, exists and the alkyl halide finally reacts with **32c** to give product. Alcohols **3**, **28**, and **33a** (as well as **26** and **27** obtained from the photolysis of **12**) were all converted to their respective acetates in near quantitative yield.



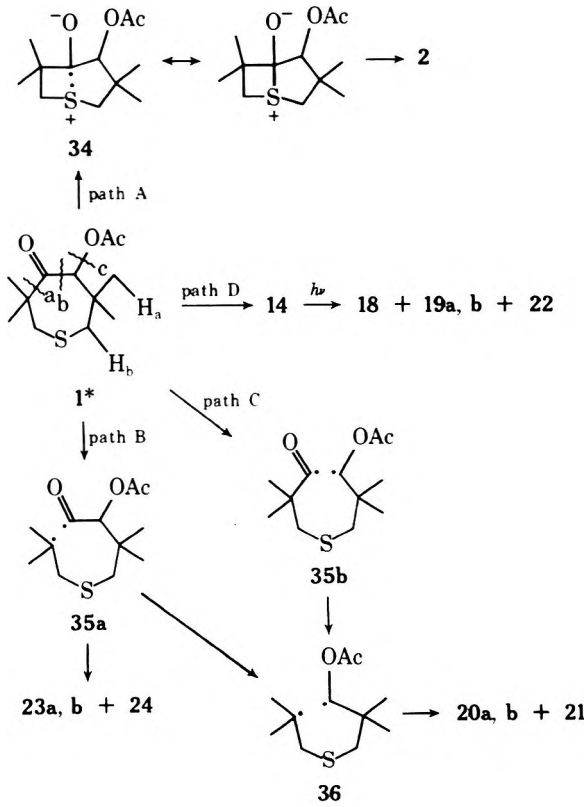
33a, R = H
b, R = Ac

Synthesized acetates were shown to be identical with corresponding acetates isolated from the photolysis of **1**.

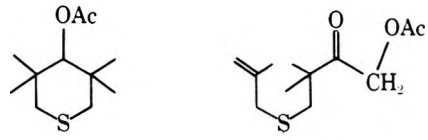
Conclusions

Photolysis of either acetate **1** (Scheme III), carbonate **12**, or ketone **14** results in the formation of the corresponding ring-contracted thiolactone as the major product. We feel that these results can best be accounted for by a one-electron transfer quenching process (e.g., via **34**, Scheme III) similar to that postulated for the photolysis of dione **6** (eq 1). The decrease in the yield of **2** upon irradiation of **1** in solvents of decreasing polarity[9] (Table I) as well as the fact that, while the production of most minor products is completely inhibited when the photolysis of **1** is carried out in the presence of air[20] (O_2, Table I, run VI), the yield of **2** is only slightly diminished under these conditions, supports an electron transfer quenching mechanism for the formation of **2**, **13**, and **22**. On the other hand, the quenching of processes leading to minor products by oxygen tends to indicate that these products probably result from either type I or type II triplet pathways. While these pathways cannot be readily distinguished in photolysis of **6**,[4a] they can be distinguished for acetate **1**. Type I reactions can occur via cleavage of either bond a or bond b of **1*** (Scheme III, paths B and C). Cleavage of bond a would lead to diradical **35a**, a likely precursor for aldehyde **23** or ester **24** (via a ketene intermediate). Loss of carbon monoxide (CO) from **35a** would give diradical **36**,[21] a likely precursor for acetate **20**, and possibly a cyclic acetate such as **37** (the equivalent of ketone **10** in the photolysis of **6** at short wavelengths). No **37** was observed in these studies. Type I cleavage of bond b (**1***) would give, via **35b** (loss of CO[22]), diradical **36** again.

Scheme III



The yield of thiolactone **2** was shown to decrease ca. 5% when it was irradiated independently in degassed methanol for 10 hr through Pyrex and nearly 40% when a Corex filter was used.[23] Since no thietane **21** was formed (nor any other monomeric products) upon irradiation of **2**, we feel that **2** is probably not a direct precursor of **21** but rather **21** is formed via diradical **36**.

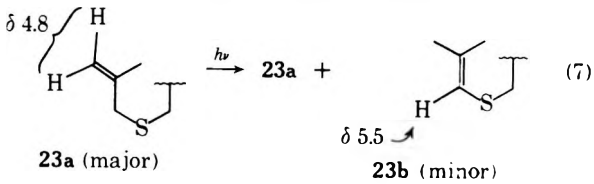


37 **38**

Type II cleavages involving either H_a or H_b (Scheme III, **1***) would lead to keto acetates **38**. No evidence for keto acetate products was obtained in these studies, leading us to agree[7] that type II processes are probably not operative in any of these systems.

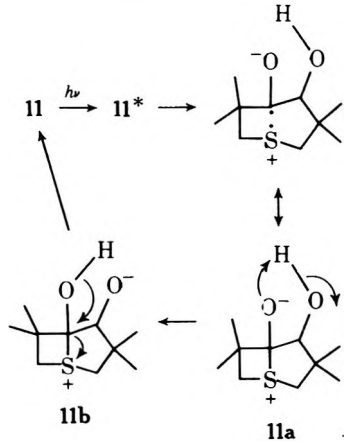
Cleavage of bond c[24] (**1***, Scheme III, path D) represents a minor pathway in the photolysis of **1** and **12** as witnessed by the formation, in low yields, of ester **18**, aldehyde **19**, and thiolactone **22** (primary photoproducts of **14**) as well as ketone **14**.

While drawn as the major isomer (e.g., **23**) for the sake of brevity, all olefinic products isolated in these studies exist as ca. 8:2 mixtures of isomers where the minor isomer has the double bond in conjugation with sulfur.[25] Their ^1H NMR spectra allow easy analysis of these isomers even though they were usually eluted as a single component off a silicic acid column. They were, however, readily separated by GLC (SE-30, Carbowax). A pure isomer of **23a** (obtained by GLC) was shown to equilibrate to an 8:2 mixture of olefins when irradiated independently through Pyrex[21] (eq 7). Loss of **23** accompanied this equilibration.



23a (major) **23b** (minor) (7)

Finally, we feel that the lack of photochemical reaction of ketol **11** can be explained best by an electron transfer quenching process involving quenching of **11*** to give a reactive ground state intermediate **11a** which is further deactivated by proton[9] transfer to give a species such as **11b** which returns to **11** in preference to undergoing ring contraction. A more direct proton transfer quenching mechanism, however, cannot be ruled out.[9] Further studies on this point are in order.



11b **11a**

We are currently studying the reactions of **2** and **3** with glycine, α-alanine, and β-alanine as part of our studies on sulfur analogs of the B complex vitamins.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncalibrated. Infrared spectra were taken on a Perkin-Elmer 337 or 457A spectrometer; ^1H NMR spectra were recorded on a Varian A-60 or Jeol MH-100 spectrometer using Me_4Si as an internal standard. Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer. Ultraviolet spectra were recorded on a Cary 14 instrument. Glpc analyses were performed using program temperature control on a Hewlett-Packard 5750 gas chromatograph equipped with 8 ft × 0.25 in. 10% Carbowax on Chromosorb P and 8 ft × 0.25 in. 10% SE-30 on Chromosorb P stainless steel columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Photochemical Studies. All photochemical reactions were performed using a Hanovia 450-W Type L, medium-pressure, mercury-arc lamp in a water-cooled quartz immersion well equipped with either a Pyrex or Corex filter. Photolysis solvents were reagent grade and were distilled prior to use. All solutions were degassed for 2 hr (unless otherwise noted) using oxygen-free N_2 and were irradiated under a blanket of N_2 with stirring. Aliquots were taken through a side arm (capped with a no-air stopper) at time intervals and the reactions followed by ^1H NMR, ir, or GLC.

A. Irradiation of Ketol 11. Ketol **11** (1.318 g, 0.0065 mol) was irradiated through Pyrex in 250 ml of N_2 degassed methanol for 14 hr to give after work-up 0.95 g (69%) of starting ketol **11**.

B. Irradiation of Acetate 1. See Table I for these data.

C. Irradiation of Carbonate 12. Carbonate **12** (2.501 g, 0.0066 mol) was irradiated through Pyrex in 250 ml of N_2 degassed methanol for 9 hr. The crude reaction, after removal of the methanol in vacuo, was treated with 3 g of zinc powder in 10 ml of acetic acid with cooling for 2 hr. Acid–base work-up gave a crude material which was chromatographed on silicic acid using hexane–ether, giving, in order of elution, photoproducts **26** (4%), **22** (5%), **14** (1%), **27** (5%), **28** (7%), and thiolactone **3** (0.47 g, 49%).

D. Irradiation of Ketone 14. Ketone **14** (50 mg) was irradiated through Pyrex in 50 ml of N_2 degassed methanol for 10 hr to give **18** (5%), **19** (6%), and **22** (48%) as determined by GLC.

3,3,6,6-Tetramethyl-5-hydroxy-1-thiacycloheptan-4-one (11) and 3,3,6,6-Tetramethyl-5-acetoxy-1-thiacycloheptan-4-one (1). Ketol **11** and its acetate **1** were synthesized according to literature procedures in good yields.

For **11**: mp (sublimed) 82–83° (lit.[12] mp 82–83°); mass spectrum (70 eV) *m/e* (rel intensity) 202 (5, M^+), 174 (2), 147 (61), 118 (11), 117 (10), 101 (12), 85 (19), 72 (20), 71 (31), 57 (61), 56 (100), 55 (22), 43 (17), and 41 (28) with a metastable ion at *m/e* 106.9; uv λ_{max} (EtOH) 294 nm (ϵ 44), 238 (530).

For **1**: mp (EtOH) 127–128° (lit.[12] mp 127–128°); ^1H NMR ($CDCl_3$) δ 0.97 (s, 3), 1.08 (s, 3), 1.21 (s, 3), 1.25 (s, 3), 2.12 (s, 3), 2.64 (AB, 2), 2.75 (br s, 2), 5.13 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 244 (2, M^+), 202 (1), 189 (83), 147 (34), 132 (10), 129 (15), 117 (10), 104 (11), 101 (17), 89 (17), 57 (41), 56 (40), 55 (17), 43 (100), and 41 (20); uv λ_{max} (EtOH) 295 nm (ϵ 44), 238 (560).

5-(2,2,2-Trichloroethylcarboxyldioxy)-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (12). 2,2,2-Trichloroethoxycarbonyl chloride (2.5 g, 0.012 mol) was added dropwise into a flask containing 50 ml of dry pyridine and 2.0 g (0.01 mol) of acyloin **11**. After allowing the mixture to stir for 24 hr at 25° under N_2, the bulk of the solvent was removed in vacuo. The remaining material was extracted with water–ether. The ether layer was dried over K_2CO_3 and evaporated to give a crude solid. Recrystallization from hexane gave 3.1 g (82%) of pure **12**: mp 141–142°; ir ($CHCl_3$) 2980, 1740, 1705, 1365, and 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 3), 1.18 (s, 3), 1.28 (s, 6), 2.64 (br s, 2), 2.74 (br s, 2), 4.73 (AB, 2, OCH_2CCl_3), 5.03 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 376 (1, M^+, 3 Cl by isotope ratio), 321 (10, 3 Cl), 185 (8), 133 (10), 131 (10), 129 (42), 101 (18), 100 (17), 69 (100), 56 (75), 55 (30), and 41 (40); uv λ_{max} (EtOH) 297 nm (ϵ 40), 238 (50).

Anal. Calcd for $C_{13}H_{19}Cl_3O_4S$: C, 41.34; H, 5.07. Found: C, 41.40; H, 5.16.

Reaction of Carbonate 12 with Zinc in Acetic Acid. Treatment of 600 mg of carbonate **12** in 10 ml of acetic acid at 25° with an equal weight of zinc dust for 12 hr gave, after careful acid–base work-up, a 91% yield of ketol **11**.

Reaction of 1 with Zinc in Acetic Acid. Synthesis of Ketone 14. Acetate **1** (3.0 g, 0.012 mol) and an equal weight of zinc dust were refluxed under N_2 for 25 hr. Fresh zinc dust was added peri-

odically. Acid–base work-up gave a neutral material from which could be isolated 120 mg (5%) of ketone **14** as an oil. Microdistillation gave a clear oil whose properties were identical with those reported:[12] mass spectrum (70 eV) *m/e* (rel intensity) 186 (4, M^+), 131 (100), 89 (10), 83 (69), 56 (39), 55 (27), and 41 (20).

Ketol **11** (5%) and acetate **1** were also recovered from this reaction.

Reduction of 11 with $NaBH_4$ in EtOH. Ketol **11** (1.5 g, 0.0075 mol) and $NaBH_4$ (0.3 g, 0.008 mol) were stirred in ethanol at 25° for 1 hr and then at 80° for an additional 3 hr. Work-up gave a crude solid which was shown by ^1H NMR to be better than 90% cis diol. Recrystallization of the solid from $CHCl_3$ gave 1.2 g (79%) of pure cis diol **15**: mp 183–185° (lit.[26] mp 179–180°); ir 3580, 3440, 2920, and 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 6), 1.09 (s, 6), 2.38 (br s, 2, absent D_2O), 2.27 (d, 2, J = 12 Hz), 2.84 (d, 2, J = 12 Hz), 3.72 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 204 (41, M^+), 130 (10), 120 (75), 115 (11), 102 (18), 101 (44), 89 (20), 86 (72), 85 (22), 83 (27), 71 (79), 69 (32), 68 (30), 57 (100), 56 (50), 55 (57), 43 (43), and 41 (58).

Anal. Calcd for $C_{10}H_{20}O_2S$: C, 58.79; H, 9.87. Found: C, 58.67; H, 10.08.

When acyloin **11** was reduced by adding it to a refluxing mixture of $LiAlH_4$ in THF cis and trans diols[15] were formed in an 85:15 ratio (determined by ^1H NMR spectra of crude diol). They could be separated by column chromatography using silicic acid with ether–hexane elution.

Reaction of Diol 15 with Triphenylphosphine in CCl_4. Synthesis of 16. Cis diol **15** (1.0 g, 0.0049 mol) and triphenylphosphine (1.7 g, 0.0065 mol) were stirred in 50 ml of CCl_4 under N_2 for 2 hr and then heated at reflux for 3 hr. After cooling the reaction mixture, hexane was added and the mixture was filtered. The filtrate was concentrated in vacuo and the residue was distilled to give 0.4 g (44%) of **16** whose properties were identical with those reported[16,26] for this material. Some dichloride **17** was also isolated from this reaction when a mixture of cis and trans diols was used.[14]

5,5-Dimethyl-1,3-dioxan-2-one (39). Cyclic carbonate **39** was synthesized according to a literature[27] procedure in 75% yield: bp 110–120° (1 mm); mp (hexane) 108–110° (lit.[27] mp 110–111°); ir ($CHCl_3$) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 6) and 3.49 (s, 4).

3,3-Dimethylthietane (30). Thietane **30** was synthesized via a modification of a literature procedure. A mixture of 11 g (0.09 mol) of carbonate **39** and 14.8 g (0.15 mol) of anhydrous potassium thiocyanate was slowly heated to ca. 120°. A slow stream of N_2 was bubbled over the reaction mixture and the volatile products collected in a Dry Ice trap. Distillation of the crude distillate gave pure **30** in 62% yield: bp 115–116° (760 mm) (lit.[28] bp 115°); ^1H NMR ($CDCl_3$) δ 1.30 (s, 6), 2.95 (s, 4); mass spectrum (70 eV) *m/e* (rel intensity) 102 (52, M^+), 87 (19), 57 (10), 56 (100), 55 (16), 46 (18), 45 (18), and 41 (75).

Synthesis of 2-Acetoxy-3,3-dimethylthietane (21). To 10 ml of dry pyridine under N_2 was added 1.2 g (1.1 mmol) of thietane **30** and 5.3 g (1.2 mmol) of lead tetraacetate. The mixture was stirred for 3 hr at 25° and poured into enough ice-cold 10% HCl to just neutralize the pyridine. The aqueous layer was quickly extracted with ether which was dried with K_2CO_3 and carefully evaporated. The residue was column chromatographed on silicic acid with hexane–ether elution. For **21**: yield 30%; bp 28–30° (1 mm); ir ($CHCl_3$) 1740 and 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 3), 1.32 (s, 3), 2.03 (s, 3), 2.76 (AB, 2, J = 9 Hz), and 3.34 (br s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 160 (4, M^+), 132 (6), 104 (5), 99 (4), 89 (7), 72 (9), 57 (13), 56 (18), and 43 (100) with metastable ions at *m/e* 108.9 ($132^2/160$) and 74.2 ($99^2/132$).

Mild hydrolysis of **21** in aqueous ethanol containing HCl followed by reduction of the reaction mixture with excess $NaBH_4$ allowed isolation (GLC) of mercaptan **31**.[18]

2-Acetoxy-3,3-dimethyl-γ-butyrothiolactone (2). For **2**: bp 85–90° (2 mm); mp (pentane) 40–41°; ir ($CHCl_3$) 2940, 1745, 1710, 1460, 1370, 1240, 1100, 1010, and 955 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 3), 1.23 (s, 3), 2.17 (s, 3), 3.14 (AB, 2, J = 12 Hz), 5.28 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 188 (1, M^+), 128 (24), 89 (9), 57 (21), 56 (23), and 43 (100) with a metastable ion at *m/e* 87.2 ($128^2/188$); uv λ_{max} (EtOH) 227 nm (ϵ 3500).

Anal. Calcd for $C_8H_{12}O_3S$: C, 51.06; H, 6.43. Found: C, 50.90; H, 6.26.

Synthesis of Methyl 5-Thia-3,3,7-trimethyl-2-hydroxyoctanoate (28). Thiolactone **2** (390 mg, 0.22 mmol) was added to 10 ml of dry methanol under N_2 in which 1 equiv of sodium metal had been dissolved. After stirring for several minutes at 25°, 2 equiv of 1-chloro-2-methylpropane was added to the flask and it was heated at reflux for 3 hr and cooled. The bulk of the methanol was removed in vacuo and the residue was extracted with water–ether. Concentration of the ether gave an oil which was shown by GLC to be a 1:1 mixture of **3** and **28**. [It was found that extraction of the original residue with water–hexane allowed isolation of nearly pure **28** (ca. 30%)]. A second extraction with ether gave **3** (ca. 30%).

For **28**: bp 94–98° (1 mm); ir ($CHCl_3$) 3540, 2940, 1730, 1250, and 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 6, J = 7 Hz), 1.01 (s, 3), 1.18 (s, 3), 1.90 (m, 1), 2.48 (d, 2, J = 6 Hz), 2.64 (AB, 2), 3.30 (d, 1, absent in D_2O), 3.85 (s, 3), 4.20 (d, 1, singlet in D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 234 (21, M^+), 232 (s) 145 (42), 144 (20), 131 (12), 129 (10), 103 (23), 89 (21), 85 (18), 83 (18), 70 (15), 57 (100), 56 (50), 55 (45), 44 (32), 43 (31), and 41 (46).

Synthesis of Methyl 5-Thia-3,3,7-trimethyl-2-acetoxyoctanoate (24). Ester **28** (40 mg) was refluxed under N_2 in 2 ml of acetic acid and 2 ml of acetic anhydride for 3 hr. Careful acid–base work-up gave acetate **24** in near quantitative yield which could be further purified by microdistillation: bp ca. 85° (1 mm); ir (CCl_4) 2980, 1750, 1370, 1240, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 6, J = 7 Hz), 1.10 (s, 6), 1.80 (m, 1), 2.13 (s, 3), 2.42 (d, 2, J = 7 Hz), 2.60 (s, 2), 3.75 (s, 3), 4.91 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 276 (12, M^+), 245 (2), 216 (10), 175 (5), 173 (4), 157 (68), 145 (35), 144 (38), 141 (13), 131 (12), 128 (10), 127 (17), 113 (10), 103 (60), 90 (10), 89 (11), 61 (15), 57 (78), 56 (18), 55 (22), 43 (100), and 41 (26).

No effort was made to obtain an analysis on this material owing to its rapid air oxidation.

2-Hydroxy-3,3-dimethyl-γ-butyrothiolactone (3). For **3**: bp ca. 50° (1 mm); ir ($CHCl_3$) 3520, 2960, 1700, 1370, 1123, 1010, 993, and 958 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3), 1.30 (s, 3), 3.05 (AB, 2), 3.98 (s, 1), 4.00 (br s, 1, OH); mass spectrum (70 eV) *m/e* (rel intensity) 146 (28, M^+), 118 (47), 89 (8), 85 (23), 72 (35), 71 (32), 57 (59), 56 (100), 55 (25), 45 (12), 43 (21), and 41 (32) with a metastable ion at *m/e* 95.5 ($118^2/146$).

Reaction of Thiolactone 3 with Acetic Acid–Acetic Anhydride. Thiolactone **3** (50 mg) was refluxed under N_2 in 2 ml of acetic acid and 2 ml of acetic anhydride for 3 hr. A careful acid–base work-up gave a near-quantitative recovery of acetylated thiolactone **2** which was identical with that isolated from photolysis mixtures of acetate **1**.

Synthesis of Methyl 5-Thia-3,3,6-trimethyl-2-hydroxyheptanoate (33a). Thiolactone **2** (370 mg, 0.2 mmol) was added to 10 ml of dry methanol under N_2 in which 1 equiv of sodium metal had been dissolved. After stirring for several minutes at 25°, 1.2 equiv of 2-bromopropane was added to the mixture and it was warmed gently for 1 hr. After removal of most of the methanol in vacuo, the mixture was extracted with water–hexane. Concentration of the hexane layer gave an oil which was distilled to give **33a** in 76% yield: bp 85–90° (1 mm); ir ($CHCl_3$) 3520, 2960, 1730, 1220, and 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 3), 1.02 (s, 3), 1.26 (d, 6, J = 7 Hz), 2.61 (AB, 2, $-SCH_2-$), 2.82 (septet, 1, J = 7 Hz), 3.30 (d, 1, absent D_2O), 3.79 (s, 3), 4.16 (d, 1, singlet in D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 220 (38, M^+), 144 (22), 131 (75), 99 (18), 90 (28), 89 (100), 85 (20), 75 (21), 57 (29), 55 (72), 47 (22), 43 (58), and 41 (31).

Synthesis of Methyl 5-Thia-3,3,6-trimethyl-2-acetoxyheptanoate (33b). Ester **33a** was heated under N_2 with acetic acid–acetic anhydride for 3 hr. Acid–base work-up gave acetate **33b** in near quantitative yield. For **33b**: bp 92–98° (1 mm); ir (CCl_4) 2950, 1750, 1370, 1235, and 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 6), 1.24 (d, 6, J = 6.5 Hz), 2.12 (s, 3), 2.60 (AB, 2), 2.76 (septet, 1, J = 6.5 Hz), 3.72 (s, 3), 4.89 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 262 (20, M^+), 202 (15), 144 (12), 143 (67), 141 (12), 131 (43), 130 (32), 128 (14), 127 (19), 113 (10), 101 (11), 99 (11), 90 (28), 89 (90), 88 (18), 75 (19), 55 (40), 47 (20), 43 (100), and 41 (18), with a metastable ion at *m/e* 156.0 ($202^2/262$).

Anal. Calcd for $C_{12}H_{22}O_4S$: C, 54.93; H, 8.45. Found: C, 54.80; H, 8.32.

4-Thia-7-hydroxy-2,6,6-trimethyl-1-heptene *O*-Acetate (20a) and Its Δ^2 Isomer 20b. For **20a**: bp ca. 50° (1 mm); ir ($CHCl_3$) 2920, 1728, 1370, 1240, and 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 6), 1.81 (br s, 3), 2.15 (s, 3), 2.43 [s, 2, $SCH_2C(CH_3)_2$], 3.09 (br 5, 2, $C{=}CCH_2S$), 3.90 (s, 2), 4.82 (m, 2, $C{=}CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 216 (27, M^+), 141 (8), 129 (17), 101 (36), 87 (15), 86 (12), 85 (12), 69 (15), 67 (16), 59 (21), 55 (42), and 43 (100).

For **20b**: ^1H NMR ($CDCl_3$) δ 0.94 (s, 6), 2.72 (s, 6), 2.08 (s, 3), 2.65 (s, 2, $C{=}CSCH_2$), 3.90 (s, 2), and 5.50 (m, 1, $C{=}CHS$); mass spectrum (70 eV) *m/e* (rel intensity) 216 (18, M^+), 156 (8), 141 (28), 129 (8), 101 (13), 100 (11), 99 (10), 89 (9), 88 (9), 85 (9), 69 (15), 57 (18), 56 (19), 55 (19), and 43 (100).

Alcohol **26**, obtained from the photolysis of **12**, was identified by its mass spectrum (M^+ 174) and its conversion to acetate **20**.

5-Thia-2-hydroxy-3,3,7-trimethyloct-7-en-1-al *O*-Acetate (23a) and Its Δ^6 Isomer 23b. For **23a**: bp ca. 85 (1 mm); ir ($CHCl_3$) 3050, 2910, 2840, 2730, 1740, 1645, 1370, 1240, 1085, 1040, and 895 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 6), 1.80 (br s, 3), 2.19 (s, 3), 2.50 (s, 2), 3.08 (br s, 2), 4.84 (m, 2, $C=CH_2$), and 4.96 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 244 (18, M^+), 216 (5), 157 (11), 143 (10), 129 (14), 115 (22), 109 (10), 101 (69), 87 (34), 67 (25), 59 (29), 56 (62), and 43 (100).

For **23b**: ^1H NMR ($CDCl_3$) δ 1.10 (s, 6), 1.72 [s, 6, $(CH_3)_2C=C$], 2.19 (s, 3), 2.70 (s, 2, SCH_2), 4.94 (s, 1), and 5.54 (br s, 1, C=CHS); mass spectrum (70 eV) *m/e* (rel intensity) 244 (28, M^+), 101 (87), and 43 (100).

A mixture of aldehydes **23** was converted to a 2,4-dinitrophenylhydrazone derivative using standard procedures: mp (EtOH) 130–131°.

Anal. Calcd for $C_{18}H_{24}N_4O_6S$: C, 50.93; H, 5.70. Found: C, 50.76, H, 5.67.

Alcohol **27**, obtained from the photolysis of **12**, was identified by its mass spectrum (M^+ 202) and its conversion to acetate **23**.

***tert*-Butyl 5-Thia-3,3,7-trimethyl-2-acetoxyoctanoate (40).** Ester **40** was identified solely on the basis of its mass spectrum and analogy to ester **24**. For **40**: mass spectrum (70 eV) *m/e* 318 (M^+), 219, 202, 171, 157, and 43.

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Registry No.—**1**, 21153-34-4; **2**, 56210-56-1; **3**, 56210-57-2; **11**, 4485-40-9; **12**, 56210-58-3; **14**, 21153-38-8; *cis*-**15**, 56210-59-4; *trans*-**15**, 56210-60-7; **16**, 56210-61-8; **20a**, 56210-62-9; **20b**, 56210-63-0; **21**, 56210-64-1; **23a**, 56210-65-2; **23b**, 56210-66-3; **23** 2,4-DNPH, 56210-55-0; **24**, 56210-67-4; **28**, 56210-68-5; **30**, 13188-85-7; **33a**, 56210-69-6; **33b**, 56210-70-9; **39**, 3592-12-9; **40**, 56210-71-0; 2,2,2-trichloroethoxycarbonyl chloride, 17341-93-4; zinc, 7440-66-6; triphenylphosphine, 603-35-0; potassium thiocyanate, 333-20-0; lead tetraacetate, 546-67-8; 1-chloro-2-methylpropane, 513-36-0; 2-bromopropane, 75-26-3.

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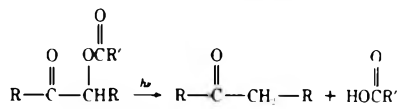

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Heterophilic Additions to Carbonyls and Thiocarbonyls. Scope and Stereochemistry

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The heterophilic additions of *Z* and *E* 1-propenyl organometallics to thiobenzophenone (1) and phenanthraquinone (25) proceed primarily with retention of configuration. These results may be used to rule out predominant reaction via a free 1-propenyl radical but do not distinguish between mechanisms involving a caged radical and direct nucleophilic addition. However, the latter process is provisionally preferred for addition of lithium reagents to 1 and organomagnesium bromides to 25, since the yields of heterophilic addition products appear to be inversely proportional to the ability of a series of organometallics to transfer an electron. It is suggested that the small amount of isomerization which is observed in the additions of (*Z*)- and (*E*)-1-propenylmagnesium bromides to 1 and 25 is due to different rates of reaction of the isomeric Grignard reagents. Attempts to observe heterophilic addition of organometallics to carbonyl and imine functions substituted by sulfur on carbon reveal only carbophilic products. Furthermore, heterophilic additions are not observed in the reactions of phenyllithium with dimethyl thiobenzamide, of benzhydryl and benzyl organometallics with aromatic thioketones, and of vinyllithium with tetraphenylcyclopentadienone.

Heterophilic additions have been reported for reactions of organometallics with a variety of carbon–heteroatom multiple bonds. Products of thiophilic addition are obtained from aromatic and aliphatic thioketones,[1,5] dithio esters,[2b-6] and trithiocarbonates.[2b-7] In the cases of many thioketones, processes after formation of the initial α-thiaorganometallic are postulated to lead to radicals,[3a-d] episulfides,[8] olefins,[6,8,9] enethiol esters,[3b,c,e,4a-c] and novel double addition products.[3d,e,4c,10] A 2,3-sigmatropic rearrangement of the initial adduct has been suggested to rationalize the ultimate carbon–carbon bond formation by an allylic organometallic with thioadamantanone,[5] and related processes could account for the carbophilic products observed on reaction of pyrrolemagnesium bromide with thiocarbonates.[11] The extent of thiophilic addition has been found to be a function of the thioketone, organometallic, and solvent and some results have been rationalized in HSAB terms.[3d] Recently it has been suggested that addition of vinyl Grignard to thiobenzophenone occurs initially at carbon and is followed by migration to sulfur,[12] although an analogous rearrangement has been definitively ruled out for the thiophilic reaction of thiobenzophenone and phenyllithium.[2b] Additions of Grignard reagents to a dithio ester,[11] a thio ester,[13] a thio amide,[14] and thio acid chlorides,[10,15] and of benzhydrylsodium to thiobenzophenone[16] are reported to give products expected for carbophilic addition, although not all products have been characterized for those cases. It is interesting that alkyl Grignard reagents react with ethyl 2,2-dimethyl thioacetoacetate exclusively at sulfur,[4d] suggesting that thiophilic addition to sulfur can even be preferred over normal addition to a carbonyl.

Addition of an organometallic to the oxygen of a carbonyl group has been reported by at least three groups. However, the fact that ethers are formed only from phenanthraquinone,[17] tetraphenylcyclopentadienone,[18] and quinol acetates[19] or an analogous cation[18] suggests that this reaction path may be limited to carbonyl functions which can provide especially stable radicals or anions on oxophilic addition.

Carbon–nitrogen bond formation between an imine and a formal carbanion can be observed if the imine is conjugated with a carbonyl group[20] or another imine.[21] Azophilic additions to oximes,[22] an oxime tosylate,[23] and azo bonds[24] have been reported.

We wish to report a product study of heterophilic additions to thiocarbonyl and carbonyl groups which provides information about the question of whether such reactions proceed by one- or two-electron processes. We also have somewhat defined the scope of heterophilic additions by failing to find this reaction path for a variety of cases.

Results

Additions of Vinyllithium, 1-Propenyllithium, Vinylmagnesium Bromide, 1-Propenylmagnesium Bromide, and Phenyl-d_5-magnesium Bromide to Thiobenzophenone. Treatment of thiobenzophenone (1) with vinyllithium in ether or vinylmagnesium bromide[12] in tetrahydrofuran gives vinyl benzhydryl sulfide (2) in 40 and 36% yields, respectively. The reaction of (*Z*)- and (*E*)-1-propenyllithium and -magnesium bromide in ether and tetrahydrofuran, respectively, give the thiophilic products (*Z*)- and (*E*)-1-propenyl benzhydryl sulfides (3) in ca. 40% yields. Isomerically pure (*E*)-3 and ca. 95% pure (*Z*)-3 were obtained by chromatography of the crude products obtained from the reaction of 1 with (*E*)- and (*Z*)-1-propenyllithium, respectively. The stereochemistry for the isomers of 3 was determined by the characteristic couplings of the propenyl group: J_E = 15.0 and J_Z = 9.4 Hz.

When the reaction of (*Z*)- and (*E*)-1-propenyllithium with 1 was quenched with deuterium oxide, the NMR spectra of the crude product showed the expected vinyl hydrogens and no detectable benzhydryl protons, indicating that the product is 3-d_1 as expected from the carbanion resulting from thiophilic addition.[2] Other products obtained from the reaction of vinyl- and 1-propenyllithium and the corresponding Grignard reagents with 1 include 24–35% benzophenone, which may arise from oxidation or hydrolysis of 1, and in the case of Grignard reagents, ca. 10% of benzhydryl mercaptan.

$$(C_6H_5)_2C{=}S + RCH{=}CHM \longrightarrow (C_6H_5)_2CHSCH{=}CHR$$

1 R = H, CH_3; M = Li, MgBr — 2, R = H; 3, R = CH_3

The stereochemical results of the reactions of (*Z*)- and (*E*)-1-propenyllithium and (*Z*)- and (*E*)-1-propenylmagnesium bromide with thiobenzophenone, as summarized in Table I, show that these additions occur with a high degree of retention of stereochemistry.[25] However, the results do reveal an apparent isomerization of up to 15% of the product from (*E*)-1-propenylmagnesium bromide.

The (*Z*)- and (*E*)-1-propenyllithiums were found to maintain geometrical integrity under the reaction condi-

Table I
Retention of Stereochemistry of the 1-Propenyl Group in 1-Propenyl Benzhydryl Sulfides (3) Obtained from Reactions of Thiobenzophenone (1) with *cis*- and *trans*-1-Propenyllithium and -magnesium Bromide at 0° in Ether and Tetrahydrofuran

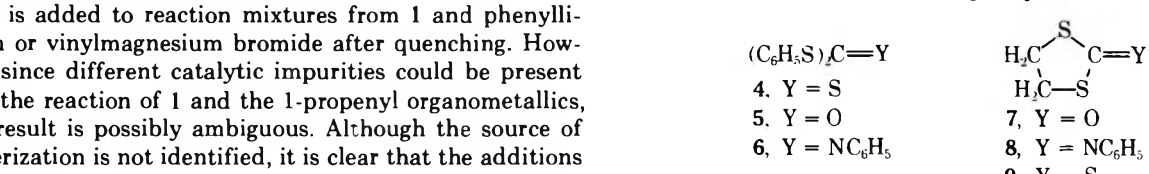
Organometallic	Isomeric purity, % Organometallic[a,b]	Isomeric purity, % Sulfide (3)[a-d]	Retention of stereochemistry, %[e]
(*E*)-CH_3CH=$CHLi$	94.7 ± 1.5	86.9 ± 2.1[f]	92
	(95.8 ± 1.9)[g]	(85.9 ± 1.8)	
	90.4 ± 0.7	84.3 ± 2.7[f]	94
	81.7 ± 0.9	73.8 ± 1.6[f]	90
	95.5 ± 0.5	91.4 ± 0.5	96
		(91.5 ± 0.8)	
	95.5 ± 0.5	91.8 ± 2.5	96
		(90.7 ± 1.1)	
	95.5 ± 0.5	91.9 ± 0.7	96
		(91.6 ± 2.0)	
(*Z*)-CH_3CH=$CHLi$	98.3 ± 0.9	94.6 ± 0.9[f]	96
	(97.0 ± 0.6)[g]		
	97.4 ± 1.0	95.1 ± 1.9	97
		(95.4 ± 1.1)	
(*E*)-CH_3CH=$CHMgBr$	77.4 ± 2.6	65.0 ± 3.5[f,h]	84
	76.9 ± 2.3	70.1 ± 3.4[f]	92
		(66.4 ± 1.7)	
	79.2 ± 4.7	68.0 ± 1.1	86
	(79.8 ± 2.0)	(70.6 ± 2.9)	
	79.2 ± 4.7	68.1 ± 1.0	86
	(79.8 ± 2.0)	(78.0 ± 0.7)	
	79.2 ± 4.7		87
	(79.8 ± 2.0)	(69.9 ± 1.4)	
(*Z*)-CH_3CH=$CHMgBr$	91.7 ± 1.9	92.6 ± 0.7[f]	101
	95.4 ± 3.7	93.4 ± 1.8	98
	(95.1 ± 0.5)	(95.9 ± 1.7)	
	95.4 ± 3.7	92.7 ± 2.5	97
	(95.1 ± 0.5)		

[a] Error limits are three times standard deviations. [b] For determination of the isomeric purities of the organometallics, see Experimental Section. The values in parentheses for Grignard reagents refer to those obtained by quench with trimethylchlorosilane. [c] Retention as determined by NMR integration. In parentheses are the values for the crude reaction products. Otherwise, the values are for the mixture of sulfides 3 isolated by column chromatography. [d] Although a correlation could be often established between the amount of benzhydryl mercaptan, the time before analysis, and the amount of isomerization, this was not a reproducible effect. For example, the reaction which gave 84% retention had less than 1% benzhydryl mercaptan present. [e] Defined as a ratio of percent of major isomer of 3 to percent of major isomer of the organometallic reagent. Error is ±4%. [f] After work-up the reaction mixture was allowed to stand at room temperature overnight before the solvent was removed in vacuo and the NMR spectra measured otherwise immediate work-up was used. [g] Isomeric purity of excess organolithium reagent immediately before quench. [h] The reaction mixture was washed with 2 *N* sodium hydroxide to remove possible benzhydryl mercaptan immediately after quench.

tions as shown by analysis of an aliquot of the reaction mixture immediately before aqueous quench. Similar analysis of the Grignard reagents was not conclusive. It was established that the equilibrium ratio of (*Z*)-3:(*E*)-3 is ca. 1.5 in favor of the *Z* isomer at 25° in ether and that some isomerization can be catalyzed by benzhydryl mercaptan, an occasional reaction product. Slightly increased isomerization is noted for experiments which were allowed to stand before analysis and in which benzhydryl mercaptan is a product (Table I) but a control experiment suggests that this can acccount for at most ca. 5% isomerization. Control experiments also establish that isomerization is negligible if (*E*)-3 is added to reaction mixtures from 1 and phenyllithium or vinylmagnesium bromide after quenching. However, since different catalytic impurities could be present from the reaction of 1 and the 1-propenyl organometallics, that result is possibly ambiguous. Although the source of isomerization is not identified, it is clear that the additions proceed largely with retention.

The similarity of the additions of the vinyl- and 1-propenyllithium and -magnesium bromide reagents to 1 is analogous to the previously reported additions of phenyllithium and phenylmagnesium bromide to the same substrate.[2] In the former case, direct thiophilic addition was established by the fact that reaction of thiobenzophenone-d_{10} with phenyllithium gives benzhydryl-d_{10}-phenyl thioether. In the present work an analogous reaction between 1-d_{10} and phenylmagnesium bromide was shown to give the same product with the same labeling. Accordingly greater than 95% of the addition is directly to sulfur for the Grignard reagent and less than 5% rearrangement occurs after initial addition to sulfur occurs under these conditions.

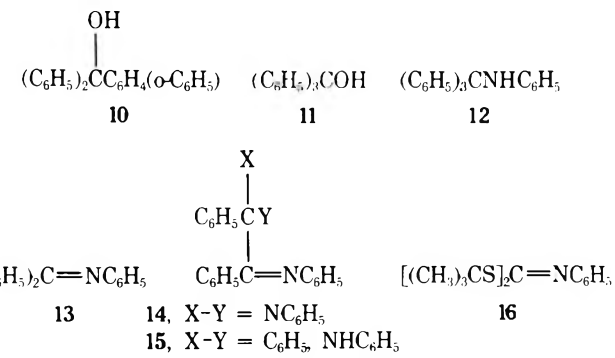
Additions of Phenyllithium to Derivatives of Dithiocarbonates. Our previous study showed that phenyl trithiocarbonate (4) reacts with phenyllithium to give tris-



(phenylthiomethane) in 66% yield at −78° although the reaction is complicated by the formation of a carbene from the initial thiophilic adduct at room temperature.[2b,7,26] To test the possibility that sulfur substitution, which would be expected to stabilize the carbanion resulting from hetero-

philic addition,[27] could promote that reaction pathway for carbonyl or imine functions, the products from the reactions of phenyllithium and the dithiocarbonates **5–8** have been investigated.

The reaction of **5** with 2 equiv of phenyllithium affords o-biphenyldiphenylcarbinol (**10**), triphenylcarbinol (**11**), thiophenol, and recovered **5** in 5, 51, 66, and 17.5% yields, respectively. The formation of **10** is attributed to 2-biphenyllithium, formed in the preparation of the organometallic from bromobenzene and phenyllithium via benzyne.[28] Hydrolysis of the phenyllithium used in this study, followed by GLC analyses, did show the presence of biphenyl along with bromobenzene, and benzene. When the imine **6** was treated with 3 equiv of phenyllithium, triphenylmethylaniline (**12**), benzophenone anil (**13**), benzophenone, and thiophenol were obtained in 66, 25, 5, and 83% yields, respectively. Presumably benzophenone arises by hydrolysis of **13** during work-up.



10 **11** **12**

13 **14**, X-Y = NC_6H_5 **16**
15, X-Y = C_6H_5, NHC_6H_5

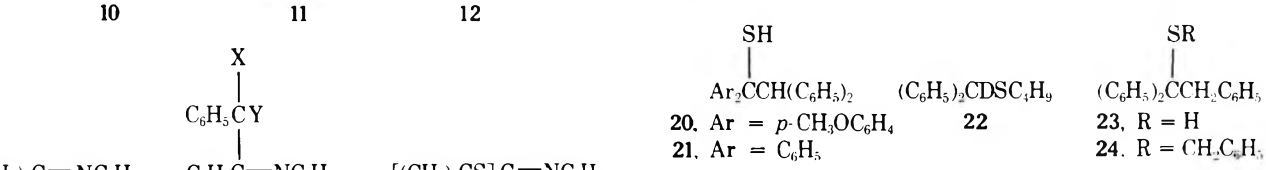
The cyclic dithiocarbonate **7** reacts with 3.3 equiv of phenyllithium to give triphenylcarbinol (**11**) and ethanedithiol in 78 and 83% yields. The reaction of the corresponding imine, however, is more complex. With 4 equiv of phenyllithium, the products from **8** include **12** and ethanedithiol in 11 and 10% yields. However, benzil dianil (**14**) and β-thiophenylethanethiol and its disulfide are also found in 47, 37, and 39% yields.

Although the reactions of **5–7** can be rationalized in a straightforward way by carbophilic addition of phenyllithium, the reaction path for **8**, while clearly not azophilic, is less apparent. To provide a model for heterophilic addition in this system, we have investigated the reaction of **9** with 2.2 equiv of phenyllithium. Treatment of the aqueous basic extract from that reaction with dimethyl sulfate gives 62% methyl dithiobenzoate and 70% thioanisole along with 21% starting material. In an attempt to determine whether the products from the reaction of **8** could arise from phenyl isocyanide the reaction of that compound with 4 equiv of phenyllithium was carried out at −23° in ether. The products are **14** (68%), a material tentatively identified as 2-anilino-*N*,1,2,2-tetraphenyl-1-imine (**15**, 2%), and benzanilide (7%). The formation of **14** finds analogy in the formation of benzilbis(cyclohexyl)imide from the reaction of cyclohexyl isocyanide with phenylmagnesium bromide[29] and may involve air oxidation of the corresponding bisenamine.[30] The reaction of 4 equiv of phenyllithium with di-*tert*-butyl phenylimidodithiocarbonate (**16**) was also examined and found to proceed normally yielding 92.5% of **12**.

These reactions of **5–8** and **18** suggest that sulfur substitution on a carbonyl or imine is not sufficient to promote heterophilic additions.

Addition of Phenyllithium to a Thio Amide. Since sulfur substitution on carbon does not promote heterophilic addition to oxygen and nitrogen, a question of interest is whether substitution on the carbon of a thiocarbonyl can inhibit the thiophilic path. Thio amides are reported to react with Grignard reagents at carbon by reduction,[14,31] and we have found that reaction of *N,N*-dimethylthiobenzamide (**17**) with 2.3 equiv of phenyllithium gives *N,N*-dimethyltriphenylmethylamine (**18**) in 50% yield, as well as 33% triphenylcarbinol and 4% benzophenone. The latter two products presumably arise by hydrolysis on work-up. Apparently, substitution of nitrogen on the thiocarbonyl carbon, like substitution of oxygen,[11,13,15] is sufficient to repress thiophilic addition.

Addition of Benzyl Sodiums and Lithiums to Aromatic Thioketone. In contrast to the thiophilic additions of other organometallics to aryl thioketones,[2,7] benzhydrylsodium is reported to add to such thiocarbonyl groups at carbon.[16] In order to determine the effect of such a structural change and of metal variation on the course of the addition, the reactions of 4,4′-dimethoxythiobenzophenone (**19**) with benzhydrylsodium and benzhydryllithium and of thiobenzophenone with benzhydryllithium have been examined. In each case products of thiophilic addition could not be isolated and the major products are the thiols **20** and **21** resulting from carbophilic additions in yields ranging from 55% (from **19**, M = Na) to 68% (from **1**, M = Li).



20, Ar = *p*-$CH_3OC_6H_4$ **22**
21, Ar = C_6H_5

Generation of the anion of dibenzhydryl sulfide with *n*-butyllithium in tetrahydrofuran followed by deuterium oxide quench gave diphenylmethane-d_1 and benzhydryl *n*-butyl sulfide-d_1 in ca. 20% yield, along with recovered undeuterated starting material. A trace of **21** was detected by NMR. This attempt to form the first intermediate in the possible heterophilic addition shows that if thiophilic addition occurs, intramolecular rearrangement to the carbophilic product would probably occur much more slowly than fragmentation to thioketone.

Since it was observed that thiobenzophenone reacts with benzhydryllithium to give **21**, the effect of benzyl structure of the organometallics was further investigated by the reaction of **1** with benzylmagnesium chloride and with benzyllithium. In the former case the reduction product benzhydryl mercaptan (8%), the carbophilic product benzyldiphenyl mercaptan (**23**, 20.5%), and the double addition product[3d,e,4c,10] benzyldiphenyl benzyl sulfide (**24**) are formed. The products with benzyllithium are benzhydryl mercaptan (12.5%) and **23** (44%) along with benzyl mercaptan.[32] Apparently benzylic structures in the organometallic repress thiophilic addition.

Additions of Vinyl- and Propenyllithium and -magnesium Bromide to Phenanthraquinone. It has been reported by Wege[17b] and Blomberg et al.[17c] that phenanthraquinone (**25**) reacts with vinyl- and phenylmagnesium bromide to give 9-vinyloxy- and 9-phenyloxy-10-hydroxyphenanthrenes. In order to determine the stereochemistry and effect of the metal ion on an oxophilic reaction, we have investigated the reaction of vinyllithium, (*E*)-1-propenyllithium, and (*Z*)- and (*E*)-1-propenylmagnesium bromide with **25**.

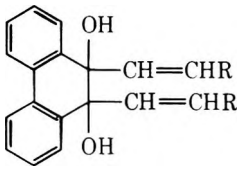
Reaction of **25** with 3.8 equiv of vinyllithium in tetrahydrofuran gives a crude product which has NMR absorptions attributable to the vinyl group of the carbophilic addition product **26** in 73% yield and no detectable absorptions (<5%) of the vinyl group of the possible oxophilic product **27**. Comparison of the physical properties of the product, isolated in 14% yield, with those reported for the trans isomer[17b] confirms the identity of **26**. The carbophilic

Table II
Retention of Stereochemistry of the 1-Propenyl Groups in 9,10-Di(1-Propenyloxy)-9,10-dihydroxy-9,10-dihydrophenanthrene (28) and 9-(1-Propenyloxy)-10-hydroxyphenanthrene (29) from Reactions of (*Z*)- and (*E*)-1-Propenylmagnesium Bromide with Phenanthraquinone (25) at 25°

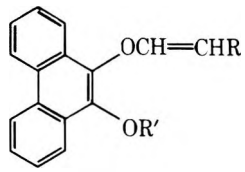
Grignard reagent	Isomeric purity[a]			Retention of stereochemistry, %[f]	
	Grignard	28	29	28	29
(*Z*)-CH_3CH=$CHMgBr$	88.3 ± 0.8	79.0 ± 0.8 (43)[d]	73.2 ± 1.3 (17)[d]	89	82
	90.3 ± 1.6[b]				
	89.4 ± 2.4[c]				
(*E*)-CH_3CH=$CHMgBr$	72.2 ± 0.7	75.6 ± 1.2 (43)[d]	89.2 ± 0.4 (29.4)[d]	103	122
	73.5 ± 1.3[b]				
	73.9 ± 0.8[c]				
(*E*)-CH_3CH=$CHMgBr$[e]	72.2 ± 0.7	75.0 ± 0.9 (27.8)[d]	88.3 ± 1.5 (15.2)[d]	102	118
	73.5 ± 1.3[e]				
	74.7 ± 0.3[c]				

[a] Determined by NMR unless otherwise noted; errors are three times standard deviations. [b] Determined by GLC of trimethylsilyl ethers. [c] Determined after reaction of 25 with the 1-propenylmagnesium bromides from the stereochemistry of the 1-(1-propenyl)-1,1-diphenylcarbinol obtained on reaction with benzophenone. [d] Values in parentheses are percent yields. [e] Inverse addition of reagents; ca. 25% 25 was recovered in this case and ca. 10% 25 was recovered for the cases shown as the first two entries. [f] Defined as ratio of percent major isomer of product to percent major isomer in organometallic. A result greater than 100% reflects an increase in the product having the same geometry as that of the major isomer of the organometallic. Errors are estimated as ±4%.

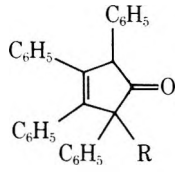
pathway is also observed on reaction of **25** with 1-propenyllithium which is 94% *E* and 6% *Z* isomers, to give a 63% yield of **28**, presumably with trans hydroxyl groups and containing 93% *E* and 7% *Z* propenyl groups. The *EE*-trans isomer of **28** was isolated in 28% yield.



26, R = H
28, R = CH_3



27, R = R' = H
29, R = CH_3; R' = H
30, R = CH_3; R' = $COCH_3$



32, R = $CH{=}CH_2$
33, R = CH_2CH_3

As reported,[17b] reaction of **25** with 3.8 equiv of vinylmagnesium bromide in tetrahydrofuran gave 22% **26** and 43% **27**, along with ca. 1% of 2-methylphenanthro[9,10-*d*][1,3]-dioxole, also noted previously as a product of cyclization of **27**. Reactions of **25** with 4 equiv of (*Z*)- and (*E*)-1-propenylmagnesium bromide gives **28** and **29**. Although **28** was obtained in analytically pure form as a mixture of stereoisomers, **29** had to be converted to a urethane for analytical characterization. The acetate, **30**, was also prepared, and separate samples of **30** containing 86% (*Z*)- and 15% (*E*)-1-propenyl groups and 4% (*Z*)- and 96% (*E*)-1-propenyl groups were subjected to reaction with 4 equiv of 1-propenylmagnesium bromide to establish that the anions of **29** retain geometry under the reaction and isolation conditions.

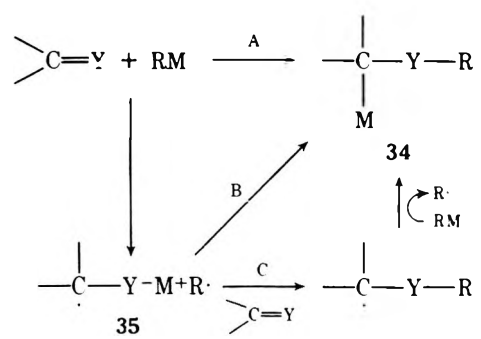
The relationship of the stereochemistries of the 1-propenyl groups of the organometallic reactants and the oxophilic and carbophilic products based on NMR analyses is presented in Table II. Those results show that there is predominant retention of geometry of the organometallic on oxophilic addition to phenanthraquinone. However, in every case there is also significantly more *E* isomer in the product than in the reactant. The fact that essentially the same stereochemistry is observed for **28** and **29** in normal and inverse addition establishes that these comparisons are free from complications due to microscopic diffusion.

Addition of Vinyllithium to Tetraphenylcyclopentadienone (31). It has been reported by Dimroth and Laufenberg that **31** undergoes oxophilic addition with *tert*-butylmagnesium chloride.[18] We have investigated the reaction of **31** with 2.2 equiv of vinyllithium and found that the product is 2-vinyl-2,3,4,5-tetraphenyl-3-cyclopenten-1-one (**32**). The structure of **32** is assigned on the basis of spectroscopic and analytical data. In particular, the nonconjugated carbonyl absorption at 1745 cm^{-1},[33] the ultraviolet absorption at λ_{max} 263 nm,[18,34] and the retention of essentially these values in **33**, the compound produced by hydrogenation of **32**, rule out the alternative structures which have a vinyl group at position 3. While oxophilic addition is not observed, it is not clear whether **32** results from 1,6 addition of vinyllithium to **31** or by rearrangement of the initial carbophilic product.[34]

Discussion

It does not seem to us that, at present, a unifying mechanism which rationalizes all the observations which have been made about heterophilic additions[1-7,10-12,17-19] can be proposed, although a rational choice between three possible pathways can be made. As outlined in Scheme I, the simplest processes would be a direct two-electron addition of the organometallic to the heteroatom to produce carbanion **34**, as shown in path A. Another route could involve initial one-electron transfer to form the caged radical **35**, which

Scheme I



could subsequently collapse to **34** as suggested in path B. A third possibility, outlined as path C, would be initiated by escape of the radical from the cage, followed sequentially by attack of the radical on the heteroatom of another substrate and attack of the resulting radical on the organometallic to produce a chain-carrying radical. Similar mechanisms and intermediate species, often involving bonding to the metal, have been suggested for these and related reactions.[2-4,7,35-38]

Analysis of the stereochemical course of additions of 1-propenyl organometallics as used by Whitesides and Casey[36] has already become a classic test for the intermediacy of free radicals in such reactions. Under the assumptions[36,37] that the rate of achievement of a 1:1 *Z*:*E* equilibrium ratio for the free propenyl radical is 10^9 sec^{-1} and that the radical would attack the ca. 0.1 *M* substrates at a diffusion controlled rate of 10^{10} l. mol^{-1} sec^{-1} it is predicted that if path C is followed the stereoisomers of **3** and **29** would be formed in ratios which would show a maximum of 67% retention in the products. If the assumption of an equilibrium constant of 1 for the equilibrating 1-propenyl radical is not correct, the calculated maximum retention would be decreased for the products from one isomer and increased, but not greater than 100%, for the products from the other isomer. In either case the predicted extent of isomerization is inconsistent with the results in Tables I and II. Accordingly the heterophilic reactions of **3** and **25** with the 1-propenyl organometallics do not appear to involve a free-radical path to a major extent.

Distinction between paths A and B is more problematical. Indeed, one possibility is that the transition state for addition has characteristics of both one- and two-electron transfers such that the usual dichotomy becomes meaningless.[39] Although quantitative product compositions are not usually known, it is interesting that the yields of thioethers from the reactions of thiobenzophenone with organolithiums are in an order benzhydryl $\simeq$ benzyl < *n*-butyl < phenyl $\simeq$ vinyl, which is the reverse of that for electron transfer from organolithiums to olefins.[40] While this result can be taken as evidence against rate-determining formation of a species analogous to **35** for these cases, it should be noted that with Grignard reagents and other thioketones, the extent of thiophilic addition does not always follow a regular order and a pronounced solvent effect on the order can be observed.[3d,8g,41] The observation of ESR signals[2,3] and the formation of benzhydryl mercaptan from the reaction of **1** and the 1-propenylmagnesium bromides also raises the possibility that radicals may be involved, although CIDNP effects were not observed. The solvent effect and the apparent lack of a pronounced metal ion effect in thiophilic additions also provide difficulties for a general HSAB interpretation.[3d]

In the case of oxophilic addition to phenanthraquinone, the facts that phenyl- and vinylmagnesium bromide add in this mode while methyl- and ethylmagnesium bromide[17b] and vinyllithium do not, in opposition to the ability of these reagents to transfer one electron to benzophenone,[40-42] might also be taken to rule out rate-determining formation of the ketyl ion pair represented by **35**. Interestingly, this order appears to be opposite to the correlation of organometallic structure and oxophilic addition observed with 2,4,5-trimethyl-2-acetoxycyclohexadien-1-one, a reaction which is believed to involve an initial one-electron transfer.[19b]

Overall, the present inference is that heterophilic additions to thiobenzophenone and phenanthraquinone probably proceed by a two-electron formation of the carbon–heteroatom bond to give the anion **34** directly. While the relative stability of the resulting anions would make this course of addition more general for the thiocarbonyl bond than for a carbonyl or imine bond, anion stability does not appear to be a singularly dominant factor in determining the reaction pathway. Thus the relative stabilities of the anions do not appear to provide a rationale for the failure of benzyl and benzhydryl organometallics to add to the sulfur of aromatic thioketones. An interesting speculation is that carbophillic additions generally proceed via initial *n* complexation with the metal ion[35] and that complexation is more favorable for the anionically stable benzyl organometallics. The preceding results do show an apparent lack of a metal ion effect in thiophilic addition. Clearly, more information is needed for formulation of detailed mechanisms.

Rearrangement after an initial heterophilic addition[5,12] has been ruled out for the addition of phenylmagnesium bromide to thiobenzophenone by the labeling studies (vide supra). The possibility of rearrangement in the reaction of benzhydryllithium with thiobenzophenone[43] is ruled out by the fact that treatment of dibenzhydryl sulfide with *n*-butyllithium followed by deuterium oxide quench gives overwhelmingly benzhydryl-*n*-butyl sulfide-d_1. Clearly fragmentation to thiobenzophenone followed by thiophilic addition of *n*-butyllithium occurs under the reaction conditions. The possibility of direct displacement followed by formation of a carbanion which is subsequently deuterated may be discounted because the starting thioether is recovered undeuterated. Nonetheless, rearrangement of an initial adduct is conceivable for some other cases.

None of the above rationalizations account for the isomerizations observed on addition of 1-propenylmagnesium bromides to **1** and **25**. Although controls show that up to 5% of the isomerizations observed could occur after product formation, the ca. 14% isomerization in heterophilic additions of (*E*)-1-propenylmagnesium bromide to thiobenzophenone and the ca. 20% isomerizations in the additions of (*Z*)- and (*E*)-1-propenylmagnesium bromide to phenanthraquinone are outside that limit. The fact that a ca. 14% isomerization was not observed for reaction of **1** with (*Z*)-1-propenylmagnesium bromide may be due to difficulty of detecting such a change when the *E* isomer makes up only ca. 8% of the Grignard reagent. For the reaction of **1** the degree of isomerization is consistent with a *Z*:*E* reactivity ratio for the organometallic reagents of 1.7 ± 0.3. A *E*:*Z* reactivity ratio of 2.9 ± 0.5[44] would similarly rationalize the isomerization observed on addition to **25**. The possibility that isomerization represents reaction of a free radical which escapes from the cage is discounted because that mechanism does not explain the greater than 100% retention enrichment of *E* isomer observed in the reaction of **25** with 1-propenylmagnesium bromides.

The reaction of **9** with phenyllithium to give phenylthiolate and dithiobenzoate further illustrates the point that in some cases secondary reactions may obscure the initial thiophilic addition.[2-5] The precedented[2b,26,45,46] mechanistic rationale involves initial thiophilic addition followed by formation of a carbene which could add phenyllithium and undergo fragmentation to lithium dithiobenzoate and ethylene. Another case in which reactions subsequent to heterophilic addition determine the structure of the product is the formation of novel double addition compound **24** from thiobenzophenone and benzylmagnesium bromide. Presumably this arises via radical formation after initial addition, as postulated by Dagonneau.[3b,47]

Experimental Section

General. Melting points were determined on a Buchi or Nalge melting point apparatus and are uncorrected; boiling points are

uncorrected. The proton chemical shifts are reported in δ (parts per million) relative to Me_4Si as internal standard. The ir spectra were measured as a Nujol mull or a KBr pellet, and the frequencies were calibrated against polystyrene. Mass spectra were obtained on a Varian MAT CH-5 spectrometer. Gas–liquid partition chromatography (GLC) was carried out on a Varian Aerograph A-90-P gas chromatograph with a 15 ft × 0.25 in. 20% XF-1150 on acid-washed Chromosorb P column unless otherwise noted. Microanalyses were performed by Mr. J. Nemeth and associates.

Compounds which are sensitive to air and moisture were handled in a dry bag under a dry nitrogen atmosphere and reactions were carried out under nitrogen. Dry ether obtained from Mallinckrodt Chemical Works was used as received. Tetrahydrofuran (THF) was dried by distillation from sodium napthalide or sodium benzophenone ketyl. The lithium metal (Lithium Corp. of America) contained 1% sodium. The magnesium turnings (Mallinckrodt analytical reagent) contained a maximum of 0.01% of heavy metal (as lead), 0.03% of iron, and 0.15% of manganese as impurities.

Extractive work-up refers to addition of the reaction mixture to excess water followed by extraction with diethyl ether, and washes of aqueous hydrochloric acid and water prior to drying ($MgSO_4$) and evaporation of the solvent. Preparative column chromatographies were carried out in silica gel or alumina.

Diphenyl dithiocarbonate (4),[48] ethylene trithiocarbonate **(9),**[49] ethylene dithiocarbonate **(7),**[50] ethylene phenylimidodithiocarbonate **(8),**[51] methyl dithiobenzoate,[52,53] and benzidianil[30,54] were prepared by literature procedures and shown to have physical and spectral properties as expected.

Diphenyl phenylimidodithiocarbonate (6) was prepared according to the procedure of Harley-Mason:[55] mp 123.5–124.5°; ir (Nujol) 1580 s (C=N), 1475 sh, 1430 sh, 1370 m, 1205 m, 1155 w, 1065 m, 1020 m, 1000 w, 985 s, 910 m, 887 m, 845 w, 765 m, 748 s, 740 m, 703 sh, and 690 cm^{-1} s; NMR (CCl_4) δ 6.6–7.5 (m, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 321 (2.4, M^+), 213 (17.1), 212 (100.0), 109 (54.9), 77 (24.8).

Anal. Calcd for $C_{19}H_{15}NS_2$: C, 70.99; H, 4.70; N, 4.36; S, 19.95. Found: C, 70.85; H, 4.65; N, 4.43; S, 20.08.

Ethylene trithiocarbonate (9) was synthesized according to the procedure of Husemann:[50] mp 35–36° (lit.[50] mp 36.5°); ir, NMR, and mass spectra are consistent with the assigned structure.

Di-*tert*-butyl phenylimidodithiocarbonate (16) was synthesized in a manner analogous to the preparation of **6** from phenyl isocyanide dichloride and *tert*-butyl mercaptan. The crude product was purified by recrystallization from ethanol to give **16** in 65% yield as slightly yellow-brown crystals: mp 62–64.5°; ir (Nujol) 1575 s, 1200 w, 918 s, 880 m, 805 vw, 753 m, and 690 cm^{-1} m; NMR (CCl_4) δ 1.47 (s, 18, *t*-C_4H_9), 6.93 (m, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 281 (3.8, M^+), 192 (15.3), 135 (21.4), 135 (12.2), 77 (12.2), 57 (100.0), 41 (15.0)

Anal. Calcd for $C_{15}H_{23}NS_2$: C, 64.00; H, 8.24; N, 4.98; S, 22.78. Found: C, 64.23; H, 8.22; N, 5.14; S, 22.84.

β-Phenylthioethanethiol (39) and Its Disulfide (40). To a solution of 2.6 g (0.044 mol) of ethylene sulfide and 4.4 g (0.04 mol) of thiophenol in 20 ml of hexane was added 10 drops of triethylamine.[56] After 7 hr of heating at reflux, distillation gave 5.0 g (73%) of **39** as a colorless liquid: bp 113–115° (1.5 mm); ir (neat) 3050 w, 2900 w, 2800 vw, 2550 w (SH), 1580 s, 1475 s, 1430 s, 1420 sh, 1265 m, 1210 m, 1135 w, 1090 m, 1070 w, 1015 m, 740 vs, 700 sh, and 690 cm^{-1} s; NMR (CCl_4) δ 1.18 (t, 1, SH, J = 7.7 Hz), 2.83 (A_2B_2X, 4, $-CH_2CH_2SH$), 7.17 (m, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 170 (32.1, M^+), 123 (34.4), 110 (100.0), 61 (56.4), 45 (51.6).

Oxidation of **39** with bromine provided **40** as a colorless liquid in 75% yield: ir (neat) 3030 w, 2900 w, 1580 s, 1475 m, 1250 m br, 1110 m, 1085 m, 1065 m, 1024 s, 738 vs, 700 w sh, and 688 cm^{-1} vs; NMR (CCl_4) δ 3.93 (A_2B_2, 8, $-CH_2CH_2-$), 7.18 (m, 10, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 338 (1.8, M^+), 141 (16.6), 138 (10.4), 137 (100.0), 135 (12.9), 110 (11.3), 109 (51.5), 77 (15.6), 65 (15.7), 59 (11.5), 45 (16.5), 39 (10.1).

Anal. Calcd for $C_{16}H_{18}S_4$: C, 56.76; H, 5.36; S, 37.88. Found: C, 56.61; H, 5.31; S, 37.77.

Phenyllithium was prepared in ethereal solutions by the reaction of lithium metal with bromobenzene[57] or by metal–halogen exchange between *n*-butyllithium and bromobenzene.[58] Phenyllithium prepared by the first method was used for the reactions with **4** and **6** and its concentration was determined by hydrolysis. Phenyllithium prepared by the second method was used for other reactions and its concentration was determined by titration with *sec*-butyl alcohol with 1,10-phenanthroline as an indicator.[59]

Vinyllithium was prepared in 93% yield from tetravinyltin (Alfa Inorganics) and *n*-butyllithium in hexane.[60] The concentration was determined by the *sec*-butyl alcohol method.[59]

Vinylmagnesium bromide was prepared by the method of Normant[61] from magnesium and vinyl bromide in THF.

(*Z*)- and (*E*)-1-Propenyllithium were prepared from ca. 97–98% isomerically pure (*Z*)- and (*E*)-1-bromo-1-propene (Chemical Samples Co.) and lithium wire at 0°.[36] The concentrations were determined by titration with *sec*-butyl alcohol.[59]

The NMR spectra of the 1-propenyllithiums were generally in good agreement with those reported[62] except that the coupling constant between the methyl protons and the geminal olefinic proton of (*E*)-1-propenyllithium was ca. 1 Hz. The NMR spectra showed no peaks which might be ascribed to the presence of unreacted 1-bromo-1-propenes. Hydrolysis of (*E*)-1-propenyllithium gave a solution which had <1% bromopropenes.[36] The isomeric purities of the latter were chemically determined by quenching three 0.5-ml aliquots of the organolithium solution with 0.5 ml of 1,2-dibromoethane, followed by GLC analysis of the resulting mixtures for isomeric 1-bromo-1-propenes.[36] The 1-propenyllithiums were shown to be geometrically stable in solution at room temperature for several days.

(*Z*)- and (*E*)-1-Propenylmagnesium bromides were prepared in THF from the isomeric 1-bromo-1-propenes and magnesium in a manner similar to that for vinylmagnesium bromide.[61] The concentration was determined by the back-titration method.[63]

The isomeric purities of 1-propenylmagnesium bromides were determined by NMR integration of the olefinic protons[64] and, in some instances, also by quench of aliquots with trimethylchlorosilane.[65] The isomer ratios obtained by GLC analysis of the (*Z*)- and (*E*)-1-propenyltrimethylsilane were in good agreement with those obtained from the NMR spectra. Unreacted 1-bromo-1-propenes were not detected in the GLC analysis of the 1-propenyltrimethylsilanes and are estimated as less than 1%.

Reaction of Thiobenzophenone (1) with Vinyllithium. To 7 ml (5.2 mmol) of 0.74 *M* vinyllithium in ether was added at room temperature 0.58 g (2.9 mmol) of **1** in 35 ml of ether over an 18-min period. After 1 hr extractive work-up provided 649 mg of an oil, which was purified by chromatography to give 264 mg (40%) of vinyl benzhydryl sulfide (**2**) obtained as an oil: ir (neat) 3077 sh, 3038 w, 1510 sh, 1584 s, 1490 s, 1449 s, 1381 w, 1339 vw, 1321 vw, 1280 w br, 1079 m, 1032 m, 956 m, 870 w br, 777 w, 747 s, 720 w, and 694 cm^{-1} s; NMR (CCl_4) δ 7.22 (m, 10, C_6H_5), 6.4–4.85 (ABX, 3, $-CH=CH_2$), 5.30 (s, 1, Ph_2CH-); mass spectrum (70 eV) *m/e* (rel intensity) 226 (2.2, M^+), 182 (10.6), 168 (16.4), 167 (100.0), 166 (12.1), 165 (29.7), 152 (16.3), 105 (27.5), 77 (17.8).

Anal. Calcd for $C_{15}H_{14}S$: C, 79.60; H, 6.23; S, 14.17. Found: C, 79.79; H, 6.24; S, 14.08.

Reaction of 1 with Vinylmagnesium Bromide. To 5.4 ml (7.4 mmol) of 1.37 *M* vinylmagnesium bromide in THF was added at 0° 727 mg (3.7 mmol) of **1** in 30 ml of THF over a 10-min period. After 2 hr at 0°, the dark brown reaction mixture was quenched with saturated aqueous ammonium chloride, filtered, and worked up extractively to give 840 mg of an oil which afforded 297 mg (36%) of **2** on chromatography.

Reaction of 1 with 1-Propenyl Organometallics. (*E*)-1-Propenyllithium. To 7.4 ml (6.2 mmol) of 0.84 *M* (*E*)-1-propenyllithium (isomeric purity 94.7 ± 1.5%) in ether was added 0.62 g (3.1 mmol) of **1** in 30 ml of ether at 0° over a 15-min period. After 1 hr of stirring, 1.5 ml of the reaction mixture was quenched with 0.5 ml of 1,2-dibromoethane. GLC analysis showed that the excess lithium reagent was 95.8 ± 1.9% *E* isomer. The remainder of the reaction mixture was quenched with 25 ml of water and after being allowed to stand overnight and worked up extractively gave 741 mg of a green-yellow oil. The NMR spectrum of this material showed it to contain (*Z*)-**3** and (*E*)-**3** in a ratio of 14.1:85.9 (±1.8%). Chromatography of a portion of this material gave 256 mg (45% overall yield for purification of all material) of **3** as an oil. The isomer ratio was found to be 13.1% (*Z*)-**3** and 86.9% (*E*)-**3** (±2.1%) by NMR.

(*Z*)-1-Propenyllithium. To 9.3 ml (6.0 mmol) of 0.65 *M* (*Z*)-1-propenyllithium (isomeric purity 98.3 ± 0.9%) in ether was added 0.60 g (3 mmol) of **1** in 25 ml of ether at 0° over a 15-min period. Work-up as for the *E* case revealed less than 1% isomerization of the lithium reagent and gave after chromatography of a portion of the crude product, 241 mg (overall yield 38%) of **3**. NMR integration of the methyl peaks showed that the isomer ratio was 94.6% (*Z*)-**3** and 5.4% (*E*)-**3** (±2.0%).

(*E*)-1-Propenylmagnesium Bromide. To 5.4 ml (5.13 mmol) of 0.95 *M* (*E*)-1-propenylmagnesium bromide (isomeric purity 79.2

± 4.7% from NMR and 79.8 ± 2.0% from GLC analysis (vide supra) in THF was added at 0° to 502 mg (2.53 mmol) of **1** in 25 ml of THF. After 1 hr, saturated ammonium chloride was added and filtration followed by extractive work-up gave 605 mg of product. The NMR spectrum of this material showed that the isomeric purity of (*E*)-**3** was 70.6 ± 2.9%. Benzhydryl mercaptan was also detected by NMR in ca. 14% yield. Chromatography of 448 mg of this oil afforded 261 mg (overall yield 58%) of **3** as an oil which was 28.1% (*Z*)-**3** and 71.9% (*E*)-**3** (±2.8).

(*Z*)-1-Propenylmagnesium Bromide. To 5.7 ml (5.4 mmol) of 0.95 *M* (*Z*)-1-propenylmagnesium bromide (isomeric purity 95.4 ± 3.7% from NMR and 95.1 ± 0.5 from GLC) was added at 0° to 540 mg (2.7 mmol) of **1** in 26 ml of THF over a 13-min period. The same work-up as for the *E* case provided 184 mg (overall yield 29%) of **3** after chromatography. The NMR analyses showed that this contained 92.7% (*Z*)-**3** and 7.3% (*E*)-**3** (±2.5%). The NMR spectrum of the crude product showed presence of benzhydryl mercaptan in 14% yield.

Characterization of the Isomeric 1-Propenyl Benzhydryl Sulfides (3). (*E*)-1-Propenyl Benzhydryl Sulfide [(*E*)-3]. To 20 ml (9.2 mmol) of 0.46 *M* (*E*)-1-propenyllithium (88% isomeric purity) was added at 0° 0.96 g (4.9 mmol) of **1** in 35 ml of ether over a 16-min period. Extractive work-up after 1 hr provided 1.153 g of a dark green oil. Chromatography of 1.054 g of this material gave 439 mg (overall yield 41%) of (*E*)-**3**: ir (neat) 3058 w, 3021 m, 2890 w, 2849 vw, 1603 m, 1587 vw sh, 1493 s, 1449 s, 1359 vw, 1326 vw br, 1295 vw, 1244 w, 1076 m, 1031 m, 937 s, 745 s, and 696 cm^{-1} s; NMR (CCl_4) δ 1.65 (m, 3, CH_3), 5.18 (s, 1, Ph_2CH–), 5.68 (non-first-order ABX_3, 2, –CH=CH–) (irradiation at δ 1.65 ppm led to collapse of this signal and appearance of the olefinic protons as an AB pattern with J = 15 Hz consistent with the trans assignment),[37e,66] 7.23 (m, 10, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 240 (8.3), 168 (17.3), 167 (100.0), 165 (26.4), 152 (14.0).

Anal. Calcd for $C_{16}H_{16}S$: C, 79.95; H, 6.71; S, 13.34. Found: C, 79.78; H, 6.68; S, 13.11.

Pure (*E*)-**3** was stable at room temperature for at least 3 days but after a week, the NMR spectrum showed small peaks due to the *Z* isomer.

(*Z*)-1-Propenyl Benzhydryl Sulfide [(*Z*)-3]. To 12 ml (7.4 mmol) of 0.62 *M* (*Z*)-1-propenyllithium (94% isomeric purity) was added 0.73 g (3.7 mmol) of **1** in 30 ml of ether at 0° over a 14-min period. After 1 hr work-up similar to that for (*E*)-**3** afforded 0.858 g of an oil which contained (*E*)-**3**:(*Z*)-**3** in a 10:90 ratio according to the NMR spectrum. Chromatography of a portion of this oil, 0.779 g, provided 254 mg (overall yield 32%) of **3**: ir (neat) 3090 vw, 3075 vw, 3050 w, 3020 m, 2900 w, 2830 vw, 1600 m, 1500 s, 1450 s, 1380 w, 1330 m, 1165 m br, 1075 m, 1030 m, 1000 vw, 930 m br, 750 s, and 700 cm^{-1} s; NMR (CCl_4) δ 1.70 (X_3 part of ABX_3, 3, CH_3, J = 1.2 and 6.4 Hz), 5.21 (s, 1, Ph_2CH–), 5.62 (AB part of ABX_3, 2, –CH=CH–, J = 1.2, 6.4, and 9.4 Hz), irradiation of the methyl signal resulted in collapse of the multiplet into a simple AB pattern with J_{AB} = 9.4 Hz,[37e,66] 7.23 (m, 10, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 240 (4.2), 168 (16.2), 167 (100.0), 166 (10.4), 165 (26.9), 152 (14.5), 58 (7.0), 43 (12.2), 32 (7.9), 31 (9.3).

Anal. Calcd for $C_{16}H_{16}S$: C, 79.95; H, 6.71, S, 13.34. Found: C, 79.84; H, 6.66; 13.19.

Equilibration of 1-Propenyl Benzhydryl Sulfides in Ether. A mixture of 109 mg of **3** containing ca. 30% *Z* and 70% *E* isomers and 10 mg of thiophenol in 5 ml of ether was gently refluxed under nitrogen. The change in the isomer ratio was periodically determined by NMR spectroscopy. After 10, 29, and 50 hr of heating, the amount of (*Z*)-**3** was found to be 49 ± 2.7, 60.3 ± 3.9, and 61.4 ± 4.5%, respectively. In another experiment, a mixture of 106 mg of **3** consisting of ca. 94% *Z* and ca. 6% *E* isomer and 16 mg of thiophenol in 3 ml of ether was stirred at room temperature under nitrogen. After 24 and 48 hr of stirring, the amount of (*Z*)-**3** decreased to 62.3 ± 1.3 and 61.6 ± 1.1%, respectively. The equilibrium constant for (*Z*)-**3**:(*E*)-**3** is ca. 1.5 at 25–35° in ether in favor of the *Z* isomer.

Stability of 1-Propenyl Benzhydryl Sulfides toward Work-up Procedures. Typical control experiments involved addition of (*E*)-**3** of known isomeric purity to a quenched reaction mixture of thiobenzophenone and phenyllithium or vinylmagnesium bromide, followed by reisolation of **3** and determination of its isomeric purity by NMR. It was shown that (*E*)-**3** was stable to that procedure and aqueous base but that 7–8% isomerization can occur in tetrahydrofuran in the presence of 1 equiv of benzhydryl mercaptan on standing 12 hr at room temperature. Accordingly, it is estimated that up to 5% isomerization could occur by a similar process in the work-up of some reactions reported in Table I. It was also shown, however, that extraction with aqueous base, immediately after quenching, did not eliminate the isomerization observed with (*E*)-1-propenylmagnesium bromide (Table I).

Reaction of thiobenzophenone-d_{10} and phenylmagnesium bromide was carried out as previously reported[2b] to give benzhydryl phenyl-d_{10} sulfide. The mass spectrum of the product shows a ratio of *m/e* 172:177 ($C_{13}H_6D_5$:$C_{13}HD_{10}$) of 2.4:100 and a ratio of *m/e* 109:114 (C_6H_5S:C_6D_5S) of 100:5.6. This fragmentation is consistent with a composition of at least 95% $C_6H_5SCH(C_6D_5)_2$.

Reaction of 5 with Phenyllithium. A solution of 0.858 g (3.5 mmol) of **5** in 50 ml of ether was added dropwise to 6.5 ml (7 mmol) of 1.08 *M* phenyllithium over a 10-min period. After 1 hr, the reaction mixture was quenched with water and worked up extractively to give 0.508 g (66%) of thiophenol and 1.317 g of pale yellow crystals. Chromatography and recrystallization (pentane) afforded (1) 0.151 g (17.5%) of **5**, mp 41–43°, mmp 41.5–43°, ir identical with that of authentic **5**; (2) 57.5 mg (4.9%) of white crystals identified as 2-biphenyldiphenylcarbinol **10**, mp 89.5–90.5° (lit.[67] mp 86–88°), ir, NMR, analysis, and mass spectrum were consistent with the assigned structure; (3) 0.468 g (51.5%) of triphenylcarbinol (**11**), mp 161.5–163° (mmp 162–164.5°). The ir, NMR, and mass spectra were identical with those of an authentic sample (Aldrich Chemical Co.).

Reaction of 6 with Phenyllithium. A solution of 0.800 g (2.5 mmol) of **6** in 50 ml of ether was added to 5.5 ml (7.5 mmol) of 1.36 *M* phenyllithium in ether over a 3-min period. After 1 hr the reaction mixture was quenched with water and worked up extractively to give 0.456 g (83%) of thiophenol and 1.181 g of an oil. Chromatography provided (1) 0.555 g (66%) of triphenylmethylaniline (**12**) obtained as a partly crystalline, light-brown glass which on two recrystallizations (hexane) afforded 203 mg of **12**, mp 144–145° (lit.[68] mp 148–149°), ir, NMR, mass spectrum, and analysis were consistent with the assigned structure; (2) 161 mg (25%) of a yellow oil which slowly crystallized and was identified as benzophenone anil **13** from comparison of its ir and NMR spectra with those of authentic material (mp 113–114°),[69] mp (from hexane) 111–113° (mmp 112–114°); (3) 24 mg (5.3%) of impure benzophenone.

Reaction of 7 with Phenyllithium. To 26 ml (13.1 mmol) of 0.507 *M* phenyllithium in ether was added at −78° 0.483 g (4 mmol) of **7** in 30 ml of ether over a 20-min period, whereupon a white precipitate appeared. After 1 hr of stirring, followed by warming to room temperature, the reaction was quenched to give 0.996 g of faintly yellow crystals, mp 147–153°. Recrystallization from cyclohexane afforded 0.814 g (78%) of **11** as white crystals: mp 160–162° (mmp 160–162°), ir and NMR spectra were identical with those of an authentic sample.

The aqueous layer provided 0.311 g (83%) of 1,2-ethanedithiol.

Reaction of 8 with Phenyllithium. To 25 ml (10 mmol) of 0.40 *M* phenyllithium was added 0.487 g (2.5 mmol) of **8** in 25 ml of ether at −23° over a 12-min period. After being allowed to stir for 1 hr at −23° and for 3 hr at room temperature, the reaction mixture was quenched with water and extractive work-up provided 869 mg of an oil.

Column chromatography provided (1) 193 mg of a yellow, viscous mixture of the disulfide of β-thiophenylethanethiol (24% overall yield) and triphenylmethyl aniline **12** (11% overall yield), identified by TLC, ir, and NMR spectra. This mixture was purified by crystallization from ether–hexane to give (1) 28 mg of **12** as brown crystals, mp 145.5–147.5° (mmp 146–149°), ir and NMR spectra as previously assigned (vide supra); (2) 82 mg of yellow, viscous **40** (15% overall yield as determined by NMR integration with methylene dichloride as standard) contaminated with small amounts of **12** and benzildianil **14**; (3) 289 mg of an oily solid, which was mainly **14** (47% overall yield as determined by NMR integration with methylene dichloride as standard) according to TLC, ir, and NMR spectra. Recrystallization from ethanol gave 137 mg of **14** as yellow crystals, mp 138–142° (mmp 141–143°), ir and NMR spectra were identical with those of authentic material.

From the aqueous layer, a liquid mixture of **39** and **40** (by NMR) was obtained in yields of 37 and 10%, respectively.

Reaction of 9 with Phenyllithium. To 9 ml (6.6 mmol) of 0.73 *M* phenyllithium in ether was added, at −78°, 0.412 g (3 mmol) of **9** in 30 ml of ether over a 30-min period. After an additional 30 min, the reaction mixture was quenched with methanol and allowed to warm to room temperature. Extractive work-up with ether after the addition of water provided a mixture of biphenyl and **9** according to the ir, NMR, and GLC (10 ft × 0.25 in. SE-30 on firebrick 188°) analyses. Integration of the NMR spectrum with 1,2-dibromoethane as reference indicated recovery of 0.63 mmol (21%) of **9**.

The brown aqueous layer from extraction was collected in an ice bath, and to it was added 0.57 ml (6 mmol) of dimethyl sulfate. After being heated to reflux for 30 min, a red oil separated and the aqueous layer became colorless. Extractive work-up gave 0.573 g of a red oil, which was a mixture of thioanisole (70% overall yield) and methyl dithiobenzoate (62% overall yield) according to the NMR spectrum. The identities were confirmed by preparative GLC (10 ft × 0.25 in. SE-30 on firebrick, 187°) and comparisons of ir, NMR, and mass spectra with those of authentic materials.

Reaction of Phenyl Isocyanide with Phenyllithium. To 35 ml (13.2 mmol) of 0.38 *M* phenyllithium was added at −23° 454 mg (4.4 mmol) of phenyl isocyanide[70] in 10 ml of ether over a 10-min period. A dark brown color developed immediately. Work-up was similar to that (vide supra) for the reaction of 8 with phenyllithium.

Chromatography provided (1) 14 mg of biphenyl; (2) 12 mg (1.2%) of yellow, weakly fluorescent material, mp 206–211°, with ir and mass spectra identical with those of material assigned as 2-anilino-*N*,1,2,2-tetraphenylethan-1-imine (**15**, vide infra); (3) 538 mg (crude yield 68%) of impure benzildianil according to its ir and NMR spectra, mp 113–121° [two recrystallizations gave material with mp 139–141, mmp 140–142°. The ethanol-insoluble portion of the residue obtained by evaporation of the mother liquors was 16 mg (1.7%) of a pale yellow solid tentatively identified as **15**: mp 213–216°; ir (Nujol) 3310 m, 1640 s, 1600 vs, 1500 s, 1480 s, 1420 m, 1375 m, 1320 s, 1280 vw, 1255 m br, 1170 m br, 1085 m, 1070 m, 1045 m, 1030 m, 1000 w, 940 w, 910 w br, 898 vw, 873 w, 846 w, 810 w br, 773 m, 750 s, 736 m, 708 s, and 692 cm^{-1} s; mass spectrum (70 eV) *m/e* (rel intensity) 438 (1.2, M^+), 345 (11.3), 259 (23.5), 258 (100.0), 257 (10.7), 181 (13.7), 180 (85.0), 77 (56.2). Further concentration of the mother liquor gave 128 mg of yellow crystals, mp 136–139°, which showed the same ir spectrum as **14**.]; (4) 61 mg (7%) of benzanilide, mp 159–161° (mmp 158–160°). The ir and NMR spectra of this compound were identical with those of authentic material (Aldrich Chemical Co.).

Reaction of 16 with Phenyllithium. To 26 ml (8 mmol) of 0.31 *M* phenyllithium in ether was added 563 mg (2 mmol) of **16** in 25 ml of ether over a 12-min period. The reaction mixture was heated at reflux for 3 hr followed by extractive work-up which afforded 732 mg of a yellow oily solid. Chromatography gave 622 mg (92.5%) of solid, which was identified as *N*-triphenylmethylaniline (**12**) containing a trace impurity by its NMR spectrum; recrystallization (hexane) gave 434 mg of light brown crystals, mp 149–151° (mmp 149–151°). The ir NMR, and mass spectra of this material were identical with those of authentic **12**.

Reaction of 17 with Phenyllithium. To 19 ml of 0.35 *M* phenyllithium in ether was added 491 mg (3 mmol) of **17** in 20 ml of ether over a 16-min period. After 2 hr at room temperature, extractive work-up provided 848 mg of an oil. Chromatography provided (1) 428 mg (50%) of *N,N*-dimethyltriphenylmethylamine (**18**), mp 90–92° [The ir and NMR spectra of this material were identical with those of an authentic sample prepared by the method of Hemilian and Silverstein.[71] Rechromatography on alumina with hexane as an eluent raised the melting point to 93–94.5° (mmp 93.5–94.5°).]; (2) 279 mg of a solid which was a mixture of benzophenone and triphenylcarbinol according to its ir and NMR spectra. The yields of these materials would be 4 and 33%, respectively. Recrystallization from cyclohexane afforded 99 mg of triphenylcarbinol, mp 156–158° (mmp 157–159°)

Reaction of Benzhydrylsodium with 19. Reaction of benzhydrylsodium[72] with **19** (Aldrich Chemical Co., mp 115–117.5°) in ether in a manner analogous to the procedure of Bergman and Wagenberg[72] gave 0.469 g (55%) of 2,2-diphenyl-1,1-di(4-methoxyphenyl)ethanethiol (**20**) as white needles: mp 149–152° (lit.[16] 155°); ir, NMR, spectrum, and analysis are consistent with the established structure.

Reaction of Benhydryllithium with 19. To 6 ml of 0.60 *M* benzhydryllithium[73] in THF was added 0.517 g (2 mmol) of **19** in 50 ml of ether over a 25 min period. After 1 hr, extractive work-up gave 1.515 g of an oil. Chromatography provided (1) 178 mg of 1,1,2,2-tetraphenylethane; (2) 711 mg of a yellow solid [Recrystallization from ethanol afforded 511 mg (60%) of pure **20**: mp 150–153° (mmp 149–152°); ir, NMR, and mass spectra were identical with authentic material. A second crop, 51 mg (6%), of impure **20**, mp 145–150° was also obtained.]; (3) 144 mg of white powder which could be recrystallized from ethanol to give 67 mg (8%) of white needles, identified as 2,2-diphenyl-1,1-di(4-methoxyphenyl)ethanol, mp 173–175° (lit.[16] 183°). The ir, NMR, mass spectrum, and analysis were consistent with the assigned structure.

Reaction of Benzhydryllithium with 1. To 10 ml (5.7 mmol) of 0.57 M benzhydryllithium[73] in THF was added 0.681 g (3.43 mmol) of **1** in 30 ml of ether over a 20-min period. After 1 hr of stirring at room temperature, extractive work-up provided 2.022 g of oily crystals which was shown by its NMR spectrum to be a mixture of diphenylmethane, 1,1,2,2-tetraphenylethanethiol (**21**), and 1,1,2,2-tetraphenylethane. Integration of the NMR spectrum with toluene as reference indicated that the yield of **21** was 84%. Recrystallization from 2-propanol gave 1.273 g of pale yellow needles, mp 155–165°. Chromatography of a 504-mg portion gave 318 mg (64% overall yield) of **21**, mp 165–167.5° (lit.[16] mp 167–168°). Recrystallization from 2-propanol raised the melting point to 166–169°; the ir, NMR, mass spectrum, and analysis were consistent with the assigned structure and different from those of independently prepared dibenzhydryl sulfide.

Dibenzhydryl sulfide was prepared in 35% yield from benzhydryl mercaptan and benzhydryl chloride, mp 63–64.5 (lit.[74] mp 65–66.5°). The ir, NMR, mass spectrum, and analysis were consistent with the assigned structure.

Reaction of Dibenzhydryl Sulfide with *n*-Butyllithium. To 0.584 g (1.6 mmol) of dibenzhydryl sulfide in 15 ml of THF was added at −23° (Dry Ice–carbon tetrachloride) 1 ml (1.6 mmol) of 1.6 M *n*-butyllithium, whereupon a brown color developed immediately. After 2 hr of stirring at −23°, the reaction mixture was quenched with 4 ml of deuterium oxide. Extractive work-up gave 634 mg of an oil. A 496-mg portion of this material was separated by chromatography into three fractions: (1) 66 mg of a colorless oil identified as diphenylmethane-d_1 (ca. 83% deuterium from NMR integration); (2) 90.7 mg (22% overall yield) of an oil identified as benzhydryl *n*-butyl sulfide-d_1 (**22**, ca. 100% deuterium) from the NMR spectrum, which was identical with that of benzhydryl *n*-butyl sulfide except that the former did not show the benzhydryl methine peak; (3) 315 mg (54% overall yield) of an oil identified as the starting sulfide without any significant deuterium incorporation according to its NMR spectrum.

Reaction of Benzylmagnesium Chloride with 1. To 4 ml (4.2 mmol) of 1.06 *M* benzylmagnesium chloride[63] was added at room temperature over a 16-min period 0.44 g (2.2 mmol) of **1** in 25 ml of ether. The reaction mixture was allowed to stir for 3 hr and worked up extractively to give 722 mg of a green oil. Chromatography provided the following.

(1) A blue oil (51 mg) was obtained, the main component of which was benzhydryl mercaptan (overall yield 8% as determined by integration of the NMR spectrum with 1,1,2,2-tetraphenylethane as a reference).

(2) A solid (189 mg) was obtained which recrystallized from 2-propanol to give 131 mg (20.5%) of benzyldiphenylmethyl mercaptan **23** as pale yellow crystals: mp 105–106.5°; ir (Nujol) 2551 vw (SH), 1600 w, 1585 sh, 1575 w, 1585 s, 1230 w, 1180 w, 1080 w, 1030 m, 1000 vw, 980 w, 955 vw, 910 w, 847 w, 785 w, 755 s, 748 sh, 703 vs, and 697 cm^{-1} s; NMR (CCl_4) δ 2.17 (s, 1, SH, exchanges with deuterium oxide in the presence of pyridine), 3.67 (s, 2, $PhCH_2$–), 6.4–7.4 (m, 15, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 257 (13.2), 256 (20.2), 200 (16.3), 199 (100.0), 198 (12.7), 180 (35.3), 178 (42.1), 167 (21.4), 165 (33.3), 121 (59.2), 91 (15.0), 77 (14.4), 45 (16.1), 28 (22.1).

Anal. Calcd for $C_{20}H_{18}S$: C, 82.71; H, 6.25; S, 11.04. Found: C, 82.62; H, 6.20; S, 11.10.

(3) Benzyldiphenyl(benzylthio)methane [**24**, 177 mg (21%)] was obtained. Recrystallization from hexane afforded 131 mg of slightly yellow crystals of **24**, mp 121.5–123.5° (lit.[75] mp 126–127°). The ir, NMR, and mass spectrum are consistent with the assigned structure.

(4) A brown oil (205 mg) was obtained which by ir and TLC analysis contained benzophenone as the major component.

Reaction of Benzyllithium with 1. To 12.5 ml (6.6 mmol) of 0.53 *M* benzyllithium[76] cooled in an ice bath was added 0.587 g (3 mmol) of **1** in 25 ml of ether over a 15-min period. After 2 hr of stirring, extractive work-up provided 1.071 g of an oil, which on chromatography gave (1) 55 mg (9%) of benzhydryl mercaptan; (2) 142 mg of a pale yellow, oily solid, which was a mixture of benzhydryl mercaptan (2%) and **23** (10%) according to the NMR spectrum (the yields are based on the NMR integration with dibenzhydryl sulfide used as internal standard); (3) 295 mg (34%) of somewhat impure **23**, mp 97–103°, which was recrystallized from ethanol to give an analytical sample, mp 107–110°. Its ir, NMR, and mass spectrum were identical with those of authentic material (vide supra). The aqueous layer was acidified and extracted with ether to give 12% benzyl mercaptan identical in TLC, ir, and NMR properties with authentic material (Aldrich Chemical Co.).

Reaction of 25 with Vinyllithium. To 18 ml (11.3 mmol) of

0.63 *M* vinyllithium in THF was added 0.626 g (3 mmol) of **25** partially suspended in 30 ml of THF over a 12-min period. After 2 hr of stirring at room temperature, the reaction mixture was gently refluxed for 45 min. Extractive work-up, after an ammonium chloride quench, provided 0.956 g of a green oil. The NMR spectrum (CCl_4) of this material showed no peaks in the regions of 6.5–7.0 and 4.0–4.9 ppm, indicating the absence of 9-hydroxy-10-vinyloxyphenanthrene.[17b] The major component was *trans*-9,10-dihydroxy-9,10-divinyl-9,10-dihydrophenanthrene (*trans*-**26**), which was present in 73% yield by NMR. Two chromatographic purifications afforded 181 mg (23%) of a light yellow solid, which was recrystallized from hexane to give 109 mg (14%) of *trans*-**26**, mp 87–88° (lit.[17b] mp 85–86°). The ir, NMR, mass spectral, and analytical data were consistent with the assigned structure.

Reaction of 25 with Vinylmagnesium Bromide. Reaction according to the procedure of Wege[17b] provided 856 mg of an oily mixture of 9-hydroxy-10-vinyloxyphenathrene (**27**) and *trans*-9,10-dihydroxy-9,10-divinyl-9,10-dihydrophenanthrene (*trans*-**26**) in ca. 56 and 32% yields, respectively, by NMR. Chromatography provided a small amount (0.8%) of 2-methylphenanthro[9,10-*d*][1,3]dioxole according to the previously assigned spectrum,[17b] mixed with **27** followed by 275 mg (39%) of **27**, mp 69–73° (lit.[17b] mp 71–73°). The ir, NMR, mass spectrum, and analysis were consistent with the assigned structure.

Reaction of 25 with (*E*)-1-Propenyllithium. To 12.5 ml (12 mmol) of 0.95 *M* (*E*)-1-propenyllithium (isomeric purity 93.5 ± 0.6%) in ether was added at room temperature 626 mg (3 mmol) of **25** in 35 ml of THF over a 20-min period. After 2 hr of stirring, the reaction mixture was quenched with saturated aqueous ammonium chloride and worked up extractively. Chromatography gave 511 mg (63%) of crude *trans*-9,10-dihydroxy-9,10-di(1-propenyl)-9,10-dihydrophenanthrene (*trans*-**28**) which contained by NMR 93 ± 1% (*E*)-1-propenyl and 7 ± 1% (*Z*)-1-propenyl groups as an oily, yellow-brown solid. The distinction between *Z* and *E* propenyl groups is made on the basis of the observed olefinic coupling constants of J_E = 15 and J_Z = 10 Hz. A portion of this material, 483 mg, was recrystallized from 20% benzene–hexane to give 278 mg of light orange crystals, mp 138–146°. Treatment of this material with decolorizing charcoal in a 25% benzene–hexane solution, followed by recrystallization from the same solvent, gave 137 mg (16%) of (*E,E*)-*trans*-**28**: mp 148–150°; ir (Nujol) 3450 s, 3365 sh, 1675 vw, 1285 vw, 1200 m, 1190 sh, 1170 vw, 1150 vw, 1070 vw, 1050 w, 1010 vw, 1000 vw, 968 s, 950 vw, 938 vw, 920 vw, 893 w, 883 vw, 856 vw, 970 vw, 770 vw, 752 s, 740 s, 740 m, 763 s, and 697 cm^{-1} br w; NMR ($CDCl_3$) δ 1.54 (d of d, 3, CH_3, J = 1.3 and 6.3 Hz), 2.21 (br s, 2, OH), 5.37–6.04 [ABX_3, 4, (*E*)-CH_A=CH_BCH_3, J_{AB} = 15.4, $J_{CH_3\text{-}H_A}$ = 1.3, and $J_{CH_3\text{-}H_B}$ = 6.3 Hz], 7.22–7.72 (m, 8, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 292 (17.8), 244 (18.4), 223 (100.0), 221 (15.4), 205 (12.7), 195 (17.2), 194 (12.1), 181 (15.8), 69 (42.7), 41 (14.2).

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.45; H, 6.92.

Reactions of 25 with Propenylmagnesium Bromides. A solution of **25** (625 mg, 3.0 mmol) in THF (35 ml) was added dropwise over 15 min under N_2 at 25° to 12.75 mmol of the 1-propenylmagnesium bromide in 25 ml of THF. After completion of the addition, the solution was stirred for an additional 2 hr before a 10-ml aliquot of the reaction mixture was withdrawn by syringe and the stereochemistry of the unreacted Grignard determined by GLC and ^1H NMR methods (vide infra).

The remainder of the reaction mixture was quenched with 25 ml of saturated ammonium chloride and worked up extractively to provide an oil that was purified by chromatography to give 9-hydroxy-10-(1-propenyloxy)phenanthrene (**29**) and 9,10-dihydroxy-9,10-di(1-propenyloxy)-9,10 dihydrophenanthrene (**28**).

The NMR spectra of crude **28** and **29** indicated each to be 80–85% pure with 8–10% **25** and 5–10% of other unidentified impurities, a result which was consistent with TLC analyses. The stereochemistries of the propenyl group of **28** and **29** shown in Table II were determined by integration of the methyl signals.

Analysis of Unreacted Grignard. Eight milliliters of the aliquot was added to benzophenone in THF at room temperature over 15 min. The stereochemistry of the product, 1-(1-propenyl)-1,1-diphenylcarbinol,[77] obtained as a pale yellow oil, was determined by NMR integration of the methyl doublets at δ 1.48 and 1.68 ppm for the *Z* and *E* isomers, respectively. The *Z* isomer had J_{AB} of 11 Hz and the *E* isomer showed a value of 15 Hz. Several control experiments established that the addition of propenyl Grignards to benzophenone occurs stereospecifically either in the presence or absence of added magnesium alkoxide.

Product Identification. The enol 9-(1-propenyloxy)-10-hydroxyphenanthrene (**29**) is air sensitive and could not be isolated in analytically pure form. The stereochemistries of the 1-propenyl groups were assigned from the NMR spectrum: (*Z*)-**29**, NMR (CCl_4) δ 1.90 (d of d, 3, CH_3, J_{AX} = 7, J_{BX} = 1.5 Hz), 4.67 (d of q, 1, CH_A, J_{AB} = 6 Hz), 6.0 (s, 1, OH), 6.06 (d of q, CH_B), 7.00–8.58 (m, 8, ArH); (*E*)-**29**, NMR (CCl_4) δ 1.58 (d of d, 3, CH_3, J_{AX} = 7, J_{BX} = 1.5 Hz), 4.00, (d of q, 1, J_{AB} = 12 Hz), 6.0 (s, br, 1, OH), 6.43 (d of q, 1), 6.93–8.50 (m, 8, ArH).

The phenylurethane of (*E*)-**29** was prepared with phenyl isocyanate.[78] Chromatography on silica gel gave a pale yellow solid which could be recrystallized from carbon tetrachloride–hexane and twice from 10% benzene–hexane to give white crystals: mp 155–160°; NMR δ 1.53 (d of d, 3, J_{AX} = 7, J_{BX} = 1.5 Hz), 5.12 (d of q, 1, J_{AB} = 12.0 Hz), 6.52 (d of q, 1), and 7.00–8.58 ppm (m, 13); ir (KBr) 3315 (NH), 1755 (sh), 1725, 1603, 1540, 1447, 1240, 1225, 1165, 1131, 1089, 759, and 740 cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 369 (P^+, 0.35), 299 (25.0), 251 (20.2), 250 (100.0), 22[illegible] (39.8), 210 (36.0), 181 (13.1), 180 (51.7), 119 (45.7), 91 (11.6).

Anal. Calcd for C, 78.02; H, 5.18; N, 3.79. Found: C, 77.75, H, 5.12; N, 3.90.

An acetate of **29** was also prepared by reaction with pyridine and acetic anhydride. Extractive work-up and chromatography gave the acetate **30** as a pale yellow oil. Numerous attempts to crystallize or obtain an analytical sample were unsuccessful: (*Z*)-**30**, NMR (CCl_4) δ 1.86 (d of d, 3, J_{AX} = 7, J_{BX} = 1.5 Hz), 2.39 (s, 3, CH_3), 4.70 (d of q, 1, J_{AB} = 6 Hz), 6.23 (d of q, 1,), 7.44–8.66 (m, 8, ArH); (*E*)-**30**, NMR (CCl_4) δ 1.47 (d of d, 3, J_{AX} = 7, J_{BX} = 1.5 Hz), 2.28 (s, 3, CH_3), 5.06 (d of q, 1, J_{AB} = 12 Hz), 6.35 (d of q, 1), 7.21–8.55 (m, 8, ArH).

The diol 9,10-di(1-propenyl)-9,10-dihydrophenanthrene (**28**), purified by recrystallization from 10% benzene–hexane, was a mixture of stereoisomers. The NMR of (*E*)-**28** is very similar to that reported for (*E*)-**26** (vide supra). The assignments to (*Z*)-**28** are δ 1.86 (m, 6, CH_3), 2.60 (br s, 2, OH), 5.1–5.8 (AB part of a non-first-order ABX_3, 4, -CH=CHCH$_3$), 7.33–7.83 (m, 8, ArH).

Control Experiments. In order to examine the stereochemical stability of the anion of **29** to the reaction conditions, and the product **29** to work-up, the anion was generated in the presence of excess Grignard by reaction of **30** with 4 equiv of (*E*)-1-propenylmagnesium bromide. Isolation of **29** showed retention of the initial geometry of **30** for both the *Z* and *E* isomer.

Reaction of Tetraphenylcyclopentadienone (31) with Vinyllithium. To 60 ml (4.4 mmol) of 0.74 *M* vinyllithium in ether was added over a 17-min period 0.771 g (2 mmol) of **31** partially suspended in 50 ml of ether. After 1 hr of stirring at room temperature, extractive work-up provided 0.859 g of a yellow-brown, oily solid. The NMR spectrum of this material showed an absence of peaks between 4.2 and 4.6 ppm expected for *O*-vinyl groups. This material was triturated with a mixture of hexane and ether to give 0.354 g (43%) of crude 2-vinyl-2,3,4,5-tetraphenylcyclopent-3-en-1-one (**32**), mp 157–161°. Recrystallization from a mixture of benzene and hexane afforded **32** as pale yellow crystals: mp 162–165°; ir (Nujol) 1748 cm^{-1} (nonconjugated C=O);[32] uv max (CH_2Cl_2) 263 nm (ε 11,600) and 235 (15,100);[33] NMR ($CDCl_3$) δ 7.30–7.00 (m, 20, C_6H_5), 6.17 (m, 1, -CH=CH$_2$), 5.42 (m, 2, -CH=CH$_2$), 4.98 (s, 1, PhCH); mass spectrum (70 eV) *m/e* (rel intensity) 413 (32.6), 412 (93.0), 385 (35.9), 384 (98.2), 307 (18.8), 294 (33.3), 293 (100.0), 292 (19.8), 291 (24.9), 289 (11.8), 279 (10.3), 278 (11.2), 267 (19.1), 265 (12.3), 229 (12.4), 228 (11.3), 216 (12.3), 215 (42.6), 205 (12.8), 204 (11.5), 203 (12.2), 202 (15.9), 191 (18.6), 179 (12.3), 178 (26.5), 168 (11.2), 167 (45.5), 165 (21.0), 153 (15.8), 152 (15.5), 151 (11.7), 128 (13.6), 115 (27.6), 105 (18.0), 91 (68.9), 50 (10.5), 44 13.7), 28 (62.9).

Anal. Calcd for $C_{31}H_{24}O$: C, 90.26; H, 5.86. Found: C, 90.54; H, 5.92.

Hydrogenation of 32. A solution of 165 mg (0.40 mmol) of **32** in 20 ml of ethyl acetate was hydrogenated in the presence of 15.5 mg of platinum oxide at room temperature under atmospheric pressure. The reduction appears to be complete within 10 min but was allowed to proceed for 3 hr. After the catalyst was removed by filtration, the filtrate was concentrated to give 168 mg of a grayish, oily solid. The NMR spectrum of this crude product indicated that the vinyl group was absent. Recrystallization of this material from a mixture of benzene and hexane afforded 91 mg (55%) of 2-ethyl-2,3,4,5-tetraphenylcyclopent-3-en-1-one (**33**) as colorless crystals: mp 149–153°; ir (Nujol) 1744 s, 1595 w, 1485 m, 1340 vvw, 1305 vw, 1275 vw, 1220 vw, 1180 w, 1165 vvw, 1150 vw, 1070 w, 1050 w, 1030 w, 1000 vw, 970 vvw, 955 vvw, 922 vvw, 915 vw, 822 vw, 800 w, 777 w, 770 m, 765 sh, 737 m, 720 m, 710 m, 698 m, and 694 cm^{-1} sh; uv

max (CH_2Cl_2) 235 nm (ε 15,600) and 267 (11,600); NMR ($CDCl_3$) δ 6.77–7.45 (m, 20, C_6H_5), 4.82 (s, 1, –CHPh–), 1.58–2.77 (m, 2, $-CH_AH_BMe$, J_{AB} = 13.3, $J_{CH_2CH_3}$ = 7.3 Hz), 0.95 (t, 3, CH_3, J = 7.3 Hz); mass spectrum (70 eV) m/e (rel intensity) 415 (23.1), 414 (60.7, M^+), 386 (26.0), 385 (83.3), 358 (34.4), 357 (100.0), 280 (21.8), 279 (58.6), 278 (12.3), 265 (14.4), 203 (12.1), 202 (12.4), 191 (12.6), 179 (14.4), 178 (24.0), 119 (10.1), 115 (20.6), 105 (24.8), 103 (12.2), 91 (39.7), 78 (23.0), 77 (22.8), 32 (19.9), 28 (78.9).

Anal. Calcd for $C_{31}H_{26}O$: C, 89.82; H, 6.32. Found: C, 89.59; H, 6.31.

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Registry No.—**1**, 1450-31-3; **2**, 54663-82-0; (*E*)-**3**, 56195-65-4; (*Z*)-**3**, 56195-66-5; **5**, 13509-36-9; **6**, 50375-41-2; **7**, 2080-58-2; **8**, 705-65-7; **9**, 822-38-8; **15**, 56195-80-3; **16**, 56247-12-2; **17**, 15482-60-7; **19**, 958-80-5; **23**, 56195-67-6; **25**, 84-11-7; (*E,E*)-*trans*-**28**, 56195-68-7; (*Z,Z*)-*trans*-**28**, 56195-69-8; (*Z*)-**29**, 56195-70-1; (*E*)-**29**, 56195-71-2; (*Z*)-**30**, 56195-72-3; **31**, 479-33-4; **32**, 56195-74-5; **33**, 56195-75-6; **39**, 17109-66-9; **40**, 56195-76-7; phenyl isocyanide dichloride, 622-44-6; *tert*-butyl mercaptan, 75-66-1; ethylene sulfide, 540-63-6; thiophenol, 108-98-5; vinyllithium, 917-57-7; vinyl bromide, 593-60-2; (*E*)-1-propenyllithium, 6386-72-7; (*Z*)-1-propenyllithium, 6524-17-0; (*E*)-1-propenyl bromide, 590-15-8; (*Z*)-1-propenyl bromide, 590-13-6; phenyllithium, 591-51-5; phenyl isocyanide, 931-54-4; benzhydrylsodium, 5152-68-1; benzhydryllithium, 881-42-5; dibenzhydryl sulfide, 1726-03-0; *n*-butyllithium, 109-72-8; benzyl chloride, 100-44-7; benzyllithium, 766-04-1

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The Peripheral Synthesis of Medium-Ring Diaza Heterocycles via β-Elimination Reactions

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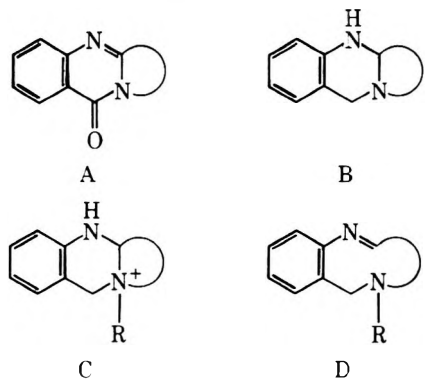
Compounds 4 and 7, respectively, obtained from the corresponding quinazolinones, were methylated to give 5 and 8 respectively. Treatment with base led to the medium-ring diaza compounds **6b** and **9**, respectively.

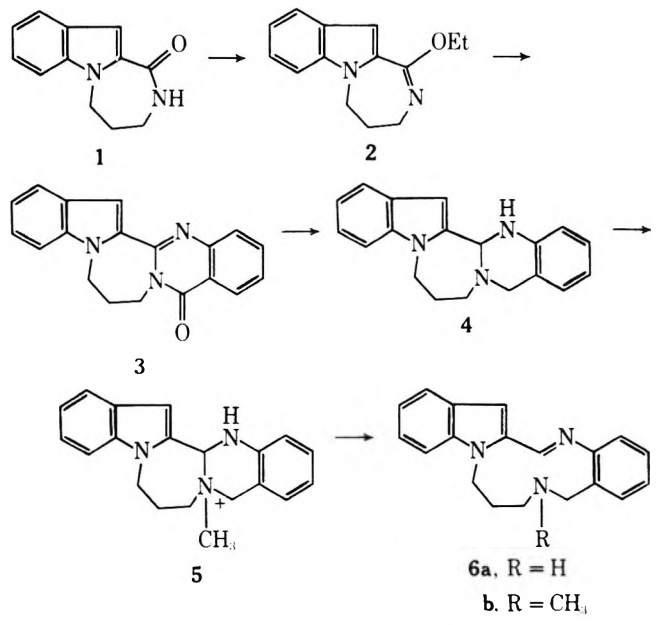
The peripheral synthesis of medium-ring azacycles as disclosed in the literature[1] involves the selective cleavage of the central bond of a fused 1-azabicycloalkanone. This was achieved via quaternization of the nitrogen in the proximity of an activating substituent leading to the selective cleavage of one nitrogen–carbon bond.

We have applied this concept to the formation of medium-ring diazacycles under nonreductive conditions. Similar to a Hofmann degradation,[2] the nitrogen–carbon bond cleavage is induced by a tetraalkylammonium salt. An aniline was placed in a 1,3 position to the ammonium salt as depicted in structure C of Scheme I. The more basic tertiary nitrogen should guarantee the selective alkylation of B by an alkyl halide to give C. We expected ring enlargement to D to occur in the presence of a suitable base via β-elimination with abstraction of a proton from the secondary amine. The precursors for B are well documented in the literature[3] and are readily prepared from o-anthranilic acid and an activated lactam, e.g., an imino ester, to give the fused quinazolinones of the general structure A. These can be reduced to the compounds of the general structure B in the presence of lithium aluminum hydride.[4]

Scheme I



Scheme II



As our starting material we selected the known[5] [1,4]diazepino[1,2-*a*]indol-1-one (**1**) (Scheme II). The imino ester **2** was prepared with the aid of Meerwein's salt following standard literature procedures.[3a,b] This activated lactam formed the novel pentacyclic quinazolinone **3** when heated with anthranilic acid in analogy to similar reactions described in the literature.[3a] Spectral and analytical data were found in agreement with the assigned structure **3**. Treatment of this compound with lithium aluminum hydride in refluxing tetrahydrofuran resulted in the reduction of both functional groups[4] of **3** to give **4**.

With dry hydrochloric acid, the base **4** was transformed into a bishydrochloride according to analytical data.

While two of the three nitrogens present in **4** are basic

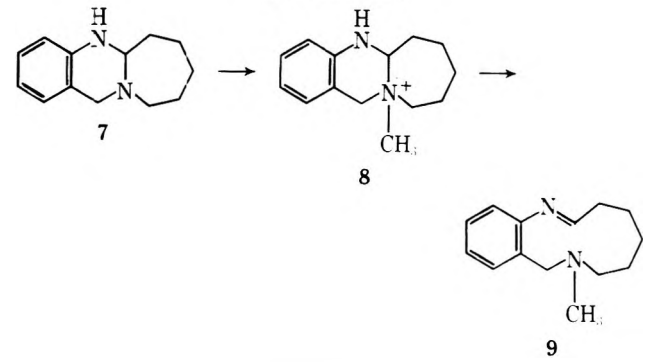
enough to form salts with a strong acid, a selective monoalkylation was observed when **4** was allowed to react with methyl iodide. From the following reaction it may be concluded that methylation of **4** took place on the tertiary nitrogen to yield **5**. The product obtained was treated with aqueous sodium hydroxide. A new crystalline substance was isolated which we assigned structure **6b** for the following reasons. Both elemental analysis and mass spectral data were in agreement with the composition $C_{20}H_{21}N_3$. The infrared spectrum of **6b** gave an absorption at 1630 cm^{-1} due to the C=N substructure. This assignment was confirmed by the NMR spectrum of **6b**, which showed a singlet at δ 8.73 ppm that is typical of CH=N. Other singlets due to the methyl group, the benzylic methylene, and the proton in position 3 of the indole appeared at chemical shifts expected for these positions. We would like to draw attention to a 2 H triplet observed at δ 4.72 ppm. This was assigned to the methylene group attached to the indole nitrogen based on examples we published earlier. There we learned that such a methylene group gives rise to a triplet when the side chain of the indole possesses a certain degree of rotational freedom, as, e.g., in 9-(3-aminopropyl)-1,2,3,4-tetrahydrocarbazole and others.[6] In the absence of this rotational freedom, e.g., 2,3,6,6a-tetrahydro-6a-ethyl-1*H*-3a,10b-diazafluoranthen-4(5*H*)-one,[7] no triplet could be observed for the corresponding methylene group. In the medium-sized ring of triazacycloundecine **6b** enough rotational freedom is present to render the two protons magnetically equivalent as observed by the presence of the triplet. Conjugation between the two aromatic ring systems of **6b** could also be observed in the ultraviolet spectrum of that compound with an absorption at 336 nm extending into the visible spectrum.

When the medium-sized ring compound **6b** was treated with hydriodic acid, the pentacyclic compound **5** was recovered. This change was accompanied by the loss of the long-wave uv absorption.

As indicated above the quinazoline **4** was converted to a bishydrochloride. This compound can exist in two tautomeric forms, one represented by the quinazoline **4**, the other by the indolo[2,1-c][1,4,8]benzotriazacycloundecine **6a**, or as an equilibrium of the two tautomeric forms. Our spectral data seems to indicate that the free base exists in the form of the quinazoline **4** while the hydrochloride exists at least to some degree if not exclusively in the medium-ring form **6a**. We were not able to obtain a NMR spectrum of the free base owing to low solubility. When **4** was dissolved in trifluoroacetic acid a singlet at δ 8.56 ppm was observed which we assigned to the CH of an imino double bond. Similar observations were made when the NMR spectrum of the bishydrochloride of **4** was recorded in Me_2SO as solvent. We anticipated a singlet in the vicinity of δ 4.0 ppm[7] corresponding to the bridgehead proton of **4**. However, it seems more likely that the partial structure CH=N gives rise to an absorption which coincides with the signals associated with the aromatic protons. Similar conclusions were reached from the interpretation of the ir and uv spectra. In particular the salt form **6a** showed an ir absorption at 1640 cm^{-1} and a uv absorption at 348 nm both of which were absent in the respective spectra of the free base **4**. In addition a direct comparison of the infrared and ultraviolet spectra of the salt with those of the medium-sized ring compound **6b** seemed to confirm that the addition salt of **4** is present either in the medium-sized ring form itself or coexists in an equilibrium with the pentacyclic form **4**.

In order to explore this novel ring opening reaction further we decided to investigate the preparation of

Scheme III



4,5,6,7,8,9-hexahydro-8-methyl-3*H*-[1,8]benzodiazacycloundecine (**9**) (Scheme III). Starting from the known 4,5,6,7-tetrahydro-3*H*-azepino[2,1-*b*]quinazolin-9-one,[3a] following the same sequence of reactions as described above for the medium-ring compound **6b**, the novel compound 4,5,6,7,8,9-hexahydro-8-methyl-3*H*-[1,8]benzodiazacycloundecine (**9**) was isolated and characterized as a liquid. In the NMR spectrum of **9** the proton on the newly generated double bond appeared as a triplet at δ 7.68 ppm, compatible with the assigned structure **9**. This compound was unstable at room temperature. Upon standing a nonvolatile substance was obtained which we did not investigate further.

In contrast to **4**, which formed a bishydrochloride, **9** gave only a monohydrochloride.

Spectral data seems to indicate the presence of the medium-ring tautomer in **7** HCl. The NMR spectrum of this compound showed a signal at δ 8.9 ppm in agreement with the presence of a N=CH. This is also supported by the ir spectrum of **7** HCl (see Experimental Section).

Direct proof for the existence of the imino double bond in **9** stems from hydrogenation experiments. After uptake of 1 mol of hydrogen the octahydro-1*H*-[1,8]benzodiazacycloundecine **10** was isolated and characterized in the form of its bishydrochloride.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and have not been corrected. Proton magnetic resonance spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in hertz or δ values (parts per million) relative to Me_4Si (tetramethylsilane) as internal standard. Infrared spectra were recorded on a Perkin-Elmer spectrometer Model 457. Ultraviolet spectra were determined in 95% ethanol with a Carey recording spectrometer Model 15. Thin layer chromatography (TLC) was carried out on glass plates coated with silica gel HF-254, E. Merck AG. Mass spectra were measured on a LKB 9000 mass spectrometer.

1-Ethoxy-3,4-dihydro-5*H*-[1,4]diazepino[1,2-*a*]indole (2). To a solution of 61.0 g (0.32 mol) of triethyloxonium fluoroborate[3b] in methylene chloride was added 45.0 g (0.275 mol) of lactam **1**[5] dissolved in methylene chloride. After 2 hr at room temperature the mixture was poured on 500 ml of 2 *N* Na_2CO_3 and worked up the usual way to give 54.5 g of crude imino ester **2**. This material was distilled in a Kugelrohr to give 35.3 g (57%) of **2**: bp 140–160° (0.3 mm); *m/e* 228 (M^+); NMR ($CDCl_3$) δ 1.38 (t, 3, J = 7.1 Hz, CH_3), 2.0–2.4 (m, 2, $CH_2CH_2CH_2$), 3.4–3.7 (m, 2, $C{=}NCH_2$) 4.17 (t, 2, J = 6.4 Hz, indole NCH_2), 4.23 (q, 2, J = 7.1 Hz, OCH_2), 6.96 (s, 1, indole C_3H), 7.0–7.3 (m, 3, C_6H_3), 7.4–7.7 (m, 1, C_6H_1); ir (film) 1670, 1650, 1620 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O$ (228.28): C, 73.7; H, 7.1; N, 12.3. Found: C, 73.6; H, 7.1; N, 12.1.

7,8-Dihydro-6*H*-indolo[2′,1′:3,4][1,4]diazepino[2,1-*b*]quinazolin-10(10*H*)-one (3). A mixture of 12.6 g (0.055 mol) of imino ester **2** and 8.2 g (0.060 mol) of anthranilic acid in 100 ml of ethanol was heated to reflux overnight. The product precipitated from the solution and was filtered off to give 11.0 g (66.5%) of **3**, mp 215–216°. A sample recrystallized from methanol gave mp 215–216°; *m/e* 301 (M^+); NMR ($CDCl_3$) δ 2.36 (m, 2, $CH_2CH_2CH_2$),

4.0–4.5 (m, 4, 2 NCH_2), 7.0–8.0 (m, 8, aromatic H), 8.2–8.5 (m, 1, C_6H_1); ir (CH_2Cl_2) 1675 (C=O), 1610, 1590 cm^{-1}; uv 218 nm (ϵ 35,420), 330 (26,460). Anal. Calcd for $C_{19}H_{15}N_3O$ (301.37): C, 75.7; H, 5.0; N, 13.9. Found: C, 75.7; H, 5.0; N, 13.9.

7,8,15,15a-Tetrahydro-6*H*,10*H*-indolo[2',1':3,4][1,4]diazepino[2,1-*b*]quinazoline (4). A solution of 6.5 g (0.022 mol) of the quinazolinone **3** in 300 ml of absolute THF was added dropwise to a suspension of 2.6 g (0.07 mol) of $LiAlH_4$ in 50 ml of absolute THF under an atmosphere of nitrogen. The mixture was heated to reflux during 3 hr. The excess of reducing agent was destroyed by slowly adding water to obtain a white precipitate which was filtered and washed with ether. The filtrate was concentrated and a solid was obtained which was recrystallized from methanol to give 4.6 g (74%) of **4**: mp 233–234°; *m/e* 289 (M^+); NMR (CF_3COOH) δ 2.5–3.0 (broad, 2, $CH_2CH_2CH_2$), 4.0–4.5 (m, 2, NCH_2), 4.5–4.9 (m, 2, NCH_2), 5.50 (s, 2, $NCH_2C_6H_4$), 7.2–8.1 (m, 9, aromatic H), 8.56 (s, 1, CH=N); ir ($CHCl_3$) 3400 (NH), 1610, 1590 cm^{-1} (weak); uv 220 nm (ϵ 35,600), 276 (10,600), 284 (10,500). Anal. Calcd for $C_{19}H_{19}N_3$ (289.37): C, 78.9; H, 6.6; N, 14.5. Found: C, 78.8; H, 6.6; N, 14.4.

A sample of **4** was suspended in methanol and treated with a stream of hydrogen chloride. The starting material dissolved and then precipitated as the yellow bishydrochloride: mp 229–231° (methanol–ether); NMR (Me_2SO-d_6) δ 1.8–2.5 (broad, 2, $CH_2CH_2CH_2$), 3.3–3.8 (m, 2, CH_2), 3.9–5.1 (m, 4, 2 CH_2), 6.37 (s, 1, indole C_3H), 6.6–8.4 (m, ~9, aromatic + CH=N), below 8.5 (3, very broad, 3 NH); ir (Nujol) 3600–2400 (NH), 1640 (C=N), 1608 cm^{-1} (aromatic); uv 270 nm (ϵ 14,200), 348 (3010). Anal. Calcd for $C_{19}H_{19}N_3$·2HCl (362.3): C, 63.0; H, 5.9; N, 11.6; Cl, 19.6. Found: C, 62.8; H, 6.1; N, 11.5; Cl, 19.8.

7,8,9,10-Tetrahydro-9-methyl-6*H*-indole[2,1-*c*][1,4,8]benzotriazacycloundecine (6b). A mixture of 2.0 g (0.007 mol) of the amine **4** and 10.0 g (0.07 mol) of methyl iodide in 50 ml of chloroform was heated to reflux for 3 hr. The solid was filtered off to yield 2.8 g (94%) of **5**, mp 212–213°. When the same reaction was carried out in methanol the product obtained had mp 231–233°. The salt was suspended in ether and after addition of 2 *N* NaOH a clear solution was obtained. The organic phase was dried over K_2CO_3 and evaporated to give 1.9 g (90%) of **6b** as a yellow solid, mp 158–159°. Recrystallization from methanol–water gave 1.4 g (66%) of **6b**: mp 161–162°; *m/e* 303 (M^+); NMR ($CDCl_3$) δ 2.35 (s, 3, CH_3), 1.7–2.7 (m, 4, $CH_2CH_2NCH_3$), 3.38 (s, 2, $C_6H_4CH_2$), 4.72 (t, 2, J = 7.0 Hz, indole NCH_2), 7.0 (s, 1, indole C_3H), 7.1–7.8 (m, 8, 2 C_6H_4), 8.73 (s, 1, CH=N); ir (CH_2Cl_2) 1630 (C=N), 1610 (weak), 1590 cm^{-1}; uv 265 nm (ϵ 11,050), 270 (11,200), 286 (8120), 298 (7040), 336 (9750). Anal. Calcd for $C_{20}H_{21}N_3$ (303.44): C, 79.2; H, 7.0; N, 13.9. Found: C, 78.8; H, 7.1; N, 13.9.

A small sample of **6b** in methanol was treated with a few drops of hydriodic acid. The solution was stirred at room temperature for 2 hr. The solvent was evaporated and the residue recrystallized from methanol–ether to give **5**: mp 239–240°; uv 215 nm (ϵ 52,800), 272 (16,390). Anal. Calcd for $C_{20}H_{21}N_3$·HI (431.35): C, 55.7; H, 5.2; N, 9.7. Found: C, 55.8; H, 5.6; N, 9.7.

5,5a,6,7,8,9,10,12-Octahydroazepino[2,1-*b*]quinazoline (7). To the suspension of 5.3 g (0.14 mol) of $LiAlH_4$ in 50 ml of THF a solution of 9.8 g (0.046 mol) of 6,7,8,9,10,12-hexahydroazepino-[2,1-*b*]quinazolin-12-one[3a] in 300 ml of THF was added dropwise. When the addition was completed the mixture was heated to reflux for 3 hr and then worked up with the usual precautions to give 8.9 g (96%) of **7** as a liquid, ir (film) 3380 (NH), 1610, 1590 cm^{-1}. A sample was treated with dry hydrogen chloride to give **7** HCl: mp 199–200°; *m/e* 202 (M^+); NMR (CF_3COOH) δ 1.6–2.4 (m, 6, 3 CH_2), 2.8–3.4 (m, 2, CH_2), 3.9–4.5 (m, 2, NCH_2), 5.63 (s, 2, $C_6H_4CH_2N$), 7.4–8.0 (m, 4, C_6H_4), 8.9 (t, 1, J = 3 Hz, N=CH); ir (Nujol) 3200 (NH), 1610, 1598 cm^{-1} (both weak); uv 242 nm (ϵ 9700), 292 (2100). Anal. Calcd for $C_{13}H_{18}N_2$·HCl (238.8): C, 65.4; H, 8.0; N, 11.7. Found: C, 65.5; H, 7.9; N, 11.4.

4,5,6,7,8,9-Hexahydro-8-methyl-3*H*-[1,8]benzodiazacycloundecine (9). A solution of 20.2 g (0.1 mol) of the amine **7** in 500 ml of $CHCl_3$ was treated with 60.0 g (0.42 mol) of methyl iodide. After 10 min at room temperature a solid started to precipitate. The mixture was stirred overnight, and the solid was collected by filtration and washed with chloroform to give **8**, mp 218–220°. This was stirred vigorously with 80 ml of 2 *N* NaOH in the presence of 300 ml of water and 500 ml of methylene chloride for 30 min. The organic layer was separated and the aqueous phase was extracted with additional methylene chloride. The combined organic phases were washed with water, dried over K_2CO_3, and concentrated to give 21.0 g of **9** as a liquid. Distillation of 17 g of the crude gave 11.5 g (64%) of pure **9**: *m/e* 216 (M^+); NMR ($CDCl_3$) δ 1.3–2.0 (m, 6, 3 CH_2), 2.12 (s, 3, NCH_3), 2.2–2.7 (m, 4, 2 CH_2), 3.40 (s, 2, $C_6H_4CH_2$), 6.6–7.4 (m, 4, C_6H_4), 7.68 (t, 1, J = 5.5 Hz, $N=CHCH_2$); ir (CH_2Cl_2) 1668 cm^{-1} (C=N); uv 244 nm (ϵ 10,340), 289 (2481).

A sample of the base was treated with dry HCl to form **9** HCl, mp 210–211°. Anal. Calcd for $C_{14}H_{20}N_2$·HCl (252.8): C, 66.5; H, 8.4; N, 11.1; Cl, 14.0. Found: C, 66.7; H, 8.1; N, 11.0; Cl, 13.8.

2,3,4,5,6,7,8,9-Octahydro-8-methyl-1*H*-[1,8]benzodiazacycloundecine (10). A solution of 6.0 g (0.028 mol) of the amine **9** in 100 ml of ethanol was hydrogenated in a Parr apparatus in the presence of 1.0 g of Pd/C (10%). A crude product was filtered through a silica gel column with benzene to give 5.2 g (86%) of **10**. A sample was treated with dry hydrogen chloride to give **10** 2HCl: mp 203–205° (ethanol–ether); *m/e* 218 (M^+); NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.1–2.0 (m, 9, 4 CH_2 + NH), 2.74 (s, 3, CH_3), 2.8–3.3 (m, 4, 2 NCH_2), 4.44 (q, 2, J = 12 Hz, $\Delta\nu$ = 10.6 Hz, $C_6H_4CH_2N$), 6.6–7.5 (m, 4, C_6H_4), 8.4–8.9 (broad, 2, NH_2); ir (Nujol) 3200–2700 (NH), 1590 cm^{-1} (weak); uv 255 nm (ϵ 11,528), 313 (2530). Anal. Calcd for $C_{14}H_{22}N_2$·2HCl (291.3): C, 57.7; H, 8.3; N, 9.6; Cl, 24.3. Found: C, 57.8; H, 8.1; N, 9.4; Cl, 24.9.

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Registry No.—**1**, 26304-37-0; **2**, 56404-31-0; **3**, 56404-30-9; **4**, 56404-29-6; **4** HCl, 56404-28-5; **5**, 56404-27-4; **6b**, 56421-60-4; **7**, 56404-26-3; **7** HCl, 56404-25-2; **8**, 56404-24-1; **9**, 56404-23-0; **9** HCl, 56404-22-9; **10** HCl, 55661-92-2; anthranilic acid, 118-92-3; methyl iodide, 74-88-4; hydriodic acid, 10034-85-2.

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2-Azacycl[3.2.2]azine. Some Electrophilic Substitutions and Addition Reactions

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Electrophilic bromination of 2-azacycl[3.2.2]azine (1), under different conditions, has afforded the 1-bromo (2), 1,4-dibromo (3), and 1,3,4-tribromo (4) derivatives. Bromination of 2-azacycl[3.2.2.]azine-4-carboxaldehyde (5) and 4-carboxylic acid (6) affords, depending upon the reaction conditions, the corresponding 1-bromo derivatives (8, 9) or the 1,4-dibromo (3) or 1,3,4-tribromo (4) compounds. Nitration of this ring system affords the 4-nitro (7) and 1,4-dinitro (10) derivatives. The 1-bromo-4-nitro-2-azacycl[3.2.3]azine (11) is obtained by bromination of the 4-nitro compound (7). Vilsmeier formylation of compound 1 affords the 1- as well as 4-formyl derivatives (12, 5). 2-Azacycl[3.2.2]azine (1) reacts with butyllithium to form the 1-butyl derivative, and with methyl iodide to give the *N*-methyl quaternary salt (14). Explanations to account for the formation of these compounds are given.

We have recently described the synthesis, CNDO/2 calculations, and ^{1}H NMR spectrum of 2-azacycl[3.2.2]azine (1).[1] As an extension of this study, we now wish to describe some of the chemical properties of this new derivative of the aromatic cycl[3.2.2.]azines.

Bromo-2-azacycl[3.2.2.]azines. The reaction of 2-azacycl[3.2.2.]azine (1) with an equimolar amount of *N*-bromosuccinimide (NBS) in the absence of peroxides, affords a monobromo (2) as well as a dibromo (3) derivative. Bromination of the monobromo compound with NBS gives the same dibromo compound. The dibromo derivative 3 becomes the only product when 2 equiv of NBS is employed. When 2-azacycl[3.2.2.]azine (1) is treated with bromine in chloroform, the dibromo derivative 3 becomes the major product, while bromine in acetic acid affords, in addition to compound 3, a small amount of a tribromo-2-azacycl[3.2.2.]azine (4). Further treatment of the dibromo derivative 3 with bromine in acetic acid under mild conditions affords the tribromo derivative 4.

The structure of the monobromo compound is readily established by an examination of its ^{1}H NMR spectrum (see Table I). The absorption of H-1 present in the parent compound (1) is absent in this derivative, while H-7 is more deshielded by 0.20 ppm. The chemical shifts of the remaining protons are essentially identical with those of the parent compound (1). Thus, bromination has afforded the 1-bromo derivative 2 (Scheme I). The structure of the dibromo compound 3 is equally easily determined as the 1,4-dibromo derivative 3 by the absence of absorptions due to H-1 and H-4 in the ^{1}H NMR spectrum. The tribromo derivative is similarly identifiable as the 1,3,4-trisubstituted compound 4 (see Table I).

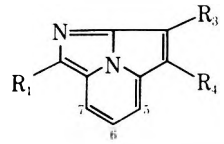
Nitro-2-azacycl[3.2.2]azines. The reaction of compound 1 at 0° with a mixture of nitric and sulfuric acids yields a mononitro derivative (7) whose ^{1}H NMR spectrum is devoid of the AB pattern due to H_3 and H_4 in the starting material while still showing the presence of H-5, H-6, and H-7 along with two singlets at τ 1.15 and 1.65, respectively. Thus, the nitro group is either substituted at C-3 or C-4, and not at C-1 as is the case in the monobromination reaction. If the nitro group is at C-4, the major deshielding effects should be on H-3 and H-5. In fact H-3 is more deshielded by 0.70 ppm and H-5 by 0.76 ppm with respect to the parent compound 1. Consequently we are dealing with the 4-nitro-2-azacycl[3.2.2.]azine (7).

Continued nitration of compound 1 yields a small amount of dinitro derivative 10, identified as the 1,4-disubstituted derivative by its mass spectral fragmentation pattern, which is very similar to that of the 1,4-dibromo compound (3) (vide infra).

The 4-nitro-2-azacycl[3.2.2]azine (7) when brominated with NBS affords a monobromomononitro compound

Table I

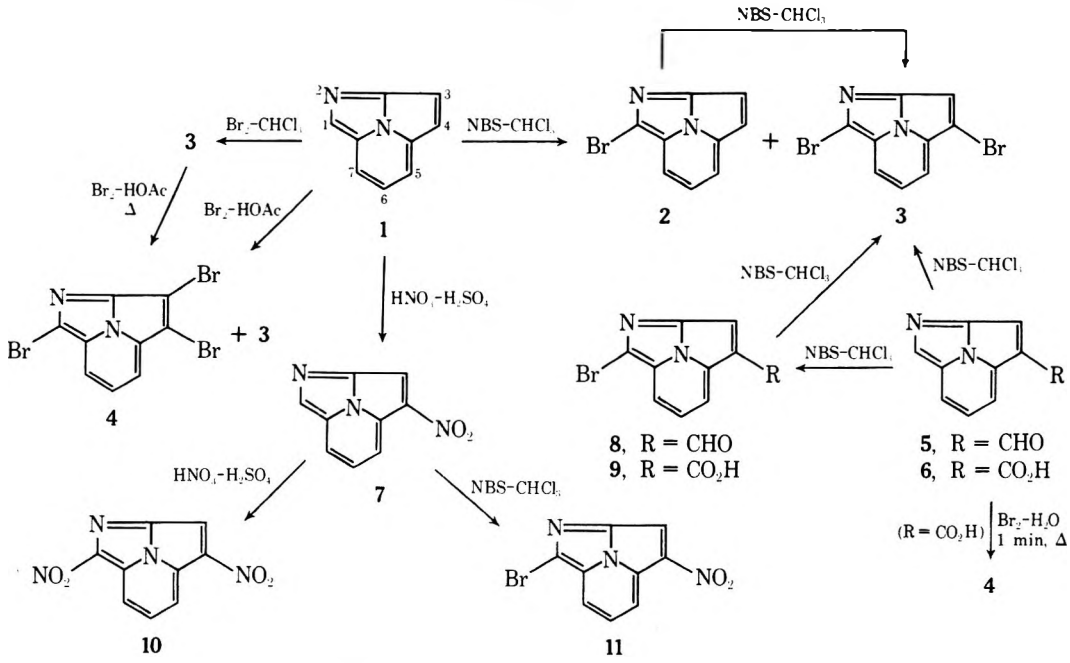
^{1}H NMR Spectral Data of Some 2-Azacycl[3.2.2]azines[a]



Compd[b]	Chemical shifts, τ						Substituents
	H_1	H_3	H_4	H_5	H_6	H_7	
1 ($R_1 = R_3 = R_4 = H$)[c]	1.55	2.35	2.70	2.04	2.49	2.18	
2 (R_1 = Br; $R_3 = R_4 = H$)		2.37	2.64	2.02	2.33	1.98	
3 ($R_1 = R_4$ = Br; $R_3 = H$)		2.31		1.89	2.23	1.97	
4 ($R_1 = R_3 = R_4$ = Br)				1.91	2.22	1.99	
5 (R_4 = CHO; $R_1 = R_3 = H$)	1.28	1.86		1.45	2.02	1.74	−0.26 (R_4)
7 ($R_4 = NO_2$; $R_1 = R_3 = H$)	1.15	1.65		1.28	1.86	1.66	
8 (R_4 = CHO; R_1 = Br; $R_3 = H$)		2.02		1.57	2.10	1.94	−0.21 (R_4)
11 (R_1 = Br; $R_4 = NO_2$; $R_3 = H$)		1.73		1.25	1.78	1.73	
13 ($R_1 = n$-C_4H_9; $R_3 = R_4 = H$)		2.33	2.65	1.88	2.32	2.00	0.65 (t), 9.2–7.6 (m) (R_1)
12 (R_1 = CHO; $R_3 = R_4 = H$)		2.24	2.42	1.45	2.06	1.45	−0.37 (R_1)

[a] Dilute solutions in $CDCl_3$. [b] $J_{14} = 1.0$; $J_{34} = 4.7$; $J_{56} = 7.8$–8.0; $J_{67} = 7.0$–7.5 Hz. [c] Taken from ref 1. In this reference, chemical shifts are given in τ and not as parts per million as printed. The Table heading ^{3}H should read ^{1}H NMR.

Scheme I



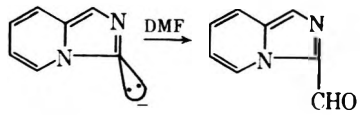
whose structure (11) (Scheme I) is readily deduced by a comparison of its ^{1}H NMR spectrum with that of 7.

Bromination of 2-Azacycl[3.2.2]azine-4-carboxaldehyde (5) and -carboxylic Acid (6). Bromination of compound 5 with NBS in chloroform yields a monobromo derivative whose structure is established as 1-bromo-2-azacycl[3.2.2.]azine-4-carboxaldehyde (8) by its ^{1}H NMR and mass spectra. This compound upon continued bromination is converted to the 1,4-dibromo derivative 3, presumable via oxidation of the carboxaldehyde to the carboxylic acid, followed by decarboxylation and bromination at C-4.

Bromination of the carboxylic acid 6 affords the 1,4-dibromo compound 3 and only traces of 1-bromo-2-azacycl[3.2.2.]azine-4-carboxylic acid (9) and its ethyl ester. The carboxylic acid 6, when treated with bromine water, yields the tribromo derivative 4 as the major product.

Formylation of 2-Azacycl[3.2.2.]azine. The treatment of the parent compound 1 under Vilsmeier formylation conditions affords two monoformyl derivatives $C_{10}H_6N_2O$ (12 and 5) in essentially equal amounts (Scheme II). One of these monoformyl derivatives (5) was identified as the 4-substituted compound by comparison with an authentic sample.[1] The other compound was shown to be the 1-formyl derivative 12 by an analysis of its ^{1}H NMR spectrum (see Table I).

Alkylation of 2-Azacycl[3.2.2.]azine. Earlier work[2,3] has shown that formylation of polyazaindenes and related compounds can be effected by initial formation of carbanions such as 15, generated by means of butyllithium, followed by treatment with dimethylformamide (DMF).

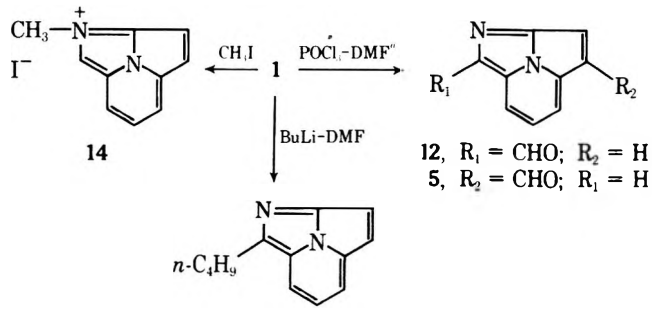


15 16

When this reaction was attempted on the cyclazine 1, a compound corresponding to a monobutyl derivative was obtained rather than the expected formyl compound. The structure of this material was established as the 1-*n*-butyl compound by comparison with an authentic sample.[6]

We have already shown that protonation of compound 1 occurs on the peripheral nitrogen atom. When the azacyclazine 1 is treated with methyl iodide, a monomethyl derivative is obtained whose ^{1}H NMR spectrum is essentially identical with that of the protonated species. Thus, not surprisingly, methylation has occurred on the peripheral nitrogen to form the quaternary salt 14.

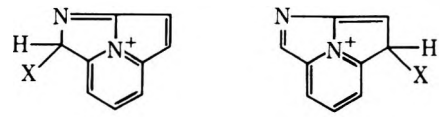
Scheme II



14 13

Discussion

If one assumes that the stabilities of the intermediates in the electrophilic substitutions are similar to those of the transition states involved, one finds that structures 17, and 18 are stabilized by the presence of a central pyridinium

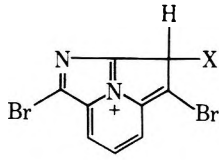


17 18

ring. Thus, one would predict that electrophilic substitution should preferentially occur at positions 1 and 4. The stabilities of intermediates 17 and 18 should be essentially the same. A comparison of these predictions with the results of the bromination reactions seems, at first glance, to contradict them. However, if one considers that the first step in the bromination reactions involves the formation of a π complex, it becomes necessary to compare the stabilities of structures 19 and 20. Clearly, because of the π-electron densities at the C_1–N_2 bond vs. the C_3–C_4 bond,[1] the π complex 19 would be more stable than 20. Thus, we can readily account for the preferential bromination at C_1 followed by introduction of the second bromine at C-4.

19 20

The introduction of the third bromine at C-3 can be rationalized in terms of the intermediate **21**. This intermedi-

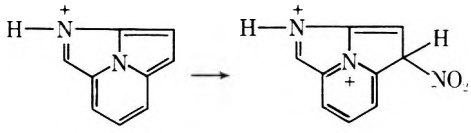


21

ate certainly would be less stable than the pyridinium ring containing ones **17** and **18**. Thus, the sequential order of the brominations is readily accounted for.

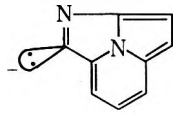
The suggested intermediacy of the π complexes **19** and **20** finds support in the observation that the Vilsmeier formylation affords the two monoformyl derivatives **12** and **5** rather than the monoformyl compound **12** and a 1,4-diformyl compound. It is of interest to note that 1,4-diacetylation occurs in cycl[3.2.2.]azine.[4]

The selective formation of the 4-nitro derivative **7** can be rationalized on the basis that under the highly acidic reaction conditions, nitration occurs on the protonated compound **22** via the intermediate **23**.



22 23

Since the reaction of butyllithium in dimethylformamide did not afford the expected formyl derivative, and when the reaction was quenched with D_2O, no deuterium was incorporated, one must conclude that anion **24** is not generat-



24

ed by butyllithium. Consequently, the *n*-butyl derivative is probably formed by a simple 1,2-addition reaction followed by oxidation of the resulting dihydro compound in a manner typical of many heterocyclic ring systems.[5]

Experimental Section

General. All melting points are uncorrected. ^{1}H NMR spectra were obtained on a Varian Associates HA-100 with Me_4Si internal standard. Mass spectra were measured with a Hitachi Perkin-Elmer RMU-6M at 80 eV. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Ga., and by the Analytical Services Division, Chemistry Department, The University of Alabama.

Bromination of 2-Azacycl[3.2.2]azine (1) with *N*-Bromosuccinimide (NBS). A. With 1 Equiv of *N*-Bromosuccinimide. To a solution of **1** (160 mg, 1.12 mmol) in 10 ml of $CHCl_3$ was added, in portions, solid NBS (214 mg, 1.2 mmol) and the reaction mixture was stirred at room temperature for 3 hr. The solvent was evaporated in vacuo and the solid residue was chromatographed on neutral Al_2O_3 (grade III), using *n*-hexane as eluent. The first fraction afforded 45 mg (13.6%) of compound **3**. The second fraction afforded 60 mg (24.1%) of compound **2** and the third fraction 90 mg (56.3%) of compound **1**. The analytical sample of **2** was prepared by sublimation (60°, 0.02 Torr): mp 72–73°; ^{1}H NMR (see Table I); mass spectrum *m/e* 222 (M^+ + 2), 220 (M^+), 141 (M^+ − 79). Anal. Calcd for $C_9H_5N_2Br$: C, 48.86; H, 2.28; N, 12.67; Br, 36.19. Found: C, 48.77; H, 2.30; N, 12.62; Br, 36.25.

B. With 2 Equiv of *N*-Bromosuccinimide: To a solution of **1** (142 mg, 1 mmol) in 10 ml of $CHCl_3$ was added solid NBS (400 mg, 2.25 mmol) and the mixture was stirred at room temperature[7] for 1 hr. The solution was filtered and the filtrate evaporated to dryness. Recrystallization of the resulting solid from ethanol–water afforded **3** as yellow crystals (280 mg, 93%): mp 121–122°; ^{1}H NMR (see Table I); mass spectrum *m/e* 302 (M^+ + 4), 300 (M^+ + 2), 298 (M^+), 219 (M^+ − 79), 140 (M^+ − 2 × 79). Anal. Calcd for $C_9H_4N_2Br_2$: C, 36.00; H, 1.33; N, 9.33; Br, 53.33. Found: C, 35.87; H, 1.34; N, 9.34; Br, 53.42.

C. With Bromine in Chloroform. To **1** (142 mg, 1 mmol) dissolved in 10 ml of $CHCl_3$ was added Br_2 (170 mg, 1.06 mmol) and the mixture was stirred at room temperature for 15 min. The reaction mixture was poured into 20 ml of water and made basic with solid Na_2CO_3. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 100 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was removed under vacuum. Recrystallization of the solid from ethanol–water gave 282 mg (94%) of 1,4-dibromo derivative **3**.

D. With Bromine in Acetic Acid. To **1** (100 mg, 0.701 mmol) dissolved in 10 ml of glacial acetic acid, Br_2 (200 mg, 1.15 mmol) was added dropwise and the reaction mixture was stirred for 15 min. The solution was diluted with H_2O, made basic with solid Na_2CO_3, and extracted with $CHCl_3$ (2 × 100 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was evaporated under reduced pressure. The crude product was chromatographed on neutral Al_2O_3 (grade III) and eluted with *n*-hexane. Compound **3** was obtained as the major product[8] (200 mg, 75%).

Nitration of 2-Azacycl[3.2.2]azine (1). To a cold solution (0°) of 1.1 ml of concentrated H_2SO_4 and 0.45 ml of concentrated HNO_3 was added **1** (180 mg, 1.27 mmol) and the mixture was allowed to warm to room temperature with stirring. After 1 hr the mixture was poured into ice–water. The abundant yellow precipitate which formed was separated by filtration, treated with an aqueous Na_2CO_3 solution, and extracted with $CHCl_3$ (2 × 100 ml). The filtrate was also made basic with Na_2CO_3 and extracted with $CHCl_3$ (100 ml). The two $CHCl_3$ extracts were combined and dried over anhydrous Na_2CO_3 and the solvent was evaporated under reduced pressure. The crude product was recrystallized from 95% ethanol to afford **7** as burnt-yellow crystals (170 mg, 72%): mp 200–201; ^{1}H NMR (see Table I); mass spectrum *m/e* 189 (M^+), 157 (M^+ − 30), 141 (M^+ − 46). Anal. Calcd for $C_9H_5N_2O_2$: C, 57.75; H, 2.67; N, 22.46. Found: C, 57.57; H, 2.78; N, 22.35. A dinitro compound (**10**, 15 mg, 5.1%) was also formed when the reaction mixture was stirred for more than 5 hr: mp 225–226°; mass spectrum *m/e* 232 (M^+), 202 (M^+ − 30), 186 (M^+ − 46), 174 (M^+ − 58), 140 (M^+ − 90). Anal. Calcd for $C_9H_4N_4O_4$: C, 46.55; H, 1.72; N, 24.13. Found: C, 46.48; H, 1.79; N, 24.46.

1-Bromo-4-nitro-2-azacycl[3.2.2]azine (11). To a solution of **7** (33 mg, 0.178 mmol) in 10 ml of $CHCl_3$ was added solid NBS (63.0 mg, 0.356 mmol) and the mixture was refluxed for 3 days. The solution was evaporated to dryness, and the residue was recrystallized from 95% ethanol. Purification by sublimation gave a burnt-yellow solid (34 mg, 81%): mp 237–238°; ^{1}H NMR (see Table I); mass spectrum *m/e* 267 (M^+ + 2), 265 (M^+), 235 (M^+ − 30), 219 (M^+ − 46), 140 (M^+ − 46 − 79). Anal. Calcd for $C_9H_4H_3O_2Br$: C, 40.60; H, 1.50; N, 15.78; Br 30.00. Found: C, 40.85; H, 1.65; N, 15.68; Br, 30.14.

1,3,4-Tribromo-2-azacycl[3.2.2]azine (4) from Compound 3. To compound **3** (80 mg, 0.267 mmol) dissolved in 10 ml of acetic acid was added Br_2 (100 mg, 0.556 mmol) and the mixture was stirred at room temperature for 10 min and then heated on a steam bath for 5 min. After cooling, the mixture was treated with aqueous Na_2CO_3 and extracted with $CHCl_3$ (3 × 100 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was evaporated in vacuo. The residue was recrystallized from methanol–benzene to give **4** as a yellow solid (86 mg, 85%): mp 199–200°; ^{1}H NMR (see Table I); mass spectrum *m/e* 382 (M^+ + 6), 380 (M^+ + 4), 378 (M^+ + 2), 376 (M^+), 297 (M^+ − 79), 218 (M^+ − 2 × 79), 139 (M^+ − 3 × 79). Anal. Calcd for $C_9H_3N_2Br_3$: C, 28.49; H, 0.79; N, 7.38. Found: C, 28.53; H, 0.81; N, 7.44.

Bromination of Compound 5. To a solution of **5** (20 mg, 0.116 mmol) in 10 ml of $CHCl_3$ was added solid NBS (50 mg, 0.281 mmol) and the reaction mixture was stirred for 36 hr. The solvent was evaporated under vacuum and the residue was chromatographed on neutral Al_2O_3 (grade III) and eluted with *n*-hexane. The first fraction afforded compound **3** (20 mg, 59%). The second fraction gave a mixture of 1-bromo-2-azacycl[3.2.2]azine-4-carboxylic acid (**9**) and its ethyl ester[9] (3 mg) as evidenced by their mass spectra: *m/e* 266 (M^+ + 2), 264 (M^+), 247 (M^+ − 17, 219 (M^+ −

45) and 294 ($M^+ + 2$), 292 (M^+), 247 ($M^+ - 45$), 219 ($M^+ - 73$), respectively.

In another separate experiment, when the reaction was run for a short period of time, the intermediate 8 was detected by ^1H NMR and mass spectrometry: ^1H NMR (see Table I); mass spectrum *m/e* 250 ($M^+ + 2$), 249 ($M^+ + 1$), 248 (M^+), 247 ($M^+ - 1$), 219 ($M^+ - 29$), 140 ($M^+ - 108$).

Bromination of Compound 6. A. With NBS in $CHCl_3$. To a solution of NBS (93 mg, 0.523 mmol) in 15 ml of $CHCl_3$, compound 6 was added in portions (50 mg, 0.269 mmol) and the mixture was stirred for 2 hr. The solution was filtered and evaporated to dryness in vacuo. Column chromatography on neutral Al_2O_3 (grade III) using *n*-hexane as the eluent gave 50 mg (62%) of compound 3.

B. With Br_2–Water. To a solution of 6 (50 mg, 0.269 mmol) in 40 ml of H_2O, Br_2 (87 mg, 0.541 mmol) was added and the mixture was stirred at room temperature for 10 min and then heated on a steam bath for 1 min. The solution was made basic with Na_2CO_3 and extracted with $CHCl_3$ (2 × 50 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was evaporated under reduced pressure. The crude product was purified by sublimation (160°, 0.2 Torr) to give 4 (82.0 mg, 80%).[10]

Formylation of 2-Azacycl[3.2.2]azine (1). A. With $POCl_3$ and DMF. To 1 (71 mg, 0.5 mmol) dissolved in 10 ml of dry DMF was added Vilsmeier reagent (0.17 g of $POCl_3$ in 1 ml of DMF) and the mixture was stirred at room temperature for 1 hr. The solution was treated with 20 ml of cold H_2O and made basic with solid Na_2CO_3. The solvent and excess DMF were removed in vacuo to give a dark solid which was chromatographed on neutral Al_2O_3 (grade III) by using *n*-hexane–chloroform (90:10) as eluent. The first fraction gave 18 mg of starting material. The second fraction afforded 1-formyl-2-azacycl[3.2.2]azine (12), a yellow solid: 30 mg (37.6%); mp 100–101°; ^1H NMR (see Table I); mass spectrum *m/e* 170 (M^+), 169 ($M^+ - 1$), 142 ($M^+ - 28$), 141 ($M^+ - 29$), 115 ($M^+ - 55$), 114 ($M^+ - 56$). Anal. Calcd for $C_{10}H_6N_2O$: C, 20.58; H, 3.52; N, 16.47; Found: C, 70.55, H, 3.46, N, 15.49.

The third fraction gave 4-formyl-2-azacycl[3.2.2]azine (5, 20 mg, 25%) as compared with an authentic sample.[1]

B. With *n*-C_4H_9Li and DMF. To a solution of 2-azacycl[3.2.2]-azine (1,70 mg, 0.49 mmol) in 15 ml of dry THF was added 0.245 ml of 2 *M* *n*-BuLi (in hexane) under a N_2 atmosphere and at 0°C. Dry DMF (36.0 mg, 0.49 mmol) was then added at once and the mixture was stirred for 1 hr, during which time the solution warmed to room temperature. The reaction mixture was treated with H_2O (20 ml) and extracted with $CHCl_3$ (2 × 50 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was removed under reduced pressure. The residue was chromatographed on neutral Al_2O_3 (grade III), using *n*-hexane as eluent. The first fraction afforded 1-butyl-2-azacycl[3.2.2]azine (13, 50 mg, 55%) as a pale fluorescing yellow liquid, identified by comparison with an authentic sample.[6] The second fraction gave starting material.

***N*-Methyl-2-azacycl[3.2.2]azinium Iodide (14).** A mixture of 2-azacycl[3.2.2]azine (1, 20 mg, 0.141 mmol) and methyl iodide (1 ml) was heated in a sealed tube on a steam bath for 15 min. The yellow solid was washed with anhydrous ethyl ether and collected by filtration. Recrystallization of the solid from ethanol gave 38 mg (95%) of burnt-yellow crystals: mp 158–159°; ^1H NMR [$(CD_3)_2SO$] δ 9.36 (s, 1 H), 8.18 (d, 1 H, J = 4.5 Hz), 8.30 (d, 1 H, J = 4.5 Hz), 8.98 (d, 1 H, J = 8.0 Hz), 8.36 (t, 3 H, J = 7.5 Hz), 8.75 (d, 1 H, J = 7.5 Hz), 4.68 (s, CH_3^-); mass spectrum *m/e* 142 ($M^+ - CH_3I$), 127 (Br^+), 115 ($M^+ - CH_3I - 27$). Anal. Calcd for $C_{10}H_9N_2I$: C, 42.24; H, 3.17, N, 9.86. Found: C, 42.13; H, 3.17; N, 9.85.

Registry No.—1, 54384-90-6; 2, 56363-23-6; 3, 56363-24-7; 4, 56363-25-8; 5, 54446-41-2; 6, 54384-89-3; 7, 56363-26-9; 8, 56363-27-0; 9, 56363-28-1; 9 Et ester, 56363-29-2; 10, 56363-30-5; 11, 56363-31-6; 12, 56363-32-7; 13, 56363-33-8; 14, 56363-34-9; NBS, 128-08-5; bromine, 7726-95-6; HNO_3, 7697-37-2; $POCl_3$, 10025-87-3; DMF, 68-12-2; *n*-C_4H_9Li, 109-72-8; methyl iodide, 74-88-4.

References and Notes

(1) O. Fuentes and W. W. Paudler, *J. Org. Chem.*, **40**, 1210 (1975).
(2) W. W. Paudler and H. G. Shin, *J. Org. Chem.*, **33**, 1638 (1968); O. Fuentes, *J. Heterocycl. Chem.*, **12**, 379 (1975).
(3) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).
(4) V. Boekelheide and R. J. Windgassen, *J. Am. Chem. Soc.*, **81**, 1459 (1959).
(5) R. A. Abramovitch and B. Vig, *Can. J. Chem.*, **41**, 1961 (1963), and earlier papers.
(6) O. Fuentes and W. W. Paudler, *J. Heterocycl. Chem.*, in press.
(7) The same product is obtained under reflux conditions.
(8) Some traces of the tribromo compound **4** were also detected.
(9) The ethyl ester is believed to be formed by an esterification reaction of the carboxylic acid and the ethanol used as stabilizing agent for $CHCl_3$.
(10) Some traces of a tetrabromo compound are formed.

Bromination Reactions of 1,5- and 1,8-Naphthyridine 1-Oxides

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The reactions of 1,5- and 1,8-naphthyridine 1-oxides with acetic anhydride in the presence of bromine have been studied in detail. The compounds formed, depending upon the reaction conditions, are the 3-bromo-, 3,6-dibromo-, and 3,7-dibromo-1,5-naphthyridines and their *N*-oxides (**2, 3, 8, 2a, 3a,** and **8a**) as well as some 7-bromo-1,5-naphthyridine 1-oxide (**7**). The 3-bromo-, 3,6-dibromo-, and their *N*-oxides (**10, 11, 10a, 11a**) are obtained from 1,8-naphthyridine 1-oxide. Along with these compounds the 1,2-dihydro-2-oxonaphthyridines as well as their 3-bromo derivatives (**4, 6, 12, 13**) along with 1,5-naphthyridine are generated. Possible mechanisms for the formation of these various reaction products are discussed.

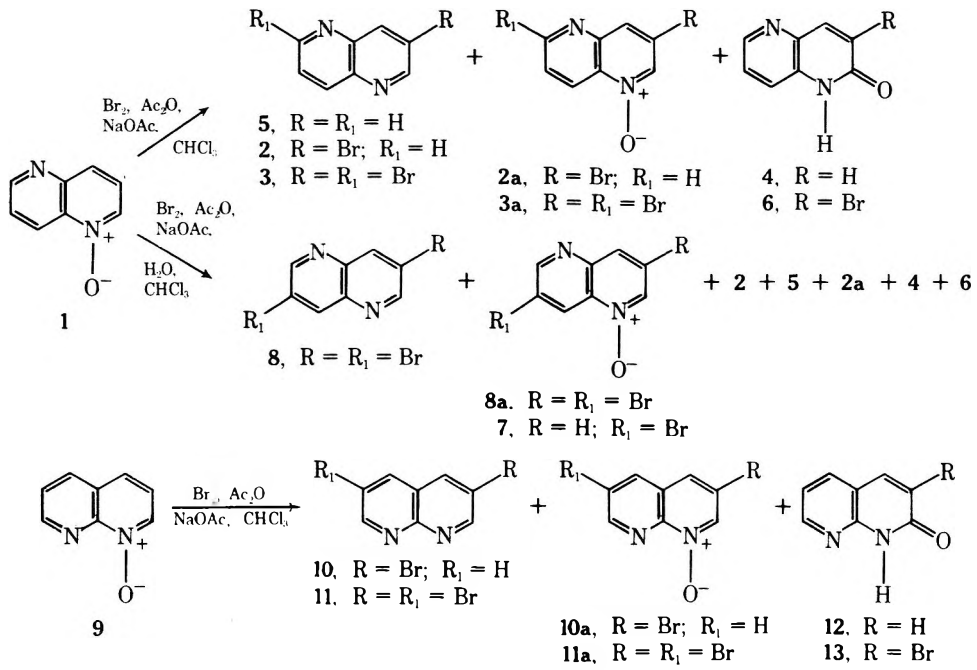
The reaction of pyridine and quinoline *N*-oxides with bromine in the presence of acetic anhydride has been reported to afford bromo derivatives resulting from substitution at positions expected to be subject to electrophilic attack. For example, quinoline *N*-oxide is reported to yield the 3,6-dibromoquinoline *N*-oxide.[1] We thought it of some interest to examine the behavior of some 1,X-naphthyridine 1-oxides under these reaction conditions and now wish to describe the results of these studies.

Results and Discussion

1,5-Naphthyridine 1-Oxide. A. Experimental Results. The reaction of 1,5-naphthyridine 1-oxide with bromine, in chloroform, and in the presence of acetic anhydride affords at least six different products. The mass spectrometrically determined molecular weights in conjunction with elemental analyses identify the compounds as a monobromo- and a dibromo-1,5-naphthyridine, a monobromo- and a dibromo-1,5-naphthyridine 1-oxide, 1,2-dihydro-2-oxo-1,5-naphthyridine, as well as its 3-bromo derivative. In addition, traces of 1,5-naphthyridine (**5**) are occasionally obtained.

The monobromo-1,5-naphthyridine is identified as the 3-bromo derivative **2** by a comparison with an authentic sample.[2] The ^1H NMR spectrum of the monobromo *N*-oxide identifies it as the 3-bromo derivative **2a**. The other

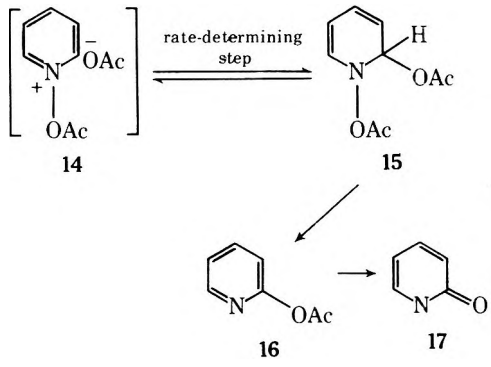
Scheme I



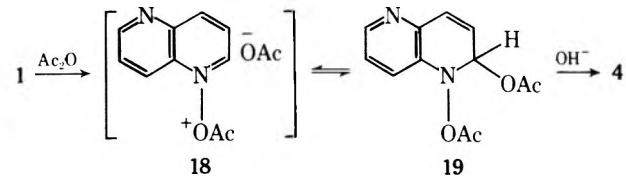
three bromine-containing products are the 3,6-dibromo-1,5-naphthyridine (**3**), its 1-oxide (**3a**), and the 3-bromo-1,2-dihydro-2-oxo-1,5-naphthyridine (**6**), as shown by their ^{1}H NMR spectra. In order to gain an understanding of this reaction variations in reaction conditions on product distributions were examined (see Table I).

In the presence of either small amounts of water (expt 4 and 5, Table I) or when 1,5-naphthyridine *N*-oxide is treated with a mixture of bromine, aqueous hydrobromic acid, and acetic acid, there are changes in some of the types of compounds formed in comparison to the "original" reaction conditions (expt 1, Table I).

B. Formation of Brominated *N*-Oxides. The mechanism of the reaction of pyridine *N*-oxide with acetic anhydride to yield 2-pyridone is well established.[3]



Since the reaction of 1,5-naphthyridine 1-oxide (**1**), under similar conditions, yields 1,2-dihydro-2-oxo-1,5-naphthyridine (**4**), we suggest that the first step in the bromination involves formation of the ion pair, **18**, which slowly collapses to the 1,2-dihydro compound, **19**. The lat-



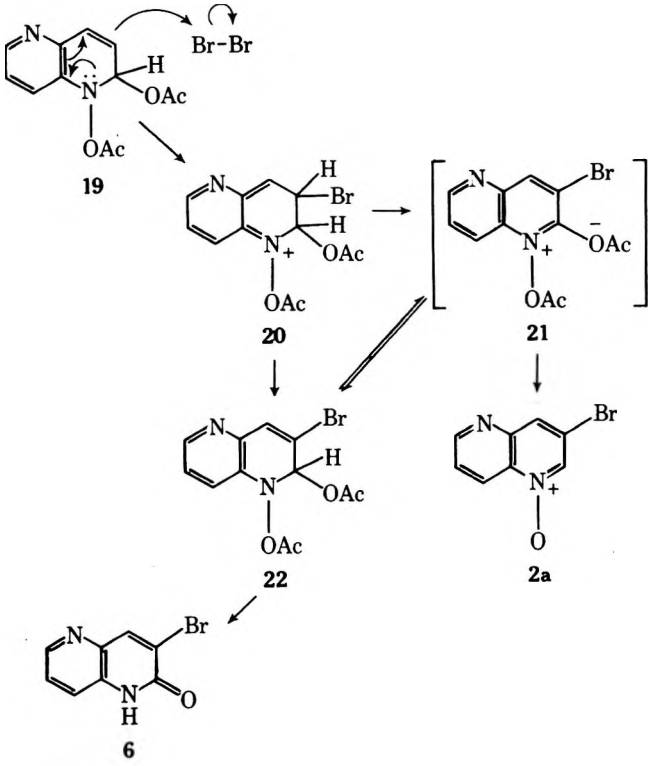
ter can react with bromine to give intermediate **20**, which may decay by two different paths. It may lose acetic acid to form the ion pair **21** or lose a hydrogen to form the dihydro compound, **22**. Structures **21** and **22** are most likely in equilibrium with one another, as are structures **18** and **19**. The ion pair **21** yields 3-bromo-1,5-naphthyridine 1-oxide (**2a**) and compound **22** affords 3-bromo-1,2-dihydro-2-oxo-1,5-naphthyridine (**6**) upon work-up with base (see Scheme II). While structure **21** can lead only to product, compound **22** can react with another molecule of bromine to give intermediate **23**, which may give either the ion pair **24** or the dihydro compound **25**. Compound **24** will yield 3,6-dibromo-1,5-naphthyridine 1-oxide (**3a**) and compound **22** will afford 3,6-dibromo-1,2-dihydro-2-oxo-1,5-naphthyridine (**23**) during work-up with base. The latter is more than likely present in trace amounts (see Scheme III).

Table I
Products and Percentage Yields for Various Bromination[a] Reactions of 1,5- and 1,8-Naphthyridine 1-Oxides

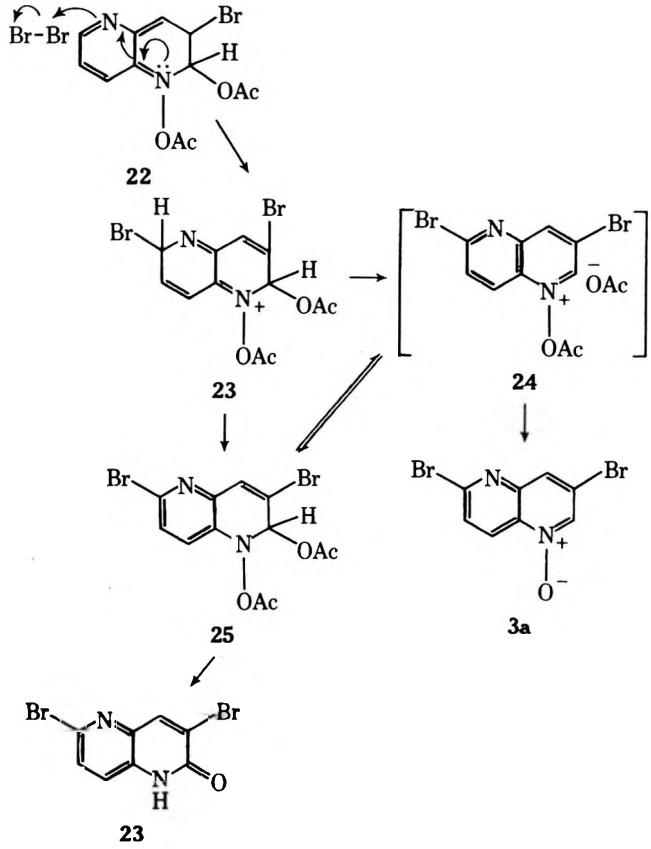
	Compd																
Expt	3	8	11	2	10	5	3a	8a	11a	2a	7	10a	1	6	13	4	12
1	2.1			2.8			3.6			5.5				6.2		61.0	
2	1.9			21.3		12.4	4.4			10.5				4.7		36.0	
3	1.0			3.8		1.8	4.1			41.5				3.9		33.8	
4		1.6		4.2		2.7		1.0		2.3	1.3		10.4	10.0		55.0	
5		1.0		2.9		3.5					7.1		61.1				
6			6.6		12.6				14.8			4.1			8.4		51.1
7									7.9			39.0			4.7		37.2

[a] Compounds obtained in less than 1.0% yield are not described.

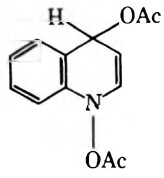
Scheme II



Scheme III



In the case of quinoline *N*-oxide the reaction is said to proceed via the 1,4-dihydro intermediate **26**.[1,4] However, since the reaction of 1,5-naphthyridine 1-oxide (**1**) with acetic anhydride yields exclusively 1,2-dihydro-2-oxo-1,5-naphthyridine (**4**), there is no justification for invoking a 1,4-dihydro intermediate in the present instance.



26

C. Formation of Deoxygenated Products. The formation of compounds **2** and **3** were initially thought to result from nucleophilic attack of bromide ion at the 3 position, with concomitant loss of acetate ion at the 1 position, followed by elimination of acetic acid. Abramovitch and coworkers[5] have noted that pyridine *N*-oxides react with imi-

Table II
^{1}H NMR Parameters and Melting Points of Some 1,5- and 1,8-Naphthyridine Derivatives[a]

Compd (no., mp, °C)	Chemical shifts, δ, ppm							Coupling constants, Hz								
	H_2	H_3	H_4	H_5	H_6	H_7	H_8	J_{23}	J_{24}	J_{34}	J_{56}	J_{57}	J_{58}	J_{67}	J_{68}	J_{78}
1,5-Naphthyridines																
3-Bromo 1-oxide (2a, 174–175°)	8.54		8.08		8.93	7.57	8.86		1.5					4.0	1.5	9.0
3,6-Dibromo 1-oxide (3a, 175–176.5°)	8.56		8.02			7.74	8.68		1.5							8.8
3,6-Dibromo (3, 192–193°)	8.98		8.49			7.73	8.21		1.8							9.0
3,7-Dibromo 1-oxide (8a, 207–208°)	8.60		8.10		9.02		8.97		1.8						2.0	
7-Bromo 1-oxide (7, 161–163°)	8.49	7.50	7.93		9.16		8.97	6.0	1.5	9.0					2.0	
1,8-Naphthyridines																
3-Bromo 1-oxide (10a, 174–176°)	8.77		7.81	8.21	7.64	9.02			2.0			1.8		5.0		
3,6-Dibromo 1-oxide (11a, 273–275°)[b]	9.39		8.83	8.91		9.29			2.0		7.8	1.8				
3-Bromo-1,2-dihydro-2-oxo (13, 304–306°)[b]			8.09	8.01	7.25	8.38						2.0		5.8		

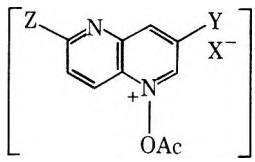
[a] Unless otherwise stated, spectra are in dilute solutions of $CDCl_3$; all compounds gave correct elemental analyses and mass spectral molecular weights. Compounds 3a and 11a were purified by recrystallization from methanol, compound 13 from water. The remaining compounds were purified by vacuum sublimation. [b] Deuterotrifluoroacetic acid solution.

doyl chlorides to form, among other products, 3-chloropyridines via nucleophilic attack of chloride ion at C-3.

When 1,5-naphthyridine 1-oxide (1) is heated with acetic anhydride either in the presence or absence of NaCl or LiCl, the naphthyridone 4 is the only product. When NaBr or LiBr are used, mixtures of the naphthyridone 4 and 1,5-naphthyridine (5) are obtained.

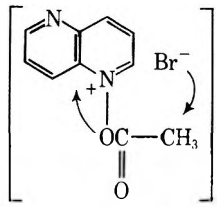
On the other hand, addition of either HI or HBr to a mixture of 1 in acetic anhydride yields only 1,5-naphthyridine (5). When either compounds 1, **2a**, or **3a** are heated with acetyl bromide alone, deoxygenation was the only reaction taking place. Acetyl chloride has nc effect upon compounds 1, **2a**, or **3a**.

Since bromine reacts with the ethanol preservative present in commercial chloroform to form hydrogen bromide, an excess of bromide ion is also present in the initial experiment. When the reaction is carried out in ethanol-free chloroform and without added bromide ion, a marked decrease in the ratio of deoxygenated to N-oxidized products is observed (see Table I). These various observations can be accounted for by invoking the initial formation of an ion pair such as **27**, **28**, or **29**. When X is an acetate ion,



27, Y = Z = H
28, Y = Br; Z = H
29, Y = Z = Br

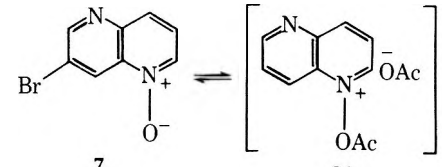
1,2-dihydro-2-oxo-1,5-naphthyridine (4) is ultimately formed. A chloride ion in the ion pair (X = Cl) inhibits this reaction and the 1,5-naphthyridine 1-oxide is recovered. On the other hand, when X^- is a bromide or iodide ion, deoxygenation takes place.



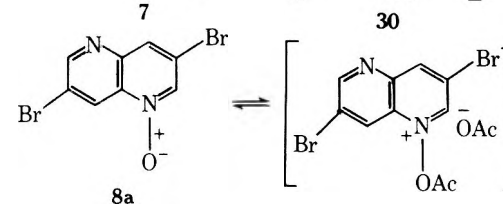
A similar nucleophilic attack has been proposed for one of the paths by which *N*-methoxypyridinium ion reacts with nucleophiles.[6] It has been shown that reaction by this path diminished with decreasing nucleophilicity of the attacking species. Since bromide and iodide ions are certainly better nucleophiles than chloride ion, this may explain the absence of deoxygenated products in the presence of the latter ion in the 1,5-naphthyridine 1-oxide reactions.

D. Formation of 7-Brominated Products. As mentioned earlier, the presence of water changes the site of substitution in the nonoxidized ring. This change is perhaps best explained by an examination of the results of expt 4 and 5. When 1,5-naphthyridine 1-oxide (1) is refluxed with acetic anhydride in chloroform for 12 hr, treated with water and a catalytic amount of HCl, and further refluxed for an additional 12 hr, starting material was quantitatively recovered. Therefore, under these conditions, intermediates **18** and **19** appear to revert back to 1,5-naphthyridine 1-oxide (1). When 3-bromo-1,5-naphthyridine 1-oxide (**2a**) is subjected to the same conditions, it is also recovered unchanged.

In light of these results we suggest the following explanation. On refluxing with acetic anhydride, structures **18** and **19** are formed. The simultaneous addition of bromine and water results in reaction of **19** by two different paths. Compound **19** may either revert back to the ion pair **18** or be brominated to form intermediate **20**. If collapse of **20** to **22** is slow, the conversion of **20** to **21** and subsequently to **2a** would predominate. This would explain the absence of any 3,6-dibrominated products. The acetic acid, hydrogen bromide, and bromine, a mixture known to be a more powerful brominating agent than bromine itself, will electrophilically brominate 1 and **2a** at C-7 to form 7-bromo-1,5-naphthyridine 1-oxide (**7a**) and 3,7-dibromo-1,5-naphthyridine 1-oxide (**8a**). In fact, when 1,5-naphthyridine 1-oxide (**1**) is treated with bromine and pyridine in chloroform, compound **7a** is obtained, albeit in low yield, as the sole product.[7] When 1,5-naphthyridine 1-oxide is treated with bromine and aqueous hydrogen bromide in acetic acid, the only products isolated are polybrominated ones. Since compounds 1 and **2a** are in equilibrium with ion pairs **18** and **21**, it is reasonable to suggest that a similar equilibrium exists between compounds **7** and **30** and compounds **8a** and **31**, and that deoxygenation occurs through these intermediates.

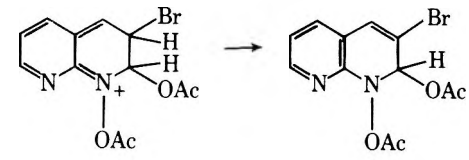


7 **30**



8a **31**

1,8-Naphthyridine 1-Oxide. Bromination of 1,8-naphthyridine 1-oxide (**9**) with bromine in chloroform in the presence of acetic anhydride follows essentially the same paths as those for 1,5-naphthyridine 1-oxide (1). A few differences in product ratios do, however, merit comment. It is interesting to note that the ratio of monobrominated to dibrominated product decreases in the 1,8-naphthyridine 1-oxide (**9**) instance. If, as suggested earlier, the collapse of **20** to **22** is slow relative to bromination, one would expect to see this effect on going from 1,5- to 1,8-naphthyridine 1-oxide. The collapse of **32** to **33** should be faster than the



32 **33**

collapse of **20** to **22** because of removal of the lone pair–N-acetoxy repulsion. This should lead to the formation of increased amounts of dibrominated products relative to monobrominated products and a corresponding decrease in the ratio (**10** + **10a**/**11** + **11a**).

Summary

One of the nonmechanistic goals of this study was to attempt to prepare the 3-bromo-1,5- and -1,8-naphthyridine 1-oxides, which were needed for another study.

A comparison of the yields of these compounds, 5 and 4.1%, respectively, obtained under the "original" experimental conditions, with those obtained, 41.5 and 39.0%, by the reaction conditions modified on the basis of this mech-

Table III
Reaction Conditions for Bromination Reactions

Expt	1,5-Naphthyridine 1-oxide, g	1,8-Naphthyridine 1-oxide, g	Commercial chloroform, ml	Ethanol-free chloroform, ml	Acetic anhydride, g	Bromine, g	Sodium acetate, g	Sodium acetate trihydrate, g	Sodium bromide, g	Water, g	Acetic acid, g
1	1.0		50		1.4	3.3	1.65				
2	1.0		50		1.4	3.3	1.65		2.12		
3	1.0			50	1.4	3.3	1.65				
4	2.0		100		2.8	6.6		3.7			
5	1.0		50			3.3	1.65			0.86	1.64
6		1.0	50		1.4	3.3	1.65				
7		1.0			1.4	3.3	1.65				

anistic study (expt 3 and 7) shows that this goal has been achieved.

Experimental Section

Melting points are uncorrected. Mass spectral analyses were performed on a Hitachi Perkin-Elmer RMU-6M spectrometer, ionizing voltage of 80 eV. ^1H NMR data were obtained with a Varian Associates HA-100 spectrometer.

Reagents. The "commercial" chloroform used was obtained from Fischer Scientific Co. and contained 0.75% ethanol. Ethanol-free chloroform was prepared by washing "commercial" chloroform with sulfuric acid and water, drying over K_2CO_3, and distillation. Unless stated otherwise, "commercial" chloroform was used. All other reagents were used as supplied by the manufactures.

Reaction of 1,5-Naphthyridine 1-Oxide (1) with Acetic Anhydride. A solution of 1,5-naphthyridine 1-oxide (1.0 g, 6.85 mmol) and acetic anhydride (1.4 g, 13.7 mmol) in $CHCl_3$ (50 ml) was refluxed for 16 hr, and cooled, and the $CHCl_3$ was removed in vacuo. The residue was dissolved in 10% aqueous NaOH (50 ml) and the aqueous solution was extracted continuously (24 hr) with $CHCl_3$. Evaporation of the dried ($MgSO_4$) $CHCl_3$ extracts and sublimation (110°, 0.1 mm) of the residue gave 1,2-dihydro-2-oxo-1,5-naphthyridine (4, 622 mg, 62.2%), mp 254–255° (lit.[9] mp 256°). Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.11; N, 19.18. Found: C, 66.18; H, 4.18; N, 19.12.

General Bromination Procedure. The following general procedure was used in expt 1–7. Reagents employed and their amounts are listed in Table III.

A solution of the naphthyridine *N*-oxide and acetic anhydride in 50 ml of $CHCl_3$ was refluxed for 12 hr and cooled, and sodium acetate, bromine, and any additional reagents (see Table III) were added. The resulting suspension was stirred at reflux for an additional 48 hr, cooled, and shaken with 10% aqueous K_2CO_3–Na_2SO_3. The aqueous layer was then adjusted to pH 7 and continuously extracted with chloroform for 24 hr. The combined $CHCl_3$ solutions were dried over $MgSO_4$ and filtered and the filtrate was evaporated to dryness. The residue was then chromatographed on neutral alumina (Brockman grade III).

In the 1,5-naphthyridine *N*-oxide experiments, the following sequence of eluents was used: 100 ml of benzene, 100 ml of 1:3 chloroform–benzene, 100 ml of 1:1 chloroform–benzene, 100 ml of 3:1 chloroform–benzene, 100 ml of chloroform, 100 ml of ethanol, 100 ml of 1:19 acetic acid–ethanol.

In the 1,8-naphthyridine *N*-oxide experiments, the sequence of eluents was 100 ml of carbon tetrachloride, 100 ml of 1:4 chloroform–carbon tetrachloride, 100 ml of 3:7 chloroform–carbon tetrachloride, 100 ml of 1:1 chloroform–carbon tetrachloride, 100 ml of chloroform, 100 ml of 1:9 methanol–chloroform, 100 ml of ethanol, 100 ml of 1:9 acetic acid–ethanol.

In each case 10-ml fractions were collected and their contents ascertained by TLC. The products and amounts of each experiment are listed in Table I and the analytical data in Table II.

Reaction of 1,5-Naphthyridine 1-Oxide (1) with Acetic Anhydride and Inorganic Halides. The reactions of 1,5-naphthyridine 1-oxide with sodium, lithium, or hydrogen bromide and also with acidified potassium iodide were carried out according to the following general procedure.

A solution of 1,5-naphthyridine 1-oxide (1, 1.0 g, 6.85 mmol) and acetic anhydride (1.4 g, 13.7 mmol) in 50 ml of $CHCl_3$ was refluxed for 12 hr and cooled, and any additional reagents were added. The stirred suspension was refluxed for a further 12 hr, cooled, and shaken with 10% aqueous NaOH (50 ml). The aqueous layer was extracted with $CHCl_3$ (5 × 25 ml). The $CHCl_3$ extracts were combined and evaporated to dryness and the residue was chromatographed on neutral alumina (Brockman Grade III). Elution with ether (300 ml) afforded any 1,5-naphthyridine present. Subsequent elution with $CHCl_3$ (300 ml) afforded any 1,5-naphthyridine 1-oxide present. Neutralization of the aqueous solution followed by continuous extraction with $CHCl_3$ and evaporation of the $CHCl_3$ extracts to dryness afforded any 1,2-dihydro-2-oxo-1,5-naphthyridine present. The identities of all products were established by comparisons with authentic samples.

(a) The reaction of 1 with acetic anhydride and NaBr (1.4 g, 13.6 mmol) afforded 1,5-naphthyridine (**5**, 0.06 g, 7%), 1,5-naphthyridine 1-oxide (1, 0.44 g, 44%), and 1,2-dihydro-2-oxo-1,5-naphthyridine (4, 0.3 g, 30%).

(b) The reaction of 1 with acetic anhydride and LiBr (1.2 g, 13.6 mmol) afforded 1,5-naphthyridine (**5**, 0.08 g, 9%), 1,5-naphthyridine 1-oxide (1, 0.418 g, 41%), and 1,2-dihydro-2-oxo-1,5-naphthyridine (4, 0.29 g, 29%).

(c) The reaction of 1 with acetic anhydride and excess anhydrous HBr afforded 1,5-naphthyridine (**5**, 0.19 g, 21.2%) and 1,5-naphthyridine 1-oxide (1, 0.73 g, 73%).

(d) The reaction of 1 with acetic anhydride, KI (2.28 g, 13.7 mmol), and 98% H_2SO_4 (0.2 ml) afforded 1,5-naphthyridine (**5**, 0.23 g, 26.0%) and 1,5-naphthyridine 1-oxide (**1**, 0.64 g, 64.0%).

Reaction of 1,5-Naphthyridine 1-Oxide (1) with Hydrogen Bromide. Anhydrous HBr was bubbled into a solution of 1,5-naphthyridine 1-oxide (1.0 g, 6.85 mmol) in $CHCl_3$ (50 ml) until the solution was saturated. The resulting suspension was stirred at reflux for 48 hr, cooled, and shaken with 10% aqueous NaOH (100 ml). The aqueous layer was extracted with $CHCl_3$ (5 × 25 ml) and the combined $CHCl_3$ solutions dried over $MgSO_4$. The $CHCl_3$ was removed to afford a quantitative recovery of starting material (1).

Reactions with Acetyl Halides. Compounds **1**, **2a**, and **3a** were treated with acetyl bromide or acetyl chloride according to the following procedure.

To a solution of the *N*-oxide (3.4 mmol) in alcohol-free $CHCl_3$ (50 ml) was added the acetyl halide (3.6 mmol) and the resulting suspension was stirred at reflux for 48 hr. The cooled reaction mixture was washed with 10% aqueous Na_2CO_3 (25 ml) and dried over $MgSO_4$. After evaporation of the $CHCl_3$, the residue was chromatographed on neutral alumina (Brockman Grade III). Elution with ether (300 ml) afforded any deoxygenated product and subsequent elution with $CHCl_3$ afforded any unreacted *N*-oxide.

(a) The reaction of 1 (0.5 g), **2a** (0.76 g), or **3a** (1.04 g) with acetyl chloride (0.28 g) afforded only starting material, **1**, **2a**, and **3a**, respectively.

(b) The reaction of 1 (0.5 g) with acetyl bromide (0.45 g) afforded 1,5-naphthyridine (**5**, 0.093 g, 21%) and starting material, **1**.

(c) The reaction of **2a** (0.76 g) with acetyl bromide (0.45 g) afforded 3-bromo-1,5-naphthyridine (**2**, 0.42 g, 59%) and starting material, **2a**.

(d) The reaction of **3a** (1.04 g) with acetyl bromide (0.45 g) afforded 3,6-dibromo-1,5-naphthyridine (**3**, 0.71 g, 72%) and starting material, **3a**.

Bromination of 1,5-Naphthyridine 1-Oxide (1) in Aqueous Acetic Acid. A solution of 1,5-naphthyridine 1-oxide (**1**, 1.0 g, 6.85 mmol), Br_2 (3.3 g, 22.55 mmol), and 48% aqueous HBr (0.1 ml) in 60% aqueous acetic acid (50 ml) was stirred at reflux for 24 hr and cooled, and the solvent was removed under an aspirator vacuum. The residue was suspended in 5% aqueous NaOAc (150 ml) and continuously extracted with $CHCl_3$ (24 hr). The precipitate formed in the $CHCl_3$ extract was filtered and the $CHCl_3$ filtrate was passed over neutral alumina (Brockman Grade III). The alumina was then washed with methanol (300 ml). The $CHCl_3$ eluate was evaporated to dryness. Mass spectrometric analysis of the residue (274 mg) gave a molecular weight of 415, indicating the presence of

three bromine atoms. The precipitate (520 mg) from the $CHCl_3$ extracts and the residue (90 mg) from the methanol eluate were shown, by TLC, to be identical. Mass spectrometric analysis gave a molecular weight of 386 indicating the presence of three bromine atoms. ^1H NMR analysis was not possible because of insufficient solubility of the two compounds in any of the common NMR solvents.

Reaction of 1,5-Naphthyridine 1-Oxide (1) with Acetic Anhydride and Dilute HCl. A solution of 1,5-naphthyridine 1-oxide (1.0 g, 6.85 mmol) and acetic anhydride (1.4 g, 13.7 mmol) in alcohol-free $CHCl_3$ (50 ml) was refluxed for 12 hr and cooled, and dilute HCl (1 ml of a 3.37% solution) was added. The solution was stirred at reflux for an additional 12 hr, cooled, and dried over Na_2CO_3. Removal of the $CHCl_3$ gave only starting material (0.98 g, 98%).

Registry No.—**1**, 27305-48-2; **2a**, 56247-21-3; **3**, 56247-22-4; **3a**, 56247-23-5; **4**, 10261-82-2; **7**, 56247-24-6; **8a**, 56247-25-7; **9**, 27284-59-9; **10a**, 56247-26-8; **11a**, 56247-27-9; **13**, 56247-28-0; acetic anhydride, 108-24-7; NaBr, 7647-15-6; LiBr, 7550-35-8; HBr, 10035-10-6; KI, 7681-11-0; acetyl bromide, 506-96-7; acetyl chloride, 75-36-5; Br_2, 7726-95-6; HCl, 7647-01-0.

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(4) For a discussion of these mechanisms see A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, N.Y. 1971, pp 231–251.
(5) R. A. Abramovitch and G. M. Singer, *J. Am. Chem. Soc.*, **91**, 5672 (1969).
(6) A. R. Katritzky and E. Lunt, *Tetrahedron*, **25**, 4291 (1969).
(7) We have already shown that Eisch bromination of 1,5-naphthyridine 1-oxide affords only, not unexpectedly, 7-bromo-1,5-naphthyridine 1-oxide (D. Pokorny, Ph D. Thesis, Ohio University, Athens, Ohio, 1972).

The Effect of Ring Size on Hydrogenation of Cyclic Allylic Alcohols

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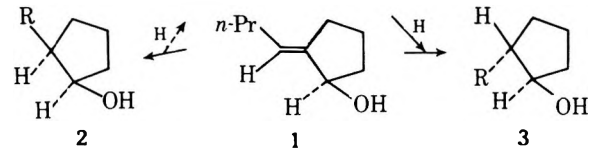
2-Butylidenecyclopentanone, 2-butylidenecyclohexanone, and 2-butylidenecycloheptanone were prepared by the Reformatsky reaction of *n*-butyraldehyde with 2-bromocyclopentanone, 2-bromocyclohexanone enol acetate, and 2-bromocycloheptanone, respectively. Reduction of 2-butylidenecyclanones with lithium aluminum hydride gave the corresponding allylic cyclanols which were characterized by their mass spectra. On catalytic hydrogenation over a variety of catalysts, the products were *cis*- and *trans*-2-butylcyclanols as well as 2-butylcyclanones. The stereochemistry of the epimeric 2-butylcyclanols was assigned by hydroxyl proton splitting in Me_2SO as observed by NMR. Alternatively, 2-butylidenecyclanones could be hydrogenated with Pd/C to 2-butylcyclanones, and reduced by lithium aluminum hydride or Raney Ni hydrogenation to *cis*- and *trans*-2-butylcyclanols.

Although product stereochemistry resulting from catalytic hydrogenation of organic compounds has been attributed to direct transfer of hydrogen,[2] compounds containing polar substituents, notably hydroxyl group, near a reducible double bond are known to exert special directing effects[3-5] in contrast with the well-known case in which the bulk of the nearby substituents is the controlling factor and imposes trans stereochemistry by sterically blocking cis approach to the catalyst surface.[6] In such instances presumably some type of attractive interaction has bound the hydroxyl group to the catalyst surface during reduction so as to enforce addition of hydrogen from the same side in spite of group's hindrance.

From their results Mitsui et al. concluded that in the case of Raney Ni the directive effect of the hydroxyl group was very efficient, but that it was small over Pd.[4d] They suggested that the difference in the affinity of nickel and palladium for the oxygen atom controlled not only the stereochemistry of the hydrogenolysis of benzyl-type alcohols, but also that of the hydrogenation of the double bond of allyl-type alcohols. To clarify the effects of hydroxyl group and also the effect of change in ring size on the stereochemistry of hydrogenation of cyclic allylic alcohols over a number of catalysts, prompted an investigation of five-, six-, and seven-membered 2-alkylidenecyclanols.

Results and Discussion

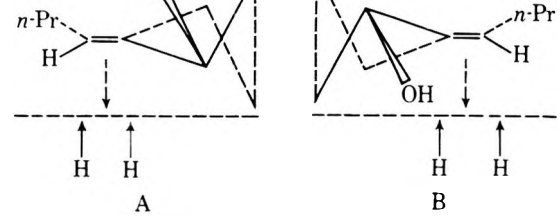
2-Butylidenecyclopentanol (1). Calculations on cyclopentane derivatives containing sp^2 hybridized atoms such as methylenecyclopentane and cyclopentanone suggest that such molecules exist in the half-chair form with the maximum puckering occurring at carbon atoms 3 and 4, i.e., away from the sp^2 hybridized atom.[7] In the hydrogenation of **1** over Raney nickel, a catalyst of low isomerizing ability,[8] 96% **3**, is obtained.



2 **1** **3**

R = *n*-Bu

From models of **1** it is found that either side of the double bond can be presented in an equally planar conformation to the catalyst. Thus steric factors cannot be responsible for this overwhelmingly one-sided addition of hydrogen. The two possible adsorption conformations of the unsaturated alcohol (A and B) differ only in that in one the



A B

OH is directed away from the catalyst surface (A), while in the other it is directed toward it (B). It is suggested that the latter is the preferred adsorption conformation, since the molecule may be adsorbed by interaction of the lone

Table I
Hydrogenation of 2-Butylidenecyclopentanol[a]

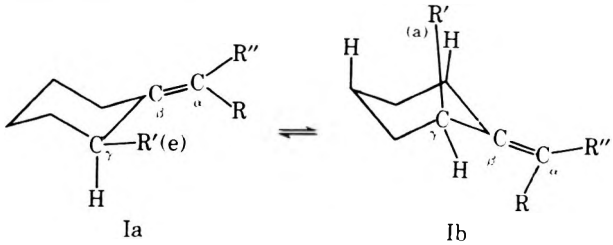
Catalyst	Conditions	2-Butylcyclopentanone[b,d]	trans-2-Butylcyclopentanol[c,d]
BDH[e] Raney nickel	95–70 atm, 16–18°, 6 hr	2	96
W_3 Raney nickel	68–55 atm, 18–24°, 6 hr	1	91
Ni_2B P-1	58–48 atm, 20–28°, 6 hr		73
Ru/C	10 atm, 2 hr	2	69
Pt/C	10 atm, 2 hr	5	55
Rh/C	10 atm, 2 hr	12	64
Pd/alumina	10 atm, 2 hr	50	66
Pd/C	10 atm, 2 hr	60	66
Pd black	10 atm, 2 hr	66	57

[a] 2-Butylidenecyclopentanol was hydrogenated over various catalysts at 10 atm pressure and room temperature for 2 hr (except Raney nickel and nickel boride catalysts, for which higher pressures and longer times were necessary). Product compositions were determined by GLC on a Carbowax column. [b] Percent of total chromatographic area. [c] Percent *trans*-2-butylcyclopentanol formed in various reductions. [d] For relative response of components see relative response of ketones and alcohols (of argon ionization detector).[9] [e] Refers to stabilized Raney nickel purchased from British Drug House.

pairs of the oxygen, as well as π electrons of the double bond with the catalyst. If it is accepted that hydrogen adds cis from the catalyst surface then addition of hydrogen to this adsorption conformation will give the trans alcohol. The alternative adsorption conformation is presumably less favored since adsorption can take place only through the double bond. Results of hydrogenation of 1 over a number of catalysts are presented (Table I).

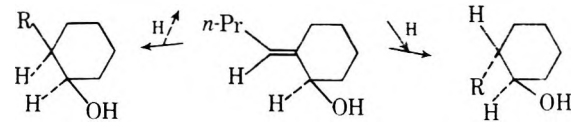
The isomerization of 1 over palladium to 13 as the main product is not surprising since endocyclic systems are almost always of lower energy than the semicyclic systems. Formation of 91% 3 can be attributed to a freshly prepared Raney nickel catalyst, which has not been deactivated by the addition of acetic acid promoting double bond migration in addition to hydrogenation.[10] The results are in good agreement with the isomerizing ability of the catalysts having the sequence Pt > Ru > Ni_2B > Ni rather than a decreasing affinity of the catalysts for adsorption through the hydroxyl group.[4e] In cases of Ni, Ni_2B, Ru/C, and Rh/C the trans isomer predominates indicating preferential adsorption of the allylic alcohol with the hydroxyl group directed toward the catalyst surface.

2-Butylidenecyclohexanol (4). An aspect of steric hindrance associated with substituted allylic groups in conformers (Ia and Ib) of I has been considered.[11]



Ia Ib

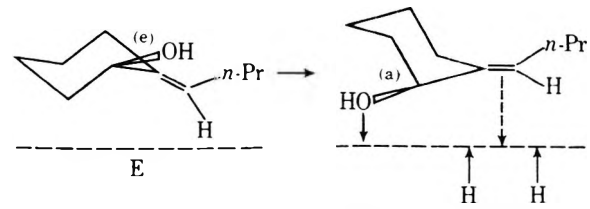
From models of Ia it is apparent that even when R′ and R are only moderate in size they will interfere with each other drastically, in fact more so than if they were 1,3 diaxially related in a cyclohexane ring. Barring a facile rearrangement of the double bond, relief of this strain can be attained most easily by conformational inversion to Ib. If R and R′ are small, the equilibrium should lie to the left. If R and R′ are medium or large in size it should lie to the right.[12] Thus if R = H and R′ = OH in the conformer Ia the strain present is that due to the interaction of C_γ equatorial OH and C_α H only, whereas in the conformer Ib the strain present is that due to the interaction of OH with two axial hydrogen atoms (two 1,3-diaxial OH–H interactions). To a first approximation it is more likely that I exists predominantly as conformer Ia, with the ring substituent equatorial.[3c] Formation of 61% 6 over Raney nickel implies



5 4 6

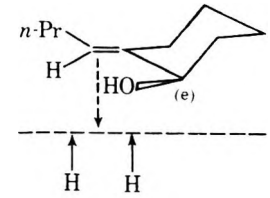
R = *n*-Bu

that the hydroxyl group is predominantly in an axial position and is directed toward the catalyst surface (C) to give the trans product from this adsorption conformation. From models of 4, with the OH group equatorial, the only conformation in which the double bond is presentable in a planar manner to the catalyst surface is that shown (D). In this conformation the OH is less favorably placed with respect to the surface for interaction to occur through the lone pairs of the oxygen. Since we get only 39% of 5, it is suggested that as the molecule approaches the catalyst surface, owing to the directing effect of the OH group, a conformational inversion takes place (E); one chair form flips into the other chair form (C). This conformation is preferred since adsorption can take place through the OH group and π electrons of the double bond. Thus, as in the case of 1, the OH group seems most probably to have a directing effect.



Preferred adsorption conformation

C

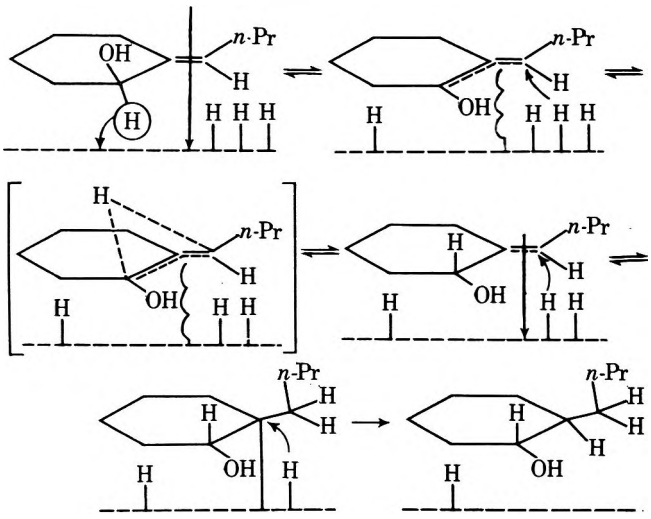


D

Although steric interactions are the most obvious aspects of the mechanism of hydrogenation, another possible explanation could be the existence of a [1,3]-sigmatropic hydrogen shift[13] (Scheme I). The occurrence of such a shift could lead to more trans product than expected from purely steric considerations. Results of hydrogenation of 4 over a number of catalysts are presented (Table II).

Over palladium there is an appreciable amount of isomerization product. Though various catalysts differ little in stereoselectivity, the stereoselectivity of the catalysts follows the sequence W_3 Raney Ni > Rh/C > Pt/C > Ru/C >

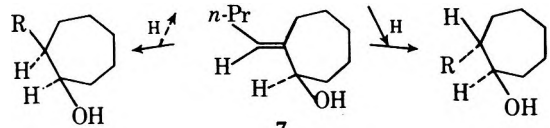
Scheme I



Ni_2B. The sequence is the reverse of that observed in 2-isopropylidene-, 2-cyclopentylidenecyclopentanol,[4e] and **1**, except over Raney nickel.

2-Butylidenecycloheptanol (7). From models the most comfortable location for the carbonyl group in cycloheptanone seemed to be at C-1, C-2, or C-7.[14] The strain appears rather small for any of these possibilities and it seems likely that the compound exists as a conformational mixture. From a study of the cyanohydrin dissociation constants of the methyl-substituted cycloheptanones, it was concluded that the cycloheptanone ring exists in a flexible-chair conformation.[15] There would seem to be little difference in the energies of the twist-chair and regular-chair conformation for cycloheptanone.

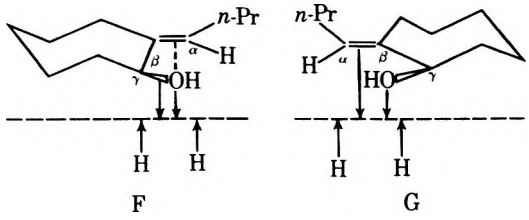
From molecular models of **7** two adsorption conformations (F and G) having minimum nonbonded interactions are possible, in which either side of the double bond can be presented in a planar conformation to the catalyst. In both



8 **7** R = *n*-Bu **9**

conformations the OH can be equally favorably placed with respect to the surface for interaction to occur through the lone pairs of oxygen.

However, the two adsorption conformations in the regular chair form differ only in that in one the OH is quasi-axial (F), and there is a distance of 1.95 Å between the C_α H and C_γ OH, while in the other the OH is quasi-equatorial (G), and there is a distance of 1.45 Å between the C_α H and C_γ OH. However, the C_α–H and C_γ–OH interactions in the two conformations can be modified in the twist-chair conformation. Since 74% **9** is obtained over Raney nickel, this suggests that the adsorption conformation (F) is the more favorable, since by addition of hydrogen cis from the catalyst surface this will give the trans alcohol.



F G

Table II
Hydrogenation of 2-Butylidenecyclohexanol[a]

Catalyst	Conditions	2-Butylcyclohexanone[b,d]	*trans*-2-Butylcyclohexanol[c,d]
W_3 Raney nickel	60–55 atm, 13–21°, 6 hr		61
Rh/C	10 atm, 2 hr	1	57
Pt/C	10 atm, 2 hr		53
Ru/C	10 atm, 2 hr		50
Ni_2B P-1	95–60 atm, 24–27°, 6 hr	1	47
Pd/C	10 atm, 2 hr	12	69
Pd black	10 atm, 2 hr	23	63

[a] 2-Butylidenecyclohexanol was hydrogenated over various catalysts at 10 atm pressure and room temperature for 2 hr (except Raney nickel and nickel boride catalysts, for which higher pressures and longer times were necessary). Product compositions were determined on a polyethylene glycol 400 column. [b] Percent of total chromatographic area. [c] Percent *trans*-2-butylcyclohexanol formed in various reductions. [d] For relative response of components see relative response of ketones and alcohols (of argon ionization detector).[9]

Table III
Hydrogenation of 2-Butylidenecycloheptanol[a]

Catalyst	Conditions	2-Butylcycloheptanone[b,d]	*trans*-2-Butylcycloheptanol[c,d]
W_3 Raney nickel	80–72 atm, 20–28°, 6 hr	2	74
Ni_2B P-1	50–40 atm, 19–21°, 6 hr	2	49
Ru/C	10 atm, 2 hr	4	55
Pt/C	10 atm, 2 hr	4	48
Rh/C	10 atm, 2 hr	16	55
Pd/C	10 atm, 2 hr	55	45
Pd black	10 atm, 2 hr	55	26

[a] 2-Butylidenecycloheptanol was hydrogenated over various catalysts at 10 atm pressure and room temperature for 2 hr (except Raney nickel and nickel boride catalysts, for which higher pressures and longer times were necessary). Product compositions were determined on polyethylene glycol 400 and polyethylene glycol 600 columns. [b] Percent of total chromatographic area. [c] Percent *trans*-2-butylcycloheptanol formed in various reductions. [d] For relative response of components see relative response of ketones and alcohols (of argon ionization detector).[9]

It seems difficult to predict precisely the factors responsible for the adsorption conformation (F) to be more favorable than the alternative adsorption conformation (G). The possibility that in the transition state the course of hydrogenation may be controlled primarily by the relative stability of the epimeric products cannot be ruled out. The occurrence of a [1,3]-sigmatropic hydrogen shift could lead to more trans product as well. Results of hydrogenation of **7** over a number of catalysts are presented (Table III).

Structure of 2-Alkylidenecyclanones. Examination of a number of ethylenic ketones in which the configuration of the conjugated system is fixed revealed that for cisoid conformation ν C=C (cm^{-1}) is considerably smaller than for the transoid conformation.[16] The differences between the ethylenic and carbonyl stretching frequencies are, however, consistently greater for s-cisoid than for s-transoid derivatives.[16] Furthermore, the ratio of the integrated band in-

Table IV
Infrared and Ultraviolet Spectra of 2-Alkylidenecyclanones

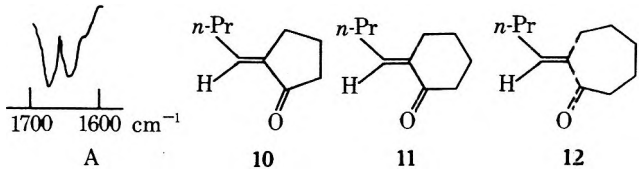
α,β-Unsaturated ketone	λ_{max} (EtOH), nm	ν C=O, cm^{-1}	ν C=C, cm^{-1}	Δ, cm^{-1}
trans-2-Butylidene-cyclopentanone	245	1715	1650	65
trans-2-Butylidene-cyclohexanone	247	1680	1615	65
trans-2-Butylidene-cycloheptanone	242	1675	1610	65

Table V
Percent *cis*-2-Alkylcyclanols Formed in Various Reductions

2-Alkylcyclanone	$LiAlH_4$	Raney nickel
2-Butylcyclopentanone	21	60
2-Butylcyclohexanone	37	63
2-Butylcycloheptanone	66	*a*

[a] Unknown, since this reduction was not performed.

tensities of the C=O and C=C stretching vibrations gives the most certain indication of the geometry of the chromophore, being low in cisoid and high in transoid systems.[17]



A 10 11 12

Numerical data for uv and ir spectra of 2-butylidenecyclanones are presented (Table IV).

The infrared spectra have characteristic absorption bands attributable to C=O and C=C stretching vibrations which are of nearly equal peak height, proving them to be rigidly cisoid systems (A).

Reduction of 2-Alkylcyclanones. The epimeric 2-alkylcyclanols were also obtained by the Pd/C-catalyzed reduction of 2-alkylidenecyclanones to give the corresponding 2-alkylcyclanones, which in turn were reduced by lithium aluminum hydride or BDH Raney nickel to give the corresponding epimeric 2-alkylcyclanols, and the results are presented (Table V).

The results obtained by the reduction of 2-butylcyclopentanone (**13**), 2-butylcyclohexanone (**14**), and 2-butylcycloheptanone (**15**) have a similar trend as has been observed by the reduction of 2-methylcyclanones by lithium aluminum hydride.[18] The reduction of **13** and **14** by lithium aluminum hydride appears to involve the attack of the reagent from the side of the butyl group, apparently the more hindered direction, to yield predominantly the more stable of the two possible alcohols (trans).[19] However, in the case of **15** (which yields the cis alcohol preferentially), reduction by lithium aluminum hydride is not consistent.[20]

To account for the formation of 60% **2** from the reduction of **13** over Raney nickel, it is suggested that steric interaction between the substituent and the atoms of the cycle combined with the requirements of a precise orientation of the carbonyl group on the catalyst directs the attack of hydrogen on the carbonyl group from the side away from the butyl group. The formation of 63% **5** from the reduction of **14** over Raney nickel is assumed to be a consequence of the ketone being adsorbed onto the catalyst in a conformation which minimizes the nonbonded interactions between the surface and the cycle, while the butyl group tends to be equatorial.[2a]

Experimental Section[21]

2-Bromocyclopentanone (16). Starting with 64 g of cyclopentanone,[22] 50 g (40%) of **16** was obtained, bp 56–58° (1.5 mm), $n^{25.5}D$ 1.5110 [lit.[22] bp 60° (2 mm), $n^{24.5}D$ 1.5114].

2-Butylidenecyclopentanone (10). Starting with 46.18 g (0.28 mol) of **16** and 30.6 g (0.42 mol) of *n*-butyraldehyde,[23] by vacuum distillation were obtained four fractions. GLC of the first three fractions indicated mainly one component present with ca. 8% of low-boiling impurities. Fraction 4 consisted mainly of 2-cyclopentylidenecyclopentanone, by comparison of its retention time with that of an authentic sample. **10** was purified by (1) vacuum fractionation (under N_2) of combined three fractions (14.18 g, 36.6%); (2) decomposing the semicarbazone with pyruvic acid (50%) in acetic acid solution;[24] or (3) preparative GLC on an NGA column (2-cyclopentylidenecyclopentanone was also recovered).

10 has bp 48–50° (0.5 mm), $n^{25.5}D$ 1.4675; darkens slowly on standing; uv λ_{max} (ethanol) 245 nm (lit.[23] 245 nm); ir 1650, 1715 cm^{-1} [lit.[23] 1655 (m), 1670 (m), 1735 cm^{-1} (s)]; NMR (CCl_4) τ 3.4–3.82 (olefinic H), 7.2–9.24 (total of alicyclic and aliphatic protons 13); its semicarbazone (50% alcohol) has mp 191–192° (lit.[23] mp 189–189.5°).

Hydrogenation of **10** over Pd/C in 95% ethanol (10 atm, 0.5 hr) gave **13** as a single component by GLC. Its semicarbazone (50% alcohol) has mp 185–186° (lit.[23] mp 186.5–187°), ir (neat) 1735 cm^{-1}.

2-Butylidenecyclopentanol (1). **10** (25 g, 0.18 mol) in dry ether (250 ml) was stirred vigorously and a suspension of $LiAlH_4$ (1.75 g, 0.046 mol) in dry ether (200 ml) was added gradually at room temperature over a period of 2 hr. The mixture was stirred for 0.5 hr after completion of the addition. The product was decomposed with dilute H_2SO_4 (300 ml, 3 *N*), and the aqueous layer was extracted with ether, washed successively with water and saturated NaCl solution, and dried (K_2CO_3). The solvent was removed after filtration, and the residue (24 g) was vacuum distilled (under N_2) to yield 20 g (78.8%) of a colorless liquid, bp 64–66° (2 mm), $n^{25}D$ 1.4740, and consisted mainly of one component, <1% **10** and traces of low-boiling impurities (GLC on NGA column). On examination, the component which originally showed a single peak on all columns tried, including Carbowax, changed into two major components (believed to be an exo to endo shift of the double bond) during preparative GLC on an NGA column. **1** (0.5 ml) was finally purified on a neutral alumina column (100 g) and eluted (9:1 hexane–methyl acetate). Presence of **1** in the various fractions was spotted by TLC (silica gel), using anisaldehyde–sulfuric acid color reagent.[25] The fractions containing pure **1** were combined and solvent removed under reduced pressure. **1** was obtained free from impurities and characterized: ir 2880, 2960, 3400 cm^{-1}; NMR (CCl_4) τ 4.3–4.8 (olefinic H), 5.6–5.9 (H adjacent to OH), 6.8–7.2 (hydroxyl H), 7.2–9.3 (aliphatic and alicyclic protons); mass spectrum *m/e* 140 (M^+).

Anal. Calcd for $C_9H_{16}O$: C, 77.14; H, 11.43. Found: C, 76.97; H, 11.22.

Its 3,5-dinitrobenzoate (alcohol) had mp 56–57°; mass spectrum *m/e* 334 (M^+).

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.39; N, 8.38. Found: C, 57.66; H, 5.58; N, 8.48.

Catalytic Hydrogenation of 1. **1** was hydrogenated over various catalysts in 95% ethanol under various conditions (see Table I). Components thus obtained were separated by preparative GLC on Carbowax column.

The first component was shown to be **13** by comparison of its retention time with that of an authentic sample on different columns. The second component was shown to be **2**: ir 2880, 2960, 3420 cm^{-1}; NMR (Me_2SO)[26] τ 5.945 (J = 4.2 Hz) (the OH proton is split into a doublet but the peak at τ 5.98 is very intense with respect to the other peak at τ 5.91); mass spectrum *m/e* 125 (M^+ 142, the observed peak corresponds to $M^+ - OH$).

Anal. Calcd for $C_9H_{18}O$: C, 76.05; H, 12.67. Found: C, 75.92; H, 12.82.

Its 3,5-dinitrobenzoate was obtained as colorless needles (ethanol), mp 69–70°, mass spectrum *m/e* 336 (M^+).

Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.14; H, 5.95; N, 8.33. Found: C, 57.27; H, 6.14; N, 8.53.

The third component was shown to be **3**: ir 2880, 2940, 3400 cm^{-1}; NMR (Me_2SO) τ 5.645 (hydroxyl H) (J = 5.4 Hz); mass

spectrum *m/e* 125 (M^+ 142, the observed peak corresponds to $M^+ - OH$).

Anal. Calcd for $C_9H_{18}O$: C, 76.05; H, 12.67. Found: C, 76.22; H, 12.59.

Its 3,5-dinitrobenzoate (ethanol) had two melting points of 34–35 and 45–46° (explained as having two distinct crystalline forms).

Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.14; H, 5.95; N, 8.33. Found: C, 57.31; H, 6.01; N, 8.31.

Reduction of 2-Butylcyclopentanone (13). 1. $LiAlH_4$. A suspension of powdered $LiAlH_4$ (25 mg) in dry ether (25 ml) was added to a stirred solution of **13** (0.5 g) in dry ether (5 ml) during ca. 0.5 hr. Stirring was continued for 15 min after completion of the addition. The product was decomposed with dilute H_2SO_4 (50 ml, 3 *N*), washed with water and saturated NaCl solution, and dried (K_2CO_3). The solvent was removed after filtration, and the residue consisted of a mixture of **2** and **3** in the ratio 21:79, respectively (GLC on Carbowax column).

2. Stabilized BDH Raney Nickel. **13** (100 mg) was hydrogenated over Raney Ni (100 mg) in 95% ethanol (25 ml) at a maximum pressure of 137.5 atm and a maximum temperature of 124° for 6 hr. The hydrogenated material was filtered to remove the catalyst and the ethanol was removed on a steam bath under reduced pressure. It consisted of a mixture of **2** and **3** in the ratio 60:40, respectively (GLC on Carbowax column).

1-Cyclohexenyl Acetate. Starting with 100 g (1.02 mol) of cyclohexanone,[27] 1-cyclohexenyl acetate was obtained as a colorless liquid: 100 g (70%); bp 32–34° (1 mm); $n^{25}D$ 1.4540 [lit.[27] bp 52–55° (4 mm)]; ir 1120 (C–O–C symmetric stretch), 1215 (C–O–C asymmetric stretch), 1740 (C=O stretch), 2920 cm^{-1}.

2-Bromocyclohexanone Enol Acetate (17). By allylic bromination of 1-cyclohexenyl acetate (50 g, 0.34 mol) with *N*-bromosuccinimide[27] in carbon tetrachloride was obtained 30 g (38.3%) of **17** as a colorless liquid, bp 52–55° (0.3–0.5 mm), $n^{25}D$ 1.5025 [lit.[27] bp 81–82° (3 mm)].

2-Butylidenecyclohexanone (11) was prepared by Reformatsky reaction of **17** and *n*-butyraldehyde by a modification (using benzene as solvent) of the reported method.[23] In a three-necked flask fitted with a mechanical stirrer, dropping funnel with a drying tube, reflux condenser, and tube for introducing nitrogen were placed zinc wool (18.2 g, 0.28 g-atom), mercuric bromide (0.37 g), *n*-butyraldehyde (30 g, 0.41 mol), and several crystals of iodine. Air was blown out by nitrogen and a solution of **17** (61 g, 0.28 mol) in anhydrous benzene (100 ml) was added gradually over a period of 2 hr. Reaction began at a bath temperature of 60°. After the end of the addition, the mixture was boiled for 0.5 hr with intensive stirring, cooled, and decomposed with hydrochloric acid (2% by volume). The water layer was repeatedly extracted with ether (6 × 50 ml). The combined ether extracts were washed with $NaHCO_3$ solution and water and dried (Na_2SO_4). The ether and benzene were distilled under reduced pressure. By vacuum distillation were obtained four fractions. GLC on a number of columns indicated fraction 3, bp 76–80° (0.5 mm), $n^{25}D$ 1.4842 (19.9 g, 46.8%), to be mainly **11** along with ca. 10% of impurities [lit.[28] bp 95–100° (3 mm), $n^{22}D$ 1.4800]. Purification of **11** on an NGA column was unsuccessful, for the presence of an unknown component (having OH group) in proximity with the main component, resulting in very poor resolution. Finally, **11** was purified by preparative GLC on a Carbowax column. GLC of the component thus obtained on various columns showed it to be mainly one component along with traces of impurities. **11** has uv λ_{max} (ethanol) 247 nm; ir[29] 1615, 1680 cm^{-1}; its semicarbazone (alcohol) had mp 140–141° (lit.[28] mp 138°).

Hydrogenation of **11** over Pd/C in 95% ethanol (10 atm, 0.5 hr) gave **14** as a major component along with ca. 2% of **5** and **6**. Its retention time was identical with that of an authentic sample on different columns. Its 2,4-DNP was obtained as orange crystals (ethanol), mp 110–111° (lit.[30] mp 110–111°), ir[31] 1700 cm^{-1}.

2-Butylidenecyclohexanol (4). A suspension of powdered $LiAlH_4$ (1.56 g, 0.041 mol) in dry ether (200 ml) was added to a stirred solution of **11** (25 g, 0.16 mol) in dry ether (250 ml) during ca. 2 hr. The reaction mixture was worked up as described for **1**. The solvent was removed after filtration and the residue (24 g), light yellow in color, was vacuum distilled to give a colorless liquid (20 g, 79%), bp 72–80° (5 mm), $n^{25}D$ 1.4958, and consisted mainly of **4** along with ca. 5% of impurities. On examination, the component which originally gave a single peak on all columns tried, including Carbowax, transformed into two major components (believed to be an exo to endo shift of the double bond) during preparative GLC on an NGA column. **4** was purified on a neutral alumina column and eluted (9:1 hexane–methyl acetate) as in the case of **1**. The sample was confirmed to be a single component (GLC on different columns): ir 2890, 2960, 3420 cm^{-1}; NMR (CCl_4) τ 4.55–4.9 (olefinic H split into a triplet), 5.9–6.25 (H adjacent to OH), 7.94 (hydroxyl H), 7.35–9.35 (aliphatic and alicyclic protons); mass spectrum *m/e* 154 (M^+).

Catalytic Hydrogenation of 4. **4** was hydrogenated over various catalysts in 95% ethanol under various conditions (see Table II). The first component was shown to be **14** by comparison of its retention time with that of an authentic sample on different columns. A mixture of the second and third components (0.5 ml) was separated by column chromatography on a neutral alumina column (100 g) and eluted (9:1 hexane–methyl acetate). The presence of epimers in the various fractions was spotted by TLC (silica gel), using anisaldehyde–sulfuric acid color reagent.[25] The possible fractions were then monitored by GLC on a polyethylene glycol 600 column. Fractions containing pure **5** and **6** were combined separately and solvent was removed under reduced pressure. Their retention times were identical with those of an authentic sample of 2-butylcyclohexanol. **5** (the component which comes out first on the column): NMR (Me_2SO)[26] τ 5.96 (hydroxyl H) (J = 4.8 Hz). **6** (the later component): NMR (Me_2SO) τ 5.73 (hydroxyl H) (J = 6.0 Hz).

Reduction of 2-Butylcyclohexanone (14). 1. $LiAlH_4$. Reduction of **14** was carried as in the case of **13**. GLC of the components (Carbowax column) resulted in **5** and **6** in the ratio 37:63, respectively.

2. Stabilized BDH Raney Nickel. **14** (200 mg) was hydrogenated over Raney Ni (100 mg) in 95% ethanol (25 ml) at a maximum temperature of 134° and maximum pressure of 112.5 atm for 6 hr. The product was analyzed (GLC on Carbowax column) and consisted of **5** and **6** in the ratio 63:37, respectively.

2-Bromocycloheptanone (18). Starting with 168 g of cycloheptanone[32] and 240 g of bromine, by vacuum distillation were obtained two fractions. Fraction 1 was a mixture of unchanged cycloheptanone and **18** (50 g), bp 50–72° (1 mm), $n^{25.5}D$ 1.5105. Fraction 2 was **18** (60 g), bp 76–80° (1 mm), $n^{25.5}D$ 1.5175 [lit.[32] bp 105° (10 mm), $n^{22}D$ 1.5137].

2-Butylidenecycloheptanone (12) was prepared by the Reformatsky reaction of **18** and *n*-butyraldehyde, by a modification (in one step) of the reported method.[23] In a three-necked flask fitted with a stirrer, reflux condenser, dropping funnel with a drying tube, and tube for introducing nitrogen were placed zinc wool (23.6 g, 0.36 g-atom), mercuric bromide (0.37 g), ethyl acetate (1 ml), *n*-butyraldehyde (32.8 g, 0.46 mol), and several crystals of iodine. Air was blown out by nitrogen, and a solution of **18** (57.04 g, 0.30 mol) in anhydrous benzene (100 ml) was added gradually over a period of 2 hr. Reaction began at a bath temperature of 60°. After the end of the addition, the mixture was boiled for 0.5 hr with intensive stirring and worked up as described in the case of **11**. By vacuum distillation were obtained four fractions. GLC on a number of columns indicated fraction 2, bp 76–80° (0.5–1 mm), $n^{25.5}D$ 1.4735, and fraction 3, bp 97–99° (1–2 mm), $n^{25.5}D$ 1.4800, to be mainly **12** (18.6 g, 37.5%) along with ca. 10% of impurities. A crude sample which had been kept for a long time at room temperature was freshly distilled to remove higher boiling components. Two peaks emerged, along with other impurities, during preparative GLC on an NGA column. One component was gradually merging with another component, and finally disappeared. The major component thus obtained was ca. 95% pure (GLC on an NGA column). It was clear that **12** was decomposing on the preparative column. A chromatographically pure sample was not obtained. **12** had uv λ_{max} (ethanol) 242 nm; ir 1610, 1675 cm^{-1}; its semicarbazone (50% alcohol) had mp 121°.

Anal. Calcd for $C_{12}H_{21}N_3O$: C, 64.54; H, 9.48; N, 18.81. Found: C, 64.75; H, 9.31; N, 18.34.

Hydrogenation of **12** over Pd/C in 95% ethanol (10 atm, 0.5 hr) gave mainly **15** with traces of **8** and **9**. Its 2,4-DNP was obtained as golden, irregular plates (alcohol), mp 81–82.5° (lit.[33] mp 80–81.5°), ir 1740 cm^{-1}.

2-Butylidenecycloheptanol (7). A suspension of powdered $LiAlH_4$ (1.425 g, 0.037 mol) in dry ether (200 ml) was added to a stirred solution of **12** (25 g, 0.15 mol) in dry ether (250 ml) during ca. 2 hr. The reaction mixture was worked up as described for **1**. After removal of the solvent under reduced pressure light pink liquid was obtained (24 g, 94.8%). GLC on an NGA column indicated it to be mainly one component along with ca. 5% of impurities. On examination, the component which originally gave a single peak on all columns tried, including Carbowax, transformed into two major components (believed to be an exo to endo shift of the double

bond) during preparative GLC on an NGA column. 7 was purified on a neutral alumina column and eluted (9:1 hexane–methyl acetate) as in the case of 1. The sample was confirmed to be a single component (GLC on various columns): ir 2870, 2940, 3400 cm^{-1}; NMR (CCl_4) τ 4.5–4.9 (olefinic H split into a triplet), 5.8–6.15 (H adjacent to OH, also split into a triplet), 8.15 (hydroxyl H), and 7.7–9.35 (aliphatic and alicyclic protons); mass spectrum *m/e* 168 (M^+).

Catalytic Hydrogenation of 7. 7 was hydrogenated over various catalysts in 95% ethanol under various conditions (see Table III). The first component was shown to be 15 by comparison of its retention time with that of an authentic sample. A mixture of the second and third components was separated by column chromatography as in case of 5 and 6. 8 (the component which comes out first on the column): ir 2900, 2960, 3460 cm^{-1}; NMR (Me_2SO)[26] τ 5.96 (hydroxyl H) (J = 4.8 Hz); mass spectrum *m/e* 170 (M^+); its 3,5-dinitrobenzoate (alcohol) had mp 53–53.5°.

Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.34; H, 6.59; N, 7.69. Found: C, 59.27; H, 6.72; N, 7.79.

9 (the later component): ir 2950, 3450 cm^{-1}; NMR (Me_2SO) τ 5.81 (hydroxyl H) (J = 4.8 Hz); mass spectrum *m/e* 170 (M^+); its 3,5-dinitrobenzoate (alcohol) had mp 83–84°.

Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.34; H, 6.59; N, 7.69. Found: C, 59.45; H, 6.41; N, 7.54.

Lithium aluminum hydride reduction of 2-butylcycloheptanone (15) was carried as described in the case of 13. GLC on a polyethylene glycol 400 column resulted in 8 and 9 in the ratio 66:34, respectively.

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Registry No.—1, 56292-34-3; 1 3,5-DNB, 56292-35-4; 2, 55166-24-0; 2 3,5-DNB, 56292-36-5; 3, 55166-25-1; 3 3,5-DNB, 56292-37-6; 4, 56292-38-7; 5, 35242-02-5; 6, 35242-05-8; 7, 56292-39-8; 8, 51113-04-3; 8 3,5-DNB, 56292-40-1; 9, 51113-00-9; 9 3,5-DNB, 56292-41-2; 10, 56292-42-3; 11, 56292-43-4; 12, 56292-44-5; 12 semicarbazone, 56292-45-6; 13, 934-42-9; 14, 1126-18-7; 14 2,4-DNP, 1166-09-2; 15, 36504-11-7; 15 2,4-DNP, 56292-46-7; *n*-butyraldehyde, 123-72-8.

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Cleavage of a Cyclopropane Ring by Singlet Oxygen

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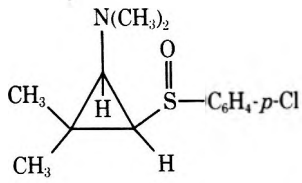
The photooxygenation of the aminocyclopropyl sulfide *cis*-2-[(*p*-chlorophenyl)thio]-*N*,*N*,3,3-tetramethylcyclopropylamine (2) afforded mainly ring opened products which can be accounted for by the formation of and subsequent cleavage of a 1,2-dioxolane intermediate. It is believed that this is the first reported singlet oxygen cleavage of a cyclopropane ring to occur via a 1,2-dioxolane intermediate.

There is currently only one reported example of the cleavage of a cyclopropane ring during the photooxygenation of a cyclopropane. This occurred during the photooxygenation of the sesquiterpene gurjunene.[1] The authors attributed this cyclopropane cleavage to the presence of the transoid vinylcyclopropane system and proposed a mechanism which was based upon this structural feature. In the course of work directed toward the synthesis of *cis*-2-[(*p*-chlorophenyl)sulfinyl]-*N*,*N*,3,3-tetramethylcyclopropylamine (**1**).[2,3] it was decided that a reasonable approach to this



1

molecule would be by the singlet oxygen oxidation of the corresponding sulfide, *cis*-2-[(*p*-chlorophenyl)thio]-*N*,*N*,-3,3-tetramethylcyclopropylamine (**2**).[3,4] Foote and Peters[5] have reported the photooxygenation of sulfides to afford the corresponding sulfoxides. However, application of their method to sulfide **2**, while affording some oxidation at the sulfur atom, afforded mainly ring opened products which can be accounted for by the formation of and subsequent cleavage of a 1,2-dioxolane intermediate. It is believed that this is the first reported singlet oxygen cleavage of a cyclopropane to occur via a 1,2-dioxolane intermediate.

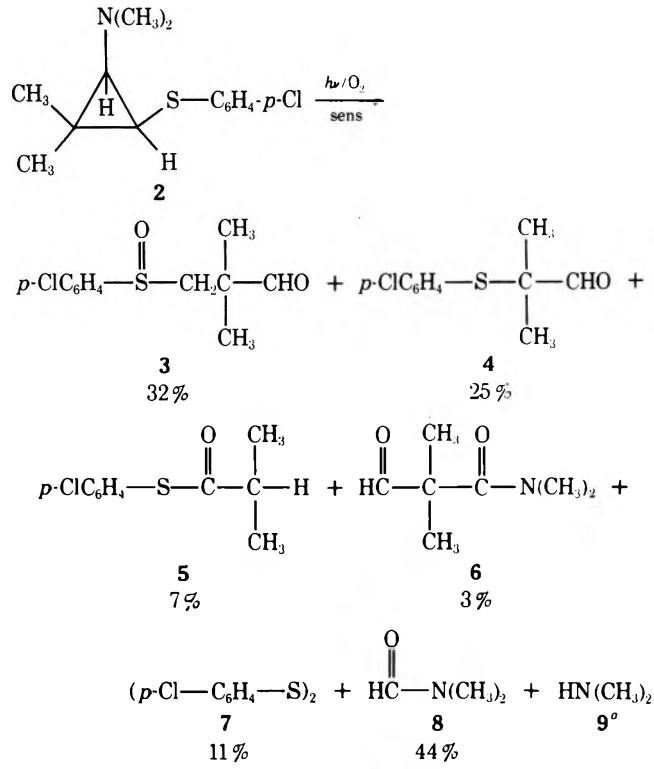
Results and Discussion

Photooxygenation of a methanol solution of **2** using Rose Bengal as a sensitizer afforded the products shown in Scheme I. The products, with the exception of dimethylamine (**9**), were isolated by column chromatography and the yields are shown in Scheme I. The reaction mixture was also examined by GLC (see Experimental Section). The yields follow: **3** (29%), **4** (30%), **5** (6%), **6** (5%), **7** (12%), and **8** (39%). These yields are in good agreement with the isolated yields (Scheme I).

Five of the seven products, **3**, **5**, **7**, **8**, and **9**, have been previously reported and were identified by comparisons of their physical constants and/or spectral data with those of the known compounds. The structure of compound **4** was assigned on the basis of elemental analysis and mass, ir, and ^{1}H NMR spectra (see Experimental Section). The structure of **6** was identified as *N*,*N*,2,2-tetramethylmalonaldehydamide by comparison with an authentic sample. Compound **6** was independently synthesized by the reaction of *N*,*N*,2-trimethylpropenylamine and phosgene to afford an iminium salt intermediate which was subsequently treated with dimethylamine and hydrolyzed. Halleux and Viehe[6] have prepared the pyrrolidine analog in a similar manner.

That the above reaction is indeed a singlet oxygen oxy-

Scheme I



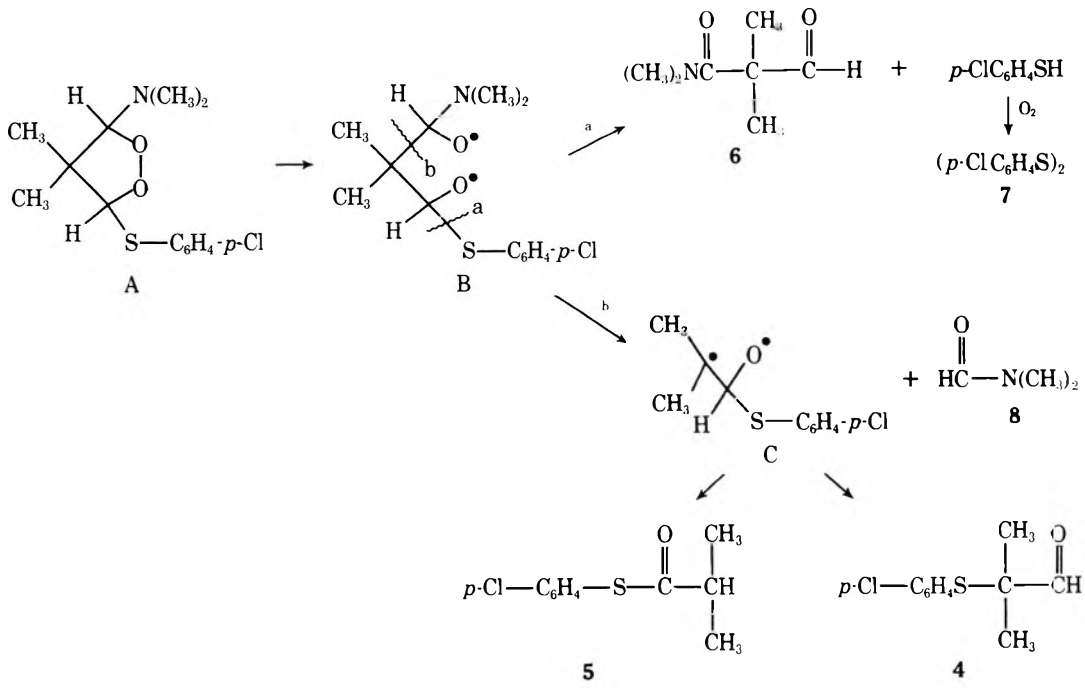
[a] Identified via GLC; yield not determined.

genation was shown by the following control reactions. When **2** was irradiated in the presence of Rose Bengal with molecular nitrogen being bubbled through the solution, in place of molecular oxygen, no reaction occurred. Nor did any appreciable reaction occur during irradiation of a solution of **2** continuously purged with molecular oxygen but in the absence of sensitizer. 1,4-Diazabicyclo[2.2.2]octane (Dabco) has been shown to inhibit singlet oxygen reactions but has little effect on free-radical reactions.[7] When an equimolar amount of Dabco was added the reaction rate was dramatically inhibited (21% completion in 14.5 hr vs. complete reaction without Dabco) with essentially no change in the product ratio (see Experimental Section).

It was also shown that the two major products **3** and **4** were relatively stable to the phooxygenation conditions. None of the other products originated from these compounds.

The photooxygenation reaction was found to be solvent dependent in that little reaction occurred in methylene chloride owing to the insolubility of Rose Bengal in this solvent. Also, little reaction occurred in acetone as a result of the rapid bleaching of the Rose Bengal. However, the use of tetrahydrofuran as the reaction solvent afforded the same products in essentially the same relative abundances as with methanol.

Scheme II



It was found that Rose Bengal was a more efficient sensitizer in methanol than either Eosin Yellow or Methylene Blue. With Eosin Yellow the reaction was much slower, requiring 41 hr for completion, as opposed to 17 hr or less with Rose Bengal. The product ratio was essentially the same (see Experimental Section). With Methylene Blue the reaction was very slow as a result of the bleaching out of the sensitizer. Additional sensitizer was added; however, the reaction was only 20% complete in 22 hr. The product ratio was the same as with Rose Bengal (^{1}H NMR).

The formation of **3** as the major product quite likely arose from the formation and subsequent hydrolysis of **1**. Indeed, examination of the reaction mixture (^{1}H NMR) before completeness of reaction showed the presence of a small amount of **1**. We have previously reported that **1** is rapidly hydrolyzed to **3** and dimethylamine.[2]

The formation of the remaining reaction products can be best rationalized in terms of the 1,2-dioxolane intermediate A[8] (Scheme II). The formation of A can be accounted for by the trapping of a 1,3 diradical generated from **2** or by attack of singlet oxygen across the electron-rich C_1–C_2 bond of **2** as in the case of electron-rich olefins.[9,10] Whether the fragmentation of A proceeds via diradical intermediates B and/or C[11] or an ionic mechanism cannot be answered with certainty at this time. However, the migration of the *p*-chlorophenylmercapto group to afford **4** can be best explained on the basis of a radical fragmentation. The vicinal migration of arylmercapto groups in radical reactions is well documented.[12,13,14] Adam and Durán have recently studied the photolysis of 1,2-dioxolanes and have observed an analogous migration of the phenyl group.[8b]

Fragmentation of B at point a (Scheme II) would lead to, after requisite hydrogen atom rearrangement, **6** and *p*-chlorothiophenol which would subsequently be oxidized to disulfide **7**. It was demonstrated that *p*-chlorophenol is rapidly oxidized to disulfide **7** under the reaction conditions. Fragmentation of B at point b would afford C, which with hydrogen rearrangement would afford **5** and with *p*-chlorophenylmercapto migration would afford **4**.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model 421 recording spectrometer, the ^{1}H NMR spectra were recorded on a Varian A-60A spectrometer, and the mass spectra were determined on an Atlas CH-4 spectrometer. GLC analyses were performed on a Hewlett-Packard dual flame gas chromatograph Model 402 using a 6-ft HIEFF-8BP Gas-Chrom-Q 100/120 (3%) column.[15] The internal standard method was used for yield determinations.

Photooxygenation of *cis*-3-[(*p*-Chlorophenyl)thio]-*N,N*-3,3-tetramethylcyclopropylamine (2). A solution of **2**[2,3] (8.0 g, 0.031 mol, 0.2 *M*) and Rose Bengal (50 mg) in anhydrous methanol (150 ml) was irradiated with 16 8-W, cool-white fluorescent lamps in a Rayonet photochemical reactor while oxygen was bubbled into the solution. The solution was maintained at 25 ± 2° by means of a cold finger. Irradiation was discontinued after 17 hr, at which time no starting material remained (TLC). The reaction was repeated twice more and the crude reaction mixtures were combined and concentrated in vacuo to afford a viscous brown oil (25 g). The oil was subjected to adsorption chromatography on silica gel (4 kg). The fractions (300 ml) and eluents were 1–27 (benzene); 28–57 (5–10% ethyl acetate in benzene, gradient elution); 58–80 (20% ethyl acetate in benzene); 81–119 (50% ethyl acetate in benzene); 120–180 (5% methanol in chloroform); and 181–200 (50% methanol in chloroform).

Concentration of fractions 18–23 afforded 1.43 g (11% yield) of bis(*p*-chlorophenyl) disulfide (**7**). The structure of **7** was determined by comparison of its ir, ^{1}H NMR, melting point, and mass spectra with those of an authentic sample.[16]

Concentration of fractions 25–30 afforded 1.4 g (7% yield) of *p*-chlorophenyl isothiobutyrate (**5**): bp 105–107° (4 mm) [lit.[17] bp 147–148° (13 mm)]; ir ($CHCl_3$) 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 6 H, J = 6.5 Hz), 2.77 (sextet, 1 H, J = 6.5 Hz), 7.32 (s, 4 H); mass spectrum *m/e* 214, 216 (M^+).

Anal. Calcd for $C_{10}H_{11}ClOS$: C, 55.93; H, 5.16; Cl, 16.51; S, 14.94. Found: C, 55.79; H, 4.90; Cl, 16.61; S, 15.15.

Concentration of fractions 33–44 afforded 4.9 g (25% yield) of 2-[(*p*-chlorophenyl)thio]-2-methylpropionaldehyde (**4**): bp 114–115° (4 mm); ir ($CHCl_3$) 1720 (C=O) and 2720 cm^{-1} (aldehyde C–H); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6 H), 7.30 (s, 4 H), 9.32 (s, 1 H); mass spectrum *m/e* 214, 216 (M^+).

Anal. Calcd for $C_{10}H_{11}ClOS$: C, 55.93; H, 5.16; Cl, 16.51; S, 14.94. Found: C, 56.01; H, 5.30; Cl, 16.79; S, 14.92.

Concentrations of fractions 109–125 afforded 7.2 g (32% yield) of 3-[(*p*-chlorophenyl)sulfinyl]-2,2-dimethylpropionaldehyde (**3**):[2] mp 61–62° (hexane); the ir, ^{1}H NMR, and mass spectra were identical with those of **3** prepared below.

Concentrations of fractions 166–180 afforded 3.0 g (44% yield) of dimethylformamide (**8**) which was identified by comparison of its ir, ^{1}H NMR, and mass spectra with those of an authentic sample.

Concentrations of fractions 186–200 afforded 0.4 g (3% yield) of

N,N,2,2-tetramethylmalonaldehydamide (**6**). The ir, ^{1}H NMR, and mass spectra were identical with those of **6** prepared below.

GLC Analysis of the Photooxygenation of 2 Using Rose Bengal in Methanol. The photooxygenation of **2** was carried out in the above described manner. The reaction was monitored by GLC and shown to be complete in 14.5 hr. The yields follow: **3** (29%), **4** (30%), **5** (6%), **6** (5%), **7** (12%), and **8** (39%). Several minor products (<1% each) were detected but no attempt was made to characterize them.

Photooxygenation of 2 Using Rose Bengal in Methanol with Dabco. A solution of **2**[2,3] (0.80 g, 3.1 mmol) (0.20 *M*), Rose Bengal (5 mg), and Dabco (0.35 g, 3.1 mmol) (0.20 *M*) in anhydrous methanol (15 ml) was irradiated as above. The reaction was monitored by GLC and after 14.5 hr only 21% reaction had occurred. GLC of the reaction products showed the relative yields to be as follows: **3** (31%), **4** (26%), **5** (8%), **6** (6%), **7** (10%), and **8** (42%). One additional minor product was formed; however, it was shown that this product arose from the irradiation of just Dabco and Rose Bengal in methanol.

Photooxygenation of 2 Using Eosin Yellow in Methanol. A solution of **2**[2,3] (2.56 g, 0.010 mol) (0.2 *M*) and Eosin Yellow (50 mg) in anhydrous methanol (50 ml) was irradiated as above. The reaction proceeded rather slowly and was shown to be complete after 41 hr. GLC of the reaction products showed the yields to be as follows: **3** (29%), **4** (25%), **5** (1%), **6** (4%), **7** (16%), and **8** (37%). It was shown that **5** slowly decomposes in this medium (without irradation) to **7** and other unidentified products. This would account for the decreased yield of **5** and the increased yield of **7** due to the prolonged reaction time (41 hr vs. 14.5 hr).

***N,N*,2,2-Tetramethylmalonaldehydamide (6).** Phosgene (10 g, 0.010 mol) dissolved in toluene (100 ml) was added dropwise to a stirred, cooled (5–10°) solution of *N,N*,2-trimethylpropenylamine (20 g, 0.20 mol) in methylene chloride (200 ml). The mixture was stirred at 5–10° for an additional 2 hr and allowed to stand at ambient temperature for 18 hr. The solution was cooled to 5–10° and dimethylamine (large excess) was bubbled into the stirred reaction mixture for 0.5 hr. The mixture was then stirred at 25° for 0.5 hr. Hydrochloric acid (18%, 100 ml) was slowly added and the mixture was stirred at 25° for 1 hr. The organic phase was separated and the aqueous phase was extracted with methylene chloride (2 × 100 ml). The combined organic fractions were washed with water (50 ml) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was distilled to afford 9.3 g (65% yield) of **6**: bp 64–65° (0.2 mm); ir (Nujol) 1635 (amide C=O), 1720 (aldehyde C=O), 2710 cm^{-1} (aldehyde C–H); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 6 H), 2.94 (s, 6 H), 9.62 (s, 1 H); mass spectrum *m/e* 143 (M^+).

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.74; H, 9.09; N, 9.56. Found: C, 58.18; H, 9.23; N, 9.56.

2,2-Dimethyl-3-[(*p*-chlorophenyl)sulfinyl]propionaldehyde (3). 2,2-Dimethyl-3-[(*p*-chlorophenyl)thio]propionaldehyde[18] (0.23 g, 1.0 mmol) in methanol (12 ml) was added dropwise to a stirred, cooled (0–5°) solution of sodium metaperiodate (0.23 g, 1.07 mmol) in methanol (12 ml). The mixture was stirred at 0–5° for 7 hr and then stirred at 25° for 12 hr. The precipitate was removed by filtration and the solvent of the residue was removed in vacuo. The residue was dissolved in methylene chloride (50 ml), extracted with water (2 × 5 ml), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was recrystallized from hexane to afford 0.18 g (73% yield) of **3**: mp 61–62°; ir (Nujol) 1090 and 1075 (S=O), 1725 (C=O), 2720 cm^{-1} (aldehyde C–H); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.39 (s, 3 H), 2.95 (s, 2 H), 7.63 (m, 4 H), 9.80 (s, 1 H); mass spectrum *m/e* 245, 247 (M + 1).

Anal. Calcd for $C_{11}H_{13}ClO_2S$: C, 53.99; H, 5.32; Cl, 14.52; S, 13.09. Found: C, 53.96; H, 5.53; Cl, 14.64; S, 12.99.

Control Experiments. Irradiation of **2** in the presence of Rose Bengal with nitrogen bubbled through the solution, in place of oxygen, afforded no reaction. Nor could any appreciable reaction be observed by irradiation of a solution of **2** continuously purged with oxygen but in the absence of sensitizer.

Acknowledgment. We are grateful to George Bronson of The Upjohn Co. for conducting much of the GLC analyses.

Registry No.—**2**, 37608-38-1; **3**, 56421-89-7; **4**, 56421-90-0; **5**, 56421-91-1; **6**, 52773-42-9; **7**, 1142-19-4; **8**, 68-12-2; singlet oxygen, 17778-80-2; *N,N*,2-trimethylpropenylamine, 6906-32-7; 2,2-dimethyl-3-[(*p*-chlorophenyl)thio]propionaldehyde, 55606-32-1; sodium metaperiodate, 7790-28-5.

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On the Electronic Structure of Phenyl Cation. A CNDO/S Treatment

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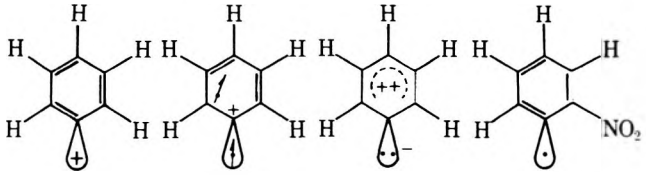
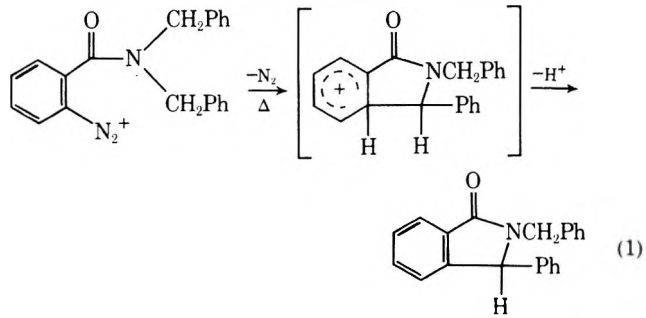
Calculations (CNDO/S with CI) on 12 electronic states of phenyl cation in the symmetric benzene geometry have been performed. The ground singlet state is predicted to be more stable than the lowest σ,π triplet state by 0.87 eV and more stable than the lowest closed-shell excited singlet state by 1.56 eV. Extension of the calculations to two other geometric configurations revealed that the various electronic states of phenyl cation can be divided into three geometric categories. Those electronic states with a vacant C-1 σ orbital prefer a highly distorted geometry in which C-1, C-2, and C-6 are colinear while those states with two electrons in the C-1 σ orbital prefer the symmetric benzene geometry. Electronic states with one electron in the C-1 σ orbital either prefer an intermediate geometry or show little discrimination between an intermediate geometry and that in which C-1, C-2, and C-6 are colinear. The conformational preferences of the various electronic states of the phenylium ion appear to be related to orbital hybridization at C-1.

In 1961, Taft suggested that the phenyl cation (1), presumably formed during the thermal hydrolysis of benzenediazonium salts, may actually exist as the σ,π-triplet diradical 2 in its ground state in its ground state.[1] This proposal was subsequently extended by Abramovitch and his coworkers, who studied the phenylation of various aromatic substrates with benzenediazonium tetrafluoroborate.[2] They obtained partial rate factors comparable to those for similar arylations with highly electrophilic radicals such as 2-nitrophenyl (4)



1 2 3 4

and argued that the phenyl cation must be endowed with radical character.[2] To rationalize the ability of aryl cations to sometimes undergo *apparent* insertion reactions typical of singlet carbenes (see eq 1),[3] structure 3 for $C_6H_5^+$ was



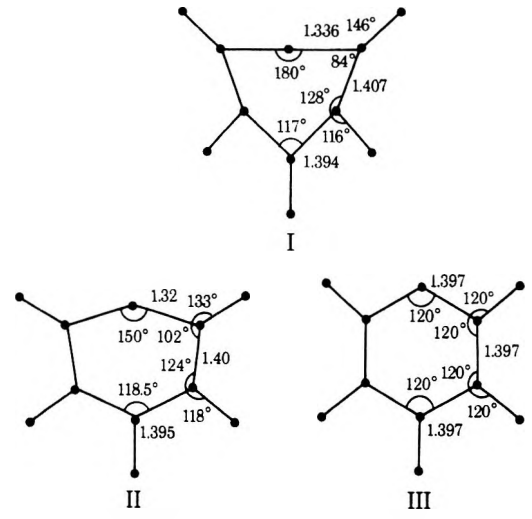
(1)

also proposed.[2a] The authors concluded that a dynamic equilibrium between 1, 2, and 3 would "account for all the reported properties of the phenyl cation."[2a]

A quantitative assessment of the possible existence of triplet diradical 2 has been published by Evleth and Horowitz,[4] who performed INDO calculations on $C_6H_5^+$ with a symmetric benzene geometry (see conformation III below). Their results place the *lowest* triplet state of phenyl cation 3.5 eV above the ground singlet state. Moreover, the electron configuration of the INDO triplet is such that all of the positive charge and both unpaired electrons reside in the σ system. That is, the triplet is of the σ,σ type and is not the σ,π triplet originally proposed by Taft. Similar calculations on the 4-aminophenyl cation, however, revealed a profound substituent effect. In this case, the lowest triplet state is predicted to be slightly more stable (0.01 eV) than the lowest singlet state, and it exhibits the σ,π configuration. Although their calculations oppose the notion of a facile interconversion between 1 and 2 for the parent cation, the authors issue a caveat regarding the accuracy of their findings since the computations were made without the inclusion of configuration interaction.[4]

More recently, Swain and his coworkers reported INDO calculations with geometry optimization (but without CI) on 1 and were led to the surprising conclusion that C-1, C-2, and C-6 are colinear in the ground singlet state of phenyl cation (see conformation I, Chart I). The calculated energy difference for the optimal geometry vs. the symmetric benzene geometry is 4.05 eV (94 kcal mol^{-1}). The linear INDO triplet was found to be 146 kcal mol^{-1} less stable than the linear INDO singlet, but the authors did not indicate whether it was of the σ,σ, σ,π, or π,π type.[5] At this point, it is well to keep in mind that conventional INDO calculations such as those described above (program QCEP 141) cannot be applied indiscriminately to any given electronic state of a molecular species. Molecular orbitals are

Chart I[a]



[a] All C–H bond lengths in each conformation were taken to be 1.084 Å.

Table I
Phenylium Ion $C_6H_5^+$ (Symmetric Benzene Geometry)
Relative State Energies in eV[a]

State	SCF	Virtual orbitals
$^1A_1(a_2^2b_1^2)$	0	0
$^3B_1(a_2^2b_1a_1)$	0.87	1.18
$^1B_1(a_2^2b_1a_1)$		0.90
$^3A_2(a_2b_1^2a_1)$	1.00	1.34
$^1A_2(a_2b_1^2a_1)$		2.17
$^1A_1(a_2^2a_1^2)$	1.56	
$^3B_2(a_2b_1a_1^2)$	2.33	
$^1A_1(b_1^2a_1^2)$	3.11	

[a] Singlets calculated with Mataga and triplets with Pariser integrals.

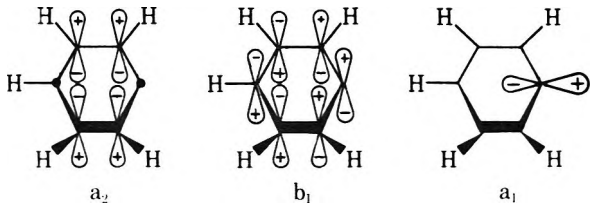
populated in such a way that only the lowest lying singlet and triplet states will be generated. Thus, in the case of phenyl cation, Evleth and Horowitz found that the singly occupied orbitals of the INDO triplet are σ orbitals.[4] Furthermore, since conventional INDO calculations cannot predict relative energies of various excited states in a reasonable manner, the conclusion that the low-lying triplet is of the σ,σ type seems doubtful.

Results and Discussion

No calculations on the electronic states of phenyl cation specifically represented by valence-bond structures 2 and 3 appear to have been performed, and, therefore, the possible coexistence of species 1, 2, and 3 remains an open question. In this paper, we report the results of CNDO/S calculations[6] with configuration interaction on 12 electronic states of phenyl cation including those represented by structures 1, 2, and 3. As described elsewhere, the CNDO/S method has been parameterized for the accurate computation of energy differences between various electronic states of a given molecular species.[6] Our computations have two unique features. First, the electrons have been "forced" to reside in either the σ or π system of phenyl cation depending on which electronic state is being studied.[7] Second, we report some of the first calculations on closed-shell singlet excited states.

Two sets of computations were performed. In the first set, the symmetric benzene geometry (conformation III) was assumed. In the second set, two other geometries were examined, namely, the geometry of Swain's linear INDO singlet[5] (conformation I) and a geometry halfway between that and the symmetric benzene geometry (conformation II). The results of the first set are summarized in Table I.

Configurations are given in terms of the three highest occupied orbitals of phenyl cation (point group C_{2v}), namely, the a_2 and b_1 π orbitals and the a_1 n orbital shown below. The a_2 and b_1 orbitals are not degenerate as they are in benzene, and, for that reason, the $^3A_2$ and $^3B_1$ states of phenyl cation differ in energy. Structures 1, 2, and 3 refer to the $a_2^2b_1^2$ singlet, the $a_2^2b_1a_1$ triplet, and the $a_2^2a_1^2$ singlet states, respectively.



a_2 b_1 a_1

Our calculations predict that the σ,π triplet 2 should be significantly less stable than 1 (0.87 eV), but the energy gap is not nearly so large as that predicted by INDO calculations between 1 and the σ,σ-triplet diradical. Likewise, the closed-shell excited singlet species 3 is predicted to be less stable than 1 by 1.56 eV. By way of comparison, CNDO/2 SCF calculations yield energy differences of 3.47 eV between 1 and 2 and 7.67 eV between 1 and 3. Also, the positive charge of the phenylium ion in all of its electronic states is significantly more delocalized than indicated by classical valence-bound structures. The computed electron densities, broken down into σ and π contributions, are summarized in Table II.

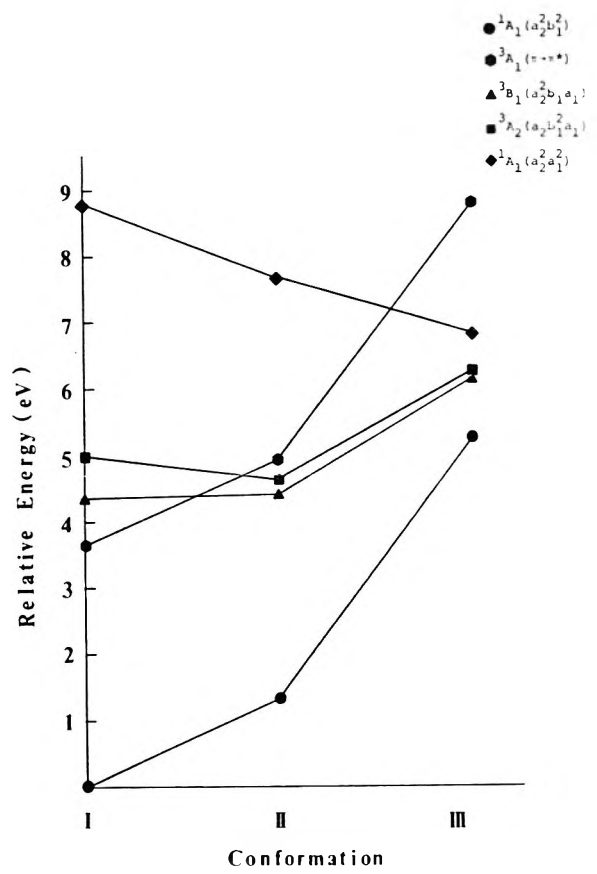
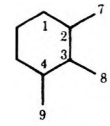


Figure 1. Relative energies of various electronic states of the phenylium ion as a function of molecular geometry.

There is little justification for the assumption that phenyl cation will prefer the symmetric benzene geometry in each of its electronic configurations. Indeed, it seems more likely that each electronic state will exhibit a unique geometry. Accordingly, we have extended our treatment to include conformations I and II for all states listed in Table I. Also, we have performed calculations on four π,π^* excited states in all three conformations. Excited-state energies were determined by adding CNDO/S excitation energies to appropriate CNDO/2 ground-state energies. The data are displayed in Table III and Figure 1.

Our CNDO/2 computations on the singlet ground state ($a_2^2b_1^2$) of phenyl cation are consistent with the finding of Swain and his coworkers that conformation I generates an energy minimum. However, the most intriguing feature of our calculations is the natural division of the electronic states of phenyl cation into three geometric categories. Those species with a vacant σ orbital (a_1) at C-1 are most stable in conformation I while excited states in which two π electrons have been transferred to the C-1 σ orbital are most stable in conformation III. For example, the singlet ground state ($a_2^2b_1^2$) prefers conformation I over conformation III by 5.26 eV, but the closed-shell excited singlet state ($a_2^2a_1^2$) prefers conformation III over conformation I by 1.96 eV. Finally, these excited states with one electron in the a_1

Table II
Phenylium Ion $C_6H_5^+$ (Symmetric Benzene Geometry) Electron Distributions



	$^1A_1(a_2^2b_1^2)$			$^1A_1(a_2^2a_1^2)$			$^1A_1(b_1^2a_1^2)$		
Atom	σ	π	Total	σ	π	Total	σ	π	Total
1	2.46	1.30	3.77	3.84	0.13	3.97	3.59	0.66	4.25
2	2.99	0.92	3.90	3.17	0.71	3.88	3.22	0.63	3.85
3	2.97	1.00	3.97	2.98	1.02	4.00	3.29	0.44	3.73
4	3.08	0.85	3.93	3.30	0.42	3.72	2.87	1.21	4.08
7	0.90		0.90	0.91		0.91	0.90		0.90
8	0.91		0.91	0.93		0.93	0.89		0.89
9	0.92		0.92	0.88		0.88	0.93		0.93
Charge	+1.02	+0.01	+1.03	−1.00	+1.99	+0.99	−0.99	+1.99	+0.98

	$^3B_1(a_2^2b_1a_1)$			$^3A_2(a_2b_1^2a_1)$			$^3B_2(a_2b_1a_1^2)$		
Atom	σ	π	Total	σ	π	Total	σ	π	Total
1	3.17	0.62	3.79	3.04	0.98	4.02	3.77	0.40	4.17
2	3.05	0.92	3.96	3.10	0.75	3.86	3.18	0.66	3.83
3	3.04	0.94	3.98	3.11	0.75	3.86	3.14	0.73	3.86
4	3.16	0.67	3.82	3.03	1.02	4.06	3.08	0.85	3.94
7	0.90		0.90	0.90		0.90	0.90		0.90
8	0.90		0.90	0.90		0.90	0.90		0.90
9	0.90		0.90	0.91		0.91	0.90		0.90
Charge	−0.01	+0.99	+0.99	0	+1.00	+1.00	−0.99	+1.99	+1.01

Table III
Phenylium Ion $C_6H_5^+$ Relative State Energies (in eV) for Various Conformations

		Energy		
State[a]	n^b	I	II	III
$^1A_1(a_2^2b_1^2)$	0	0	1.32	5.26
$^3A_1(\pi-\pi^*)$	0	3.64	4.93	8.78
$^3B_1(a_2^2b_1a_1)$	1	4.36	4.40	6.13
$^3B_2(\pi-\pi^*)$	0	3.91	5.64	9.33
$^1B_1(a_2^2b_1a_1)$	1	4.50	4.59	6.16
$^1B_2(\pi-\pi^*)$	0	4.62	6.28	10.18
$^1A_1(\pi-\pi^*)$	0	5.50	7.24	10.30
$^3A_2(a_2b_1^2a_1)$	1	4.99	4.63	6.26
$^1A_2(a_2b_1^2a_1)$	1	5.54	5.51	7.45
$^1A_1(a_2^2a_1^2)$	2	8.78	7.67	6.32
$^3B_2(a_2b_1a_1^2)$	2	9.84	8.40	7.58
$^1A_1(b_1^2a_1^2)$	2	10.92	9.12	8.37

[a] States marked $\pi \rightarrow \pi^*$ involve various mixtures of such promotions. [b] The number of electrons occupying orbital a_1.

orbital either prefer an intermediate geometry (not necessarily conformation II which lies exactly halfway between conformations I and III) or show little descrimination between conformations I and II. It seems clear that the driving force behind the conformational preferences of the phenylium ion can be related to the state of hybridization of C-1. Thus, when the C-1 σ orbital is vacant, it acquires 100% p character (sp hybridization at carbon), but when the C-1 σ orbital contains two electrons, it tends toward maximum s character (sp^2 hybridization at carbon). A singlet electron in the C-1 σ orbital distorts the symmetric benzene geometry but not necessarily all the way to conformation I. It is comforting to note the estimation of excited-state energies by the addition of CNDO/S excitation energies to CNDO/2 ground-state energies agrees with chemical intuition.

Finally, it can be seen from the data in Table III that the triplet diradical 2 ($a_2^2b_1a_1$) is clearly not the ground state of phenyl cation. Indeed, both the $^3A_1$ and $^3B_1$ $\pi \rightarrow \pi^*$ triplet excited states are predicted to be of lower energy than 2. Further, the singlet species 3 ($a_2^2a_1^2$) in its most stable conformation is placed 6.82 eV above 1 in its most stable conformation. Hence, we are forced to conclude, within the framework of our calculations, that the $a_2^2b_1a_1$ triplet and $a_2^2b_1^2$ singlet states of phenyl cation may not be accessible through the thermal decomposition of benzenediazonium salts, and the rate factors of Abramovitch should probably be explained in some other way.

Registry No.—Phenylium ion, 17333-73-20.

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The Solution of a Classical Problem. Tautomerism and Isomerism in the α-Methylglutaconic Acid Series

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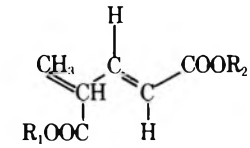
All four isomeric diethyl α-methyl- and γ-methylglutaconates (diethyl 3-methyl-1-propene-1,3-dicarboxylate and 1-methyl-1-propene-1,3-dicarboxylate, respectively) have been prepared for the first time, and their interconversions studied under acid-catalyzed, base-catalyzed, thermal, and photochemical conditions. The compounds previously believed to belong to the α-methyl series were actually γ-methyl derivatives, but were readily converted thermally into the α-methyl isomers, the *Z* product predominating largely. Base-catalyzed reactions, on the other hand, converted the diethyl α-methylglutaconates into the (*E*)-γ-methylglutaconate. The pure α-methylglutaconic acids could not be isolated. The readily obtained (*E*)-γ-methylglutaconic acid was converted into its *Z* isomer, through the anhydride, by treatment with either heat or acid followed by hydrolysis. The stable form of the anhydride was not the expected hydroxypyrone isomer(s), although the latter were observed by NMR in strong acids. No interconversion of 2-methyleneglutaric acid or ester with α- or γ-methylglutaconic acids or esters was observed in the presence of heat, light, acid, or base. However, the interconversion in the presence of a hydrogen transfer catalyst was confirmed.

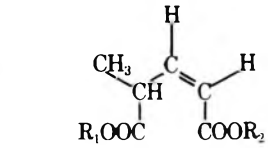
For half a century following the first preparation of the parent compound,[1] heated polemics were associated with the progress toward understanding the tautomerism and isomerism of glutaconic acids. Three research groups were more particularly involved, those of Feist, Thorpe, and Kon, who contributed a total of 49 publications on this subject, and for a long time the debate was centered on the existence of a special type of tautomerism for the three-carbon system, comprising the "normal" and "labile" forms. In the former, a "mobile" hydrogen was attached to the central carbon of the system, which still remained acyclic, while in the latter there was one localized double bond, with the possibility of cis–trans isomerism about it. Five isomeric forms were thus recognized, two cis, two trans, and one "normal", this last one being due to "retarded mobility". The concept of "normal" structures passed away around 1930, and the remaining problem consisted in establishing the position of the double bond in unsymmetrical systems, and determining the stereochemistry about it. The last piece of structural work with acyclic, alkyl-substituted, glutaconic acids was due to Fitzgerald and Kon, and appeared in 1937.[2] The field became dormant until 1952, when the long-debated structure of Feist's acid was finally shown to be 3-methylenecyclopropane-*trans*-1,2-dicarboxylic acid,[3] and thus proved not to be that of a glutaconic acid after all. However, the structures of the other alkylglutaconic acid derivatives were not reinvestigated at that time. The isolation of unsymmetrically substituted glutaconic acids from natural sources[4] made such a study particularly desirable, and we therefore decided to isolate and study the interconversion of the four α-methyl- and γ-methylglutaconic acids, the simplest monosubstituted members of this group. In this traditional nomenclature, the α position refers to the allylic carbon, and the β and γ positions to the vinylic carbons of the propene-1,3-dicarboxylic acid system.

Until this work was completed, only two isomers were known, one cis and one trans, which had been shown by ozonolysis to belong to different tautomeric series.[2] During the preparation of this article a publication appeared which described some isomerization reactions of methylglutaconic esters,[5] but confused the situation even further by claiming the participation of the isomeric methyleneglutaric esters (5), which had not been previously implicated, and which we proved not to be involved at all.

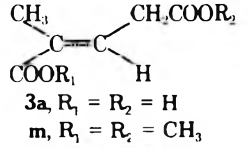
We repeated the condensation of diethyl malonate with chloroform,[1] followed by methylation and hydrolysis, and obtained the crystalline product melting at 144–145°. The assignment to the α-methylglutaconic acid structure **1a** had been essentially based on the assumption that no double bond migration had occurred during the hydrolysis and decarboxylation, and had been supported by ozonolysis, which yielded (from the diester) oxalic and methylmalonic esters.[2] The NMR analysis has now proved this product to belong to the γ-methyl series instead, with one methyl as a singlet, only one vinyl, and two methylene protons. That it was indeed the *E* isomer **3a** became apparent from subsequent chemical observations and NMR data (Table I). The mother solution could be crystallized, and melted at 112–113°, giving the appearance of a pure compound, while being actually a mixture of **1a**, **3a**, and **4a** as shown by NMR. Through the anhydride, the conversion of **3a** into an



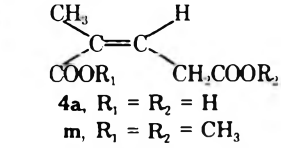
1a, $R_1 = R_2 = H$
m, $R_1 = R_2 = CH_3$
e, $R_1 = R_2 = C_2H_5$



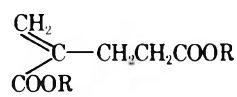
2a, $R_1 = R_2 = H$
m, $R_1 = R_2 = CH_3$
e, $R_1 = R_2 = C_2H_5$



3a, $R_1 = R_2 = H$
m, $R_1 = R_2 = CH_3$
e, $R_1 = R_2 = C_2H_5$
11m, $R_1 = H$; $R_2 = CH_3$
e, $R_1 = H$; $R_2 = C_2H_5$
16m, $R_1 = CH_3$; $R_2 = H$
e, $R_1 = C_2H_5$; $R_2 = H$



4a, $R_1 = R_2 = H$
m, $R_1 = R_2 = CH_3$
e, $R_1 = R_2 = C_2H_5$
12m, $R_1 = H$; $R_2 = CH_3$
e, $R_1 = H$; $R_2 = C_2H_5$
17m, $R_1 = CH_3$; $R_2 = H$
e, $R_1 = C_2H_5$; $R_2 = H$



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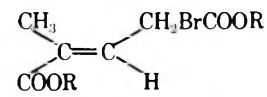

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Table I
NMR (Coupling Constants) of the Glutaconic Acid Derivatives

Compd	Solvent	CH_3	OCH_2CH_3[a]	OCH_3	CH_2	β-Vinyl	γ-Vinyl	C–H
1e	$CDCl_3$	1.34	1.27, 4.19			7.06	5.90	3.38
		(7)	1.30, 4.22			(8, 16)	(1.5, 16)	(1.5, 7, 8)
2e	$CDCl_3$	1.31	1.21, 4.00			6.37	5.84	4.48
		(7)	1.23, 4.16			(9, 11.5)	(11.5)	(7, 9)
3a	Me_2SO-d_6	1.74[c]			3.22[b]	6.78[b]		
3m	$CDCl_3$	1.90[c]		3.74	3.31[b]	6.81[b]		
				3.78				
3e	$CDCl_3$	1.87	1.27, 4.19		3.23	6.97[b]		
		(1)	1.30, 4.22		(7)			
11e	$CDCl_3$	1.87[c]	1.27, 4.23		3.27[b]	7.09[b]		
15e	$CDCl_3$	1.93	1.33, 4.22			7.04		5.05
		(1)	4.25			(1, 11)		(11)
15m	$CDCl_3$	2.03		3.88		7.13		5.16
		(1)		3.92		(1, 11)		(11)
16e	$CDCl_3$	1.86[c]	1.27, 4.18		3.28[b]	6.92[b]		
4a	Me_2SO-d_6	1.85[c]			3.48[b]	6.18[b]		
4m	$CDCl_3$	1.99[c]		3.74	3.61[b]	6.26[b]		
				3.78				
4e	$CDCl_3$	1.99[c]	1.26, 4.25		3.60[b]	6.28[b]		
			1.30, 4.20					
12m	$CDCl_3$	1.98[c]		3.73	3.65[b]	6.42[b]		
12e	$CDCl_3$	1.98	1.27, 4.18		3.62	6.40[b]		
		(1, 1.5)			(1.5, 7)			
17e	$CDCl_3$	1.96[c]	1.29, 4.23		3.63[b]	6.20[b]		

[a] J = 7 Hz. [b] J = 1 and 7 Hz. [c] J = 1 and 1 Hz.

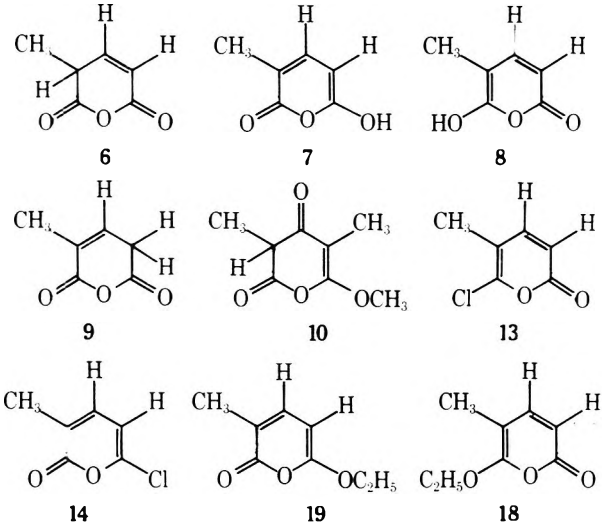
isomer melting at 125–126° could be performed as reported by Fitzgerald and Kon, and the NMR proved this to be the *Z* isomer **4a**, in agreement with the conclusions derived from ozonolysis.

The Anhydride of (*Z*)-γ-Methylglutaconic Acid. Prior to Fitzgerald and Kon's work, two isomeric acids were known, melting at 145[1,6–13] and 118°,[7] which were obtained by saponification of ester precursors, and which were believed to be the *trans*- and *cis*-α-methylglutaconic acids, respectively. It is probable that the latter was very similar to our sample melting at 113°. Feist and Pomme reported that an anhydride could not be formed by treating either acid with acetyl chloride at reflux, or with thionyl chloride in refluxing ether.[6] However, they obtained an anhydride melting at 85° which was formulated as **6**, when either acid was treated with phosphorus pentachloride in order to form their monoacid chloride. They found the hydrolysis of **6** with water not to proceed readily, and they also found that its treatment with aqueous base containing some casein yielded the then expected acid melting at 118°.[6] Thole and Thorpe agreed with the above formulation of the anhydride, and reported the same product to be formed by treatment of the acid melting at 145° with 2 equiv of acetyl chloride in a sealed tube at 100°.[3] However, they believed that this compound was enolized to **7** during distillation, and ruled out the isomeric structure **8** on the basis of a permanganate oxidation reaction.

Thole and Thorpe agreed with Feist and Pomme on the results of the alkaline hydrolysis,[7] but they also observed the slow formation of the trans acid by treatment with warm water. Unfortunately, the melting point of this product was not recorded, and structure **9** was not considered for the anhydride. Fitzgerald and Kon observed that the hydrolysis of the "hydroxy anhydride" with cold water yielded a small amount of what they believed to be a purer cis acid, melting at 125–126°.[2] Unfortunately, their structure determination of the isomeric acids by ozonolysis involved prior conversion to the methyl esters with diazomethane, and distillation of the methyl esters. The thermal isomerization reactions discussed below could only give misleading results, although the published experimental results cannot even be reconciled in detail with the now expected outcome.

Since the trans acid is now known to be **3a** rather than **1a**, a reformulation of the anhydride was desirable. As noted earlier, the acetyl chloride reaction with **3a** yielded mixtures rich in chlorinated products, and was not convenient for obtaining the anhydride itself, which we first encountered during the distillation of the monoester **16e**, and later in the thermolysis of the acid **4a**. The anhydride, which melted at 75°, was unquestionably that of a γ-methylglutaconic acid and had structure **9**, since its NMR spectrum showed one vinyl proton at 6.74, the two methylene protons at 3.58, and the methyl at 2.30 ppm. The isomeric structures **6**, **7**, and **8** are clearly ruled out by this spectrum.

Surprisingly, the enolization of this anhydride proved quite difficult. It did not occur upon distillation, as claimed earlier, and no change in the NMR was apparent when hydrogen chloride was bubbled into the $CDCl_3$ solution for 5 min, or when the compound was heated in trifluoroacetic acid for 62 hr at 100°. Compound **10** is another example in which the enolization to a hydroxypyrone system is known not to occur readily.[14] However, the facile thermal enolization of an acyclic anhydride was described,[15] but is most certainly benefiting from the stabilization of the monoenol by intramolecular hydrogen bending to the other carbonyl. The enolization of **9** was observed when 1 drop of concentrated sulfuric acid was added to the trifluoroacetic acid solution. The NMR then showed a singlet at 2.28 ppm for the methyl, and doublets at 6.72 and 8.38 ppm for the ring protons. The coupling constant of 8 Hz suggested a rapid exchange between the two enolic structures **7** and **8**, in which the values of ca. 9 and 7 Hz, respectively, would have been expected.[7,16]



Treatment of the acidic solution with ice water gave a mixture of the two γ-methylglutaconic acids containing 29% of **3a** and 71% of **4a**, from which a pure sample of the latter was obtained by fractional crystallization. It melted at 125–126°, and thus was probably identical with Fitzgerald and Kon's material.[2] The comparison between the NMR spectra of the products melting at 145 and 125° clearly supported the formulation as trans and cis acids, respectively (Table I). The only other reaction which we performed on this anhydride was a treatment with ethanol at reflux, which gave **12e** in good yield, resulting from nucleophilic attack at the less hindered carbonyl.

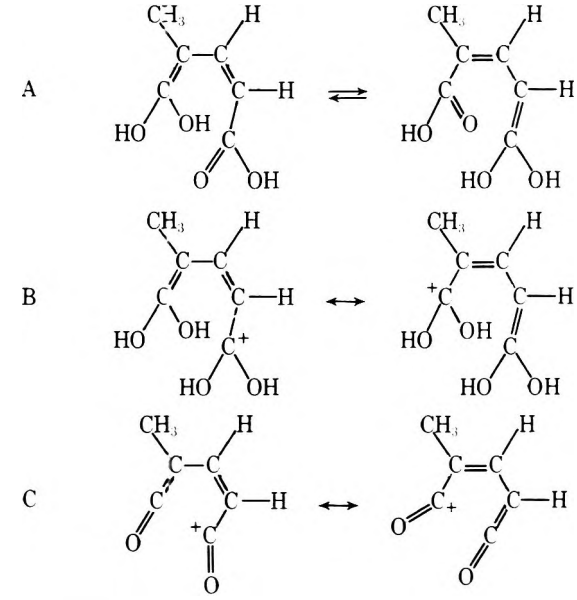
The treatment of **3a** with an excess of acetyl chloride yielded a crystalline product, mp 39–40°, which was an equimolar mixture of **13** and **14**, as shown by the mass spectral and NMR analyses. The separation of the components of this mixture proved difficult, but pure **13**, mp 69–70°, was found to be the only product eluted by column chromatography over silica gel. It was probably identical with the product melting at 71°, and believed by Thole and Thorpe to have structure **14**. We did not investigate whether **13** had isomerization into **14** on the column or had been selectively hydrolyzed. It is now known that the isomer **13**, melting at 75°, may be obtained pure by acid-catalyzed isomerization of **14** in the presence of acetyl chloride.[5]

The (*E*)- and (*Z*)-γ-Methylglutaconic Acids. A. Acid-Catalyzed Reactions. As indicated above, the pure acids **3a** and **4a** were obtained in this work, and the ozonolysis of the latter was uneventful, yielding pyruvic and malonic acids, in contrast to the published reports with the corresponding esters.[2] In order to explore the possibility of isomerizing the double bond to the less substituted positions, **3a** was treated with acid, and the reaction followed by NMR.

Very little change was observed in fluorosulfonic acid at room temperature, but after 10 min at 100° new peaks appeared, a singlet at 1.72 (3 H) and two doublets at 6.18 (1 H) and 7.76 ppm (1 H), with a coupling constant of 8 Hz (after cooling of a similar sample to the usual probe temperature, the chemical shifts were 2.20, 6.62, and 8.28 ppm, respectively). Quenching of the hot solution with ice water yielded a 1:2.5 mixture of **3a** and **4a**, and a similar behavior was observed for a solution of **3a** in concentrated sulfuric acid.

When pure **4a** was dissolved in either of the two acids, the spectrum of the above intermediate was obtained immediately. The mode of formation of this intermediate, as well as its reaction with ethanol to yield the monoester **12**, suggested it to be the anhydride or an equivalent. This was supported by the spectrum of **9** in these acids, which was indistinguishable from that generated from either **3a** or **4a**, and which probably represented **7** and **8** in rapid equilibrium. Furthermore, when a sample of **3a** was heated for 40 hr at 100° in trifluoroacetic acid, a 1:1 mixture of the starting material and the anhydride **9** *in its ketonic form* was obtained.

The conversion of **3a** into a *Z* species in acid could be rationalized by the formation of any of the three sets of structures A, B, or C, in addition to the enolized forms **7** and **8** of the cyclic anhydride **6** or **9**. All have the proton distribution required by the observed NMR spectrum (note that the hydroxyl peaks were not detected experimentally, and thus cannot be used for structural assignments).



Structures A and B follow from the well-known protonation of carboxylic acids in mineral acids.[17] Structure C may be viewed as vinylogous to the methylketenylacylium ion observed by Conrow and Morris upon acid treatment of methylmalonic acid.[18]

We have no direct proof for dismissing the structures A–C. There is a need for a driving force which will explain the formation of the *Z* intermediate from the *E* diacid. In the absence of any obvious stabilizing elements for the *Z* configuration in the acyclic structures A–C, their thermal isomerization to the electronically preferred *E* configuration should have taken place. Consequently, the most satisfying explanation involves a structure in which the *Z* configuration is locked, such as in the anhydride, which is obtained here in its enolized forms **7** and **8** in a manner similar to that described for maleic acid.[19]

Unsaturated and aromatic anhydrides have been reported to be quite stable in superacids,[20] and to undergo reversible protonation at the oxygen rather than at the carbon atoms, and this also applied to unsaturated acids.[19] The same is seen here with **9**, judging from the chemical shifts of the pyrone ring protons in comparison with those of the vinyl protons in the starting material.

The kinetics of the thermal reaction of **3a** to the anhydride could be easily followed by NMR from the disappearance of the methyl signal at 1.50 and the appearance of the signal at 1.70 ppm. A good first-order plot was obtained, and from the rate constants at four different temperatures, an activation energy of 16.5 kcal/mol was determined for the overall cis–trans isomerization about the double bond.

B. Base-Catalyzed Reactions. Since the acid-catalyzed isomerization of **3a** and **4a** did not yield any detectable quantity of the α-methylglutaconic acid isomers, we turned to base-catalyzed treatments. The conversion of α,β-unsat-

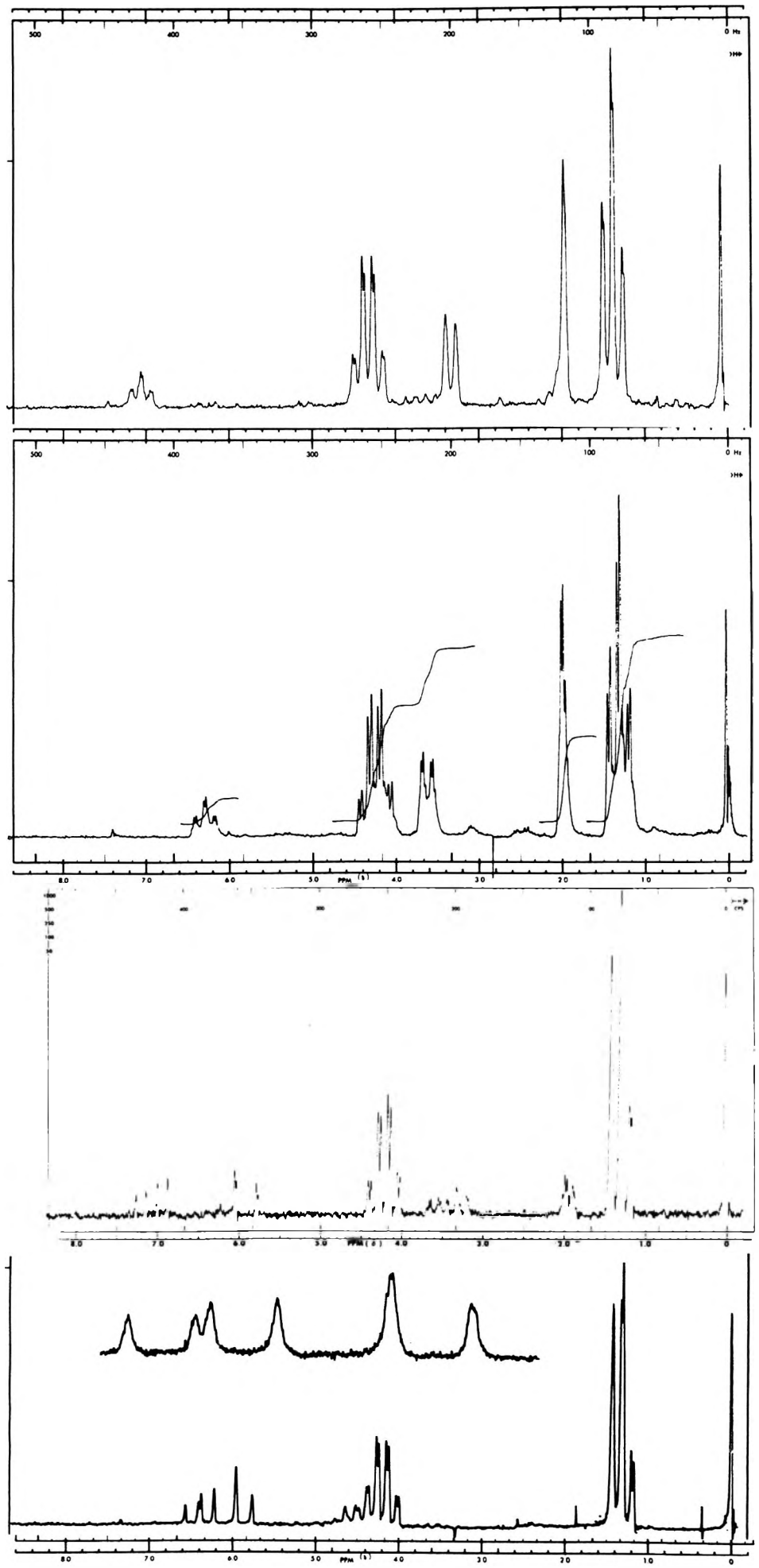


Figure 1. NMR spectra of the four isomeric diethyl α-methyl- and γ-methylglutaconates. From top to bottom: **3e, 4e, 1e,** and **2e.** (The sample of **1e** is contaminated with small amounts of **3e** and **4e.**)

urated acids into their β,γ-unsaturated isomers has long been known, most notably through the early work of Fittig and his group, followed by Kon and Linstead and their coworkers.[21]

The acidic nature of the methylene protons in **3a** was indicated by their exchange in deuterium oxide, which was complete after 20 min at 90°.[22] When **3a** was refluxed in alkaline solution for 6 days a mixture containing 75% of a 5:1 mixture of **3a** and **4a** and 25% of one α-methylglutaconic acid isomer was obtained. The new acid was recognized in the NMR by a methyl doublet at 1.20 (J = 6 Hz), and the γ-vinyl proton as a doublet at 5.73 ppm (J = 16 Hz). Although the other signals were masked by those of the starting material, the magnitude of this coupling constant indicated the E configuration for the product, which was therefore **1a**. Unfortunately, it could not be obtained pure following either fractional crystallization or chromatography.

C. Thermal Reactions. When a pure sample of **3a** was heated under vacuum at 160°, its isomer **4a** slowly sublimed in the pure state. After 12 hr at ca. 30 Torr, 60% of the original sample had been isomerized and this procedure was the simplest for obtaining pure **4a**. When there was no cold area for the product to condense on, the anhydride **9** was found to be the major product, and the thermal treatment of the Z acid **4a** under the same conditions also yielded the anhydride **9**. It appeared, therefore, that the cis–trans isomerization of **3a** was followed by anhydride formation, but no double bond migration to the α-methylglutaconic acid system was detected in these experiments.[23]

D. Photochemical Reactions. The irradiation of either **3a** or **4a** in anhydrous ether at 253.7 nm for 2 hr yielded an equimolar mixture of these two acids, without the formation of any detectable quantity of the isomeric α-methylglutaconic acids **1a** or **2a**, as observed by NMR.[24]

Diethyl Methylglutaconates. The difficulties encountered in attempting to isolate the acid **1a** which was produced in the base-catalyzed isomerization of **3a** prompted us to handle the esters instead, with the hope that their preparative gas chromatographic separation would be feasible, and would allow the isolation of **1e** and **2e** in pure form.

The Wittig reaction is usually the method of choice for introducing a double bond regiospecifically, but the condensation of ethyl 2-formylpropionate with carboethoxymethylenetriphenylphosphorane, at room temperature or below, actually yielded an equimolar mixture of **2e** and **3e**, rather than the expected mixture of **1e** and **2e**. The slow isomerization of **2e** into **3e** by the basic phosphorane reagent[25] was demonstrated in a control experiment, and thus explained the formation of the latter product. The distillation of the reaction mixture under vacuum in a spinning band column afforded three fractions, pure **2e** in the first, and mixtures of **1e** and **4e** in the second and third (95:5 and 20:80, respectively). The residue contained a mixture of all four isomers **1e**–**4e**.

Essentially pure samples of **1e** and **4e** were obtained by preparative gas chromatography, and the independent existence of all four isomeric α-methyl- and γ-methylglutaconic esters was thus finally demonstrated experimentally, as shown in Figure 1.

Other synthetic approaches toward the α-methylglutaconic ester series were not as successful. For example, the Doebner condensation of ethyl 2-formylpropionate with monoethyl malonate[12] yielded **3e** exclusively, as did the zinc reduction of the allylic bromide **15e**.

A. Thermal Isomerization Reactions. Surprisingly, the distillation of a sample of **3e** which was pure from NMR yielded a major fraction which was the pure Z isomer **4e**. Some starting material, as well as **1e** and **2e**, was observed in the other fractions. This isomerization was completely suppressed by lowering the pot temperature from 230 to 150° during the distillation, and this thermal reaction therefore provided an inviting avenue into the α-methylglutaconic acid series. It also created problems for the GLC analyses, and made a sample of either **3e** or **4e**, which was known to be pure from NMR, appear to be contaminated by three other components. This was corrected by lowering the temperature of the injection block to ca. 180°, and in these conditions none of the esters **1e**–**4e** was found to be isomerized in the gas chromatography. Unfortunately, we did not succeed in obtaining a complete separation of the peaks for the isomers **1e** and **4e**. However, the separation was sufficient for qualitative measurements, which closely paralleled the NMR analyses.

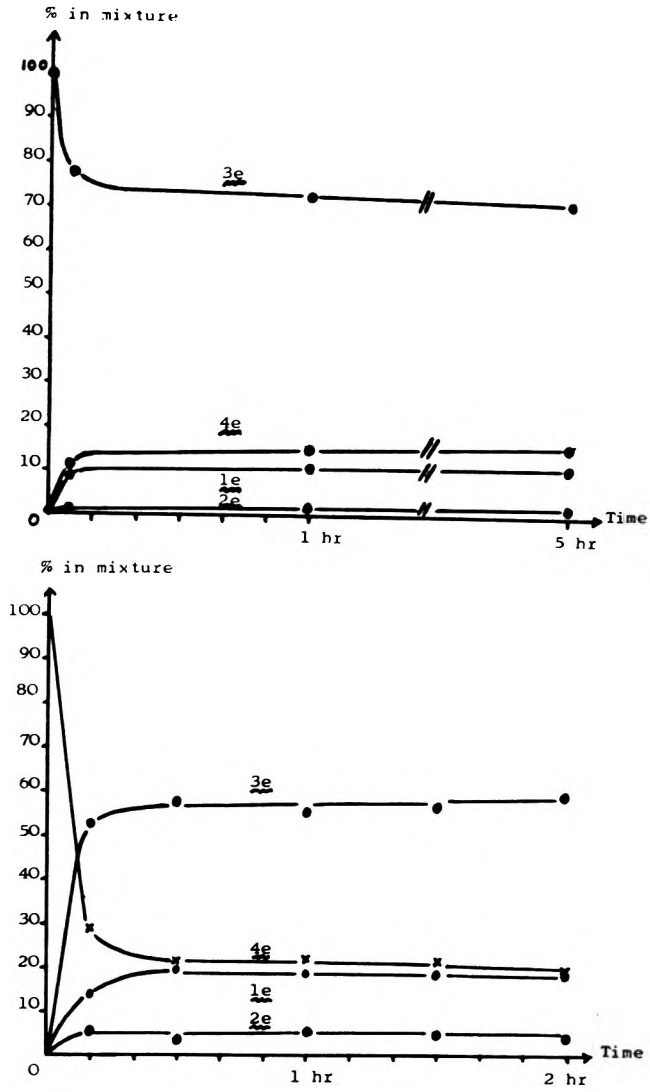


Figure 2. The thermal isomerization of **3e** at 260°, and of **4e** at 265°. (The accuracy of the GLC analyses is ca. ±10%, and the small amounts of polymeric materials were neglected.)

While the occurrence of the thermal isomerization of the esters had been dramatically demonstrated, the kinetics and equilibrium concentrations were more difficult to measure, because of competing polymerization and/or decomposition reactions which yielded insoluble materials, especially at higher temperatures. Smooth curves were obtained for the isomerization of **3e** at 260° and **4e** at 265°, which showed that the cis–trans isomerization proceeded faster than the double bond migration (Figure 2). Poorer results were obtained in the thermal treatment of the other isomers, which was accompanied by extensive polymerization. These thermal reactions require further study, and we hope to be able to report on their course in the near future.

The thermal isomerization reactions described above un-

Table II
NMR of the Anhydride Derivatives

Compd	Solvent	CH_3	CH_2	Vinyl	Ethyl
9	$CDCl_3$	2.03 (m)	3.58 (m)	6.74 (m)	
7 ⇌ 8	H_2SO_4	2.30		6.74 (8), 8.32 (8)	
	FSO_3H	2.20		6.62 (8), 8.28 (8)	
13	$CDCl_3$	2.05		6.15 (9), 7.21 (9)	
14	$CDCl_3$	2.05 (1)		6.09 (7), 7.05 (7, 1)	
18	$CDCl_3$	1.99 (1.5)		5.34 (9), 7.24 (9, 1.5)	1.41 (7), 4.20 (7)

doubtedly help explain the results of Fitzgerald and Kon's experiments.[2] As a check, the acid **3a** was esterified with diazomethane and yielded **3m** which was pure from NMR. Vacuum distillation with a pot temperature of 210–230° yielded **4m** as the major product, but one fraction containing about 40% of **1m** was also obtained. The residue was a mixture of all four isomers.

B. Acid-Catalyzed Reactions. The only attempt at isomerizing the diethyl γ-methylglutaconate system into the α-methyl isomer was by treating **4e** with concentrated sulfuric acid for 10 min at 100°. Dilution with water and extraction yielded a 1:1 mixture of the *E,Z* pair of **3a** and **4a**, without any evidence for double bond migration.

C. Photochemical Isomerization Reactions. A photoequilibrium of all four isomeric esters was observed upon irradiation of either **2e** or **3e** at 253.7 nm in benzene for 70 hr. The equilibrium mixture contained 6% of **1e**, 2% of **2e**, 47% of **3e**, and 45% of **4e**.

D. Base-Catalyzed Isomerization Reactions. All the chemical syntheses which utilized base-catalyzed reactions had yielded the pure (*E*)-γ-methylglutaconic diester **3e**, resulting from isomerization of the initially formed α-methylglutaconic diester. The facile isomerization of the *Z* diester **2e** was confirmed by an independent treatment with pyridine, which resulted in complete disappearance of the starting material, and formation of **3e**.

Monoethyl γ-Methylglutaconates. The treatment of the anhydride **9** with ethanol had yielded a monoethyl ester, identified as **12e**, and the synthesis of the isomeric monoesters was desirable for spectroscopic comparison. One single isomer was isolated from the Doebner condensation of ethyl 2-formylpropionate with malonic acid.[11,12,27] The NMR analysis showed it to belong to the γ-methyl series, and to be *E* from the allylic coupling constant of 7.5 Hz. This product was therefore **16e** and the original assignment of **12e** was confirmed by the comparison of the NMR spectra as well as the ultraviolet spectra. As expected for the conjugated acid **12e**, the absorption maximum shifted from 213 to 218 nm in going from pH 1 to 9, whereas there was no bathochromic shift in the spectrum of the nonconjugated acid **16e** when base was added. Cis–trans isomerization but no appreciable double bond migration took place in **16e**, either thermally during distillation, or photochemically upon irradiation at 253.7 nm in benzene for 15 hr. In the thermal treatment, the formation of both the anhydride **9** and the ethoxypyrone **18** competed with the isomerization. The structural assignment of this latter was based mainly on the NMR spectrum, which showed the two adjacent ring protons with a coupling constant of 9 Hz. As seen in the chloroanhydride **14**, the isomeric ethoxypyrone **19** would have been expected to show a coupling constant of 7 Hz for these adjacent protons. The 1.3:1 mixture of **16e** and **17e** which was formed by irradiation of **16e** could not be separated into its components by chromatography over silica gel. Similarly, a mixture of **11e** and **12e** (1:1.3) was obtained by photolysis of the former in the same conditions, but could not be separated into its components. However, all four isomeric monoesters could be easily identified by their NMR spectra (Table I).

Conclusion

Although the synthesis of the α-methylglutaconic acids is still to be performed, the main part of this article described the synthesis and interconversion of the four isomeric diethyl α-methyl- and γ-methylglutaconates.

Diethyl methyleneglutarate (**5**) was not detected in this work by either NMR or GLC analyses, and its independent treatment under thermal, photochemical, or base-catalyzed conditions did not result in any noticeable isomerization to the methylglutaconic esters. The Swiss workers' claim to the contrary[5] needed to be explained. We repeated their hydrogen transfer reaction in the presence of rhodium chloride, and confirmed that both **3e** and **5** yielded a mixture of **5**, **3e**, **4e**, and **1e**, and that **2e** was not a reaction product. A major additional component was obtained, however, which was identified as diethyl α-methylglutarate, the product of reduction. Contamination by some rhodium catalyst and/or difficulties with the NMR analyses are therefore the most logical explanations for the recently published results.

Experimental Section

(*E*)-γ-Methylglutaconic Acid (3a). From 227.4 g of diethyl malonate and 56 ml of chloroform,[1] there was obtained 70 g of recrystallized sodio-1,1,3,3-tetracarboethoxypropene: NMR (Me_2SO-d_6) 1.23 (t, 7 Hz, 12 H), 4.04 (q, 7 Hz, 8H), and 8.06 ppm (s, 1 H). Methylation of 49.0 g with 9.1 ml of methyl iodide yielded 38.0 g of 1,1,3,3-tetracarboethoxybutene: bp 160–161° (0.5 Torr); NMR ($CDCl_3$) 1.28 (m, 12 H), 1.67 (s, 3 H), 4.23 (m, 8 H), and 7.52 ppm (s, 1 H). Reflux overnight in a solution of 38 g of potassium hydroxide in 200 ml of water, followed by acidification to pH 3 and ether extraction, yielded 11.4 g of recrystallized **3a**: mp 144–145°; ir 3100 (br), 1700, 1600, 1450, 1370, 1280, 1140, 900 cm^{-1}; mol wt 144 (mass spectrum). Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.55. Found: C, 49.72, H, 5.40. The NMR of the mother liquor showed a mixture of **1a**, **3a**, and **4a**.

(*Z*)-γ-Methylglutaconic Acid (4a). A solution of 0.598 g of **3a** in 1 ml of either fluorosulfonic acid or sulfuric acid was heated at 100° in an oil bath for 2 hr. The light brown solution was quenched with 5.0 g of ice water and extracted with 25 ml of ether, which was dried and concentrated, yielding 0.278 g of a mixture of 29% **3a** and 71% **4a** by NMR. Repeated crystallizations from chloroform yielded 0.202 g of **4a**: mp 125–126° (lit. 125–126°); ir (Nujol) 3100 (br), 1690, 1670, 1630, 1360, 1310, 930 cm^{-1}. The starting material (0.028 g) was recovered from the mother solution.

Ozonolysis of 3a. A solution of 4.7 g of **3a** in 150 ml of ethyl acetate was ozonized at −80°, concentrated under vacuum at room temperature, treated with 100 ml of water, and warmed over a steam bath for 15 min. The solution was concentrated, and the residue esterified with ethanol and sulfuric acid at reflux for 24 hr. Distillation yielded 0.620 g of ethyl pyruvate, bp 153–155°, and 0.460 g of diethyl malonate, bp 198–199°, identified by comparison of their NMA and GLC with authentic samples.

γ-Methylglutaconic Anhydride (9). A. A solution of 3.0 g of **3a** in 10 ml of acetic anhydride was refluxed for 2 hr. The dark brown solution was distilled and yielded 1.0 g of **9** at 140–144° (3 Torr). After recrystallization from CCl_4 **9** had mp 74–76°; mol wt 126 (mass spectrum); ir ($CHCl_3$) 1820, 1760, 1380, 1220, 1070 cm^{-1}. Anal. Calcd for $C_6H_6O_3$: C, 57.10; H, 4.76. Found: C, 57.00; H, 4.73.

B. A solution of 0.050 g of **3a** in 0.5 ml of trifluoroacetic acid was heated in an NMR tube at 100° for 62 hr. The NMR spectrum showed a 1:1 mixture of **3a** and **9**.

Reaction of (*E*)-γ-Methylglutaconic Acid with Acetyl Chloride. A solution of 3 g of **3a** in 6 ml of acetyl chloride was refluxed for 24 hr, concentrated, and distilled, and yielded 2.2 g, bp 80–81° (4 Torr), mp 39–40°, mol wt 144 (mass spectrum), of a mixture of **13** and **14**. Chromatography over silica gel of 1.0 g of this mixture yielded 0.70 g of crude **13**, eluted with chloroform–ether. After recrystallization from petroleum ether it had mp 69–70°; NMR ($CDCl_3$) 2.05 (s, 3 H), 6.15 (d, J = 9 Hz, 1 H), and 7.21 ppm (d, J = 9 Hz, 1 H); ir ($CHCl_3$) 3000, 1640, 1555, 1530, 1100, and 935 cm^{-1}. Anal. Calcd for $C_6H_5O_2Cl$: C, 49.82; H, 3.47; Cl, 24.30. Found: C, 49.92; H, 3.35; Cl, 24.00. By difference, the NMR of **14** was 7.05 (d, d, J = 7, 2 Hz, 1 H), 6.09 (d, J = 7 Hz, 1 H), and 2.05 ppm (d, J = 2 Hz).

Deuterium Exchange of 3a. A solution of 0.050 g of **3a** in 0.5 ml of deuterium oxide had the following NMR at room temperature: 1.48 (s, 3 H), 3.01 (d, J = 6 Hz, 2 H), and 6.52 ppm (t, J = 6 Hz, 1 H). Complete disappearance of the methylene protons was observed after 20 min at 90°, and the 6.52-ppm signal had become a broad singlet.

Deuterium Exchange with 4a. A solution of 0.302 g of **4a** in 2 ml of 40% sodium deuteroxide (prepared by careful reaction of sodium hydride with deuterium oxide) was stirred at room temperature for 5 min. I was acidified with deuterium chloride and extracted with 5 ml of ether which was dried and evaporated, yielding 0.175 g of **3a**-d_4: NMR (Me_2SO-d_6) 1.73 (s, 3 H) and 6.66 ppm (br s, 1 H); mol wt 148 (mass spectrum).

Kinetic Study of the Reaction of 3a in Sulfuric Acid. The NMR probe temperature was adjusted to 75, 80, 85, and 90° utilizing the relative chemical shifts of the ethylene glycol protons. All rate determinations were run in duplicate starting from 0.050 g of **3a** in 0.5 ml of concentrated sulfuric acid. The progress of the reaction was followed by the decrease in the integration for the methyl peak at 1.50 ppm in the starting material. The plot of log $(I_t - I_e)$ vs. time was linear, where I_t and I_e are the values of the integration at time t and at equilibrium. The rate constants were derived from the slope of this plot at each temperature and were 4, 5.29, 7.06, and 10.3 × 10^{-2} min^{-1} at 75, 80, 85, and 90°, respectively. The equilibrium constants were 1.25, 1.41, 1.67, and 2.16 at these temperatures. The activation energy of 16.5 kcal/mol was obtained from the plot of log k vs. $1/T$.

Reaction of 4a with Concentrated Acids. A solution of 0.300 g of **2a** in 1 ml of concentrated sulfuric acid at room temperature showed NMR peaks at 1.70 (s, 3 H), 6.11 (d, J = 8 Hz, 1 H), and 7.76 ppm (d, J = 8 Hz, 1 H). The hydroxyl proton was not seen even at −80°. The solution was quenched with 5 g of ice–water and extracted with 10 ml of ethyl acetate which was washed, dried, and evaporated. There was obtained 0.240 g of starting material, mp 125–126°. A similar result was observed with fluorosulfonic acid.

(*Z*)-γ-Methylglutaconic Acid-d_3. A solution of 0.250 g of **4a** in 1 ml of concentrated sulfuric acid was quenched immediately in deuterium oxide. After work-up as above, there was obtained 0.212 g of **4a**-α-d_1-dicarboxyl-d_2: NMR (Me_2SO-d_6) 1.88 (s, 3 H), 3.48 (d, J = 6 Hz, 1 H), 6.16 (br s, 1 H); mol wt 147 (mass spectrum).

Isomerization of 3a in Base. A solution of 0.242 g of **3a** in 8 ml of 30% aqueous potassium hydroxide was refluxed for 6 days, acidified to pH 1, and extracted with 10 ml of ether, which was dried and evaporated. The NMR of the crude product indicated 75% of a 5:1 mixture of **3a** and **4a** and 25% of **1a**. From this, there was obtained 0.132 g of a solid, which was a 3:1 mixture of **3a** and **4a** from NMR. It could not be fractionated by crystallization or TLC.

Isomerization of 4a in Base. A solution of 0.050 g of **4a** in 5 ml of 40% aqueous potassium hydroxide was stirred at room temperature for 5 min. Following work-up as as above, the crude solid product gave an NMR spectrum identical with that of **3**, and melted at 144–145° after recrystallization from water.

Thermal Isomerization of 3a. A Pyrex vessel containing 1.0 g of **3a** was heated in a sand bath at 160° for 12 hr at 30 Torr. Part of the sample had sublimed and was mostly **4a**. The latter was purified by fractional crystallization from 1:1 chloroform–hexane, and melted at 125–126°. In another experiment, the anhydride **9** was the major product when **3a** was placed in a tube which was sealed under 30 Torr and heated at 180° for 8 hr.

Thermal Isomerization of 4a. A Pyrex vessel containing 0.500 g of **4a** was heated in a sand bath at 170–175° for 7 hr at 30 Torr. After cooling, 25 ml of hot carbon tetrachloride was added. The solution yielded 0.214 g of **9**, mp 75–76°.

Photochemical Isomerization of 3a. A solution of 1.0 g of **3a** in 20 ml of anhydrous ether was irradiated at 254 nm in a Rayonet reactor for 2 hr. After evaporation of the solvent, a 1:1 mixture of **3a** and **4a** (NMR) was obtained.

Photochemical Isomerization of 4a. The above procedure was followed, using 0.033 g of **4a** in 5 ml of ether, and yielded an equimolar mixture of **3a** and **4a**. Although there were signals in the region of 0.9–1.4 ppm, the corresponding vinyl doublets expected from **1a** of **2a** were not detected.

(*Z*)-4-Carbomethoxy-2-methyl-2-butenoic Acid (12m). A solution of either **4a** (0.180 g) or **9** (0.102 g) in 2 ml of concentrated sulfuric acid at room temperature was quenched immediately in 5 ml of chilled methanol. After dilution with 10 ml of water and extraction with three 10-ml portions of ether which were subsequently dried and concentrated, 0.106 g of **12m** was obtained: mp 71–72° after recrystallization from chloroform–hexane (1:4); ir ($CHCl_3$) 3600 (br), 3100, 1720, 1680, 1640, and 1510 cm^{-1}; uv (EtOH) λ_{max} 218 nm (ε 3800) in a buffer at pH 9, 213 nm (ε 3400) at pH 1. Anal. Calcd for $C_7H_{10}O_4$: C, 53.10; H, 6.34. Found: C, 52.80; H, 6.30.

(*Z*)-4-Carboethoxy-2-methyl-2-butenoic Acid (12e). A. A solution of 0.514 g of **4a** or 0.259 g of **9** treated with ethanol as above yielded **12e** (0.245 and 0.208 g, respectively): mp 56–58° after recrystallization from hexane; ir ($CHCl_3$) 3600 (br), 3100, 1720, 1680, and 1515 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 55.71; H, 7.00.

(*E*)-4-Carboethoxy-3-pentenoic Acid (16e). A solution of 13.0 g of freshly distilled ethyl formylpropionate, 11.0 g of malonic acid, and 10 ml of purified pyridine was heated on a steam bath for 4 hr, poured over 50 g of ice, stirred until the ice melted, and acidified to pH 2 with cooling. The precipitate was washed with a small amount of cold water, dried, and recrystallized from hexane, yielding 8.0 g of **16e**: mp 66–67°; ir ($CHCl_3$) 3500 (br), 2900, 1710, 1700, 1640, 1360, 1080, and 1030 cm^{-1}; uv (EtOH) λ_{max} 225 nm (ε 8590) at pH 9, 225 nm (ε 8045) at pH 1. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 55.73; H, 7.03.

Photolysis of 16e. A solution of 3.0 g of **16e** in 50 ml of spectrograde benzene was irradiated at 254 nm for 15 hr, and yielded a 1.3:1 mixture of **16e** and **17e**. These isomers could not be separated by chromatography or selective extraction with base.

Photolysis of 12e. A solution of 0.974 g of **12e** in 5 ml of benzene was irradiated at 254 nm for 15 hr, and yielded a 1.31:1 mixture of **12e** and **11e** which could not be separated.

Thermolysis of 16e. Distillation of 3.0 g of **16e** in a spinning band apparatus gave a major fraction (1.44 g) of **9**, bp 102–103° (3.5 Torr). It was recrystallized from carbon tetrachloride and melted at 75–76°. A minor fraction (0.031 g), bp 142–144° (3.5 Torr), contained mainly **18** with a trace of **9**. When this experiment was repeated, only **9** was isolated. The residual liquid was a ca. 1:1 mixture of **16e** and **17e**.

Wittig Reaction of Ethyl Formylpropionate with Carboethoxymethylenetriphenylphosphorane. A solution of 21.4 g of the phosphorane in 250 ml of absolute ethanol was added dropwise with stirring at room temperature to 8.0 g of ethyl formylpropionate.[28] After stirring for 48 hr the solution was concentrated under vacuum at room temperature, and 250 ml of petroleum ether was added. The precipitate was filtered and washed with an additional 50 ml of solvent. The combined extracts were concentrated at room temperature, and yielded 5.14 g of **2e** and **3e** in equal amounts (NMR), with a trace of triphenylphosphine oxide. The same results were obtained at −5°. Distillation in a spinning band apparatus (pot temperature 225°) yielded three fractions. The first was 1.64 g of pure **3e** (NMR and GLC): bp 70–72° (4.7 Torr); ir (neat) 3000, 1730, 1710, 1640, 1410, 1390, 1370, 1310, 1300, 1290, 1210, 1030, 945, and 830 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00. Found: C, 59.85; H, 7.83. The second fraction, 2.12 g, bp 77–80° (4.7 Torr), contained ca. 95% of **4e** and 5% of **1e**. The former was purified by preparative GLC, and had ir (neat) 2995, 1730, 1710, 1645, 1450, 1440, 1365, 1315, 1230, 1180, 1135, 1030, 855, and 840 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00. Found: C, 59.72; H, 7.89. The last fraction [0.73 g, bp 83–86° (4.7 Torr)] was a mixture of 20% **4e** and 80% **1e**, and the latter was obtained at least 95% pure by preparative GLC. The residue from distillation was a mixture of the four isomers **1e**–**4e**.

Condensation of Ethyl Formylpropionate with Monoethyl Malonate. A mixture of 26.0 g of freshly distilled ethyl formylpropionate, 26.4 g of monoethyl malonate, and 20 ml of pyridine was refluxed overnight,[2] diluted with water, acidified to pH 2, extracted with two 50-ml portions of ether, which were dried and concentrated at 30°, and yielded 14 g of **3e** pure from NMR and GLC: ir (neat) 2980, 1730, 1710, 1645, 1440, 1380, 1260, 1180, 1120, 1050, 860, 740 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00. Found:

C, 59.82; H, 7.92. Distillation of this product in a 6-in. Vigreux column with a pot temperature of 230° yielded 1.9 g at 78–82° (4.7 Torr) which contained 20% of **2e**, 30% of **1e**, and 50% of **4e** from GLC. There was also obtained 3.0 g, bp 82–83° (4.7 Torr), which was pure **4e**.

Diethyl (*E*)-α-Bromo-γ-methylglutaconate (15e). A mixture of 12.0 g of **3e**, 13.0 g of *N*-bromosuccinimide, a trace of benzoyl peroxide, and 150 ml of carbon tetrachloride was refluxed for 48 hr. The filtrate was washed with 100 ml of 10% bicarbonate and 100 ml of water. The organic phase was dried and concentrated. Distillation yielded 5.0 g of starting material and 4.3 g of **15e**: bp 130–133° (0.25 Torr); ir (neat) 2995, 1735, 1710, 1640, 1440, 1365, 1255, 1280, 1210, 1025, 980, 860, and 750 cm^{-1}. Anal. Calcd for $C_{10}H_{15}O_4Br$: C, 43.00; H, 5.37; Br, 28.25. Found: C, 42.91; H, 5.30; Br, 27.97.

Reduction of 15e. Zinc dust (2.3 g) was added to 1.3 g of **15e** in 2 ml of glacial acetic acid, and the mixture was stirred for 1 hr.[26] It was filtered, diluted with 50 ml of water, and extracted with 25 ml of ether which was dried and concentrated, yielding 0.7 g of **3e**.

Thermal Isomerizations. Neat samples of diesters (ca. 0.050 g) in sealed tubes were heated in a sand bath for various lengths of time. After cooling, the tubes were opened, acetone was added, and the solution was analyzed by GLC utilizing a 4 ft × 0.25 in. glass column of 15% diethylene glycol succinate on Chromosorb W, an injection temperature of 180°, and an oven at 50° which was heated at 4°/min. In all these experiments, a dark, insoluble material had been formed.

Irradiation of 4e. A solution of 0.200 g of **4e** in 5 ml of benzene was irradiated at 254 nm for 70 hr, and was shown by GLC to contain 2% of **2e**, 6% of **1e**, 44% of **4e**, and 48% of **3e**.

Irradiation of 3e. A solution of 0.300 g of **3e** in 5 ml of benzene was irradiated at 254 nm for 70 hr, and was shown by GLC to contain 2% of **2e**, 5% of **1e**, 46% of **4e**, and 47% of **3e**.

Dimethyl (*E*)-γ-Methylglutaconate (3m). Diazald (42 g) was used to prepare an ether solution of diazomethane, and 6.5 g of **3a** was added to it. Concentration under vacuum yielded 8.72 g of **3m**, judged to be pure from NMR: ir (neat) 2950, 1740, 1720, 1660, 1440, 1260, 1200, 1180, 1130, 1020, 1010, and 740 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 6.99. Found: C, 55.54; H, 6.92. A 3-g sample of the ester was distilled in a spinning band apparatus with a pot temperature of 210–230°, and yielded 2.3 g of **4m**: bp 68–69° (6 Torr); ir (neat) 2950, 1740, 1710, 1650, 1420, 1240, 1200, 1180, 1140, 1020, 1000, and 850 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 6.99. Found: C, 55.61; H, 6.84. A minor fraction (0.240 g), bp 73–76° (6 Torr), contained ca. 40% of **1m** and 60% starting material from GLC.

Dimethyl 2-Methyleneglutarate (5m). A mixture of 34.0 g of methyl acrylate, 1.0 g of tributylphosphine, and 0.2 g of hydroquinone in 80 ml of *tert*-butyl alcohol was refluxed for 7.5 hr,[29] concentrated under vacuum, and distilled to yield 9.5 g of **5m**: bp 74–77° (9.5 Torr); NMR ($CDCl_3$) 2.62 (m, 4 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 5.64 (s, 1 H), and 6.24 ppm (s, 1 H); ir ($CHCl_3$) 3000, 2950, 1710, 1610, 1430, 990, and 950 cm^{-1}.

Diethyl 2-Methyleneglutarate (5e). A mixture of 20.0 g of ethyl acrylate, 1.0 g of tributylphosphine, and 0.2 g of hydroquinone in 80 ml of *tert*-butyl alcohol was refluxed for 7.5 hr, concentrated under vacuum, and distilled to yield 12.5 g of **5e**: bp 92–94° (3 Torr); NMR ($CDCl_3$) 1.25 (t, J = 7 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 2.58 (broad s, 4 H), 4.16 (q, J = 7 Hz, 2 H), 4.20 (q, J = 7 Hz, 2 H), 5.20 (s, 1 H), and 6.20 ppm (s, 1 H); ir (neat) 2900, 1730, 1720, 1630, 1370, 1300, 1260, 1190, 1140, 1045, 950, 890, 860, and 820 cm^{-1}.

2-Methyleneglutaric Acid (5a). A mixture of 8.0 g of **5m**, 7.82 g of potassium hydroxide, and 25 ml of water was refluxed for 2 hr, cooled, and brought to pH 1. The precipitate was filtered and recrystallized from ether to yield 3.1 g of **5a**: mp 130–136° (lit.[29] mp 129–130°); NMR (Me_2SO-d_6) 2.43 (m, 4 H), 5.62 (s, 1 H), 6.07 (s, 1 H), and 12.40 ppm (br s, 2 H); ir ($CHCl_3$) 3500, 3000, 2950, 2400, 1710, 1620, 1430, 990, and 950 cm^{-1}.

Acid Treatment of 5a. A solution of 0.30 g of **5a** in 3 ml of concentrated sulfuric acid was heated in an oil bath at 100° for 1 hr. The dark brown solution was diluted with 10 ml of water and extracted with 10 ml of ether. The extract was dried and concentrated and yielded 0.17 g of crystalline starting material.

Base Treatment of 5a. A solution of 0.500 g of **5a**, 0.600 g of potassium hydroxide, and 20 ml of water was refluxed for 18 hr, cooled, adjusted to pH 1, and extracted with 20 ml of ether. The extract was dried and concentrated, and yielded pure starting material.

Irradiation of 5a. A solution of 0.200 g of **5a** in 5 ml of methanol was irradiated at 254 nm for 15 hr. Evaporation of the solvent yielded the starting material.

Rhodium Chloride Treatment of 5e. A mixture of 0.050 g of **5e**, 0.030 g of rhodium(III) chloride dihydrate, 0.010 g of hydroquinone, and 0.5 ml of ethanol was heated in a sealed glass tube for 4.5 hr at 210°.[5] The mixture was concentrated and filtered after addition of 2 ml of carbon tetrachloride. The filtrate was shown by GLC to contain 25% of an unknown component, 8% of starting material, 10% of **4e**, 8% of **1e**, and 49% of **3e**.

Rhodium Chloride Treatment of 3e. The above procedure was repeated exactly with **3e**. GLC analysis showed the reaction mixture to contain 13% of the unknown, 7% of **5e**, 9% of **4e**, 8% of **1e**, and 63% of **3e**.

Diethyl 2-Methylglutarate. The unknown product in the rhodium chloride experiments gave no peaks above *m/e* 156 in the mass spectrum, compared to *m/e* 154 for each of the isomers **1e–4e**, which were not distinguishable by this technique, and **5e**. The diethyl 2-methylglutarate structure was therefore indicated and this product was prepared in 83% yield by hydrogenation of **5e** over 5% palladium on charcoal catalyst. It had bp 121–122° (3.3 Torr), NMR ($CDCl_3$) 1.18 (d, J = 6 Hz, 3 H), 1.25 (t, J = 7.5 Hz, 6 H), 1.7–2.7 (complex, 5 H), and 4.16 ppm (q, J = 7.5 Hz, 4 H), and was identical (GLC and mass spectrum) with the above unknown.

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Registry No.—**1e**, 53358-20-6; **2e**, 56298-60-3; **3a**, 53358-21-7; **3e**, 53358-19-3; **3m**, 53358-16-0; **4a**, 53358-22-8; **4e**, 53358-18-2; **4m**, 53358-15-9; **5a**, 3621-79-2; **5e**, 5621-43-2; **5m**, 5621-44-3; **7**, 56298-61-4; **8**, 56298-62-5; **9**, 56298-63-6; **11e**, 56298-64-7; **12e**, 56298-65-8; **12m**, 56298-66-9; **13**, 53358-24-0; **14**, 53358-25-1; **15e**, 56298-67-0; **15m**, 56298-68-1.

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Torsional Isomerism and Configurational Assignments in Amides Containing Three Asymmetric Centers. A Method for Distinguishing Meso and DL Secondary Amines[1a,b]

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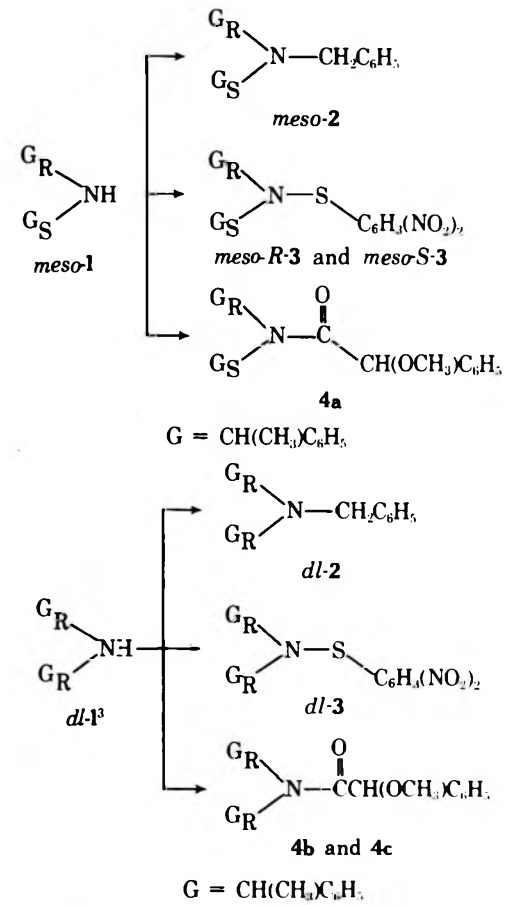
The amides of 1-methoxyphenylacetic acid (*O*-methylmandelic acid) and *dl*- and *meso*-bis(1-phenylethyl)amine were prepared and their NMR spectra obtained under conditions of both slow and rapid torsion about amide bonds. The diastereomeric amides prepared from the meso amine could be interconverted by torsion about the configurationally labile amide bond. The diastereomeric amides prepared from the racemic amine could be separated since they differed in configuration at asymmetric carbon atoms, while the amide bond was not a configurational unit. The free energies of activation for torsion about the amide bond were determined using NMR spectroscopy. The values obtained for the amides prepared from the meso amine (15.6–15.9 kcal/mol) were nearly the same as those obtained for the two amides prepared from the *dl* amine (15.6 and 16.0 kcal/mol), although the stereochemical processes were different, isomerization in the former and topomerization in the latter two compounds. The configurations of the four amides were assigned and it was shown how the stereochemical behavior of the amides could be used to distinguish between meso and *dl* secondary amines.

Torsion about carbonyl to nitrogen bonds is slow enough on the NMR time scale to render this moiety a labile stereochemical unit. Since barriers to rotation generally fall within the range of 5–25 kcal/mol, the stereochemistry of amides is most conveniently studied by observing the coalescence of NMR resonances from diastereotopic groups, although in some cases the barrier is high enough to permit the isolation of a single isomer and the measurement of the rate of isomerization using conventional kinetics.[2] The diastereotopic groups whose NMR resonances coalesce can reside either in the same molecule (for example, in *N,N*-dimethylacetamide) or in different, isomeric molecules (for example, in *N*-methyl-*N*-ethylacetamide). In the former case, we speak of groups which are diastereotopic by internal comparison and the stereochemical process which results in coalescence is a topomerization, while in the latter case, the two groups are diastereotopic by external comparison and the stereochemical process is an isomerization which reversibly interconverts two diastereomeric molecules.

This paper deals with amides which exhibit chemical shift nonequivalence and undergo coalescence which is a reflection of either isomerization or topomerization *depending upon the stereochemistry of the substituents attached to the amide moiety.*

In addition, the ability to distinguish between topomerization and isomerization using NMR spectroscopy can be used to distinguish between diastereomeric meso and *dl* secondary amines **1**.[3] NMR methods based upon the magnetic nonequivalence of diastereotopic groups[4] and upon the introduction of pseudo-asymmetry[5] have been developed. The symmetry arguments used in the present approach offer some advantages over those of previous methods.

The method of Hill and Chan[4] involves conversion of the secondary amines **1** into tertiary amines **2**, which bear a prochiral atom, such as that in a benzyl group, attached to nitrogen. The two benzyl methylene protons in *dl*-**2** are diastereotopic and appear as an AB quartet while those in *meso*-**2** are enantiotopic. The observation of chemical shift nonequivalence allows an unambiguous assignment of the *dl* configuration to the parent amine. However, the obser-



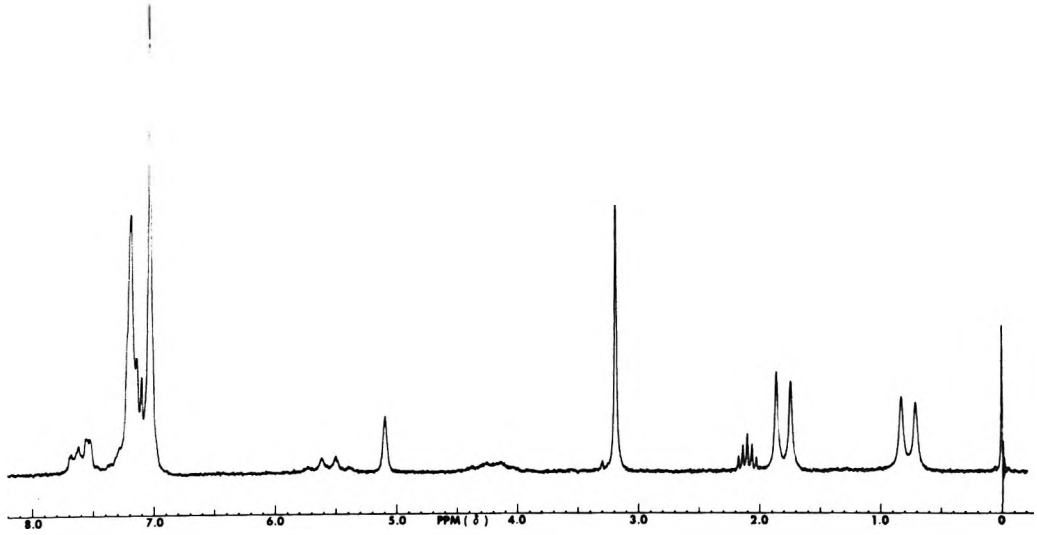


Figure 1. NMR spectrum of (*RS,RS*)-*N,N*-bis(1-phenylethyl)-(*SR*)-1-methoxyphenylacetamide (**4b**) at −18° in toluene-d_8.

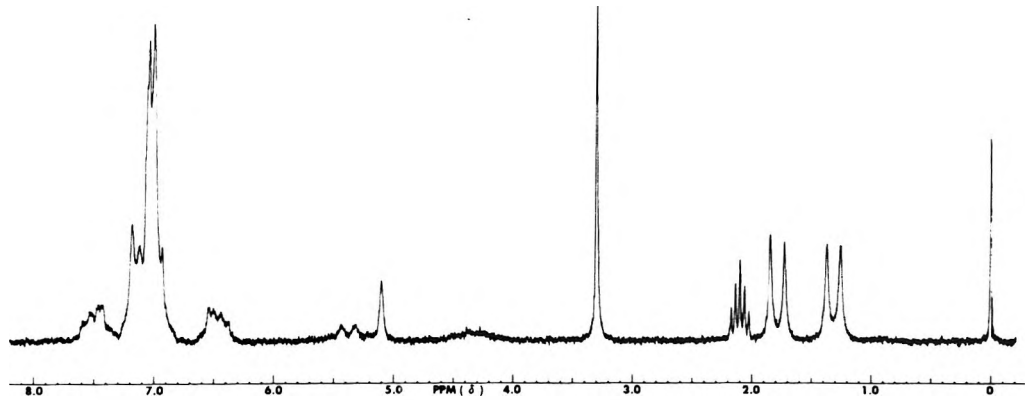


Figure 2. NMR spectrum of (*RS,RS*)-*N,N*-bis(1-phenylethyl)-(*RS*)-1-methoxyphenylacetamide (**4c**) at −18° in toluene-d_8.

vation of a singlet does not ensure that the amine has the meso configuration unless the possibility of accidental equivalence can be excluded.[6]

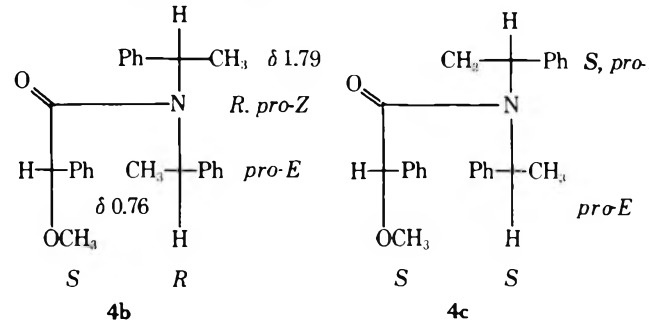
The method involving pseudo-asymmetry[5] is complementary in that it can provide an unambiguous assignment for the meso isomer. Reaction of the achiral amine *meso*-**1** with 2,4-dinitrobenzenesulfenyl chloride produced two diastereomeric product sulfenamides, *meso*-*R*-**3** and *meso*-*S*-**3**, which differed in configuration at the pseudo-asymmetric axis of the S–N bond. Since stereomutation via torsion about the S–N bond was slow on the NMR time scale, the equilibrium mixture of torsional diastereomers gave rise to two unequally intense *C*-methyl doublets, one for each of the two diastereomers. Although the sulfenamide produced from *dl*-**1** consists of a single diastereomer, it also gave rise to two doublets, but of equal intensity, since the two methyl groups within a molecule are diastereotopic.

Results and Discussion

The introduction of a third chiral center provides an additional means of distinguishing amines **1**. A convenient means of adding an additional unit of chirality is reaction with a chiral acid chloride, here 1-methoxyphenylacetyl chloride, to produce amides **4**. The introduction of the amide linkage introduces a further element of stereochemical complexity which is of utility in making the configurational assignment.

If we disregard, for the moment, the complexity introduced by slow rotation about the amide bond, reaction of *dl*-**1** with racemic 1-methoxyphenylacetyl chloride yields two diastereomeric amides,[7] (*RS,RS,SR*)-**4** (**4b**) and (*RS,RS,RS*)-**4** (**4c**), which give rise to observably different NMR spectra. Since the reaction occurs with asymmetric induction, one of the diastereomeric amides, **4b**, is produced in excess over the other. The assignment of the *RS,RS,SR* configuration to the major isomer **4b** was made by carrying out the reaction with optically active amine and acid chloride. Reaction of (*S,S*)-**1** with (*R*)-1-methoxyphenylacetyl chloride gave rise to a single diastereomer (*S,S,R*)-**4** whose NMR spectrum was identical with that of **4b**.

The low-temperature NMR spectra of both **4b** and **4c** (Figures 1 and 2) exhibit pairs of doublets for the phenethyl groups indicating that torsion about amide bonds is slow on the NMR time scale. The doublets in **4b** are centered at δ 1.79 and 0.76 while those in **4c** appear at δ 1.78 and 1.31. The differences in chemical shifts between **4b** and **4c** can arise only from diastereomeric interactions between the phenethyl groups and the asymmetric 1-methoxybenzyl moiety. It seems most reasonable to assume that the methyl group in **4b** which exhibits the greatest chemical shift relative to the corresponding methyl group in **4c** derives



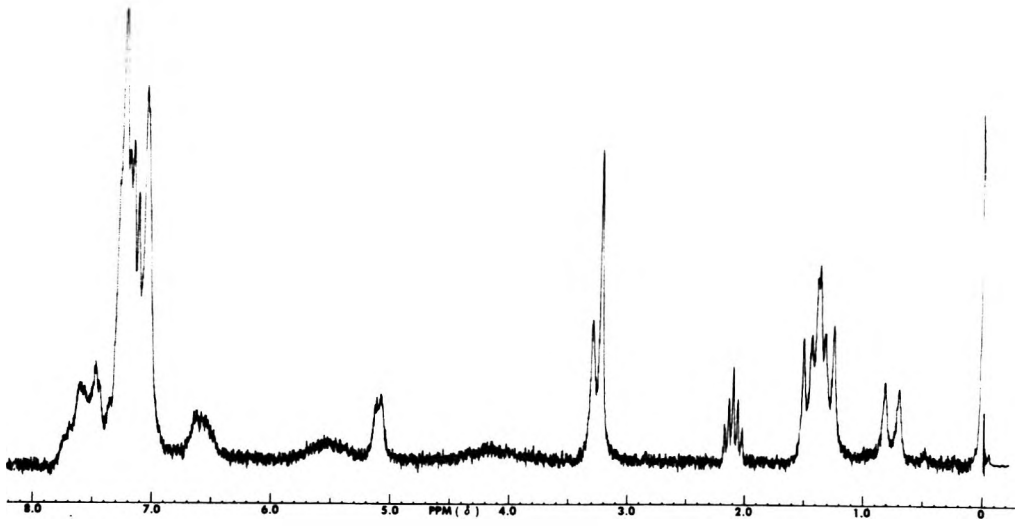
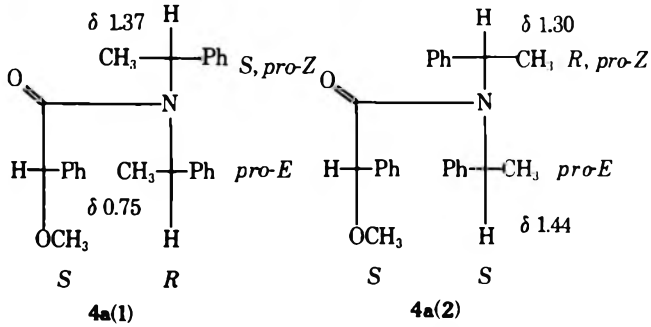


Figure 3. NMR spectrum of amides **4a** prepared from *meso*-bis(1-phenylethyl)amine and *dl*-1-methoxyphenylacetic acid at −18° in toluene-d_8.

from the *pro-E* phenethyl methyl group. Thus, we may tentatively assign the doublets in **4b** at δ 0.76 and 1.79 to the *pro-E* and *pro-Z* methyl groups, respectively.[9]

One possibility for this dramatic upfield shift is that the methyl group in **4b** lies within the shielding cone of the phenyl ring in the acyl group. Since interchanging the position of the methyl groups and phenyl groups in the phenethyl moieties converts **4b** into its diastereomer **4c**, we may ask whether one of the phenethyl phenyl groups suffers a similar upfield shift in **4c**. Inspection of the spectrum of **4c** reveals that two aromatic protons suffer a similar upfield shift and appear as an unstructured multiplet at δ 6.5. This upfield shift is in accord with a model which involves upfield shifts for protons in the phenethyl moiety which lie in the shielding cone of the 1-methoxybenzyl phenyl ring. This observation of upfield shifts for the methyl protons in **4b** and aromatic protons in **4c** provides the basis for the assignment of configurations in the meso amides **4a**.

Reaction of *meso*-**1** with 1-methoxyphenylacetyl chloride yields amide **4a**, which represents a single diastereomer on the isolation time scale. However, the amide bond is a labile configurational unit and, on the NMR time scale, two torsional diastereomers are present, **4a(1)** and **4a(2)**. The



presence of two diastereomers in equilibrium is evident from the NMR spectrum (Figure 3) which features two singlets for the *O*-methyl groups and four doublets for *C*-methyl groups (K_{eq} = 1.4 at −18°).

A tentative assignment of the configuration **4a(2)** to the major isomer can be made on the basis of the analysis of chemical shifts of phenethyl methyl and aromatic protons made for the *dl* amides **4b** and **4c**. The low-temperature spectrum of **4a** features four doublets arising from phenethyl methyl groups since all four phenethyl moieties are diastereotopic and anisochronous. One methyl doublet, which integration revealed as deriving from the minor isomer, suffers a considerable upfield shift and appears at nearly the same chemical shift as the *pro-E* methyl group in **4b**. By analogy we assign this doublet to the *pro-E* methyl group in **4a(1)**, since this isomer also has phenethyl and 1-methoxybenzyl groups with opposite configurational designations in a geometry where interaction can occur. A complementary upfield shift of aromatic protons was observed. Integration indicates that the broad unstructured multiplet at ca. δ 6.6 derives from a pair of aromatic protons in the major isomer. Since the cis phenethyl and methoxybenzyl moieties in **4a(2)** have the same configurational relationship as those in **4c**, which also exhibits a pair of shielded aromatic protons, this provides further support for our assignment of the configuration of **4a(2)** to the major isomer.[10]

Table I
Dynamic Nuclear Magnetic Resonance Data

Compd[a]	$\Delta\nu$, Hz[b]	T_c, °C[c]	$\Delta G^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kJ/mol
4a[f]	3.4	12	15.7,[d] 15.9[e]	65.5,[d] 66.3[e]
4a[g]	31	36	15.6,[d] 15.8[e]	65.3,[d] 66.1[e]
4a[h]	4.1	14	15.7,[d] 15.8[e]	65.4,[d] 66.2[e]
4b	23	32	15.6	65.2
4c	52	51	16.0	66.8

[a] All data refer to solutions (ca. 15% w/v) in toluene-d_8. [b] Chemical shift differences at the coalescence points were obtained by extrapolation of shifts measured at temperatures below the coalescence point. [c] The temperature is considered accurate to ±2°. This results in uncertainties in the free energies of activation of ±0.1 kcal/mol (±0.5 kJ/mol). [d] Free energy of activation for conversion of minor isomer to major isomer. [e] Free energy of activation for conversion of major isomer to minor isomer. [f] Signals from methoxy methyl groups. [g] Signals from *C*-methyl groups which exhibit the larger chemical shift difference [*pro-E* in **4a(1)** and *pro-Z* in **4a(2)**]. [h] Signals from *C*-methyl groups which exhibit the smaller chemical shift difference [*pro-Z* in **4a(1)** and *pro-E* in **4a(2)**].

Torsion about amide bonds in **4a**, **4b**, and **4c** becomes rapid on the NMR time scale at elevated temperatures and the spectra of all three compounds exhibited coalescence of *C*-methyl doublets (and *O*-methyl singlets for **4a**) when the temperature was increased. The coalescence temperatures, chemical shift differences, and free energies of activation derived from calibration curves based upon complete line shape analysis[11] are given in Table I. While the free energies of activation are comparable for all three amides, the stereochemical description of the process which results in coalescence in **4b** or **4c** is quite different from the process

Table II
Characterization of Amides

Compd	Mp, °C	Anal., % C	H	N
Calcd for $C_{25}H_{27}NO_2$		80.4	7.3	3.8
rac-4a	83–84°	80.33	7.05	3.64
rac-4b	105–116°	80.15	7.18	3.58
(*S,S,R*)-4b	117.5–118°			
rac-4c	95–96°	80.31	7.25	3.62

which results in coalescence in **4a**. When rotation about the amide bond is rapid the diastereotopic *pro-E* and *pro-Z* phenethyl groups in **4b** become homotopic (equivalent) on the NMR time scale (as do those in **4c**) and a single doublet is observed as an averaged chemical shift. The exchange in these compounds is between groups residing in the same molecule, groups which are diastereotopic by internal comparison.[12] By contrast, torsion about the amide bond in **4a(1)** does not interchange the *pro-E* and *pro-Z* groups. These remain diastereotopic and anisochronous even when rotation about amide bonds is rapid on the NMR time scale. Rather, rapid rotation about amide bonds exchanges the *pro-E* group in **4a(1)** with the *pro-Z* group in **4a(2)**. As a result, the high-temperature limit spectrum of **4a** features two equally intense methyl doublets. This amide is unusual in that the two constitutionally equivalent moieties at nitrogen cannot be rendered isochronous by torsion about the amide bond. Since the reversible isomerization involves the interchange of groups which are diastereotopic by external comparison,[12] we might describe this stereochemical process as an *intermolecular topomerization*. By the same token, the exchange which results from the degenerate isomerization of **4b** (or **4c**) might be termed an *intramolecular topomerization* in order to distinguish it from the present situation.

Although the stereochemical process which results in coalescence in **4a** is different from that which takes place in **4b** and **4c**, the structural change is similar and the barriers are not very different. The barriers obtained for **4** are within the range which might be expected considering the barriers reported for similar amides.[2]

Experimental Section

Spectra were recorded on a Varian A-60A spectrometer equipped with a V-6040 variable-temperature accessory. Temperatures were determined using methanol and ethylene glycol spectra as described in the Varian manual. Melting points were measured on a Thomas-Hoover oil bath apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter using a 1-dm cell.

1-Methoxyphenylacetyl Chloride (*O*-Methylmandelyl Chloride). 1-Methoxyphenylacetic acid and thionyl chloride (1.5 equiv) were heated under reflux in benzene for 1 hr. The solvent and excess thionyl chloride were removed under reduced pressure. The NMR spectrum of the residual oil exhibited only the resonances ascribed to the acid chloride (in $CDCl_3$, δ units) OCH_3, s, 3.49; CH, s, 5.00; C_6H_5, m, 7.45.

(*RS,SR,RS*)-*N,N*-Bis(1-phenylethyl)-1-methoxyphenylacetamide (4a). A solution of 0.40 g (2.2 mmol) of freshly prepared *dl*-1-methoxyphenylacetyl chloride in 20 ml of benzene was added dropwise over a period of 1 hr, at room temperature, to a stirred solution of 0.96 g (4.3 mmol) of *meso*-bis(1-phenylethyl)amine[5] in 30 ml of benzene. The reaction mixture was allowed to stand at room temperature for 20 hr and the solvent was evaporated in vacuo. The residue, composed of solid and oil, was triturated with hexane and the insoluble amine hydrochloride was removed by filtration. The mother liquor was washed successively with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and water, and then dried over magnesium sulfate. Evaporation of the solvent followed by recrystallization from hexane–pentane (1:1) afforded white crystals, mp 83–84°.

(*RS,RS,SR*)- and (*RS,RS,RS*)-*N,N*-Bis(1-phenylethyl)-1-methoxyphenylacetamide (4b and 4c). Racemic bis(1-phenylethyl)amine was treated with racemic 1-methoxyphenylacetyl chloride in the same manner as described above for the meso amine. Upon evaporation of the hexane mother liquor, the product was revealed to be a ca. 5:1 mixture of two diastereomeric amides, **4b** and **4c**. Treatment of the mixture with benzene–hexane resulted in crystallization of **4b** which was recrystallized from hexane, mp 105–106°. The benzene–hexane mother liquor was evaporated, dissolved in hexane–pentane, and left to stand for 1 week. Two kinds of crystals formed, colorless, transparent cubes and white granules. The former were separated mechanically and recrystallized from hexane–pentane (2:1) affording pure **4c**, mp 95–96°.

(*S,S,R*)-*N,N*-Bis(1-phenylethyl)-1-methoxyphenylacetamide (4b). Optically active (−)-*S,S*-bis(1-phenylethyl)amine was prepared by catalytic hydrogenation of (−)-*S*-1-phenylethylidene-1-phenylethylamine as previously reported[13] at 0° in ethyl acetate solvent, resulting in 87% asymmetric induction. The final separation of *S,S* amine from meso amine was accomplished by recrystallization of the benzoate salt of the *S,S* amine from 2-propanol,[14] mp 112–113°. The free amine was obtained by treatment with sodium bicarbonate, extraction with ether, and removal of solvent in vacuo: $[\alpha]^{25}D$ −187.9° (*c* 6.87, benzene) [lit.[13b] $[\alpha]^{25}D$ −197.3° (*c* 3.65, benzene)]. The optically active amine was treated with the acid chloride of (−)-(*R*)-1-methoxyphenylacetic acid[15] as described above. Recrystallization from hexane afforded white crystals in 52% yield, mp 117.5–118°, $[\alpha]^{26.4}D$ −73.4° (*c* 6.10, benzene). The NMR spectrum was identical with that of racemic **4b**.

Registry No.—*meso*-**1**, 21003-57-6; *rac*-**1**, 21003-56-5; (−)-(*S,S*)-**1**, 56210-72-1; **4a**, 56210-73-2; *rac*-**4b**, 56271-09-1; (−)-**4b**, 56271-10-4; *rac*-**4c**, 56271-11-5; *dl*-1-methoxyphenylacetylchloride, 56271-12-6; *dl*-1-methoxyphenylacetic acid, 7021-09-2; (−)-(*R*)-1-methoxyphenylacetic acid, 3966-32-3.

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(5) (a) D. Kost and M. Raban, *J. Am. Chem. Soc.*, **94**, 2533 (1972); (b) M. Raban, S. K. Lauderback, and D. Kost, *ibid.*, in press.

(6) The symmetry argument based upon resolvability has the same property, in that resolution provides unambiguous assignment of the *dl* isomer, while an inability to achieve optical activation can arise from extraneous experimental factors.

(7) Except for the preparation of optically active **4b** described below, all experiments were performed using racemic materials. The first two configurational designations refer to the configurations of the phenylethyl substituents at nitrogen; the third refers to the configuration at the asymmetric carbon atom in the *O*-methylmandelyl moiety. The symbol (*RS,RS,SR*)-**4** denotes the racemic mixture of (*R,R,S*)-**4** and (*S,S,R*)-**4**.[8] Both enantiomers, of course, give rise to identical NMR spectra under the conditions employed.

(8) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem.*, **78**, 413 (1966); *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).

(9) The assignment of the two methyl doublets in **4c** is less certain. An assignment could be made by assuming that the *pro-Z* methyl group lies downfield relative to *pro-E* methyl group in **4c**, also possibly as a result of deshielding by the anisotropic carbonyl group. However, in *N,N*-dimethylamides, the *N*-methyl group cis to oxygen (*pro-Z*) appears at higher field than that of the *pro-E* methyl.[2] Furthermore, analysis of the spectra of the meso amides **4a**, vide infra, demonstrates unequivocally that in one isomer the *pro-Z* methyl group lies upfield with respect to the *pro-E* methyl group (this isomer seems to be related to **4c**). However, in the other isomer (which has some similarities with **4b**) the *pro-Z* methyl group lies downfield. Using this analogy to the meso isomers a reversed assignment could be made. Independent of which assignment is correct, we can be sure that one of the methyl groups in **4b** suffers a dramatic upfield shift relative to its counterpart in **4c**.

(10) The assignment of the remaining *C*-methyl doublets follows naturally from the assignment of the doublet at δ 0.75 to the *pro-E* methyl in **4a(1)**. Integration indicated that the doublet at δ 1.37 also derived from the minor isomer; thus it can be assigned to the *pro-Z* methyl group in **4a(1)**. The assignment of the two methyl groups in **4a(2)** follows from the coalescence at higher temperatures, vide infra. Analysis of spectra below and above the coalescence point indicated that the signal at δ 0.75 in **4a(1)** coalesces with that at δ 1.30 in **4a(2)** and the signal at δ 1.37 coalesces with that at δ 1.44. Since rapid rotation about the amide

bord exchanges the *pro-E* methyl in **4a**(1) with the *pro-Z* methyl in **4a**(2), the later must give rise to the doublet at δ 1.30.
(11) D. Kost, E. H. Carlson, and M. Raban, *Chem. Commun.*, 656 (1971).
(12) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).
(13) (a) G. G. Overberger, N. P. Marullo, and R. G. Hiskey, *J. Am. Chem. Soc.*, **83**, 1374 (1961); (b) T. Yoshida and K. Harada, *Bull. Chem. Soc. Jpn.*, **45**, 3706 (1972).
(14) D. Kost, unpublished results.
(15) (a) J. v. Braun, E. Anton, and K. Weissbach, *Ber.*, **63**, 2847 (1930); (b) W. Reeves and I Christoffel, *J. Am. Chem. Soc.*, **72**, 1480 (1950).

Synthesis of Mono- and Bis(trimethylsilyl)anthracenes

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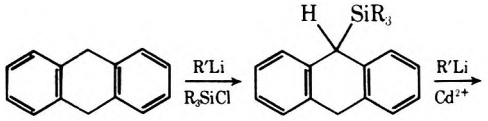
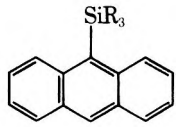
Synthesis of the previously unknown 1-, 2-, and 9-trimethylsilylanthracenes and of the 9,10- and 1,3-bis(trimethylsilyl)anthracenes has been accomplished. Aromatization of 9-trimethylsilyl-9,10-dihydroanthracene via the dianonic intermediate generated with the *n*-butyllithium–TMEDA reagent and cadmium chloride afforded 9-trimethylsilylanthracene in overall yield exceeding 90%. Reaction of trimethylsilyl chloride with the anthracene–lithium–TMEDA complex gave *cis*- and *trans*-9,10-bis(trimethylsilyl)-9,10-dihydroanthracene and *trans*-1,2-bis(trimethylsilyl)-1,2 dihydroanthracene. Aromatization of the trans-9,10 isomer afforded 9,10-bis(trimethylsilyl)anthracene, while similar reaction of the trans-1,2 isomer led to 1- and 2-trimethylsilylanthracene and 1,3-bis(trimethylsilyl)anthracene. Details of the mechanisms of these reactions and the 270-MHz NMR spectra are discussed.

Synthesis of the isomeric trialkylsilylanthracenes has not previously been achieved. Reaction of 9-bromoanthracene with Mg and Me_3SiCl reportedly afforded only the parent hydrocarbon.[1] In our experience, cross metalation of 9-bromoanthracene with *n*-butyllithium, followed by Me_3SiCl, failed to furnish 9-trimethylsilylanthracene (**2**), although analogous reaction of 9-bromophenanthrene gave 9-trimethylsilylphananthrene in good yield (95%).[2]

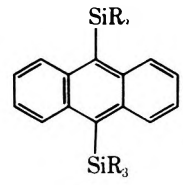
Synthesis of **2** has now been accomplished through reaction of Me_3SiCl with 9-lithio-9,10-dihydroanthracene[3] at −78° followed by aromatization with *n*-butyllithium–TMEDA and cadmium(II) chloride.[4] The overall yield exceeded 90%. The intermediacy of the dianion of 9-trimethylsilylanthracene was evidenced by the success of the second step and by the characteristic purple color of the solution before the addition of the cadmium salt. The ability of the trimethylsilyl group to stabilize the adjacent negative charge contrasts with the contrary effect of the *tert*-butyl group in this regard; similar reaction of 9-*tert*-butyl-9,10-dihydroanthracene was found earlier to afford a dimeric product arising from the 10-monoanion.[4] Attempted aromatization of 9-trimethylsilyl-9,10-dihydroanthracene (**1**) with trityl trifluoracetate in trifluoroacetic acid,[5] a reagent found to be effective in dehydrogenation of many hydroaromatic compounds, furnished anthracene as the sole product. Undoubtedly, this is a consequence of the facility of acidic cleavage (protodesilylation) of aryl silanes.[2]





2

Attempted synthesis of 9,10-bis(trimethylsilyl)anthracene (**3**) through repetition of the sequence of trimethylsilylation and aromatization on **1** was not successful owing to preferential formation of the monoanion at the 9 position. Reaction of **1** with *n*-butyllithium (10% excess) in tetrahydrofuran at 0° afforded a deep red solution of the monoanion which failed to undergo trimethylsilylation with Me_3SiCl. Similar reaction employing a large excess (200%) of the lithium reagent also failed, as might have been anticipated from the known resistance to formation of the anthracene dianion via deprotonation in ethereal solvents.[4]



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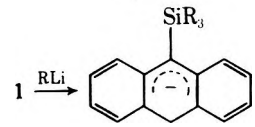
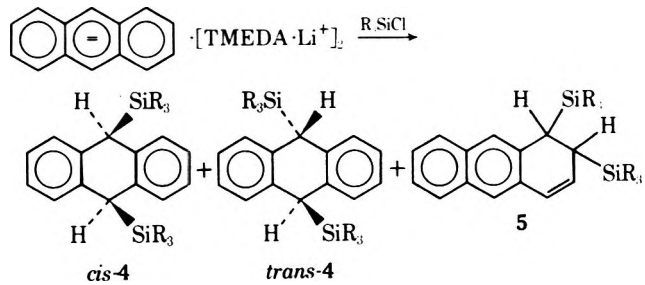


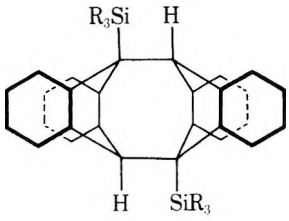
However, reaction of Me_3SiCl with the anthracene dianion in the form of its lithium *N,N,N',N'*-tetramethylethylenediamine complex generated by the method described[4] gave a mixture of *cis*- and *trans*-9,10-bis(trimethylsilyl)-9,10-dihydroanthracene (*cis*- and *trans*-**4**) and 1,2-bis(trimethylsilyl)-1,2-dihydroanthracene (**5**) in a molar ratio of 10:5:4 by NMR analysis. Similar reaction with the addition of Me_3SiCl carried out at 0° afforded a cleaner product with *cis*- and *trans*-**4** and **5** in the molar ratio 10:1:5. Chromatography on basic alumina and recrystallization furnished the pure compounds as crystalline solids melting at



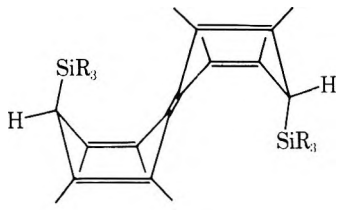
cis-4 *trans*-4 5

67–68, 172, and 126°, respectively. The cis isomer was found to be somewhat unstable, exhibiting a tendency toward decomposition during chromatography or purification by other means.

A minor additional product (~3%), mp 138–139°, was also isolated. It was identified as a dimer of **2** on the basis of microanalysis and the NMR spectrum which exhibited methyl, benzylic, and aromatic protons in the ratio 18:2:16. The methyl and benzylic signals appeared as singlets at δ −0.11 and 4.01, respectively, while the aromatic protons furnished two multiplets with the downfield multiplet (δ 8.09–8.50) equivalent to four protons, which are presumably those flanking the Me_3Si group ($H_{1,1',8,8'}$). The face-to-face (**6a**) and tail-to-tail (**6b**) structures are most consistent with this data and cannot at present be distinguished.



6a

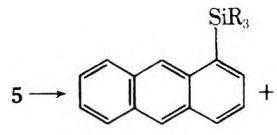


6b

The integrated NMR spectra of **4** and **5** were consistent with their structural assignments. The cis and trans stereoisomers of **4** were assigned on the basis of the relative chemical shifts of the benzylic protons (δ 3.83 and 3.66, respectively) in comparison with those of the analogous *cis*- and *trans*-9,10-bis-*tert*-butyl compounds (δ 3.97 and 3.83, respectively).[3] The structure of the 1,2-bis(trimethylsilyl) compound **5** was distinguished from alternative structures, such as the 1,4 isomer, by the 270-MHz NMR spectrum, which displayed singlets at high field δ −0.09 and −0.02 for the trimethylsilyl protons. The allylic and benzylic protons appeared as a doublet at δ 1.96 ($J_{2,3}$ = 7 Hz) and a broad singlet at δ 2.45, respectively, while the vinyl region showed an AB pattern with doublets at δ 5.90 and 6.31 ($J_{3,4}$ = 10 Hz) with additional coupling ($J_{2,3}$ = 7 Hz) of the H_3 proton to the allylic hydrogen. Tentatively, the trimethylsilyl groups are assigned as trans with the bulky groups in the axial orientation, known to be preferred by related dihydroaromatic ring systems;[3,7] coupling between the benzylic and allylic protons was not detected, consistent with the normally small couplings exhibited by diequatorial protons in these ring systems.

Dehydrogenation of **4** with *n*-butyllithium–TMEDA and cadmium(II) chloride[4] furnished the previously unknown 9,10-bis(trimethylsilyl)anthracene (**3**) isolated as a crystalline solid, mp 112–113°, and **2** in a molar ratio of 5:8.5.

Dehydrogenation of the *trans*-1,2-bis(trimethylsilyl) compound **5** with alkyllithium–TMEDA reagent failed to afford 1,2-bis(trimethylsilyl)anthracene as anticipated, but instead furnished the previously unknown 1- and 2-trimethylsilylanthracene (**7** and **8**) plus a disilyl derivative of anthracene. The latter on the basis of the NMR spectral data appears to be not the anticipated 1,2 isomer, but rather 1,3-bis(trimethylsilyl)anthracene (**9**). The NMR spectrum of the latter compound exhibited characteristic singlet peaks at δ 7.73 and 8.12 in the aromatic region assigned to H_2 and H_4, respectively; other features of the spectrum were entirely consistent with this assignment. Conversely, the spectrum lacked the characteristic AB quartet pattern anticipated for the H_3, H_4 protons of the 1,2 isomer. Therefore, the latter structure may be rejected. The 1 and 2 isomers, **7** and **8**, were also readily distinguished through their NMR spectra. The 9,10 protons of **8** appeared as a broad singlet at δ 8.30 in the region expected for anthracene itself, whereas H_9 of **7** appeared at lower field (δ 8.53) than H_{10} (δ 8.30), indicating the presence of the bulky trimethylsilyl group in the adjacent 1 position. Other features of both spectra were also consistent with these assignments.



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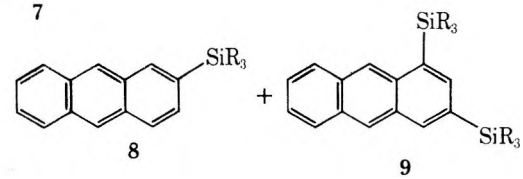


8 **9**

Finally, *trans*-**4** underwent smooth epimerization to *cis*-**4** on treatment with the alkyllithium reagent quenching reaction with water rather than $CdCl_2$. This stereochemical result is similar to that observed previously with the analogous 9,10-dialkyl-9,10-dihydroanthracenes.[3]

Discussion

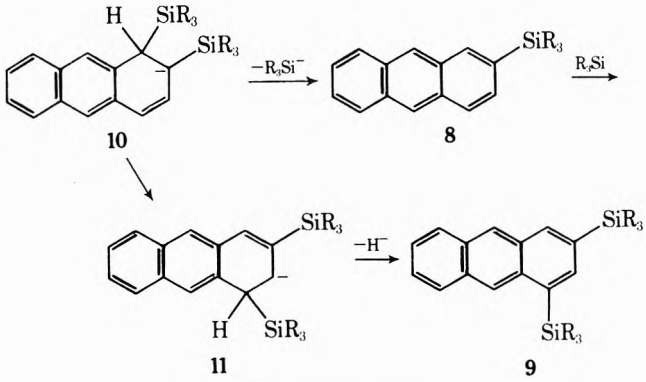
The foregoing syntheses of the mono- and bis(trimethylsilyl)anthracenes provide convenient synthetic access to this class of compounds. It is likely that this synthetic approach will prove applicable to the preparation of other aryl silanes.

The origin of the 1,2-bis(trimethylsilyl) isomer, **5**, though not immediately obvious, is explicable as a consequence of the structure of the anthracene–lithium–TMEDA complex.[8] According to X-ray crystallographic analysis, the anthracene dianion is somewhat puckered with a lithium ion centered above the face of the central ring and the second lithium ion situated on the opposite face of the polycyclic ring system and centered over one of the outer rings. Although maximum charge density is expected at the 9,10 positions, significant negative charge is localized in one of the outer rings, facilitating electrophilic attack of the relatively bulky trimethylsilyl reagent at least partially in this region. While the stereochemistry of **5** could not be assigned with certainty, it is most probably trans. In the trans isomer the bulky Me_3Si groups would be expected to occupy the diaxial positions, and the resulting diequatorial 1,2 protons would be expected to show a coupling constant (J_{calcd} = 4.1 Hz)[9] somewhat smaller than the equivalent protons of the cis isomer (J_{calcd} = 5.2 Hz) due to the smaller dihedral angle. However, no coupling could be detected in the high-resolution NMR spectrum of **5**, and the stereochemistry remains uncertain.

The observed cis stereochemical preference in the trimethylsilylation of anthracene is unexpected in view of the recent evidence that the stereochemistry of alkylation of the alkylanthracenyl anion is predominantly sterically controlled with larger groups leading to transalkylation.[3] Also, Russian workers have reported[10] that interaction of anthracene with lithium metal in ether (70 hr), followed by reaction with Me_3SiCl, furnished a major product of unspecified stereochemistry melting at 168–170°, which is presumably *trans*-**4** (mp 172°). Thus, the present result appears anomalous. One explanation is that *trans*-**4** is indeed the initial product which is transformed to *cis*-**4** via subsequent epimerization. This is consistent with previous findings[3] with the 9,10-dialkyl-9,10-dihydroanthracenes. Also, *trans*-**4** on treatment with the alkyllithium–TMEDA reagent in refluxing cyclohexane was found to undergo smooth transformation to *cis*-**4**. While this explanation appears attractive, it is inconsistent with the observation of a decreased proportion of *trans*-**4** at lower temperature (0°),

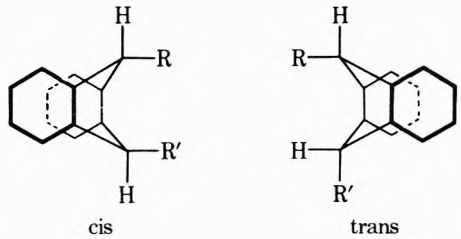
a condition less favorable for epimerization. Therefore, further investigation will be required to solve this problem, which is outside the scope of the present study.

Dehydrogenation of the *trans*-1,2-bis(trimethylsilyl) compound **5** followed an unexpected course. In place of the anticipated 1,2-bis(trimethylsilyl)anthracene were found 1- and 2-trimethylsilylanthracene (**7** and **8**) plus 1,3-bis(trimethylsilyl)anthracene (**9**). From a purely synthetic viewpoint this is fortunate, since it provides convenient synthetic access to the remaining two monotrimethylsilyl isomers of anthracene. The origin of **7** and **8** is explicable in terms of basic elimination of trimethylsilane from **5** via an intermediate such as **10**. Formation of **9** is less obvious. The possible pathways include (1) nucleophilic attack of the trimethylsilyl anion on **7** or **8** to produce an intermediate such as **11** followed by hydride loss, or (2) direct formation of **11** from **10** through migration of a trimethylsilyl group followed by similar hydride loss.[11] No attempt was made to distinguish between these two pathways.



Formation of the monoanion at the 9 position of **1** on treatment of the latter with butyllithium is deserving of comment. That a monoanion is indeed present is confirmed by the characteristic deep red color of the solution which is quite different from the intensely purple color of the anthracene dianion.[3,4] 9-Alkyl-9,10-dihydroanthracene under similar conditions affords the 10 monoanion, which undergoes facile alkylation.[4] Since trimethylsilylation was not observed, the monoanion of **1** must bear the charge in the relatively inaccessible 9 position. Stabilization of a negative charge by the trimethylsilyl group is consistent with previous observations of the directive effect of this group in the Birch reduction of silylnaphthalenes.[12]

The NMR data on more careful inspection reveal several interesting facts concerning the structures of the silylated derivatives of anthracene. Thus, the *cis*- and *trans*-9,10-bis(trimethylsilyl) isomers, *cis*- and *trans*-**4**, exhibit only one singlet peak for the benzylic protons of each isomer. In earlier studies[3,7] NMR analysis of the closely related 9-alkyl- and 9,10-dialkyl-9,10-dihydroanthracenes demonstrated existence of this ring system in a nonplanar boat structure with the alkyl groups preferentially occupying the pseudo-axial positions. Thus the cis isomers exist principally as the diaxial conformer, while the trans isomers exhibit strong preference for the conformer bearing the bulkier group in the axial position. With large groups, ring flattening due to transannular interaction was detected, and the 9,10-bis(*tert*-butyl) derivatives exhibited only a single peak in the benzylic region for both isomers. It appears, therefore, that *cis*- and *trans*-**4**, owing to the large steric demands of the trimethylsilyl groups, similarly exist in "flattened" conformations with the trans isomers closely approaching planarity.



Introduction of the trimethylsilyl group into anthracene markedly affected the chemical shifts in the NMR spectrum of the nearby aromatic protons. Substitution of this group into the 1 position, as in **7** and **9**, caused a shift of H_9 0.23 ppm downfield, while substitution in the 9 position led to a shift of H_{10} in the same ring upfield from δ 8.30 to 8.14. Evidently, both through-space and inductive effects are important. It is interesting that similar effects are found in the analogous *tert*-butyl derivatives of anthracene. The H_2 proton of 1-*tert*-butylanthracene appears downfield 0.58 ppm from the meso protons of anthracene, while the H_{10} proton of 9-*tert*-butylanthracene exhibited an upfield shift from δ 8.30 to 8.22.[13]

Experimental Section

Materials and Methods. NMR spectra were recorded on a Varian T-60 or Bruker 270-MHz spectrometer; CCl_4 was employed as the solvent and Me_4Si as internal standard for the 270-MHz spectra and cyclohexane (s at δ 1.43 relative to the Me_4Si) as internal standard for the 60-MHz spectra. Ether, cyclohexane, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), and tetrahydrofuran (THF) were purified by distillation from $LiAlH_4$. *n*-Butyllithium (15% in hexane) was obtained from Apache Chemicals. Cadmium chloride was dried in vacuo at 100° overnight and stored in airtight vials. Trimethylsilyl chloride (Alfa Ventron) was redistilled before use. Microanalyses for C and H correct to ±0.3% were obtained for all new compounds from Atlantic Microlabs, Inc.

9-Trimethylsilyl-9,10-dihydroanthracene (1). The procedure employed was essentially that found most effective for the monoalkylation of 9,10-dihydroanthracene.[3,4] To a stirred solution of 9,10-dihydroanthracene (7.2 g, 40 mmol) in THF (200 ml) at −33° under nitrogen was added a solution of *n*-butyllithium in hexane (44 mmol). The resulting brownish-red solution was stirred for 30 min, then the temperature was lowered to −78°, and stirring was continued for an additional 30 min. Upon addition of Me_3SiCl (6 ml) the solution became pale yellow. Addition of water and ether followed by conventional work-up afforded a pale yellow solid product, chromatography of which on Florisil (30 g) eluted with hexane (600 ml) gave pure **1** (9.8 g, 97%). Recrystallization from petroleum ether gave **1** as white crystals (9.2 g): mp 116° (lit.[6] mp 112–113°); NMR δ 0.05 (s, 9, CH_3), 3.61 (s, 1, H_9), 3.96 (apparent s, 2, H_{10}), and 7.13 ppm (apparent s, 8, aromatic).

9-Trimethylsilylanthracene (2). To a solution of **1** (2.52 g, 10 mmol) in cyclohexane (60 ml) and TMEDA (30 ml) was added a solution of *n*-butyllithium (40 mmol) in hexane. The resulting purple solution was heated at reflux for 1 hr, then allowed to cool for 5 min and the color discharged by addition of $CdCl_2$ (3.7 g, 20 mmol). Addition of water and ether followed by conventional work-up gave a brown oil. Chromatography of the latter on Florisil (20 g) eluted with petroleum ether (500 ml) gave **2** (2.4 g, 95%) as a pale yellow oil. Crystallization from petroleum ether furnished crystalline **2** (2.2 g): mp 60–61°; NMR δ 0.63 (s, 9, CH_3), 7.03–7.43 (m, 4, aromatic, $H_{2,3,6,7}$), 7.57–7.83 (m, 2, aromatic, $H_{4,5}$), 8.14 (s, 1, H_{10}), and 8.10–8.47 ppm (m, 2, aromatic, $H_{1,8}$).

Reaction of Trimethylsilyl Chloride with the Lithium–TMEDA Complex of the Anthracene Dianion. To a solution of 9,10-dihydroanthracene (3.6 g, 20 mmol) in cyclohexane (120 ml) and TMEDA (60 ml) was added *n*-butyllithium (80 mmol) in hexane. The resulting purple solution was refluxed for 1 hr under nitrogen and allowed to cool for 5 min; then Me_3SiCl (12 ml) was added. The resulting exothermic reaction subsided in 5 min. Stirring was continued for 30 min more, then the reaction mixture was worked up by a conventional extraction procedure with ether. Rapid chromatography through a column of Florisil (20 g) eluted with petroleum ether (500 ml) gave a partially crystalline pale yellow oil (6 g), NMR analysis showed *cis*- and *trans*-**4** and **5** in a molar ratio of 10:5:4. The cis isomer was found to be somewhat unstable, necessitating appropriate care to minimize loss through decomposition during chromatography or purification by other

means. Crystallization of the product mixture from petroleum ether gave colorless crystals of *trans*-4 (0.85 g). The second crop (0.55 g) contained in addition to *trans*-4 yellow crystals of a minor additional component which was readily separated mechanically or by dissolving the *trans*-4 in petroleum ether. This new compound on recrystallization from ether–petroleum ether gave needles: mp 138–139°; NMR δ −0.11 (s, 9, CH_3), 4.01 (s, 1, benzylic), 6.07–7.56 (m, 6, aromatic), and 8.09–8.30 ppm (m, 2, aromatic). The dimeric structure **6** was tentatively assigned. Recrystallization of the combined *trans*-4 from petroleum ether gave pure *trans*-4 (1 g): mp 172°; NMR δ −0.15 (s, 18, CH_3), 3.66 (s, 2, benzylic), and 6.89 ppm (s, 8, aromatic).

Chromatography of the remainder of the product (4.5 g) on basic alumina (180 g) gave in order of elution with petroleum ether **5** (700 mg), a 1:1 mixture of *trans*-4 and **5** (550 mg), and *trans*-4 (350 mg). Further elution with 10% benzene in petroleum ether gave *cis*-4 (900 mg), and final elution with benzene furnished anthracene and a trace of *cis*-4 (600 mg). Rechromatography of the *cis*-4 on basic alumina (30 g) gave pure *cis*-4 (800 mg): mp 67–68; NMR δ 0.02 (s, 18, CH_3), 3.83 (s, 2, benzylic), and 6.92 ppm (s, 8, aromatic). Recrystallization of the fractions containing **5** from petroleum ether gave a total of 850 mg of pure **5**: mp 126°; NMR δ −0.09 (s, 9, CH_3), −0.02 (s, 9, CH_3), 1.96 (d, 1, $J_{2,3}$ = 7 Hz, H_2), 2.45 (s, 1, H_1), 5.90 (d of d, 1, $J_{3,4}$ = 10, $J_{2,3}$ = 7 Hz, H_3), 6.31 (d, 1, $J_{3,4}$ = 10 Hz, H_4), 7.09 (s, 1, H_9 or H_{10}), 7.15 (s, 1, H_9 or H_{10}), 7.17–7.25 (m, 2, $H_{6,7}$), and 7.33–7.58 ppm (m, 2, $H_{5,8}$).

Similar reaction with the trimethylsilylation carried out at lower temperature (0°) gave a cleaner product shown by NMR analysis to contain *cis*- and *trans*-4 and **5** in the molar ratio 10:1:5, the most striking difference being the depressed yield of the trans isomer.

9,10-Bis(trimethylsilyl)anthracene (3). To a solution of *trans*-4 (325 mg, 1 mmol) in cyclohexane (12 ml) and TMEDA (6 ml) was added a solution of *n*-butyllithium (3 mmol) in hexane. The resulting solution was heated at reflux for 2 hr; the purple color of the dianion developed after the first hour. The solution was allowed to cool for 5 min, then the color was discharged by addition of $CdCl_2$ (0.74 g, 4 mmol). The mixture was stirred for another 30 min while metallic cadmium was precipitating. Water was added and the mixture was extracted with ether and worked up by conventional procedure to furnish a brown oil (280 mg). Chromatography on neutral alumina (50 g) eluted with petroleum ether gave **3** (110 mg) and **2** (140 mg). Recrystallization of the former from petroleum ether gave pure **3** as greenish-yellow needles: mp 112–113°; NMR δ 0.67 (s, 18, CH_3), 7.23–7.43 (m, 4, $H_{2,3,6,7}$), and 8.22–8.42 ppm (m, 4, $H_{1,4,5,8}$). Recrystallization of the latter from the same solvent gave pure **2** as yellow crystals, mp 61°.

The product mixture from a similar reaction on heating in a solution of 10% concentrated HCl in refluxing acetic acid for 2 hr underwent protodesilylation to furnish anthracene almost quantitatively.

Epimerization of *trans*- to *cis*-4. Treatment of *trans*-4 with *n*-butyllithium and TMEDA according to the procedure employed for synthesis of **2** from **1** except that $CdCl_2$ was not employed afforded pure *cis*-4 free of *trans*-4 (95% yield).

Dehydrogenation of *trans*-1,2-Bis(trimethylsilyl)-1,2-dihydroanthracene (5). Dehydrogenation of **5** (324 mg, 1 mmol) with the *n*-butyllithium–TMEDA reagent according to the general procedure[4] which was employed for synthesis of **2** gave a pale yellow oil (320 mg). Chromatography on Florisil (5 g) eluted with petroleum ether (200 ml) gave a colorless oil (250 mg) shown by NMR analysis to contain 1- and 2-trimethylanthracene (**7** and **8**) and 1,3-bis(trimethylsilyl)anthracene (**9**) in the molar ratio 4:1:2. A second chromatography on Florisil (50 g) eluted with the same solvent afforded initially **9** (80 mg) followed by the mixture of **7** and **8** (150 mg) which proved difficult to separate. However, pure samples of each were obtained by rechromatography of the early fractions rich in **7** on neutral alumina and of the later fraction rich in **8** on basic alumina.

Compound **7** was obtained as a colorless oil: NMR δ 0.53 (s, 9, CH_3), 7.15–7.67 (m, 4, $H_{2,3,6,7}$), 7.73–8.10 (m, 3, $H_{4,5,8}$), 8.30 (s, 1, H_{10}), and 8.53 ppm (s, 1, H_9). Compound **8** was a solid which was recrystallized twice from petroleum ether to afford colorless plates: mp 161–161.5°; NMR δ 0.36 (s, 9, CH_3), 7.27–7.57 (m, 3, $H_{3,6,7}$), 7.77–8.13 (m, 4, $H_{1,4,5,8}$), and 8.30 ppm (apparent s, 2, $H_{9,10}$). Compound **9** was also an oil: NMR δ 0.37 [s, 9, 3-Si(CH_3)$_3$], 0.54 [s, 9, 1-Si(CH_3)$_3$], 7.27–7.50 (m, 2, $H_{6,7}$), 7.73 (s, 1, H_2), 7.80–8.07 (m, 2, $H_{5,8}$), 8.12 (s, 1, H_4), 8.37 (s, 1, H_{10}), and 8.54 ppm (s, 1, H_9); the peaks at 7.73 and 8.12 designated as singlets appeared to exhibit a small additional coupling ($J \simeq 2$ Hz) not well resolved.

Acknowledgment. Support of this research by the U.S. Public Health Service (N01-CP-033385) is gratefully acknowledged. The HX-270 Bruker superconducting NMR spectrometer was provided through the University of Chicago Cancer Research Center Grant CA-14599. We also wish to thank Dr. Peter W. Rabideau for helpful discussion concerning assignment of several of the structures based on NMR spectral data.

Registry No.—**1**, 18002-83-0; **2**, 56272-35-6; **3**, 56272-36-7; *trans*-**4**, 56272-37-8; *cis*-**4**, 56272-38-9; *trans*-**5**, 56272-39-0; **7**, 56272-40-3; **8**, 56272-41-4; **9**, 56272-42-5; 9,10-dihydroanthracene, 613-31-0; Me_3SiCl, 75-77-4.

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Synthesis of Substituted 7,7,8,8-Tetracyanoquinodimethanes

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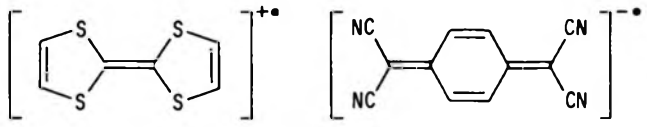
Twenty-one 7,7,8,8-tetracyanoquinodimethanes substituted with Me, Et, *i*-Pr, F, Cl, Br, I, OMe, OEt, O-*i*-Pr, O-*i*-Bu, O-*i*-C_5H_{11}, -O-CH_2OCH_2-, SMe, and CN groups are reported along with several TCNQ dianion salts.

The charge transfer complex between tetrathiofulvalene and tetracyanoquinodimethane (TTF·TCNQ) 1 shows high



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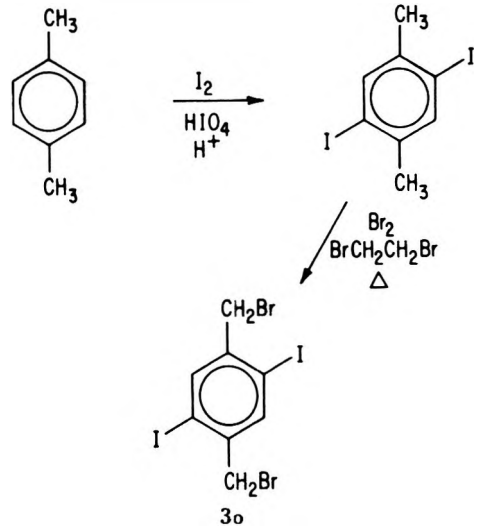
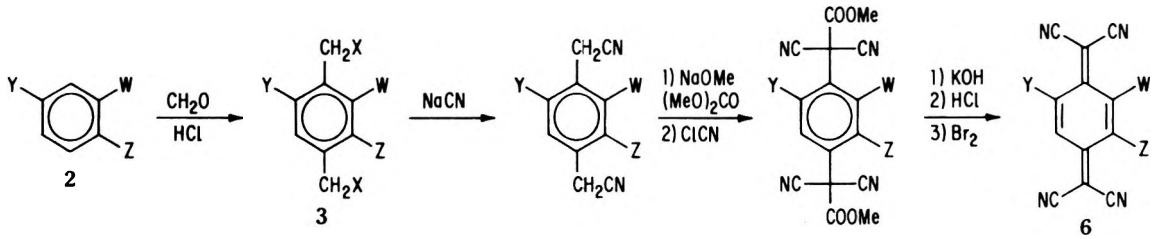
metallic electrical conductivity from room temperature down to ~60 K.[1-6] This chemistry has already been expanded by the preparation of selenium,[7] tetrathiomethoxy,[8] dimethyl,[2] tetramethyl,[9] benzo,[10,11] and tetramethylene[11] analogs of tetrathiofulvalene. Syntheses are reported here of a rather complete series of substituted TCNQ's, extended TCNQ's, and related anion salts that may aid in the systematic analysis of charge transfer salt conductivity.[12]

Substituted 7,7,8,8-tetracyanoquinodimethanes were synthesized according to procedures disclosed or claimed in Du Pont patents.[13] These syntheses most frequently started with the corresponding *p*-xylylene dihalide **3**. *p*-Xylylene dihalides **3b–g, 3j–l,** and **3p–s** were prepared by direct bischloromethylation of the appropriately substituted benzene, as shown in Scheme I. *p*-Xylylene dihalides, **3a, 3h, 3i, 3m,** and **3n** were prepared according to Scheme II, starting with *p*-xylenes **7** or terephthalic acids **8**. The terephthalic acids were converted first to their acid chlorides, then reduced to glycols, and treated with hydrogen halide to give *p*-xylylene dihalides. 1,4-Bis(bromomethyl)-2,5-di-



3o

Scheme I



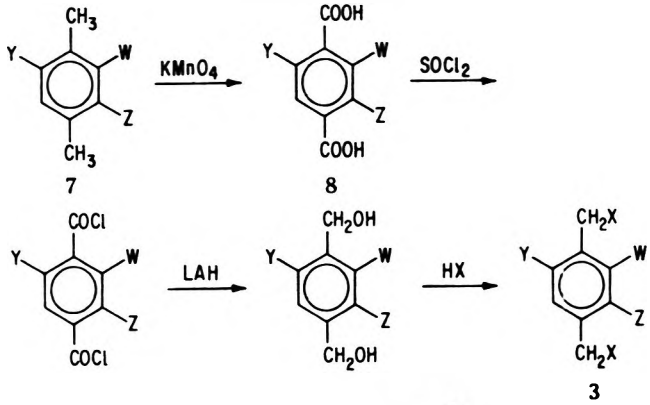
Y	Z
2b, OMe,	OMe[a]
c, OMe,	OEt[b]
d, OMe,	O-*i*-Pr[c]
e, OMe,	O-*i*-Bu[d]
f, OMe,	O-*i*-C_5H_{11}[e]
g, OEt,	SMe
j, Cl,	Me
k, Br,	Me
l, I,	Me
p, OMe,	OCH_2Ph
q, Me,	Me
r, Et,	Et
s, *i*-Pr,	*i*-Pr

X	Y	Z	W[f]
3a, Br,	OMe,	H	
b, Cl,	OMe,	OMe[a]	
c, Cl,	OMe,	OEt[b]	
d, Cl,	OMe,	O-*i*-Pr[c]	
e, Cl,	OMe,	O-*i*-Bu[d]	
f, Cl,	OMe,	O-*i*-C_5H_{11}[e]	
g, Cl,	OEt,	SMe	
h, Cl,	Cl,	H	
i, Cl,	Br,	H	
j, Cl,	Cl,	Me	
k, Cl,	Br,	Me	
l, Cl,	I,	Me	
m, Cl,	Cl,	Cl	
n, Cl,	Br,	Br	
o, Br,	I,	I	
p, Cl,	OMe,	$-OCH_2OCH_2-$	
q, Cl,	Me,	Me	
r, Cl,	Et,	Et	
s, Cl,	*i*-Pr,	*i*-Pr	

Y	Z	
6a, OMe,	H	TCNQ(OMe)
b, OMe,	OMe[a]	$TCNQ(OMe)_2$
c, OMe,	OEt[b]	TCNQ(OMe)(OEt)
d, OMe,	O-*i*-Pr	TCNQ(OMe)(O-*i*-Pr)
e, OMe,	O-*i*-Bu[d]	TCNQ(OMe)(O-*i*-Bu)
f, OMe,	O-*i*-C_5H_{11}[e]	TCNQ(OMe)(O-*i*-C_5H_{11})
g, OEt,	SMe	TCNQ(OEt)(SMe)
h, Cl,	H	TCNQCl
i, Br,	H	TCNQBr
j, Cl,	Me	TCNQClMe
k, Br,	Me	TCNQBrMe
l, I,	Me	TCNQIMe
m, Cl,	Cl	$TCNQCl_2$
n, Br,	Br	$TCNQBr_2$
o, I,	I	$TCNQI_2$
p, OMe,	$-OCH_2OCH_2-$	$TCNQ(OMe)(OCH_2OCH_2)$
q, Me,	Me	$TCNQ(Me)_2$
r, Et,	Et	$TCNQ(Et)_2$
s, *i*-Pr,	*i*-Pr	$TCNQ(i\text{-}Pr)_2$

[a] Me = CH_3. [b] Et = C_2H_5. [c] *i*-Pr = $CH(CH_3)_2$. [d] *i*-Bu = $CH_2CH(CH_3)_2$. [e] *i*-C_5H_{11} = $CH_2CH_2CH(CH_3)_2$. [f] Substituent W is hydrogen unless otherwise specified.

Scheme II

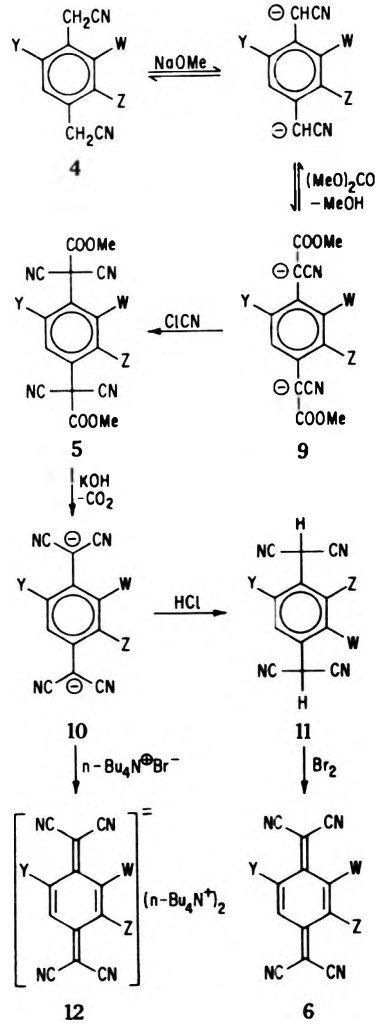


3a, X = Br; Y = OMe; Z = H
h, X = Y = Cl; Z = H
i, X = Cl; Y = Br; Z = H
m, X = Y = Z = Cl
n, X = Cl; Y = Z = Br

7a, Y = OMe; Z = H
h, Y = Cl; Z = H
i, Y = Br; Z = H
8m, Y = Z = Cl
n, Y = Z = Br

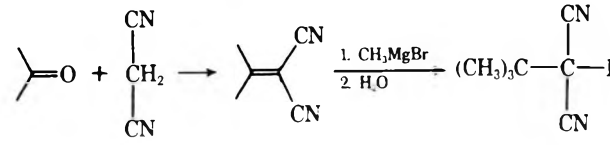
iodobenzene (**3o**) was prepared by oxidative iodination of *p*-xylene[14] followed by halogenation with bromine.

Once the *p*-xylylene dihalides had been obtained, the syntheses of TCNQ's **6a–s** ran closely parallel, as summarized in Scheme I and detailed below. Reaction of *p*-xylylene dihalide **3** with sodium cyanide gives *p*-xylylene dicyanide **4**. Treatment of **4** with sodium methoxide in benzene–dimethyl carbonate establishes an equilibrium with dianion **9** which may be driven to completion by distilling off a benzene–methanol azeotrope. Distilling cyanogen chloride into the same pot affords a good yield of tetracyanodiacetate **5**. Treatment of **5** with KOH or NaOH hydrolyzes and decarboxylates the ester groups to dianion **10**. This dianion may be precipitated as air-sensitive bis(tetra-*n*-butylammonium) salt **12** but most frequently is converted to dihydro TCNQ **11** with hydrochloric acid. Dihydro TCNQ **11** need not be purified extensively and can be oxidized directly to TCNQ **6** with bromine.



The first step in $TCNQF_4$ **15**, $TCNQ(CN)_2$ **16**, and $TCNDQF_8$ precursor **17** syntheses involved initial nucleophilic displacement of aromatic halogen by the *tert*-butyl malononitrile anion (Scheme III). Thermolysis of **13** and **14** with loss of isobutylene, followed by oxidation, gave TCNQ's **15** and **16**. Bis(tetra-*n*-butylammonium) salt **17** may be used for incorporation of the octafluorotetracyanodiphenoquinodimethane moiety in complexes by metathesis. Octafluorotetracyanodiphenoquinodimethane was not isolated as a neutral compound.[15]

tert-Butylmalononitrile (**19**) was prepared by condensing acetone with malononitrile[16] and then adding mathylmagnesium bromide.



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Experimental Section

The synthetic procedures described in this report are of a highly repetitive nature. TCNQ's **6a–s**, for example, were all prepared by the sequence of steps shown in Scheme I. Within this sequence actual experimental conditions vary sufficiently that four detailed examples are necessary in the Experimental Section: TCNQIMe **6l**, $TCNQ(i\text{-}Pr)_2$ **6s**, $TCNQ(OMe)_2$ **6b**, and $TCNQCl_2$ **6m**. The syntheses of the remaining TCNQ's in the **6a–s** series can then be described in terms of one of these four model compounds. Necessary data are summarized in Table I, the numbering of formulas corresponding to intermediates shown in Scheme I. Table I indicates melting points, yields, and conditions (by reference to the appropriate model TCNQ, **6l**, **6s**, **6b**, or **6m**, in the Experimental Section). Generally the crude product from each step was run directly into the next step after withdrawal of a small sample for purification and analysis.

Full spectral data for all TCNQ's in this paper are included in Table II. Frequently NMR spectra could not be taken of the TCNQ's as a result of low solubility complicated by radical anion formation with solvent impurities.

Those preparations requiring hydrogen halide–formaldehyde mixtures may generate the carcinogens, chloromethyl methyl ether and bis(chloromethyl) ether.[17]

2-Iodo-5-methyl-7,7,8,8-tetracyanoquinodimethane (6l). A. 2,5-Bis(chloromethyl)-4-iodotoluene (3l). A 200-g (0.92 mol) sample of *p*-iodotoluene was melted in the bottom of a flask held at 50°C in an oil bath, and then 80 g of powdered zinc chloride was added with mechanical stirring followed by 80 g (2.7 mol) of paraformaldehyde. Hydrogen chloride gas was blown over the surface of the reaction mixture. It became necessary to replace the oil bath with occasional ice bath cooling in order to control the temperature. Once the exotherm moderated, the mixture was heated to ~70°C and 4 g of zinc chloride plus 4 g (0.13 mol) of paraformaldehyde added every hour for the next 6–7 hr. The cooled reaction mixture was beaten to near homogeneity with 1 l. of methylene chloride. One liter of water was added and then solid sodium sulfite with stirring until the iodine color disappeared. The organic layer was separated, washed with 2 × 1000 ml of water, dried over magnesium sulfate, treated with decolorizing carbon, and filtered. Stripping on a rotary evaporator with periodic addition of hexane gave a slurry. Vacuum filtration gave 76 g of pink solid, that was recrystallized from toluene as 48.66 g (16%) of pale yellow needles, mp 139–144°C. The material was suitable for the next step: ^1H

Scheme III

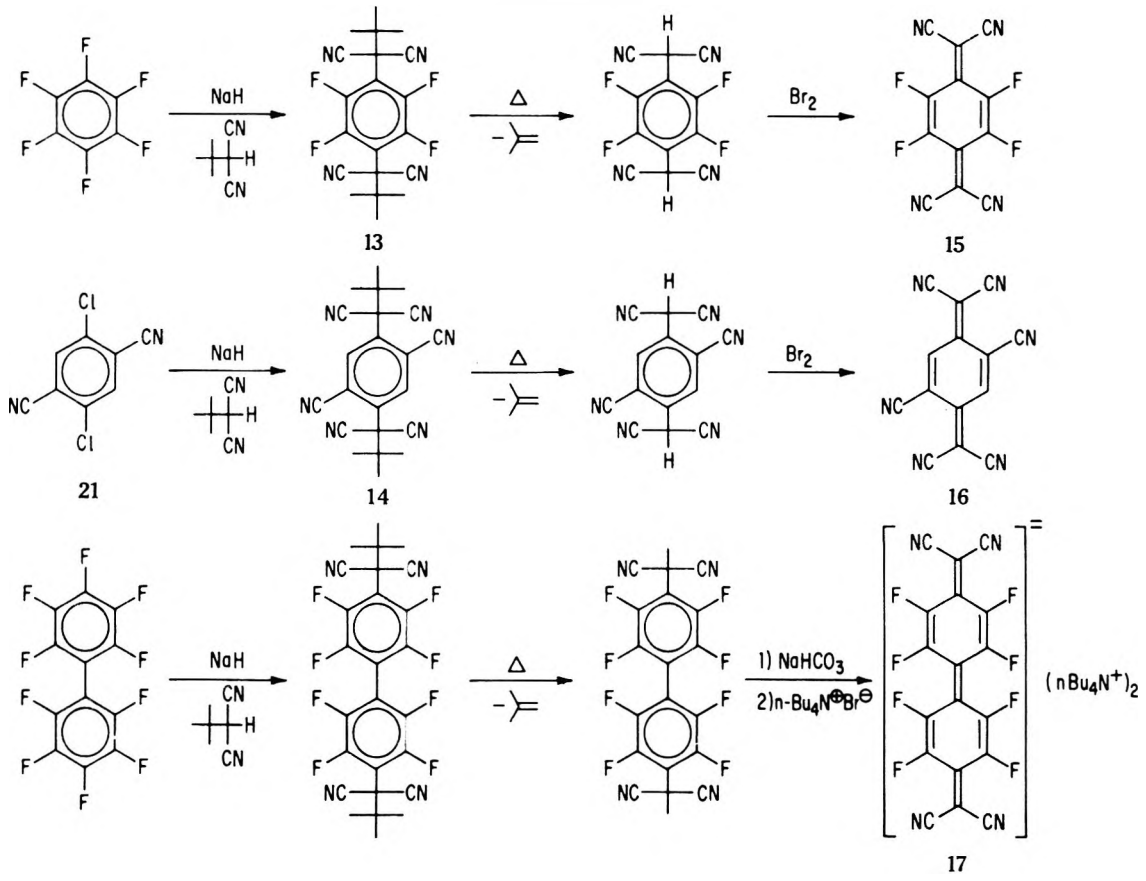
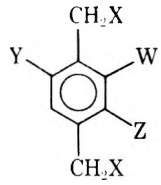
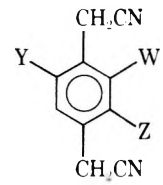
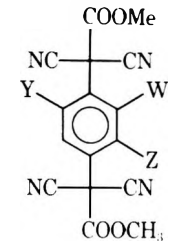


Table I[j]
TCNQ Precursors







3a	HBr gas + glycol in CH_2Cl_2	4a	66%[a,h]
3b	64–65%,[h] mp 167–169°C[b,i]	4b	81%, mp 198–200°C[b,i]
3c	68%, mp 132–133°C[b]	4c	80%, mp 155–157°C[b]
3d	63%, mp 92–95°C[b]	4d	78%, mp 125–127°C[b]
3e	80%, mp 102–105°C[b]	4e	82%, mp 111–112°C[b]
3f	83%, mp 84–86°C[b]	4f	50%, mp 116–117°C[b]
3g	54%, 132–133°C[c]	4g	93%, mp 160–161°C[b]
3h	95%, mp 48–49°C[a]	4h	96%, mp 62–63°C[a]
3i	78%, mp 55–57°C[a]	4i	100%, mp 64–66°C[a]
3j	45%, mp 105–107°C[d]	4j	31%, mp 135–137°C[b]
3k	56%, mp 123–128°C[d]	4k	mp 162–166°C[b]
3l	16%, mp 142–144°C[d]	4l	52%, mp 181–185°C[d]
3m	100%, mp 98–100°C[a]	4m	90–96%, mp 184–186°C[a]
3n	91%, mp 121–123°C[a]	4n	89%, mp 212–213°C[a]
3o	22%, mp 217–223°C[e]	4o	44%, mp 250–255°C[f]
3p	mp 146–147°C[b]	4p	91%, mp 168–170°C[b]
3q		4q	87%, mp 152–155°C[b]
3r	80%, mp 74–76°C[g]	4r	90%, mp 140–141°C[g]
3s	80–82%, mp 129–131°C[g]	4s	100%, mp 188–190°C[g]

5a	23%,[h] mp 153–155°C[i]
5b	95%, mp 200–201°C
5c	70%, mp 143–144°C
5d	62%, mp 144–147°C
5e	51%, mp 108–109°C
5f	73%, mp 104–105°C
5g	53%, mp 139–140°C
5h	82%, mp 128–130°C
5i	75%, mp 121–124°C
5j	74%, mp 166–170°C
5k	66%, mp 190–192°C
5l	34%, mp 203–207°C
5m	68–80%, mp 187–189°C
5n	89%, mp 222–224°C dec
5o	36%, mp 230–236°C
5p	67%, mp 162–164°C
5q	100%, mp 181–183°C
5r	67%, mp 177–178°C
5s	96%, mp 228–229°C

[a] Procedure similar to that for $TCNQCl_2$. [b] Procedure similar to that for $TCNQ(OMe)_2$. [c] Procedure similar to that for $TCNQ(OMe)_2$ except acetic acid not included in reaction mixture. [d] Procedure similar to that for $TCNQICH_3$. [e] Reflux 2,5-diiodo-*p*-xylene 8–10 hr with Br_2 in $BrCH_2CH_2Br$, recrystallize from $BrCH_2CH_2Br$. [f] DMF, CF_3COOH, NaCN, 0°C. [g] Procedure similar to that for $TCNQ(i\text{-}Pr)_2$. [h] Yields most frequently of crude material for next step. [i] Melting points generally of analytical sample. [j] See introduction to Experimental Section.

Table II
Tetracyanoquinodimethanes[b]

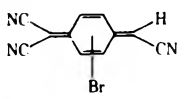
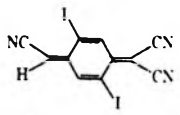
TCNQ	Mp, °C	Ir (KBr), μ	^{1}H NMR,[a] δ	Parent mass spectrum	Yield, %
TCNQ(OMe), 6a	214–215	4.48 6.20 6.42 6.48 8.03 8.87 10.03 12.65		234.0517 (calcd 234.0541) impurity at mass 250	87
TCNQ(OMe)$_2$, 6b	300–305	4.52 6.39 6.55 8.07 9.93 12.64	4.03, 6 H, s 6.45, 2 H, s	264.0593 (calcd 264.0647)	83–98
TCNQ(OMe)(OEt), 6c	243–244	4.48 6.36 6.49 8.05 11.64	1.59, 3 H, t 4.03, 3 H, s 4.25, 2 H, q 6.42, 1 H, s 6.44, 1 H, s	278.0781 (calcd 278.0803) impurity at mass 280, probably TCNQH$_2$(OMe)(OEt)	96–98
TCNQ(OMe)(O-*i*-Pr), 6d	193–195	4.48 6.37 6.51 8.05 8.67 11.65	1.5, 6 H, d 4.2, 3 H, s ~5.1, 1 H, m 6.7, 2 H, s	292.0933 (calcd 292.0959)	93
TCNQ(OMe)(O-*i*-Bu), 6e	219–220	4.47 6.37 6.48 8.04 10.06 11.63	1.13, 6 H, d 2.32, 1 H, m 3.93, 2 H, d 4.03, 3 H, s 6.43, 1 H, s 6.45, 1 H, s	306.1099 (calcd 306.1116)	52–98
TCNQ(OMe)(O-*i*-C$_5$H$_{11}$), 6f	228–230 dec	4.49 6.38 6.52 8.04 8.68 11.67	0.97, d 1.84, m 4.02, s 4.19, t 6.44, s	320.1276 (calcd 320.1272)	92
TCNQ(OEt)(SMe), 6g	232–233 dec	4.48 6.22 6.57 11.73	6.86, 1 H, s 6.61, 1 H, s 4.28, 2 H, q 2.64, 3 H, s 1.58, 3 H, t	294.0547 (calcd 294.0575)	93–95
TCNQCl, 6h	210–212	4.48 6.54 9.68 10.94 11.98	7.2–7.7, m	238.0025 (calcd 238.0046)	93–96
TCNQBr, 6i	203–204	4.48 6.48 6.57 9.83 10.96 12.00	7.4–7.8, m	281.9541 (calcd 281.9541) Possible contamination with 	95
TCNQClMe, 6i	260–265 dec	4.48 6.48 9.77 10.98	2.69, 3 H, s 7.32, 1 H, s 7.61, 1 H, s	252.0181 (calcd 252.0202)	84–93
TCNQBrMe, 6k	265 dec	4.48 6.50 9.89 10.97	2.67, 3 H, s 7.35, 1 H, s 7.86, 1 H, s	295.9691 (calcd 295.9698)	75

Table II
(*Continued*)

TCNQ	Mp, °C	Ir (KBr), μ	^{1}H NMR,[a] δ	Parent mass spectrum	Yield, %
$TCNQICH_3$, 6l	285–287	4.48 6.53 6.58 10.01 10.98	8.22, 1 H, s 7.36, 1 H, s 2.66, 3 H, s	343.9571 (calcd 343.9760)	49
$TCNQCl_2$, 6m	305 dec	4.47 6.50 6.55 9.37 9.96 10.92		271.9668 (calcd 271.9656)	93–96
$TCNQBr_2$, 6n	316–318 dec	4.51 6.53 6.60 9.52 10.02 10.98		359.8644 (calcd 359.8647)	94
$TCNQI_2$, 6o	>348	4.52 6.56 6.67 9.63 10.17 11.01		455.8405 (calcd 455.8372) Possible contamination with TCNQBrI and 	51
$TCNQ(OMe)(OCH_2OCH_2)$, 6p	>400	4.50 6.40 6.56 7.94 9.66 10.54	4.03, 3 H, s 5.12, 2 H, s 5.42, 2 H, s 6.41, 1 H, s	292.0576 (calcd 292.0596)	89
$TCNQ(Me)_2$, 6q	277–279	4.48 6.40 6.53 9.67 10.33 11.05	2.67, 6 H, s 7.30, 2 H, s	232.0738 (calcd 232.0748)	80
$TCNQ(Et)_2$, 6r	174–175	4.48 6.43 6.55 6.85 9.53 10.95 12.37	1.3, 3 H, t 3.0, 2 H, s 7.3, 1 H, s	260.1052 (calcd 260.1061)	92–98
$TCNQ(i\text{-}Pr)_2$, 6s	193–195	4.50 6.40 6.58 9.18 11.23	7.50, 2 H, s 3.77, 2 H, m 1.33, 12H, d	288.1371 (calcd 288.1371)	86
$TCNQF_4$, 15	295–300	4.47 6.23 7.45 10.23		276.0034 (calcd 276.0059)	72–85
$TCNQ(CN)_2$, 16	>360	4.50 6.54 8.88 10.02 11.03 (mineral oil)		254.0344 (calcd 254.0341)	78

[a] Most proton NMR spectra were taken at 220 MHz using Fourier transform methods to enhance signal strength: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; values given in δ parts per million; all spectra in $CDCl_3$ except 6d (CD_3COCD_3) and 6r (CD_3CN).
[b] Satisfactory analytical values (±0.4% for C, H, N) for every compound in table were included in original manuscript. Ed.

NMR ($CDCl_3$, Me_4Si) 3 H singlet δ 2.4, 2 H singlet 4.53, 2 H singlet 4.62, 1 H singlet 7.3, and 1 H singlet 7.8.

Recrystallization of a small sample from 1,2-dichloroethane gave white needles, mp 142–144°C.

Anal. Calcd for $C_9H_9Cl_2I$: C, 34.32; H, 2.88; Cl, 22.51; I, 40.29. Found: C, 34.97; H, 3.14; Cl, 22.24; I, 39.28; C, 34.94; H, 3.06; Cl, 22.12; I, 39.21.

B. 2,5-Bis(cyanomethyl)-4-iodotoluene (4l). A 1.4-g (4.5 mmol) sample of 2,5-bis(chloromethyl)-4-iodotoluene (mp 137–146°C) was added to a mixture of 1 g (20 mmol) of sodium cyanide, 1.2 ml of water, and 2.8 ml of dioxane with magnetic stirring. The mixture thickened nearly to a gel over several days. Vacuum filtration, washing with water, sucking dry, and crystallizing from ethanol–acetone gave 0.69 g (52%) of white solid, mp 181–185°C, acceptable for use in the next step.

Anal. Calcd for $C_{11}H_9IN_2$: C, 44.62; H, 3.06; N, 9.46. Found: C, 44.82; H, 3.22; N, 9.01; C, 44.80; H, 3.26.

^1H NMR ($CDCl_3$, Me_2SO-d_6–Me_4Si) 3 H singlet δ 2.4, 4 H singlet 3.9, 1 H singlet 7.4, 1 H singlet 7.9.

C. Dimethyl α,α,α′,α′-Tetracyano-2-iodo-5-methyl-1,4-phenylenediacetate (5l). A three-neck 500-ml round-bottom flask was equipped with a N_2 inlet, strong mechanical stirrer, steam bath, and distillation head. The reaction vessel was charged with 100 ml (1 mol) of dimethyl carbonate, 18 g (0.33 mol) of sodium methoxide, and 38.6 g (0.13 mol) of 2,5-bis(cyanomethyl)-4-iodotoluene. The thick solution turned pink and cleared considerably on warming with a steam bath. Within several minutes, however, a yellow precipitate formed that only the most vigorous stirring kept from gelling. An additional 100 ml of benzene was added and the slurry heated to reflux. The mixture became so thick that several hundred more milliliters of benzene were added. After ~2 hr of refluxing, 100–200 ml of solvent was allowed to distil off with replacement by benzene. The reaction mixture was cooled to 0 to −10°C with a wet ice–acetone bath as 25 ml (~0.5 mol) of liquid cyanogen chloride was blown in on a nitrogen stream. The solution loosened up markedly and was stirred at room temperature overnight. Vacuum filtering the thick slurry gave solid that was later combined with additional solid from reducing the filtrate on a rotary evaporator. This solid was ground in a mortar and added to water with stirring. Vacuum filtration, grinding up again, adding to water with stirring, and vacuum filtering a second time gave 30 g of light green solid. This solid was taken up in methylene chloride, treated with decolorizing carbon and magnesium sulfate, and filtered. Stripping to a heavy slurry on a rotary evaporator, adding methanol, and filtering gave 20.7 g (34%) of white solid, softening 190°C, mp 203–207°C.

Anal. Calcd for $C_{17}H_{11}IN_4O_4$: C, 44.18; H, 2.40; N, 12.12. Found: C, 44.01; H, 2.28; N, 12.43.

^1H NMR ($CDCl_3$, Me_4Si) 3 H singlet δ 2.5, 6 H doublet 4.0, 1 H singlet 7.7, 1 H singlet 8.2.

D. 2-Iodo-5-methyl-7,7,8,8-tetracyanoquinodimethane (6l). Ten grams (0.022 mol) of dimethyl α,α,α′,α′-tetracyano-2-iodo-5-methyl-1,4-phenylenediacetate was added with stirring to 14 g of potassium hydroxide (0.22 mol) in 200–300 ml of water under nitrogen. The clear yellow solution obtained after 15 min was acidified by slow addition of 30 ml (0.37 mol) of concentrated hydrochloric acid in 30 ml of water (foaming). The precipitate was vacuum filtered and washed with water. The damp precipitate was stirred with 200 ml of water and treated with excess bromine water. The resulting orange solid was filtered, ground with mortar and pestle, and treated with excess bromine water as before. Vacuum filtration gave brick red solid that was taken into 2000 ml of methylene chloride, treated with magnesium sulfate and decolorizing carbon, and filtered. Stripping this filtrate to a slurry of red solid on a rotary evaporator, filtering, dissolving in methylene chloride, treating with decolorizing carbon, and stripping again gave 3.65 g (49%) of dark red crystals, mp 283–287°C.

Anal. Calcd for $C_{13}H_5N_4I$: C, 45.38; H, 1.46; N, 16.28. Found: C, 45.36; H, 1.47; N, 16.02; C, 45.28; H, 1.52; N, 15.74.

Gradient sublimation of 2 g of this material at 170–190°C (0.01–0.05 mm) for several days gave a 1.79-g middle cut of spectacular purple lumps, mp 285–287°C. Anal. Found: C, 45.18; H, 1.45; N, 16.01; C, 45.18; H, 1.44; N, 16.00.

2,5-Diisopropyl-7,7,8,8-tetracyanoquinodimethane (6s). A. 1,4-Bis(chloromethyl)-2,5-diisopropylbenzene (3s). Into a 1-l., round-bottom flask fitted with mechanical stirrer, thermometer, condenser, and gas inlet tube were charged 243 g (1.5 mol) of *p*-diisopropylbenzene, 120 g (4.0 mol) of paraformaldehyde, and 150 g of pulverized anhydrous zinc chloride. A rapid stream of dry hydrogen chloride was passed into the vigorously stirred reaction mixture at 70 ± 2°C. The temperature was increased to 80 ± 1°C for 1 hr. It was necessary to add 50 ml of cyclohexane toward the end of the reaction in order to stir the reaction mixture. The reaction mixture was cooled, and the solid dichloride was collected and washed with cold water and finally with petroleum ether. The filter cake was taken up in methylene chloride, and the solution was washed twice with dilute hydrochloric acid and once with water. The resulting solution was treated with decolorizing charcoal and anhydrous magnesium sulfate, and the filtrate was concentrated until crystals began to separate. Anhydrous ether was added and the concentration continued until most of the methylene chloride had been displaced. After cooling, the crystals were collected and washed with cold methylene chloride followed by a washing with petroleum ether. After drying, there was obtained 300–318 g (80–82%) of dichloride, mp 129–131°C.

Anal. Calcd for $C_{14}H_{20}Cl_2$: C, 64.87; H, 7.78; Cl, 27.36. Found: C, 64.87; H, 7.81; Cl, 27.56.

B. 1,4-Bis(cyanomethyl)-2,5-diisopropylbenzene (4s). Into a mechanically stirred suspension of 11 g of finely powdered sodium cyanide in 55 ml of dimethyl sulfoxide was added in small portions 25.4 g (0.1 mol) of 1,4-bis(chloromethyl)-2,5-diisopropylbenzene. The temperature was maintained at 45–50°C by controlling the rate of addition of the dichloride and by means of external cooling. The mixture was stirred for an additional 1–5 hr at 50°C and diluted to 500 ml with cold water, the dinitrile was collected and washed with water, and the washed filter cake was dissolved in about 200 ml of methylene chloride. After drying, the filtrate was concentrated until crystals separated, ether was added, and the concentration was continued with subsequent additions of ether until the solvent was essentially ether. The yield of granular crystals melting at 188–190°C was 74 g (100%).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.67; H, 8.31; N, 11.79.

C. Dimethyl α,α,α′,α′-Tetracyano-2,5-diisopropyl-1,4-phenylenediacetate (5s). A mechanically stirred mixture of 24 g (0.1 mol) of 1,4-bis(cyanomethyl)-2,5-diisopropylbenzene, 100 ml (1.0 mol) of dimethyl carbonate, and 14 g (0.2 mol) of sodium methoxide was stirred until the exothermic reaction (to 50°C) had subsided and 50 ml of benzene was added. In order to stir the thick reaction mixture, it was necessary to add an additional 50 ml of dimethyl carbonate and 50 ml of benzene. The thick reaction mixture was stirred on total reflux for 3 hr, and then the benzene–methanol binary was distilled during the course of 1 hr and the distillation was continued for an additional 1 hr. After cooling to 5°C, 16 ml of cyanogen chloride was distilled into the reaction mixture at 5–10°C. The nearly colorless reaction mixture was warmed slowly to 50°C during the course of about 1 hr. After stirring overnight at room temperature, the reaction mixture was evaporated under reduced pressure to dryness by means of a Rinco evaporator. The crude solid mixture of dimethyl α,α,α′,α′-tetracyano-2,5-diisopropyl-1,4-phenylenediacetate and sodium chloride was stirred with cold water in a Waring Blendor. The tetracyanodiacetate was collected, washed with water, and, after air drying, dried over phosphorus pentoxide under reduced pressure. The yield of nearly colorless material was 39 g (96%). Crystallization from methylene chloride–ether gave colorless crystals, mp 228–229°C.

Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.00; H, 5.46; N, 13.78. Found: C, 64.76; H, 5.18; N, 13.86; C, 64.79; H, 5.27; N, 13.74.

D. 2,5-Diisopropyl-7,7,8,8-tetracyanoquinodimethane (6s). To an aqueous solution of 120 ml of 5% potassium hydroxide warmed to about 70°C was added 10.0 g of dimethyl α,α,α′,α′-tetracyano-2,5-diisopropyl-1,4-phenylenediacetate, and the solution was stirred for about 1 min, whereupon a homogeneous solution was obtained. The solution was acidified carefully by the addition of 6 *N* hydrochloric acid, and the solid was treated with a slight excess of bromine water (positive test with starch–potassium iodide paper).

The bright yellow precipitate was collected, washed with cold water, and dissolved in methylene chloride, and the solution was concentrated to a small volume. Anhydrous ether was added slowly whereupon the TCNQ(*i*-Pr)$_2$ separated as bright yellow crystals during continued concentration. After cooling, the crystals were collected, washed with ether, and dried. The yield was 6.1 g (86%) of bright yellow crystals, mp 193–195°C.

Anal. Calcd for $C_{18}H_{16}N_4$: C, 74.97; H, 5.59; N, 19.43. Found: C, 75.03; H, 5.66; N, 19.71.

2,5-Dimethoxy-7,7,8,8-tetracyanoquinodimethane (6b). A. 1,4-Bis(chloromethyl)-2,5-dimethoxybenzene (3b). A slow

stream of dry hydrogen chloride was passed into a mechanically stirred mixture of 82 g (0.6 mol) of *p*-dimethoxybenzene, 45 g (1.5 mol) of paraformaldehyde, 100 ml of glacial acetic acid, and 200 ml of concentrated hydrochloric acid at 50–55°C for a period of 2 hr. It was necessary to cool the reaction mixture externally until the exothermic reaction ceased. Crystals of the dichloride started to separate within about 15 min after the start of the reaction, and at the end of 2 hr, a crystalline, thick reaction mass was obtained. The reaction product was collected by suction filtration and washed with about 2 l. of cold water. The moist filter cake was dissolved in about 2 l. of methylene chloride and the organic layer was treated with decolorizing charcoal and anhydrous magnesium sulfate. The resulting colorless filtrate was concentrated to a thick paste of colorless crystals, the mixture was cooled to 0°C, and the dichloride was collected, washed with cold methylene chloride, and, after air drying, dried under reduced pressure over phosphorus pentoxide–potassium hydroxide. The yield of colorless crystals, mp 167–169°C, was 90–92 g (64–65%).

Anal. Calcd for $C_{14}H_{12}O_2Cl_2$: C, 51.08; H, 5.15; Cl, 30.16. Found, C, 50.83; H, 5.32; Cl, 30.27; C, 50.83; H, 5.24.

B. 1,4-Bis(cyanomethyl)-2,5-dimethoxybenzene (4b). To a mechanically stirred suspension of 35 g (0.7 mol) of sodium cyanide in 200 ml of dimethyl sulfoxide was added in small portions 71 g (0.3 mol) of 2,5-dimethoxy-1,4-xylylene dichloride. The temperature was maintained at 50°C by controlling the rate of addition of the dichloride and by means of external cooling. The reaction mixture was maintained at 50°C for an additional 1 hr after the addition of the dichloride was completed and then the temperature was increased to 85°C for 5 min. After cooling to about 40°C, the reaction mixture was diluted to a volume of about 1 l., and the precipitated dinitrile was collected and washed with water until essentially neutral. The moist filter cake was dissolved in about 2 l. of methylene chloride, and the organic layer was dried and concentrated until a thick paste of crystals was obtained. After cooling to room temperature, the dinitrile was collected and washed in turn with methylene chloride and ether. After drying under reduced pressure over phosphorus pentoxide at 50°C, there was obtained 51 g (81%) of 2,5-dimethoxy-1,4-xylylene dicyanide: mp 198–200°C; ^{1}H NMR ($CDCl_3$, Me_4Si) 4 H singlet δ 3.7, 6 H singlet 3.9, 2 H singlet 7.0.

Anal. Calcd for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.53; H, 5.35; N, 13.00.

C. Dimethyl $\alpha,\alpha,\alpha',\alpha'$-Tetracyano-2,5-dimethoxy-1,4-phenylenediacetate (5b). A mechanically stirred mixture of 43 g (0.2 mol) of 2,5-dimethoxy-1,4-xylylene dicyanide, 250 ml (2.5 mol) of dimethyl carbonate, and 27 g (0.5 mol) of sodium methoxide was warmed to 70°C whereupon a spontaneous reaction occurred, the temperature increased to 80°C, the sodium methoxide partially dissolved, and after a few minutes a solid began to precipitate. About 50 ml of benzene was added and the reaction mixture was refluxed for 3 hr. The benzene–methanol binary was removed by distillation during the course of 1 hr, additional benzene being added as required. The suspension of the disodium derivative of dimethyl α,α-dicyano-2,5-dimethoxy-1,4-phenylenediacetate was cooled to 5°C and 35 ml of cyanogen chloride was distilled into the reaction mixture at 5–10°C. After a slight exothermic reaction, the temperature was increased to 65°C during the course of about 2 hr. After stirring overnight at room temperature, the temperature of the reaction mixture was increased to 50°C, and the reaction mixture was evaporated to dryness in a Rinco evaporator under reduced pressure in a bath at 50–60°C. The solid residue of dimethyl $\alpha,\alpha,\alpha',\alpha'$-tetracyano-2,5-dimethoxy-1,4-phenylenediacetate and sodium chloride was stirred in a Waring Blendor with cold water. The crude ester was collected and washed with cold water, and the moist filter cake was dissolved in methylene chloride. The organic layer was treated with decolorizing carbon and anhydrous magnesium sulfate, and the filtrate was concentrated until crystals began to separate. Addition of ether precipitated the tetracyanodiacetate. After cooling to −5°, the colorless crystals were collected, washed with cold ether, and dried. The yield of compound melting at 200–201°C was 72 g (95%).

Anal. Calcd for $C_{18}H_{14}O_6N_4$: C, 56.54; H, 3.69; N, 14.66. Found: C, 56.62; H, 3.85; N, 14.60.

^{1}H NMR ($CDCl_3$, Me_4Si) 2 H singlet δ 7.3 and 12 H singlet 4.0.

D. 7,7,8,8-Tetracyano-2,5-dimethoxyquinodimethane (6b). To 3.8 g (0.1 mol) of dimethyl $\alpha,\alpha,\alpha',\alpha'$-tetracyano-3,5-dimethoxy-1,4-phenylenediacetate was added 40 ml of 10% aquous potassium hydroxide solution and the mixture was stirred until a homogeneous solution was obtained. The solution was acidified by the addition of 6 *N* hydrochloric acid, and a slight excess of bromine water was added to the suspension of the dihydro compound. The resulting red product was collected, washed with cold water, and dissolved in about 600 ml of methylene chloride. The organic layer was dried, treated with decolorizing charcoal, and concentrated to a small volume, whereupon deep red crystals of $TCNQ(OMe)_2$ separated. The crystals were collected, washed with methylene chloride, and dried. The yield was 2.2–2.6 g (83–98%), mp 300–305°C dec.

Anal. Calcd for $C_{14}H_8O_2N_4$: C, 63.63; H, 3.05; N, 21.20. Found: C, 63.32; H, 2.85; N, 21.22.

2,5-Dichloro-7,7,8,8-tetracyanoquinodimethane (6m). A. 1,4-Bis(hydroxymethyl)-2,5-dichlorobenzene. Into a 3-l., four-necked flask fitted with reflux condenser, mechanical stirrer, thermometer, and dropping funnel was added 17 g (0.45 mol) of $LiAlH_4$ followed by the addition of 300 ml of anhydrous ether. All reactions were carried out under an atmosphere of nitrogen. The stirrer was started and the mixture was refluxed for 0.5 hr. The steam was turned off and a solution of 68 g (0.25 mol) of 2,5-dichloroterephthalcyl chloride (prepared from 2,5-dichloroterephthalic acid and thionyl chloride in the presence of a few drops of dimethylformamide) in 600 ml of anhydrous ether was added dropwise over the course of 1 hr. The reaction mixture refluxed gently at this rate for an additional period of 1 hr. Ethyl acetate (30 ml) was added dropwise followed by the careful addition of 35 ml of water. Hydrogen evolution usually ceased before the addition of the water was complete. A solution of 30 ml of concentrated hydrochloric acid and 400 ml of water was added and the ether was evaporated in a stream of nitrogen while stirring vigorously at 20–25°C. To the resulting gray suspension of the glycol was added about 100 ml of concentrated hydrochloric acid and the mixture was warmed to 50°C. The reaction mixture was filtered, and the filter cake was washed first with dilute hydrochloric acid, then with water until the washings were neutral. The yield of colorless crystals melting at 198–200°C was 52 g (99%). Crystallization from methanol–ether did not change the melting point.

Anal. Calcd for $C_8H_8O_2Cl_2$: C, 46.40; H, 3.90. Found: C, 46.69; H, 3.77.

B. 1,4-Bis(chloromethyl)-2,5-dichlorobenzene (3m). Replacement of the hydroxyl groups in 1,4-bis(hydroxymethyl)-2,5-dichlorobenzene requires extremely vigorous conditions, but by heating the glycol with hydrogen chloride and hydrochloric acid, an essentially quantitative yield of dichloride was obtained.

A mixture of 100 g (0.49 mol) of 1,4-bis(hydroxymethyl)-2,5-dichlorobenzene, 400 ml of concentrated hydrochloric acid, and 100 g of hydrogen chloride was heated in a bomb with agitation at 120°C for 8 hr. After cooling, the tube was vented and the solid dichloride was collected, washed with water, and dissolved in methylene chloride. After the methylene chloride layer was dried, the solution was concentrated until crystals began to separate. Ether was added slowly to displace the methylene chloride. After cooling thoroughly, the crystals were collected, washed with cold ether, and dried. An analytical sample crystallized in this manner melts at 98–100°C.

Anal. Calcd for $C_8H_6Cl_4$: C, 39.38; H, 2.48; Cl, 58.14. Found: C, 39.41, H, 2.41; Cl, 57.95.

^{1}H NMR ($CDCl_3$, Me_4Si) 2 H singlet δ 7.6, 4 H singlet 4.6.

C. 1,4-Bis(cyanomethyl)-2,5-dichlorobenzene (4m). Sixteen unsuccessful attempts were made to prepare the dinitrile from the dichloride by the usual procedures. If hydrogen cyanide is not present, intractable products are obtained. The following procedure gave the desired compound in excellent yield.

Into a 500-ml three-necked flask fitted with mechanical stirrer, thermometer, and stopper was charged 210 ml of dimethyl sulfoxide and 29 g (0.6 mol) of finely powdered sodium cyanide was added to the stirred reaction mixture. After cooling to 20°C, 35 ml of liquid hydrogen cyanide was added slowly, the resulting mixture was cooled to 12°C, and 49 g (0.2 mol) of 1,4-bis(chloromethyl)-2,5-dichlorobenzene was added in one portion. The reaction mixture was stirred at 14–16°C for 0.5 hr, then the temperature was allowed to increase slowly to 20–22°C during about 1 hr. The reaction mixture was diluted to about 1500 ml with cold water, and the precipitate was collected and washed with cold water until the washings were neutral. The moist filter cake was dissolved in about 1500 ml of methylene chloride at the reflux temperature, and the organic layer was separated, treated with decolorizing charcoal, and dried with anhydrous magnesium sulfate. The nearly colorless filtrate was concentrated to a thick paste of colorless crystals. After cooling in ice, the crystals were collected and washed in turn

with cold methylene chloride, ether, and pentane. After drying at 60°C (10–15 mm) over phosphorus pentoxide, the yield was 40.5–43.6 g (90–96%). The compound melts at 184–186°C.

Anal. Calcd for $C_{10}H_6N_2Cl_2$: C, 53.36; H, 2.69; N, 12.45; Cl, 31.50. Found: C, 53.49; H, 2.47; N, 12.16; Cl, 31.40.

^1H NMR ($CDCl_3$–CF_3COOH, Me_4Si) 2 H singlet δ 7.7, 4 H singlet 4.0.

D. Dimethyl α,α,α′,α′-Tetracyano-2,5-dichloro-*p*-phenylenediacetate (5m). Into a jacketed Waring blender were charged 45 g (0.02 mol) of 1,4-bis(cyanomethyl)-2,5-dichlorobenzene, 28 g of sodium methoxide, and a mixture of 225 ml of dimethyl carbonate and 75 ml of dried benzene. The stirrer was started and as soon as the exothermic reaction had ceased, the reaction mixture was heated to gentle reflux. All operations were carried out under an atmosphere of nitrogen. It was necessary to add additional benzene (about 150–200 ml) in order to obtain a mixture that could be stirred. The reaction mixture was stirred at gentle reflux for a period of about 3 hr, then the binary of methanol and benzene was allowed to distil during the course of about 1 hr. The reaction mixture was cooled to 20°C and 30–32 ml of cyanogen chloride was distilled into the stirred mixture, the temperature being maintained at 20°C during the addition of the cyanogen chloride and for an additional 0.5 hr. The temperature was gradually increased to 35–40°C during the course of about 1.5 hr and the orange-colored suspension was transferred to a 2-l. round-bottom flask and evaporated to dryness on a Rinco evaporator in a bath at 70–80°C. The resulting solid was scraped from the walls of the flask, transferred to a funnel, and washed with cold water until the washings were essentially colorless. The moist filter cake was dissolved in ca. 450–500 ml of methylene chloride, the aqueous layer was separated, and the organic layer was dried with anhydrous magnesium sulfate and treated with decolorizing charcoal. The resulting reddish-orange filtrate was stirred with a few grams of aluminum oxide (Woelm neutral). The resulting light yellow filtrate was concentrated until crystals began to separate, then ether was added so as to maintain a constant volume. The tetracyano-*p*-phenylenediacetate separated as colorless crystals. After cooling in ice the crystals were collected and washed with −40 to −30°C ether until the washings were colorless, then with pentane. The yield of dried product melting at 186–187°C was 53.3–63.3 g (68–80%). Crystallization from methylene chloride–ether gave colorless crystals melting at 187–189°C. A total of 20 runs (9 at low yield, 11 at the above indicated range) were made.

Anal. Calcd for $C_{16}H_8O_4N_4Cl_2$: C, 49.13; H, 2.06; N, 14.32; Cl, 18.13. Found: C, 48.94; H, 2.09; N, 13.97; Cl, 18.63.

^1H NMR ($CDCl_3$, Me_4Si) 2 H singlet δ 8.1, 6 H singlet 4.1.

E. 2,5-Dichloro-7,7,8,8-tetracyanoquinodimethane (6m). To a solution of 39.1 g (0.1 mol) of dimethyl α,α,α′,α′-tetracyano-2,5-dichloro-*p*-phenylenediacetate in 125 ml of dioxane at 70–75°C was added, slowly and with swirling, 400 ml of a 10% aqueous potassium hydroxide solution at 70–75°C. (The reaction is very exothermic at the start and the alkali solution must be added slowly and with care to prevent boil over.) The addition of the alkali required about 1.5 min and the temperature of the solution was about 75°C. After stirring for an additional period of 2 min, the solution was cooled rapidly in a mixture of ice–salt to 20–25°C and about 75 ml of 6 *N* hydrochloric acid was added slowly with stirring. The mixture was cooled to 10–12°C and transferred to a 3-l. beaker and a few pieces of ice were added. The solution was acidified by the dropwise addition of 3 *N* hydrochloric acid and an excess of bromine water was added. The resulting bright yellow suspension of the tetracyanoquinodimethane was warmed rapidly to 40°C on a steam bath and stirred for 0.5 hr at this temperature. The amount of bromine water added should be sufficient to produce a red coloration to the aqueous solution. Otherwise only part of the dihydrotetracyanoquinodimethane is oxidized. The bright yellow precipitate was collected by filtration and washed with cold water until the washings were colorless and free of bromine and bromide ion. The moist filter cake was divided into four portions and one portion was dissolved in about 3.5–4.0 l. of refluxing methylene chloride. The methylene chloride solution was transferred to another 5-l. flask, the solution was dried with anhydrous magnesium sulfate, and the filtrate was concentrated using two 3-l. flasks. The methylene chloride was recovered for use in purifying the other portions of the filter cake. Crystals of the compound separated during the concentration and the process was continued to a small volume. The yellow-orange crystalline product was collected and washed twice with methylene chloride and several times with ether. The yield of $TCNQCl_2$ was 25.4–26.2 g (93–96%).

Anal. Calcd for $C_{12}H_2N_4Cl_2$: C, 52.78; H, 0.74; N, 20.52; Cl, 25.97. Found: C, 52.75; H, 0.63; N, 20.65; Cl, 25.93; C, 52.51; H, 0.60; N, 20.68.

***tert*-Butylmalononitrile (19).** A solution of 159 g (1.5 mol) of isopropylidenemalononitrile[16] in 200 ml of anhydrous benzene was added to 550 ml (1.6 mol) of 3 *M* methylmagnesium bromide in diethyl ether at 30–35°C under an atmosphere of nitrogen. The mixture was stirred at 45–47°C for 1 hr and poured onto excess ice. The mixture was made faintly acidic with 20% sulfuric acid. The aqueous layer was extracted once with 1:1 ether–benzene. The combined organic layers were washed twice with water, made faintly acidic with dilute hydrochloric acid, and washed twice with saturated sodium chloride solution. After drying with anhydrous magnesium sulfate and concentration under reduced pressure, the residue was distilled, giving 136 g (75%) of *tert*-butylmalononitrile, bp 80–85°C (7 mm), as a waxy solid that melted at about 80°C: ^1H NMR ($CDCl_3$, Me_4Si) 9 H singlet δ 1.3, 1 H singlet 3.6.

Anal. Calcd for $C_7H_{10}N_2$: C, 68.81; H, 8.25; N, 22.94. Found: C, 68.66; H, 8.40; N, 22.73.

2,3,5,6-Tetrafluoro-7,7,8,8-tetracyanoquinodimethane (15). A. 2,3,5,6-Tetrafluoro-1,4-bis(*tert*-butyldicyanomethyl)benzene (13). To a magnetically stirred suspension of 2.88 g (0.12 mol) of sodium hydride in 30 ml of glyme was added a solution of 15 g (0.12 mol) of *tert*-butylmalononitrile in 15 ml of glyme. The addition was carried out at 10–15°C under an atmosphere of nitrogen. To the resulting homogeneous solution was added 9.3 g (0.05 mol) of hexafluorobenzene (**20**) and the reaction mixture was heated to reflux. After about 2 hr, a white solid began to precipitate and appeared complete after about 12–16 hr. Most of the glyme was removed by distillation under reduced pressure, the reaction mixture was diluted with water, and the precipitate was collected, washed until neutral with water, then washed with methanol until the washings were colorless, and finally washed with ether. The yield of nearly colorless to light yellow 2,3,5,6-tetrafluoro-1,4-bis(*tert*-butyldicyanomethyl)benzene (**13**) was 15.7 g (81%). Colorless crystals, mp 295–300°C dec, were obtained after crystallization from a large volume of acetone.

Anal. Calcd for $C_{20}H_{18}N_4F_4$: C, 61.53; H, 4.65; N, 14.35; F, 19.47. Found: C, 61.58; H, 4.61; N, 14.47; F, 19.44.

B. 2,3,5,6-Tetrafluoro-7,7,8,8-tetracyanoquinodimethane (15). Diphenyl ether (350 ml) was heated to reflux with stirring under an atmosphere of nitrogen and 7.8 g (0.02 mol) of 2,3,5,6-tetrafluoro-1,4-bis(*tert*-butyldicyanomethyl)benzene (**13**) was added rapidly in one portion. The resulting solution was heated to reflux for 3.0–3.5 min, cooled with air to 195°C, then cooled to 40°C with cold water. An equal volume of ether was added followed by the addition of 100 ml of 4% sodium bicarbonate solution. The resulting mixture was shaken vigorously, and the organic layer was extracted with three 30-ml portions of 1% sodium bicarbonate solution. The combined aqueous layers were filtered and extracted once with ether. To the resulting aqueous solution was added 7.5 g of potassium acetate and 5 ml of acetic acid. Bromine water was added until a positive test for free bromine was obtained, the precipitated $TCNQF_4$ was filtered and washed with water, and the moist filter cake was dissolved in about 2.5 l. of methylene chloride at 25°C. The aqueous layer was separated, the organic layer was treated with anhydrous magnesium sulfate and decolorizing charcoal, and the clear, bright yellow filtrate was concentrated until a thick paste of yellow crystals of $TCNQF_4$ was obtained. The crystals were collected and washed with cold methylene chloride followed by a wash with ether. The yield of yellow crystals was 4.0–4.7 g (72–85%), mp 295–300°C dec.

Anal. Calcd for $C_{12}N_4F_4$: C, 52.20; H, 0.00; N, 20.29; F, 27.52. Found: C, 52.02; H, 0.00; N, 20.17; F, 27.43.

2,5-Dicyano-7,7,8,8-tetracyanoquinodimethane (16). A. 2,5-Dicyano-1,4-bis(*tert*-butyldicyanomethyl)benzene (14). To a suspension of 1.68 g (0.07 mol) of sodium hydride in 10 ml of glyme was added a solution of 5.91 g (0.07 mol) of *tert*-butylmalononitrile in 15 ml of glyme at 10°C. To the resulting solution was added 5.91 g (0.3 mol) of 2,5-dichloroterephthalonitrile (**21**) and the reaction mixture was refluxed with stirring under an atmosphere of nitrogen for 20 hr. Most of the glyme was removed by evaporation under reduced pressure, the residue was diluted with water, and the solid material was collected, washed neutral with water, then with methanol until the washings were colorless, and finally with ether. The yield of nearly colorless crystals of **14**, mp 265°C dec, was 8.6 g (78%). Crystallization of a small portion from methylene chloride gave colorless crystals.

Anal. Calcd for $C_{22}H_{20}N_6$: C, 71.72; H, 5.47; N, 22.81. Found: C, 71.39; H, 5.31; N, 22.58.

B. 2,5-Dicyano-7,7,8,8-tetracyanoquinodimethane (16). To

150 ml of diphenyl ether at 230°C was added rapidly in one portion 1.3 g of 2,5-dicyano-1,4-bis(*tert*-butyldicyanomethyl)benzene (**14**). The mixture was stirred at this temperature for 3 min, cooled rapidly to 40°C, and diluted with an equal volume of ether and 100 ml of 1% sodium bicarbonate was added. The organic layer was extracted with 100 ml of a 1% sodium bicarbonate solution and with two 15-ml portions of 1% sodium bicarbonate and the combined aqueous solutions were filtered. The deep red solution was neutralized with hydrochloric acid and bromine water was added to the resulting solution until the anion radical disappeared and a brownish-yellow precipitate was obtained. The crude $TCNQ(CN)_2$ was isolated by filtration (very slow), washed with water, and dried. The crude $TCNQ(CN)_2$ was dissolved in a large volume of hot acetonitrile and the filtered solution was concentrated to a small volume under reduced pressure. The deep yellow crystals were collected, washed with ether, and dried.

Anal. Calcd for $C_{14}H_2N_6$: C, 66.14; H, 0.79; N, 33.06. Found: C, 65.94; H, 0.79; N, 33.19.

Bis(tetra-*n*-butylammonium)-2,2′,3,3′,5,5′,6,6′-octafluoro-7,7,7′,7′-tetracyanodiphenoquinodimethanide (17). A solution of 1 g of **18** and 2 g of sodium bicarbonate in 700 ml of water was pressure filtered under N_2 into 3 g of tetra-*n*-butylammonium bromide in 100 ml of water. The precipitate was pressure filtered under N_2 the next day and blown dry, 1.97 g (94%) of light tan powder, mp, 197–200°C.

Anal. Calcd for $C_{50}H_{72}N_6F_8$: C, 66.06; H, 7.98; N, 9.24. Found: C, 66.21; H, 7.99; N, 9.30; C, 66.07; H, 7.94; N, 9.24.

^{19}F NMR (CH_2Cl_2, $CFCl_3$) multiplets 144.4 and 147.9 ppm downfield from $CFCl_3$.

Bis(tetra-*n*-butylammonium)-7,7,8,8-tetracyanoquinodimethanide (12). A solution of 3 g of sodium hydroxide in 100 ml of water was stirred under nitrogen with 3 g of dimethyl $\alpha,\alpha,\alpha',\alpha'$-tetracyano-1,4-phenylenediacetate (**5**, Y = W = Z = H). The clear orange solution that resulted after about 1 hr was treated with decolorizing carbon and pressure filtered under nitrogen into 10 g of tetra-*n*-butylammonium bromide in 300 ml of water. Washing with water and blowing dry under nitrogen for about 1 week affords 6.22 g (95%) of light tan solid, that turns deep orange on prolonged exposure to air, mp ~100°C dec. Store under nitrogen.

Anal. Calcd for $C_{44}H_{76}N_6 \cdot \frac{1}{2}H_2O$: C, 75.70; H, 11.12; N, 12.04. Found: C, 76.12; H, 10.77; N, 12.14; C, 76.09; H, 10.69; N, 11.96.

^1H NMR ($CDCl_3$, Me_4Si) δ 0.5–2.0, m, 28 H; 2.9–3.4, m, 8 H; 7.3, s, intensity decreases on storage relative to *n*-Bu_4N absorptions.

Registry No.—**2b**, 150-78-7; **2c**, 5076-72-2; **2d**, 20744-02-9; **2e**, 54929-09-8; **2f**, 20744-00-7; **2g**, 33733-78-7; **2j**, 106-43-4; **2k**, 106-38-7; **2l**, 624-31-7; **2p**, 6630-18-8; **2q**, 106-42-3; **2r**, 105-05-5; **2s**, 100-18-5; **3a**, 46045-95-8; **3b**, 3752-97-4; **3c**, 56403-19-1; **3d**, 56403-20-4; **3e**, 56403-21-5; **3f**, 56403-22-6; **3g**, 56403-23-7; **3h**, 10221-08-6; **3i**, 56403-24-8; **3j**, 56403-25-9; **3k**, 56403-26-0; **3l**, 56403-27-1; **3m**, 50987-90-1; **3n**, 56403-28-2; **3o**, 56403-29-3; **3p**, 56403-30-6; **3q**, 6298-72-2; **3r**, 56403-31-7; **3s**, 28782-17-4; **4a**, 56403-32-8; **4b**, 38439-93-9; **4c**, 56403-33-9; **4d**, 56403-34-0; **4e**, 56403-35-1; **4f**, 56403-36-2; **4g**, 56403-37-3; **4h**, 56403-38-4; **4i**, 56403-39-5; **4j**, 56403-40-8; **4k**, 56403-41-9; **4l**, 56403-42-0; **4m**, 56403-43-1; **4n**, 56403-44-2; **4o**, 56403-45-3; **4p**, 56403-46-4; **4q**, 1134-68-5; **4r**, 56403-47-5; **4s**, 56403-48-6; **5a**, 56403-49-7; **5b**, 21172-01-0; **5c**, 56403-50-0; **5d**, 56403-51-1; **5e**, 56403-52-2; **5f**, 56403-53-3; **5g**, 56403-54-4; **5h**, 56421-59-1; **5i**, 56403-55-5; **5j**, 56403-56-6; **5k**, 56403-57-7; **5l**, 56403-58-8; **5m**, 21004-02-4; **5n**, 56403-59-9; **5o**, 56403-60-2; **5p**, 56403-61-3; **5q**, 21004-07-9; **5r**, 56403-62-4; **5s**, 21004-00-2; **6a**, 56403-63-5; **6b**, 21003-99-6; **6c**, 28998-01-8; **6d**, 29075-37-4; **6e**, 28998-09-6; **6f**, 28998-03-0; **6g**, 56403-64-6; **6h**, 56403-65-7; **6i**, 56403-66-8; **6j**, 56403-67-9; **6k**, 56403-68-0; **6l**, 56403-69-1; **6m**, 21004-03-5; **6n**, 56403-70-4; **6o**, 56403-71-5; **6p**, 56403-72-6; **6q**, 1487-82-7; **6r**, 56403-73-7; **6s**, 21004-01-3; **12**, 56403-74-8; **13**, 29097-86-7; **14**, 29097-88-9; **15**, 29261-33-4; **16**, 29097-90-3; **17**, 56403-76-0; **18**, 56403-77-1; **19**, 4210-60-0; **20**, 392-56-3; **21**, 1897-43-4; zinc chloride, 7646-85-7; paraformaldehyde, 30525-89-4; sodium cyanide, 143-33-9; dimethyl carbonate, 616-38-6; sodium methoxide, 124-41-4; cyanogen chloride, 506-77-4; potassium hydroxide, 1310-58-3; isopropylidenemalononitrile, 13166-10-4; tetra-*n*-butylammonium bromide, 1643-19-2.

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Synthesis of a Model Depsipeptide Lactone Related to the Quinoxaline Antibiotics

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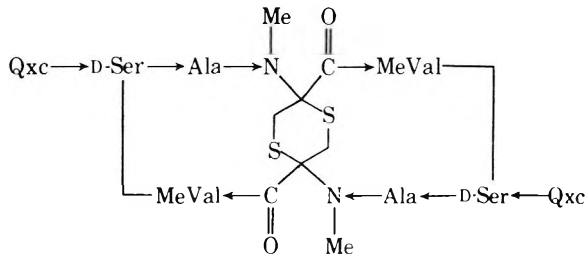
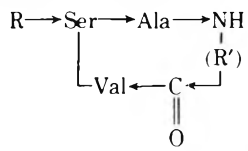
The depsipeptide lactone, *N*-benzyloxycarbonyl-L-seryl-L-alanyl-5-aminovaleryl-L-valine (serine hydroxyl) lactone (**2**), has been synthesized as a simple synthetic model for a portion of the depsipeptide lactone moiety common to the quinoxaline antibiotics. Synthesis involved condensation of *N*-benzyloxycarbonyl-L-serine 2,4-dinitrophenyl ester with L-alanine 4-(methylthio)phenyl ester to give dipeptide **6**. Depsipeptide bond formation in the preparation of tridepsipeptide **7** was effected using *N,N'*-dicyclohexylcarbodiimide in pyridine. Condensation of deblocked **7** with *N-tert*-butyloxycarbonyl-5-aminovaleric acid gave tetradepsipeptide **8**. Cyclization to give depsipeptide lactone **2** was effected by oxidation of **8** to the 4-(methylsulfonyl)phenyl active ester, deprotection, and cyclization under conditions of high dilution.

The quinoxaline antibiotics[1] are a group of bicyclic depsipeptide antibiotics that have been reported active against gram-positive bacteria[2] and certain tumors[3] and to inhibit RNA synthesis.[4] Echinomycin (**1**), a representative



1

Qxc = 2-quinoxalinecarbonyl



2. R = carbobenzoxy; R' = $-(CH_2)_4-$

3. R = Qxc; R' = 1,4-cyclohexylene

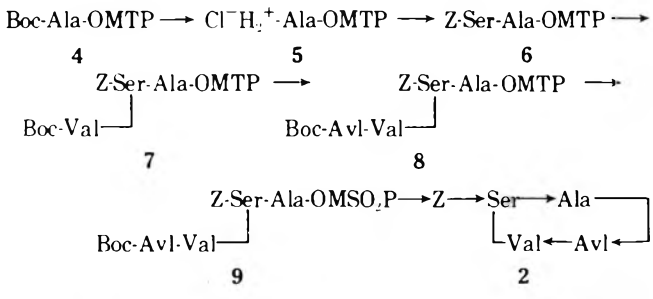
member of the above antibiotics, originally was reported[1a] to possess two 16-membered peptide lactone rings composed of a unit each of L-alanine, D-serine, and L-*N*-methylvaline and interconnected by a 1,4-dithiane amino acid moiety formally derivable from two *N*-methyl-L-cysteine residues; the lactone bonds are found to occur between the serine and valine residues. The structure of echinomycin recently has been revised[5] in which a thioacetal group is present rather than the dithiane moiety.

Pursuant to the synthesis of echinomycin, the depsipeptide lactone, *N*-benzyloxycarbonyl-L-seryl-L-alanyl-5-aminovaleryl-L-valine (serine hydroxyl) lactone (**2**), has been prepared as a simple synthetic model for a portion of the depsipeptide sequence common to the quinoxaline antibiotics.

An initial goal was to incorporate *cis*-4-aminocyclohexanecarboxylic acid[6] into a model system (**3**) representing hemiechinomycin. However, attempts to do so were not successful and 5-aminovaleric acid was used, therefore, in place of the above cyclohexane amino acid to provide a model system containing the same ring size as well as the tridepsipeptide sequence of *O*-(valyl)serylalanyl present in hemiechinomycin. The model lactone **2** includes substitution of L-serine for D-serine, and absence of *N*-methylamino acids and of the 2-quinoxalinecarbonyl function as normally found in the quinoxaline antibiotics.

N-tert-Butyloxycarbonyl-L-alanine was converted to the 4-(methylthio)phenyl ester **4** by condensation with 4-(methylthio)phenol[7] using *N,N'*-dicyclohexylcarbodiimide. The rationale[8] for use of the 4-(methylthio)phenyl ester as a carboxyl protective group relates to the fact that this group subsequently can be activated to the 4-(methylsulfonyl)phenyl active ester for use in the final cyclization step.

Deprotection of **4** with hydrogen chloride in acetic acid yielded L-alanine 4-(methylthio)phenyl ester hydrochloride (**5**) in a yield of 85%. Coupling of **5** with the known[9] 2,4-dinitrophenyl ester of *N*-benzyloxycarbonyl-L-serine furnished dipeptide **6** in 85% yield.



MTP = 4-(methylthio)phenyl Avl = 5-aminovaleryl

MSO_2P = 4-(methylsulfonyl)phenyl

Formation of the depsipeptide bond in **7** was effected in 95% yield by condensation of dipeptide **6** with an excess of *N-tert*-butyloxycarbonyl-L-valine using *N,N'*-dicyclohexylcarbodiimide in pyridine.[10] Attempts at depsipeptide bond formation employing the carbonyldiimidazole or the mixed anhydride methods were not successful.

The *tert*-butyloxycarbonyl group in tridepsipeptide **7** was selectively removed with 70% trifluoroacetic acid,[11] followed by condensation with *N-tert*-butyloxycarbonyl-5-aminovaleric acid via the carbodiimide method to give tetradepsipeptide **8** in 63% yield. Oxidation[12] of the 4-(methylthio)phenyl ester in **8** with *m*-chloroperoxybenzoic acid gave in 91% yield the 4-(methylsulfonyl)phenyl ester **9**. Treatment of **9** with trifluoroacetic acid for 0.5 hr was followed by cyclization in chloroform containing 2% triethylamine to give cyclic depsipeptide **2** in 79% yield. The overall yield of depsipeptide **2** from L-alanine 4-(methylthio)phenyl ester **5** was 37%.

These studies provide a model for approaches to the synthesis of the quinoxaline antibiotics. The tridepsipeptide **7** should prove to be a key intermediate in future studies. Thus, incorporation into **7** of an appropriate cystine derivative would provide an approach to the triostin family of the above antibiotics, while incorporation of other amino

acid moieties would allow preparation of analogs and of other model systems that may be of interest.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were recorded on a Varian A-60 or XL-100 spectrometer. Infrared spectra were recorded on a Beckman IR-20A spectrophotometer. Solvents were removed in vacuo on a Buchler rotary evaporator. Thin layer chromatography was performed on commercially available silica gel plates with or without fluorescence indicator; components were located under ultraviolet irradiation and with iodine vapors. The solvent system used was chloroform–methanol–acetic acid (85:10:5). Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.

***N*-*tert*-Butyloxycarbonyl-L-alanine 4-(Methylthio)phenyl Ester (4).** Using the method reported by Johnson and Trask,[7] 7.56 g (40 mmol) of *N*-*tert*-butyloxycarbonyl-L-alanine was dissolved in 80 ml of methylene chloride, following which 8.64 g (42 mmol) of *N,N'*-dicyclohexylcarbodiimide was added. After stirring for 10 min at room temperature, 5.88 g (42 mmol) of 4-(methylthio)phenol was added and the reaction mixture was stirred overnight at room temperature. The dicyclohexylurea was removed by filtration and washed with methylene chloride. The filtrate was washed with 10% sodium bicarbonate and water and the solid obtained was recrystallized from ethyl acetate–hexane to give 8.9 g (72%) of **4**: mp 93–95°; TLC R_f 0.83; $[\alpha]^{20}D$ −56° (c 1.5, EtOH); NMR ($CDCl_3$) δ 7.1 (q, 4 H, *S*-phenyl), 5.2 (d, 1 H, NH), 4.5 (m, 1 H, α-H), 2.5 (s, 3 H, *S*-methyl), 1.5 (d, 12 H, alanyl methyl, *tert*-butyl). Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.9; H, 6.79; N, 4.49. Found: C, 58.05; H, 6.81; N, 4.36.

L-Alanine 4-(Methylthio)phenyl Ester Hydrochloride (5). *N*-*tert*-Butyloxycarbonyl-L-alanine 4-(methylthio)phenyl ester (**4**, 7.0 g, 22.5 mmol) was dissolved in 50 ml of saturated hydrogen chloride in glacial acetic acid and allowed to stand overnight at room temperature. Addition of dry ether precipitated the hydrochloride, which was recrystallized from methanol–diethyl ether to yield 4.7 g (85%) of **5**: mp 180–182°; TLC R_f 0.31; $[\alpha]^{20}D$ +4° (c 1.5, EtOH); NMR (trifluoroacetic acid) δ 7.4 (m, 4 H, phenyl), 4.6 (m, 1 H, α-H), 2.5 (s, 3 H, *S*-methyl), 1.9 (d, 3 H, alanyl methyl). Anal. Calcd for $C_{10}H_{14}ClNO_2S$: C, 48.5; H, 5.69; N, 5.66; Cl, 14.33. Found: C, 48.35; H, 5.70; N, 5.51; Cl, 14.49.

***N*-Carbobenzoxy-L-seryl-L-alanine 4-(Methylthio)phenyl Ester (6).** To a solution of 4.72 g (19 mmol) of L-alanine 4-(methylthio)phenyl ester hydrochloride (**5**) in 120 ml of chloroform was added 2.04 g (20 mmol) of triethylamine and 7.70 g (19 mmol) of *N*-carbobenzoxy-L-serine 2,4-dinitrophenyl ester.[9] The reaction mixture was stirred overnight at room temperature, during which time the product precipitated from the solution. The precipitate was filtered and washed with ethyl acetate to give 5.03 g of white solid, mp 169–170°. The filtrate was evaporated in vacuo and the residue was washed with 10% sodium bicarbonate, water, and 10% citric acid and triturated with ether to give 2.65 g of a white solid, mp 167–168°. Both solids were combined and recrystallized from ethyl acetate–ethanol to yield 7.0 g (85%) of product. It was observed that the above 2,4-dinitrophenyl ester, and on occasion **5**, showed a second component on TLC analysis. However, use of these less pure materials did not affect the yield or purity of **6**: TLC R_f 0.76; $[\alpha]^{20}D$ −35° (c 1.5, DMF); NMR (Me_2SO-d_6) δ 7.2 (q, 9 H, benzyl aromatic and *S*-phenyl), 5.2 (s, 2 H, benzyl), 5.0–4.0 (m, 2 H, α hydrogens), 3.7 (d, 2 H, seryl methylene), 3.5 (s, 1 H, OH), 2.5 (s, 3 H, *S*-methyl), 1.4 (d, 3 H, alanyl methyl). Anal. Calcd for $C_{21}H_{24}N_2O_6S$: C, 58.3, H, 5.61; N, 6.48. Found: C, 58.45; H, 5.43; N, 6.45.

***N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-L-valyl)-L-alanine 4-(Methylthio)phenyl Ester (7).** To a precooled solution of *N*-carbobenzoxy-L-seryl-L-alanine 4-(methylthio)phenyl ester (**6**, 7.68 g, 17.7 mmol) and *N*-*tert*-butyloxycarbonyl-L-valine (6.41 g, 29.5 mmol) in 100 ml of anhydrous pyridine was added 6.46 g (31.3 mmol) of *N,N'*-dicyclohexylcarbodiimide. The reaction mixture was stirred for 4 hr at 0° and then overnight at room temperature. The solvent was removed in vacuo; ethyl acetate was added to the residue and precipitated dicyclohexylurea was removed by filtration. The filtrate was evaporated in vacuo and the material obtained was recrystallized from ethyl acetate–petroleum ether (bp 60–90°) to afford 10.58 g (95%) of **7**: mp 128–130°; TLC R_f 0.92; ir (film) carbonyl absorption at 1740, 1690, 1670 cm^{-1}; $[\alpha]^{20}D$ −32° (c 1.5, EtOH); NMR ($CDCl_3$) δ 7.3 (m, 10 H, NH, *S*-phenyl, and benzyl aromatic), 6.0 (d, 1 H, NH), 5.2–3.8 (m, 8 H, NH, benzyl, α hydrogens, seryl methylene), 2.4 (s, 3 H, *S*-methyl), 2.3–1.7 (m. 1 H, valyl methine), 1.5 (d, 12 H, alanyl methyl and *tert*-butyl), 0.8 (q, 6 H, valyl isopropyl hydrogens). Anal. Calcd for $C_{31}H_{41}N_3O_9S$: C, 58.9; H, 6.55; N, 6.65. Found: C, 58.99; H, 6.41; N, 6.64.

***N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-5-aminovaleryl-L-alanine 4-(Methylthio)phenyl Ester (8).** *N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-L-valyl)-L-alanine 4-(methylthio)phenyl ester (**7**, 8.0 g, 12.7 mmol) was dissolved in 50 ml of 70% aqueous trifluoroacetic acid and the solution was allowed to stand at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in 100 ml of ethyl acetate. The ethyl acetate solution was washed three times each with cold 10% sodium bicarbonate solution and saturated sodium chloride solution and was dried over anhydrous sodium sulfate. Evaporation in vacuo gave 4.96 g of a white solid which was dissolved in 90 ml of methylene chloride. The reaction mixture was cooled to 0° and 2.16 g (9.9 mmol) of *N*-*tert*-butyloxycarbonyl-5-aminovaleric acid[13] and 2.03 g (9.9 mmol) of *N,N'*-dicyclohexylcarbodiimide were added. The reaction mixture was stirred at 0° for 1 hr and then at room temperature overnight. The dicyclohexylurea was removed by filtration and washed with methylene chloride. The filtrate was evaporated in vacuo and the residue was crystallized from chloroform–petroleum ether (bp 90–120°) to yield 5.86 g (63%) of product, mp 157–160°. The product was recrystallized from chloroform–ether: mp 163–166°; TLC R_f 0.62; $[\alpha]^{23}D$ −20° (c 1.5, DMF); NMR ($CDCl_3$) δ 7.7 (d, 1 H, NH), 7.1 (q, 9 H, *S*-phenyl and benzyl aromatic), 6.3 and 5.9 (two d, 2 H, NH), 5.1 (s, 2 H, benzyl), 4.9–4.0 (m, 5 H, α hydrogens and seryl methylene), 3.1 (m, 2 H, valeryl H-5), 2.5 (s, 3 H, *S*-methyl), 2.4–1.2 (m, 19 H, valeryl H-2 to 4, alanyl methyl, valyl methine), 0.8 (d, 6 H, valyl isopropyl hydrogens). Anal. Calcd for $C_{36}H_{50}N_4O_{10}S$: C, 59.2; H, 6.89; N, 7.66. Found: C, 59.40; H, 6.82; N, 7.74.

***N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-5-aminovaleryl-L-valyl)-L-alanine 4-(Methylsulfonyl)phenyl Ester (9).** To a solution of 5.60 g (7.7 mmol) of *N*-carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-5-aminovaleryl-L-valyl)-L-alanine 4-(methylthio)phenyl ester (**8**) in 90 ml of dioxane was added 4.10 g (23.8 mmol) of *m*-chloroperoxybenzoic acid. After stirring overnight at room temperature, the solvent was removed in vacuo. The residue was dissolved in 90 ml of chloroform and washed with cold 10% sodium bicarbonate and cold saturated salt-solution. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed in vacuo to give 5.29 g of white solid, which was recrystallized from chloroform–petroleum ether (bp 60–90°) to yield 5.10 g (91%) of **9**: mp 133–136°; TLC R_f 0.65; $[\alpha]^{23}D$ −14° (c 1.5 DMF); NMR ($CDCl_3$) δ 8.1–7.2 (m, 10 H, *S*-phenyl and benzyl aromatic), 6.4 and 5.9 (two d, 2 H, NH), 5.1 (s, 2 H, benzyl), 4.9–4.0 (m, 5 H, α hydrogens and seryl methylene), 3.05 (m, 5 H, *S*-methyl and valeryl H-5), 2.5–1.1 (m, 19 H, valeryl H-2 to 4, valyl methine, alanyl methyl, *tert*-butyl), 0.9 (d, 6 H, valyl isopropyl hydrogens). Anal. Calcd for $C_{36}H_{50}N_4O_{12}S$: C, 56.7; H, 6.60; N, 7.34. Found: C, 56.58; H, 6.70; N, 7.14.

***N*-Carbobenzoxy-L-seryl-L-alanyl-5-aminovaleryl-L-valine (Serine Hydroxyl) Lactone (2).** *N*-Carbobenzoxy-L-seryl-*O*-(*N*-*tert*-butyloxycarbonyl-5-aminovaleryl-L-valyl)-L-alanine 4-(methylsulfonyl)phenyl ester (**9**, 5.0 g, 6.6 mmol) was dissolved in 22 ml of trifluoroacetic acid. After standing for 0.5 hr, the solvent was removed in vacuo. The residue was dissolved in 60 ml of chloroform and this solution was added dropwise over a period of 4 hr to a stirred solution of 2% triethylamine in chloroform (900 ml). After stirring for 2 days, the chloroform solution was washed with 10% sodium bicarbonate, saturated sodium chloride solution, and 10% citric acid solution. The solution was dried over anhydrous sodium sulfate and evaporated in vacuo to give 2.8 g of white solid. The product was recrystallized from chloroform–ether to yield 2.55 g (79%) of **2**: mp 262–264°; TLC R_f 0.45, 0.76 (EtOH–H_2O, 80:20), 0.67 (*n*-BuOH–AcOH–H_2O, 4:1:1); $[\alpha]^{23}D$ −57 (*c*, 1.5, DMF); ir (film) carbonyl absorption at 1725, 1685, 1635, and 1530 cm^{-1}; NMR (trifluoroacetic acid) δ 7.8 (d, 4 H, NH), 7.4 (s, 5 H, benzyl aromatic), 5.3 (s, 2 H, benzyl), 4.8 (s, 5 H, α hydrogens and seryl methylene), 3.3–1.3 (m, 12 H, valeryl, alanyl methyl, and valyl methine), 1.1 (d, 6 H, valyl isopropyl hydrogens); mol wt (osmometry) 486 ± 20 (DMF, 37°). Anal. Calcd for $C_{24}H_{34}O_7N_4$: C, 58.8; H, 6.98; N, 11.4. Found: C, 58.5; H, 6.98; N, 11.0.

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Registry No.—**2**, 56411-59-7; **4**, 56411-60-0; **5**, 56411-61-1; **6**, 56411-62-2; **7**, 56411-63-3; **8**, 56411-64-4; **9**, 56411-65-5; *N-tert*-butyloxycarbonyl-L-alanine, 15911-69-0; 4-(methylthio)phenol, 1073-72-9; *N*-carbobenzoxy-L-serine 2,4-dinitrophenyl ester, 5249-65-0; *N-tert*-butyloxycarbonyl-L-valine, 13734-41-3; *N-tert*-butyloxycarbonyl-5-aminovaleric acid, 27219-07-4; *m*-chloroperoxybenzoic acid, 937-14-4.

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Structures of the 1:1:1 Adducts of the "Nitroso–Isonitrile–Isocyanate" Reaction. Possible Intermediacy of a Carbodiimide *N*-Oxide[1]

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Reaction of a nitrosoalkane with an isonitrile in the presence of an isocyanate affords 1:1:1 adducts, $RR'R''C_2N_3O_2$. Adducts **1** (R = R′ = R″ = *tert*-butyl) and **2** (R = *tert*-butyl; R′ = R″ = phenyl) are substituted 3-imino-1,2,4-oxadiazolidin-5-ones (C), proved by synthesis from the corresponding carbodiimides. Adducts **3** (R = *tert*-butyl; R′ = isopropyl; R″ = phenyl) and **4** (R = R′ = *tert*-butyl; R″ = phenyl) are assigned as substituted 2-imino-1,3,4-oxadiazolidin-5-ones (D) based on acid-catalyzed conversion to **13a** and **13b** (assigned as 3-amino-1,3,4-oxadiazolin-5-ones) and on base-catalyzed isomerization to substituted 1,3,4-triazolidine-2,5-diones (F, **16a, 16b**), proved by synthesis. Adduct **5** is assigned as a substituted 3,5-diimino-1,4,2-dioxazolidine (A) on the basis of thermal isomerization to **4** and decomposition to di-*tert*-butyldiaziridinone (**19**, R = R′ = *tert*-butyl) and phenyl isocyanate. The relation of these structures to the course of the "nitroso–isonitrile–isocyanate" reaction is discussed. The results are in good agreement with the earlier suggestion of the intermediacy of a carbodiimide *N*-oxide (from RNO + RNC) and trapping of this species by the isocyanate. Adduct **1** loses carbon dioxide at 150°, affording tri-*tert*-butyldiaziridinimine (**10**), providing a new entry to this novel small-ring heterocyclic system.

Some years ago we described a novel route to a small-ring heterocyclic system: reaction of a nitrosoalkane with an isonitrile to give a diaziridinone (diazacyclopropanone) (Scheme I). Several lines of evidence pointed to an intermediate. In the presence of R″NCO (the best trapping agents were alkyl or aryl isocyanates), no diaziridinone was observed; instead, adducts of composition RNO + R′NC + R″NCO were formed. The rate of disappearance of RNO and R′NC was independent of the concentration of R″NCO. The intermediacy of a carbodiimide *N*-oxide was suggested. Heterocycles of type A and C (Scheme I) seemed the best candidates for the 1:1:1 adducts. In this paper, the structures of several of the adducts are established, both supporting Scheme I and providing some unexpected extensions.

Results

The adducts **1–5** are listed in Table I. Adducts **1–4**, although showing some differences in the infrared carbonyl region, were generally similar in mass spectra (primary fragmentation patterns are loss of carbon dioxide and isobutylene units),[2] in thermal stability (decomposition at 120°), and in sensitivity to acid. Adduct **5**, a much more labile material, differed from **1–4** in the infrared (e.g., compare the similarly substituted **3** vs. **5**), and in mass spectra (loss of R′NCO, no primary loss of carbon dioxide). Thermal decomposition of **5** at 80° afforded a mixture of **4**, diaziridinone, and phenyl isocyanate.[2] Our hypothesis early in the present study was that adducts **1–4** were heterocycles of type C (Scheme I) (3-imino-1,2,4-oxadiazolidin-5-one) and that adduct **5** was of type A (3,5-diimino-1,4,2-dioxazolidine). This hypothesis, shown to be correct for **1** and **2**, facilitated establishment of structure C for these adducts. As will be shown later in the paper, adducts **3** and **4** do *not* possess structure C. Structure A remains the best formulation for **5**.

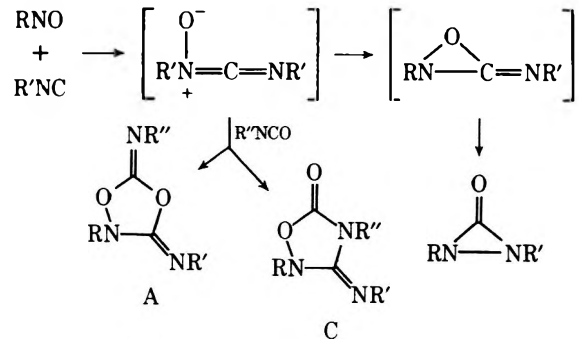
Table I
1:1:1 Adducts. Composition $RR'R''C_2N_3O_2$ (RNO + R′NC + R″NCO)

Compd	R	R′	R″	Ir, cm^{-1}
1	*t*-Bu	*t*-Bu	*t*-Bu	1789, 1700
2[a]	*t*-Bu	C_6H_5	C_6H_5	1804, 1687
3	*t*-Bu	*i*-Pr	C_6H_5	1809, 1717
4	*t*-Bu	*t*-Bu	C_6H_5	1811, 1710
5	*t*-Bu	*t*-Bu	C_6H_5	1775, 1700

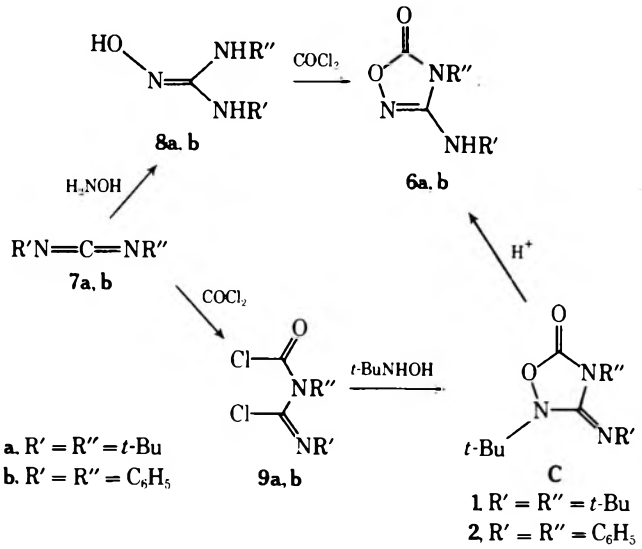
[a] Minor one of three adducts (**2**, **4**, and **5**) isolated from reaction of $(CH_3)_3CNO$, $(CH_3)_3CNC$, and C_6H_5NCO (see ref 2).

Adducts 1 and 2. Concentrated hydrochloric acid effected rapid loss of a *tert*-butyl group. The structures of the new products, **6a** and **6b**, were established by synthesis in high yield from the carbodiimides **7a** and **7b** (Scheme II). Assignment of the endocyclic C=N structure to **6** rather than the tautomeric exocyclic C=N form is based on the

Scheme I



Scheme II



differences in the infrared between **1** and **6** (see Table II). A related synthesis of a compound of type **6** (R′ = R″ = cyclohexyl) has been reported.[3] Syntheses of **1** and **2** were achieved via the phosgene–carbodiimide adducts, **9** (reactive, unstable materials).[4] Ring closure with *tert*-butylhydroxylamine afforded **1** and **2** in low yield (Scheme II).

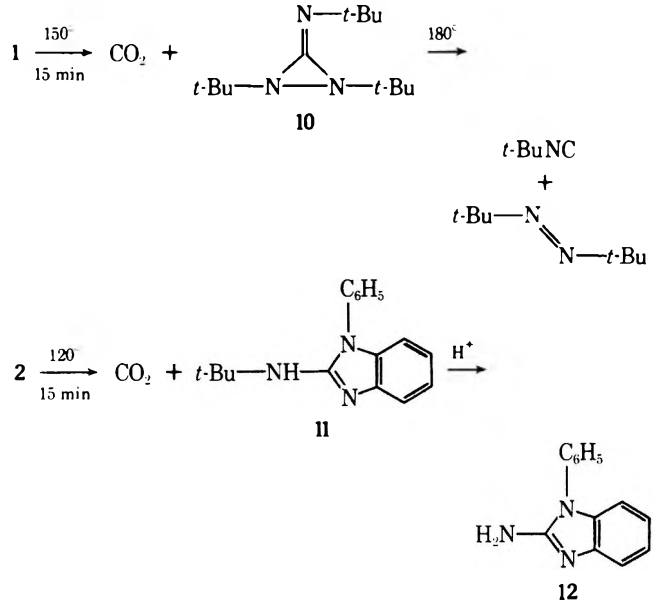
The syntheses of **6a** and **6b** establish the correctness of the direction of addition of the *tert*-butylhydroxylamine shown in Scheme II. Determination of the direction of addition with a less hindered alkylhydroxylamine was not investigated. Synthesis of several compounds of the same heterocyclic system as **1** and **2** (C, R = CH_3; R′ = R″ = cyclohexyl or aryl) has been reported by condensation of CH_3NHOH with the carbodiimide followed by cyclization with $ClCOOCH_3$.[3,5] Hydrolysis (HCl, ethanol) of the compounds in which R = CH_3 resulted in replacement of the imino group by oxygen.[5]

Table II
1:1:1 Adducts and Acid Cleavage Products. Infrared Bands in the Carbonyl Region

Structure found in		Adducts, ir, cm^{-1}		Acid cleavage products ir, cm^{-1}
Scheme II	**1**	1789, 1700	**6a**	1768, 1615
Scheme II	**2**	1804, 1687	**6b**	1777, 1611
Eq 3[a]	**14**	1797, 1700	**6c**[a]	1768, 1605
Scheme VI	**3**	1809, 1717	**13a**	1790, 1778, 1660
Scheme VI	**4**	1811, 1710	**13b**	1785, [b]1772, 1675
Scheme IV	**16a**[c]	1778, 1720	**18a**	1765, 1695

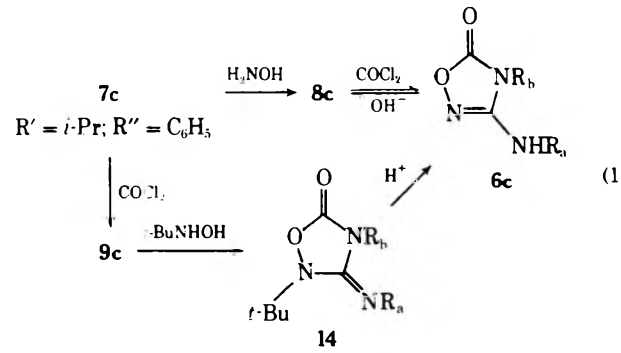
[a] Structure not established. See text. [b] Shoulder. [c] **16b** (Scheme IV), 1773(m), 1720 cm^{-1} (vs).

Scheme III



Thermal decomposition of **1** (Scheme III) afforded the novel small-ring heterocycle, tri-*tert*-butyldiaziridinimine (**10**), identical with that described by Quast and Schmitt.[6] Thus, thermolysis of compounds of type **1** provides a new entry to this novel small-ring heterocyclic system. (Further heating of **10** resulted in fragmentation to the azoalkane and *tert*-butyl isonitrile.) Under similar conditions **2** afforded the *tert*-butylaminobenzimidazole **11**, established by acid degradation to **12**, a known compound.[7]

Adducts 3 and 4. These 1:1:1 adducts, like **1** and **2**, lost carbon dioxide on heating at 120°, and readily lost a *tert*-butyl group by the action of acid. It seemed probable that they were also of structural type C, although there were differences in the infrared of the acid degradation products, **13a** and **13b**, compared with **6a** and **6b** (e.g., **13a**, 1790, 1778, 1660 cm^{-1}; **6a**, 1768, 1615 cm^{-1}). The infrared differences were not considered compelling because of the possibilities for isomers of C (including syn–anti forms) and for isomers of **6** (endocyclic vs. exocyclic C=N). In the expectation that **3** was similar in structure to **1** and **2**, isopropylphenylcarbodiimide **7c** was subjected to the reactions of Scheme II. The reactions of the carbodiimide **7c** with hydroxylamine and with phosgene afforded single products, **8c** and **9c**, each of which was cyclized (eq 1).



(1)

Compound **14** (not isolated in pure form) was related to **6c** by acid-catalyzed loss of isobutylene. The synthetic sequences (eq 1) might afford two isomers of **6c** and of **14** (R_a = *i*-Pr; R_b = C_6H_5; and vice versa).

Unfortunately, only one isomer of **6c** was obtained (from **8c** or from **14**) and that one not identical with **13a**, the acid degradation product of **3** (and correspondingly, **14** was not identical with **3**). However, the synthetic compound **6c**

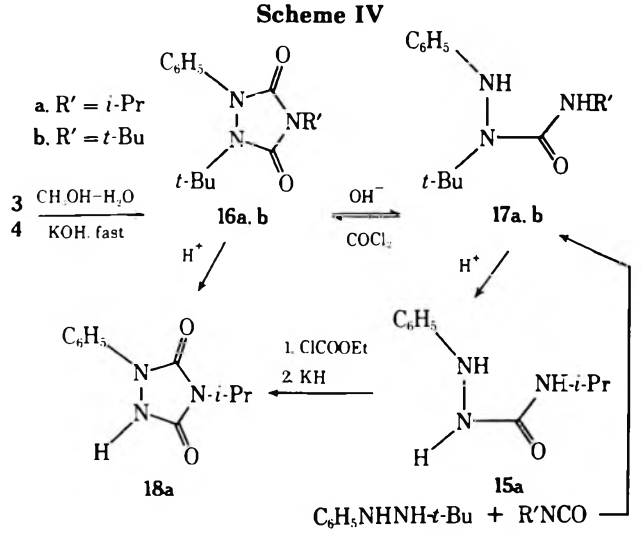
showed greater similarity in the infrared to **6a** and **6b**, the acid degradation products of **1** and **2**, than to **13a** and **13b**, the acid degradation products of **3** and **4**. A further indication that compounds **13a** and **13b** were not of the same structural type as **6a** and **6b** came from alkaline hydrolysis. Compound **6c** was reconverted to the hydroxyguanidine **8c** by base; compound **13a** was converted to semicarbazide **15a**, established by synthesis (eq 2).

$$3 \xrightarrow{H^+} \mathbf{13a} \xrightarrow{OH^-} \underset{\mathbf{15a}}{C_6H_5NHNHCONH\text{-}i\text{-}Pr} \qquad (2)$$

Action of Base on 3 and 4. Treatment of adduct **3** with base effected rapid (3–4 sec), quantitative conversion to an isomer **16a**. Further reaction with base converted **16a** to semicarbazide **17a**. A similar sequence was shown for adduct **4**.

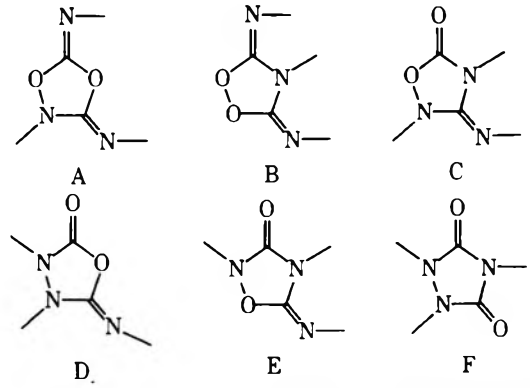
Compounds **16a** and **16b**, the products of base isomerization of **3** and **4**, were more stable to heat and to acid than their precursors. Their conversion by base to the semicarbazides suggested that they might be urazoles, proved by degradation and synthesis of **16a** and **16b** and by synthesis of the semicarbazides **17a** and **17b** (Scheme IV).

Scheme IV



Structures for adducts 3 and 4 may be assigned on the basis of the available physical and chemical data. Compounds **3** and **4** (as well as **1**, **2**, **5**, **16a**, and **16b**) have the composition $RR'R''C_2N_3O_2$, indicating the presence of three rings and/or double bonds. The acid and base degradations of **3** and **4** place one substituent on each of the three nitrogens, ruling out the presence of nitrogen–oxygen or nitrogen–nitrogen double bonds. Each of the two carbons may have a maximum of one double bond, and thus the presence of a ring is required. The infrared spectra strongly indicate the presence of two double bonds (C=N or C=O). Both must be exocyclic to the ring, restricting the ring size to five membered or less. Rings smaller than five membered would require the presence of nitrones or $R\text{-}N^-\text{-}N^+(R)=$, for which there is no evidence in the infrared. Consequently, only five-membered rings were considered. Lastly, there is no carbon–carbon bond in the products of acid or base degradations of **3** and **4**, strongly suggesting the absence of such a bond in the skeletons of **3** and **4**. Thus, possible systems for **3** and **4** are shown in Scheme V. Principal considerations in the assignment of one of the heterocyclic systems of Scheme V to **3** and **4** are the presence of an N–N bond in the products of base degradations (e.g., conversion of **3** to **17a**)[8] and the thermal (and mass spectral) loss of carbon dioxide.

Scheme V[a]



[a] **Consideration of A (3,5-Diimino-1,4,2-dioxazolidine).** Structure A is assigned to the labile adduct **5** on the basis of the mass spectral data (presence of an $M - C_6H_5NCO$ peak, absence of peaks associated with loss of carbon dioxide), chemical reactions, and possible mode of formation. Compound **5** could only be isolated when the RNO + R′NC + R″NCO reaction was carried out at 40° and worked up after 10% reaction. Heating of **5** at 80° in solution afforded adduct **4**, phenyl isocyanate, and di-*tert*-butyldiaziridinone.[2]

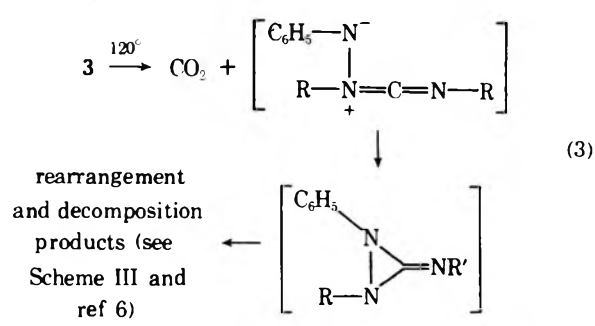
Consideration of B (3,5-Diimino-1,2,4-dioxazolidine). Structure B is rejected on the basis of the loss of carbon dioxide in the thermolysis and mass spectra of **3** and **4**. One might also expect peroxygen species B (unknown) to be of lower thermal stability than that shown by **3**.

Consideration of C (3-Imino-1,2,4-oxadiazolidin-5-one). Structure C has been established by synthesis (Scheme II) for **1** and **2**. Compounds **3** and **4** differ from **1** and **2** toward acid and toward base. In particular, **3** and **4** are converted to semicarbazides **17a** and **17b** by aqueous nonalcoholic base. No satisfactory route exists for the *hydroxide*-catalyzed (see ref 8) conversion of C to these products. Structure C is rejected for **3** and **4** on these grounds.

Consideration of E (5-Imino-1,2,4-oxodiazolidin-3-one). Structure E, like C, is rejected for **3** and **4** on the basis of the lack of a satisfactory route for *hydroxide*-catalyzed (see ref 8) conversion of E to the semicarbazides. Also, the loss of carbon dioxide in the thermolysis and mass spectra of **3** and **4** is hard to reconcile with E.

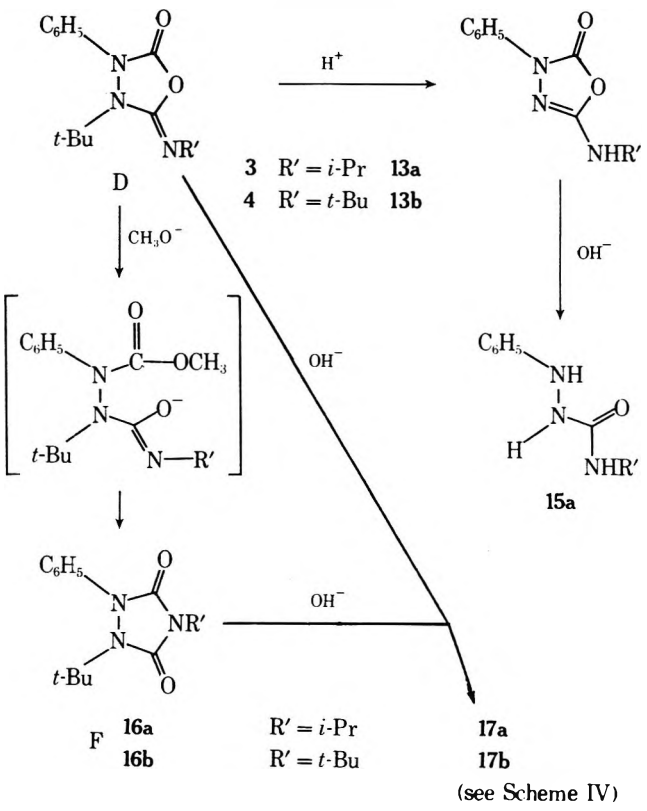
Consideration of F (Urazole, 1,3,4-Triazolidine-2,5-dione). Structure F has been established by synthesis (Scheme IV) for **16a** and **16b**, the products of base-catalyzed isomerization of **3** and **4**, and cannot also be the structure for **3** and **4**.

Compounds **3** and **4** are assigned structure D (2-imino-1,3,4-oxadiazolidin-5-one). It accounts for the chemical and physical data, and is nicely in accord with a reasonable mode of formation of adducts **3** and **4**. A brief indication of the grounds on which systems A, B, C, E, and F are *not* suitable for **3** and **4** is given in Scheme V. Assignment of structure D to **3** and **4** and analysis of the reactions under acidic and basic conditions are shown in Scheme VI. The thermal decomposition of **3** affords carbon dioxide and a mixture of products. It is of interest that **3** is of comparable thermal stability to **1** and **2** although rather different in structure. Possibly, breakdown of **3** may proceed as shown in eq 3.

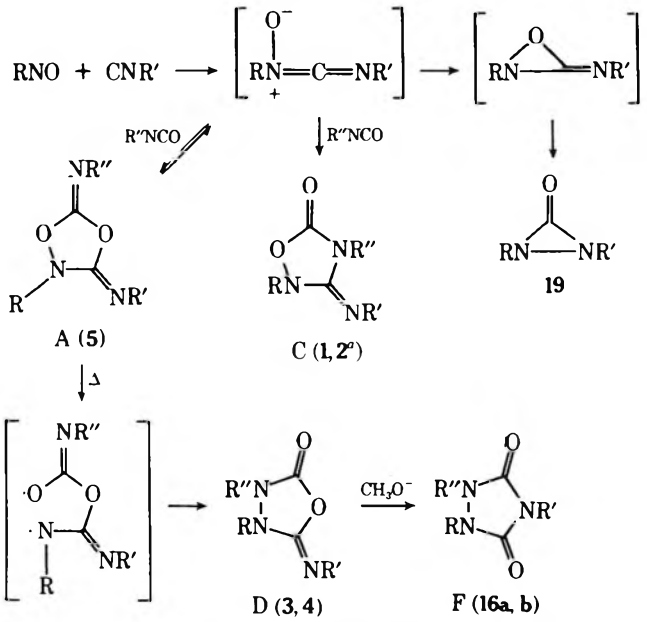


(3)

Scheme VI



Scheme VII



[a] Exact origin of adduct 2 (i.e., origin of C_6H_5NC for this case) is unclear (see Table I, footnote *a*).

An overall summary of the probable modes of formation and interconversion of the different types of adducts is shown in Scheme VII and eq 4. Attention is also directed to the sequence in eq 5.

$$\underset{A}{5} \xrightarrow{80^\circ} \underset{D}{4} \xrightarrow{CH_3O^-} \underset{F}{16b} \xrightarrow{OH^-} 17b \qquad (4)$$

$$R_1C_2N_3O_2 \xrightarrow{150^\circ} R_1CN_3 \xrightarrow{180^\circ} R_2N_2 \xrightarrow{200^\circ} R_2 + N_2 \qquad (5)$$

1 → 10 + CO_2 → + RNC → + RH + R(−H) (200°: RNC → RCN)

With respect to the "nitroso–isonitrile–isocyanate" reaction, the rigorous establishment of structure C for the 1:1:1 adducts 1 and 2, and the strong evidence for the sequence leading to structure F (eq 4) provide support for the original suggestion of the intermediacy of a carbodiimide *N*-oxide. In the absence of a trapping agent, this species closes to the oxaziridinimine, which then isomerizes to the diaziridinone.[2,9] The oxaziridinimine could also lead to structures A and C, and cannot be excluded as the trappable intermediate, but it would not appear to be a reactive dipolar species (e.g., compare nitrones and oxaziridines in cycloaddition reactivity).[10]

In the cases examined to date, the reaction of RNO with R'NC in the presence of a trapping agent R''NCO has afforded rather complex mixtures from which the adducts 1–5 were isolated in low yield. Thus it is not possible to say which path predominates, C or A → D. As noted earlier in this paper, the spectral properties of C and D are similar. Distinction between these may be made by the action of alkoxide which effects rapid isomerization of the compounds of type D to F (urazoles), and only slowly reacts with the compounds of type C (affording colored solutions and product mixtures). For R = *tert*-butyl, distinction between C and D may also be made by acidic degradation and infrared analysis. Distinctive bands are summarized in Table II. A third indication may be seen in the mass spectra:[2] adducts 1 and 2 of type C do not show ions of *m/e* R'NCO; adducts 3 and 4 show these ions in 17 and 8% abundance, relative to the base peaks for 3 and 4. None of the adducts 1–4 shows an ion for M − R''NCO. Adduct 5 (type A) shows ions for both M − R''NCO and for R''NCO.

Experimental Section

General. Infrared spectra have the following notations: vs, very strong; s, strong; m, medium; w, weak; br, broad. Nuclear magnetic resonance spectra (NMR) are reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si) with the following notations: s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet; br, broad. Adducts 1–5 were obtained by the literature procedures.[2]

Carbodiimides. Diphenylcarbodiimide was prepared by the method of Hunger in 70% yield: bp 112–114° (1.5 mm) [lit.[11] bp 119° (0.07 mm)]; ir (CCl_4) 2120 (vs), 2090 (sh, s), 1570 (m), 1470 cm^{-1} (m). **Isopropylphenylcarbodiimide** was prepared by the method of Hinton and Webb in 56% yield: bp 63–64° (0.3 mm) [lit.[12] bp 56–57° (0.1 mm)]; ir (CCl_4) 2110 (sh, m), 2120 (vs), 2040 (sh, s), 1590 (s), 1495 cm^{-1} (s). **Di-*tert*-butylcarbodiimide** was prepared by the general procedure of Campbell.[13a] *tert*-Butyl isocyanate (100 g, 1.01 mol) was dissolved in 200 ml of tetralin and 10 g of 1-ethyl-3-methyl-3-phospholene 1-oxide as a catalyst was added and refluxed for 1 week. The di-*tert*-butylcarbodiimide was distilled from the reaction mixture at 80–90 mm and the 105–120° fraction was redistilled on a spinning band column, affording 19.89 g (25% yield) of di-*tert*-butylcarbodiimide as a clear liquid: bp 59° (20 mm) [lit.[13b] bp 58° (15 mm)]; ir (CCl_4) 2970 (s), 2915 (m), 2130 (sh, m), 2095 cm^{-1} (vs).

***N*-Hydroxyguanidines (8a–c).** A solution of hydroxylamine hydrochloride (0.1 g, 1.44 mmol) in 1 ml of ethanol was added to di-*tert*-butylcarbodiimide (0.22 g, 1.44 mmol) in ethanol and stirred overnight. The solvent was removed under high vacuum and the solid residue was dissolved in water. Dropwise addition of a cold concentrated solution of KOH while cooling to 0° afforded a white solid; the solid was extracted into ether and dried over $MgSO_4$. The ether was then removed under reduced pressure affording 0.14 g (43% yield) of ***N*-hydroxy-*N'*,*N''*-di-*tert*-butylguanidine (8a).** It was recrystallized from THF and heptane: mp 117–117.5°; ir (CCl_4) 3609 (w), 3500–2400 (br, m), 2985 (s), 1645 (s), 1225 (m), 1205 (m); NMR ($CDCl_3$) 1.32 (s, 18 H), 3.1 (br, s, 2 H), 4.83 ppm (br, s, 1 H).

Anal. Calcd for $C_9H_{21}N_3O$: C, 57.71; H, 11.30; N, 22.44. Found: C, 57.55; H, 11.35; N, 22.36.

***N*-Hydroxy-*N'*,*N''*-diphenylguanidine (8b)** was prepared by the same procedure in 25% yield: mp 149–151° (lit.[14] mp 151°); ir ($CHCl_3$) 3560 (m), 3380 (s), 3500–2400 (m, broad), 1640 (vs), 1590

(vs), 1480 cm^{-1} (vs); NMR ($CDCl_3$) 3.80 (br, s, 3 H), 6.80–7.43 ppm (br, m, 10 H). ***N*-Hydroxy-*N'*-isopropyl-*N''*-phenylguanidine (8c)** was obtained as white crystals: mp 133–134°; ir (CCl_3H) 3480 (w), 3395 (m), 1650 (vs), 1600 (s), 1500 cm^{-1} (vs); NMR ($CHCl_3$ + D_2O) 1.13 (d, 6 H), 3.58 (sept, 1 H), 6.8–7.5 ppm (m, 5 H).

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.2; H, 7.82; N, 21.8. Found: C, 62.34; H, 8.07; N, 21.74.

Phosgene–Carbodiimide Adducts, 9a–c. A phosgene solution (1.25 g, 0.0126 mol) in 10 ml of CH_2Cl_2 was added dropwise under N_2 by means of a cannula to di-*tert*-butylcarbodiimide (1.94 g, 0.0126 mol) in 15 ml of CH_2Cl_2 with stirring and cooling. Removal of the solvent by a stream of N_2 afforded *N,N'*-di-*tert*-butylchloroformamidine-*N*-carbonyl chloride (**9a**) as a yellow oil. The major bands in the ir were similar to those reported in the isopropyl case;[4] ir (CCl_4) 2975 (s), 1760 (vs), 1693 (s), 1395 (m), 1368 (s), 1290 cm^{-1} (s); NMR (CCl_4) 1.52 (s, 9 H), 1.40 ppm (s, 9 H). ***N,N'*-Di-*tert*-butylchloroformamidine-*N*-carbonyl chloride (9a)** was unstable to heat and attempted distillation resulted in decomposition. Compounds **9b** and **9c** were prepared in the same way: **9b**, yellow oil, ir (CCl_4) 1755 (vs), 1660 (vs), 1590 (s), 1487 cm^{-1} (s) (lit.[4] ir 1755, 1660 cm^{-1}); **9c**, a light yellow oil, ir (CCl_4) 1750 (vs), 1660 cm^{-1} (s), NMR (CCl_4) 1.23 (d, 6 H), 3.82 (sept, 1 H), 7.32 ppm (s, 5 H).

Pyrolysis of Adduct 1. A 300-mg sample of compound 1 sealed in a Pyrex tube at 0.4 mm was heated at 150° for 15 min. Upon cooling, a solid separated. The remaining oil was carefully decanted and the solid was washed several times with pentane. A melting point showed the solid to be starting material; ir (CCl_4) of the remaining oil showed absorption at 1790 (vs), 1767 (sh, m), 1697 (m), 1380 (m), 1365 cm^{-1} (s). Gas-liquid partition chromatographic analysis was performed on an Aerograph Model 200, using helium carrier gas and thermal conductivity detectors with the following column: a 1.5 ft × 0.125 in. Teflon tube packed with 20% (w/w) silicone oil SE-30 on a 60–80 mesh Chromosorb P diatomite with a column temperature of 100° and employing a flow rate of 600 ml/min, revealed two peaks with relative areas of 1:13.7 and retention times of 5 and 11.5 min, respectively. The second peak, *N,N',N''*-tri-*tert*-butyldiaziridinimine (**10**), was collected: ir (CCl_4) 2970 (vs), 2900 (sh, w), 2865 (m), 1790 (vs), 1362 cm^{-1} (vs); NMR (CCl_4) 1.08 (s, 9 H), 1.10 (s, 9 H), 1.23 ppm (s, 9 H) [lit.[6] ir 1790 cm^{-1}; NMR (10°, CCl_4) 1.09 (s, 9 H), 1.17 (s, 9 H), 1.25 ppm (s, 9 H)]. Further heating of **10** resulted in decomposition to *tert*-butyl isonitrile and to 2,2'-dimethyl-2,2'-azopropane.

Conversion of Compound 1 to Compound 6a. To a 100-mg sample of compound 1, 1 ml of concentrated HCl was added at room temperature. There was vigorous bubbling, but the solid did not go into solution. After 3 min, the solid was filtered and washed several times with distilled water. The solid was dried (crude mp 114–117°) and recrystallized from THF and heptane, affording compound **6a** as white crystals: mp 116–117°; ir (CCl_4) 3460 (w), 1768 (vs), 1615 (s), 1512 (s), 1390 (m), 1365 cm^{-1} (s); NMR ($CDCl_3$) 1.37 (s, 9 H), 1.67 (s, 9 H), and 3.93 ppm (s, 1 H).

Anal. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.31; H, 8.98; N, 19.70. Found: C, 56.31; H, 9.10; N, 19.78.

Synthesis of 3-*tert*-Butylamino-4-*tert*-butyl-1,2,4-oxadiazolin-5-one (6a). A phosgene solution (0.040 g, 0.48 mmol) in 0.2 ml of CH_2Cl_2 was added slowly by means of a microsyringe to a stirring solution of *N*-hydroxy-*N',N''*-di-*tert*-butylguanidine (**8a**, 0.09 g, 0.484 mmol) in 15 ml of anhydrous ether buffered with 12 drops of triethylamine. After stirring at room temperature for 15 min, the solid was filtered and the ether laver was evaporated to dryness under vacuum. The solid residue was recrystallized from THF and heptane, affording white crystals, mp 116–117°, of **6a**, shown to be identical with the **6a** from acid-catalyzed decomposition of 1 by ir and mixture melting point.

Synthesis of 2,4-Di-*tert*-butyl-3-*tert*-butylimino-1,2,4-oxadiazolidin-5-one (1). A solution of *tert*-butylhydroxylamine[15] (4.45 g, 0.0504 mol) in 25 ml of CH_2Cl_2 was added dropwise under N_2 to a stirred and cooled (0°) solution of *N,N'*-di-*tert*-butylchloroformamidine-*N*-carbonyl chloride (**9a** 3.19 g, 0.0126 mol) in 15 ml of CH_2Cl_2, and left standing overnight at room temperature. The solvent was removed in vacuo and the residual oil was extracted into pentane (only part of it was soluble) and washed with H_2O several times. The pentane layer was dried over $MgSO_4$ and removed in vacuo, affording a clear oil. Upon standing in the refrigerator overnight, part of it crystallized. The crystals were filtered and washed with cold pentane, affording a 10% yield, mp 104–106°, ir identical with that of compound **1**, and a mixture melting point showed no depression.

Pyrolysis of Adduct 2. A 200-mg sample of compound 2 sealed in a Pyrex tube evacuated to 0.04 mm was heated at 120° for 45 min, after which the bubbling had ceased: ir (CCl_4) 3420 (m), 2120 (vw), 1622 cm^{-1} (s). The brown oil crystallized upon standing (10 min). The solid was triturated with a small portion of ether, filtered, and washed two times with pentane. It was crystallized from THF and heptane, affording 1-phenyl-2-(*tert*-butylamino)benzimidazole (**11**) as white crystals: mp 139–141°; ir ($CHCl_3$) 3420 (m), 1622 (s), 1601 (s), 1390 (m), 1368 cm^{-1} (s); NMR ($CDCl_3$) 1.47 (s, 9 H), 4.40 (s, 1 H), and 6.67–7.67 ppm (m, 9 H).

Anal. Calcd for $C_{17}H_{19}N_3$: C, 76.94; H, 7.22; N, 15.84. Found: C, 77.10; H, 7.09; N, 15.77.

Conversion of 1-Phenyl-2-(*tert*-butylamino)benzimidazole (11) to 1-Phenyl-2-aminobenzimidazole (12). 1-Phenyl-2-*tert*-butylaminobenzimidazole (40 mg, 0.151 mmol) was dissolved in 3 ml of concentrated HCl at room temperature and allowed to stand for 2 days. Addition of a cold concentrated solution of KOH with cooling resulted in a white precipitate. The mixture was extracted with ether and dried over $MgSO_4$. The ether was then removed and the yellow solid residue was recrystallized from THF and heptane, affording 7.8 mg (25% yield) of 1-phenyl-2-aminobenzimidazole (**12**) as white crystals: mp 149–151° (lit.[7] mp 151–152°); ir ($CHCl_3$) 3485 (w), 3390 (w), 1630 (s), 1610 (m), 1598 cm^{-1} (m); NMR ($CDCl_3$) 4.92 (br, s, 2 H), 6.20–7.34 ppm (br, m, 9 H).

Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.03. Found: C, 74.74; H, 5.08; N, 19.98.

The compound was converted to the picrate in ethanol. The picrate was recrystallized from ethanol, mp 256° dec (lit.[7] mp 251–253°).

Conversion of Compound 2 to Compound 6b. To a 150-mg sample of compound 2, 1 ml of concentrated HCl was added at room temperature. The solid appeared to dissolve, the solution turned slightly pink, and a white solid precipitated. The solid was filtered and washed several times with distilled water. It was dried (crude mp 158–161°) and recrystallized from THF and heptane, affording compound **6b** as a white solid: mp 161.5–162°; ir ($CHCl_3$) 3410 (m), 1777 (vs), 1611 cm^{-1} (vs); NMR ($CDCl_3$) 2.87 (s, 1 H), 6.67–8.0 ppm (m, 10 H).

Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.4; H, 4.35; N, 16.6. Found: C, 66.20; H, 4.36; N, 16.50.

Synthesis of 3-Phenylamino-4-phenyl-1,2,4-oxadiazolin-5-one (6b). To a slurry of *N*-hydroxy-*N',N''*-diphenylguanidine (**8b** 0.264 g, 1.14 mmol) in 20 ml of ether, a solution of 340 mg of KOH in 20 ml of water was added. To this stirred and cooled (0°) mixture, a solution of phosgene (114 mg, 1.44 mmol) in 1 ml of CH_2Cl_2 was added dropwise. At the first drop, a visible reaction took place. After addition was complete, the organic layer was separated, dried over $MgSO_4$, and evaporated. The brown solid residue was triturated with ether several times until only a faint yellow color remained. It was then recrystallized from THF and heptane, affording white crystals, mp 160–161°. Ir was identical with that of compound **6b**, and mixture melting point showed no depression.

Synthesis of 2-*tert*-Butyl-4-phenyl-3-phenylimino-1,2,4-oxadiazolidin-5-one (2) was achieved from *tert*-butylhydroxylamine and *N,N''*-diphenylchloroformamidine-*N*-carbonyl chloride (**9b**) by the procedure used to synthesize 1: mp 102–103°, shown to be identical with the 1:1:1 adduct 2 by ir and mixture melting point.

Synthesis of compound 6c was achieved from *N*-hydroxy-*N'*-isopropyl-*N''*-phenylguanidine (**8c**) and phosgene by the procedure described above for **6b**. Compound **6c** was obtained as white crystals: mp 136–137.5°; ir ($CHCl_3$) 3400 (w), 1768 (vs), 1605 (vs), 1520 cm^{-1} (s); NMR ($CDCl_3$) 1.15 (d, 6 H), 3.35–4 (m 2 H), 7–7.5 ppm (m, 5 H).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.16. Found: C, 60.19; H, 5.87; N, 19.22.

Synthesis of 14 and Acid-Catalyzed Conversion to 6c. A solution of *tert*-butylhydroxylamine[15] (1.8 g, 0.02 mol) in 15 ml of CH_2Cl_2 was added dropwise to a stirred and cooled (0°) solution of *N*-isopropyl-*N'*-phenylchloroformamidine-*N*-carbonyl chloride (**9c**, 1.30 g, 5 mmol) in 20 ml of CH_2Cl_2. The reaction was complete in 1 hr. The solvent was removed in vacuo, and the oily residue was dissolved in pentane. The pentane layer was washed with water several times, dried, and evaporated, affording a clear oil, **14**, ir (CCl_4) 1790 (m), 1755 (m), 1700 cm^{-1} (vs), clearly different from 3. No further purification was attempted. Treating part of the pentane solution with dilute HCl afforded **6c**, identical with the synthetic material.

Pyrolysis of Adduct 3. A 100-mg sample of compound **3** sealed in a Pyrex tube at 0.4 mm was heated at 120° until no additional gas evolution could be detected (~30 min). Ir of the oily mixture revealed many bands in the carbonyl region, and no attempt was made to separate the components: ir (CCl_4) 1779 (s), 1712 (s), 1660 (vs), 1615 (s), 1595 cm^{-1} (s). Formation of carbon dioxide was established by mass spectral analysis of the gas phase.

Conversion of Adduct 3 to 2-Isopropylamino-4-phenyl-1,3,4-oxadiazolin-5-one (13a). To a 100-mg sample of compound **3**, 1 ml of concentrated HCl was added at room temperature. An oily layer formed and solidified upon standing (3 min). The solid was filtered and washed with distilled water several times. It was recrystallized from THF and heptane, affording compound **13a** (90% yield): mp 104–106°; ir (CCl_4) 3420 (m), 1790 (s), 1778 (s), 1660 cm^{-1} (s); NMR ($CDCl_3$) 1.25 (d, 6 H), 3.72 (sept, 1 H), 4.53 (d, 1 H), 6.90–7.90 ppm (m, 5 H).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 5.9; N, 19.18. Found: C, 60.11; H, 5.95; N, 18.97.

Conversion of Adduct 3 to 1-Isopropyl-3-phenyl-4-*tert*-butyltriazolidine-2,5-dione (16a). Compound **3** (16.6 mg, 0.06 mmol) was dissolved in 2 ml of 20% KOH in ethanol. After 1–2 min, the solution was added to H_2O and extracted with ether three times. The organic layers were combined and dried over $MgSO_4$. The ether was removed in vacuo, affording a solid residue. The solid was recrystallized two times from THF and heptane, affording 13 mg (81% yield) of compound **16a** as white crystals: mp 93–94°; ir (CCl_4) 2975 (m), 1778 (s), 1720 (vs), 1412 (vs), 1385 (s), 1367 cm^{-1} (s); NMR ($CDCl_3$) 1.32 (s, 9 H), 1.43 (d, 6 H), 4.40 (sept, 1 H), 6.55–7.16 ppm (br, m, 5 H).

Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.45; H, 7.69; N, 15.26. Found: C, 65.50; H, 7.57; N, 15.38.

Conversion of Adduct 3 to 4-Isopropyl-1-phenyl-2-*tert*-butylsemicarbazide (17a). Compound **3** (0.10 g, 0.365 mmol) was added to 0.5 g of KOH dissolved in 5 ml of ethanol and heated at 75° for 30 min. The reaction mixture was added to water and extracted with ether several times. The ether layers were combined, dried, and evaporated in vacuo. The resulting solid residue was recrystallized from THF and heptane, affording compound **17a** in 62% yield as white crystals: mp 162– 163.5°; ir ($CHCl_3$) 3418 (m), 2960 (m), 1653 (s), 1595 (s), 1495 (s), 1475 cm^{-1} (s); NMR ($CDCl_3$) 1.07 (d, 6 H), 1.43 (s, 9 H), 4.0 (sept split, 1 H), 3.50–5.91 (br, m, 2 H), 6.35–7.36 ppm (br, m, 5 H).

Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.30; N, 16.85. Found: C, 67.40; H, 9.49; N, 16.85.

Subjection of compound **3** to the action of KOH in aqueous dioxane afforded only **17a** with no evidence for **16a** (the *alkoxide* isomerization product of **3**, see above).

***N*-*tert*-Butyl-*N*′-phenylhydrazine.** 1-*tert*-Butyl-2-phenyldiazene[16] (320 mg, 1.95 mmol) in 9 ml of ethanol was hydrogenated with platinum. The mixture was filtered by means of a cannula through a sintered funnel under a N_2 atmosphere and the ethanol was removed in vacuo, affording the hydrazine in nearly quantitative yield as a clear white oil, highly reactive toward air.

4-Isopropyl-1-phenyl-2-*tert*-butylsemicarbazide (17a). To a solution of *N*-*tert*-butyl-*N*′-phenylhydrazine (~300 mg) in 2 ml of $CHCl_3$, an excess of isopropyl isocyanate (340 mg, 4 mmol) was added by means of a syringe through a no-air stopper. The solution was heated to 70° for 2 hr and left at room temperature overnight. The $CHCl_3$ was removed in vacuo and the solid residue was recrystallized from THF and heptane, affording 250 mg (50% yield) of the semicarbazide **17a** as white crystals, mp 162–163°. A mixture melting point with the slower formed product obtained from the base treatment of compound **3** showed no depression and comparison of their ir spectra showed them to be identical.

1-Isopropyl-3-phenyl-4-*tert*-butyltriazolidine-2,5-dione (Urazole 16a). An excess of phosgene was bubbled through a solution of 1-phenyl-2-*tert*-butyl-4-isopropylsemicarbazide (~15 mg) dissolved in 1 ml of CH_2Cl_2. The reaction only went to ⅔ completion shown by NMR. After 4 days, the solvent was removed and the solid residue was digested with hot hexane. The hexane was decanted and left standing, affording urazole **16a** as white crystals, mp 92–94°. A mixture melting point with the first-formed product obtained from base treatment of compound **3**, and comparison of their ir spectra showed them to be identical.

Conversion of 4-Isopropyl-1-phenyl-2-*tert*-butylsemicarbazide (17a) to 4-Isopropyl-1-phenylsemicarbazide (15a). 4-Isopropyl-1-phenyl-2-*tert*-butylsemicarbazide (5 mg) was dissolved in 0.5 ml of concentrated HCl and left overnight at room temperature. The solution was cooled in an ice bath and concentrated KOH was added dropwise until no further precipitate was formed. The solid 4-isopropyl-1-phenylsemicarbazide (**15a**), was filtered and air dried: mp 143–147° (lit.[17] mp 145–147°); ir ($CHCl_3$) 3498 (m). 2981 (m), 1670 (vs), 1530 (s), 1485 cm^{-1} (s), NMR ($CDCl_3$) 1.10 (d, 6 H), 5.63 (br, s, 2 H), 6.07 (br, s, 1 H), 6.66–7.46 (m, 5 H); shown to be identical with an authentic sample by ir and mixture melting point.

Conversion of 1-Isopropyl-3-phenyl-4-*tert*-butyltriazolidine-2,5-dione (Urazole 16a) to 1-Isopropyl-3-phenyltriazolidine-2,5-dione (Urazole 18a). Urazole **16a** (69.5 mg, 0.244 mmol) was dissolved in 1 ml of concentrated HCl (heating gently) and left overnight at room temperature. It was diluted with 4 ml of H_2O, affording 27 mg (50% yield) of 1-isopropyl-3-phenyltriazolidine-2,5-dione (**18a**) as white crystals: mp 109–111°; ir ($CHCl_3$) 1765 (m), 1695 (vs), 1595 (m), 1495 (m), 1435 cm^{-1} (s); NMR ($CDCl_3$) 1.52 (d, 6 H), 4.40 (sept, 1 H), 7.1–7.62 (m, 6 H).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.16. Found: C, 60.07; H, 5.87; N, 19.22.

1-Isopropyl-3-phenyltriazolidine-2,5-dione (Urazole 18a). To a slurry of 1-phenyl-4-isopropylsemicarbazide (**15a**, 0.69 g, 3.67 mmol) in 20 ml of CH_2Cl_2 was added an excess of ethyl chloroformate. The reaction was monitored by NMR. When the reaction was complete (overnight) the solvent was removed and the solid residue recrystallized from THF and heptane, affording 1-carboethoxy-1-phenyl-4-isopropylsemicarbazide as a light yellow powder: mp 126–128°; ir ($CHCl_3$) 3700–3120 (br, m), 2945 (m), 1715 (s), 1681 (s), 1595 (w), 1518 cm^{-1} (m); NMR ($CDCl_3$) 1.10 (d, 6 H), 1.28 (t, 3 H), 4.27 (q, 2 H), 4.90 (br, s, 1 H), 5.03 (br, s, 1 H), 7.0–7.31 (m, 5 H). A solution of this material (537 mg, 1.27 mmol) in 3 ml of dry DME was added to a slurry of KH (excess) in 5 ml of DME. After the bubbling stopped, the flask was sealed with a no-air stopper and the reaction was heated at 90° for 5 hr. The solvent was removed in vacuo and the solid residue was dissolved in water and filtered. Acidification of the aqueous solution with dilute HCl resulted in a red oil that was extracted into pentane. The pentane layer was dried and removed in vacuo and the solid residue recrystallized from water, affording urazole **18a** in 32% yield, mp 143–147°. A mixture melting point with the compound obtained from the reaction of 1-isopropyl-3-phenyl-4-*tert*-butyltriazolidine-2,5-dione (**16a**) with concentrated HCl showed no depression and comparison of their ir spectra showed them to be identical.

Alkaline hydrolysis of 13a under the conditions described above for **3** → **16a** afforded 4-isopropyl-1-phenylsemicarbazide,[17] shown to be identical with an authentic sample by ir and mixture melting point.

Alkaline hydrolysis of 6c under the above conditions regenerated **8c**, *N*-hydroxy-*N*′-isopropyl-*N*″-phenylguanidine.

Conversion of Adduct 4 to 1,3-Di-*tert*-butyl-4-phenyltriazolidine-2,5-dione (Urazole 16b). Compound **4** (~10 mg) was dissolved in 0.5 ml of methanol and three drops of a concentrated solution of KOH (0.5 g KOH in 0.5 ml of H_2O, 0.5 ml of CH_3OH) were added. The reaction was instantaneous as shown by NMR. The solvent was removed in vacuo and the solid recrystallized from pentane, affording 1,3-di-*tert*-butyl-4-phenyltriazolidine-2,5-dione (**16b**) in 80% yield: mp 119.5–121°; ir (CCl_4) 1773 (m), 1720 (vs), 1595 (w), 1370 cm^{-1} (s); NMR (CCl_4) 1.29 (s, 9 H), 1.59 (s, 9 H), 6.80–7.50 (m, 5 H); shown to be identical by ir and mixture melting point with an authentic sample of urazole **16b** prepared from 1-phenyl-2,4-di-*tert*-butylsemicarbazide and phosgene by the procedure described above for the synthesis of **16a**.

Conversion of Adduct 4 to 2,4-Di-*tert*-butyl-1-phenylsemicarbazide (17b). Compound **4** (~10 mg) was dissolved in 0.5 ml of methanol and 3 drops of a concentrated KOH solution (0.5 g of KOH in 0.5 ml of H_2O, 0.5 ml of CH_3OH) were added. Water was then added until the solution started to turn cloudy. It was heated for 30 min and the methanol removed in vacuo. The solid residue was dissolved in CH_2Cl_2, dried, and evaporated. The solid residue was recrystallized from THF and heptane, affording 1-phenyl-2,4-di-*tert*-butylsemicarbazide (**17b**): mp 172–173°; ir ($CHCl_3$) 3420 (m), 2965 (s), 1660 (vs), 1600 (s), 1500 and 1480 (vs, doublet), 1450 (s), 1388 (m), 1360 cm^{-1} (s); NMR ($CDCl_3$) 1.29 (s, 9 H), 1.31 (s, 9 H), 5.4–5.9 (br, 2 H), 6.65–7.3 (m, 5 H); identical in ir and mixture melting point with an authentic sample prepared from *N*-*tert*-butyl-*N*′-phenylhydrazine and *tert*-butyl isocyanate (see synthesis of **17a**, above).

Acid hydrolysis of 4 under the conditions described above for **3** → **13a** afforded as the first-formed product **13b**, ir (CCl_4) 1785 (sh), 1772 (s), 1675 (m), 1617, 1603 cm^{-1}. Longer exposure to acid effected further changes, loss of the second *tert*-butyl, ir (CCl_4)

1785 (s), 1680 (m), 1660 (s), 1600 cm^{-1}. The product was not characterized further.

Registry No.—**1**, 55871-81-3; **2**, 19656-65-6; **3**, 55871-82-4; **4**, 55871-83-5; **6a**, 55871-84-6; **6b**, 55871-85-7; **6c**, 55871-86-8; **7a**, 691-24-7; **7b**, 622-16-2; **7c**, 14041-89-5; **8a**, 42136-40-3; **8b**, 34362-08-8; **8c**, 55871-87-9; **9a**, 55871-88-0; **9b**, 55871-89-1; **9c**, 55871-90-4; **10**, 22975-87-7; **11**, 55871-91-5; **12**, 43023-11-6; **13a**, 55871-92-6; **13b**, 55871-93-7; **14**, 19656-62-3; **15a**, 55871-94-8; **16a**, 55871-95-9; **16b**, 55871-96-0; **17a**, 55871-97-1; **17b**, 55871-98-2; **18a**, 55871-99-3; 1-carboethoxy-1-phenyl-4-isopropylsemicarbazide, 55872-00-9.

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A *trans*-1,2-*cis*-4,5-Germacradienolide and Other New Germacranolides from *Tithonia* Species[1]

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Isolation and structure determination of two new germacranolides, tifruticin (**1a**) and deoxyfruticin (**4a**), from *Tithonia fruticosa* Canby and Rose are described. Deoxyfruticin is the first naturally occurring *trans*-1,2-*cis*-4,5-germacradienolide. Structures were determined by chemical transformations and extensive use of ^1H and ^{13}C NMR spectrometry. Structures are suggested for tirotundin and its ethyl ether, two new germacranolides from *Tithonia rotundifolia* (Mill.) Blake.

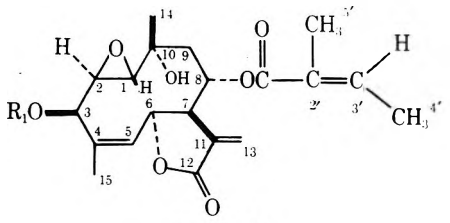
As part of our search for secondary metabolites of Compositae with potential biological activity, we have examined collections of *Tithonia fruticosa* Canby and Rose and *Tithonia rotundifolia* (Mill.) Blake (Heliantheae, subtribe Helianthinae). The former yielded two closely related new germacranolides, tifruticin (**1a**) and deoxyfruticin (**4a**). Although only small amounts of these compounds were available, the complete structure and stereochemistry has been elucidated. *T. rotundifolia* afforded the new germacranolide tirotundin and its ethyl ether, for which structures **9a** and **9b** are suggested in preference to **10a** and **10b**.

Trifruticin (**1a**), mp 141°, $C_{20}H_{26}O_7$ (mass spectrum and elemental analysis), $[\alpha]^{22}D$ −22°, was a conjugated γ-lactone (ir bands at 1760 and 1640 cm^{-1}, strong uv end absorption) and had at least one hydroxyl group (ir band at 3400 cm^{-1}). In the ^1H NMR spectrum of **1a**, the proton under the (secondary) hydroxyl group was located at 4.46 ppm by D_2O exchange and by its paramagnetic shift to 5.33 ppm on acetylation of tifruticin to **1b**. In the 270-MHz NMR spectrum of the latter compound, all signals were well separated; hence decoupling experiments on **1b** afforded the full structure of tifruticin.

The NMR spectrum of **1b** (Table I) exhibited the typical two doublets of H_a and H_b in partial structure A at 6.38 and 5.92 ppm. Spin decoupling experiments involving H_a and H_b established the location of the H_c multiplet at 3.22 ppm. Irradiation at the frequency of H_c converted a doublet of doublets at 5.05 ppm to a doublet (J = 10 Hz) and a multiplet at 5.21 ppm was also simplified. Thus H_d and H_e are at 5.05 and 5.21 ppm, respectively, or the reverse. If it be assumed provisionally that the signal at higher field is H_d, as is generally the case, the signal at lower field could be assigned tentatively to a proton on a carbon carrying a conjugated ester function whose presence was indicated by an ir band at 1700 cm^{-1}.

Since the low-resolution mass spectrum of tifruticin displayed diagnostically important peaks at m/e 278 (M^+ − 100), 260 (M − 100 − 18), and 83 (base peak), the inference was drawn that a five-carbon ester side chain was present. The nature of the ester (partial structure B) was revealed by the NMR spectrum, which had a vinyl multiplet at 6.20 ppm coupled to a three-proton multiplet at 2.01 ppm and another methyl multiplet at 1.88 ppm, all characteristic of an angeloyl group.

Irradiation at the frequency of H_e (5.21 ppm) affected the H_c multiplet, collapsed a doublet of doublets at 2.22 ppm to a doublet (J = 15 Hz), and affected a partially obscured one-proton signal near 2.00 ppm. Irradiation near 2 ppm collapsed the doublet of doublets at 2.22 ppm to a doublet (J = 6 Hz) and converted the 5.21-ppm multiplet to a triplet, thus demonstrating that H_e was adjacent to a methylene group (H_f). Irradiation at the frequency of H_c (5.05 ppm) collapsed a broadened doublet at 5.52 ppm to a broad singlet. The broadening of this signal (H_g) could be traced to a small coupling with a narrowly split three-proton multiplet at 2.10 ppm. Thus partial structure A could be extended to C, where the symbol ■ represents quaternary carbon.



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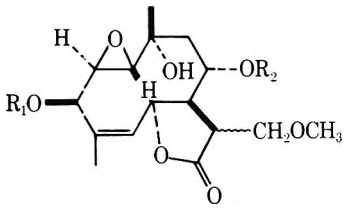
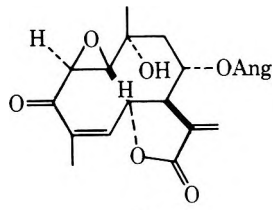
b, R = Ac



2a, R_1, R_2 = H
b, R_1, R_1 = Ac



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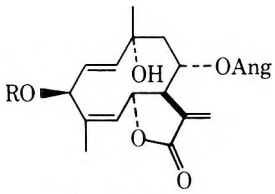
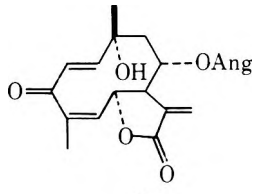


4a, R = H
b, R = Ac



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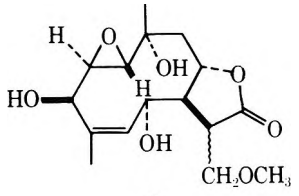

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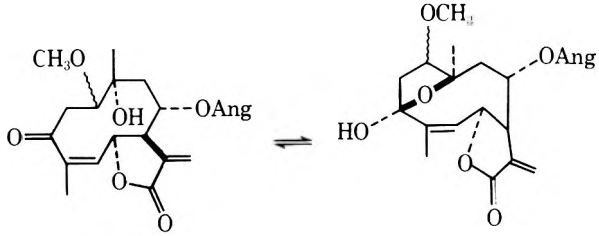
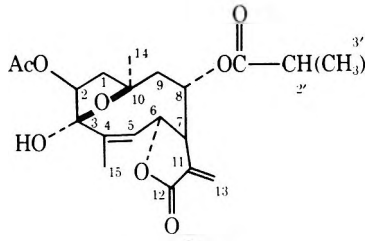


7a **7b**



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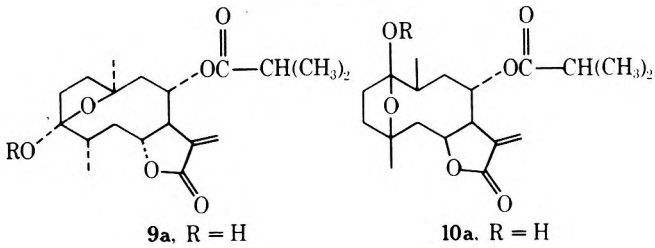


9a, R = H
b, R = Et

10a, R = H
b, R = Et

It was further shown that a somewhat broadened doublet at 3.36 ppm (H_i, J = 2.5 Hz) and a sharp doublet at 3.15 ppm (H_j) constituted an AB system, the broadening of H_i being due to coupling with the proton under the acetate at 5.33 ppm (H_h, vide supra). The chemical shift of the AB system suggested that it represented two protons in an epoxide ring which is included in partial structure D.

Six of the seven oxygen atoms and 20 of the 22 carbon atoms of tifruticin were accounted for by C and D. The remaining two carbons and one oxygen had to be assigned to the grouping CH_3COH where the hydroxyl is tertiary, since the ir spectrum of **1b** still exhibited hydroxyl absorption and the NMR spectra of **1a** and **1b** displayed a three-proton singlet at 1.39 ppm typical of methyl on carbon attached to oxygen.

All of the above information was accommodated by formulas **1a** (devoid of stereochemistry) or E with the proviso mentioned earlier that the proton under the lactone oxygen (H_d) is represented by the signal at 5.05 ppm, i.e., that the lactone ring is closed to C-6. This was confirmed as follows.

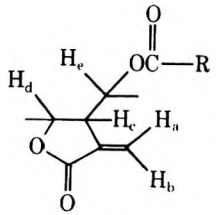
Methanolysis of **1a** (NaOMe, MeOH) gave **2a** by loss of the ester side chain and addition of the elements of methanol to the α,β-unsaturated lactone. The proton under the newly freed hydroxyl function (H_e) now appeared as a multiplet at 3.94 ppm (Table I), and was further identified by its paramagnetic shift on acetylation to **2b**. Decoupling experiments on **2a** confirmed that the H_d signal had remained at 5.03 ppm and was coupled to a vinyl proton at 5.44 ppm, whereas the 3.94-ppm signal was coupled to a methylene group. Hence the lactone ring of tifruticin is closed to C-6.

That the secondary hydroxyl group of tifruticin was allylic and that formula E must be rejected was established by MnO_2 oxidation of **1a** to the α,β-unsaturated ketone **3** [double-strength ir band at 1700 cm^{-1}, uv λ_{max} 235 nm (ϵ 9000)] in whose NMR spectrum (Table I) the H-2 signal was shifted downfield to 4.07 ppm. Finally the ^{13}C NMR spectrum of **1a** (Table II) was fully consonant with the assigned structure **1a**.

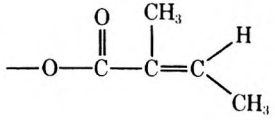
Before discussing the stereochemistry of tifruticin, mention should be made of deoxytifruticin (**4a**), which was isolated from *T. fruticosa* in very low yield and whose purification was attended with considerable difficulties (see Experimental Section). The NMR spectrum of **4a** (Table I) resembled that of **1a** with the exception that the AB system of H-1 and H-2 was displaced downfield by 2.5 ppm, an observation which, taken together with the empirical formula $C_{20}H_{26}O_6$, suggested that the epoxide ring of **1a** had been replaced by a double bond. This was in complete harmony with the ^{13}C NMR spectrum (Table II) and could be confirmed by peracid oxidation of **4a** to **1a**, and of **4b** to **1b**.

MnO_2 oxidation of **4a** afforded the cross conjugated dienone **5**. The ir spectrum of this substance exhibited a very strong band at 1650 cm^{-1} attributable to the new chromophore. The uv spectrum showed the expected maximum at 250 nm (ϵ 8500), while in the NMR spectrum of **5** the resonances of H-1 and H-2 had moved still further downfield, in agreement with the postulated structure.

As regards the stereochemistry of **1a** and **4a**, if the usual assumption be made that the C-7 side chain is β oriented as in all sesquiterpene lactones of authenticated absolute stereochemistry, the value of $J_{6,7}$ (10 Hz) requires that H-6 and H-7 have a trans relationship, i.e., that the lactone ring by trans fused and H-6 be β. Furthermore, NaOH hydrolysis of **2a** followed by acidification resulted in isolation of a product **6** with a reorientated lactone ring. Although shortage of material prevented adequate characterization, the NMR spectrum exhibited the H-6 and H-8 signals near 4.5 ppm and the H-5 signal at 5.00 ppm. This suggested that



A



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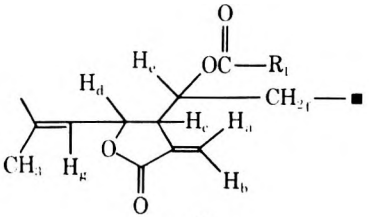
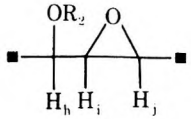


C



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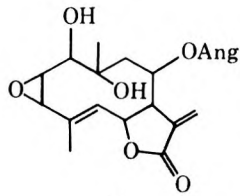

E

Table I
^{1}H NMR Spectra of Compounds from Tithonia[a]

Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15[b]	H-3'	H-4'[b]	H-5'[b]	Misc
1a	3.30[c]	3.30[c]	4.46 br	5.55 dd (10, 1.5)	5.19 dd (10, 10)	3.22 m (10, 3.3, 3.1, 4)	5.19 m	2.15 dd (15, 6) *e*	6.35 d (3.3) 5.88 d (3.1)	1.38	2.01 d (1.5)	6.17 m (7, 1.5)	1.96 m (7, 1.5)	1.88	
1b	3.15 d (2.5)	3.36 d br (2.5)	5.33 br	5.52 d br (10, 1.5)	5.05 dd (10, 10)	3.22 m (10, 3.3, 3.1, 4)	5.21 m	2.22 dd (15, 6) *e*	6.38 d (3.3) 5.92 d (3.1)	1.39	2.10 d (1.5)	6.20 m (7, 1.5)	2.01 m (7, 1.5)	1.88 m	2.04 (Ac)
2a	*e*	*e*	4.44 br	5.44 d br (10, 1.5)	5.03 dd (10, 10)	2.38 m	3.94 m	*e*	*e*	1.42	1.96 d (1.5)				3.44 (OMe)
2b	3.16 d (2.5)	3.33 d br (2.5)	5.32 br	5.44 d br (10, 1.5)	4.92 dd (10, 10)	*e*	5.14 m	*e*	3.62 dd (10, 3) 3.86 dd (10, 2)	1.43	2.07 d (1.5)				3.33 (OMe) 2.04, 2.04 (Ac)
3	3.02 d (3.0)	4.07 d (3.0)		5.74 d br (10, 1.5)	4.54 dd (10, 10)	3.38 m (10, 4, 3.3, 3.1)	5.47 m	2.16[c]	6.38 d (3.3) 5.98 d (3.1)	1.42	20.6 d (1.5)	6.20 m (7, 1.5)	2.01 m (7, 1.5)	1.89 m	
4a	5.77 d (17)	6.08 dd (17, 1.5)	4.69 br (1.5)	5.27 d br (10, 1.5)	5.77 dd (10, 10)	3.05 m (10, 3.3, 3.0, 4)	5.18 m	2.14 dd (15, 6) *e*	6.34 d (3.3) 5.82 d (3.0)	1.38	1.97 d (1.5)	6.22 m (7, 1.5)	2.02 m (7, 1.5)	1.87 m	
4b	5.60 d (17)	6.07 dd (17, 1.5)	5.48 br (1.5)	5.25 d br (10, 1.5)	5.57 dd (10, 10)	3.05 m (10, 4, 3.3, 3.0)	5.18 m	2.19 dd (15, 6) *e*	6.35 d (3.3) 5.82 d (3.0)	1.37	2.02 br (1)	6.22 m (7, 1)	2.02 m (7, 1)	1.87 br	2.13 (Ac)
5	6.49 d (17)	6.25 d (17)		5.87 d br (9, 1.5)	5.40 d br[f] (9)	3.55 m[f]	5.40 m	2.53 dd (15, 6)	6.36 d (3.3) 5.82 d (3.0)	1.53	1.95 d (1.5)	6.08 m (7, 1.5)	1.92 m (7, 1.5)	1.75 m	

7	4.02 dd (10, 6)	2.60 dd (14, 6)		5.64 d br (5, 1)	5.72 dd (5, 5)	4.13 m	5.42 m	*e*	6.26 d (2.1) 5.60 d (2.0)	1.54	1.82 br	6.05 m	1.90 m	1.73 br	3.39 (OMe)
8[f]	*e*	5.36 d br	*e*	5.60 d[g]	5.50 m	4.06 m	5.50 m		6.23 d (2.4) 5.60 d (2.0)	1.50	1.77 t (1.5)	1.05 d (7)	1.07 d (7)		2.12 (Ac)
9a	*e*	*e*	*e*	*e*	4.57 dd br (7, 10.5, 1)	4.11 m (7, 3.4, 3.0, 1.5)	5.54 m	*e*	6.25 d (3.4) 5.54 d (3.0)	1.45	1.13 d (7)	1.05 d (7)	1.08 d (7)		
9b	*e*	*e*	*e*	*e*	4.50 dd br (7, 10.5, 1)	4.05 m (7, 3.4, 3.0, 1.5)	5.55 m	*e*	6.24 d (3.4) 5.53 d (3.0)	1.42	1.04 d (7)	1.02 d (7)	1.02 d (7)	1.12 t (7)[b] 8.33 m 3.50 m	

[a] Run in $CDCl_3$ at 270 MHz on a Bruker HFX-270 instrument with Me_4Si as internal standard. Values are in parts per million; d, doublet; t, triplet; br, broadened singlet; m, multiplet. Unmarked signals are singlets. Figures in parentheses are coupling constants in hertz. [b] Intensity three protons. [c] Intensity two protons. [d,d] Center of AB system. [e] Signal in methylene envelope or obscured. [f] $J_{6,7} < 1$; $J_{7,8} < 1$. [g] From ref 4, run at 90 MHz.

Table II
^{13}C NMR Spectra of Tifruticin and Congeners[a]

Signal no.	1a	4a	Assignment[b]	9a	Assignment[b]
1	169.3 s	169.4 s	C-1′	176.1 s	C-1′
2	167.3 s	168.0 s	C-12	169.4	C-12
3	143.8 s	146.8 s	C-4	137.2 s	C-11
4	140.1 d	140.7 d	C-3′	121.4 t	C-13
5	134.9 s	135.5 s	C-11	108.8 s	C-3
6	127.1 s	127.1 s	C-2′	81.3 d	C-6
7	126.8 d	125.9 d	C-5	80.0 s	C-10
8	122.9 t	122.6 t	C-13	69.8 d	C-8
9	74.4 d	73.9 d[c]	C-6	47.9 d	C-7
10	69.9 d[c]	72.9 d[c]	C-3	43.4 d	C-4
11	67.4 s	70.8 s	C-10	42.2 t[c]	C-9
12	67.1 d[c]	68.9 d	C-8	38.9 t[c]	C-1
13	60.0 d[d]	131.9 d[d]	C-1	38.4 t[c]	C-2
14	56.9 d[d]	130.5 d[d]	C-2	38.0 t[c]	C-5
15	51.2 d	51.3 d	C-7	34.1 d	C-2′
16	41.3 t	43.8 t	C-9	26.9 q	C-14
17	27.8 q	29.5 q	C-14	19.1	C-15
18	25.4 q	25.1 q	C-15	18.7	C-3′
19	20.5 q	20.4 q	C-4′	18.6	C-4
20	15.9 q	15.9	C-5′		

[a] Run in $CDCl_3$ on Bruker HFX-270 instrument. [b] Tentative assignments based on predicted shifts, comparisons with data in the literature (for references see W. Herz, I. Wahlberg, C. S. Stevens, and P. S. Kalyanaraman, *Phytochemistry*, in press) and spectra of lactones of known structure in our files. [c,d] Probable assignments, may be interchanged.

the C-8 side chain of **1a** and **4a** was α oriented (for further evidence on this point, vide infra), since germacranolides containing lactonizable α-oxygen groups at C-6 and C-8 preferably lactonize toward C-8.[2]

The small paramagnetic shift (0.2 ppm) of the H-5 signal accompanying the oxidation of **1a** to **3** was noteworthy and could be explained most satisfactorily by assuming that the carbonyl group at C-3 was twisted somewhat out of the plane of the C-4, C-5 double bond, a situation which could arise only if the double bond were cis.[3] The correctness of this deduction was demonstrated by the existence in **1a** of a nuclear Overhauser effect between H-15 and H-5. Irradiation at the frequency of the methyl group attached to C-4 produced a 12.5% enhancement in the integrated intensity of the H-5 signal.

The 1,2 double bond of **4a** must be trans because of the high value of $J_{1,2}$ (15 Hz); consequently deoxytifruticin represents the first example of a *trans*-1,2-*cis*-4,5-germacradienolide. Since epoxidation with *m*-chloroperbenzoic acid is known to proceed stereospecifically, H-1 and H-2 of **1a** are also trans. Now H-1 and H-6 of **3** are shifted upfield relative to H-1 and H-6 of **1a** and **1b** (Table I) presumably because these protons are located within the shielding cone of the new ketone group. Since H-6 is β, H-1 must be β also and H-2 is α. The small value of $J_{2,3}$ (<1 Hz) further indicates that the dihedral angle between H-2 and H-3 of **1a** and **1b** is close to 90°, in which case H-3 must be α oriented (models).

The chance observation that the uv absorption of **5** decreased on standing in methanol solution offered not only a clue to the stereochemistry at the remaining center C-10, but also provided additional evidence for the previous conclusions about the stereochemistry of tifruticin. That the product (**7**) of this transformation had been formed by addition of the elements of methanol to the conjugated C-1, C-2 double bond was indicated by its mass spectrum, the presence of a methoxyl signal in the NMR spectrum, and the upfield shifts of H-1 and H-2 (Table I). However, the ir

band at 1700 cm^{-1} was relatively weak compared with the analogous band of **3** which represents the combined cyclopentenone–conjugated ester chromophore. Consequently we assumed that **7** was predominantly in the hemiketal form **7b,** a surmise which was strengthened by comparison of the NMR spectrum of **7** with that of woodhousin (**8**,[4] Table I). In fact, since the chemical shifts of H-5, H-6, H-7, H-8, H-13, H-14, and H-15 and the coupling constants involving H-5, H-6, H-7, and H-8 were so similar, it was concluded that the stereochemistry of **7,** and hence that of **1a,** at C-5, C-6, C-7, C-8, and C-10 was the same as that of woodhousin.

We have commented previously[5] on the unusual low-field shift of the H-7 resonance (~4.1 ppm) in woodhousin and certain other cis C-4, C-5 germacranolides (erioflorin[4] and its congeners,[6] heliangin[7]) similar to **7.** In these compounds, H-7 is strongly deshielded by the oxygen atom attached to C-10.[8] The H-7 resonance of **7** is also strongly deshielded; models show that H-7 comes close to the acetal oxygen only if the absolute configuration of **7** at C-10 is *R* (if the absolute configuration of C-7 is as written) and the C-3 hydroxyl is α. Therefore the tertiary hydroxyl group on C-10 of tifruticin (**1a**) is α.[10]

The CD curve of **3** exhibits a negative Cotton effect, while that of **1a** is positive although no change has occurred in orientation of the lactone ring and stereochemistry at C-6. This reinforces our earlier conclusion[11] that the empirical rule relating the sign of the lactone Cotton effect to the type of lactone ring closure[12] is not generally applicable to *cis*-Δ^4-germacranolides. Similarly, $J_{7,13}$ for **7** is <3 in violation of Samek's rule,[13] as is true for other *cis*-Δ^4-germacranolides,[14] while $J_{7,13}$ for **1a, 1b, 3, 4a, 4b,** and **5** is >3. Obviously, the magnitude of $J_{7,13}$ depends on the conformation of the unsaturated germacranolide ring system and not on the stereochemistry of the lactone ring fusion per se.

The main sesquiterpene lactone constituent of *T. rotundifolia* was named tirotundin, $C_{19}H_{28}O_6$, mp 141°, $[\alpha]D$ −77°. The ^1H NMR spectrum (Table I) indicated the presence of partial structure A; this was confirmed by spin decoupling in the manner described for tifruticin, which also permitted identification of the H_d resonance as the more shielded of two signals in the ester region (4.57 vs. 5.54 ppm). Appropriate peaks at 1.05, 1.08 (two methyl doublets), and 2.44 ppm (septet) and fragmentation under electron impact (diagnostically important peaks at *m/e* 264, 247, and 71, the last base peak) showed that the ester side chain was isobutyrate.

The occurrence of the H_c multiplet at the same low frequency (4.11 ppm) as in **7** suggested that tirotundin might be a saturated (because of the analysis and the upfield shift of H_d) hemiketal of the woodhousin type, especially since the ir spectrum exhibited hydroxyl absorption and the NMR spectrum contained no signal indicative of a primary or secondary hydroxyl group. This deduction was supported by the ^{13}C NMR spectrum (Table II), which contained a singlet at 108.8 ppm, characteristic of tetravalent carbon carrying two oxygens, and another singlet at 80.0 ppm which must represent the carbon atom at the other terminus of the acetal linkage. The latter is also attached to a methyl group (^1H methyl singlet at 1.45, ^{13}C methyl quartet at 26.9 ppm).

The foregoing information leads to formulas **9a** (devoid of stereochemistry) or **10a.** Since the methylene signals of tirotundin were not sufficiently well separated at 270 MHz even in the presence of shift reagents to permit their unambiguous identification by double resonance, it was not possible to decide unequivocally between these two alternatives. However, irradiation at the frequency of H-5 did not appear to affect a partially obscured doublet of doublets, an observation which appears to favor the biogenetically more plausible **9a** over **10.** Moreover, the paramagnetic chemical shift of H-7 is highly characteristic of germacranolides containing an oxygen bridge linking C-3 and C-10 (vide supra); compounds of type **10** are so far unknown. Unfortunately, several attempts to distinguish between the two possibilities by chemical means failed.

The minor constituent of *T. rotundifolia* which had formula $C_{21}H_{32}O_6$ was easily recognized as the ethyl acetal of tirotundin **9b** or **10b** (mass spectrum, Tables I and II) possibly formed from tirotundin during the isolation process one stage of which employs ethanol or during the tedious chromatographic purification by reaction with trace amounts of ethanol in chloroform.

Since the chemical shifts of H-7 and H-8 are the same as those of the corresponding signals in the spectra of **7** and woodhousin, the C-8 ester side chain of tirotundin and its acetal is undoubtedly α oriented also. Because $J_{7,13a} > 3$ and the lactone Cotton effect is negative, the lactone ring is trans fused;[16] hence H-6 is β. Now if the gross structure of tirotundin is **9a,** inspection of the various models of **9a** with H-6 and H-8β and H-7α reveals that H-7 approaches the tetrahydrofuran oxygen only when the configuration at C-10 is *S* and C-3 OH is α (*R* configuration) as represented in the formula. Finally, the chemical shift of the C-10 methyl group suggests that it is cis to the hydroxyl at C-3, hence α oriented; this would also be the thermodynamically favored orientation in the ketol corresponding to **9a.**

Experimental Section

Experimental details have been specified previously.[16]

Extraction of *Tithonia fruticosa*. Above-ground parts of *T. fruticosa* Canby and Rose, wt 0.45 kg, collected by Mr. Juan Arguelles near Curahui, Sonora, Mexico in 1959 under USDA auspices (Arguelles No. 124 and 129, A. 5307 and A. 5308) was extracted with $CHCl_3$ and worked up in the usual fashion.[17] The crude gum, wt 6.0 g, was chromatographed over 200 g of silicic acid, 200-ml fractions being collected in the following order: 1–10 (Bz), 11–20 (Bz–$CHCl_3$, 10:1), 21–30 (Bz–$CHCl_3$, 1:1), 31–40 (Bz–$CHCl_3$, 1:10), 41–50 ($CHCl_3$), 51–60 ($CHCl_3$–MeOH, 20:1). Fractions 32–38 gave a mixture of two lactonic components which was separated into its constituents by preparative tlc on silica gel $PF_{255-366}$ (solvent hexane–ethyl acetate 3:2). The plate (20 × 40 cm, thickness 1 mm) was developed *six times;* after each development the plate was fully dried by leaving it in a hood for 1 hr. The two bands did not separate when the plate was developed only twice or three times. The upper band (**4a**) was obtained as a gum which could not be induced to crystallize, ir bands at 3400, 1760, 1700, 1650, 1240, 1150, 1080, 1040 and 850 cm^{-1}, high uv end absorption (ϵ_{230} 7000, ϵ_{210} 18,000, MeOH), CD curve (MeOH) λ_{max} 240 nm, $[\theta]$ +6300. The low-resolution MS exhibited M^+ at *m/e* 362 [not seen in high-resolution MS which displayed the first peak ($M^+ - C_5H_8O_2$, 2.5%) at *m/e* 262.1176 (calcd for $C_{15}H_{18}O_4$, 262.1159) and the base peak at 83 (C_5H_8O)].

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; O, 26.49. Found: C, 66.05; H, 7.52; O, 26.15.

The lower band (**1a**) was recrystallized from ethyl acetate: yield 0.29 g; mp 141°; $[\alpha]^{22}D$ −22° (*c* 1.1, $CHCl_3$); ir bands at 3400, 1760, 1700, 1640, 1140, 1040, 960, and 870 cm^{-1}; uv end absorption (ϵ_{230} 7000, ϵ_{210} 18,000); CD curve λ_{max} 257 nm, $[\theta]$ −4990 (MeOH). It did not react with $NaIO_4$ or with acetone–toluenesulfonic acid. The low-resolution MS exhibited M^+ at *m/e* 378; this was not seen in the high-resolution MS which displayed the first peak ($M^+ - C_5H_8O_2$) at *m/e* 278.1171 (1.3%) (calcd for $C_{15}H_{18}O_5$, 278.1153); other significant peaks were at 260 (1.6%, $M^+ - C_5H_8O_2 - H_2O$), 164 (13.5%, $C_{10}H_{12}O_2$), and 83 (100, C_5H_7O).

Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93; O, 29.60. Found: C, 62.96; H, 6.64; O, 29.52.

Acetyltifruticin (1b) and Acetyldeoxytifruticin (4b). Acetylation of 15 mg of **1a** with acetic anhydride–pyridine gave **1b** as a gum, ir bands at 3400, 1760, 1740, 1710, 1650, 1235, 1150, 1040, 910, 740 cm^{-1}. The low-resolution mass spectrum exhibited diagnostic peaks at *m/e* 420 (M^+), 378 ($M^+ - C_2H_2O$), 360 (M^+ –

$C_2H_4O_2$), 320 ($M^+ - C_5H_8O_2$), 260 ($M^+ - C_2H_4O_2 - C_5H_8O_2$), 243 ($M - C_5H_8O_2 - C_2H_4O_2 - OH$), 83 ($C_5H_7O$, base peak).

Anal. Calcd for $C_{22}H_{28}O_8$: mol wt, 420.1784. Found: mol wt, 420.1780 (MS).

Acetylation of 20 mg of **4a** gave 20 mg of **4b** as a gum, ir bands at 3400, 1760, 1740, 1700, 1650, 1235, 1140, 1030 and 920 cm^{-1}. The low-resolution MS gave significant ions at *m/e* 404 (M^+), 344 ($M^+ - C_2H_4O_2$), 304 ($M^+ - C_5H_8O_2$), 244 ($M^+ - C_2H_4O_2 - C_5H_8O_2$), 226 ($M^+ - C_2H_4O_2 - C_5H_8O_2 - H_2O$), 83 ($C_5H_7O$, base peak).

Anal. Calcd for $C_{22}H_{38}O_7$: C, 65.33; H, 6.98; O, 27.69. Found: C, 65.11; H, 6.66; O, 27.85.

Reaction of 5 with Methanol. TLC analysis of a solution of **5** in MeOH indicated partial conversion to a less polar substance. The product **7** was separated by preparative TLC on silica gel (benzene–ethyl acetate, 2:1) as a gum which had ir bands at 3400, 1760, 1700 (weaker than the band at 1760), 1650, 1230, 1120, and 1000 cm^{-1}; uv end absorption (ϵ_{210} 19,500); diagnostic peaks in low-resolution MS at *m/e* 392 (M^+), 374 ($M^+ - H_2O$), 342 ($M^+ - H_2O - CH_3OH$), 292 ($M^+ - C_5H_8O_2$), 260 ($M^+ - C_5H_8O_2 - CH_3OH$), 83 (C_5H_7O, base peak).

Anal. Calcd for $C_{21}H_{28}O_7$: mol wt, 392.1835. Found: mol wt, 392.1837 (MS).

MnO_2 Oxidation of 1a. A solution of 20 mg of **1a** in 5 ml of AR $CHCl_3$ was stirred with 100 mg of active MnO_2 until TLC indicated disappearance of starting material (10 hr), filtered, washed, dried, and evaporated at reduced pressure. The residue was purified by preparative TLC on silica gel (Bz–ethyl acetate, 1:1): yield 15 mg of **3**; mp 215–217°; ir bands at 3400, 1760, 1700 (double strength), 1650, 1240, 1150, and 1040 cm^{-1}; uv (MeOH) λ_{max} 235 nm (ϵ 9000), strong end absorption (ϵ_{210} 21,000); diagnostic peaks in the low-resolution MS at *m/e* 376 (M^+), 358 ($M^+ - H_2O$), 276 ($M^+ - C_5H_8O_2$), 259 ($M^+ - C_5H_8O_2 - OH$), 83 (C_5H_7O, base peak).

Anal. Calcd for $C_{20}H_{24}O_7$: mol wt, 376.1522. Found: mol wt, 376.1519 (MS).

Conversion of 1a to 2a. A solution of 80 mg of **1a** in 5 ml of anhydrous MeOH was allowed to stand for 4 hr with 100 mg of MeONa (nitrogen atmosphere), diluted with water, and extracted with ethyl acetate. The washed and dried residue was evaporated and the residue purified by preparative TLC on silica gel ($CHCl_3$–MeOH, 20:1) to provide 20 mg of gummy **2a**, ir bands at 3400, 1760, 1050, and 980 cm^{-1}. Acetylation of 10 mg of **2a** gave **2b**, which did not crystallize: ir bands at 1760, 1735, 1240, 1030, and 980 cm^{-1}; diagnostic peaks in the low-resolution MS at *m/e* 412 (M^+), 370 ($M^+ - C_2H_2O$), 352 ($M^+ - C_2H_4O_2$), 310 ($M^+ - C_2H_4O_2 - C_2H_2O$), 292 ($M^+ - 2C_2H_4O_2$), 43 ($C_2H_3O$, base peak).

Anal. Calcd for $C_{20}H_{28}O_9$: mol wt, 412.1733. Found: mol wt, 412.1729 (MS).

Epoxidation of 4a and 4b. A solution of 4 mg of **4a** in 2 ml of $CHCl_3$ was allowed to stand, with stirring, with 25 mg of *m*-chloroperbenzoic acid for 1 hr, diluted with water, and extracted with $CHCl_3$. The washed and dried extract was evaporated and the residue purified by preparative TLC (Bz–ethyl acetate, 1:1). The product was identical with **1a** in every respect. Similarly, **4b** afforded **1b**.

When the reaction time was extended, a mixture of products resulting from epoxidation of ring and ester side chain double bonds was obtained.

MnO_2 Oxidation of 4a. A solution of 10 mg of **4a** in 3 ml of AR $CHCl_3$ was stirred with 50 mg of active MnO_2, the reaction being monitored by TLC. When all of **4a** had disappeared (3 hr), the mixture was filtered, washed, dried, and evaporated at reduced pressure. The residue was purified by TLC on silica gel (Bz–ethyl acetate, 2:1). This gave **5** as a gum: wt 7 mg; ir bands at 3400, 1760, 1700, 1650 (very strong), 1250, 1130, 1040, 950 cm^{-1}; uv (MeOH) λ_{max} 250 nm (ϵ 8500); the low-resolution MS gave significant peaks at *m/e* 350 (M^+), 260 ($M^+ - C_5H_8O_2$), 243 ($M^+ - C_5H_8O_2 - OH$), 83 (C_5H_7O, base peak).

Anal. Calcd for $C_{20}H_{24}O_6$: mol wt, 360.1573. Found: mol wt, 360.1570 (MS).

Extraction of *Tithonia rotundifolia*. Above-ground parts (wt 13.5 kg) of *T. rotundifolia* (Mill.) Blake, collected by E. L. Tyson (Tyson no. 6446) on Nov 27, 1971 midway between Chorrera and Capira, Panama, along the Interamerican Highway, was extracted with $CHCl_3$ and worked up as usual.[15] The crude gum, wt 20 g, was chromatographed over 700 g of silicic acid, 500-ml fractions being collected in the following order: 1–10 (Bz), 11–20 (Bz–$CHCl_3$, 10:1), 21–30 (Bz–$CHCl_3$, 1:1), 31–40 (Bz–$CHCl_3$, 1:10), 41–50 ($CHCl_3$), and 51–60 ($CHCl_3$–MeOH, 20:1). Fractions 29–45, which showed the same two spots on TLC, were combined and the two substances were separated by preparative TLC (five 20 × 40 cm plates, silica gel, solvent Bz–ethyl acetate, 2:1). The less polar compound (probably **9b**) was recrystallized from ethyl acetate: yield 0.5 g; mp 125°; $[\alpha]^{22}D$ −55° (*c* 1.2, $CHCl_3$); ir bands at 1760, 1730, 1650, 1250, 1150, and 1040 cm^{-1}. The low-resolution MS exhibited significant peaks at *m/e* 380 (M^+), 292 ($M^+ - C_4H_8O_2$), 264 ($M^+ - C_4H_8O_2 - C_2H_4$), 246 ($M^+ - C_4H_8O_2 - C_2H_4 - H_2O$), 71 ($C_4H_8O$, base peak).

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48; O, 25.23. Found: C, 65.72; H, 8.47; O, 24.94.

The more polar compound (probably **9a**) was recrystallized from ethyl acetate: yield 3.1 g; mp 141°; $[\alpha]^{22}D$ −77° (*c* 2.0, $CHCl_3$); CD curve (MeOH) δ_{max} 263 nm, $[\theta]$ −1560; ir bands at 3400, 1760, 1735, 1650, 1230, 1150, 1030, and 960 cm^{-1}; significant peaks in the low-resolution MS at *m/e* 352 (M^+), 334 ($M^+ - H_2O$), 264 ($M^+ - C_4H_8O_2$), 246 ($M^+ - C_4H_8O_2 - H_2O$), 71 (C_4H_7O, base peak).

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01; O, 27.24. Found: C, 64.30; H, 7.72; O, 26.80.

Registry No.—**1a**, 56377-69-6; **1b**, 56377-59-4; **2a**, 56377-60-7; **2b**, 56377-61-8; **3**, 56377-62-9; **4a**, 56377-63-0; **4b**, 56377-64-1; **5**, 56377-65-2; **7b**, 56377-66-3; **9a**, 56377-67-4; **9b**, 56377-68-5.

References and Notes

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Total Synthesis of Steroids. VI. Synthesis of 14β-Hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione and Related Compounds

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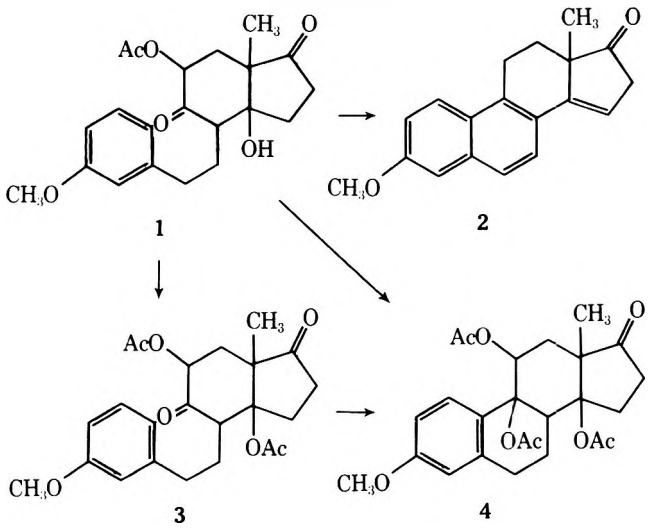
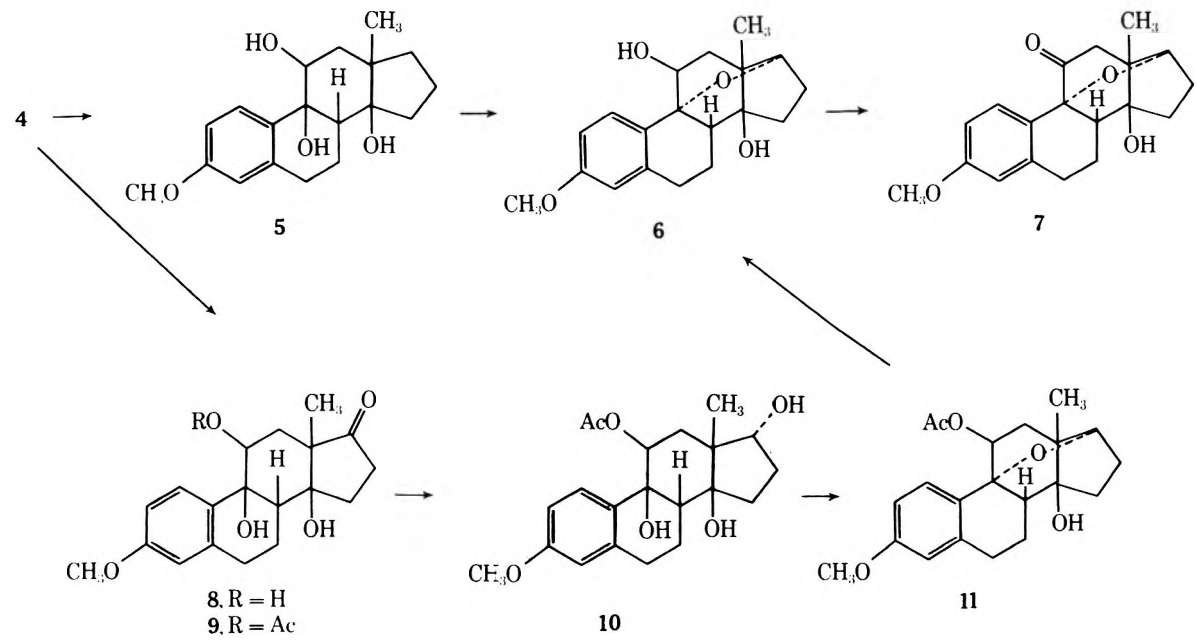
Cyclization of 11β-acetoxy-14β-hydroxy-3-methoxy-9,10-secoestra-1,3,5(10)-triene-9,17-dione (1) by acetyl *p*-toluenesulfonate in acetic anhydride gave tetracyclic triacetate 4. The stereochemistry of the latter was elucidated on spectral grounds and by conversion to 14-isoestrone 3-methyl ether (21). Further transformation of 4 led to the new 11-keto-9α,17α-epoxy compound 7.

Total synthesis of 11β-acetoxy-14β-hydroxy-3-methoxy-9,10-secoestra-1,3,5(10)-triene-9,17-dione (1) and its cyclization to the methyl ether of 14-dehydroequilenin (2) were reported previously.[1] In the present paper we describe a cyclization of compound 1 which is not accompanied by aromatization of ring B and other reactions. When the cyclization of 1 was carried out in acetic anhydride (Scheme I) in the presence of *p*-toluenesulfonic acid or acetyl *p*-toluenesulfonate, a new triacetate 4 was obtained in 70% yield. When the reaction was carried out for a short time in acetic anhydride with a smaller amount of *p*-toluenesulfonic acid the secodiacetate 3 could be isolated. Triacetate 4 was readily isolated because it precipitated directly from the reaction mixture. The structure of this triacetate was proved by reactions presented in Schemes II–IV and by examination of the spectra of compounds obtained from 4. The reduction of triacetate 4 with $LiAlH_4$ afforded tetraol 5 which, upon acidification, readily gave the internal ether 6. Oxidation of ether 6 with Collins[2] or Jones[3] reagents yielded 11-keto compound 7 in which the ether group remained unchanged. Proof of the oxygen bridge between carbon atoms 9 and 17 was obtained in the following way. Alkaline hydrolysis of triacetate 4 gave triol 8 in which the secondary hydroxyl group at carbon atom 11 was easily acetylated to the monoacetate 9. This acetate was then reduced with $NaBH_4$; according to the literature[4] the 17-hydroxyl group should have the α configuration, as always occurs in the case of a cis C/D ring junction. A solution of compound 10 in alcohol treated at room temperature with *p*-toluenesulfonic acid gave the dehydrated compound 11, which upon hydrolysis gave the same internal ether 6. The NMR spectrum of compound 11 exhibits a signal of proton at C-11 (5.20 ppm) and a signal of proton at C-17 (3.97 ppm). In the spectrum of the keto compounds 7 the signal

Scheme I



Scheme II

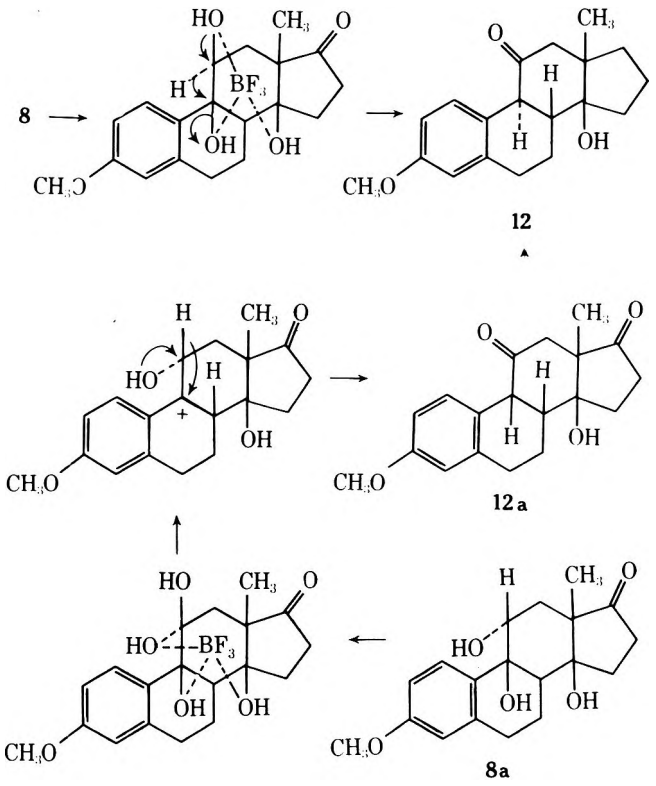


of proton at C-17 (4.15 ppm) is still present. This shows clearly that the oxygen bridge is located between carbon atoms 9 and 17.

In order to prove that the alkaline hydrolysis did not cause any rearrangements at carbon atoms 9 and 11, the acetylation of monoacetate **9** to the triacetate **4** was carried out with acetic anhydride and *p*-toluenesulfonic acid as a catalyst. This series of reactions constitutes a proof of the cis C/D ring fusion; otherwise the formation of 9,17-epoxy compound would be impossible. Since the internal ethers **6** or **11** were formed in quantitative yields, the mechanism of the intramolecular reaction was probably of the SN2 type, and therefore the hydroxyl group at the carbon atom 9 should have the β configuration. In the case of the hydroxyl group in the α configuration, the free or solvated carbonium ion at C-9 should have existed before its collapse to the internal ether, which would have caused the formation of dehydrated side products as will be shown[5] later.

The triol **8** could be easily converted to diketone **12** in good yield by action of boron trifluoride etherate. The rate

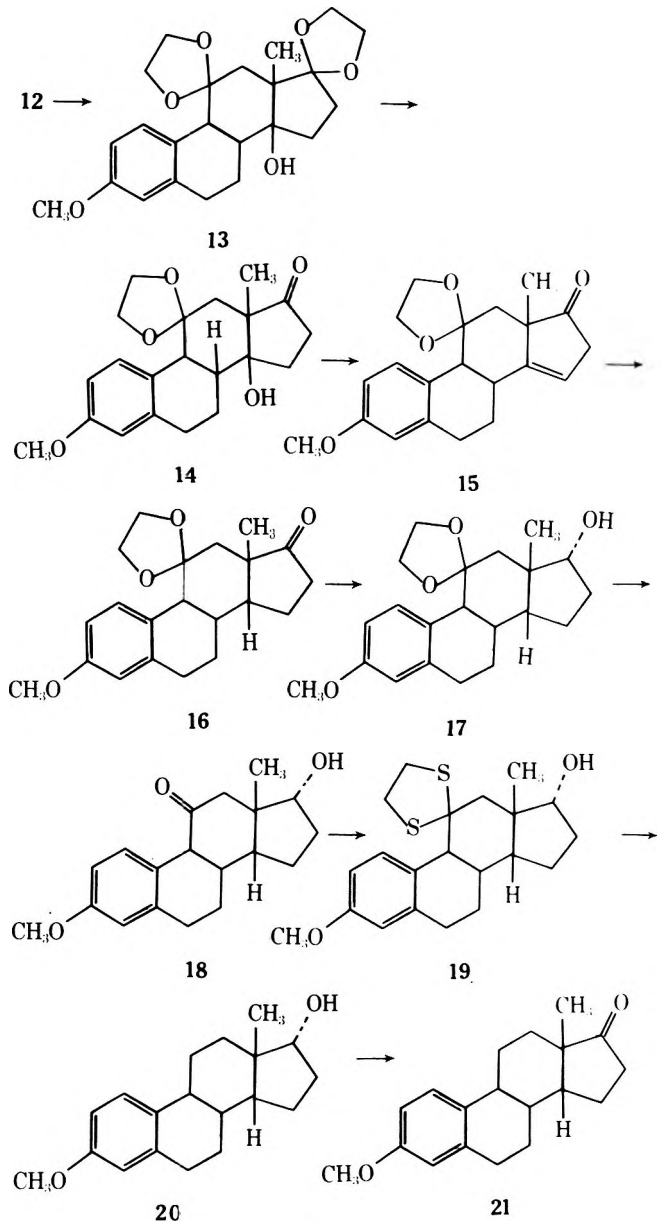
Scheme III



of this rearrangement at room temperature is very fast. The new diketone **12** is different from that obtained earlier[6] (8-isoestrane derivative) and, according to its NMR data, contains a trans B/C ring junction; the coupling constant between protons at C-8 and C-9 was 13 Hz. Since the hydrogen at C-8 has the β configuration (vide infra), the hydrogen at C-9 must be α as a result of the pinacol-like rearrangement of triol **8**. In the starting triol **8** the hydroxyl group at C-11 should have the β configuration. If the hydroxyl group at C-11 had the α configuration as in **8a**, the action of BF_3 should have resulted in the formation of **12a** with cis B/C ring junction. A fast epimerization of **12a** to **12** with a trans B/C ring junction is improbable.

The configuration of the hydroxyl group at C-11 could not be established by an examination of the NMR spectra of compounds **1**, **3**, **4**, **8**, **9**, or **10** because of the presence of cis C/D and B/C ring junctions and the resulting possibility of two chair conformations. Proof for the structure of diketone **12** was obtained by the series of reactions presented in Scheme IV.

Scheme IV



The diketone **12** was transformed to the known 3-methoxy-14β-estra-1,3,5(10)-trien-17-one (**21**) with melting point and ir spectrum identical with those of compound **21** as reported by Johnson and his coworkers.[7] Since compound **21** has the trans B/C ring junction it is assumed that diketal **13** and ethylene thioketal **19** have the same geometry. A similar series of reactions has been conducted with the 8-iso analog of **12** and was described in detail in our previous paper.[6]

Experimental Section[8]

11β,14β-Diacetoxy-3-methoxy-9,10-secoestra-1,3,5(10)-triene-9,17-dione (3). A solution of *p*-toluenesulfonic acid (0.10 g) in Ac_2O (2 ml) was added to a mixture of compound **1** (2.0 g, 5.35 mmol) and acetic anhydride (10 ml) at room temperature. When the substrate was consumed (2 hr), the mixture was quenched with water and neutralized with $NaHCO_3$. Then it was extracted with chloroform and the chloroform solution was washed with an aqueous $NaHCO_3$ solution, dried, and evaporated to dryness in vacuo. The residue was recrystallized from 10 ml of methanol and gave 2.0 g (90%) of **3**: mp 99–100°; NMR δ 1.2 (s, 3, CH_3), 2.08 (s, 3, CH_3CO at C-11), 2.2 (s, 3, CH_3CO at C-14), 5.28 (q, 1, at C-11), 6.8–7.5 ppm (m, 4, at C-1, C-2, C-4, and C-10); ir 1725, 1740 cm^{-1}.

Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.72; H, 6.30.

9β,11β,14β-Triacetoxy-3-methoxyestra-1,3,5(10)-trien-17-one (4). A solution of **1** (6.0 g, 16 mmol) in Ac_2O (25 ml) was added to the acetyl *p*-toluenesulfonate[9] obtained from *p*-toluenesulfonic acid (6.1 g, 32 mmol) in Ac_2O (20 ml). The mixture was allowed to stand for 24 hr at room temperature and then the precipitated compound **4** was filtered. It was washed with acetic acid (20 ml), water, and cold methanol (10 ml), giving 5.15 g (70%) of compound **4**: mp of crude 202–204°; after recrystallization from chloroform–methanol mixture, mp 211–213°; NMR δ 1.07 (s, 3, CH_3), 1.78 (s, 3, CH_3CO at C-11), 2.14 (s, 6, 2 CH_3CO at C-9 and C-14), 3.82 (s, 3, CH_3O), 5.43 (q, 1, at C-11), 6.68 (d, 1, J = 2.5 Hz at C-4), 6.82 (2 d, 1, J_{1-2} = 8.5, J_{2-4} = 2.5 Hz, at C-2), 7.4 ppm (d, 1, J = 8.5 Hz, at C-1); ir (Nujol) 1735, sh 1740 cm^{-1}.

Anal. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 64.55; H, 6.31.

9β,11β,14β-Trihydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (8). A solution of NaOH (2.62 g, 65.4 mmol) in 50 ml of methanol was added to **4** (10 g, 21.8 mmol) in 100 ml of methanol and was refluxed for 1 hr. Then methanol was evaporated in vacuo. The residue was treated with benzene (50 ml), and the precipitate (12.4 g) was filtered and washed with 50 ml of benzene. The product consisted of a mixture of CH_3COONa and compound **8**, but for further reactions, acetylation or dehydration, its purification is not necessary. A pure compound **8** could be extracted with a mixture of acetone and chloroform (1:2). It melted at 185–189°; NMR (CD_3COCD_3) δ 1.25 (s, 3, CH_3), 3.75 (s, 3, CH_3O), 4.45 (t, 1, at C-11), 6.55 (m, 2, at C-2 and C-4), 7.3 ppm (d, 1, J = 9 Hz, at C-1); ir 3450, 1735 cm^{-1}.

11β-Acetoxy-9β,14β-dihydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (9). The above-described mixture of compound **8** and CH_3COONa (1 g) in 5 ml of pyridine was treated with acetic anhydride (2 ml) and allowed to stand for 24 hr. Then 10 ml of water was added and after cooling in an ice box 0.6 g (94%) of **9** was filtered off: mp 210–212°; after recrystallization from a mixture of acetone and water, mp 222–223.5°; NMR (CD_3COCD_3) δ 1.15 (s, 3, CH_3), 1.80 (s, 3, CH_3CO), 3.76 (s, 3, CH_3O), 5.53 (t, 1, at C-11), 6.7 (m, 2, at C-2 and C-4), 7.1 ppm (d, 1, J = 8 Hz, at C-1); ir 3520, 1720 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.37; H, 7.00. Found: C, 67.45; H, 7.05.

11β-Acetoxy-3-methoxyestra-1,3,5(10)-triene-9β,14β,17α-triol (10). To a solution of **9** (1 g, 2.67 mmol), $NaHCO_3$ (0.3 g) in methanol (10 ml) and water (2 ml), 0.50 g (1.31 mmol) of $NaBH_4$ was added at room temperature. When the reduction was completed, water (50 ml) was added to the reaction mixture and compound **10** (0.85 g, 84%) was filtered off: mp 200–202°; NMR (CD_3COCD_3) δ 1.15 (s, 3, CH_3), 1.75 (s, 3, CH_3CO), 3.75 (s, 3, CH_3O), 4.1 (m, 1, at C-17), 5.54 (t, 1, at C-11), 6.65 (m, 2, at C-2 and at C-4), 7.05 ppm (d, 1, J = 9 Hz, at C-1); ir 3500, 1710 cm^{-1}.

Anal. Calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 66.91; H, 7.51.

11β-Acetoxy-3-methoxy-9α,17α-epoxyestra-1,3,5(10)-trien-14β-ol (11). To a solution of **10** (1.0 g, 2.66 mmol) in 10 ml of methanol, 0.50 g of *p*-toluenesulfonic acid was added and the mixture was left for 2 hr. Then it was diluted with water (10 ml) and the precipitate **11** was filtered off, giving 0.93 g (98%): mp 168–170°; NMR δ 0.9 (s, 3, CH_3), 1.70 (s, 3, CH_3CO), 3.72 (s, 3, CH_3O), 3.97 (d, 1, at C-17), 5.20 (q, 1, at C-11), 6.55 (d, 1, J = 2.5 Hz, at C-4), 6.70 (2, d, 1, J_{2-4} = 2.5, J_{1-2} = 9 Hz, at C-2), 7.25 ppm (d, 1, J = 9 Hz, at C-1); ir 3450, 1720 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.37. Found: C, 70.21; H, 7.49.

3-Methoxy-9α,17α-epoxyestra-1,3,5(10)-triene-11β,14β-diol (6). Method A. To a solution of **4** (1 g, 2.18 mmol) in 20 ml of tetrahydrofuran, $LiAlH_4$ (0.350 g, 9.21 mmol) was added. The mixture was stirred for 1.5 hr, then ethanol (5 ml) and water (1 ml) were added. The inorganic salts were filtered off and were washed with chloroform (50 ml) and the filtrate was evaporated to dryness. The residue was dissolved in methanol (5 ml) and was acidified with *p*-toluenesulfonic acid (pH about 2). The mixture was left for 1 hr at room temperature. Then one-half of the methanol was removed and water (5 ml) was added. The precipitate **6** (0.59 g, 85%) after recrystallization from benzene had mp 164–165°; NMR δ 0.90 (s, 3, CH_3), 3.84 (s, 3, CH_3O), 4.0 (d, 1, at C-17), 4.24 (q, 1, at C-11), 6.75 (d, 1, J_{2-4} = 2.5 Hz, at C-4), 6.9 (2 d, 1, J_{1-2} = 9, J_{2-4} = 2.5 Hz, at C-2), 7.45 ppm (d, 1, J = 9 Hz, at C-1); ir 3500 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.32; H, 7.62.

Method B. Compound **6** was obtained by simple reduction of compound **11** with $LiAlH_4$ by the standard procedure. The yield was 95%.

14β-Hydroxy-3-methoxy-9α,17α-epoxyestra-1,3,5(10)-trien-11-one (7). Jones reagent[3] was added dropwise at room temperature with stirring to a solution of **6** (1.0 g, 3.17 mmol) in acetone (20 ml) until the time when the yellow color of the solution was permanent. After compound **6** had been oxidized, ten drops of 2-propanol was added and the reaction mixture was filtered. The acetone solution was evaporated to about 5 ml and then water (10 ml) was added. The precipitated **7** (0.85 g, 85%) had mp 230–235°; NMR δ 1.05 (s, 3, CH_3), 3.85 (s, 3, CH_3O), 4.15 (d, 1, at C-17), 6.75 (d, 1, at C-4), 6.92 (2 d, 1, at C-2), 7.27 ppm (d, 1, at C-1); ir 3480, 1720 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.69; H, 6.94.

14β-Hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione (12). Freshly distilled Et_2O-BF_3 (2 ml) was added to a solution of **8** (1.0 g, 3.01 mmol) in dry acetone (50 ml) at room temperature and after 1 min water (10 ml) was added. The solvent (30 ml) was evaporated in vacuo and the precipitated **12** was filtered off. The filtrate was extracted with chloroform, washed with an aqueous saturated solution of $NaHCO_3$, and dried. After the evaporation of chloroform the residue was treated with benzene (5 ml) and an additional amount of **12** was obtained, 0.71 g (75%): mp 215–217°; NMR δ 1.0 (s, 3, CH_3), 3.70 (s, 3, CH_3O), 3.90 (d, 1, J = 13 Hz, at C-9), 6.65 (m, 2, at C-2 and C-4), 7.05 ppm (d, 1, at C-1); ir 3500, 1705, 1740 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.65; H, 6.98.

11,11,17,17-Bis(ethylenedioxy)-3-methoxyestra-1,3,5(10)-trien-14β-ol (13). A mixture of compound **12** (1.0 g, 3.18 mmol), benzene (100 ml), ethylene glycol (1 ml), and *p*-toluenesulfonic acid (0.050 g) was refluxed using a Dean-Stark separator for 10 hr. When the ketalization was complete the mixture was cooled, washed with aqueous Na_2CO_3 solution, and dried. The benzene solution was evaporated to dryness and to the residue methanol (10 ml) was added. The precipitated **13** (1.15 g, 2.89 mmol, 90%) was filtered off and washed with cold methanol: mp 219–220°; NMR δ 1.07 (s, 3, CH_3), 3.72 (s, 3, CH_3O), 6.55 (m, 2, at C-2 and C-4), 7.75 ppm (d, 1, J = 9 Hz, at C-1); ir 3500 cm^{-1}.

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.74; H, 7.68.

14β-Hydroxy-11,11-ethylenedioxy-3-methoxyestra-1,3,5(10)-trien-17-one (14). The solution of *p*-toluenesulfonic acid (15 mg) in 1 ml of water was added to a solution of **13** (1.30 g, 3.24 mmol) in benzene (30 ml) and acetone (10 ml). The mixture was stirred at 50°. When diketal **13** had changed to monoketal **14** the mixture was treated with an aqueous solution of Na_2CO_3. Then it was dried and the solvent was removed in vacuo. To the residue methanol (5 ml) was added and the precipitate was filtered off, giving 1.00 g (86%) of **14**: mp 225–226°; NMR δ 1.08 (s, 3, CH_3), 3.75 (s, 3, CH_3O), 3.90 (m, 4, OCH_2CH_2O), 6.74 (m, 2, at C-2 and C-4), 7.95 ppm (d, 1, J = 9 Hz, at C-1); ir 3500, 1735 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.52; H, 7.19.

11,11-Ethylenedioxy-3-methoxyestra-1,3,5(10),14-tetraen-17-one (15). To a solution of **14** (1.0 g, 2.8 mmol) in pyridine (10 ml), $SOCl_2$ (0.5 ml) was added at 0°. The mixture was stirred for 5 min and then treated with water (20 ml). The crystalline **15** was filtered off and washed with water and cold methanol, giving 0.80 g (84%) of **15**: mp 159–163°; NMR δ 1.32 (s, 3, CH_3), 3.82 (s, 3, CH_3O), 3.95 (m, 4, OCH_2CH_2O), 5.77 (br s, 1, at C-15), 6.75 (m, 2, at C-2 and C-4), 8.02 ppm (d, 1, J = 9 Hz, at C-1); ir 1740 cm^{-1}.

11,11-Ethylenedioxy-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (16). The hydrogenation of **15** (1.00 g, 2.94 mmol) was carried out at atmospheric pressure in a toluene solution using 1.0 g of 10% Pd on $CaCO_3$. When the hydrogen absorption ceased, the catalyst was filtered off and toluene was evaporated in vacuo. To the residue, methanol (5 ml) was added and the precipitate **16** was filtered off. It was washed with cold methanol and dried, giving 0.95 g (95%) of **16**: mp 154–156°; NMR δ 1.24 (s, 3, CH_3), 3.74 (s, 3, CH_3), 3.90 (m, 4, OCH_2CH_2O), 6.60 (m, 2, at C-2 and C-4), 7.90 ppm (d, 1, J = 9 Hz, at C-1); ir 1740 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.81; H, 7.79.

11,11-Ethylenedioxy-3-methoxy-14β-estra-1,3,5(10)-trien-17α-ol (17). To a solution of **16** (1.00 g, 2.92 mmol) in ether (20 ml) and toluene (15 ml), $LiAlH_4$ (0.100 g, 2.63 mmol) was added at room temperature. The mixture was stirred for 10 min and water

(1 ml) was added. The inorganic precipitate was filtered off and washed with ether (50 ml) and the filtrate was evaporated. The residue was treated with hexane and the precipitated **17** was filtered off to yield 0.90 g (90%), mp 119–120°, ir no C=O band.

17α-Hydroxy-3-methoxy-14β-estra-1,3,5(10)-trien-11-one (18). A mixture of compound **17** (1.00 g, 2.91 mmol), methanol (20 ml), and 10% hydrochloric acid (2 ml) was heated under reflux for 15 min. The solvent (15 ml) was evaporated and then compound **18** was filtered off and washed with water, giving 0.73 g (86%): mp 189–191°; NMR δ 1.10 (s, 3, CH_3), 3.80 (s, 3, CH_3O), 3.95 (br s, 1, at C-17), 6.75 (m, 2, at C-2 and C-4), 7.25 ppm (d, 1, J = 9 Hz, at C-1); ir 3500, 1705 cm^{-1}.

17α-Hydroxy-3-methoxy-14β-estra-1,3,5(10)-trien-11-one Ethylene Thioketal[10] (19). To a solution of compound **18** (1.0 g, 3.33 mmol) in 5 ml of ethanedithiol, $Et_2O{\cdot}BF_3$ (1 ml) was added at 10° and the mixture was allowed to stand at room temperature for 2 hr. When compound **18** could no longer be detected in the mixture (by TLC) the reaction mixture was diluted with ether and washed with 1 N sodium hydroxide solution until the ethanedithiol odor was eliminated. Upon drying and evaporation, the ether solution gave a crude mercaptal **19** (1.10 g, 88%): mp 90–91°; NMR δ 1.35 (s, 3, CH_3), 3.80 (s, 3, CH_3O), 3.95 (br s, 1, at C-17), 6.70 (m, 2, at C-2 and C-4), 8.75 ppm (d, 1, J = 9 Hz, at C-1); ir 3500 cm^{-1}, no C=O band.

Anal. Calcd for $C_{21}H_{28}S_2O_2$: C, 67.07; H, 7.45. Found: C, 67.2; H, 7.36.

3-Methoxy-14β-estra-1,3,5(10)-trien-17α-ol (20). Freshly prepared Raney nickel (from 8 g of alloy) was added to a solution of compound **19** (0.200 g, 0.532 mmol) in methanol (20 ml). The resulting suspension was heated under reflux for 5 min with rapid stirring with a magnetic bar. The nickel was then removed by filtration and the solvent was evaporated. The residue, recrystallized from methanol, yielded 0.140 g (89%) of compound **20**: mp 103–104°; NMR δ 1.04 (s, 3, CH_3), 3.76 (s, 4, CH_3O and H at C-17), 6.70 (m, 2, at C-2 and C-4), 7.25 ppm (d, 1, J = 9 Hz, at C-1); ir 3400 cm^{-1}.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.82; H, 9.10.

3-Methoxy-14β-estra-1,3,5(10)-trien-17-one (21). To a solution of **20** (0.100 g, 0.35 mmol) in 5 ml of acetone, Jones reagent[3] was added dropwise at room temperature until the time when the yellow color of the solution became permanent. When compound **20** was oxidized a few drops of 2-propanol were added and the inorganic solid was removed by filtration. Acetone was evaporated and the residue was washed with water. The precipitate was recrystallized from methanol, yielding 0.080 g (80.5%) of compound **21**, mp 120–121°, whose ir spectrum in $CHCl_3$ was identical with that described by Johnson et al.[7]

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Registry No.—**1**, 55923-92-7; **3**, 55887-37-1; **4**, 55923-93-8; **6**, 55887-38-2; **7**, 55904-18-2; **8**, 55871-08-4; **9**, 55887-39-3; **10**, 55887-40-6; **11**, 55887-41-7; **12**, 55923-94-9; **13**, 55903-63-4; **14**, 55923-95-0; **15**, 55903-64-5; **16**, 55887-42-8; **17**, 55923-96-1; **18**, 55923-97-2; **19**, 55923-98-3; **20**, 55923-99-4; **21**, 55924-00-0.

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(8) All melting points are uncorrected. The NMR spectra were determined in $CDCl_3$ unless otherwise stated with a Jeol apparatus at 100 MHz using Me_4Si as an internal standard. The ir spectra were obtained in KBr unless otherwise stated with a Unicam SP 200 spectrophotometer. All the reactions were monitored by thin layer chromatography. All the compounds were obtained as racemates and for the sake of simplicity prefixes *dl* or *rac* have been omitted.
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Total Synthesis of Steroids. VII. Synthesis of 14β-Estra-4-ene-3,11,17-trione and Related Compounds

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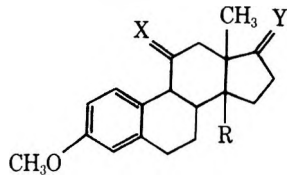
Transformation of 14β-hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione to 3-methoxy-14β-estra-1,3,5(10)-triene-11,17-dione, 14β-estra-4-ene-3,11,17-trione, and 3-methoxy-8α-estra-1,3,5(10)-triene-11,17-dione as well as to other compounds is described. The stereochemistry of the products was elucidated on spectral grounds and by convertion to known compounds.

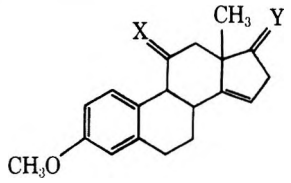
In part VI on total synthesis of steroids[1] a method of preparation of 9β,11β,14β-trihydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**12**) and 14β-hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione (**1**) was described. The present work is concerned with a transformation of **1** and **12** into estrane derivatives. Compound **1** can be easily dehydrated with thionyl chloride in pyridine to unsaturated diketone **2**. A catalytic hydrogenation of C-14 double bond in diketone **2** and compounds **4**, **7**, **9**, **10** and **11** (Scheme I) leads to 3-methoxy-14β-estra-1,3,5(10)-triene-11,17-dione (**3**) irrespectively of the substitution at C-11 and C-17 by a hydroxyl, keto, or ketal function, similarly to the known reduction of 14-dehydroestrone methyl ether.[2]

In order to obtain compounds with the natural configuration at carbon atom 14 the following series of reactions was carried out (Scheme II). The known[1] triol **12** was oxidized by Collins' method[3] to diketone **13**, which was dehydrated in hot acetic acid with p-toluenesulfonic acid to pentaene **14**. This compound could also be obtained by dehydration of the known compound[4] **15**, which was produced by either a monodehydration of **13** or an oxidation of **16**. The preparation of **16** and the proof of its structure will be described later. Catalytic hydrogenation of pentaene **14** in toluene solution over $Pd/CaCO_3$ catalyst gave tetraene **17** as in the case of reduction of 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one.[5] The uv spectrum of **17** was

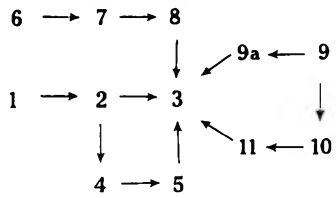
Scheme I



1, X = Y = O; R = OH
3, X = Y = O; R = H
5, X = ξOH, ξH; Y = βOH, αH; R = H
6, X = Y = OCH_2CH_2O; R = OH
8, X = Y = OCH_2CH_2O; R = N
9a, X = OCH_2CH_2O; Y = O; R = H



2, X = Y = O
4, X = ξOH, ξH; Y = βOH, αH
7, X = Y = OCH_2CH_2O
9, X = OCH_2CH_2O; Y = O
10, X = OCH_2CH_2O; Y = βOH, αH
11, X = O; Y = βOH, αH

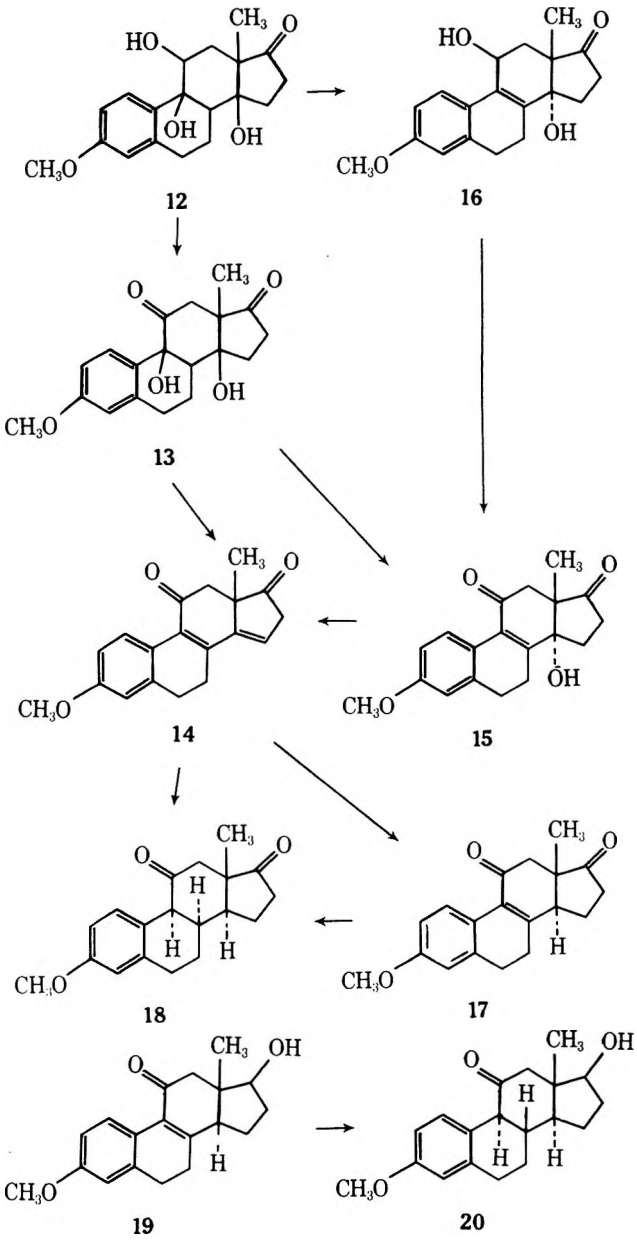


almost identical with that of **15.** In order to prove that the hydrogenation of the 14(15) double bond took place from the α side, tetraene **17** was hydrogenated in an alcoholic solution and gave the known compound **18** identical in all respects with an authentic sample.[6] Compound **18** was also prepared by a direct hydrogenation of pentaene **14** over palladium catalyst in an alcoholic solution.

The reduction of the 8(9) double bond of compound **19** to **20** with the natural configuration was carried out by Smith[7] and by Birch.[8] These authors obtained a 60% yield of compound **20,** but their substrate **19** had the β-hydroxyl group at C-17 instead of the keto group which is present in compound **17.** We have shown[1] that the treatment of triol **12** with $Et_2O{\cdot}BF_3$ gives diketone **1** but the acidification of the same triol **12** with *p*-toluenesulfonic acid in alcoholic solution yields the unsaturated compound **16** in which a change of configuration at C-14 takes place. TLC showed that the first step of this reaction was a dehydration and the second step was a change of configuration at C-14. The mechanism of this reaction was not investigated further but it is probable that a change of configuration at C-14 takes place through the SN1 type reaction to the thermodynamically favored diastereoisomer. It is known[9] that cinnamyl alcohol exchanges the hydroxyl group under acidic conditions. The acetyl derivative **22** was obtained by acetylation of **16** and by dehydration of known monoacetate[1] **23** (Scheme III).

These reactions proved that there was no change of configuration at C-11. Catalytic hydrogenation of **16** gave compound **24** as the major product and compounds **25** and **26** as by-products. The known[10] compound **27** was obtained by oxidation of **24** with Jones[11] reagent. The structure of **27** was established unambiguously. It was shown earlier[1] that the configuration of the hydroxyl group at C-11 could not

Scheme II



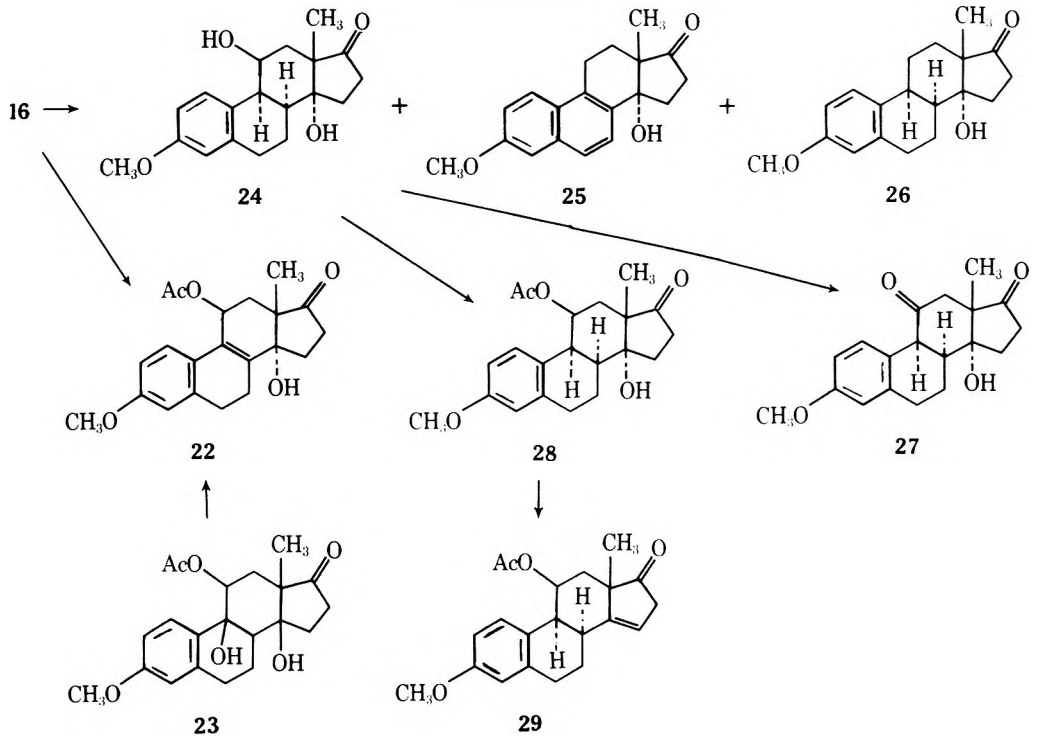
be demonstrated by NMR, owing to a flexibility of the steroidal nucleus at the cis B/C and C/D ring junctions. Confirmation of the β configuration of the hydroxyl group at C-11 in triol **12** and other related compounds was obtained from the NMR spectrum of compound **29.** Compound **29** has a double bond between C-14 and C-15 and consequently has only one chair conformation. The signal of the proton at C-11 (5.62 ppm) in the NMR spectrum of **29** has a total width of 10 Hz, clearly showing the axial β geometry of the hydroxyl at C-11.

In order to obtain some other new 19-norsteroids, diketals **6** and **8** were reduced by sodium in liquid ammonia and the products were hydrolyzed to the hitherto unknown triketones **31, 32,** and **34** (Scheme IV). The hydrogen atom at C-10 was assumed to have the trans configuration with respect to the hydrogen atom at C-9.[12]

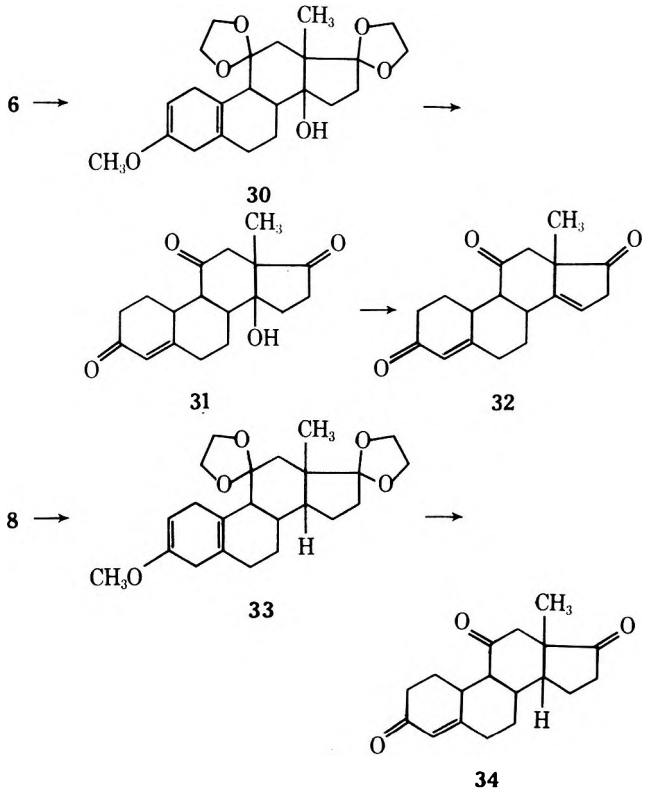
Experimental Section[13,14]

3-Methoxyestra-1,3,5(10),14-tetraene-11,17-dione (2). To a solution of **1** (1.00 g, 3.19 mmol) in dry pyridine, 0.5 ml of $SOCl_2$ was added at 0°. The mixture was stirred for 5 min and water (25 ml) was added. The crystalline product was filtered off and washed with water and cold methanol. The yield of **2** was 0.81 g (86%). Crude **2** melted at 143–145°; NMR δ 1.2 (s, 3, CH_3), 2.55 (s, 2, at

Scheme III



Scheme IV



C-16), 3.55 (d, 1, J = 12 Hz, at C-9), 3.8 (s, 3, CH_3O), 5.87 (t, 1, at C-15), 6.7 (m, 2, at C-2 and C-4), 7.05 ppm (d, 1, J = 9 Hz, at C-1); ir 1710, 1735 cm^{-1}.

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.94; H, 6.83.

3-Methoxy-14β-estra-1,3,5(10)-triene-11,17-dione (3) via Compounds 4 and 5. To a solution of **2** (1.00 g, 3.38 mmol) in ether (50 ml), 200 mg (5.26 mmol) of $LiAlH_4$ was added at room temperature. The mixture was stirred for 10 min and water (2 ml) was added. The inorganic precipitate was filtered off and washed with ether (50 ml). The filtrate was evaporated, and the crystalline compound **4** (ir showed the absence of C=O band) was hydrogenated without purification to compound **5** over palladium on charcoal under atmospheric pressure in ethyl alcohol solution. The standard Jones oxidation[11] of **5** afforded 0.60 g of **3**: mp 202–205°; NMR δ 1.1 (s, 3, CH_3), 3.75 (s, 3, CH_3O), 3.85 (d, 1, J = 12 Hz, at C-9), 6.55 (m, 2, at C-2 and C-4), 7.05 ppm (d, 1, J = 9 Hz at C-1); ir 1710, 1738 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.50; H, 7.39.

3-Methoxy-14β-estra-1,3,5(10)-triene-11,17-dione (3) by Hydrogenation of 2, 7, and 9. The hydrogenation of **2**, **7**, or **9** was carried out at atmospheric pressure in toluene solution over 10% $Pd/CaCO_3$. Compounds **3**, **8**, and **9a** were obtained in 95% yield. The hydrolysis of the ketal groups of compounds **8** and **9a** was carried out in boiling methanol containing some 10% hydrochloric acid. In both the cases compound **3** was obtained. Compound **9a** was identical in all respects with that described earlier.[1] Compound **8**: mp 161–162; NMR δ 1.1 (s, 3, CH_3), 3.8 (s, 3, CH_3O), 3.95 (s, 8, ketal groups), 6.7 (m, 2, at C-2 and C-4), 8.0 ppm (d, 1, at C-1); ir no C=O band.

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.35; H, 7.91.

11,11,17,17-Bis(ethylenedioxy)-3-methoxyestra-1,3,5(10),14-tetraene (7). To a solution of **6** (0.500 g, 1.24 mmol) in dry pyridine (5 ml), $SOCl_2$ (0.3 ml) was added at 0°. The mixture was stirred for 10 min at 0° and water (10 ml) was added dropwise. The crystalline product **7** was filtered off and washed with water and cold methanol: yield 0.43 g (90%); mp 151–153°; NMR δ 1.25 (s, 3, CH_3), 3.8–4.0 (m, 11, CH_3O and ketal groups), 5.4 (s, 1, at C-15), 6.72 (m, 2, at C-2 and C-4), 8.0 ppm (d, 1, at C-1).

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.69; H, 7.40.

3-Methoxy-14β-estra-1,3,5(10)-triene-11,17-dione (3) by Transformation of 10. The reduction of the 14(15) double bond of compound **10** was carried out under atmospheric pressure in toluene solution over 10% $Pd/CaCO_3$. The resulting saturated compound was hydrolyzed without isolation with 10% hydrochloric acid in a methanolic solution. Methanol and hydrochloric acid were removed and the residue was oxidized with Jones reagent[11] to compound **3**. Also the ketal group in compound **10** was hydrolyzed before the hydrogenation and the resulting compound **11** was hydrogenated without purification over 10% $Pd/CaCO_3$ in toluene solution. The crude product was oxidized by Jones reagent to the same compound **3**.

11,11-Ethylenedioxy-3-methoxyestra-1,3,5(10),14-tetraen-17-ol (10). To a solution of **9** (0.80 g, 2.2 mmol) in 20 ml of THF and 20 ml of methanol, $NaBH_4$ (0.050 g) was added at room tem-

perature. At the end of the reaction one-half of the solvent was evaporated under reduced pressure and the residue was diluted with water. The solid **10** was recrystallized from a mixture of benzene and hexane to give 0.60 g (74.5%) of **10**: mp 138–140°; NMR δ 1.1 (s, 3, CH_3), 3.8 (s, 3, CH_3O), 3.9 (m, 5, OCH_2CH_2O and at C-17), 5.25 (s, 1, at C-15), 6.7 (m, 2, at C-2 and C-4), 8.0 ppm (d, 1, J = 9 Hz, at C-1); ir 3550 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.50; H, 7.71.

9β,14β-Dihydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione (13). A mixture of CrO_3 (3 g, 30.0 mmol) and pyridine (4.75 g) in 60 ml of methylene chloride was stirred under reflux for 1 hr and compound **12** (1.00 g, 3.1 mmol) in 50 ml of methylene chloride was added. When the oxidation of **12** was complete (1 hr) the reaction mixture was filtered in order to remove the chromium salts and the last traces of them were removed by passing through a 5-cm layer of alumina. The solvent was evaporated and the residue was recrystallized from acetone–hexane mixture and gave 0.71 g (71.4%) of **13**: mp 201–203; NMR [$(CD_3)_2SO$] δ 1.0 (s, 3, CH_3), 3.82 (s, 3, CH_3O), 6.82 (m, 2, at C-2 and C-4), 7.12 ppm (d, 1, J = 9 Hz, at C-1); ir 1730, 3450 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.86; H, 6.76.

3-Methoxyestra-1,3,5(10),8(9),14-pentaene-11,17-dione (14). A mixture of **13** (0.500 g, 1.51 mmol) and p-toluenesulfonic acid (0.050 g) in 5 ml of acetic acid was heated under nitrogen up to 110° for 40 min. After cooling, the mixture was diluted with 5 ml of water, and the blue precipitate of **14** was filtered and washed with water and cold methanol. It was used without further purification for the hydrogenation: yield 0.39 g (87.5%); mp of crude 155–160°; uv max (95% EtOH) 255 nm (ϵ 12,000), 371 (5100); NMR δ 1.3 (s, 3, CH_3), 3.22 (2 d, 2, at C-16), 3.80 (s, 3, CH_3O), 6.3 (t, 1, at C-15), 6.75 (m, 2, at C-2 and C-4), 8.0 ppm (d, 1, at C-1).

14α-Hydroxy-3-methoxyestra-1,3,5(10),8(9)-tetraene-11,17-dione (15). A mixture of **13** (0.50 g, 1.51 mmol) and p-toluenesulfonic acid (0.050 g) in 5 ml of acetic acid was stirred at room temperature until the substrate **13** disappeared. Then it was diluted with water (5 ml). The precipitate **15** was filtered and washed with water and cold methanol. After recrystallization from ether 0.30 g (63.5%) of **15** was obtained. It was identical in all respects with the compound described earlier.[4] Compound **15** was also obtained by an oxidation of **16** with Jones reagent[11] which gave an 85% yield.

11β,14α-Dihydroxy-3-methoxyestra-1,3,5(10),8(9)-tetraen-17-one (16). To a solution of **12** (0.500 g, 1.50 mmol) in 5 ml of 90% ethanol, 0.05 g of p-toluenesulfonic acid was added at room temperature. After 2 hr the substrate **12** almost disappeared, and 2 ml of water was added. The precipitated **16** was filtered and was recrystallized from aqueous acetone: yield of **16** 0.30 g (63.5%); mp 185–196°; NMR (CD_3SOCD_3) δ 1.05 (s, 3, CH_3), 3.75 (s, 3, CH_3O), 4.34 (m, 1, at C-11), 6.7 (m, 2, at C-2 and C-4), 7.25 ppm (d, 1, J = 9 Hz, at C-1); ir 3350, 1730 cm^{-1}; uv max (95% EtOH) 276 nm (ϵ 16,000).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.62; H, 6.96.

3-Methoxyestra-1,3,5(10),8(9)-tetraene-11,17-dione (17). The hydrogenation of **14** (1.00 g, 3.4 mmol) was carried out under atmospheric pressure in a toluene solution using 1.00 g of 10% Pd/$CaCO_3$. When the hydrogen absorption ceased, the catalyst was removed by filtration and the toluene was evaporated under reduced pressure. Methanol (5 ml) was added to the residue, and the precipitate was filtered and washed with cold methanol. After drying it gave 0.80 g (80%) of the product **17**: mp 143–146°; NMR δ 0.97 (s, 3, CH_3), 3.77 (s, 3, CH_3O), 6.70 (m, 2, at C-2 and C-4), 7.84 ppm (d, 1, J = 9 Hz, at C-1); uv max (95% EtOH) 247 nm (ϵ 16,400), 287 (3730), 297 (3990), 322 (4170).

3-Methoxy-8α-estra-1,3,5(10)-triene-11,17-dione (18). The hydrogenation of **17** (0.500 g, 1.69 mmol) was carried out under atmospheric pressure in ethanol solution using 0.50 g of 10% Pd/$CaCO_3$. At the end of the reaction the catalyst and ethanol were removed and the residue was recrystallized from methanol to give 0.40 g (80%) of **18** which turned out to be identical in all respects with a sample kindly supplied by Professor H. Smith of Wyeth Laboratories.[6]

11β-Acetoxy-14α-hydroxy-3-methoxyestra-1,3,5(10),8(9)-tetraen-17-one (22). Method A. A solution of **16** (0.200 g, 0.638 mmol) in pyridine (2 ml) and acetic anhydride (2 ml) was allowed to stand overnight at room temperature and was evaporated under reduced pressure. The residue was dissolved in chloroform (10 ml) and was washed with water, then dried and evaporated to dryness. After recrystallization from an acetone–hexane mixture it gave 0.20 g (88%) of **22**: mp 180–190°; NMR δ 1.2 (s, 3, CH_3), 2.0 (s, 3, CH_3CO), 3.8 (s, 3, CH_3O), 5.75 (t, 1, at C-11), 6.8 ppm (m, 3, at C-1, C-2, and C-4); ir 3500, 1740, 1715 cm^{-1}; uv max (95% EtOH) 278 nm (ϵ 16,000).

Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.76; H, 6.79. Found: C, 70.69; H, 6.81.

Method B. A solution of **23** (0.500 g, 1.33 mmol) and p-toluenesulfonic acid (0.100 g) in 90% ethanol (10 ml) was allowed to stand at room temperature. After 2 hr the substrate disappeared, 2 ml of water was added, and the precipitated **22** (0.300 g, 63.2%) was filtered and recrystallized from an acetone–hexane mixture.

11β,14α-Dihydroxy-3-methoxy-8α-estra-1,3,5(10)-trien-17-one (24), 14α-Hydroxy-3-methoxyestra-1,3,5,6,8(9)-pentaen-17-one (25), and 14α-Hydroxy-3-methoxy-8α-estra-1,3,5(10)-trien-17-one (26). The hydrogenation of **16** (1.00 g, 1.32 mmol) was carried out under atmospheric pressure in ethanol over 1.0 g of 10% Pd/C. The reaction mixture was separated by column chromatography on silica gel 100–200 mesh using a mixture of hexane–ethyl acetate (2:1) as eluent. After chromatography three compounds, **24** (0.71 g), **25** (0.080 g), and **26** (0.070 g), were isolated. **24**: mp 158–160°; NMR δ 1.3 (s, 3, CH_3), 3.72 (s, 3, CH_3O), 4.12 (m, 1, at C-11), 6.65 (m, 2, at C-2 and C-4), 7.0 ppm (d, 1, J = 9 Hz, at C-1); ir 3500, 1730 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.07; H, 7.59.

25: mp 151–153°; NMR δ 1.1 (s, 3, CH_3), 3.9 (s, 3, CH_3O), 7.5 ppm (m, 5, at C-1, C-2, C-4, C-6, and C-7); ir 3500, 1725 cm^{-1}; uv max (95% EtOH) 267 nm (ϵ 5180), 278 (5290), 287 (3460), 319 (1235), 333 (1630); mass spectrum m/e 296. **26**: mp 145–149°; NMR δ 1.1 (s, 3, CH_3), 3.8 (s, 3, CH_3O), 6.75 (m, 3, at C-2 and C-4), 7.12 ppm (d, 1, J = 8 Hz, at C-1); ir 3550, 1735 cm^{-1}; uv max (95% EtOH) 279 nm (ϵ 2180), 287 (1920); mass spectrum m/e 300.

14α-Hydroxy-3-methoxy-8α-estra-1,3,5(10)-triene-11,17-dione (27). Compound **27** was obtained by an oxidation of **24** with Jones reagent[11] using the standard procedure. It was identical in all respects with the compound described earlier.[10]

11β-Acetoxy-14α-hydroxy-3-methoxy-8α-estra-1,3,5(10)-trien-17-one (28). A mixture of **24** (0.500 g, 1.58 mmol), pyridine, and acetic acid anhydride (2 ml) was refluxed for 1 hr, during which the substrate disappeared. Then water (5 ml) was added, and the precipitated **28** was filtered and recrystallized from ether. The yield of **28** was 0.49 g (86.5%): mp 193–195°; NMR δ 1.3 (s, 3, CH_3), 1.8 (s, 3, CH_3CO), 3.8 (s, 3, CH_3O), 5.38 (q, 1, at C-11), 6.7 (m, 2, at C-2 and C-4), 7.1 ppm (d, 1, J = 9 Hz, at C-1); ir 3450, 1730, 1710 cm^{-1}.

Anal Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.10; H, 7.23.

11β-Acetoxy-3-methoxy-8α-estra-1,3,5(10),14-tetraen-17-one (29). To a solution of **28** (0.250 g, 0.70 mmol) in pyridine (2 ml), 2 drops of $SOCl_2$ was added at 0°. When the substrate disappeared, water (3 ml) was added, and the precipitated **29** was filtered and recrystallized from methanol. The yield of **29** was 0.220 g (93%): mp 143–144°; NMR δ 1.4 (s, 3, CH_3), 1.78 (s, 3, CH_3CO), 3.8 (s, 3, CH_3O), 5.58 (q, 1, at C-11), 5.9 (t, 1, at C-15), 6.75 (m, 2, at C-2 and C-4), 7.1 ppm (d, 1, J = 8.5 Hz, at C-1); ir 1735 cm^{-1}.

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.97; H, 7.23.

11,11,17,17-Bis(ethylenedioxy)-3-methoxyestra-2,5(10)-dien-14β-ol (30). A solution of **6** (1.00 g, 2.49 mmol) in *tert*-butyl alcohol (15 ml) and THF (30 ml) was added to liquid ammonia (200 ml) and 1.0 g of metallic sodium was added in small portions. After 4 hr the solution was treated with methanol until a disappearence of blue color and 3 g of NH_4Cl was added. Ammonia was allowed to evaporate, water (100 ml) was added, and the solvents, THF, *tert*-butyl alcohol, and some water, were distilled off under reduced pressure. The precipitated **30** was filtered and was washed with water and methanol. The yield of **30** was 0.925 g (92.5%): mp of crude product 193–203°; ir 3500 cm^{-1}; NMR δ 1.05 (s, 3, CH_3), 3.55 (s, 3, CH_3O), 4.0 (m, 8, OCH_2CH_2O), 4.62 ppm (t, 1, at C-2).

14β-Hydroxyestra-4-ene-3,11,17-trione (31). A solution of **30** (0.800 g, 1.98 mmol) in methanol (50 ml) and 10% HCl (5 ml) was refluxed for 0.5 hr and methanol was evaporated under reduced pressure. The precipitated **31** was filtered and was washed with water. It was recrystallized from acetone–hexane mixture and gave 0.480 g (80%) of **31**: mp 205–207°; NMR δ 1.05 (s, 3, CH_3), 5.82 ppm (s, 1, at C-4); ir 3450, 1730, 1710, 1660, 1620 cm^{-1}; uv max (95% EtOH) 240 nm (ϵ 14,000).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.25; H, 7.54.

Estra-4,14-diene-3,11,17-trione (32). To a solution of **31** (0.400 g, 1.32 mmol) in dry pyridine, $SOCl_2$ (0.1 ml) was added at −10°. The mixture was stirred at this temperature for 10 min and water (5 ml) was added. The solvent was evaporated to dryness under reduced pressure and the crystalline **32** was washed with water and recrystallized from benzene–hexane mixture. The yield of **32** was 0.300 g (80%): mp 130–132°; NMR δ 1.13 (s, 3, CH_3). 3.1 (s, 2, at C-16), 5.9 ppm (s, 2, at C-4 and C-15); ir 1740, 1705, 1660, 1625 cm^{-1}; uv max (95% EtOH) 238 nm (ε 16,500).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.93; H, 7.15.

14β-Estra-4-ene-3,11,17-trione (34). The diketal **8** was reduced by the Birch method by the procedure used in the case of compound **30.** The intermediate **33** was not isolated in pure form, but was hydrolyzed to compound **34** in methanol containing some 10% hydrochloric acid. The yield of **34** was 85%: mp 173–175°; NMR δ 1.18 (s, 3, CH_3), 5.9 ppm (s, 1, at C-4); ir 1730, 1700, 1660, 1620 cm^{-1}; uv max (95% EtOH) 239 nm (ε 16,000).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.38; H, 7.82.

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Registry No.—**1,** 55923-94-9; **2,** 55871-06-2; **3,** 55903-62-3; **6,** 55903-63-4; **7,** 55925-20-7; **8,** 55871-07-3; **9,** 55903-64-5; **10,** 55903-65-6; **12,** 55871-08-4; **13,** 55871-09-5; **14,** 55871-10-8; **15,** 55871-11-9; **16,** 55871-12-0; **17,** 24510-25-6; **18,** 24510-29-0; **22,** 55871-13-1; **23,** 55871-14-2; **24,** 55871-15-3; **25,** 55871-16-4; **26,** 55903-66-7; **28,** 55871-17-5; **29,** 55871-18-6; **30,** 55871-19-7; **31,** 55871-20-0; **32,** 55871-21-1; **34,** 55903-67-8.

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(14) All the compounds were obtained as racemates and for the sake of simplicity, prefixes *dl* or *rac* have been omitted. For the preparation of optically active compounds see part VIII, *J. Org. Chem.*, **40,** 3135 (1975). Compounds **1, 6, 9,** and **12** were obtained according to procedures described in ref 1.

Total Synthesis of Steroids. IX.[1] Synthesis of 11-Oxidized 19-Norandrostanes

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Reactions of *rac*-3-methoxy-14α-hydroxy-8α-estra-1,3,5(10)-triene-11,17-dione (**1a**) leading to *rac*-11-keto-8,14-bisdehydroestradiol 3-methyl ether (**20**) and analogous compounds are described. The Birch reduction of **20** followed by hydrolysis and Jones oxidation produced *rac*-19-norandrost-4-ene-3,11,17-trione (**22**), having the natural geometry at all chiral centers.

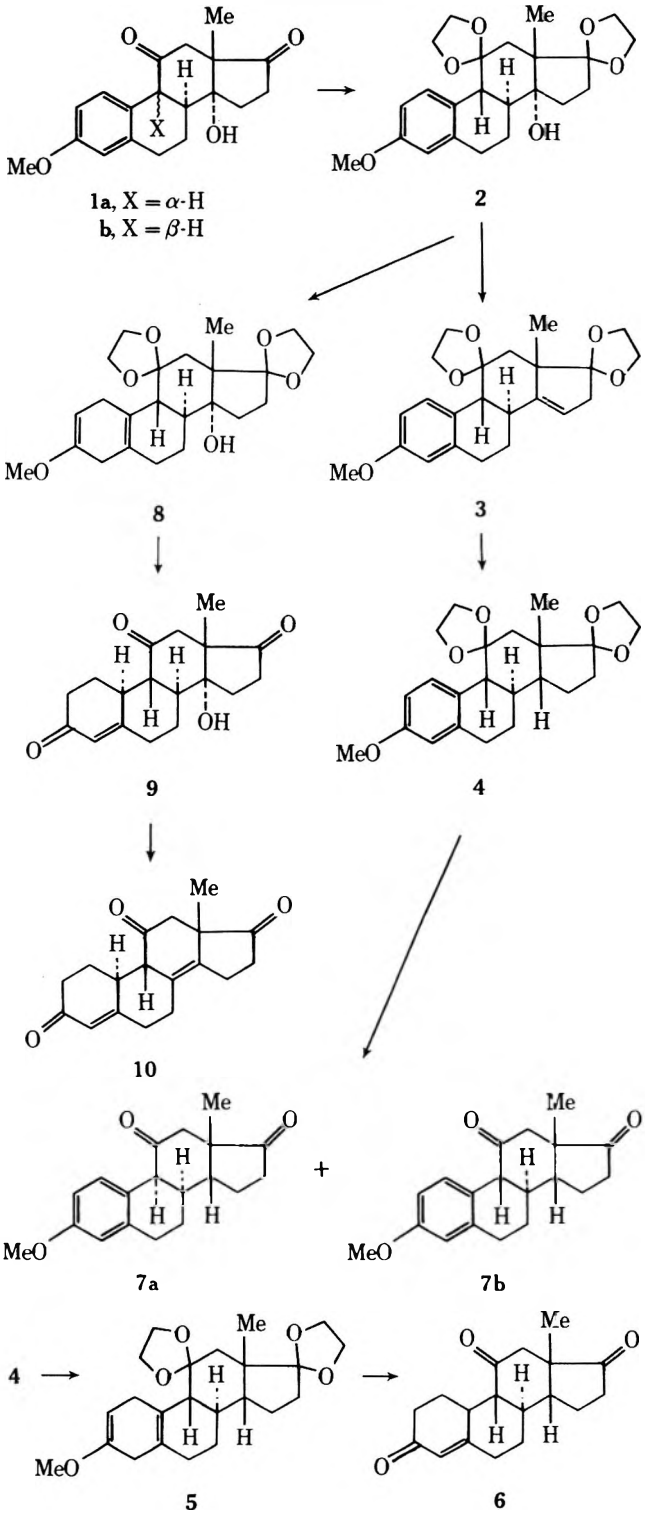
The total synthesis of a mixture of *rac*-3-methoxy-14α-hydroxy-8α-estra-1,3,5(10)-triene-11,17-dione (**1a**) and its epimer **1b** was described earlier.[2] This mixture gave on ketalization a single diketal **2** (Scheme I), whose further transformations are the subject of our present communication.

The diketal **2** was dehydrated with thionyl chloride in pyridine to form the unsaturated intermediate **3,** which was subsequently catalytically hydrogenated to the saturated diketal **4.** The latter compound was then reduced by the Birch method and yielded on hydrolysis the 19-norsteroid **6** with cis geometry of C/D ring junction. Acid hydrolysis of the diketal **4** afforded an unseparable mixture of diketones **7a** and **7b** epimeric at C-9. Birch reduction of the diketal **2,** followed by acid hydrolysis produced the 19-nor compound **9,** which was dehydrated to the diene trione **10.**

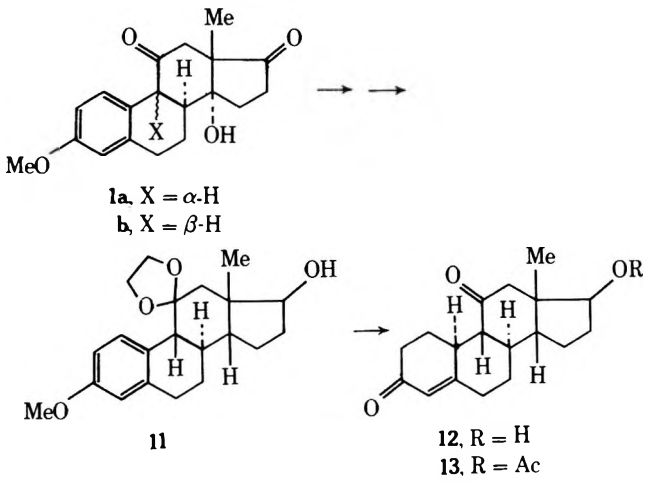
The synthesis of the 17-hydroxy 19-norsteroid **12** was achieved by Birch reduction, followed by acid treatment, of the monohydroxy ketal **11** (Scheme II); the latter compound has been prepared from the diketal **2** as described before.[2] In all cases of Birch reduction described above and below, a new chiral center was created at carbon 10. According to the literature,[3] such a reduction of the aromatic A ring, followed by acid hydrolysis of the enol ether groups, leads predominantly to products with trans geometry of the hydrogen at C-10 with respect to H-9; consequently the compound **6** is a racemic mixture of 13-isoestranes (or 19-nor-13-isoandrostanes, respectively), and therefore compounds **9, 10,** and **12** have also the geometry as presented.

In order to secure the possibility of changing the configuration at carbon atoms 8 and 9, we attempted the introduction of the double bond at the B/C ring junction. In fact, dehydrogenation of **1a,b** with DDQ gave the desired compound[4] **15** (Scheme III), but only in poor yield (22%); the main reaction product was a 8,14-seco compound, **16.** This disappointing result can be explained in the following way. As is known from the literature,[5] the DDQ dehydrogenation of saturated ketones consists of β-axial hydride ion abstraction from the ketone enolate, followed by the stabilization of the intermediate carbonium ion by reorganization of electrons to α,β-unsaturated ketone. In our case, however, the intermediate carbonium ion **14** formed from the enolate **1c** can stabilize in two competing ways, a and b, as depicted in Scheme III. The tricyclic compound **16** was re-

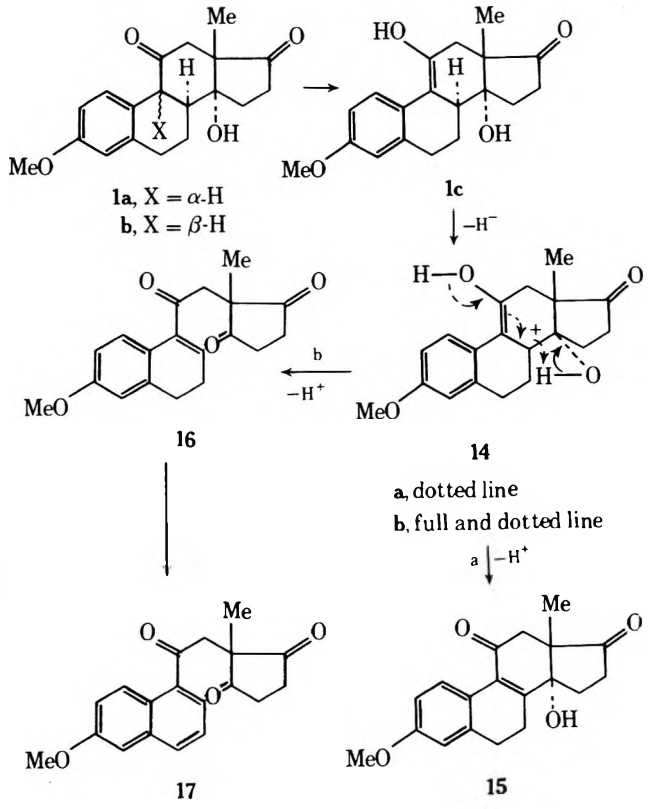
Scheme I



Scheme II



Scheme III



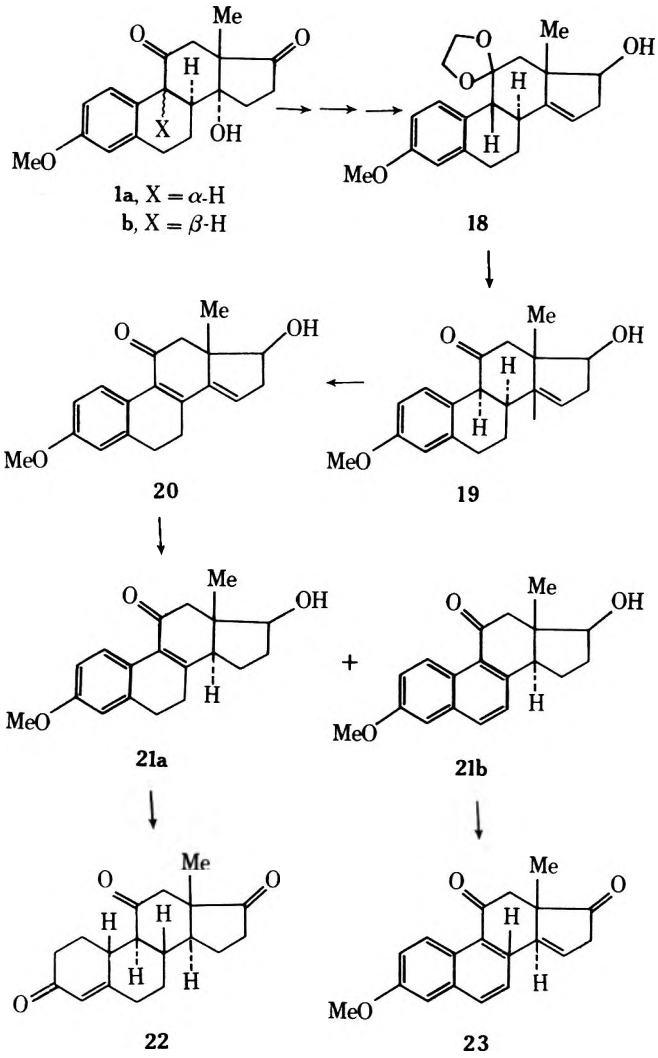
cently described by Harnik et al.[6] The reaction proceeds apparently toward the more favored, sterically less strained product **16**. We also observed in a separate experiment that the rate of the dehydrogenation reaction of compound **1a** is much higher than that of **1b**. This is caused by the tendency to remove the strong 1,4 interaction between H-9 and the angular methyl group in the C ring which must assume in **1a** the boat conformation.

All attempts to cyclize the compound **16** failed; its structure was additionally proved by dehydrogenation to the naphthalene derivative **17**, obtained also in our laboratory earlier.[7]

A better approach to the compounds with natural geometry at chiral centers 8 and 9 is presented in Scheme IV. Acid hydrolysis of the 17-hydroxy ketal[2] **18** yielded the hydroxy ketone **19**, which according to its ^{1}H NMR spectrum has cis B/C ring junction, and which smoothly underwent the dehydrogenation with DDQ to the pentaene **20** in good yield. This compound gave on catalytic reduction a mixture of two products: the main product was the desired tetraene **21a** (68.2%), with trans C/D ring junction, and the minor one appeared to be 11-oxo-17-dihydroequilenin methyl ether (**21b**). Its structure was confirmed by the oxidation to the known 11-oxoequilenin methyl ether[8,9] (**23**).

The tetraene **21a** was reduced according to Birch[10] and Smith[11] to 11-oxoestradiol methyl ether; however, yields were not satisfactory. Therefore we carried out the Birch reduction to its completion (the styrenic double bond and the aromatic system); upon hydrolysis and Jones oxidation of the hydroxyl at C-17, we obtained compound **22**, *rac*-19-norandrost-4-ene-3,11,17-trione, in good overall yield. The spectral and analytical data of **22** were identical with

Scheme IV



those described in the literature.[12] The direct comparison of the melting points and ir spectra with those of an authentic sample kindly supplied by H. Smith confirmed the structure of **22**.

Further work on the synthesis of optically active compounds of this series is in progress.

Experimental Section[13,14]

3-Methoxy-11,11,17,17-bis(ethylenedioxy)-8α,9β-estra-1,3,5(10),14-tetraene (3). The solution of 2.5 g (6.2 mmol) of the hydroxy diketal[2] **2** in 50 ml of pyridine was treated with 0.5 ml of thionyl chloride and allowed to stand for 20 min at room temperature. The reaction mixture was then poured into 1 l. of cold water, and the precipitate was filtered and dried, giving 2.3 g (96%) of **3**: mp 146–148° (from MeOH); ^{1}H NMR 1.38 (s, 3, CH_3), 3.85 (s, 3, OCH_3), 4.00 (s, 4, OCH_2CH_2O at C-17), 5.55 (s, 1, H-15), 6.75 (m, 2, H-2 and H-4), 7.45 ppm (d, 1, J = 9 Hz, H-1).

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.82; H, 7.30.

3-Methoxy-11,11,17,17-bis(ethylenedioxy)-8α,9β,14β-estra-1,3,5(10)-triene (4). The solution of 1.0 g (2.61 mmol) of compound **3** in 100 ml of toluene was hydrogenated at room temperature in the presence of 1 g of 10% Pd/$CaCO_3$ catalyst. The equimolar amount of hydrogen was consumed within 4 hr, and the reaction mixture was worked up in the standard manner, giving 1 g (quantitative yield) of the diketal **4**: mp 154–155° (from benzene–hexane); ^{1}H NMR 1.22 (s, 3, CH_3), 3.88 (s, 3, OCH_3), 4.00 (s, 4, OCH_2CH_2O at C-17), 6.75 (m, 2, H-2 and H-4), 7.5 ppm (d, 1, J = 9 Hz, H-1).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.09; H, 7.72.

13α-Estra-4-ene-3,11,17-trione (6). Metallic sodium (3 g) was added in small portions to the solution of 1 g (2.6 mmol) of the diketal **4** in 20 ml of THF and t-BuOH (3:1) and 200 ml of liquid ammonia. After 3 hr the solution was decolorized by addition of some methanol, and subsequently 7 g of NH_4Cl was added. Ammonia was evaporated, the residual solution was diluted with 100 ml of water, a portion of organic solvents was removed in vacuo, and the remaining solution was extracted with chloroform. The organic solution was evaporated in vacuo after drying with anhydrous $MgSO_4$, leaving ca. 1 g of an oil, which was then treated at room temperature with 5 ml of 3 N HCl in 50 ml of methanol. After 2 hr the solution was worked up in the usual way, giving 0.6 g (82%) of **6**: mp 185–190° (from MeOH); uv max (95% EtOH) 240 nm (ε 16,600); ir 1740 (CO at C-17), 1720 (CO at C-11), and 1670 cm^{-1} (CO at C-3); ^{1}H NMR 1.22 (s, 3, CH_3), 5.98 ppm (s, 1, H-4).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.59; H, 7.84.

3-Methoxy-8α,14β-estra-1,3,5(10)-triene-11,17-dione (7a) and 3-Methoxy-8α,9β,14β-estra-1,3,5(10)-triene-11,17-dione (7b). The solution of 0.5 g (1.3 mmol) of the diketal **4** in 100 ml of methanol and 0.5 ml of 10% HCl was refluxed for 2 hr. The reaction solution was then worked up in the usual manner, and 0.33 g (86%) of the oily mixture of **7a** and **7b** was obtained. All attempts to separate the epimers by chromatography failed: uv max (95% EtOH) 278 nm (ε 1980) and 285 (1800); ir (film) 1740 (CO at C-17), 1720 cm^{-1} (CO at C-11); ^{1}H NMR 1.15 and 1.20 (2 s, CH_3), 3.60 (d, $J_{9,8}$ = 10 Hz, H-9 in **7b**), 3.82 (s. 3, OCH_3), 3.90 (d, $J_{9,8}$ = 6 Hz, H-9 in **7a**), 6.8 (m, H-2, H-4, and H-1 from **7a**), 7.2 ppm (d, H-1 from **7b**).

3-Methoxy-14α-hydroxy-11,11,17,17-bis(ethylenedioxy)-8α,9β-estra-2,5(10)-diene (8). The solution of 0.95 g (2.4 mmol) of the diketal[2] **2** in 30 ml of THF–t-BuOH mixture (3:1) and 150 ml of liquid ammonia was treated portionwise with 3 g of metallic sodium. After ½ hr the solution was worked up in the standard manner, giving 0.88 g (93%) of **8**: mp 159–161° (from MeOH); ir 3520 cm^{-1} (OH); ^{1}H NMR 1.12 (s, 3, CH_3), 3.60 (s, 3, OCH_3), 3.95 (s, 8, OCH_2CH_2O), 4.80 ppm (s, 1, H-2).

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.60; H, 8.20.

14α-Hydroxy-8α,9β,10α-estra-4-ene-3,11,17-trione (9). Compound **8** was refluxed with 3 N HCl in methanol for 1 hr, giving in almost quantitative yield the product **9**: mp 208–209° (from benzene); uv max (95% EtOH) 241 nm (ε 16,350); ir 3400 (OH), 1740 (CO at C-17), 1720 (CO at C-11), 1660 cm^{-1} (CO at C-3); ^{1}H NMR 1.20 (s, 3, CH_3), 5.95 ppm (s, 1, H-4).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 72.01; H, 7.17.

9β,10α-Estra-4,8(14)-diene-3,11,17-trione (10). A solution of 0.4 g (1.3 mmol) of compound **9** in 20 ml of pyridine was dehydrated with thionyl chloride at −70°, giving 0.35 g (95%) of **10**: mp 180–183° (from MeOH); uv max (95% EtOH) 233 nm (ε 13,900); ir 1740 (CO at C-17), 1700 (CO at C-11), and 1670 cm^{-1} (CO at C-3); ^{1}H NMR 1.13 (s, 3, CH_3), 5.90 ppm (s, 1, H-4).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.09; H, 7.09.

17α-Acetoxy-13α-estra-4-ene-3,11-dione (13). The hydroxy ketal **11** (0.1 g, 0.3 mmol) was reduced with sodium in liquid ammonia as above, and 0.075 g (89%) of oily **12** was obtained. This oil was acetylated with acetic anhydride in pyridine and after the normal work-up 0.084 g (98%) of the acetate **13** was obtained: mp 153–156° (from MeOH); uv max (95% EtOH) 240 nm (ε 16,840); ir 1735 (CO from acetate), 1700 (CO at C-11), 1660 (CO at C-3), and 1620 cm^{-1} (C=C); ^{1}H NMR 1.1 (s, 3, CH_3), 2.0 (s, 3, CH_3COO), 4.8 (t, 1, H-17), 5.9 ppm (s, 1, H-4).

Anal. Calcd for $C_{20}H_{27}O_4$: C, 72.70; H, 7.93. Found: C, 72.47; H, 8.07.

3-Methoxy-14α-hydroxyestra-1,3,5(10),8(9)-tetraene-11,17-dione (15) and 3-Methoxy-8,14-secoestra-1,3,5(10),8-tetraene-11,14,17-trione (16). The solution of **1a** or **1b** or a mixture of **1a,b** (1 g, 3.2 mmol) and 0.76 g (3.3 mmol) of dichlorodicyano-p-benzoquinone (DDQ) in 50 ml of benzene was refluxed for 5 hr. The precipitated hydroquinone (0.75 g, quantitative yield) was then filtered off, and the filtrate was evaporated in vacuo, dissolved in 25 ml of methylene chloride, and washed several times with 10% aqueous NaOH and then with water. The organic layer was then dried with anhydrous $MgSO_4$ and filtered and the solvent was evaporated in vacuo. The residue was treated with 10 ml of ether and compound **15** (0.22 g, 22%) precipitated: mp 205–235° dec; uv max (95% EtOH) 203 nm (ε 33,200), 246 (14,650), 287 (3470), 297 (4010) and 318 (4550); ir 3500 (OH), 1740 (CO at C-17), 1650 cm^{-1} (CO at C-11).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.80; H, 6.38.

The filtrate was evaporated and the residue was crystallized from methanol, giving 0.73 g (74%) of **16**: mp of dried sample 112–116° (lit.[6] mp 76–86° solvated and 118–122° after drying in vacuo at 70°); uv max (95% EtOH) 204 nm (ε 29,600), 247 (14,350), 289 (4040), 313 (3210); ir 1720 (CO at C-14 and C-17), 1650 cm^{-1} (CO at C-11); ^1H NMR (of the MeOH solvate) 1.18 (s, 3, CH_3), 3.01 (d, 4, 2 H-15 and 2 H-16), 3.5 (s, CH_3OH), 3.65 (s, 2, 2 H-12), 3.88 (s, 3, OCH_3), 6.73 (m, 2, H-2 and H-4), 7.05 (t, 1, H-8), 7.55 ppm (d, 1, J = 9 Hz, H-1).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.42; H, 6.53.

3-Methoxy-8,14-secoestra-1,3,5,6,8-pentaene-11,14,17-trione (17). Compound **16** (0.5 g, 1.6 mmol) was dehydrogenated with 0.36 g (1.6 mmol) of DDQ in the manner described above, giving after standard work-up 0.45 g (90%) of compound **17**, mp 115° (from ether), spectrally identical with compound prepared earlier.[7]

3-Methoxy-17β-hydroxy-8α-estra-1,3,5(10),14(15)-tetraen-11-one (19). The solution of hydroxy monoketal[2] **18** (1 g, 2.9 mmol) in 100 ml of methanol and 10 ml of 10% aqueous HCl was left at room temperature for 2 hr. Standard work-up yielded 0.83 g (95%) of **17** as an oil: ir 3500 (OH) and 1710 cm^{-1} (CO at C-11); ^1H NMR 1.0 (s, 3, CH_3), 3.4 (s, 3, OCH_3), 4.0 (t, 1, H-17), 5.2 (s, 1, H-15), 6.75 ppm (m, 3, H-1, H-2, H-4).

3-Methoxy-17β-hydroxyestra-1,3,5(10),8,14-pentaen-11-one (20). Dehydrogenation of **19** (0.8 g, 2.7 mmol) with DDQ (0.61 g, 2.7 mmol) was carried out in the manner described above, giving 0.75 g (95%) of **20**: mp 134–137°; ir 3400 (OH) and 1650 cm^{-1} (CO); uv max (95% EtOH) 264 nm (ε 21,000) and 358 (11,500); ^1H NMR 1.1 (s, 3, CH_3), 3.78 (s, 3, OCH_3), 4.2 (t, 1, H-17), 5.92 (s, 1, H-15), 6.72 (m, 2, H-2 and H-4), 8.02 ppm (d, 1, J = 9 Hz, H-1).

3-Methoxy-17β-hydroxyestra-1,3,5(10),8(9)-tetraen-11-one (21a) and 3-Methoxy-17β-hydroxyestra-1,3,5,6,8(9)-pentaen-11-one (21b). The solution of **20** (0.7 g, 2.36 mmol) in 100 ml of toluene was hydrogenated in the presence of 0.7 g of 10% Pd/$CaCO_3$ in the manner described above, giving 0.67 g (96%) of crystals, which were a mixture of **21a** and **21b**. After chromatography on 70 g of silica gel with hexane–ethyl acetate (3:1) as eluents we obtained (a) 0.16 g (22.8%) of **21b** [mp 194–198° (from ether); uv max (95% EtOH) 249 nm (ε 23,900), 322 (4700), and 357 (3590); ir 3450 (OH), 1650 (CO), and 1620 cm^{-1} (C=C); ^1H NMR 0.8 (s, 3, CH_3), 3.9 (s, 3, OCH_3), 4.1 (t, 1, H-17), 7.12 (m, 4, H-2, H-4, H-6, H-7), and 7.9 ppm (d, 1, J = 9 Hz, H-1); *m/e* 296], and (b) 0.48 g (68.2%) of **21a** [mp 196–203° (from ether); uv max (95% EtOH) 248 nm (ε 16,850); ir 3420 (OH), 1640 cm^{-1} (CO); ^1H NMR 0.88 (s, 3, CH_3), 3.75 (s, 3, OCH_3), 3.98 (t, 1, H-17), 6.7 (m, 2, H-2 and H-4) and 7.95 ppm (d, 1, J = 9 Hz, H-1); *m/e* 298].

Estra-4-ene-3,11,17-trione (22). The compound **21a** (0.2 g, 0.67 mmol) was reduced with sodium in liquid ammonia in the manner described above, and then oxidized carefully by Jones reagent. The product was separated by TLC using a mixture of benzene–methanol–acetone (9:1:1) as eluent to give 0.090 g (50%) of **22**: mp 180–185°; uv max (95% EtOH) 240 nm (ε 12,600); ir 1740, 1720, 1660, and 1620 cm^{-1}; ^1H NMR 0.9 (s, 3, CH_3) and 5.85 ppm (s, 1, H-4) [lit.[12] mp 185–189°; uv max 239 nm (ε 14,300); ir 1740, 1720, 1660, and 1620 cm^{-1}].

3-Methoxyestra-1,3,5,6,8(9)-pentaene-11,17-dione (23). Compound **21b** (0.1 g, 0.34 mmol) was oxidized with Jones reagent, giving 0.070 g (77.5%) of **23**: mp 218–221° (from MeOH) (lit.[8] mp 224°, lit.[9] mp 195–196°); uv max (95% EtOH) 250 nm (ε 27,000), 320 (6460), and 361 (3660) [lit.[9] 245 nm (ε 13,500), 315 (2500)]; ir 1730, 1670, and 1620 cm^{-1}; ^1H NMR (CD_3COCD_3) 0.8 (s, 3, CH_3), 3.9 (s, 3, OCH_3), 7.3 (m, 4, H-2, H-4, H-6, H-7), and 8.1 ppm (d, 1, J = 9 Hz, H-1).

Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.19; H, 6.16.

Registry No.—**1a**, 51606-68-9; **1b**, 51606-67-8; **2**, 51510-11-3; **3**, 51510-17-9; **4**, 55903-69-0; **6**, 55903-70-3; **7a**, 55903-71-4; **7b**, 55903-72-5; **8**, 55903-73-6; **9**, 55903-74-7; **10**, 55871-48-2; **11**, 51510-15-7; **12**, 55871-49-3; **13**, 55871-50-6; **15**, 55871-11-9; **16**, 51270-60-1; **17**, 41021-02-7; **18**, 51510-14-6; **19**, 55871-51-7; **20**, 55871-61-9; **21a**, 18656-76-3; **21b**, 55903-75-8; **22**, 21317-72-6; **23**, 16373-41-4.

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(13) Melting points were measured on a micro hot plate, and are not corrected. Ir spectra were determined in KBr tablets with an Infracord instrument, and ^1H NMR spectra were measured with a Jeol 100-MHz spectrometer in $CDCl_3$ solution (accuracy ±0.5 Hz) and are given in δ values. The microanalyses were performed in our microanalytical laboratory (head Z. Celler, M.S.).
(14) All compounds were obtained as racemates and for the sake of simplicity the prefixes (*dl* or *rac*, respectively) have been omitted.

Notes

Total Synthesis of Steroids. VIII. Synthesis of Optically Active 19-Norsteroids Oxidized in Position 11

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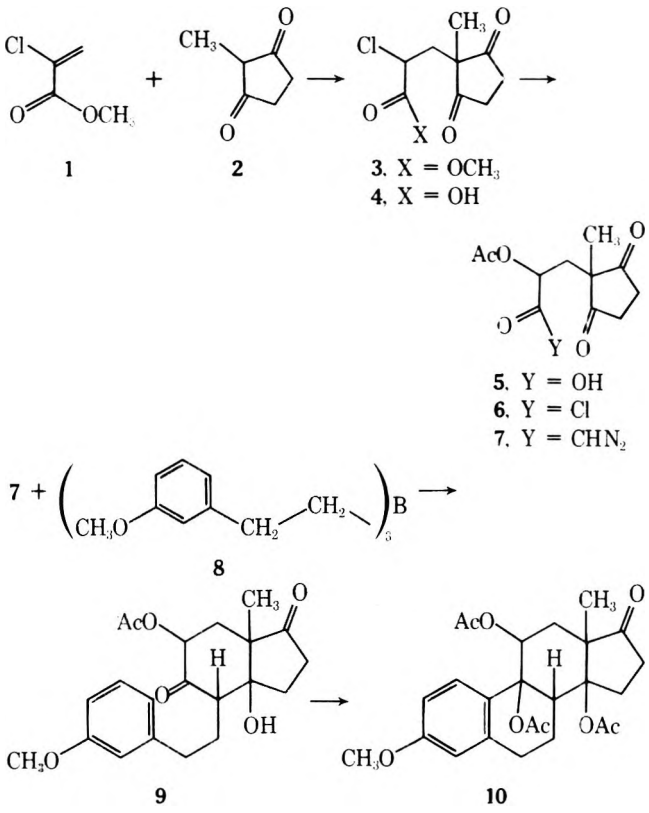
The total synthesis of 11-oxidized *rac*-19-norsteroids was recently described.[1-3] One of the substrates in that work was *rac*-2-methyl-2-(β-acetoxy-β-carboxyethyl)cyclopentane-1,3-dione (**5**) (Scheme I). In the present paper we report resolution of the compound **5** into enantiomers by means of α-phenylethylamine as a resolving agent. When the synthesis was carried out with optically pure acid **5**, optically pure steroids were obtained.

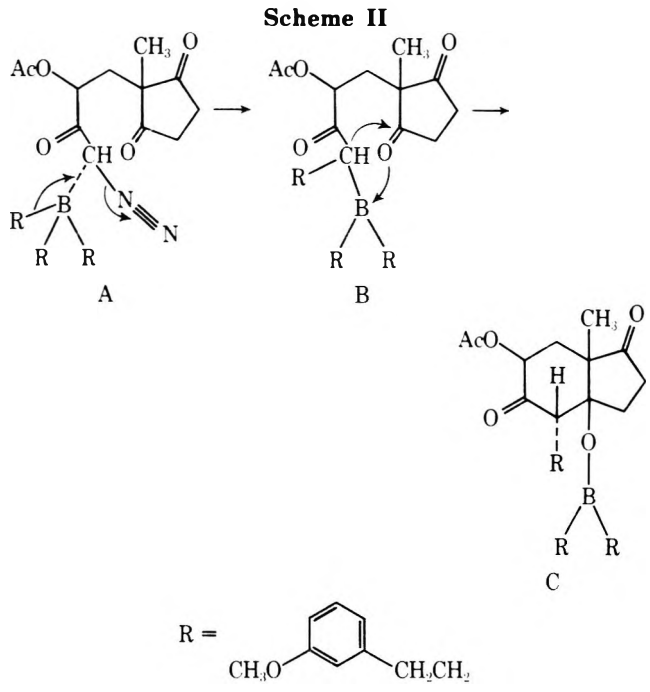
Scheme I



In the case of racemic acid **5** the seco compound **9** was obtained in crystalline form but when the starting acid **5** was optically active, the seco compound was an oil. The optical purity of triacetate **10** was determined by examination of the NMR spectrum of its mixture with tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium. In the NMR spectrum of the racemic triacetate **10** containing the chiral europium complex, the signals of protons of the angular methyl group as well as those of the two acetoxy groups appeared as doublets. In the case of optically active triacetate **10** the corresponding signals in the NMR spectrum of **10** containing the chiral europium complex were shifted but appeared as singlets. The optical purity of the triacetate **10** was at least 95%, which indicates that the asymmetric induction of the creation of new chiral centers was also 95%. The (−) diazo ketone **7** and then the (+) triacetate **10** were obtained from the (−) acid **5**. The (+) triacetate **10** was transformed by known[2] reactions to (+)-3-methoxy-14β-estra-1,3,5(10)-trien-17-one, the specific rotation of which was identical with the reported value.[4] Since the structure of triacetate **10** is known, it was possible to ascertain that the acid **5** with negative specific rotation has the *S* configuration and is a precursor of steroids with the natural configuration at the chiral centers.

In addition to the preceding papers[1-3] we would like to suggest a reaction mechanism for the reaction of diazo ketone **7** with the boron compound **8** which leads to tricyclic secodione **9**. As the first step we propose the formation of complex A, which rearranges stereospecifically with elimination of molecular nitrogen to intermediate B. (Scheme II). The latter undergoes cyclization to the next intermediate C, which under hydrolytic conditions is converted to secodione **9**. The boron compound **8** attacks diazo ketone **7** only from the less hindered side (opposite to the acetoxy group); thus a new chiral center is formed at the 8 carbon atom of compound **9**. The next step is most probably a concerted and stereospecific 1,2 shift of one phenylethyl group, accompanied by nitrogen elimination. The intermediate B thus formed undergoes further rearrangement owing to complexing of boron by the carbonyl oxygen, which is the driving force for the cyclization to intermediate C in a stereospecific manner.

Scheme II



Experimental Section

2-Methyl-2-(β-carbomethoxy-β-chloroethyl)cyclopentane-1,3-dione[6] (3). A solution of 2-methylcyclopentane-1,3-dione (2, 16.8 g, 0.15 mol) and 2.0 g of KOH in 150 ml of methanol and methyl α-chloroacrylate (1, 12 g, 0.1 mol) was refluxed for 12 hr under nitrogen. Methanol was distilled off, and 100 ml of benzene was added to the residue. The unreacted 2-methylcyclopentane-

1,3-dione (2, 6 g) was filtered off and the filtrate after distillation in vacuo afforded 18.6 g (80%) of 3: bp 100° (0.14 mmHg); mp 48–49.5°; NMR δ 1.17 (s, 3, CH_3), 2.36 (d, 2, CH_2), 2.77 (s, 4, CH_2CH_2), 3.67 (s, 3, CH_3O), 4.30 ppm (t, 1, CHCl).

Anal. Calcd for $C_{10}H_{13}ClO_4$: C, 51.65; H, 5.60. Found: C, 51.49; H, 5.61.

2-Methyl-2-(β-carboxy-β-chloroethyl)cyclopentane-1,3-dione[6] (4). A mixture of compound 3, (23.3 g, 0.1 mol) and 50 ml of concentrated hydrochloric acid was heated under reflux for 0.5 hr and then 10 ml of the acid was distilled off. Compound 4 crystallized out upon cooling; it was filtered and washed with 20 ml of ice-water. The product was dried in air: yield 17.5 g (80%); mp 117–119°; NMR δ 1.15 (s, 3, CH_3), 2.46 (d, 2, CH_2), 2.80 (s, 4, CH_2CH_2), 4.40 ppm (t, 1, CHCl).

Anal. Calcd for $C_9H_{11}ClO_4$: C, 49.6; H, 5.04. Found: C, 50.08; H, 5.09.

2-Methyl-2-(β-carboxy-β-acetoxyethyl)cyclopentane-1,3-dione (5). Compound 4 (21.85 g, 0.1 mol) was dissolved in an aqueous solution of 16.8 g (0.20 mol) of sodium bicarbonate and the mixture was refluxed for about 2 hr until all the substrate disappeared (checked by TLC). Then the solution was evaporated and the residue was treated with 60 ml of acetic acid and 15 ml of acetic anhydride. The mixture was refluxed for about 0.4 hr to convert the hydroxy acid completely into the acetoxy acid 5. Then the acetic acid was almost completely removed by distillation under reduced pressure and the residue was treated with 100 ml of acetone and 10 ml of concentrated hydrochloric acid. Sodium chloride was filtered off and the acetone was evaporated in order to reduce the volume of the solution to about 50 ml. Then 50 ml of benzene was added, and the crystals of acetoxy acid 5 were filtered off and recrystallized from a mixture of benzene and acetone. The pure product melted at 162–163°: yield 20.6 g (85%); NMR δ 1.15 (s, 3, CH_3), 2.03 (s, 3, CH_3CO), 2.33 (d, 2, CH_2), 2.77 (s, 4, CH_2CH_2), 4.97 ppm (t, 1, CH).

Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.5; H, 5.78. Found: C, 54.8; H, 5.80.

(−)-S-2-Methyl-2-(β-carboxy-β-acetoxyethyl)cyclopentane-1,3-dione (5). The solution of (−)-α-phenylethylamine (35.5 g, 0.293 mol) in ethanol (100 ml) was mixed with the solution of racemic acetoxy acid 5 (71.0 g, 0.293 mol) in 400 ml of ethanol and allowed to crystallize in the cold for 3 hr. The crystalline precipitate was recrystallized twice from ethanol (130 ml), yielding 33.0 g (62%) of the salt. The free (−) acid 5 was obtained by stirring the methanolic solution of salt with Dowex 50W, filtering off the resin, and concentrating the filtrate to afford 22.0 g of pure (−) acetoxy acid 5: mp 139–141°; $[\alpha]^{18}D$ −16.15° (c 9.5, MeOH).

Acid Chloride of 2-Methyl-2-(β-carboxy-β-acetoxyethyl)-cyclopentane-1,3-dione (6). The acetoxy acid 5 (2.42 g, 0.01 mol) was treated with 25 ml of dry $CHCl_3$ and 3 ml of thionyl chloride and the mixture was refluxed for about 0.5 hr. Then the excess thionyl chloride and chloroform were distilled off, using reduced pressure at the end of the distillation. The crystalline acid chloride 6 was used in further reactions.

2-Methyl-2-(2′-acetoxy-3-keto-4′-diazobutyl)cyclopentane-1,3-dione (7). Acid chloride 6 obtained by the above described method from 2.42 g (0.01 mol) of acid 5 dissolved in 25 ml of dry ether and was added dropwise at 0–10° to a solution of diazomethane in ether prepared from 6 g (0.058 mol) of nitrosomethylurea. Then the mixture was cooled to −50° and 2.30 g (86.7%) of diazo ketone 7 (mp 66–67°) was filtered off, $[\alpha]^{13}D$ −55.7° (c 6.5, CH_3OH).

11β-Acetoxy-14β-hydroxy-3-methoxy-9,10-secoestra-1,3,5(10)-triene-9,17-dione (9). A solution of $LiAlH_4$ (0.228 g, 0.006 mol) in 20 ml of anhydrous THF was treated dropwise at −10° with BF_3-Et_2O (1.134 g, 0.008 mol) and then a solution of *m*-methoxystyrene (3.3 g, 0.0230 mol) in 10 ml of anhydrous THF was added. The mixture was stirred under argon for about 1 hr at room temperature and subsequently a solution of diazo ketone 7 (1.8 g, 0.007 mol) in 10 ml of dry benzene was dropped in, causing an evolution of nitrogen. The mixture was allowed to stand for 3 hr, and then 6 ml of glacial acetic acid was added. The solvents were removed in vacuo, and the residual liquid was poured into 100 ml of water and extracted with benzene (3 × 50 ml). The organic layer was washed with water (3 × 50 ml) and dried with anhydrous Na_2SO_4. After evaporation of solvents in vacuo the residue was washed with pentane (3 × 20 ml) and hexane (2 × 20 ml) in order to remove low molecular weight impurities. The remaining oil was dissolved in 50 ml of benzene, and 5 ml of *t*-BuOOH was added. The mixture was left overnight and filtered and then the solvents were removed from the filtrate in vacuo. The residue was again washed with hexane (2 × 20 ml) and the remaining resin was pure enough for the next step.[2]

All the compounds listed below[5] were obtained using the procedures described for the racemic compounds.[2,3]

9β,11β,14β-Triacetoxy-3-methoxyestra-1,3,5(10)-trien-17-one (10), mp 244–245°, $[\alpha]D$ (room temperature) 61.4° (c 5.4, $CHCl_3$); **14β-hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione,** mp 227–229°, $[\alpha]D$ (room temperature) 355.0° (c 6.4, HMPT); **3-methoxy-14β-estra-1,3,5(10)-triene-11,17-dione,** mp 172–173°, $[\alpha]D$ (room temperature) 435.0° (c 4.7, $CHCl_3$); **11,11,17,17-bis(ethylenedioxy)-3-methoxy-14β-estra-1,3,5(10)-triene,** mp 127–128°, $[\alpha]D$ (room temperature) 145.0° (c 0.5, $CHCl_3$); **11,11,17,17-bis(ethylenedioxy)-3-methoxyestra-1,3,5(10)-trien-14β-ol,** mp 164–166°, $[\alpha]D$ (room temperature) 106.2° (c 0.32, EtOH); **11,11-ethylenedioxy-3-methoxyestra-1,3,5(10),14-tetraen-17-one,** mp 121–122°, $[\alpha]D$ (room temperature) 301.0° (c 0.46, EtOH); **11,11-ethylenedioxy-3-methoxy-14β-estra-1,3,5(10)-trien-17-one,** mp 133–134°, $[\alpha]D$ (room temperature) 185.0° (c 0.23, EtOH); **17α-hydroxy-3-methoxy-14β-estra-1,3,5(10)-trien-11-one,** mp 175–176°, $[\alpha]D$ (room temperature) 270.0° (c 0.1, $CHCl_3$); **14β-estra-4-ene-3,11,17-trione,** mp 226–227; $[\alpha]_{578}$ (room temperature) 375.0° (c 0.13, $CHCl_3$); **14β-hydroxyestra-4-ene-3,11,17-trione,** mp 202–204°, $[\alpha]_{578}$ (room temperature) 278.0° (c 0.42, $CHCl_3$); **11,11-ethylenedioxy-14β-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one,** mp of crude 196–204°, $[\alpha]D$ (room temperature) 121.0° (c 0.21, EtOH); **3-methoxy-14β-estra-1,3,5(10)-trien-17-one,** mp 112–114°, $[\alpha]D$ (room temperature) 180.0° (c 0.2, $CHCl_3$) [lit.[4] mp 112–113°, $[\alpha]D$ (room temperature) 179° (c 0.2, $CHCl_3$)].

Registry No.—**1**, 80-63-7; **2**, 765-69-5; **3**, 55836-13-0; **4**, 55836-14-1; (±)-**5**, 55836-15-2; (−)-(*S*)-**5**, 55902-71-1; (−)-(*S*)-**5** (−)-α-phenylethylamine, 55902-72-2; **6**, 55836-16-3; **7**, 55836-17-4; **8**, 55836-18-5; **9**, 55836-19-6; **10**, 55836-20-9; (−)-α-phenylethylamine, 2627-86-3; 14β-hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione, 55902-73-3; 3-methoxy-14β-estra-1,3,5(10-triene-11-17-dione, 55902-74-4; 11,11,17,17-bis(ethylenedioxy)-3-methoxy-14β-estra-1,3,5(10)-triene, 55836-21-0; 11,11,17,17-bis(ethylenedioxy)-3-methoxyestra-1,3,5(10)-trien-14β-ol, 55902-75-5; 11,11-ethylenedioxy-3-methoxyestra-1,3,5(10),14-tetraen-17-one, 55902-76-6; 11,11-ethylenedioxy-3-methoxy-14β-estra-1,3,5(10)-trien-17-one, 55836-22-1; 17α-hydroxy-3-methoxy-14β-estra-1,3,5(10)-trien-11-one, 56452-85-8; 14β-estra-4-ene-3,11,17-trione, 55902-78-8; 14β-hydroxyestra-4-ene-3,11,17-trione, 55836-23-2; 11,11-ethylenedioxy-14β-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one, 55902-79-9; 3-methoxy-14β-estra-1,3,5(10)-trien-17-one, 17748-69-5.

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(1) A. R. Daniewski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **21**, 17 (1973)
(2) Part VI: A. R. Daniewski, *J. Org. Chem.*, **40**, 3124 (1975).
(3) Part VII: A. R. Daniewski, *J. Org. Chem.*, **40**, 3127 (1975).
(4) P. Grabbe, A. Cruz, and J. Iriarte, *Can. J. Chem.*, **46**, 349 (1968).
(5) Melting points were determined on a micro hot plate, and are not corrected. Specific rotations were determined on a Perkin-Elmer 141 polarimeter.
(6) A. R. Daniewski and M. Kocór, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **20**, 395 (1972).

Total Synthesis of Steroids. X.[1] Synthesis of 3-Methoxyestra-1,3,5(10),8,14-pentaen-17-one

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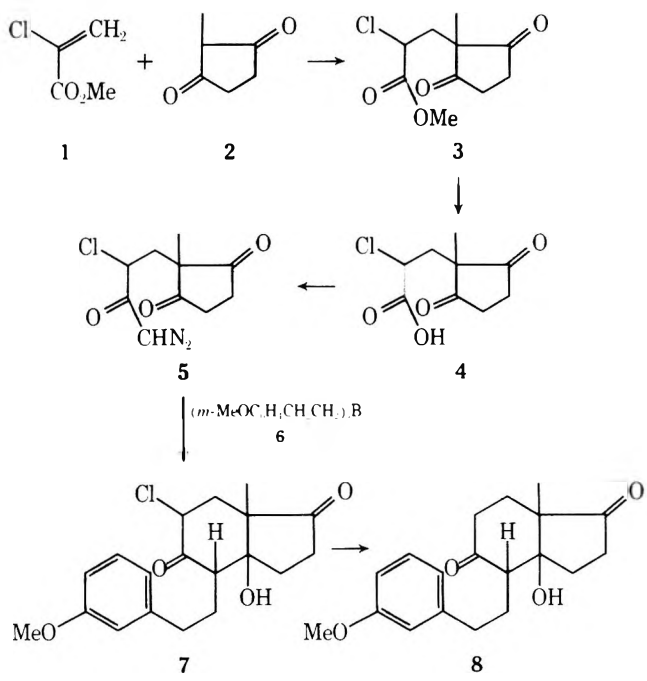
We recently published a series of papers[1-3] on the total synthesis of 11-oxygenated steroids, which were obtained either as racemates or as optically active compounds. Now we wish to describe the total synthesis of pentaene **10**,

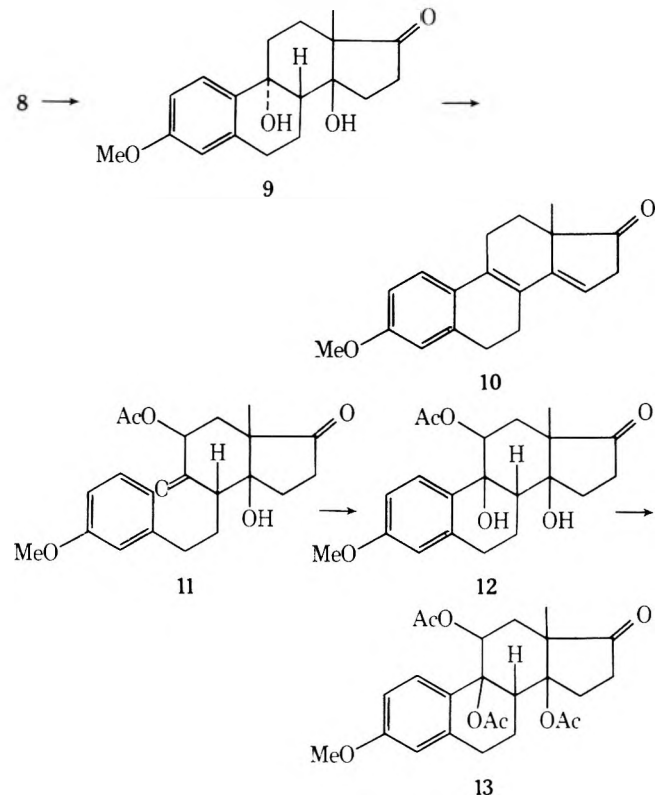
Scheme I



which serves as the key intermediate in the synthesis of estrone and its derivatives.

The racemic α-chloro acid **4** (Scheme I) was easily synthesized by the condensation of methyl α-chloroacrylate (**1**) with 2-methylcyclopenta-1,3-dione (**2**) and was resolved into enantiomers by crystallization of its salt with (−)-ephedrine. Further reaction was carried out either with the racemic **4** or with one of the antipodes, and thus we were able to obtain 8,14-bisdehydroestrone methyl ether (**10**) either as a racemate or as one of the enantiomers. The chloro acid **4** was converted via its acid chloride into diazo ketone **5**. The latter compound could be crystallized as the racemate but remained liquid as the (−) antipode. Its condensation with boron compound **6** yielded the tricyclic 11-chloro secodiene **7**, to which we assigned the same geometry as the corresponding 11-acetoxy compound **13** obtained previously.[3] Compound **7** could not be obtained in crystalline form but the dechlorinated product **8**, prepared by zinc dust reduction of the former, was crystalline both as the racemate and the (−) enantiomer. The dione **8** was cyclized using acetyl *p*-toluenesulfonate in acetic anhydride to the pentaene **10**. Surprisingly, the analogous conditions of cyclization[3] led to the formation of the triacetate **13** from the corresponding 11-acetoxy compound **11**. These different cyclization results can be explained as follows. In compound **11** the acetoxy group assumes the β geometry as it was proved earlier,[3] and therefore the attack of the carbonium ion at C-10 must take place from the top of the aromatic ring. Hence the newly formed OH group at C-9 in **12** assumes β geometry and the B/C ring junction becomes cis; such geometry prevents the elimination of water. The cyclization reaction is accompanied by acetylation, giving rise to the triacetate **13**. The lack of a significant steric hindrance at C-11 in **8** causes the attack of carbonium ion at C-9 below the plane of the aromatic ring, leading to the formation of an intermediate **9** with α geometry of the newly formed hydroxyl group at C-9 (trans B/C ring junction). Consequently, the trans diaxial elimination of water from C-9 and C-8, and then from C-14 and C-15, can occur very easily, producing the pentaene **10** (Scheme II). Further experiments on cyclization proved that the best conditions for the cyclization of **8** involved the use of glacial acetic acid as a solvent, and a few drops of perchloric acid obtained by mixing commercial 70% $HClO_4$ with acetic anhydride. The racemic pentaene **10** has identical physical properties with those of the compound known from literature.[4] The pentaene **10** obtained from the α-chloro acid **4** with the optical rotation of −13° has a specific rotation of −103° and mp 143°, i.e., exactly the same values as reported[5] for the compound with natural geometry at C-13, meaning that the optical purity of **10** as well as that of the intermediates was 100%. The overall yield with respect to the chloro acid **4** was quite high (40%).

Scheme II



Experimental Section[6]

(−)-(*S*)-2-Methyl-2-(2′-carboxy-2′-chloroethyl)cyclopentane-1,3-dione (4). The solution of (−)-ephedrine (7.2 g, 0.0435 mol) in methanol (25 ml) was mixed with the solution of chloro acid **4** (9.5 g, 0.0435 mol) in 50 ml of methanol and allowed to crystallize in the cold for 3 hr. The crystalline precipitate was recrystallized twice from methanol, yielding 4.17 g (50%) of the salt. The free (−) acid **4** was obtained by stirring the acetone slurry of the salt with Dowex 50W, filtering off the resin, and concentrating the filtrate to afford 2.35 g of pure (−) chloro acid **4** (50%), mp 72–73°, $[\alpha]^{18}D$ −13° (c 2.8, EtOH).

2-Methyl-2-(2′-chloro-3′-keto-4′-diazobutyl)cyclopentane-1,3-dione (5). The chloro acid **4** (4.37 g, 0.02 mol) was treated with 4 ml of $SOCl_2$ in benzene–hexane (1:1) solution and the mixture was refluxed for 0.5 hr until the acid was dissolved. The excess of thionyl chloride and solvent were then distilled off in vacuo. The optically active acid chloride was an oil, whereas the racemic product crystallized from the concentrated solution. The acid chloride obtained as described above from 4.37 g (0.02 mol) of **4** was dissolved in 25 ml of dry ether and treated dropwise at 0–10° with a solution of diazomethane in ether (prepared from 12 g of nitrosomethylurea). The mixture was then cooled down to −60° and 3.70 g (76.3%) of diazo ketone **5**, mp 74–76°, was obtained. In the case of optically active diazo ketone **5**, ether and the excess of diazomethane were distilled off in vacuo and the oily diazo ketone **5** was used for the next step: ir 2120, 1730 cm^{-1}; ^1H NMR δ 1.15 (3, s, CH_3), 2.4 (2, d, J = 8.5 Hz, CH_2), 2.85 (4, s, $-CH_2CH_2-$), 4.4 (1, t, J = 8.5 Hz, CHCl), 5.9 ppm (1, s, CHN_2).

3-Methoxy-11β-chloro-14β-hydroxy-9,10-secoestra-

1,3,5(10)-triene-9,17-dione (7). A solution of $LiAlH_4$ (0.228 g, 0.006 mol) in 20 ml of anhydrous THF was treated dropwise at about −10° with BF_3·Et_2O (1.134 g, 0.008 mol) and then a solution of *m*-methoxystyrene (3.3 g, 0.0230 mol) in 10 ml of anhydrous THF was added. The mixture was stirred under argon for about 1 hr at room temperature and subsequently a solution of diazo ketone **5** (1.7 g, 0.007 mol) in 10 ml of dry benzene was dropped in, causing an evolution of nitrogen. The mixture was allowed to stand for 3 hr, and then 6 ml of glacial acetic acid was added. The solvents were removed in vacuo, and the residual liquid was poured into 100 ml of water and extracted with benzene (3 × 50 ml). The organic layer was washed with water (3 × 50 ml) and dried with anhydrous Na_2SO_4. After evaporation of solvents in vacuo the residue was washed with pentane (3 × 20 ml) and hexane (2 × 20 ml) to remove low molecular weight impurities. The remaining oil was dissolved in 50 ml of benzene, and 5 ml of *t*-BuOOH was added. The mixture was left overnight and filtered and then the solvents were removed from the filtrate in vacuo. The residue was again washed with hexane (2 × 20 ml) and the remaining resin was sufficiently pure for the next step. The pure compound **7** (oil) was obtained by preparative TLC using hexane–ethyl acetate (4:1) for developing: ir 3480, 1730, 1720 cm^{-1}; ^1H NMR δ 1.35 (3, s, CH_3), 3.37 (1, q, at C-8), 3.78 (3, s, CH_3O), 4.25 (1, t, at C-11), 6.7–7.2 ppm (4, m, at C-1, C-2, C-4, and C-10).

3-Methoxy-14β-hydroxy-9,10-secoestra-1,3,5(10)-triene-9,17-dione (8). The solution of compound **7** in ether (50 ml) was treated with 2 g of activated zinc dust. The mixture was stirred for about 2 hr and after the substrate disappeared (by TLC), the unreacted zinc was filtered off and the filtrate, worked up in the usual manner, gave compound **8** (1.45 g, 70% with respect to the starting chloro diazo ketone): mp of racemic **8** 132–133.5°, mp of optically active **8** 136–137°; $[\alpha]^{18}D$ −2.46° (*c* 3.4, EtOH); ir 3425, 1725 cm^{-1}; ^1H NMR δ 1.25 (3, s, CH_3), 3.78 (3, s, CH_3O), 6.7–7.2 ppm (4, m, at C-1, C-2, C-4, and C-10).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 72.12; H, 7.65. Found: C, 71.97; H, 7.70.

3-Methoxyestra-1,3,5(10),8(9),14-pentaen-17-one (10). Method A. Acetyl *p*-toluenesulfonate prepared according to the literature[7] from 300 mg of *p*-toluenesulfonic acid was added to the solution of the seco compound **8** (500 mg) in 5 ml of acetic anhydride. The mixture was heated up to 50° for 1 hr and then it was poured into 50 ml of water with stirring. The acids were neutralized with aqueous sodium hydrogen carbonate and then the mixture was extracted with benzene (3 × 10 ml). The benzene layer was dried with anhydrous Na_2SO_4 and chormatographed on silica gel, giving 265 mg (60%) of the pentaene **10**, mp 107°, whose ir spectrum was identical with that of the compound obtained by method B.

Method B. Perchloric acid (70%, 5.0 g) was added dropwise to cold acetic anhydride (10 ml). Five drops of this solution was added to the solution of the seco compound **8** (0.5 g) in 5 ml of acetic acid. The mixture turned orange and after 15 min was poured into water (50 ml), and the precipitate was filtered off. It gave after recrystallization from methanol 360 mg (80%) of compound **10**, mp 142–143°, $[\alpha]^{18}D$ −103° (*c* 0.6, $CHCl_3$).

Registry No.—(±)-**4**, 55836-14-1; (−)-(*S*)-**4**, 55923-89-2; (−)-(*S*)-**4** (−)-ephedrine salt, 55923-90-5; **5**, 55887-35-9; **7**, 55887-36-0; (±)-**8**, 56142-64-4; (−)-**8**, 55923-91-6; **10**, 5182-24-1; (−)-ephedrine, 299-42-3.

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(6) The chloro acid **4** was obtained by us previously [*Bull. Acad., Pol. Sci., Ser. Sci. Chim.*, **20**, 395 (1972)]. All melting points are uncorrected. The ^1H NMR spectra were determined in $CDCl_3$ in a Jeol apparatus at 100 MHz using Me_4Si as the internal standard. The ir spectra were obtained in KBr in a Unicam SP 200 spectrophotometer. All the reactions were monitored by TLC.
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Orientation in Dehydrohalogenation of 2-Iodobutane Promoted by Ramified Tertiary Aldoxide Bases in Dimethyl Sulfoxide

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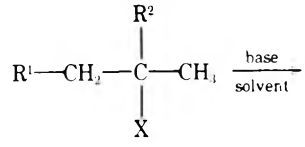
Positional orientation[1] in base-promoted β eliminations from **1** (where R^1 = alkyl, R^2 = H;[2] R^1 = R^2 = alkyl;[3] or R^1,R^2 = constituents of a carbocyclic ring[3] and X = halogen or arenesulfonate) is strongly influenced by base association.[2,4] In solvents of low polarity, such as *t*-BuOH,



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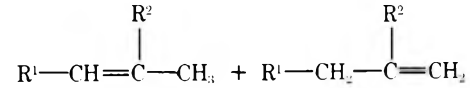

2 **3**

Et_3COH, and toluene, alkali metal oxyanion bases exist predominantly as ion pairs and aggregates of ion pairs.[4] Unfavorable steric interactions of such associated[5] bases in transition states leading to internal olefin **2** (the Saytzeff product) produces much higher proportions of the thermodynamically less stable alkene **3** (the Hofmann product) than is formed with dissociated[5] oxyanion bases. This effect is illustrated in Table I for eliminations from 2-iodobutane induced by associated (system no. 1–4) and dissociated (system No. 5–8) alkoxide bases.

Table I
Olefinic Products from Reactions of 2-Iodobutane with Alkoxide Bases in Various Solvents at 50°

System no.	Base	Solvent	% 1-butene	*trans*-2-Butene/*cis*-2-butene	Ref
1	*t*-BuOK	*t*-BuOH	34	2.17	6
2	Et_3COK	Et_3COH	49.3	1.50	7
3	*t*-BuOK	Toluene	36.1	1.70	7
4	Et_3COK	Toluene	46.8	1.75	7
5	EtOK	EtOH	11.7	3.25	8
6	EtONa	DMSO	17.1	3.32	9
7	*t*-BuOK	DMSO	20.7	2.99	9
8	Et_3COK	DMSO	20.9	3.13	10

Synthetic utility of the Hofmann orientation control provided by associated bases is lessened by a low reactivity when compared with that of dissociated bases.[6] A search was therefore initiated for a base species which would combine the orientation control of an associated base with the higher reactivity of a dissociated one.

Previous studies have demonstrated a correlation between base strength and positional orientation for eliminations promoted by dissociated oxyanion bases in Me_2SO.[8,9,10] However, certain highly hindered bases, such as potassium 2,6-di-*tert*-butylphenoxide, yield greater proportions of 1-butene than would be anticipated from their base strengths. The increased fraction of terminal olefin is attributed to the onset of base steric effects.[10,11] Since synthetic routes to very hindered tertiary alcohols are now available,[12,13] ramified tertiary alkoxides appeared to be promising candidates for dissociated bases with the requisite steric properties.

Table II
Olefinic Products from Reactions of 2-Iodobutane[a] with Potassium Alkoxides in Me_2SO at 50°

System no.	Alkoxide	Registry no.	% 1-butene	trans-2-Butene: cis-2-butene
9	Di-*tert*-butyl-*n*-octadecylmethoxide[b]	56348-30-2	24.5 ± 0.2[c]	3.31
10	Tricyclohexylmethoxide[d]	54637-79-5	27.2 ± 0.6	3.04
11	Tri-2-norbornylmethoxide[d]	56343-31-3	29.4 ± 0.5	3.41

[a] [2-BuI] = 0.1 *M*. [b] [ROK] = 0.25 *M*. [c] Standard deviation from repetitive analysis of trapped butene mixture. [d] [ROK] = saturated solution.

Olefinic products observed in reactions of 2-iodobutane with potassium tricyclohexylmethoxide, tri-2-norbornylmethoxide, and di-*tert*-butyl-*n*-octadecylmethoxide in Me_2SO at 50° are recorded in Table II. A nitrogen gas sweep technique[14] was employed to prevent isomerization by removing butenes from the reaction vessel.

For all three bases, the high *trans*-:*cis*-2-butene ratios indicate dissociated base species[2] and the percentage of 1-butene is higher than would be expected on the basis of estimated base strength alone.[10,11] However, only with the most ramified dissociated base, tri-2-norbornylmethoxide, does the proportion of terminal alkene approach that reported with *t*-BuOK–*t*-BuOH (Table I, system no. 1), a base–solvent system in which base association plays an important role.[2,4]

Dehydrohalogenation of alkyl halides by oxyanion bases in Me_2SO is very rapid.[15] It might be anticipated that greater selectivity for the production of 1-butene by ramified, dissociated alkoxide ion bases might be exhibited at lower temperatures. Reactions of 2-iodobutane with potassium *tert*-butoxide and tri-2-norbornylmethoxide in DMF at −28° were therefore investigated. The results, which are presented in Table III, reveal that, when compared with *tert*-butoxide, tri-2-norbornylmethoxide is even less selective in DMF at −28° than in Me_2SO at 50°.

Table III
Olefinic Products from Reactions of 2-Iodobutane[a] with Potassium Alkoxides in DMF at −28°

Entry no.	Alkoxide	% 1-butene	trans-2-Butene: cis-2-butene
12	*tert*-Butoxide[b]	12.9 ± 0.3[c]	4.93
13	Tri-2-norbornylmethoxide[d]	15.4 ± 0.2[d]	5.82

[a] [2-BuI] = 0.1 *M*. [b] [ROK] = 0.25 *M*. [c] Standard deviation from repetitive analysis of the trapped butene mixture. [d] [ROK] = saturated solution.

In conclusion, the proportion of Hofmann orientation product which can be obtained in eliminations from 2-iodobutane induced by ramified, dissociated, tertiary alkoxide bases in Me_2SO is less than that reported using associated oxyanion bases. The concept of sterically hindered dissociated bases which combine the orientation control of associated bases with high reactivity therefore appears to be unworkable.

Experimental Section

Reagents. Analytical reagent grade Me_2SO and DMF were kept over molecular sieves. Tricyclohexylmethanol, tri-2-norbornylmethanol, and *t*-BuOK (Aldrich) were used directly. Di-*tert*-butyl-*n*-octadecylmethanol was provided by Dr. H. Quast, University of Würzburg, West Germany.

Base–solvent solutions of *t*-BuOK in Me_2SO and DMF were prepared by dissolving the base in the appropriate solvent. Other base–solvent solutions were prepared by previously employed methods[11] except that KH was used instead of NaH.

Procedure. For the reactions at 50°, the experimental procedure and GLC analytical techniques previously reported[11] were utilized. For the reactions at −28°, a bromobenzene–liquid nitrogen slush bath was used to cool the reaction vessel and a 20-min reaction period was employed.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Registry No.—2-Iodobutane, 513-48-4; potassium *tert*-butoxide, 865-47-4.

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(1) Positional orientation refers to the relative amounts of internal and terminal alkenes that are formed.
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A Facile One-Step Synthesis of 3,5,5-Trisubstituted 2(5*H*)-Furanones

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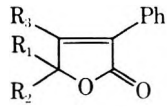
In the course of our studies dealing with the photochemical rearrangements of α,β-unsaturated lactones,[1] we required a number of 3,5,5-triaryl substituted 2(5*H*)-furanones. A survey of the literature revealed that there are no convenient methods to synthesize lactones of this type. An attractive route to several of the desired compounds was suggested by some recent work of Liotta[2] and Durst.[3] These authors showed that when the potassium salt of an acid is solubilized by complexation with crown ethers,[4,5] the anionic portion becomes sufficiently nucleophilic to react smoothly and quantitatively with a wide variety of organic substrates. For example, carboxylate salts were found to undergo phase transfer reaction with α-bromoacetophenone in nonpolar solvents to give phenacyl esters by an SN2 process in quantitative yield.[3] The present paper describes an application of the carboxylate displacement reaction which allows various α,α-dialkyl and diaryl acetaldehydes to be converted into 3,5,5-trisubstituted 2(5*H*)-furanones in high yield.

Using a slight modification of the Durst procedure,[3] potassium phenylacetate (1) was treated with an α-bromo substituted aldehyde (2) in the presence of 18-crown-6 to

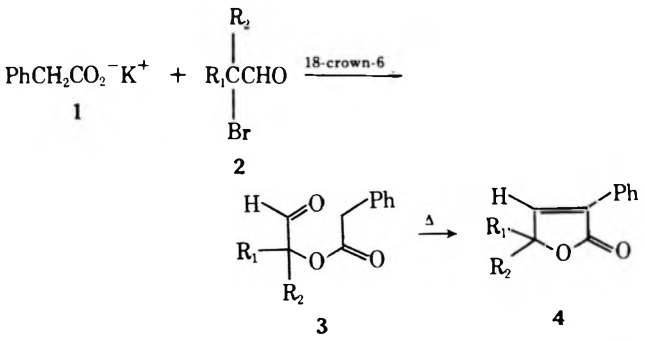
Table I
Synthesis of Trisubstituted 2(5*H*)-Furanones



Example	Product[a]	Procedure	Yield, %[b]	Mp, °C	Registry no.
1	$R_1 = R_2 = Ph$; $R_3 = H$	B	90	152–153	36859-02-6
2	$R_1 = Ph$; $R_3 = H$; $R_2 = p\text{-}CH_3OC_6H_4$	B	81	139–140	56258-94-7
3	$R_1 = Ph$; $R_2 = H$; $R_3 = p\text{-}CH_3OC_6H_4$	A	80	120–121	56258-95-8
4	$R_1 = H$; $R_3 = Ph$; $R_2 = p\text{-}CH_3OC_6H_4$	A	75	112–113	56258-96-9
5	$R_1 = Ph$; $R_3 = H$; $R_2 = p\text{-}BrC_6H_4$	B	62	134–135	56258-97-0
6	$R_1 = Ph$; $R_3 = H$; $R_2 = p\text{-}CNC_6H_4$	B	20	117–118	56258-98-1
7	$R_1 = R_3 = Ph$; $R_2 = H$	A, B	80	125–126	7404-46-8
8	$R_1 = R_3 = CH_3$; $R_2 = H$	B	90	69–70	5109-73-9

[a] Structures were assigned on the basis of physical and spectral properties. Satisfactory analyses were obtained on all new compounds. [b] No attempts were made to optimize the yields.

form an aldehydo ester **3** which could be cyclized to a five-membered unsaturated lactone **4** on further heating. We



found that either acetonitrile or benzene can be used as the solvent, with the reaction proceeding faster in acetonitrile than in benzene. The reactions could be carried out by utilizing one of two different procedures. Procedure A involved heating a mixture of the appropriate α-bromo carbonyl compound with potassium phenylacetate in acetonitrile for 1 hr. In this case the catalyst concentration was 0.05 *M*. Removal of the solvent afforded the aldehydo ester **3** (or desyl ester when desyl bromide was used) in quantitative yield. Cyclization of **3** to the desired 2(5*H*)-furanone system was accomplished by treating **3** with 1 equiv of sodium hydride in dimethyl sulfoxide at 70° for 1–3 hr. A more convenient procedure (B) involved refluxing a mixture of **1** and **2** in benzene in the presence of 18-crown-6 (0.25 equiv) for 1–3 days. The solvent was removed under vacuum and the residue was washed with benzene through a short column (4–5 g) of dry column silica gel. Removal of the solvent afforded the desired 2(5*H*)-furanone (see Table I).

It is interesting to note that the reaction of "naked" phenylacetate with tertiary substituted bromo aldehydes proceeds quickly and quantitatively to afford the corresponding esters in high yield. The substitution reaction occurred even when 2-bromo-2-methylpropanal was used as the substrate. Virtually no elimination product could be detected in this reaction. This result is in direct contrast to that obtained by Liotta in the reaction of "naked" fluoride with tertiary halides. His results showed that the "naked" fluoride reagent produced much larger quantities of alkene products.[6] The above observation confirms Liotta's claim that "naked" fluoride is a much stronger base than "naked" acetate.[2,6] The mechanism for the displacement reaction on the tertiary aldehydic bromide may involve attack of solubilized acetate on a tight ion pair rather than by an SN2 substitution path. Further work needs to be done before this point can be established.

Experimental Section

Synthesis of 3,5-Diphenyl-4-(*p*-anisyl)-2(5*H*)-furanone. Procedure A. To a stirred solution of 2.2 g of 4′-methoxybenzoin in 50 ml of carbon disulfide was added a solution of 1.36 g of bromine in 5 ml of carbon disulfide. After stirring for 2 hr the reaction mixture was quenched by the addition of 20 ml of a 1% aqueous sodium thiosulfate solution. The reaction mixture was washed with water and dried over sodium sulfate. Removal of the solvent gave α-bromo-4′-methoxybenzoin in quantitative yield. The crude bromo ketone was taken up in 75 ml of acetonitrile and 1.50 g of potassium phenylacetate and 132 mg of 18-crown-6 was added to the solution. The mixture was heated at reflux for 1 hr. Removal of the solvent left a yellow oil which was taken up in 100 ml of dry dimethyl sulfoxide. To this mixture was added 270 mg of sodium hydride. The reaction mixture was stirred at room temperature for 2 hr and then warmed to 70° for 10 min. The cooled reaction mixture was poured into cold water and extracted several times with ether. The ether layer was washed with a 2% hydrochloric acid solution and then repeatedly with water. Evaporation of the dried ethereal layer gave 3,5-diphenyl-4-(*p*-anisyl)-2(5*H*)-furanone as a white solid in 80% yield: mp 120–121°; ir (KBr) 1755 cm^{-1}; NMR ($CDCl_3$) δ 3.62 (s, 3 H), 6.03 (s, 1 H), 6.51 (d, 2 H, J = 8.0 Hz), 6.92 (d, 2 H, J = 8.0 Hz), 7.09–7.41 (m, 10 H); *m/e* (70 eV) 342 (M^+).

Synthesis of 3,5,5-Triphenyl-2(5*H*)-furanone. Procedure B. To a stirred solution of 2.32 g of diphenylacetaldehyde (Aldrich) in 50 ml of carbon disulfide was added a solution of 1.35 g of bromine in 5 ml of carbon disulfide. After stirring for 1 hr the reaction mixture was quenched by the addition of 20 ml of a 1% aqueous sodium thiosulfate solution. The reaction mixture was washed with water and dried over sodium sulfate. Removal of the solvent gave α-bromodiphenylacetaldehyde in nearly quantitative yield: ir (film) 1695 cm^{-1}; NMR (CCl_4) δ 9.61 (s, 1 H), 7.22 (m, 10 H). The crude bromo aldehyde was taken up in 125 ml of benzene and 1.50 g of potassium phenylacetate and 662 mg of 18-crown-6 was added to the solution. The mixture was heated at reflux for 24 hr with an attached Dean-Stark tube. At the end of this time the solution was concentrated under reduced pressure to 20 ml and passed through a short silica gel column with benzene to remove the crown ether.

Evaporation of the solvent and recrystallization of the solid from methanol gave 3,5,5-triphenyl-2(5*H*)-furanone in 90% yield: mp 152–153°; ir (KBr) 1750 cm^{-1}; NMR ($CDCl_3$) δ 7.98 (s, 1 H), 7.31 (m, 15 H); uv (95% ethanol) 265 and 275 nm (ε 18,200 and 16,800); *m/e* (70 eV) 312 (M^+).

Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.28; H, 5.05.

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Registry No.—1, 13005-36-2; 2 (R_1 = R_2 = Ph), 36930-94-6; 4′-methoxybenzoin, 4254-17-5; diphenylacetaldehyde, 947-91-1.

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Preparation of 2,5-Diamino-4,6-dichloropyrimidine[1]

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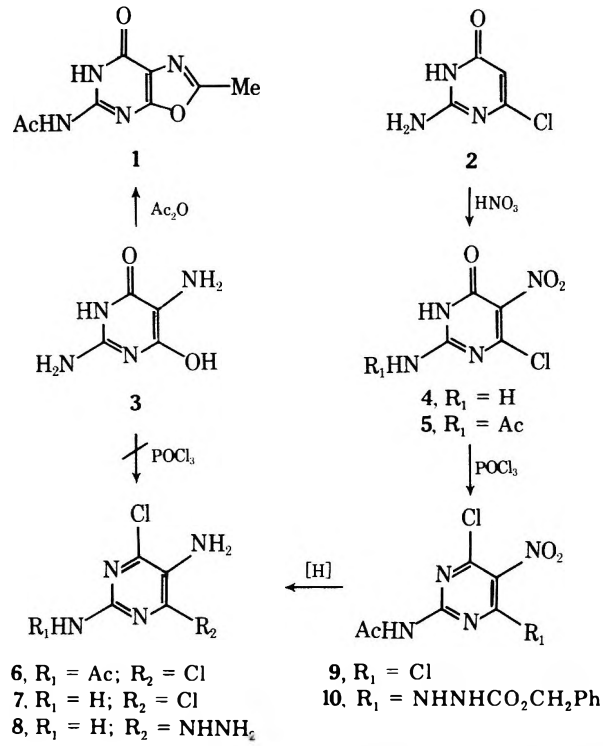
The projected routes for the synthesis of some condensed pyrimidine ring systems used 2,5-diamino-4,6-dichloropyrimidine (7) as a key intermediate. Previously, this compound was obtained in two steps from 2,4,6-trichloro-5-nitropyrimidine, which was prepared by the chlorodehydroxylation of 5-nitrobarbituric acid.[2] In one experiment in our laboratories, treatment of 5-nitrobarbituric acid with $POCl_3$ gave a 4% yield of the desired product. In two other experiments, the addition of *N,N*-dimethylaniline to the $POCl_3$ mixture gave a violet, exothermic reaction (induction period) resulting in the loss of the reactants. For this reason another route for the preparation of 7 was sought.

The chlorination of 3 with $POCl_3$ to give 7 directly was unsuccessful, apparently because of degradation of the ring system. To block the amino groups, 3 was treated with hot Ac_2O, but this reaction resulted in the formation of the oxooxazolopyrimidine 1. Chlorination of 1 gave a mixture of products containing one to four chlorine atoms (mass spectrum), and the investigation of this approach was terminated.

In the successful route, the 5-nitropyrimidine 4[3] was prepared from 2[4] and purified by conversion to its acetylamino derivative 5. Treatment of 5 with refluxing $POCl_3$ gave the dichloropyrimidine 9. In some runs this product was contaminated with a minor impurity, presumably the corresponding 2-aminopyrimidine resulting from deacetylation of 9. This impurity was reconverted to 9 by recrystallization of the sample from Ac_2O. In one experiment, the product was contaminated with 5, apparently resulting from hydrolysis of 9 during the work-up of the acidic reaction medium. Treatment of 9 with an equimolar amount of benzyl carbazate at room temperature gave a 37% yield of 10. Since it is known that the chloro group of 2,4-diamino-6-chloro-5-nitropyrimidine is replaced by amines under mild conditions,[5] the reaction of 9 with 2 equiv of the carbazate was not attempted.



Hydrogenation of 9 in the presence of Raney nickel gave the 5-amino compound 6. Replacement of one chloro group and removal of the 2-acetyl group was accomplished by treatment of 6 with ethanolic hydrazine at room temperature to give 8. In some preparations of 6, this product was contaminated with the corresponding deacetylated compound 7. Treatment of either 6 or a mixture of 6 and 7 with ethanolic HCl hydrolyzed the 2-acetyl group to give 7. The reason for the considerable difference between the melting points of 7 and that previously prepared[2] is unknown. The use of 7 in the preparation of a pteridine has been reported.[6]

Experimental Section[7]

***N*-(6,7-Dihydro-2-methyl-7-oxooxazolo[5,4-*d*]pyrimidin-2-yl)acetamide (1).** A mixture of 3 hemisulfate (6.0 g, 31 mmol) and Ac_2O (60 ml) was heated with stirring at 100° for 3.5 hr. The solid that deposited from the resulting solution was collected by filtration and washed with Et_2O: yield 3.3 g (50%); mp 294°. For analyses a portion of this sample (0.5 g) was recrystallized from H_2O yield, 0.3 g; mp 303°; λ_{max} (ε × 10^{-3}) pH 7 253 nm (15.0), 279 (11.3); $\bar{\nu}_{max}$ 1670 cm^{-1}.

Anal. Calcd for $C_8H_8N_4O_3$: C, 46.16; H, 3.88; N, 26.92. Found: C, 46.30; H, 4.27; N, 27.39.

***N*-(6-Chloro-3,4-dihydro-5-nitro-4-oxopyrimidin-2-yl)acetamide (5).** Solid 2 (10 g, 69 mmol) was added with stirring at 17.5° to 140 ml of of a 1:1 mixture of concentrated sulfuric acid–nitric acid (*d* 1.49–1.50). The solid dissolved in several minutes and the temperature rose to 35°. After 50 min the solution was poured with stirring into crushed ice (500 g). The solid that deposited was collected by filtration, washed with water, and dried in vacuo over P_2O_5. The resulting crude sample of 4[3] was extracted with acetone (4 × 500 ml), and the combined extract was evaporated to dryness in vacuo. The resulting solid was suspended in acetic anhydride (100 ml) containing 2 drops of concentrated sulfuric acid, and the whole was heated in a preheated oil bath at 90° for 30 min. The resulting hot solution was filtered, and the filtrate was cooled to deposit 5: yield 8.7 g; mp 260° dec (Kofler Heizbank); λ_{max} (ε × 10^{-3}) pH 7 242 nm (10.2), 278 sh (3.72), 356 (2.02); $\bar{\nu}_{max}$ 1680 cm^{-1}.

Anal. Calcd for $C_6H_5ClN_4O_4$: C, 30.95; H, 2.15; Cl, 15.27; N, 24.10. Found: C, 30.71; H, 2.29; Cl, 14.83; N, 23.73.

Concentration of the acetic anhydride filtrate to a volume of about 15 ml deposited a second crop of product: yield, 1.4 g; mp 260° dec.

***N*-(5-Amino-4,6-dichloropyrimidin-2-yl)acetamide (6).** A solution of **9** (7.2 g, 29 mmol) in a mixture of DMAC (40 ml) and EtOH (750 ml) was hydrogenated in the presence of Raney nickel (7 g wet, washed with H_2O and EtOH) at room temperature and atmospheric pressure. The theoretical amount of H_2 was absorbed within 5 hr. The reaction mixture was filtered (Celite) under N_2, and the colored filtrate was evaporated in vacuo to give a gummy solid. This residue was triturated with Et_2O, and the brown solid was collected by filtration and dried in vacuo over P_2O_5 for 4 hr: yield 2.8 g (44%); mp 135–138° dec; λ_{max} ($\epsilon \times 10^{-3}$) pH 7 263 nm (12.1), 318 (4.79); $\bar{\nu}_{max}$ 1665 cm^{-1}.

Anal. Calcd for $C_6H_6Cl_2N_4O$: C, 32.60; H, 2.74; N, 25.34. Found: C, 32.37; H, 2.94; N, 25.09.

The Et_2O wash was evaporated to dryness to give a yellow solid, yield 3.9 g. TLC (silica gel, 9:1 $CHCl_3$–MeOH) indicated that this residue was a mixture of **6** and the corresponding deacetylated compound, **7** (see below).

2,5-Diamino-4,6-dichloropyrimidine (7). The mixture of **6** and **7** (3.9 g) obtained in the preparation of **6** was suspended in 6 *M* ethanolic HCl (40 ml) and stirred at room temperature for 3 hr. The solid was collected by filtration, washed with Et_2O, and dried in vacuo over P_2O_5: yield, 3.0 g; mp >264°.

Anal. Calcd for $C_4H_4Cl_2N_4$·HCl·0.25C_2H_6O: C, 23.81; H, 2.36; N, 24.68. Found: C, 23.86; H, 2.63; N, 24.80.

An additional amount of **7** (0.2 g) was obtained from the ethanol filtrate.

A portion of the first crop (1.0 g) was suspended in H_2O (25 ml), and the pH was adjusted to 7 by the addition of solid $NaHCO_3$. After stirring for 10 min, the mixture was heated at 50° for 15 min. After cooling the cream-colored solid was collected by filtration, washed with water, and dried in vacuo over P_2O_5: yield 0.6 g; mp 188–191° dec (lit.[2] mp 260–261°). In some samples decomposition occurred before melting unless the melting point was taken rapidly: λ_{max} ($\epsilon \times 10^{-3}$) pH 7 245 nm (13.0), 341 (4.84); $\bar{\nu}_{max}$ 1645 cm^{-1}; M^+ *m/e* 178, 180, 182.

Anal. Calcd for $C_4H_4Cl_2N_4$: C, 26.84; H, 2.25; N, 31.30. Found: C, 26.94; H, 2.49; N, 31.56.

2,5-Diamino-4-chloro-6-hydrazinopyrimidine (8). A suspension of **6** (1.0 g, 4.5 mmol) in EtOH (20 ml) containing anhydrous hydrazine (1.2 ml) was stirred at room temperature for 72 hr. The brown solid was collected by filtration, washed with Et_2O and then H_2O, and dried in vacuo over P_2O_5: yield 0.47 g (53%); mp >260°; λ_{max} ($\epsilon \times 10^{-3}$) pH 7 305 nm (5.05); $\bar{\nu}_{max}$ 1620 cm^{-1}.

Anal. Calcd for $C_4H_7ClN_6$·H_2O: C, 24.94; H, 4.71; N, 43.63. Found: C, 24.57; H, 4.36; N, 43.58.

An additional amount of crude **8** (0.28 g) was obtained from the water wash.

***N*-(4,6-Dichloro-5-nitropyrimidin-2-yl)acetamide (9).** A mixture of **5** (10.0 g, 43 mmol) and $POCl_3$ (200 ml) was refluxed for 4 hr. The resulting solution was concentrated under reduced pressure to a smaller volume (50 ml) and poured with vigorous stirring into an ice–H_2O mixture (1000 ml). The brown solid that precipitated was collected by filtration, washed with water (1000 ml), and dried in vacuo over P_2O_5: yield 7.3 g (67%); mp 206–207° dec. Although this material analyzed correctly for **9**, the melting point was increased by recrystallization of a sample (0.5 g) from hot Ac_2O: yield 0.25 g; mp 224°. This sample was homogeneous on TLC (silica gel, EtOAc, R_f 0.9) except for a spot at the origin: λ_{max} ($\epsilon \times 10^{-3}$) pH 7 240 nm (13.0), 247 sh (12.9), 275 sh (7.57), 340 br sh (0.95); $\bar{\nu}_{max}$ 1705 cm^{-1}; M^+ *m/e* 250, 252, 254.

Anal. Calcd for $C_6H_4Cl_2N_4O_3$: C, 28.71; H, 1.61; N, 22.32. Found: C, 28.88; H, 1.63; N, 22.48.

Benzyl 3-(2-Acetylamino-4-chloro-5-nitropyrimidin-6-yl)carbazate (10). A suspension of **9** (1.0 g, 4.0 mmol) in dioxane (40 ml) containing benzyl carbazate (0.68 g, 4.1 mmol) was stirred at room temperature for 60 hr. The solid was collected by filtration, washed sparingly with Et_2O, and dried in vacuo over P_2O_5 to give the dioxanate complex of **10**: yield 0.69 g (37%); mp 185–186° dec; λ_{max} ($\epsilon \times 10^{-3}$) pH 7 235 nm sh (10.8), 341 (11.1); $\bar{\nu}_{max}$ 1735 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}ClN_6O_5$·$C_4H_8O_2$: C, 46.11; H, 4.51; N, 17.93. Found: C, 46.05; H, 4.84; N, 17.80.

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.—**1**, 56145-01-8; **2**, 1194-21-4; **3**, 40769-69-5; **5**, 51471-45-5; **6**, 56145-02-9; **7**, 55583-59-0; **7** HCl, 56145-03-0; **8**, 56227-23-7; **9**, 56145-04-1; **10** dioxane, 56145-06-3; acetic anhydride, 108-24-7; hydrazine, 302-01-2; benzyl carbazate, 5331-43-1.

References and Notes

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1,3-Bridged Aromatic Systems. XIV. The Effect of Configuration on the Course of Reactions of Alcohols with Thionyl Chloride and with Phosgene

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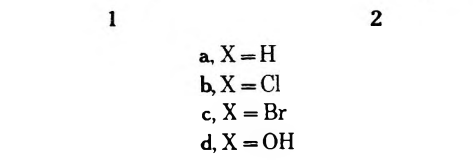
Continuing studies[1] of the chemistry of anti chloride **2b** and anti bromide **2c** have been inhibited by their lack of availability. While the syn bromide **1c** is readily available[2] by bromination of **1a** with *N*-bromosuccinimide, the anti chloride and bromide have only been obtained as by-products from reactions of the *N*-oxide of **1a** with acid halides.[1,3,4,5]



1 **2**

a, X = H
b, X = Cl
c, X = Br
d, X = OH

We have now observed that the anti chloride **2b** can be obtained conveniently and in high yield from the readily available anti alcohol **2d** by reaction with thionyl chloride in hot benzene. The reaction is stereoselective and occurs with complete retention of configuration.

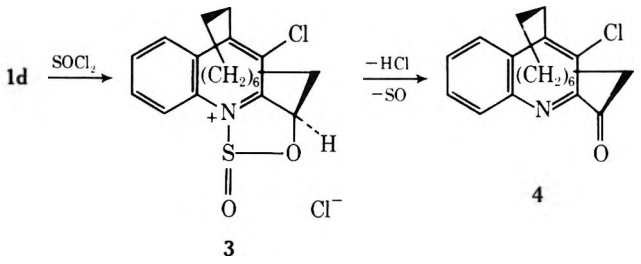
Similar results were obtained with thionyl bromide; the yield of pure anti bromide **2c** was >67% and no syn bromide, which would be formed if inversion occurred at the benzylic carbon atom,[6] was detected.

By contrast, reaction of the corresponding syn alcohol **1d** with thionyl chloride in hot benzene did not lead to the syn

chloride but rather to the ketone **4**; the yield of **4** is essentially quantitative. Conversion of **1d** to **4** with thionyl chloride in benzene occurs at room temperature (>80% yield after 5 hr) but is slower in tetrahydrofuran (complete after 15 hr at 32°).

Inspection of models show that the expected intermediate halosulfite ester can, in the syn series, form the intramolecular salt **3**. One possible mechanism for the formation of **4** would involve proton removal by halide ion from **3** with elimination of sulfur monoxide (SO) as shown in Scheme I. Failure to form halide, normally expected by reaction of alcohols with thionyl chloride, is not surprising in view of the known reluctance of these cyclophane systems to undergo SN2 substitution reactions.[1-5] Similar results were obtained with redistilled thionyl bromide in benzene; ketone **4** was isolated pure in 67% yield.

Scheme I



Reactions of *syn*-**1d** with phosgene in hot benzene led to the formation of ketone **4** (59% isolated pure); in this case carbon monoxide was identified as a reaction product, a result anticipated by the sequence shown in Scheme I.

This rather unusual oxidation of pyridine methanols is apparently limited to rather strained systems which cannot undergo SN2 substitution reactions. The product derived by reaction of thionyl chloride with 2-hydroxymethylpyridine was examined closely. The yield of 2-chloromethylpyridine hydrochloride[7] was nearly quantitative; no oxidation occurred as evidenced by the absence of aldehyde products.

Attempts to isolate intermediate **3** were made by carrying out the reaction of **1d** with thionyl chloride in benzene at room temperature; solvent benzene was removed in vacuo at 32°. After 1 hr the product was mostly **1d** but contained some ketone **4**; after 6 hr the product was mostly ketone **4** (85% isolated pure by recrystallization). In no case did we detect any S=O functions as evidenced by the absence of ir absorptions at ν_{S-O} 1000–1100 cm^{-1}. In another experiment **1d** in tetrahydrofuran was treated with *n*-butyllithium and the resulting lithium alkoxide[4] was treated with thionyl chloride in hexane. After 1 hr at 32° the product was a mixture of unreacted alkoxide (42% isolated as **1d**) and ketone **4** (31% subsequently isolated pure). There was no evidence for S–O groups as judged by lack of absorption by the crude product at 1000–1100 cm^{-1}. We conclude from these experiments that the rate-determining step in the formation of **4** is formation of **3** which collapses rapidly to products.

Since carbon monoxide was formed in reactions of **1d** with phosgene, sulfur monoxide was an expected product from the reaction of **1d** with thionyl chloride; however, attempts to trap SO by conducting such reactions in the presence of excess *trans*-1,4-diphenylbutadiene[8] and with excess isoprene[9] were unsuccessful.

Experimental Section

I. Reactions of Anti Alcohol 2d. A. With Thionyl Bromide. A mixture of **2d**[2] (0.318 g, 0.001 mol) and excess thionyl bromide (freshly distilled at reduced pressure) was heated at 90° for 2 hr. Excess thionyl bromide was removed (70–75° under water aspirator pressure) and the residue was dissolved in chloroform. The organic extract was washed with 5% potassium hydroxide (25 ml) and the residue (0.375 g, mp 145–151°), obtained from the dried chloroform, was recrystallized from chloroform–petroleum ether[10] to give pure anti bromide **2c** (0.33 g, 87% yield, mp and mmp[2] 151–152°). Similar results were obtained when benzene was employed as solvent.

B. With Thionyl Chloride. The reaction with thionyl chloride was carried out at reflux as in A above. The yield of anti chloride **2b** (mp and mmp[11] 143–145° from chloroform–petroleum ether[10]) was 82%.

II. Reactions of Syn Alcohol 1d. Formation of Ketone 4. A. With Thionyl Chloride. A mixture of **1d** (0.318 g, 0.001 mol), thionyl chloride (0.238 g, 0.002 mol), and benzene (25 ml) was heated at the reflux temperature for 5 hr. The residue obtained by removal of solvent and excess thionyl chloride (rotary evaporator) was dissolved in chloroform and was washed with 5% potassium hydroxide. The ketone **4** (0.280 g, 88% yield, mp and mmp 136–138°[2] from petroleum ether[10]) was obtained from the dried chloroform.

When the reaction was carried out in benzene at room temperature (6 hr) the yield of pure **4** was 86%. The reaction was incomplete after 5 hr reflux when tetrahydrofuran was used as solvent; the yield of **4** was 72% after 12 hr at reflux and 70% after 15 hr at 32°.

B. With Thionyl Bromide. The reaction of **1d** (0.318 g) with thionyl bromide was carried out as in IA. The crude product was chromatographed (silica gel–petroleum ether[10]/ether, 95:5, as eluent) to give 280 mg of **4** (mp 129–134°), mp and mmp 136–138[2] from chloroform–petroleum ether,[10] 67% yield). No syn bromide **1c** was detected.

C. With Phosgene. A mixture of syn alcohol **1d** (0.952 g, 0.003 mol), dry benzene (2.5 ml), and phosgene [24 ml of a 12.5% solution of phosgene (0.03 mol) in benzene] was stirred (magnetic stirrer) and heated at the reflux temperature under a nitrogen atmosphere. The solution was flushed occasionally with a slow stream of nitrogen which was passed through a test solution (25 ml) for carbon monoxide prepared from phosphomolybdic acid and palladium chloride.[12] The color of molybdenum blue in the test solution due to carbon monoxide formation was evident after 2 hr; the color darkened indicating continued evolution of carbon monoxide, over a 5-hr period.[13] Benzene and phosgene were then removed from the mixture (water aspirator) and the residue was recrystallized twice from chloroform–petroleum ether[10] to give pure ketone **4** (60% yield, mp and mmp 136–138°).

Registry No.—**1d**, 25866-36-8; **2b**, 52019-95-1; **2c**, 42880-45-5; **2d**, 25907-82-8; **4**, 25859-31-8; thionyl bromide, 507-16-4; thionyl chloride, 7719-09-7; phosgene, 75-44-5.

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(3) W. E. Parham and K. B. Sloan, *Tetrahedron Lett.*, 1947 (1971).
(4) W. E. Parham, K. B. Sloan, K. R. Reddy, and P. E. Olson, *J. Org. Chem.*, **38**, 927 (1973).
(5) The syn and anti alcohols were previously shown to be unreactive to prolonged action of concentrated HBr; cf. W. E. Parham, K. B. Sloan, and J. B. Biasotti, *Tetrahedron*, **27**, 5767 (1971).
(6) Syn and anti bromides **1c** and tosylates do not undergo SN2 displacement reactions; however, both syn-**1c** and *anti*-**2c** undergo SNi reactions with silver acetate with complete retention of configuration (cf. ref 1).
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(8) R. M. Dodson and R. F. Sauers, *Chem. Commun.*, 1189 (1967).
(9) (a) P. Chas and D. M. Lemal, *J. Am. Chem. Soc.*, **95**, 921 (1973); (b) *ibid.*, **95**, 923 (1973).
(10) Bp 30–60°.
(11) W. E. Parham and P. E. Olson, *J. Org. Chem.*, **39**, 2916 (1974).
(12) Test solution: (a) 100 g of phosphomolybdic acid is dissolved in 200 ml of cold water; (b) 0.1 g of $PdCl_2$ is dissolved in 10 drops of concentrated HCl and brought to 50 ml with water. 100 ml of test solution consists of 80 ml of a and 20 ml of b. F. Feigl, "Spot Tests in Inorganic Chemistry", American Elsevier, New York, N.Y., 1956, pp 327–329.
(13) The color developed was comparable to that observed from the carbon monoxide gas generated by heating oxalic acid (50 mg) with polyphosphoric acid (1.0 g). This test is quite sensitive to carbon monoxide. No color changes in the test solution were observed in blank experiments employing (1) nitrogen used in the experiment, (2) repetition of experiment IIC but omitting syn alcohol **1d**.

Reactions of Sodium Naphthalenide with Aromatic and Aliphatic Esters

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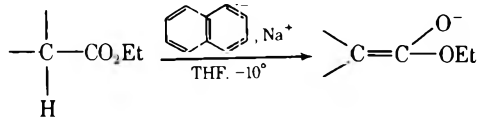
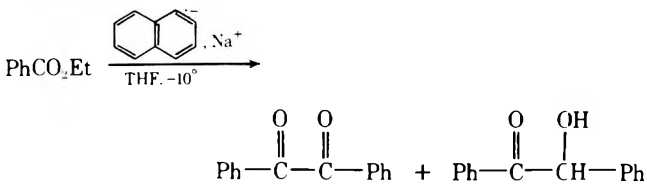
The considerable attention devoted to the chemistry of sodium naphthalenide has derived, in part, from observations that this radical anion is both a strong base[1] and a powerful reducing agent.[2] Its reactions with esters were of interest to us from several respects. (1) Naphthalenides have been used as bases for condensation reactions without evaluation of other possible functions, such as electron transfer. (2) It was desirable to determine if the product trend noted in the reactions of carbonyl compounds would be repeated by a closely related functional group.[3] (3) Few functional groups have demonstrated competitive proton abstraction and reduction. For esters such a competition was viewed as being clearly possible. (4) Extant reports on the reactions of aromatic radical anions with esters were in conflict.[4]

We have found that deprotonation is the main reaction for esters in which the α carbon possesses a hydrogen. This



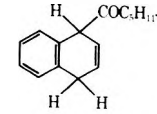
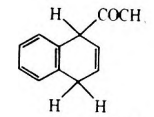
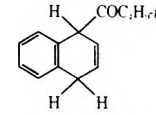
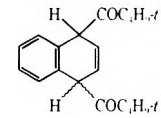
observation is based upon the disappearance (GLC) of ethyl ethanoate and ethyl hexanoate upon addition of these esters to a sodium naphthalenide solution. The major portion of these esters was regenerated upon quenching the reactions with water, followed by adjustment of the pH to 5–7 with dilute hydrochloric acid and GLC analysis. However, proton abstraction was not the only reaction which occurred. Aliphatic esters (Table I) also formed acylation products of naphthalene. While the yields of these products were not high, the fact that they were formed at all is significant. This type of naphthalene product has not been recorded previously. Machtinger reported the reaction of ethyl laurate with sodium naphthalenide to yield the analogous ketone containing a fully aromatic naphthalene moiety.[4a] This is clearly not the case for the esters we have examined; the NMR spectra are in accord only with the 1,4-dihydro derivatives. The products we have observed are analogous to the adduct reported by Kaplan et al. in their study of the reaction of sodium biphenylide with ethyl laurate.[4b]

The reaction of ethyl benzoate (Table II) provides a striking contrast to the reactions of alkyl esters. No acylation products of naphthalene could be detected. The only ester-derived products were benzil and benzoin.



The following conclusions are apparent. (1) Sodium naphthalenide interacts with aliphatic esters in a capacity other than strictly as a base; its use to effect enolate formation is not advised. (2) The differing fates of aliphatic and aromatic esters are analogous to those observed for the reactions of aliphatic and aromatic carbonyl compounds.[3] Deprotonation and acylation occur with aliphatic esters. In its reaction with ethyl benzoate, sodium naphthalenide functions exclusively as a reducing agent. (3) Conceptually, the naphthalene acylation products may arise via a number of routes; those analogous to the alternatives described for the reactions of carbonyl compounds are most likely.[3] These possibilities involve either electron transfer or nucleophilic attack as key steps. The routes to benzil and benzoin are not certain but the "unified acyloin condensation mechanism" discussed recently by Bloomfield, Owsley, Ainsworth, and Robertson must be considered as an attractive alternative to the traditional radical coupling or dianion mechanisms.

Table I
Reaction of Sodium Naphthalenide with Aliphatic Esters[a]

Compd	Naphthalenide: ester	Product	Yield, %
Ethyl hexanoate	2:1		35
Ethyl ethanoate	2:1		11
Ethyl dimethylpropanoate	2:1		13
			40

[a] Yields are based upon ester.

Table II
Reaction of Sodium Naphthalenide with Ethyl Benzoate

Ratio naphthalenide:benzoate	% benzil	% benzoin
4:1	5	86
1:1	38	27

Experimental Section

All melting points are uncorrected and were taken with a Fisher-Johns melting point apparatus. Ir spectra were determined on a Perkin-Elmer Model 710 infrared spectrometer. NMR spectra were recorded on a Varian A-60A spectrometer using Me_4Si as an internal standard. Mass spectra were determined by the University of Kentucky Mass Spectroscopy Center with a Perkin-Elmer RMU7 spectrometer; the ionizing voltage was 70 eV. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Starting Materials. Tetrahydrofuran was purified by distillation under nitrogen from benzophenone sodium ketyl. Reagent grade esters were dried over magnesium sulfate and distilled before use. Reagent grade naphthalene was used directly. Baker Analyzed metallic sodium was cleaned of its oxide coating before use.

General Procedure for the Preparation of Sodium Naphthalenide. To 800 ml of dry, deoxygenated, cooled (−10°) THF containing 60.0 g (0.47 mol) of naphthalene was added 10.0 g (0.435 mol) of metallic sodium over a 30-min period. The dark green color of the naphthalenide formed within 1 min. The mixture was stirred under nitrogen for 12–15 hr before three 5-ml aliquots were removed, quenched in 50-ml portions of water, and titrated for total base with standardized hydrochloric acid solution to a phenolphthalein end point.

General Procedure for the Reaction of Sodium Naphthalenide with Esters. To the sodium naphthalenide solution cooled to ca. −10° was added via addition funnel a solution of the ester dis-

solved in 50 ml of dry THF. The temperature rose to about 10° during the 2 min required; the color changed from dark green to dark brown. After 2–5 min ice water was added and the pH adjusted to 5–7 with 6 *M* hydrochloric acid. The organic products were isolated by extraction with ether, washing with water, and drying over magnesium sulfate. The ethers were evaporated under vacuum and the products were separated by column or thin layer chromatography from silica gel. Some lots of silica gel caused partial decomposition upon column chromatography, so it was necessary to partially deactivate these by first washing the column with 1% ethyl ether–99% petroleum ether. Crude product fractions were combined and further purified by vacuum distillation. Yields are based upon ester.

Reaction of Ethyl Dimethylpropanoate with Sodium Naphthalenide. To 0.435 mol of sodium naphthalenide in 800 ml of THF was added 28.0 g (0.22 mol) of ethyl dimethylpropanoate. Isolation of the products as described in the general procedure and elution from a silica gel column with 50% petroleum ether–50% benzene resulted in the isolation of 7.0 g (0.033 mol, 15%) of crude 1-(2,2-dimethyl-1-propanoyl)-1,4-dihydronaphthalene. Distillation at 0.2 mm gave 5.6 g (0.026 mol, 12%) of the pure product: bp 113–116°; NMR (CCl_4) 1.13 (s, 9 H), 3.35 (broad m, 2 H), 4.82 (AB, 2 H), 5.93 (m, 2 H), 7.06 ppm (m, 4 H); ir (CCl_4) 3100, 1680, 1650, 750 cm^{-1}; MS *m/e* (rel intensity) 214 (3), 155 (30), 130 (14), 129 (100), 128 (59), 127 (25), 85 (10), 57 (54). Anal. Calcd for $C_{15}H_{18}O$: C, 84.11; H, 8.41. Found: C, 83.68; H, 8.32.

Further elution of the silica gel column with 10% ethyl ether–90% benzene yielded 14.2 g (0.044 mol, 43% based on ester) of crude 1,4-bis(2,2-dimethyl-1-propanoyl)-1,4-dihydronaphthalene, mp 51–59°. Recrystallization from ethanol yielded 7.3 g (0.024 mol, 22%) of the pure product: mp 95–97°; NMR (CCl_4) 1.10 and 1.27 (s, 18 H), 3.52 (m, 2 H), 4.20 (AB, 2 H), 5.97 (m, 2 H), 7.10 ppm ($A_2'B_2'$, 4 H); ir (CCl_4) 3100, 1680, 1650, 750 cm^{-1}; MS *m/e* (rel intensity) 298 (5), 215 (30), 119 (42), 106 (50), 85 (63), 57 (100). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.54; H, 8.72. Found: C, 80.27; H, 8.63.

Reaction of Ethyl Hexanoate with Sodium Naphthalenide. To 0.22 mol of sodium naphthalenide in 500 ml of dry THF was added 15.7 g (0.11 mol) of distilled ethyl hexanoate. Isolation as described in the general procedure followed by elution from a silica gel column with 10% ethyl ether–90% benzene resulted in the isolation of 11.5 g (0.50 mol, 46%) of crude 1-hexanoyl-1,4-dihydronaphthalene. Distillation resulted in the isolation of 8.4 g (0.38 mol, 33%) of the pure product: bp 113–116° (0.2 mm); NMR (CCl_4) 0.80–1.62 (m, 9 H), 2.10–2.45 (m, 2 H), 3.45 (m, 2 H), 4.33 (AB, 2 H), 5.95 (m, 2 H), 7.13 ppm (br s, 4 H); ir (CCl_4) 3070, 3050, 1700, 1650, 670 cm^{-1}; MS *m/e* (rel intensity) 228 (4), 157 (13), 155 (16), 131 (20), 130 (53), 129 (100), 128 (70), 127 (23), 99 (15). Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.79; H, 8.70.

Reaction of Ethyl Acetate with Sodium Naphthalenide. To 0.435 mol of sodium naphthalenide solution was added 19.5 g (0.22 mol) of distilled ethyl acetate. After 2 min, the reaction was quenched with ice water and the organic materials isolated in the usual manner. The 75 g of crude products was directly distilled without preliminary chromatography to yield 4.2 g (0.024 mol, 11%) of 1-ethanoyl-1,4-dihydronaphthalene: bp 100–109° (0.5 mm); NMR (CCl_4) 1.85 (s, 3), 3.46 (m, 2 H), 4.30 (AB, 2 H), 6.03 (m, 2 H), 7.16 ppm (br s, 4 H); ir (CCl_4) 3100, 1700, 725 cm^{-1}; MS *m/e* (rel intensity) 172 (8), 155 (28), 129 (13), 128 (93), 127 (100), 126 (44), 125 (10). Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.37; H, 6.87.

Reaction of Ethyl Benzoate with Sodium Naphthalenide. To 0.435 mol of sodium naphthalenide in 800 ml of THF was added 16.5 g (0.11 mol) of ethyl benzoate. Elution of the column resulted in the isolation of 9.9 g (0.047 mol, 86% based on ester) of benzil, mp 130–131°, and 0.55 g (0.0026 mol, 5% based on ester) of benzoin, mp 94–96°.

Proton Abstraction by Sodium Naphthalenide. To two 0.1 *M* tetrahydrofuran solutions of sodium naphthalenide at −10°C were added either 1.0 equiv of ethyl ethanoate or ethyl hexanoate. Analysis by GLC (10% polyphenyl ether on Anakrom ABS, 80/90 mesh, 125°, flow 0.5 cm^3/sec; 10% FFAP on Chromosorb W, 60/80 mesh, 125° flow 0.5 cm^3/sec) failed to detect either ester. Upon quenching with 10% hydrochloric acid, followed by GLC analysis, the major portions of these esters were regenerated.

Registry No.—Sodium naphthalenide, 3481-12-7; naphthalene, 91-20-3; sodium, 7440-23-5; ethyl dimethylpropanoate, 3938-95-2; ethyl hexanoate, 123-66-0; ethyl acetate, 141-78-6; ethyl benzoate, 93-89-0; 1-(2,2-dimethyl-1-propanoyl)-1,4-dihydronaphthalene, 56282-07-6; 1,4-bis(2,2-dimethyl-1-propanoyl)-1,4-dihydronaphthalene, 56282-08-7; 1-hexanoyl-1,4-dihydronaphthalene, 56282-09-8; 1-ethanoyl-1,4-dihydronaphthalene, 56282-10-1; benzil, 134-81-6; benzoin, 119-53-9.

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In Situ Reduction of Nitroxide Spin Labels with Phenylhydrazine in Deuteriochloroform Solution. A Convenient Method for Obtaining Structural Information on Nitroxides Using Nuclear Magnetic Resonance Spectroscopy

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Stable nitroxide free radicals have enjoyed wide use both in the study of biological systems with spin-labeling techniques[2] and in studies of the nature of bi- and polyradical systems.[3] Doxyl (4,4-dimethyloxazoline-*N*-oxyl) nitroxides are particularly important since the ring system can be either rigidly attached at the site of a ketone group[4] or readily assembled using the reaction of an organometallic reagent with an appropriate nitrone.[5] Owing to the paramagnetic nature of the nitroxide spin labels, however, one cannot conveniently gain the valuable structural information on these molecules afforded by NMR spectroscopy.[6] It occurred to us that essentially the same structural information could be obtained from the NMR spectra of the corresponding *N*-hydroxy amines, if a convenient method were available to prepare these normally air- and sometimes moisture-sensitive molecules quantitatively from the nitroxide, preferably in the NMR tube. We have therefore investigated the in situ reduction of a series of nitroxides in $CDCl_3$ using phenylhydrazine.[7]

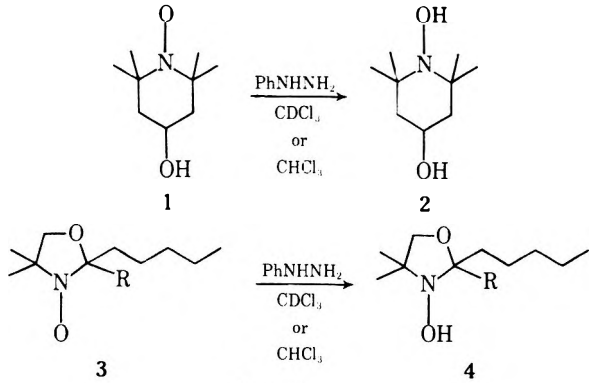
Thus, in situ reduction of the representative nitroxides **1**, **3a–c**, and **6**[8] in $CDCl_3$ with a solution of phenylhydrazine in $CDCl_3$ led smoothly to the corresponding *N*-hydroxy amines **2**, **4a–c**, and **7**[9] (Table I). The NMR spectrum of **2** was identical, except for absorption at δ ~7.3 (ArH), with that of pure **2** prepared from **1** by the method of Rosantsev.[7] When the phenylhydrazine reduction was carried out on a more concentrated solution of **1** (65.7 mg in 0.2 ml of $CDCl_3$), *N*-hydroxy amine **2** precipitated, recrystallization of which gave 53 mg (80%) of **2**, mp 155–159° (lit.[10] mp

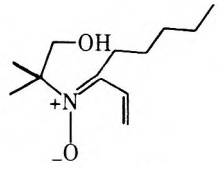
Table I
100-MHz NMR Spectra ($CDCl_3$) of Several *N*-Hydroxy Amines and Nitrone 5

Compd	Spectrum
2	δ 1.17 (6 H, s), 1.22 (6 H, s), 1.3–2.1 (4 H, m), 4.01 (1 H, m)
4a	δ 0.89 (3 H, m), 1.21 (3 H, s), 1.25 (3 H, s), 1.33 (3 H, s), 1.1–1.7 (8 H, m), 3.59 (1 H, d, J = 9 Hz), 3.65 (1 H, d, J = 9 Hz)
4b	δ 0.8–1.0 (6 H, m), 1.20 (6 H, s), 1.1–1.9 (10 H, m), 3.50 (2 H, s)
4c	δ 0.90 (6 H, m), 1.24 (6 H, s), 1.2–1.8 (20 H, m), 3.63 (2 H, s)
4d	δ 0.89 (3 H, m), 1.19 (3 H, s), 1.23 (3 H, s), 1.1–1.9 (8 H, m), 3.69 (2 H, s), 5.25 (1 H, m, J_{AB} = 2, J_{AC} = 11 Hz), 5.42 (1 H, m, J_{AB} = 2, J_{BC} = 18 Hz), 6.13 (1 H, d of d, J_{AC} = 11, J_{BC} = 18 Hz)
5	δ 0.90 (3 H, m), 1.60 (6 H, s), 1.1–1.8 (6 H, m), 2.65 (2 H, m), 3.73 (2 H, s), 5.45 (1 H, d, J = 11 Hz), 5.52 (1 H, d, J = 17 Hz), 5.99 (1 H, d of d, J = 11, 17 Hz)
7	δ 0.88 (3 H, t, J = 7 Hz), 1.13 (3 H, s), 1.16 (3 H, s), 1.1–1.7 (6 H, m)

158°). Structure assignments of the other *N*-hydroxy amines were verified by comparison of the respective NMR spectra with those of the crude substances synthesized by the nitrone method.[5,8] Additionally, nitroxides **1** and **3a** were recovered from the NMR experiments by copper-catalyzed oxidation[5,11] of the *N*-hydroxy amines **2** and **4a** in 90% yield after preparative TLC and shown to be identical with the original nitroxides by melting point in the case of **1** and by ir and mass spectral fragmentation pattern[12] in the case of **3a**.

When vinyl nitroxide **3d**[5] was reduced with phenylhydrazine, a time-dependent NMR spectrum was observed

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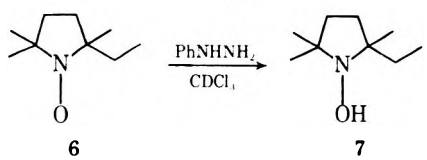

which, at first, corresponded to a ~3:1 mixture of *N*-hydroxy amine **4d** and its ring-opened nitrone isomer **5**. This latter substance was also observed as the major product when the vinyllithium–nitrone reaction[5,8] was carried out at 0°. After about 30 min the NMR spectrum of the phenylhydrazine reduction mixture corresponded to a ~1:2 mixture of **4d** and **5** together with some products of decomposition. Interestingly, when **3d** (9.7 mg in 0.3 ml of $CDCl_3$) was treated with an eight- to tenfold excess of 97% hydrazine, there was no immediate reaction. After 3 hr the yellow color had faded and the NMR spectrum was that of only **4d** plus hydrazine. Evaporation of the $CDCl_3$ and treatment of the residue with cupric ion in methanol gave back nitroxide **3d** in 86% yield after preparative TLC. The unusual propensity of **4d** to undergo ring opening to **5** undoubtedly is related to the added presence of the conjugated system in **5**.

Experimental Section

NMR spectra were recorded on a Varian XL-100 spectrometer using Me_4Si as an internal standard. Phenylhydrazine was freshly distilled. A fresh standard solution (0.03 *M*) of phenylhydrazine in $CDCl_3$ was made up prior to each series of experiments and used within a 0.5-hr period owing to the known slow reaction of phenylhydrazine with $CHCl_3$.[13] The progress of the reduction could be monitored visually by the disappearance of the yellow-orange color of the nitroxide. Comparative runs with crude phenylhydrazine gave identical NMR spectra but the resulting reduced solutions were always colored. The use of 0.5 molar equiv of phenylhydrazine minimizes the extraneous absorption in the aromatic region of the NMR spectrum. Otherwise, an excess of reagent has no undesirable effects.

General Phenylhydrazine Reduction Procedure. To a solution of ~5 mg of the nitroxide in 0.3 ml of $CDCl_3$ in an NMR tube was added ~0.5 ml (0.50 molar equiv) of 0.03 *M* phenylhydrazine in $CDCl_3$. After ~15 min at 25° the yellow-orange color had faded and the NMR spectrum was that of the corresponding *N*-hydroxy amine (Table I). Alternatively, a small drop of phenylhydrazine can be added directly to the nitroxide–$CDCl_3$ solution without using the standard solution when absorptions in the δ ~7.3 region are not of interest.

General Procedure for Recovery of the Nitroxide after Reduction. The solvent was evaporated from the reduced NMR sample. The residue was dissolved in 1 ml of MeOH containing 1 mg of cupric acetate monohydrate[5,11] and stirred under air for ~1 hr. The solution quickly became dark purple and then slowly changed to the characteristic yellow-orange color of the nitroxide. Concentration followed by preparative TLC over silica gel gave the pure nitroxide in high yield.

Acknowledgment. This investigation was supported by the National Science Foundation (09413) and Public Health Service Research Grant CA-17338 from the National Cancer Institute.

Registry No.—**1**, 2564-83-2; **2**, 3637-10-3; **3a**, 16263-51-7; **3b**, 55011-35-3; **3c**, 55011-36-4; **3d**, 55011-37-5; **4a**, 55011-31-9; **4b**, 55011-32-0; **4c**, 55011-33-1; **4d**, 55011-34-2; **5**, 56348-28-8; **6**, 56348-29-9; **7**, 4604-54-0; phenylhydrazine, 100-63-0.

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One-Bond and Two-Bond Homolytic Scission of *tert*-Butyl *p*-Nitrophenylperacetate[1]

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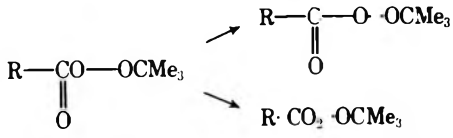
It is accepted that some *tert*-butyl peresters thermally decompose by one-bond scission (eq 1a) while others decompose by simultaneous scission of two bonds (eq 1b) so

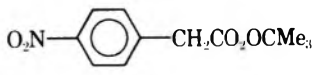


(1a)

(1b)

as to produce carbon dioxide in the primary step.[2-5] However, the proposal that a few peresters decompose simultaneously by both pathways[4,6] remains controversial.[3,5,7]

R groups which can become reasonably stable radicals (R·), such as diphenylmethyl,[2,6] trityl,[8] *tert*-butyl,[2,4,7,9,10] *p*-methoxybenzyl[3,6,11,12] and *p*-methylbenzyl,[6,11,12] lead to decomposition via path 1b, while phenyl,[2,13] vinyl,[14] methyl,[2-4] and ethyl[4] groups promote one-bond scission (eq 1a). One perester which has been proposed to decompose by both routes is *tert*-butyl *p*-nitrophenylperacetate (**1**).[6]

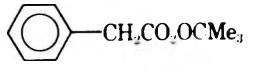


1

In this paper we present the results of a study of the effect of pressure on decomposition of **1** in the solvent cumene. We feel that the data indicate that **1** decomposes only by two-bond scission; however, the results are not unambiguous.

Results and Discussion

The rates of decomposition of **1** (cumene, 85°) at various pressures are given in Table I along with data for unsubstituted *tert*-butyl phenylperacetate (**2**) under the same conditions. The atmospheric pressure data for these two peresters give the solid point in Figure 1.[15] This Hammett plot for decomposition of ring-substituted *tert*-butyl phenylperacetates was drawn using data obtained by Bartlett (chlorobenzene, 90.7°)[11] and by Behar (cumene, 79.6°)[12]



2

Table I
Rate Constants for Decomposition of *tert*-Butyl *p*-Nitrophenylperacetate (1) and *tert*-Butyl Phenylperacetate (2) in Cumene at 85°

Perester	*P*, atm	$k \times 10^5$, sec^{-1}
1	1	3.10 ± 0.06
	1250	2.74 ± 0.04
	2000	2.73 ± 0.07
	3000	2.65 ± 0.04
	4000	2.71 ± 0.06
	6000	2.02 ± 0.07
2	1	13.2
	2000	12.3
	4000	10.6

[a] Ranges reported are derived from least-squares analysis of the kinetic data.

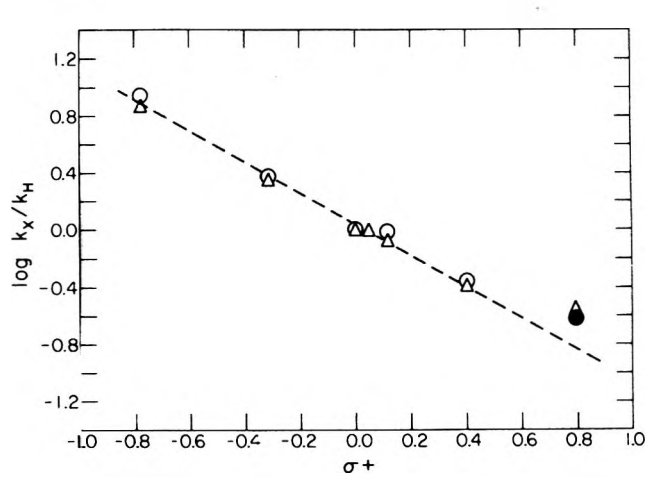
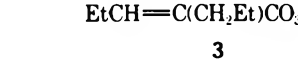


Figure 1. Plot of log (k_X/k_H) vs. σ^+ for thermal decomposition of ring substituted *tert*-butyl phenylperacetates where, from left to right, X = *p*-MeO, *p*-Me, H, *m*-Me, *p*-Cl, *m*-Cl, and *p*-NO_2 in chlorobenzene at 90.7° (△), cumene at 79.6° (○), and cumene at 85° (●)

and the fit of this solid point provides justification for comparison of these studies of **1** to the earlier data.[11,12] A question had been raised that the apparent positive deviation of Bartlett's point for **1** in chlorobenzene from the best straight line through the other points (Figure 1) might reflect induced decomposition.[11] The congruence of our data point for **1** in cumene with that for **1** in chlorobenzene suggests, however, that induced decomposition is probably not important. It seems unlikely that it would occur to the same extent in these two different solvents.

The data for **2** were determined at 85° not only to provide results for the Hammett plot, but to see if the same pressure dependence obtained in the earlier study[12] was observed. A comparison of the earlier data for **2** at 79.6° with those determined here at 85° (Figure 2) show that this is the case.

The data for **1** are plotted in Figure 2 along with those for *tert*-butyl phenylperacetate, *tert*-butyl trimethylperacetate,[7] *tert*-butyl dimethylperacetate[7] and the cis and trans isomers of *tert*-butyl 2-propyl-2-peroxypentenoate (**3**).[14] These latter two peresters decompose by one-bond



3

scission[14] (path 1a) while the trimethylperacetate is generally accepted to decompose by two-bond scission.[2,4,7,9,10] It seems to us that two families of curves are visible in this figure and that the data for **1** fall within that family with a

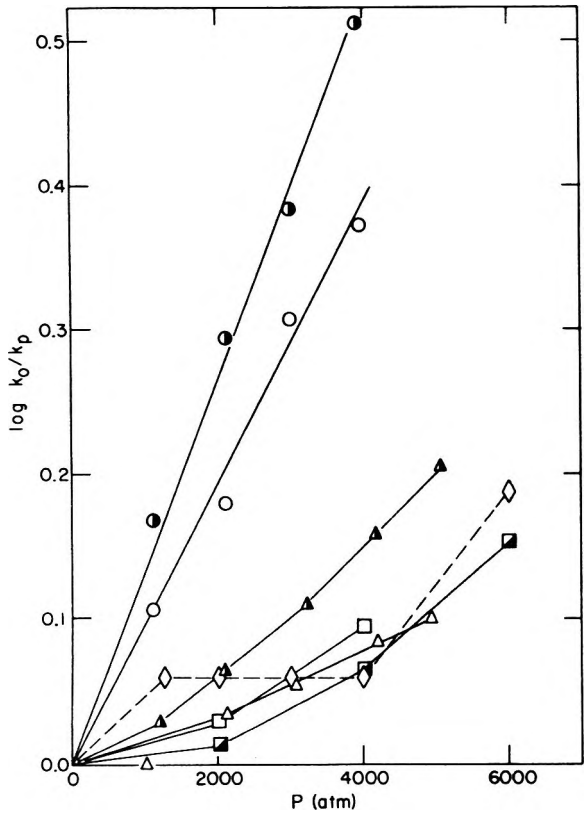


Figure 2. Pressure dependence of the decomposition rates of *cis*- (○) and *trans*- (◑) *tert*-butyl 2-propyl-2-peroxypentenoate, *tert*-butyl phenylperacetate (◪, 79.6°; □, 85°), *tert*-butyl trimethylperacetate (△), *tert*-butyl dimethylperacetate (▲), and *tert*-butyl *p*-nitrophenylperacetate (◇).

small pressure dependence that we have argued[5,7] is characteristic of a two-bond scission decomposition mechanism.[16]

The interpretation that 1 decomposes by two-bond scission would be consistent with kinetic isotope studies reported by Koenig.[3] The basis for proposing that 1 and some other peresters[17] decompose simultaneously by two mechanisms has been derived primarily from the effects of varying medium viscosity on the observed rates of decomposition of these peresters.[4,6] It is assumed that variation in the viscosity of solvents will not affect the rate of decomposition of peresters decomposing by path 1b, but that increasing viscosity will retard decomposition by path 1a because separative diffusion of the first formed radicals (k_d, eq 2)

$$\mathrm{RCO_2OCMe_3} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overline{\mathrm{RCO_2\cdot \cdot OCMe_3}} \overset{k_d}{\searrow} \quad (2)$$
$$\overset{k_r}{\searrow}$$

will be retarded causing the radicals to revert to starting perester (k_{-1}) a greater percentage of the time.

This "viscosity test" has been very useful in probing the decomposition mechanisms of a variety of free-radical initiators. Large rate retardations have been observed for various phenylazotriphenylmethanes, dialkyl peroxides, and diacyl peroxides, clearly demonstrating that one-bond scission occurs with "cage return" of the primary geminate radicals.[4,6] Conversely, a variety of symmetrical azo compounds as well as certain *tert*-butyl phenylperacetates including the *p*-methoxy and *p*-methyl substituted compounds show no rate dependence on viscosity suggesting two-bond scission decomposition mechanisms.[4,6]

However, in the cases of the peresters proposed to decompose by both paths the dependences of decomposition rates on solvent viscosity have been small and irregular. Since perester decompositions seem to involve polar contributions in the homolytic scission transition states,[5,7,11,12] we have suspected that the small effects observed with viscosity variation could be due to a combination of experimental uncertainty and solvation effects. Viscosity variation is accomplished by changing the solvent.[18]

Several years ago we showed that the effect of externally applied pressure on the rates of solution phase initiator decompositions could be used as a diagnostic test for one- *vs.* two-bond scission.[5,19] Pressure increases the viscosity of the solvent causing k_d to decrease, thus leading to a marked retardation of the apparent rate of initiator decomposition when cage return can occur (eq 2). The effect is similar to that of the viscosity test with two important distinctions: (1) the medium is not varied to achieve the viscosity change; and (2) all homolytic scission reactions, whether occurring by one- or two-bond scission, are retarded to some extent by pressure because homolytic scission leads to an expanded transition state.

The first point is an advantage because changes in solvation with medium variation are avoided. The second requires that a baseline be established for the pressure effect on homolytic scission processes uncomplicated by return. Extensive studies of a variety of radical initiators indicate that activation volumes for homolytic scission without return are less than or equal to +5 cm^3/mol, while activation volumes for scission complicated by return are substantially greater. Decomposition of 1 shows an overall pressure dependence less than that corresponding to a ΔV^* of +5 cm^3/mol. Between 1 and 1250 atm the apparent ΔV^* is +3 cm^3/mol, there is no significant effect of pressure on rate between 1250 and 4000 atm, and the ΔV^* between 4000 and 6000 atm is +4 cm^3/mol. Thus, we feel that 1 should be classified as a two-bond scission initiator. It is always possible that one-bond scission (path 1a) could occur without return and our data cannot distinguish this from two-bond scission. However, if the solvent dependence of the decomposition rate of 1 at atmospheric pressure[6] is due to an effect on diffusion which competes with return, we would have expected a much larger ΔV^* value in these pressure studies than that which was observed.

A troubling aspect of our results for 1 is the apparent plateau in the log k vs. P plot (Figure 2). Outside of experimental error, we have no ready explanation for this other than that it could indicate a mixture of mechanisms. In this case the shape of the curve would suggest a competition between a pressure-retarded process and one that was pressure accelerated. This would not be consistent with competing one- and two-bond scission (eq 1a and 1b) because both of these reactions would be pressure retarded. It could indicate the presence of induced decomposition facilitated by increasing pressure. This would lead to an apparent rate increase offsetting the pressure-induced retardation associated with bond scission. We have argued earlier against induced decomposition based on the comparative results in cumene and chlorobenzene. Also our prejudice is that any induced decomposition process would not overshadow the large ΔV^* value expected for one-bond scission with return. Thus we stand behind our interpretation of two-bond scission with the hope that future studies might clarify the unusual aspects of the data obtained here.

Experimental Section

Materials. All solvents were carefully purified. *tert*-Butyl hydroperoxide (Lucidol) was distilled (bp 34–35°, 18–20 mm) and its purity confirmed by iodimetric titration.

***tert*-Butyl Phenylperacetate.** This perester was synthesized from phenylacetyl chloride and *tert*-butyl hydroperoxide as previously reported:[13] ir 1775 cm^{-1}; NMR δ 7.04, 3.24, 1.06 with respective areas of 5, 2, and 9.

***tert*-Butyl *p*-Nitrophenylperacetate.** This perester was synthesized from *p*-nitrophenylacetyl chloride (mp 45.6–46.6°, ir 1800 cm^{-1}) and *tert*-butyl hydroperoxide by the procedure described by Bartlett and Rüchardt.[11] The compound was a crystalline solid: ir 1775 cm^{-1}; NMR δ 8.10, 7.40, 3.61, 1.20 with respective areas of 2, 2, 2, and 9.

Kinetic Studies. Thermal decomposition of 0.1 *M* solutions of the respective peresters in carefully purified cumene was monitored by infrared spectroscopy as previously described.[13] The high-pressure apparatus and procedures concerning its use in kinetic studies have been described in detail.[12,13]

Registry No.—**1**, 29540-08-7; **2**, 3377-89-7; *cis*-**3**, 33509-65-8; *trans*-**3**, 33509-66-9; *tert*-butyl trimethylperacetate, 927-07-1; *tert*-butyl dimethylperacetate, 109-13-7; *tert*-butyl *p*-methoxyphenylperacetate, 27396-21-0; *tert*-butyl *p*-tolylperacetate, 27396-20-9; *tert*-butyl *m*-tolylperacetate, 56391-29-8; *tert*-butyl *p*-chlorophenylperacetate, 27396-18-5; *tert*-butyl *m*-chlorophenylperacetate, 27396-17-4; *tert*-butyl hydroperoxide, 75-91-2.

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(15) The solid point corresponds to log $k_{p\text{-}NO_2}/k_H$ from Table I.
(16) The only other pressure data available for a one-bond scission perester are limited results for *tert*-butyl perbenzoate (R = phenyl)[15] which give a ΔV^* (and pressure dependence) even greater than those for the vinyl peresters.
(17) Besides *tert*-butyl *p*-nitrophenylperacetate, it had been suggested that *tert*-butyl phenylperacetate and *tert*-butyl dimethylperacetate also might simultaneously decompose by paths 1a and 1b[4,6] but the evidence was weak. In any case, earlier data reported by us seem to rule out this possibility for the latter two systems.[7,12]
(18) (a) Traylor[18b] has seen evidence for solvent effects using homologous saturated hydrocarbon solvents in which to decompose d-*tert*-butyl hyponitrite ($Me_3CON{=}NOCMe_3$), a compound most certainly decomposing via two-bond scission.[18c] (b) H. Kiefer and T. Traylor, *J. Am. Chem. Soc.*, **89**, 6667 (1967). (c) R. C. Neuman, Jr. and R. J. Bussey, *ibid.*, **92**, 2440 (1970).
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Chelation and the Nucleophilicity of α-Ketoaldehyde and α-Diketone Monophenylhydrazones

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Certain properties of hydrazones have been attributed to chelation. Thus, Fieser and Fieser[1] suggested that chelation of saccharide bishydrazones (osazones) was responsible for their stability, and Chapman[2] attributed to chelation the fact that osazone formation did not proceed beyond C-2 to give, for example, tris- or tetrakishydrazones. Further, it was suggested[3–5] that osazones form mono-*N*-acyl derivatives and not diacylated ones, because chelation inhibited the acylation of the imino nitrogen whose proton was involved in hydrogen bonding. By analogy, it was assumed that chelation was the reason why the bishydrazones of benzil and phenylglyoxal could only undergo monoacylation.[6–7]

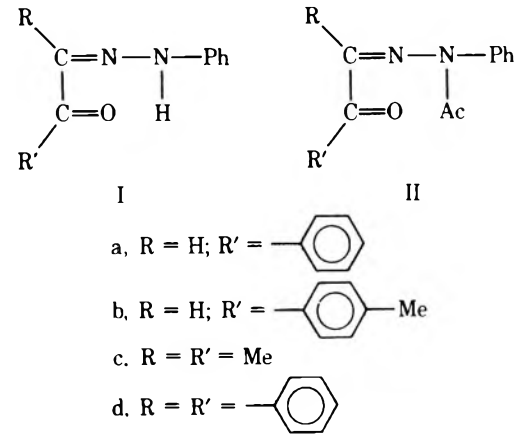
Table I
Summary of ^{1}H NMR Parameters[a]

Compd	Solvent	CH	NH	Aromatic	HC=	$-CH_3$
Ia	*b*	14.66	12.1	6.8–8.4	7.36, 7.91	
Ib	*b*	14.60	12.1	6.8–8.4	7.40, 7.96	2.28
Ic	*a*		8.1	6.9–7.4		2.01, 2.05
Id	*d*		7.9	7.4–8.1		
IIa	*c*			7.0–8.1	7.41	3.55
IIb	*b*			7.1–8.2	7.20	2.28, 2.50

[a] Chemical shift in δ from Me_4Si. [b] Pyridine-d_5. [c] Me_2SO-d_6. [d] $CDCl_3$.

To verify whether involvement of the imino protons of hydrazones in hydrogen bonding inhibited the ability of the imino nitrogen to undergo acylation, we studied the acetylation of substituted α-ketoaldehyde monophenylhydrazones and α-diketone monophenylhydrazones.

It was found that in substituted α-ketoaldehyde monophenylhydrazones of type I (R = H; R′ = Ar), acetylation occurred readily, affording the *N*-acetyl derivatives IIa or IIb. The latter compounds were completely colorless, unlike the starting monophenylhydrazones, which were yellow. On the other hand, substituted α-diketone monophenylhydrazones I (R = R′ = Me or Ph) resisted acetylation even on prolonged boiling with acetic anhydride.



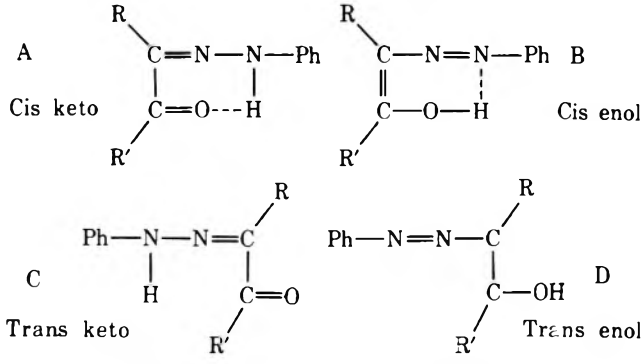
A correlation could be made between the reactivity of α-ketoaldehyde monophenylhydrazones (Ia and Ib) and their existence in chelated tautomeric forms. Their ^{1}H NMR spectra (see Table I) showed two resonances in the downfield region of the spectrum, one at δ 12.1 and one at δ 14.6, which together integrated for one exchangeable proton, suggesting their existence as equilibrium mixtures. The chemical shift of the signal at δ 12.1 was comparable to that of the chelated imino protons of bisarylhydrazones[8–10] and the signal at δ 14.6 was quite close to that of chelated enolic protons in bisaroylhydrazones.[11] Accordingly, the observed resonances at δ 12.1 and 14.6 were assigned to the chelated keto structure A and the enol structure B, respectively. Analogous keto–enol tautomerisms have been observed in bisaroylhydrazones.[11,12] The existence of compounds Ia and Ib in the form of tautomeric mixtures was also appar-

Table II

Compd	Mp, °C	Formula	Anal. %	C	H	N	Ir, cm^{-1}, C=O	Uv, λ, nm (log ε)
Ia	124–126	$C_{14}H_{12}N_2O$	F	74.81	5.27	12.44	1620	λ_{max} 375 (4.33), 284 (s) (4.24), 258 (4.38), 203 (4.32)
			C	74.98	5.39	12.49		λ_{min} 315 (3.56), 219 (3.95)
Ib	95–98	$C_{15}H_{14}N_2O$	F	75.47	5.81	11.72	1610	λ_{max} 380 (4.30), 286 (4.30), 245 (4.06), 206 (4.12)
			C	75.61	5.92	11.76	1595	λ_{min} 313 (3.26), 275 (3.94), 220 (3.88)
Ic	123–124	$C_{10}H_{12}N_2O$	F	68.54	6.92	16.12	1630	λ_{max} 338 (4.43), 295 (s) (3.91), 238 (4.11)
			C	68.16	6.86	15.90		λ_{min} 263 (2.76, 212 (3.50)
IIa	115–117	$C_{16}H_{14}N_2O_2$	F	72.38	5.29	10.42	1690	λ_{max} 284 (4.24), 206 (4.42)
			C	72.17	5.30	10.52	1624	λ_{min} 238 (4.12)
IIb	137–139	$C_{17}H_{16}N_2O_2$	F	72.72	5.62	9.92	1695	λ_{max} 286 (4.26), 206 (4.28)
			C	72.84	5.57	9.99	1650	λ_{min} 245 (3.66)

ent from the signals of their nonexchangeable protons, which were paired. Thus, two identical multiplets were observed at δ 8.3 and 8.1 for Ia and at δ 8.28 and 8.05 for Ib. Also, a pair of resonances for the azomethine proton was detected. The detection of separate signals for each of the two forms of Ia and Ib suggested that the exchange rate between the two forms was slow on the ^{1}H NMR time scale and that the mean lifetime of the proton in either state was longer than 0.1 sec.[13] From the integration of the different pairs of resonances, it could be determined that the ratio of form A to form B was 2:1 in both compounds Ia and Ib.

Acetylation of α-ketoaldehyde monophenylhydrazones Ia and Ib afforded *N*-acetyl derivatives (IIa and IIb), which existed in one form, and did not show any pairing of signals. The α-diketone monophenylhydrazones (Ic and Id), which did not react with acetic anhydride, existed also in one form. The chemical shift of their exchangeable proton occurred at about δ 8, and they were tentatively assigned the unchelated trans keto structures C. No enolic structures (D) could be detected for these compounds.



The ^{1}H NMR results were not inconsistent with the ir and uv spectra of compounds Ia–c and IIa,b (see Table II). Compounds Ic and Id, which resisted acetylation, showed a well-defined carbonyl absorption at ν 1630 and 1655 cm^{-1}, respectively. Similar carbonyl absorptions appeared at ν 1642 and 1650 cm^{-1} in the spectra of their *N*-acetyl derivatives IIa and IIb, which also showed acetamido bands at ν 1690 and 1695 cm^{-1}, respectively. Acetamido bands occur between ν 1690 and 1695 cm^{-1} in the spectra of N-acylated sugar osazones,[3,4,14] which show no C=N absorption in the ν 1610–1700-cm^{-1} region.[15] The latter is in support of the fact that the absorptions at ν 1630–1650 we observed are carbonyl absorptions. Compounds Ia and Ib showed only one band at ν 1620 and 1610 cm^{-1}, respectively.

In the ultraviolet–visible regions, the spectra of the reactive hydrazones Ia and Ib (see Table II) showed an absorption around λ 285 nm which appeared at the same wavelength in the spectra of their acetates IIa and IIb. In addition, compounds Ia and Ib showed two absorptions each, one around λ 250 nm and one around λ 380 nm, which were absent in the spectra of their acetates. Since the *N*-acetyl derivatives IIa and IIb are fixed in the keto form and lack the absorptions around λ 250 and 380 nm, these two bands in compound Ia and Ib were assigned to the enol form B and the absorption around λ 285 nm was assigned to the keto form A.

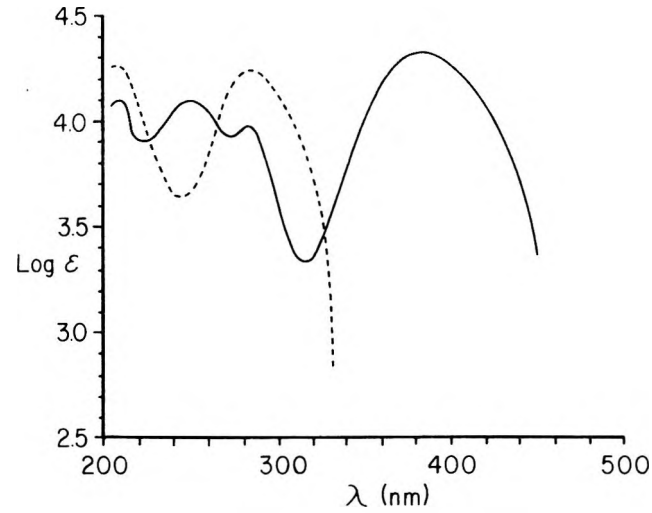


Figure 1. Ultraviolet–visible spectra of Ib (—) and IIb (---).

The reactivity of compounds Ia and Ib toward acetic anhydride can be attributed to the hydrogen bonding of the imino proton which enhances the nucleophilicity of the nitrogen of the imino group involved in chelation. The reactive forms of the tautomers of Ia and Ib seem to be the cis keto forms A in which hydrogen bonding would weaken the covalent N–H bond and render the nitrogen more nucleophilic. Another reason for the reactivity of compounds Ia and Ib could be that hydrogen bonding stabilizes an intermediate in the reaction.

It could be argued that in the cis enol form B the nucleophilicity of the oxygen might be enhanced to yield an *O*-acetyl derivative. However, no ester could be detected in the products of acetylation of Ia and Ib.

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were recorded at 100 MHz with a Varian HA-100 spectrometer. Thin layer chromatography (TLC) was performed on plates of silica gel precoated with a fluorescent indicator (Eastman Kodak Catalog No. 6060). Microanalyses were performed by Mr. M. P. Gilles, Department of Chemistry and Chemical Engineering, Michigan Technological University.

Acetylation Experiments. A. A solution of the substituted phenylglyoxal monohydrazone (1 g) in dry dimethylaniline (5 ml) was treated with acetyl chloride (10 ml) and set aside at room tem-

perature for 24 hr. The mixture was poured on crushed ice and the mono-*N*-acetyl derivative which separated out was filtered off, washed, and crystallized from ethanol.

B. A suspension of the phenylglyoxal monohydrazone (1 g) was heated under reflux with acetic anhydride (15 ml) for 5 hr. The mixture was poured on crushed ice and the mono-*N*-acetyl derivative which separated out was worked up as in A; (see Table II).

Registry No.—Ia, 5335-28-4; Ib, 56421-95-5; Ic, 13732-32-6; Id, 6630-86-0; IIa, 33877-94-0; IIb, 56404-20-7; acetyl chloride, 75-36-5; acetic anhydride, 108-24-7.

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Lithium–Ammonia Reduction of Benzyl Alcohols to Aromatic Hydrocarbons. An Improved Procedure

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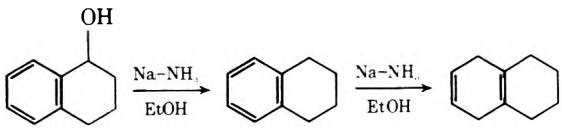
Some time ago Birch reported the reduction of a few benzyl alcohols to the corresponding aromatic hydrocarbons in sodium–ammonia–ethanol solutions.[1] The general procedure was to add small pieces of sodium periodically to a solution of the benzyl alcohol and ethanol in liquid ammonia. What was disconcerting to us was that these conditions were almost exactly those reported previously by the same researcher to reduce aromatic compounds to the corresponding 1,4-dihydro derivatives.[2] Since this work had been done long before gas–liquid partition chromatography or nuclear magnetic resonance spectroscopy, it seemed conceivable to us that under these conditions some overreduction might have occurred and mixtures obtained but not detected.



Since we had recently established that benzyl alcohols and their alkoxides are efficiently reduced to aromatic hydrocarbons in lithium–ammonia solutions that were quenched with ammonium chloride,[3] we undertook a careful comparative study of the two procedures using a selection of benzyl alcohols. The lithium–ammonia–ammonium chloride method involves the addition of the benzyl alcohol in THF to a solution of lithium in ammonia, and then the resultant mixture is rapidly quenched with ammonium chloride.

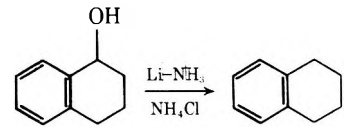
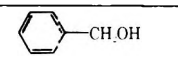
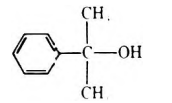
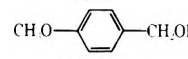
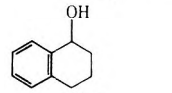
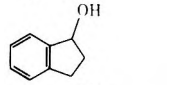
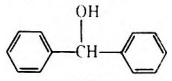
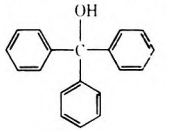


Table I

Registry no.	Benzyl alcohol	Na–NH_2–EtOH[a] products[b] Aromatic hydrocarbon	1,4-Dihydro derivative	Li–NH_3–NH_4Cl[a] products[b] Aromatic hydrocarbon	1,4-Dihydro derivative
100-51-6		100[c]		100[c]	
617-94-7		100[c]		100[c]	
105-13-5		64	12[d]	100[c]	
529-33-9		75	25	100[c]	
6351-10-6		85	15	100[c]	
91-01-0		94	6[e]	91	9
76-84-6		82	18[e]	88	12

[a] The reaction conditions are described in the Experimental Section. [b] Analyzed by GLC (% of volatiles). [c] Isolated in excellent yield (greater than 95%) in repeated experiments after column chromatography. [d] Plus 2,5-dihydro alcohol (10%) and unreacted alcohol (14%). [e] Predominantly the mono-1,4-dihydro derivative.

Table I summarizes the outcome of this study. The results of sodium–ammonia–ethanol reduction of benzyl alcohol, phenyldimethylcarbinol, and *p*-methoxybenzyl alcohol are substantially the same as were previously reported.[1] However extension of this procedure to other benzyl alcohols, such as 1-tetralol, 1-indanol, benzhydrol, and triphenylcarbincl, resulted, in most cases, in substantial overreduction. In contrast, the lithium–ammonia–ammonium chloride procedure was much more selective. All of the benzyl alcohols except benzhydrol and triphenylcarbinol yielded exclusively the corresponding aromatic hydrocarbon.

Evidently the major difference between the two reduction procedures is that the aromatic hydrocarbon product is overexposed to the strong proton source in the sodium–ammonia–ethanol procedure, while such contact is minimized in the lithium–ammonia–ammonium chloride method.

Experimental Section

General Comments. The reductions were performed under a dry N_2 atmosphere in dry glassware. Sodium metal was cut in small pieces, lithium wire (0.32 cm) was cut in 0.5-cm pieces, and both were rinsed in petroleum ether just prior to use. Anhydrous NH_3 was distilled through a KOH column into the reaction vessel. THF was freshly distilled from $LiAlH_4$. Analysis of reaction mixtures was accomplished by gas–liquid partition chromatography

(GLC) using a 4 ft × 6 mm (all glass) 4% silicone gum rubber UCC-W-982 (methyl vinyl) on 80–100 mesh HP Chromosorb W (AW, DMCS) column; and by gas–liquid partition chromatography–mass spectrometry (GLC–MS). All products gave satisfactory spectral and analytical data; mixtures were compared by GLC and GLC–MS with authentic samples.

Lithium–Ammonia–Ammonium Chloride. To a pear-shaped metal–ammonia reaction vessel containing a stirred mixture of 105 mg of Li (15 mg-atoms, six pieces) in 20 ml of NH_3 and 10 ml of THF was added (10 min) a solution of 741 mg (4.99 mmol) of 1-tetralol in 10 ml of THF. After 10 min, ca. 1.2 g of NH_4Cl was cautiously added (ca. 2 min) to discharge the blue color, and the NH_3 was allowed to evaporate. After the residue had been partitioned between brine and Et_2O, the organic phase was dried, filtered, concentrated, and analyzed by GLC and GLC–MS. Following column chromatography, 646 mg (98%) of tetralin was obtained as a colorless oil.

Sodium–Ammonia–Ethanol. To a stirred mixture of 741 mg (4.99 mmol) of 1-tetralol and 500 mg (10.96 mmol) of EtOH in 20 ml of NH_3 was added six pieces of Na (253 mg, 11 mg-atoms) over a 14-min period to maintain a dark blue solution. Approximately 12 min later the mixture turned white and then the NH_3 was allowed to evaporate. Work-up as described above yielded a mixture of tetralin (75%) and 5,8-dihydrotetralin (25%).

Registry No.—Toluene, 108-88-3; 1-methylethylbenzene, 98-82-8; 1-methoxy-4-methylbenzene, 104-93-8; 1,2,3,4-tetrahydronaphthalene, 119-64-2; 2,3-dihydro-1,4-indene, 496-11-7; 1,1′-methylenebis(benzene), 101-81-5; 1,1′,1″-methylidynetris(benzene), 519-73-3.

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Transfer of Oxygen to Organic Sulfides with Dimethyl Sulfoxide Catalyzed by Hydrogen Chloride. Preparation of Disulfoxides

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The transfer of oxygen from a sulfoxide to a sulfide has been reported,[3] but with limited success as a preparative method. Thus, Bordwell and Pitt[3a] isolated dibenzyl sulfoxide in 17% yield from a tarry mixture obtained by refluxing an acetic acid solution of dibenzyl sulfide and fourfold excess 1-thiacyclopentane 1-oxide in the presence of sulfuric acid. Barnard[3b] observed oxygen exchange up to ca. 7% equilibration between ^{35}S-labeled cyclohexyl methyl sulfoxide and a large excess of inactive cyclohexyl methyl sulfide by heating the mixture with acetic acid containing a trace of perchloric acid. Searles and Hays[3c] prepared di-*n*-propyl, di-*n*-butyl, and tetramethylene sulfoxides by heating the respective sulfides with Me_2SO for several hours at 160–175°. The reaction was accompanied by considerable pyrolysis. They were unsuccessful in catalyzing the reaction with acids.

In connection with an investigation of metal ion complexes of 2,5-dithiahexane 2,5-dioxide (**1**),[4] one of us attempted to prepare the ligand by transferring oxygen from Me_2SO to 2,5-dithiahexane. In the absence of catalysts no reaction occurred, even on boiling the mixture for many hours at approximately 180°. However, the addition of small amounts of hydrogen chloride to the mixture catalyzed the reaction at about 100° and afforded the desired disulfoxide in good yield.[5]

Since the method has advantages over the procedures with conventional oxidizing agents, we report here the preparation of disulfoxides from sulfides of the type $RS(CH_2)_nSR$ ($n \geq 2$, R = alkyl or benzyl). We were unable to *isolate* sulfoxides from formals ($n = 1$), or from other mercaptals and mercaptoles. Instead we obtained oxidative cleavage, generating formaldehyde (or the analogous carbonyl compounds), the disulfide RSSR, and dimethyl sulfide—a consequence of the rapid acid-catalyzed decomposition of monosulfoxides $RS(O)CR'_2SR$,[6] which would form initially by O-transfer from Me_2SO.

In recent years, the effects of halogen halides, and particularly HCl, on sulfoxide behavior, including racemization,[7] and O-exchange[8] reactions, have been investigated intensively.[9] A common intermediate appears to be the halosulfonium ion, e.g., Me_2SCl, whose formation, via protonated sulfoxide, is kinetically dependent on both H^+ and halide ion, and usually rate determining. The completion of the process would involve relatively fast reactions with nucleophilic agents, e.g., H_2O regenerates the sulfoxide, halide ion effects racemization (specifically by Cl^- or Br^-), or reduction to sulfide (especially by I^-). Modena[9] includes sulfides among the nucleophiles which would react with halosulfonium ions. Accordingly, O-transfer with Me_2SO would proceed as follows.

$$Me_2SO \xrightleftharpoons[\text{several steps}]{2HCl} \underset{+H_2O}{Me_2\overset{+}{S}Cl\ \bar{Cl}} \xrightleftharpoons{R_2S} \underset{+Me_2S}{R_2\overset{+}{S}Cl\ \bar{Cl}} \xrightleftharpoons{H_2O} R_2SO + 2HCl$$

This course would appear to be more reasonable than direct involvement of protonated sulfoxide by nucleophilic attack of sulfide on oxygen,[3a,10] and would explain catalysis by halogen acid specifically as opposed to acids in general.

The advantages of the HCl-catalyzed Me_2SO method include cheapness of reagent, the absence of overoxidation which inevitably occurs with conventional oxidizing agents,[11] and the relatively simple isolation and purification of the product. The reaction is unfortunately limited to nonaromatic sulfides.

The disulfoxide preparations are summarized in Table I. The crude products usually have a wide melting range, expected of a mixture of diastereoisomers (*dl* pair and meso). Recrystallization was used to isolate at least one isomer, both in the case of **3** and **4**.

Infrared Spectra. All products absorb most intensely at ca. ν 1000–1050 cm^{-1}, typical of the sulfoxide SO stretching frequency (see Table I). As a test of oxidation methods—Me_2SO vs. commonly used oxidizing agents—we prepared **1**α and **2** with H_2O_2 in acetic acid,[12a,b] and **1**α also with sodium metaperiodate,[13] and determined their ir spectra. In the sulfoxide region the analogous spectra are indistinguishable. Thus, whether produced by Me_2SO or the other methods, **1**α shows a broad band with a maximum at ca. 1018 cm^{-1} and **2**, distinct bands at 1019 (more intense) and 1044 cm^{-1}.[14] However, elsewhere in the spectrum, as shown in Table II, there are significant differences. We offer the following explanations for extra bands in the spectra of products of peroxide and periodate oxidation.

Compound 1α. Shoulders at 1307, 1318, and 1324 cm^{-1} and the band at 1139 cm^{-1} suggest the sulfone group.[15a,b] The bands at 508 and 520 cm^{-1} (peroxide method) and at 538 and 551 cm^{-1} (periodate method) may also be associated with sulfone.[15b] A band at 1267 cm^{-1} appears in the

Table I
Disulfoxides $RSO(CH_2)_nSOR$

Compd	n	R	Name	Yield, %	Mp, °C Crude	Mp, °C Recryst (solvent)	Ir max, ν (KBr), cm⁻¹	Anal C, % Calcd	Anal C, % Found	Anal H, % Calcd	Anal H, % Found
1	2	Me	1,2-Bis(methylsulfinyl)ethane	73	125–164	α 169–170[a] (ethanol)	1018	31.15	31.33[b]	6.54	6.58[b]
2	2	Et	1,2-Bis(ethylsulfinyl)ethane	62	146–148	149–149.5[c] (ethanol)	1019				
3	2	Pr	1,2-Bis(propylsulfinyl)ethane	63	140–147	α 161–162.5[c] (benzene–hexane, 3:2 v/v)	1012	45.68	45.84	8.70	8.70
						β 111–112[d] (benzene–hexane, 1:2 v/v)	1013	45.68	45.68	8.70	8.61
4	2	$PhCH_2$	1,2-Bis(benzylsulfinyl)ethane	82	140–191	α 228–229[e] (ethanol)	1020	62.71	62.96	5.92	5.92
						β 196–197[e] (*p*-xylene)	1020	62.71	62.79	5.92	5.89
5	3	Me	1,3-Bis(methylsulfinyl)propane[f]	65	114–116	117–118 (tetrahydrofuran)	1050	35.69	35.09	7.19	6.85
6	4	Me	1,4-Bis(methylsulfinyl)butane[g]	71	117–121	120–122[h] (ethyl acetate)	1035	39.53	39.76	7.74	7.95
7	4	Pr	1,4-Bis(propylsulfinyl)butane	25	125–127	126–127.5 (tetrahydrofuran)	1015	50.38	50.54	7.30	9.22
8	5	Me	1,5-Bis(methylsulfinyl)pentane[f,g]	52		113–114 (ethanol)	1019	42.83	42.49	8.22	8.65
9	6	Me	1,6-Bis(methylsulfinyl)hexane[f,i]	59	94–104	106–108[h] (benzene)	1021	45.68	45.20	8.63	8.92

[a] Reference 12a reports mp 163–164°. [b] Analysis courtesy of GAF Corp.; also found S, 41.44, 41.12 (calcd: S, 41.57). [c] Reference 12b reports that oxidation with either H_2O_2 or HNO_3 gives only one disulfoxide with mp 150°. [d] Percent ratio α:β, 60:40. [e] Percent ratio α:β, 84:16. [f] Very hygroscopic. [g] We thank C. W. Muhlhausen for preparing compounds 6 and 8. [h] D. Jerchel, L. Dippelhofer, and D. Renner, *Chem. Ber.*, 87, 947 (1954), report compound 6, mp 110–111°, compound 9, mp 113–114°. [i] Purification was not very satisfactory. There appeared to be two very hygroscopic compounds present.

spectrum of the unoxidized 1,2-bis(methylthio)ethane,[16] suggesting the presence of some unoxidized sulfide in both the peroxide and periodate oxidation products.

Compound 2. Bands at 1318 and 1137 cm^{-1} (peroxide method) may arise from the sulfone group.[15a,c] Also the band at 528 cm^{-1} compares with the 533-cm^{-1} band of the disulfone,[15c] and contrasts with the absence of bands in the region 450–600 cm^{-1} for the disulfoxide prepared with Me_2SO. No explanation is offered for the band at 743 cm^{-1}, which is absent in the spectrum of the Me_2SO product.

In conclusion, it appears that disulfoxides produced by the Me_2SO O-transfer method are purer than the respective products of conventional oxidants, and probably free of sulfone contamination.

Experimental Section

The sulfides were prepared by standard methods[17] or purchased from commercial sources and used as received. Other chemicals were reagent grade. Melting points were determined in the Fisher-Johns or the Gallenkamp apparatus and were corrected. Carbon and hydrogen analysis were carried out in the F. B. Strauss Microanalytical Laboratory, Oxford, England. Infrared analyses were run in the Perkin-Elmer 457 grating infrared spectrophotometer.

General Procedure. In a well-ventilated hood, a mixture of 10–100 mmol of bis sulfide with 50–100% excess Me_2SO and 2–6 mol % HCl[18] was heated in a steam bath or oil bath at 80–100° until the evolution of dimethyl sulfide (Me_2S) subsided. The Me_2S was trapped in an ice bath or allowed to escape. After cooling to room temperature, the disulfoxide mixture was filtered, washed with ether or benzene to remove excess Me_2SO and unreacted sulfide, and recrystallized from alcohol or other solvent (see Table I). Except for evaporation losses, the HCl appeared in the filtrates.

Sample Preparation. 1,2-Bis(methylsulfinyl)ethane (1). A mixture of 10.4 g (85 mmol) of 1,2-bis(methylthio)ethane,[16] 20 ml (21.3 g, 273 mmol) of Me_2SO, 0.18 g (2 mmol) of 12 *M* HCl, and a few boiling chips in an erlenmeyer flask was heated overnight on the steam bath. After cooling, the mixture was filtered with suction, and the solid was washed three times with a few milliliters of benzene and dried, giving 9.6 g of mixed disulfoxides. Heating the filtrate for an additional 3 hr[19] gave 0.5 g, total 10.1 g (77%), mp 125–164°. Three crystallizations from ethanol gave mp 169–170° (lit.[12a] α, 163–164°; β, 128–130°).

Table II
Comparison of Ir Spectra of Disulfoxides Prepared with Me_2SO and Analogous Products Prepared with H_2O_2 or $NaIO_4$, ν (KBr), cm^{-1}

1,2-Bis(methylsulfinyl)ethane (1α) ν, cm^{-1}			1,2-Bis(ethylsulfinyl)ethane (2) ν, cm^{-1}	
Me_2SO	H_2O_2	$NaIO_4$	Me_2SO	H_2O_2
1298[a]	1298[b]	1298[b]	*e*	1318[f]
c	1267	1267		
1122	1122	1122	1125	1125
d	1139	1139	*g*	1137
			h	743[i]
	508			
j	528	538	*j*	528
		552		

[a] Single narrow band. [b] Shoulders at 1307, 1318, and 1324 cm^{-1}. [c] No band at 1267 cm^{-1}. [d] No band at 1139 cm^{-1} (cf. twin bands 1122 and 1139 cm^{-1} in case of H_2O_2 and $NaIO_4$ products). [e] No band at 1318 cm^{-1}. [f] Single narrow band. [g] No band at 1137 cm^{-1} (cf. twin bands at 1125 and 1137 cm^{-1} in case of H_2O_2 product). [h] No band at 743 cm^{-1}. [i] Single narrow band. [j] No bands at 450–600 cm^{-1}.

The disulfoxides 2-9 listed in Table I were prepared similarly. Except for the bis(benzylsulfinyl) compounds (4), the disulfoxides are substantially water soluble and several were sufficiently hygroscopic to present difficulties in handling and analysis.

Compounds 1 and 2 (Method of Bell and Bennett).[12] The procedure with hydrogen peroxide in glacial acetic acid gave essentially the results previously reported: **1α**, mp 164–165°; **1β**, mp 129–130.5° (lit.[12a] α, 163–164°; β, 128–130°); **2**, mp 146–147° (lit.[12b] 150°). The ir spectrum of **1β** is essentially the same as that of **1α**.

Compound 1α (Method of Leonard and Johnson).[13] The procedure with $NaIO_4$ was essentially as described, except that the water solution of the product was deionized by passing successively through Dowex 1-X4 and Dowex 50W-X8 resins, followed by evaporation and three crystallizations from ethyl acetate, mp 165–167° (lit.[12a] 163–164°).

Registry No.—**1**, 10349-04-9; **2**, 10483-95-1; *dl*-**3**, 56391-04-9; *meso*-**3**, 56348-32-4; *dl*-**4**, 56348-33-5; *meso*-**4**, 56348-34-6; **5**, 56348-35-7; **6**, 56348-36-8; **7**, 56348-37-9; **8**, 56348-38-0; **9**, 50512-41-9; Me_2SO, 67-68-5; 1,2-bis(methylthio)ethane, 6628-18-8; 1,2-bis(ethylthio)ethane, 5395-75-5; 1,2-bis(propylthio)ethane, 22037-97-4; 1,2-bis(benzylthio)ethane, 24794-19-2; 1,3-bis(methylthio)propane, 24949-35-7; 1,4-bis(methylthio)butane, 15394-33-9; 1,4-bis(propylthio)butane, 56348-39-1; 1,5-bis(methylthio)pentane, 54410-63-8; 1,6-bis(methylthio)hexane, 56348-40-4.

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(16) Product of Aldrich Chemical Co.: ir (neat, NaCl disks).
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(18) 12 *M* HCl was added to the mixture or premixed with Me_2SO to concentration of 0.2–0.5 *M* HCl. Premixed solutions, stored on the shelf for months, retained their titer and reactivity.
(19) *Caution.* Benzene should be trapped to avoid noxious vapors.

A Convenient New Procedure for Synthetic Reactions of Gaseous Alkenes via Automatic Gasimetry

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Syntheses involving gaseous alkenes often prove problematic, especially where stoichiometric control of reagents is desired. Where justified by continual need, a variety of systems have been developed, e.g., the use of constant-pressure controllers coupled with wet test flow meters. In most cases, however, the occasional user resorts to one of three methods. Either the gas is passed through the reaction mixture in considerable excess (resulting in loss and disposal requirements for considerable quantities of flammable gas) or contained in gas burets (cumbersome for all but very small scale), or else the reaction is run in a pressurized autoclave (with complications for subambient temperature operation). Of these three, only the gas buret is readily amenable to stoichiometric control. In connection with other work, we have had occasion to carry out such reactions and find a marked convenience in quantitative automatic gasimetry.

Quantitative automatic gasimetry[1] has proven valuable both in synthesis and in reaction studies. With this technique—first employed in hydrogenation—the gaseous reagent is generated as needed to supply the reaction at a constant pressure, the gas being generated by automatically controlled mixing of two solutions. In addition to hydrogen,[1,2] HCl,[3] CO,[4] O_2,[5] and CO_2[6] have been utilized. In many cases considerably higher yields are obtained through ready optimization of reaction times.[3,5]

Gaseous alkenes are readily prepared by addition of the corresponding 1,2-dibromoalkane to a hot suspension of zinc powder in ethylene glycol. Of the numerous methods envisioned which have been tested, this alone met the requirements: rapid *and* quantitative alkene generation; lack of gel or precipitate formation; and available, inexpensive reagents. Reactions were carried out in an apparatus (Figure 1) modified from the hydrogenator previously described[1] by addition of heating for the generator and insertion of a U-tube packed with porous $CaCl_2$ as a trap between the generator and reactor. The concentration of neat

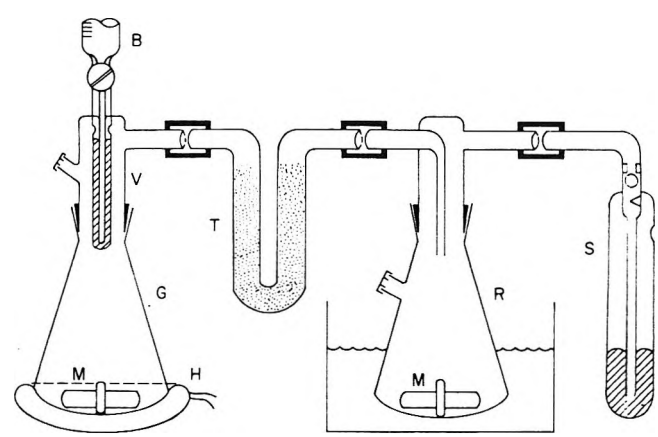
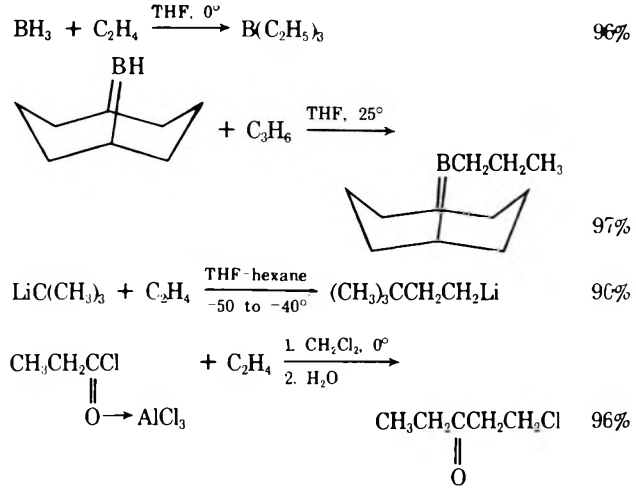


Figure 1. Automatic gasimeter adapted from Brown[a] hydrogenator (Delmar Scientific Glass Division of Coleman Instruments Co., Maywood, Ill.): ////, mercury; B, buret containing dibromide; V, mercury valve for regulating addition of dibromide to maintain constant gas pressure; G, generator flask; H, heating mantle; M, poly-TFE covered magnetic stirring bar; T, trap packed with $CaCl_2$; R, reactor flask; S, mercury safety bubbler with anti-back-up check valve.

Scheme I[a]



[a] 0.95–1.05 equiv of alkene uptake in all cases.

1,2-dibromoethane and 1,2-dibromopropane, 11.6 and 9.6 *M*, respectively, proved excessive for use with common laboratory-scale reactions (10–200 mmol); 2–5 *M* solutions of the dibromoalkane in diethylene glycol or ethylcarbitol were employed.

The technique has proven useful for hydroboration,[7] anionic addition of organolithium,[8] and aliphatic acylation,[9] as shown in Scheme I. The last reaction has particular potential, as β-chloroethyl ketones are precursors of two versatile synthetic intermediates—isomerically pure vinyl ketones and Mannich bases of methyl ketones.[10]

Experimental Section

Ethylene (General Procedure). A 5 *M* solution of 1,2-dibromoethane (dried over $CaCl_2$, 94.0 g, 43.1 ml. per 100 ml solution) in diethylene glycol or similar solvent was placed in the buret. The 250-ml generator flask was charged with 35–40 g of technical zinc *powder* and 100 ml of ethylene glycol. The mixture in the generator was aggitated with a magnetic stirrer and heated to 90–100°. The apparatus was purged with dry nitrogen and the reaction mixture was introduced into the reactor. Then 0.5 ml of 1,2-dibromoethane was added to the generator. When gas evolution was observed at the bubbler, 8–9 ml of *neat* 1,2-dibromoethane was added to maintain vigorous gas evolution, purging the reactor with ethylene (~2.5 l. is produced). Upon cessation of gas evolution, stirring was begun in the reactor; the stirring rate was adjusted so that ethylene uptake did not exceed 7.5 mmol/min.

A parallel procedure was used to generate propylene from 1,2-dibromopropane. With 5.0 *M* dibromide solution, 20.5–21 ml produced 100 mmol of alkene.

***B*-Ethyl-9-borabicyclo[3.3.1]nonane.** A 125-ml reaction flask (magnetic stirring bar, injection port sealed with a rubber septum) was attached to the gas generator and purged with dry nitrogen. Into the flask was placed 56 ml (25.0 mmol) of 0.44 *M* 9-borabicyclo[3.3.1]nonane (9-BBN) in THF.[11a] The flask was placed in a 20° water bath and purged with ethylene; reaction was initiated by slowly bringing the stirrer up to the desired speed. After an initial surge saturating the solution with ethylene (0.09 mmol of C_2H_4/ml of solution) absorption continued until 25.0 mmol of ethylene had been consumed in 1.0 hr. Prolonged further stirring had no effect. Hydrolysis of a sample of the reaction mixture with THF–methanol showed no active hydride remaining.[11b] Oxidation of the reaction mixture at 0° with $NaOH$–H_2O_2[12] produced 24.3 mmol of ethanol by GLC (decane standard, UCON Polar liquid phase), a yield of 97% based on B–H or on ethylene.

***B*-*n*-Propyl-9-borabicyclo[3.3.1]nonane.** In the manner described for the *B*-ethyl compound, 9-BBN was reacted with propylene. The solution dissolves 0.55 mmol of propylene/ml. The reaction was complete in 1.0 hr, absorbing 26.1 mmol of propylene. The yield was 97% based on B–H, 93% based on propylene.

1-Chloro-3-pentanone. The 1:1 complex of propionyl chloride with aluminum chloride was ethenated in dichloromethane (2.0 *M* concentration) at 0° as described by McMahon et al.[10c] After 60 min (104 mmol of C_2H_4 used) the reaction mixture was hydrolyzed with 6.5 molar equiv of water and the $AlCl_3 \cdot 6H_2O$ sand was separated. GLC of the filtrate (decane standard, polyester column) showed 96% yield of 1-chloro-3-pentanone.

Neohexyllithium. *tert*-Butyllithium was ethenated at −40 to −50° in pentane–THF as described by Bartlett et al.[8] in 90% yield, based on reaction of the product with methyl borate and then oxidation to neohexyl alcohol.[13]

Registry No.—1,2-Dibromoethane, 106-93-4; ethylene, 74-85-1; propylene, 115-07-1; *B*-ethyl-9-borabicyclo[3.3.1]nonane, 52102-17-7; 9-borabicyclo[3.3.1]nonane, 280-64-8; *B*-*n*-propyl-9-borabicyclo[3.3.1]nonane, 1127-78-2; 1-chloro-3-pentanone, 32830-97-0; propionyl chloride 1:1 complex with aluminum chloride, 36379-65-4; neohexyllithium, 6909-52-0; *tert*-butyllithium, 594-19-4.

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Basicity of the Carbonyl Group. V. Applicability of the Taft–Pavelich Equation to Cyclic Systems with Reference to the Complexation Enthalpy of Cyclic Ketones Using Boron Trifluoride

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Experimental calorimetric data verify the Taft–Pavelich equation for inductive and steric effects in substituted five- and six-membered rings.

The use of linear free energy relationships of the form $\log k/k_0 = \rho^*\sigma^* + \delta E_s$ (I) (the Taft–Pavelich equation) has spread to numerous fields of experimental science[1] since the initial work of Taft[2] on the separation of the polar and steric effects of substituents.

We have recently shown[3] that eq II

$$\Delta H^0_R = (3.74 \pm 0.22)\,\sigma^* - (0.77 \pm 0.17)E_s - 18.21 \text{ kcal mol}^{-1} \quad \text{(II)}$$

can be applied in a satisfactory manner to the reaction enthalpy of CH_3COR ketones with boron trifluoride over a

Table I
Complexation Enthalpies (kcal mol^{-1}) of Saturated Cyclic Ketones

Ketone	$\Sigma\sigma^{*}$ [a]	$-\Delta H^0_{calcd}$ [b]	$-H^0_{exp}$ [c]	$\Delta H^0_{exp} - \Delta H^0_{calcd}$	h [d]	δE_s [e]	Registry no.
Cyclopentanone	−0.200	19.29	18.94 ± 0.10	0.35	0	0	120-92-3
2-Methyl-	−0.290	19.62	18.83 ± 0.21	0.79	0.44	0.36 ± 0.08	1120-72-5
2,2-Dimethyl-	−0.400	20.04	18.20 ± 0.09	1.84	1.49	1.19 ± 0.26	4541-32-6
2,3-Dimethyl-	−0.310	19.70	18.93 ± 0.27	0.77	0.42	0.36 ± 0.08	14845-37-5
2,4,4-Trimethyl-	−0.315	19.72	18.90 ± 0.07	0.82	0.47	0.36 ± 0.08	4694-12-6
2,2,4-Trimethyl-	−0.415	20.09	18.31 ± 0.24	1.78	1.43	1.19 ± 0.26	28056-54-4
Cyclohexanone	−0.230	19.40	18.62 ± 0.20	0.78	0.07	0	108-94-1
2-Methyl-	−0.325	19.76	18.54 ± 0.19	1.22	0.51	0.36 ± 0.08	583-60-8
3-Methyl-	−0.240	19.44	18.85 ± 0.11	0.59	−0.12	0	591-24-2
4-Methyl-	−0.260	19.51	18.90 ± 0.31	0.61	−0.10	0	589-92-4
2,2-Dimethyl-	−0.425	20.13	18.04 ± 0.18	2.09	1.38	1.19 ± 0.26	1193-47-1
3,3,5-Trimethyl-	−0.290	19.62	18.77 ± 0.09	0.85	−0.14	0	873-94-9

[a] Values taken from ref 1 and 2 or calculated by the method of W. A. Seth Paul and A. Van Duyse, *Spectrochim. Acta, Part A*, 28, 211 (1972). [b] Calculated by means of eq II. [c] Experimental value, and 95% confidence interval (0.5 *M* in CH_2Cl_2). The experimental method has been described: J. F. Gal, L. Elegant, and M. Azzaro, *Bull. Soc. Chim. Fr.*, 1150 (1973); 411 (1974). [d] Difference between the value ($\Delta^+H^0_{exp} - \Delta H^0_{calcd}$ for the α-substituted and the α-unsubstituted ketone (0.35 kcal for the cyclopentanone and mean value of 0.71 kcal for cyclohexanones). [e] Calculated steric effect; see text.

Table II
Complexation Enthalpies (kcal mol^{-1}) of 1-Cyclohexen-2 one

Ketone	$\Sigma\sigma^{*}$ [a]	$-\Delta H^0_{calcd}$ [b]	$-\Delta H^0_{exp}$ [c]	$\Delta H^0_{exp} - \Delta H^0_{calcd}$	h [d]	δE_s [e]	Registry no.
1-Cyclohexen-2 one	+0.210	17.75	19.53 ± 0.19	−1.78	+0.11	0	930-68-7
5,5-Dimethyl-	+0.195	17.81	19.60 ± 0.24	−1.79	+0.10	0	4694-17-4
4-Methyl-	+0.185	17.85	19.70 ± 0.09	−1.85	+0.04	0	5515-76-4
4,4-Dimethyl-	+0.150	17.98	20.10 ± 0.26	−2.12	−0.23	0	1073-13-8
4,4,6-Trimethyl-	+0.050	18.39	19.47 ± 0.19	−1.08	+0.81	0.36 ± 0.08	13395-73-8
4,4,6,6-Tetramethyl-	−0.060	18.76	19.37 ± 0.22	−0.61	+1.28	1.19 ± 0.26	32264-57-6
3-Methyl-	−0.115	18.97	21.40 ± 0.04	−2.43	+0.06	0	1193-18-6
3,5-Dimethyl-	−0.125	19.01	21.60 ± 0.22	−2.59	−0.10	0	1123-09-7
3,5,5-Trimethyl-	−0.165	19.16	21.60 ± 0.16	−2.44	+0.05	0	78-59-1

[a-e] See Table I.

range of 4.5 kcal (correlation coefficient 0.9833, standard deviation 0.30 kcal, number of data points 14, confidence level >>99%).

In the present communication, we demonstrate that eq II can be used to analyze the variation in the reaction enthalpies of methylcyclopentanones, -cyclohexanones, and -cyclohexenones[4] with BF_3 by separating the inductive and steric effects of the substituents.

Our analysis of the contribution of the inductive effect of the methylene groups of the ring is based on two hypotheses.

(1) The inductive effect is equal to the effects of two "pseudo-substituents" obtained by dividing the ring with a plane passing through the C–O bond axis and bisecting the carbonyl π bond. If a carbon atom occurs in this plane, it is included in each of the two pseudo-substituents.

(2) The inductive effects of the two pseudo-substituents are additive toward the carbonyl group.

The additivity of the inductive effects is a well-known experimental fact. For example, the ionization potential of R_1COR_2 ketones is linearly related to ($\sigma^*_{R_1} + \sigma^*_{R_2}$).[5]

Moreover, the ionization potentials of 3-pentanone and of cyclopentanone as well as those of 4-heptanone and of cyclohexanone are practically identical. This justifies the mode of separation adopted.

The σ^* parameters for the five- and six-membered rings have been evaluated elsewhere;[6] they are only slightly different from the $\Sigma\sigma^*$ (pseudo-substituents).

Using the ρ^* value obtained for aliphatic ketones and the reaction enthalpy of acetone (taken as the reference Lewis base) $\Delta H^0_0 = -18.54$ kcal mol^{-1}, we can calculate a ΔH^0_{calcd} (Table I) in which the steric effect is identical with that of the reference compound. The difference $\Delta H^0_{exp} - \Delta H^0_{calcd}$ is remarkably constant *for an identical substitution α to the carbonyl group in the same ring*. For cyclopentanone itself, this value is 0.35 kcal and the average for the four cyclohexanones which are not substituted at the α position is 0.71 kcal. The smaller experimental reactivities of the rings compared to the calculated ones may be the result of the approximation of the inductive effect or of a more marked steric effect in the rings relative to acetone. The latter alternative is the most likely: it is known that the steric effect increases in going from an aliphatic system to a cyclic system and then to a bicyclic system.[7]

Qualitatively, a steric effect in the same order can be obtained by examining the values of E_s—$E_s(i\text{-Pr}) < E_s$ (cyclopentyl) $< E_s$ (cyclohexyl)[2]—or the values of E_s calulated for the polymethylene cyclic groups.[8]

$$E^c_s(CH_2)_4 = -0.04;\ E^c_s(CH_2)_5 = -0.15$$

If this contribution to ΔH^0_R due to cyclization is deduced from the values $\Delta H^0_{exp} - \Delta H^0_{calcd}$ for the α-substituted carbonyl compounds, the steric effect of these substituents can be obtained (Table I, column h). For an α-methyl group, we obtain a contribution of 0.44 ± 0.03 kcal (average for cyclopentanones) and of 0.51 kcal (2-methylcyclohexa-

none). For *gem*-dimethyl substitution, we obtain 1.46 ± 0.03 kcal (average for 2,2-dimethylcyclopentanones) and 1.38 kcal (2,2-dimethylcyclohexanone). These values are remarkably close for the two types of rings and correspond, moreover, to the product δE_s, taking the δ value of eq II, E_s (α-methyl) = E_s (i-Pr) and E_s (α-dimethyl) = E_s (t-Bu) (Table I, last column).

The equation obtained for aliphatic ketones is therefore applicable to analogous cyclic systems (i.e., substituted on one side of the carbonyl group).

Equation II cannot be applied[3] to ketones bearing substituents situated on both sides of the carbonyl group, because the angle of the C=O → B bond differs from 180°.[9] The steric effect with regard to BF_3 is therefore not additive and much greater in these systems.

Taking into account the cyclization effect, we obtain

$$\Delta H_R^0 = 3.74\ \Sigma\sigma^*\ (\text{pseudo-substituents}) - 0.77E_s + \Delta H_0^0 \qquad \text{(III)}$$

with $\Delta H_0^0 = -18.19$ kcal mol^{-1} for the cyclopentanones and -17.83 kcal mol^{-1} for the cyclohexanones, taking into account the conventions used previously for the values of σ^* and E_s.

Equation III reproduces the values of the ΔH_{exp}^0 within the limits of accuracy of eq II.

The same method has been applied to the complexation enthalpies of cyclohexenones (Table II).[10]

In this series, one can equally observe the constancy of the term $\Delta H_{exp}^0 - \Delta H_{calcd}^0$ for an identical substitution α to the carbonyl group and to the double bond. The latter assumes a negative value because of the increase in basicity due to conjugation with the carbonyl. This effect is increased by the substitution of the double bond by a methyl group in position 3. The calculated steric effect (Table II, column h) is similar to that obtained with saturated ketones. Equation III can therefore be used with $\Delta H_0^0 = -20.43$ kcal mol^{-1} (-21.03 for a methyl group in position 3).

In conclusion, our method of analysis of inductive and steric effects in these ring systems enables us to calculate the complexation enthalpies of cyclic ketones with BF_3 with a very fair degree of accuracy, comparable to that of experimental values. Recently, others approaches have been proposed for the evaluation of steric or inductive effects in cyclic compounds: computation by molecular mechanics[11] or from experimental data.[12]

We feel that an important result of our work is the demonstration that only "classical" parameters (σ^*, E_s) are necessary to describe the basicity of aliphatic and cyclic ketones, using the same Taft–Pavelich equation. It has also been stated that E_s values will correlate structural or reactivity data provided that the concerned groups are in a structural surrounding which does not induce an important conformational preference of the group.[13] In our case, the cyclization of the alkyl chain reduces the steric effect to that of atoms or groups close to the function, i.e., at the α position of the carbonyl. This effect is thus easily evaluated from an equivalent substituent. Work is in progress on several series of mono- and bicyclic carbonyl compounds containing substituents possessing a wider range of inductive and steric effects. The behavior of more hindered systems such as t-BuCOR ketones is also under investigation.

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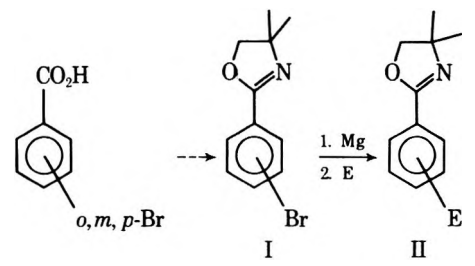
Oxazolines. XVII. Regioselective Metalation of 2-Aryl Oxazolines. A Route to Polydeuteriobenzoic Acids

Summary: The ortho-lithiation of 2-aryl oxazolines with *n*-BuLi has been shown by deuterium incorporation studies to provide a source of deuteriated benzoic acids.

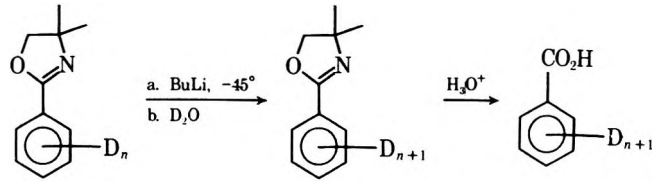
Sir: We recently reported[1] a method for the elaboration of bromobenzoic acids via the Grignard reagent of their 4,4-dimethyl-Δ^2-oxazoline derivatives, I (eq 1). We wish to describe an extension of this work which obviates the need for the ortho bromo substituent and enables the preparation of polysubstituted benzoic acid derivatives through consecutive metalations of the aromatic ring.

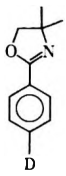
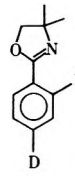
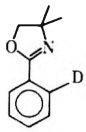
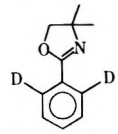
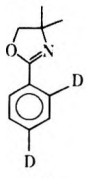
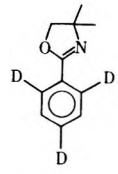
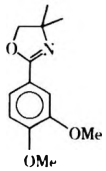
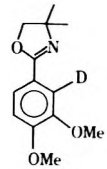
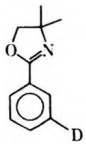
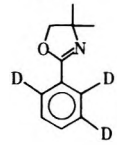


I II (1)

It is well known that anisole and benzamides undergo metalation with organolithium reagents predominantly in the ortho position.[2] Precoordination of the lithium base with the adjacent lone pairs followed by abstraction of the adjacent ortho proton has been proposed as a possible

Table I
Deuteration of Phenyl Oxazolines



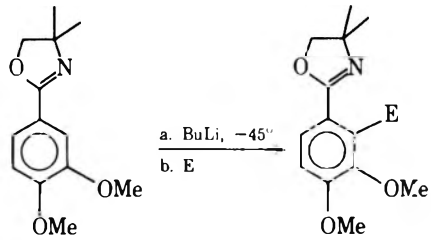
Entry	Oxazoline[a]	Conditions[b]	Product[c] (%)[d]	Benzoic acid % yield[d]	Benzoic acid Deuterium ratio[e] $d_0:d_1:d_2:d_3:d_4$
1		A	 (90)	76	0:9:100:6:0
2		B	 (90)	82	0:13:100:5:0
3		B	 (92)	79	0:0:21:100:7
4		A	 (95)	71	3:100:13:0:0
5		C	 (88)	77	0:4:44:100:11

[a] Oxazolines were prepared as previously described.[1] Monodeuterio compounds were conveniently obtained by halogen–metal exchange of the bromides with *n*-BuLi (THF, −78°) followed by D_2O quenching. [b] Method A, stirred with 1.1 equiv of *n*-BuLi for 1.5 hr and quenched at −45° with D_2O; method B, stirred with 1.1 equiv of *n*-BuLi for 6 hr before quenching at −45°; method C, oxazoline sequentially subjected to conditions A and B. [c] Deuterium incorporation was complete within the limits of NMR spectroscopy. [d] Yields are for distilled or recrystallized materials. [e] Mass spectral data at 70 eV.

mechanism. We now report the rapid and efficient metalation of oxazolines II (E = D) with *n*-BuLi in THF at −45°. Table I shows a series of experiments run to determine the extent and position of metalation. The ease of metalation and the high selectivity observed are particularly noteworthy. The low temperature employed both limits unwanted side reactions[3] and provides a large isotope effect enabling selective hydrogen abstraction[4] (entries 2, 3, and 5). Entry 4 illustrates the ability to have other substituents on the ring. In this case, the 3-methoxy group enhances metalation in the 2 position through participation of its lone pairs in the coordination step.

The following procedure is illustrative. To 0.405 g (2.3 mmol) of 2-(4-deuteriophenyl)-4,4-dimethyl-Δ^2-oxazoline in 30 ml of THF under N_2 at −45° (Dry Ice–chlorobenzene bath) was added 1.1 ml of 2.3 *M* *n*-BuLi in hexane (2.6 mmol, 1.1 molar equiv) and the solution was stirred for 1.5 hr. Excess D_2O (1–2 ml) was then added; the mixture was allowed to warm to ambient temperature and poured into ether. After washing, drying ($MgSO_4$), and concentration there was obtained a clear oil which on distillation (bulb to bulb, pot temperature 60° at 0.05 mmHg) afforded 0.365 g (90%) of 2-(2,4-dideuteriophenyl)-4,4-dimethyl-Δ^2-oxazoline, pure by NMR analysis. Direct hydrolysis of this material in 20 ml of 4.5 *N* HCl (reflux, 4 hr) gave 0.195 g (76%) of fine needles (mp 121°) after recrystallization from water. The benzoic acids obtained in this manner were all analyzed for deuterium content by mass spectral techniques (Table I). The desired deuteriobenzoic acids were formed in 80–87% isotopic yield except for entry 5 which was performed in sequence in a single vessel. In this instance the trideuteriobenzoic acid was obtained in 63% isotopic yield. These experiments have not been optimized and further effort should produce higher yields of the intended deuterio derivatives.

In addition to deuteration, other electrophiles were added to the o-lithiated aryl oxazolines. As expected,[2] substituted derivatives were obtained in high yields.[5] Thus III, after addition of *n*-butyllithium, was treated with dimethyl disulfide or *N*-chlorosuccinimide and furnished IV [92%;



III IV, E = SMe V, E = Cl

oil; ir (film) 1655 cm^{-1}; NMR (CCl_4) δ 7.2 (d, 1), 6.7 (d, 1), 4.0 (s, 2), 3.9 (s, 6), 2.4 (s, 3), 1.33 (s, 6)] and V [90%; oil; ir (film) 1650 cm^{-1}; *m/e* (70 eV) 270 (M^+), 272 (M + 2); NMR ($CDCl_3$) δ 7.5 (d, 1), 6.9 (d, 1), 4.1 (s, 2), 3.9 (s, 3), 3.8 (s, 3), 1.4 (s, 6)].

The versatility of oxazolines to serve as precursors to a variety of functional groups[6] amplifies the usefulness of these reactions and we are currently applying the above findings to the preparation of aromatics present in natural products.

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(3) At higher temperatures, the butyllithium will slowly add to the C=N link of the oxazolines giving rise to small quantities of 2-(*n*-butyl)-2-aryl oxazolidines.
(4) K_H/K_D is calculated to be 14 at −45° from the equation $K_H/K_D = e^{(1200/T\ 99\times T)}$
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Reduction of Organic Halides by the System Titanocene Dichloride–Magnesium

Summary: A titanocene dichloride–magnesium system reduces organic halides under mild conditions and in good yield.

Sir: The chemical reactivity of titanocene, generated by the reduction of titanocene dichloride (I), has been the subject of considerable interest.[1] Recent evidence[1e,2] suggests the following scheme for the reduction of I with sodium under argon.

$$\mathrm{I} \rightarrow (\pi\text{-Cp})_2\mathrm{TiCl} \rightarrow \underset{\mathrm{II}}{[(\pi\text{-Cp})_2\mathrm{Ti}]_{1,2}} \rightarrow [(\pi\text{-Cp})(\mathrm{C_5H_4})\mathrm{TiH}]_2 \rightarrow [(\pi\text{-Cp})(\mathrm{C_5H_4})\mathrm{TiH}]_x$$

Titanocene,[3] or its dimer (i.e., II), has been implicated in the various reductions induced by this system.[1c,e,f]

It has been shown[4] that the organotitanium species generated by the action of powdered magnesium on I reduces molecular nitrogen. Presumably the action of magnesium on I proceeds via a sequence similar to that shown above. We have investigated the reactions of the titanocene dichloride–magnesium system with organic halides and found that they are reduced in good yield.

The reducing system was generated by the addition of excess finely powdered magnesium to a stirred solution of I under argon. A color change from the characteristic red color of I to green, then black, was noted.[4] The compound to be reduced was rapidly added to this system at 0°. The reaction was then immediately quenched by the addition of the resultant mixture to water. The product was isolated by ether extraction.

The efficiency of this reducing system is illustrated by the reduction of azo compounds.[5] The reductions of diethyl azodicarboxylate (75%), dimethyl azodicarboxylate (77%), diphenyl azodicarboxylate (67%), and azobenzene (75%) are representative and proceed in the yields specified.

It should be noted that the azo compounds were recovered unchanged from exposure to magnesium powder alone under identical conditions. Furthermore, comparable yields of hydrazo products were obtained by filtering the reducing system to remove the unreacted magnesium prior to the addition of the azo compounds.

Table I
Reduction of Organic Halides by the Titanocene Dichloride–Magnesium System

Halide	Product[a]	Yield, %[b]
1-Bromononane	Nonane	84
1-Chlorodecane	Decane	87
1-Chlorononane	Nonane	79
2-Chlorooctane	Octane	87
2-Bromobiphenyl	Biphenyl	89
2-Bromooctane	Octane	87
Diethyl bromomalonate	Diethyl malonate	79
2-Bromocycloheptanone	Cycloheptanone	68[c]
2-Bromonaphthalene	Naphthalene	85

[a] All compounds were identified by comparison of their physical and spectral properties with those of authentic samples. [b] Yields were determined by GPC analysis. [c] A 10% yield of cycloheptanol was also isolated from this reduction.

The reduction of organic halides[6-8] proceeds smoothly at 0° in the presence of the reducing system under investigation. Both alkyl and aryl halides are reduced smoothly and under mild conditions. In addition, both alkyl bromides and chlorides are easily reduced in contrast with a recent report presumably involving $(\pi\text{-Cp})_2\text{TiH}$.[8] The results for a number of alkyl and aryl halides are included in Table I.

$$\text{RX} + (\pi\text{-Cp})_2\text{TiCl}_2 \xrightarrow{\text{Mg}} \xrightarrow{\text{H}_2\text{O}} \text{RH}$$

When the reaction mixture was quenched with deuterium oxide, rather than water, the product hydrocarbons did not contain deuterium, thereby excluding the possibility that the product is formed by hydrolysis of a Grignard reagent formed from the halide and unreacted magnesium. This is further supported by the observation that GPC analysis reveals the presence of hydrocarbon product even prior to hydrolysis. Moreover, when an ether solution of the Grignard reagent derived from *n*-decyl bromide was added to the precooled (vide supra) reducing medium at 0° and hydrolyzed with deuterium oxide, the hydrocarbon product, obtained in 85% yield, was 88% decane-d_1. This suggests that the hydrocarbon produced directly in the reducing medium does not derive by attack of an initially formed Grignard reagent with the organometallic consistuents of the medium.

When a sample of 1-chlorodecane was subjected to an equimolar amount of titanocene-d_{10}[9] (96.0% deuterium) in THF, an 87% yield of decane (70.0% decane-d_1 by mass spectral examination) was obtained after hydrolysis with water. This indicates that the reducing hydrogen originates from the cyclopentadienyl ligands.[10,11]

Table I summarizes the results of the reduction of some representative alkyl and aryl halides. In addition, α-halo ketones and esters can be reduced. The yields recorded are all good.

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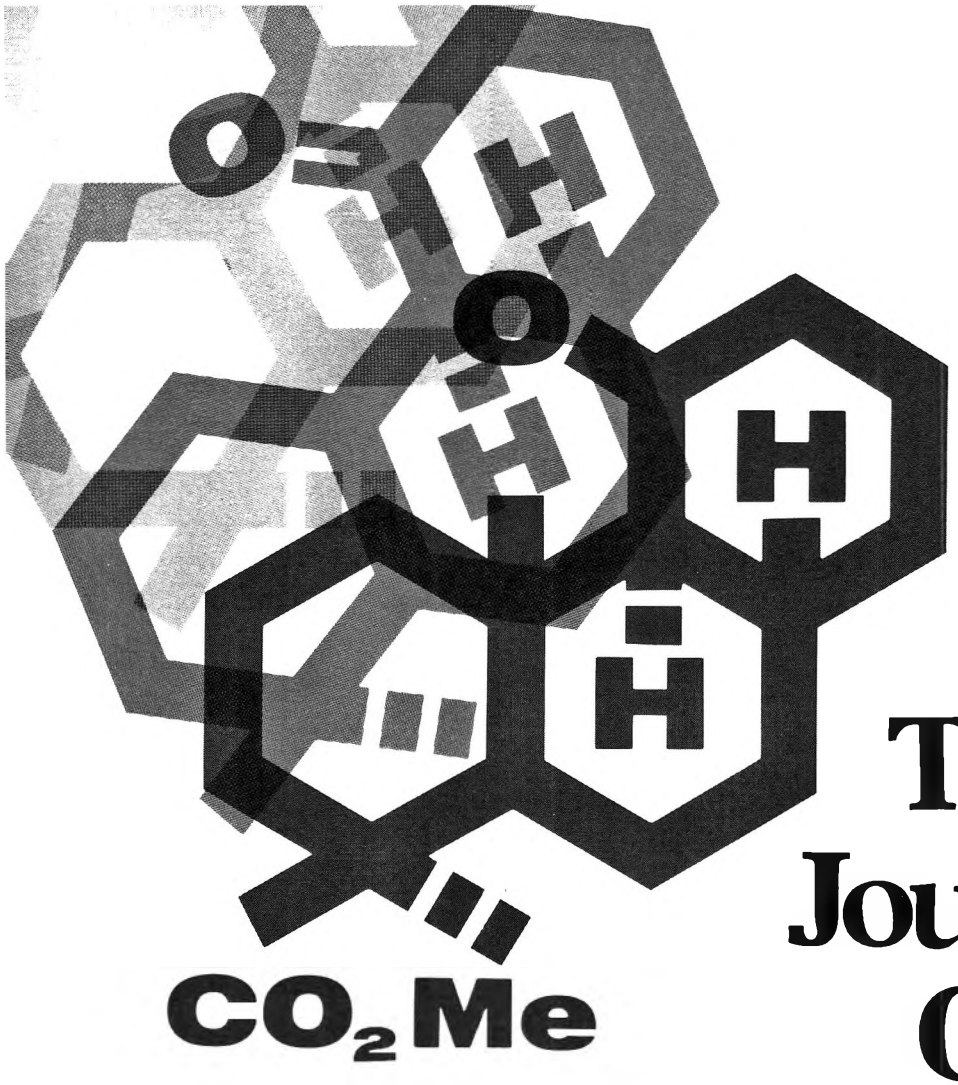

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Trifluoromethyl Reagents

Trifluoroacetic Anhydride

One of the most important uses of **trifluoroacetic anhydride (TFAA)** is in the preparation of peroxytrifluoroacetic acid,[1] a remarkable oxidizing agent. **Peroxytrifluoroacetic acid,** readily prepared from 90% hydrogen peroxide and **TFAA** in methylene chloride,[1] is the reagent of choice for Baeyer-Villiger oxidations,[2] hydroxylation of olefins,[3] epoxidation in the presence of sodium carbonate,[3] oxidation of anilines to nitrobenzenes[4] and the preparation of pyridine *N*-oxides which cannot be formed with peroxybenzoic and peroxyacetic acids.[4]

TFAA readily acylates primary and secondary alcohols and has been used to protect 11-hydroxy groups in steroids,[5] 1-halosugar hydroxyls,[5] and an amine[5] in the synthesis of a D-glucosamine nucleoside. In addition, **TFAA** enables the esterification of highly hindered acids and alcohols; *e.g.*, a mixture of mesitoic acid and mesitol in **TFAA** yielded mesityl mesitoate in high yield.[6] Mixed anhydrides useful in preparing malonic anhydrides for pyrolysis to ketenes are obtained in 50-60% yield simply by refluxing a mixture of **TFAA** and a carboxylic acid.[5] The reaction of **TFAA** with trimethylamine *N*-oxide forms *N,N*-dimethylformaldiimmonium trifluoroacetate which gives Mannich bases in higher yields[7] than classical Mannich conditions.

TFAA also catalyzes the acylation of activated aromatic compounds, olefins and acetylenes. A mixture of cyclohexene, acetic acid and **TFAA** yields cyclohexenyl methyl ketone in 48% yield.[5] **TFAA** is far superior to phosphorus pentoxide for the cyclization of a phenothiazinecarboxylic acid (93% yield).[5] Beckmann rearrangements which give water-soluble amides have been performed in higher yield using **TFAA** because of much simpler product isolation.[5]

Trifluoroacetic Acid

Trifluoroacetic acid (TFA) is useful for cleaving *N*-benzyloxycarbonyl (*N*-carbobenzoxy), *t*-butoxy and benzyl groups[8] as well as trichloroethyl esters and replaces acetic acid for the HBr cleavage of protective groups.[8] **TFA** enables a one-step synthesis of flavones from phenols and malonic acid,[9] efficiently catalyzes thioketal formation,[10] and is useful in olefin cyclization developed by Johnson.[8,11] **TFA** is also a good solvent for nmr spectroscopy.

Trifluoromethanesulfonyl- (CF_3SO_3-), a Better Leaving Group

Conductivity measurements in acetic acid have established that **trifluoromethanesulfonic acid,** a stable, nonoxidizing liquid, is the strongest proton acid known. The acid readily forms oxonium compounds from oxygen-containing substrates.

Trifluoromethanesulfonic anhydride, trifluoromethanesulfonyl chloride and **silver trifluoromethanesulfonate** are useful for preparing trifluoromethanesulfonate esters. The excellent leaving ability of the $CF_3SO_3^-$ anion is evident from the 41,500 times faster generation of vinyl cations from the trifluoromethanesulfonate ester (triflate) than from the analogous tosylate.[12] Vinyl triflates have been used in a novel, convenient synthesis of *t*-butylacetylene from pinacolone, a reaction of potential general application.[13]

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