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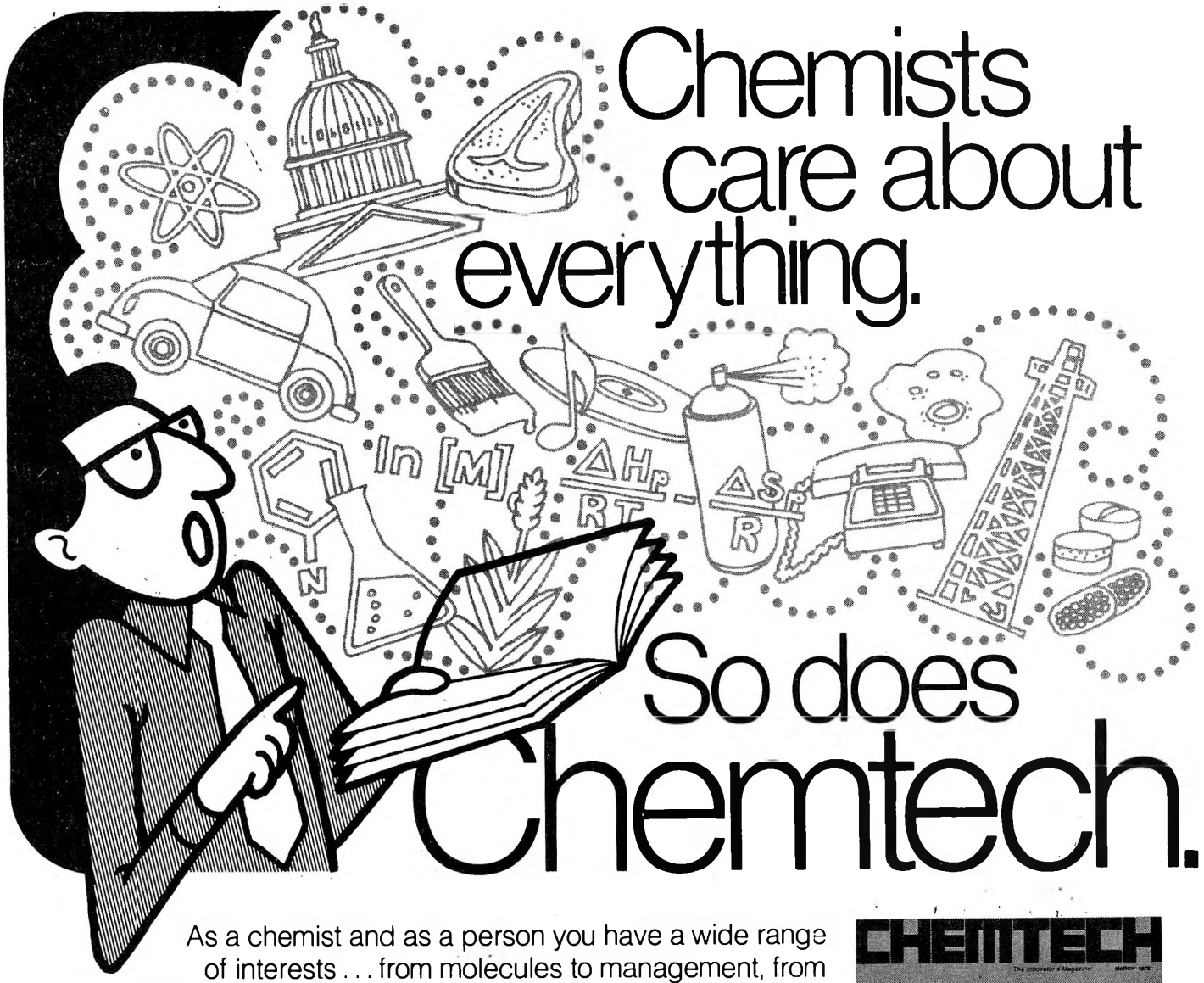

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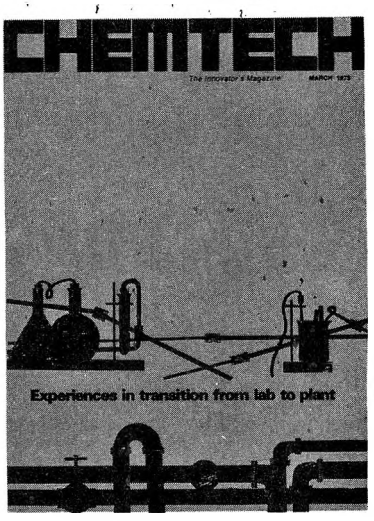

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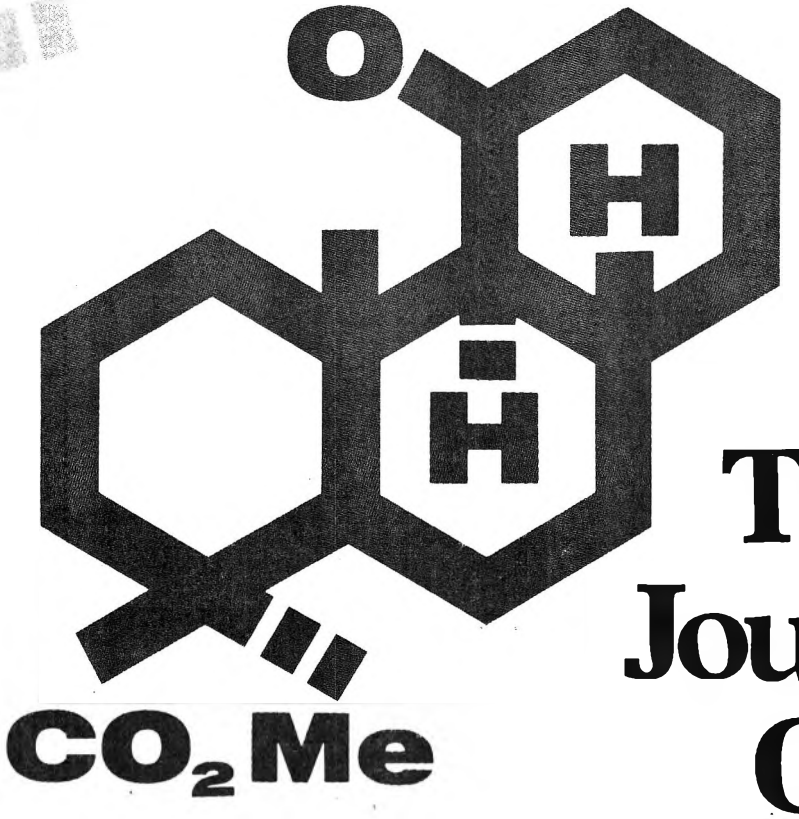

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JANUARY 7, 1977

Dehydrogenation and Coupling Reactions in the Presence of Iodine and Molten Salt Hydrogen Iodide Acceptors

Charles T. Adams, Stanley G. Brandenberger,* J. B. DuBois, George S. Mill, M. Nager, and Davis B. Richardson

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Received June 20, 1976

Organic compounds are dehydrogenated cleanly and in high yield at 500–650 °C by iodine in the presence of molten salt hydrogen iodide acceptors; iodine is generated in situ by oxidation of the molten metal iodide-containing salt. This method provides a direct route to molecules not readily available by other synthetic methods. For example, *p*-diisopropenylbenzene is obtained in 72% yield by dehydrogenation of *p*-diisopropylbenzene. These reactions occur by a free-radical mechanism, and for structures which give rise to stable free-radical intermediates coupled, dehydrogenated products are obtained. Examples include *p*-xylene from isobutane or 2-methylpropene, *trans*-stilbene from toluene, and naphthalene from toluene and propene. This chemistry has been extended to nonhydrocarbons, and coupling to give nitrogen–nitrogen and carbon–nitrogen bonds has been observed. Benzonitrile is obtained from the reaction of aniline/toluene, and quinoline from aniline/propene.

The high-temperature reactions of iodine with hydrocarbons to form unsaturated hydrocarbons and hydrogen iodide have been investigated by Mullineaux and Raley.[1-3] They found that at temperatures above 400 °C a variety of paraffins react with stoichiometric amounts of iodine to yield the corresponding olefins and diolefins along with an equivalent amount of hydrogen iodide. In this way ethane and propane gave ethylene and propene, respectively; butenes, along with 1,3-butadiene, were obtained from butane; and isopentane gave a mixture of methylbutenes and isoprene.[2] With paraffins containing a chain of six or more carbon atoms, aromatization resulted. Thus benzene was obtained from hexane; toluene from heptane; and C_8 aromatics from octane or octene-1. As expected, cyclohexane was converted almost exclusively to benzene.[3] A free-radical mechanism was proposed for these reactions.[2,3]

Although the yields of olefins and diolefins far exceed those obtainable by catalytic dehydrogenation at any reasonable conditions, the extent of dehydrogenation is equilibrium limited.[2] As a consequence of this equilibrium limitation, the maximum extent of dehydrogenation, especially to diolefins, is far short of complete conversion of the paraffin to the desired product, e.g., 1,3-butadiene. This equilibrium effect can be offset partially by introduction of oxygen which oxidizes the product hydrogen iodide to iodine; however, some product degradation to carbon monoxide and smaller hydrocarbons is obtained along with increased conversion to dehydrogenated products.[2]

Iodine/hydrocarbon dehydrogenation processes whereby the equilibrium limitation is circumvented have been reported.[4-6] In these processes, three stepwise reactions are involved: (1) reaction of oxygen with a metal iodide to give elemental iodine, (2) reaction of the liberated iodine with the organic reactant to give a dehydrogenated product and hydrogen iodide, and (3) reaction of the hydrogen iodide with metal hydroxide to re-form metal iodide. With reaction 3, the equilibrium limitation is removed, and the overall chemistry is reaction 4, reaction of oxygen with the organic compound to give a dehydrogenated product and water. The hydrogen iodide acceptor may be either solid[6] or molten.[4,5] The present discussion will be limited to molten salt mixtures which serve both as the source of iodine and as the hydrogen iodide acceptor in a cyclic operating mode. The patent literature of both the acceptor and nonacceptor chemistry has been reviewed.[7]

$$MI_2 + H_2O + \tfrac{1}{2}O_2 \rightarrow M(OH)_2 + I_2 \quad (1)$$

$$I_2 + C_nH_{2n+2} \rightarrow C_nH_{2n} + 2HI \quad (2)$$

$$2HI + M(OH)_2 \rightarrow MI_2 + 2H_2O \quad (3)$$

$$\tfrac{1}{2}O_2 + C_nH_{2n+2} \rightarrow C_nH_{2n} + H_2O \quad (4)$$

The results presented in the present paper serve to extend and define the scope of iodative dehydrogenation reactions of both hydrocarbons and nonhydrocarbons.

Results and Discussion

Dehydrogenation of Hydrocarbons. Ethane. Results obtained with ethane over two molten salts are presented in Table I. In both cases 75–80% conversion of ethane was obtained with a selectivity to ethylene of greater than 90%. There is, however, some hydrocarbon degradation, especially to carbon oxides, with a resultant inefficient utilization of oxygen; with an increased oxygen to hydrocarbon ratio, still higher ethane conversions could be achieved. It is not unexpected, of course, that with concurrent introduction of oxygen and

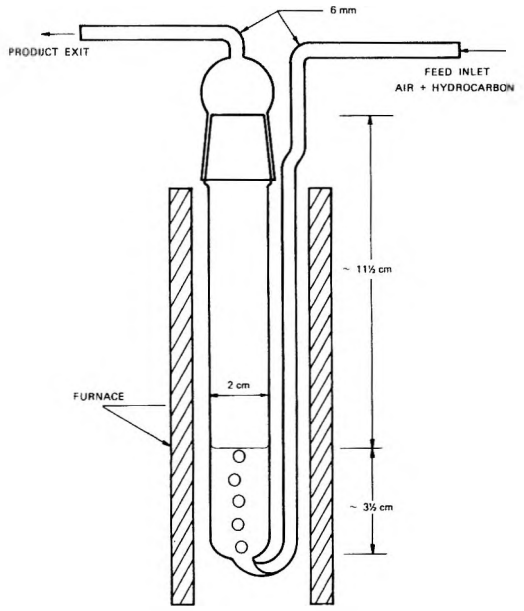


Figure 1. Single vessel for dehydrogenations in the presence of molten salts.

Table I. Dehydrogenation of Ethane and Butane

	Ethane		Butane	
Salt	LiI	PbI_2	LiI	LiI
Temp, °C	595	595	565	565
O_2/hydrocarbon (molar)	0.5	0.5	1.0	1.4
Residence time, s	1.0	1.0	3.0	3.0
Conversion, wt %	78	75	75	92
Product selectivity, % carbon				
Methane	0.8	1.4	3.5	2.4
Ethylene	97.2	93.4	6.0	6.0
Ethane			2.5	1.7
Propene	0.1	0.5	10.5	6.1
1,3-Butadiene	0.2	0.8	68.3	75.6
Butenes			4.8	2.3
Other products	0.9	1.2	2.8	2.3
Carbon oxides	0.7	2.6	1.6	3.6

hydrocarbon into a single vessel at 565 °C some carbon oxide formation would occur (Figure 1).

Butane. The effect of oxygen/hydrocarbon ratio on conversion is shown for butane dehydrogenation over molten lithium salts (Table I). At a ratio of 1.4, a butane conversion of 92% with a selectivity to 1,3-butadiene of 75.6 is obtained. The ratio of diolefin to olefin is relatively insensitive to conversion level or oxygen to hydrocarbon ratio. From this result, it is reasonable to conclude that the allylic hydrogens of the butenes formed as primary products are much more reactive than the secondary (or primary) hydrogens of butane.

Isopentane. Similar results are obtained with isopentane which yields isoprene as the major product (Table II). At an oxygen/isopentane ratio of 1.3, conversion of isopentane is 95.5% with an isoprene selectivity of 80.4%. Although isoprene is the major product, significant quantities of monoolefins are obtained, and the amount of monoolefin produced is dependent on the oxygen/isopentane ratio. This result suggests that the tertiary hydrogen of isopentane is considerably more reactive than secondary and primary hydrogens of *n*-butane.

In this case and in all subsequent examples, lithium iodide served as the source of iodine, and the reaction was carried out in a circulating lithium iodide/lithium hydroxide salt system containing separate iodide oxidation and hydrocarbon dehydrogenation zones (Figure 2).

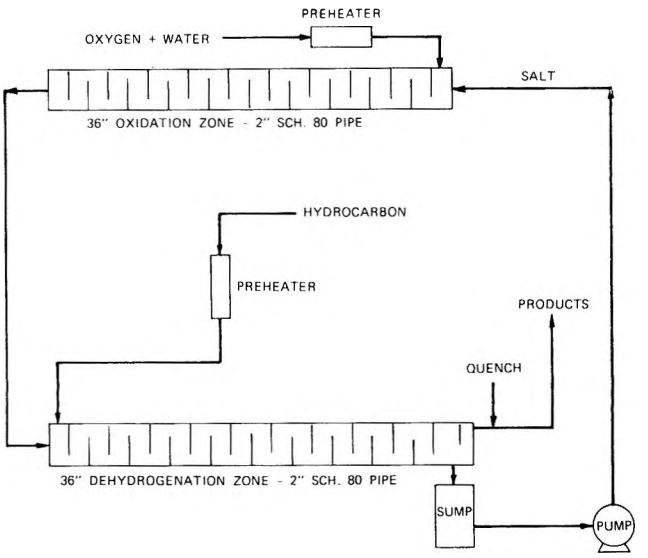


Figure 2. Reaction system with separate oxidation and dehydrogenation reactors.

Table II. Dehydrogenation of Isopentane at 565 °C and 2 s Residence Time

O_2/C_5H_{12} mole ratio	0.6	0.9	1.3
Isopentane conversion, %	62.4	77.3	95.5
Selectivity, wt % carbon			
Methane	2.4	1.5	0.7
Ethane + ethylene	1.2	0.9	0.8
Propene	1.9	1.8	2.4
1,3-Butadiene	1.2	1.2	1.0
2-Methylpropene	11.9	5.9	2.6
Isoprene	55.1	67.0	80.4
Methylbutenes	23.9	12.4	5.4
C_{6+}	1.7	8.2	1.3
Carbon oxides	0.8	1.1	5.3

Alkylbenzenes. Alkylbenzenes are readily converted to the corresponding alkenylbenzenes as illustrated by the data in Table III. The dehydrogenations of ethylbenzene and isopropylbenzene are extremely clean, yielding the alkenylbenzenes in 95% selectivity even at very high conversions. Propylbenzene is converted primarily to a mixture of *cis*- and *trans*-propenylbenzene and allylbenzene. It is noteworthy that with the longer alkyl side chain, fragmentation reactions become significant. For example, methane and styrene are formed in approximately equal molar amounts.

Dialkylbenzenes also are subject to iodative dehydrogenation. The relative amounts of olefin and diolefin obtained are dependent on the oxygen/hydrocarbon ratio. *p*-Diisopropenylbenzene has been prepared in 72.9% selectivity at a conversion level of 98.9% (Table III).

Relatively large amounts of higher boiling residue are obtained in this system as also was the case for the isopropylbenzene and propylbenzene dehydrogenations. The origin of this high-boiling material will be discussed in more detail below.

Butylbenzene. Hydrocarbons with a carbon chain of six or more undergo aromatization in the presence of iodine; e.g., hexane is aromatized to benzene and heptane to toluene.[2] These reactions also have been reported for molten salt acceptor systems.[4] An interesting extension of the aromatization reaction is illustrated by the data in Table III. Butylbenzene is dehydrogenated by iodine at 565 °C to yield naphthalene with 72% selectivity. The reaction sequence for this aromatization presumably is analogous to cyclization of hexatriene followed by dehydrogenation of the cyclohexadiene inter-

Table III. Dehydrogenation of Alkylaromatics

	Ethyl-benzene	Isopropyl-benzene	Propyl-benzene	*p*-Diisopropyl-benzene		Butyl-benzene
Temp, °C	580	565	540	565	565	565
Residence time, s	3	3	1.6	2.0	2.0	1.5
O_2/hydrocarbon mole ratio	0.6	0.6	0.6	1.0	1.6	1.0
Hydrocarbon conversion, %	96.0	99.0	77.0	90.8	98.9	83.0
Selectivity, wt % carbon						
C_1–C_7	2.4	0.6	3.9	0.4	0.5	8.7
Ethylbenzene		0.1	0.3			1.6
Styrene	96.1	0.4	6.1			10.7
Isopropylbenzene			0.1			
Allylbenzene			7.7			
Isopropenylbenzene		94.7	0.6			
cis-Propenylbenzene			17.9			
trans-Propenylbenzene			54.9			
p-Isopropylisopropenylbenzene				37.0	13.0	
p-Diisopropenylbenzene				56.4	72.9	
Naphthalene						72.0
Other products		1.6	7.0	5.4	10.5	6.0
Carbon Oxides	1.5	2.6	1.5	0.9	3.0	1.0

Table IV. Relative Reactivities of Hydrocarbons at 540 °C

Compd	Relative rate	Hydrogen type (no.)	Relative hydrogen reactivity
Cyclohexane	1.0	Secondary (12)	1
Methycyclohexane	1.5	Tertiary (1)	8
Tetralin	15.8	Benzylic (4)	46
Cyclohexene	36.6	Allylic (4)	109

mediate as proposed for the aromatization of hexane to benzene.[2]

Hydrocarbon Reactivity. The relative reactivities of several hydrocarbons have been inferred from the preceding data. In additional competitive-rate experiments, the influence of structure on dehydrogenation rate was investigated. Equimolar mixtures of two hydrocarbons were reacted with a limited amount of iodine and the conversion of each compound determined. Assuming that hydrogen abstraction to form the initial hydrocarbon radical is the slow step in dehydrogenation, then for compounds A and B

$$\frac{dA}{dB} = \frac{k_A}{k_B}\frac{[A][I]}{[B][I]}$$

and

$$\frac{k_A}{k_B} = \frac{\log([A]/[A_0])}{\log([B]/[B_0])}$$

Results obtained for a series of six-membered ring compounds containing different hydrogen types are summarized in Table IV. In all experiments the reaction gave the expected aromatic product in high selectivity. Tertiary hydrogens are more reactive than secondary hydrogens; benzylic and allylic hydrogens are the most reactive. These results are consistent with the order or reactivity to be expected for a process in which a free radical is the intermediate. The high selectivity obtained with the iodine atom can be attributed to the relatively low hydrogen–iodine bond strength and the consequent low reactivity of the iodine atom.

Coupling Reactions of Hydrocarbons. For the reaction systems discussed above, radical coupling has not been significant. However, in the investigations of Mullineaux and Raley, coupled products (e.g., *p*-xylene from 2-methylpropene) were detected in minor amounts,[1] and in the presence of a hydrogen iodide acceptor, which permits higher radical concentrations, coupling is found to occur extensively with certain hydrocarbons. Benzene was obtained in 58.6% yield from propene;[4] isobutane or 2-methylpropene yielded *p*-xylene, and a mixture of 2-methylpropene and propane gave toluene in addition to benzene and *p*-xylene.[5]

Table V. Dehydro Coupling of Hydrocarbons

Temp, °C	595	620	565	595	540
O_2/hydrocarbon (molar)	0.6	0.6	0.65	0.3	0.3
Residence time, s	2	2.4	2.0	2.5	2.5
Conversion, wt %	61.2	41.0	37.5	11.3	12.7
Reactant composition, mol %					
Toluene	100	50	16.7		
Propene		50	83.3		64.3
Isopropenylbenzene				100	35.7
Product selectivity, % carbon					
Benzene		19.7	37.2		12.9
Styrene		1.7	1.3	4.8	1.8
Ethylbenzene		0.2	0.1		
Iodobenzene		3.7	7.4		
Iodotoluene		0.7	0.1		
1,2-Diphenylethane	10.7				
cis-Stilbene	3.9	1.7	0.1		
trans-Stilbene	72.2	13.5	0.7		
1,2-Diphenylacetylene	1.1		0.2		
Naphthalene		42.3	16.2		
Biphenyl		0.3	0.5		61.5
p-Terphenyl				87.5	9.1
Other products	11.1	10.8	14.8	5.9	7.3
Carbon oxides	1.0	5.4	21.4	1.8	7.5

Toluene. Aromatics also have been found to participate in coupling processes. Toluene is converted cleanly to *trans*-1,2-diphenylethylene (*trans*-stilbene); a minor product is the intermediate 1,2-diphenylethane. Reaction conditions and product composition are given in Table V. In a competitive experiment with a feed containing equimolar amounts of tetralin and toluene, no coupled products of toluene were observed in the presence of a limited amount of oxygen (0.25 oxygen/hydrocarbon). Since both compounds contain benzylic hydrogen, radical stabilities and rates of radical formation should be comparable. The absence of coupling indicates that (1) reaction of the radical derived from tetralin to give dehydrogenated products is fast compared to coupling and (2) hydrogen abstraction from tetralin by the benzyl radical is fast compared to radical coupling. The conclusion reached from these results is that coupling can occur only in the absence of

a feasible dehydrogenation process. Consistent with this view is the observation that propene undergoes coupling whereas butene-1 dehydrogenates to 1,3-butadiene.

Toluene/Propene. Toluene does participate in coupling and cross-coupling reactions in the presence of propene.[5] Detailed results are given in Table V. The major products are benzene (propene coupling), stilbene (toluene coupling), and naphthalene (toluene/propene coupling). With an equimolar feed, allyl radical coupling is moderately favored relative to benzyl radical coupling. Naphthalene is the major product which is consistent with the expected statistical bias in favor of the cross-coupling reaction. Considerable control over product composition can be exercised by varying feed composition. At a feed ratio of five propene/toluene (molar), stilbene formation is effectively suppressed.

The dehydrocoupling results discussed above provide the outline of a general reaction sequence leading to the observed coupled products:

(1) Dehydrogenation occurs until a radical not capable of giving a stable product by loss of an additional hydrogen atom is produced. In general this radical will be either an allyl- or benzyl-type radical.

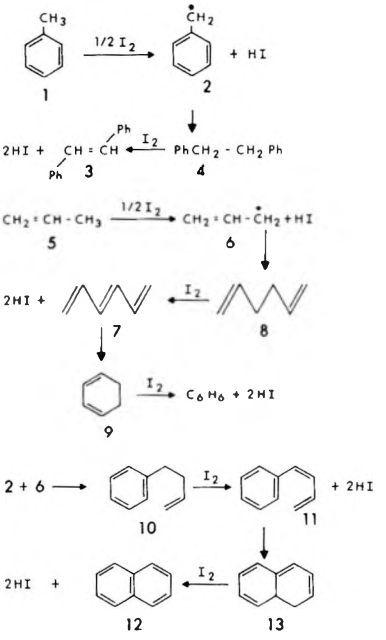
(2) The radicals thus produced will couple.

(3) Further dehydrogenation will occur, if possible.

(4) If a conjugated triene is formed, it will cyclize to the cyclohexadiene with subsequent dehydrogenation to an aromatic product.

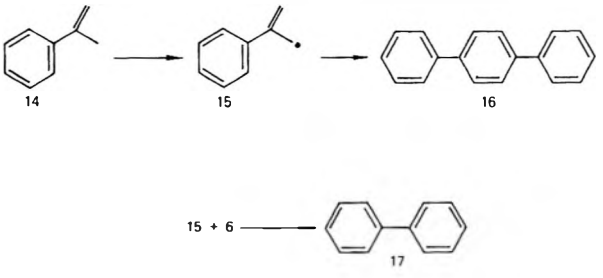
These reactions are illustrated for the allyl and benzyl systems in Scheme I.

Scheme I. Coupling Reactions of Toluene and Propene



The chemistry outlined in Scheme I serves as a basis for consideration of other dehydro coupling reactions. Returning to the isopropenylbenzene system (Scheme II) it is seen that

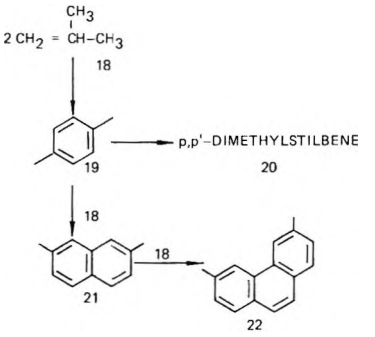
Scheme II. Reactions of Isopropenylbenzene



dehydro coupling can lead to *p*-terphenyl (**16**); cross-coupling of propene and isopropenylbenzene should yield biphenyl (**17**) in addition to terphenyl and benzene. As shown by the data in Table V, these expected products are indeed obtained in high selectivity.

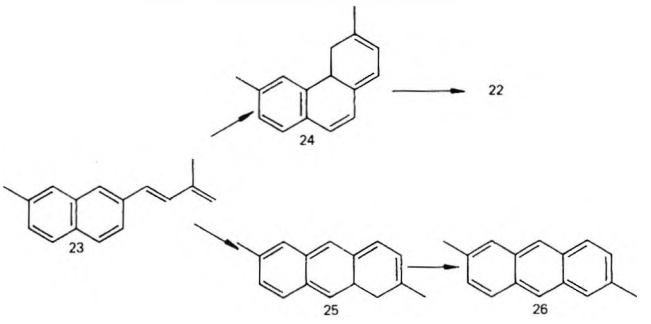
***p*-Xylene/2-Methylpropene.** Some additional dehydro coupling reactions are outlined in Scheme III. From a mixed

Scheme III. Some Coupling Reactions of 2-Methylpropene and *p*-Xylene



p-xylene/2-methylpropene feed, *trans*-*p*,*p*'-dimethylstilbene (**20**), 2,7-dimethylnaphthalene (**21**), and 3,6-dimethylphenanthrene (**22**) are obtained; the amount of each is dependent on *p*-xylene/2-methylpropene ratio and the oxygen/hydrocarbon ratio. An interesting phenomenon is the absence of 2,6-dimethylanthracene (**26**) which could arise from the alternative cyclization mode for the coupled 2,7-dimethylnaphthalene/2-methylpropene (Scheme IV). Consideration

Scheme IV. Aromatization Routes Leading to Phenanthrenes and Anthracenes



of the cyclization reaction (Scheme IV) suggests that considerably more π-electron localization and loss of aromaticity would occur during cyclization to the anthracene thus favoring formation of 3,6-dimethylphenanthrene (**22**). To test the generality of this effect, the dehydro coupling of 2-methylnaphthalene and propene was investigated. Of the two possible products, phenanthrene was favored over anthracene by at least a factor of 50.

Reactions of Nonhydrocarbons. Reaction with iodine at high temperature is not limited to hydrocarbons. For example, it has been shown that propionitrile is dehydrogenated to acrylonitrile at 535 °C in the iodine/molten salt system.[4] The reactions of nitrogen-containing compounds have been extended to include nitrogen–nitrogen and nitrogen–carbon coupling reactions.

Aniline. Formation of a nitrogen–nitrogen bond by iodative dehydro coupling is demonstrated by results obtained with aniline (Table VI). The expected primary dehydro coupled product, azobenzene (**30**), is indeed found, albeit in low selectivity. However, other products formed in higher selectivity indicate that extensive dehydro coupling to azobenzene occurred. Thus benzene and iodobenzene are major products

Table VI. Dehydro Coupling of Nonhydrocarbons

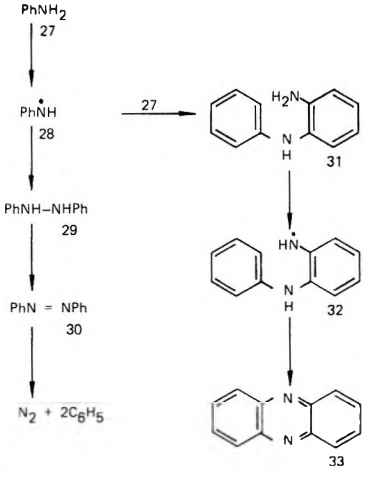
Temp, °C	620	620	620	620
O_2/reactant (molar)	0.5	0.8	0.8	0.75
Residence time, s	4.0	2.0	4.0	2.0
Conversion, wt%	23.0	40.5	75.2	24.5
Reactant composition, mol %				
Aniline	100	50		50
Toluene		50		
N-Benzylideneaniline			100	
Propene				50
Product selectivity, % carbon				
Benzene	19.1	9.3	15.4[b]	49.5
Iodobenzene	20.5	5.3	1.0	11.0
Toluene			7.2	
Aniline			10.9	
o-Iodoaniline	3.2	0.5		
Azobenzene	5.0			
Phenazene	28.0	9.3		
Carbazole	7.3	2.8		
Benzonitrile		20.2	29.8	
Quinoline				14.3
Biphenyl			11.2	
Stilbenes + diphenylacetylene		35.3		
Other products	9.6[a]	9.1	21.0	9.0
Carbon oxides	7.4	8.2	3.5	16.1

[a] In addition, 0.11 mol of N_2 per 100 g carbon feed also produced. [b] By difference.

and are assumed to arise via intermediate phenyl radicals formed by the thermal decompositon of azobenzene. In support of this hypothesis, molecular nitrogen is a reaction product.

To provide additional evidence for this reaction scheme, the thermal decomposition (no iodine present) of azobenzene in the presence of toluene was investigated. As expected the decomposition of azobenzene does lead to benzene and nitrogen. Formation of benzene requires a source of hydrogen atoms for abstraction by the intermediate phenyl radical. In this experiment the source was toluene as indicated by the products from benzyl radical coupling, 1,2-diphenylethane and *trans*-stilbene. The iodative dehydro coupling reactions of aniline are outlined in Scheme V.

Scheme V. Dehydro Coupling Reactions of Aniline

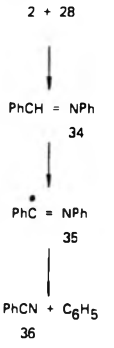


Two other major products of this reaction, phenazine and carbazole, involve nitrogen–carbon bond formation. Formation of these products can be rationalized either by homolytic substitution mechanisms or by a radical coupling mechanism. If the latter mechanism is operative the free-radical character of the anilino radical is shared to a considerable extent by the aromatic ring.

Aniline–Toluene. The above results with aniline demonstrate the formation and coupling of anilino radicals. Since toluene dehydro couples cleanly to give stilbene, it can be anticipated that with a mixture of toluene and aniline cross-coupling reactions will occur to give compounds containing carbon–nitrogen bonds. Results obtained in an aniline–toluene coupling experiment are given in Table VI. As expected the self-coupling products of toluene (diphenylacetylene, *cis*- and *trans*-stilbene) and of aniline (benzene and iodobenzene) are found. In addition phenazine and carbazole are again observed.

The major product containing a carbon–nitrogen bond is benzonitrile. Although unexpected, a straightforward pathway, outlined in Scheme VI, exists for benzonitrile formation

Scheme VI. Formation of Benzonitrile from Toluene and Aniline



via toluene–aniline dehydro coupling. Coupling of benzyl (**2**) and anilino radicals (**28**) leads to *N*-benzylideneaniline (**34**), the carbon–nitrogen analogue of stilbene. This product, however, contains only one more abstractable hydrogen. The radical thus formed fragments to give benzonitrile (**36**) and the phenyl radical.

The proposed reaction scheme has been tested in an experiment starting with a benzene solution of *N*-benzylideneaniline (Table VI). Benzonitrile is indeed a major product. Further support for the reaction scheme is provided by the formation of significant quantities of toluene and aniline. This reversal of the dehydro coupling reaction presumably is brought about by the hydrogen iodide released by the iodative dehydrogenation and fragmentation of *N*-benzylideneaniline.

It is interesting to observe that the fate of the phenyl radical differs in this experiment. In the absence of large quantities of the hydrogen donors toluene and aniline, an appreciable quantity of the coupled product, biphenyl, is formed.

Aniline–Propene. To explore further the possibilities of carbon–nitrogen bond formation by dehydro coupling, the aniline–propene system was chosen. The results of the aniline–propene experiment are given in Table VI. As would be expected benzene from the self-coupling of propene is a major product. In addition the products from aniline alone also are found. The major product from cross-coupling of aniline and toluene is quinoline. Thus the reaction appears to proceed in a straightforward manner via coupling of anilino and allyl radicals followed by dehydrocyclization to quinoline.

Conclusions

The chemistry demonstrated and discussed above provides a facile route to many compounds not readily available by other synthetic methods. In general the products are easily predicted and are obtained in high yield. For cross-coupling reactions product mixtures are of course obtained, although even in these cases product composition can be controlled by feed composition and oxygen/feed ratio. There are many ob-

vious variations of the chemistry outlined here. These include divinylbenzenes from diethylbenzene and coupling reactions to yield substituted stilbenes and numerous substituted aromatics.

Experimental Section

Two flow reactor systems were utilized. One of these was a single heated vessel containing the molten salt (Figure 1). Air (or oxygen) and hydrocarbon were introduced concurrently into the vessel, and after bubbling through the molten salt, the gaseous products left the vessel via a single exit line. A more elaborate system (Figure 2) consisted of separate salt oxidation and hydrocarbon dehydrogenation zones and was equipped with a pump to permit continuous recycle of the molten salt. The U configuration was mounted horizontally. The 2-in., schedule 80 pipe was baffled internally to promote gas–liquid contacting. The total system was heated by electrical resistance wire and insulated to maintain a uniform temperature. Care was taken to eliminate all cold spots which could lead to formation of salt plugs. Liberation of iodine occurred in the oxidation zone, and iodative dehydrogenation of the hydrocarbon, followed by reaction of hydrogen iodide, occurred in the dehydrogenation zone.

In general, gaseous products were analyzed by mass spectrometry. Liquid products were analyzed by either packed-column or capillary gas chromatography. As required, separated products were trapped and identified by mass spectrometry or by ultraviolet, infrared, or nuclear magnetic resonance spectroscopy. More complex product mixtures were handled by coupled capillary gas chromatography/mass spectrometric techniques.

To illustrate experimental procedures the dehydrogenation of *p*-diisopropylbenzene to *p*-diisopropenylbenzene is described fully.

Procedure. The reactor used in this case was the baffled pipe (Figure 2). After the salt mixture had melted, salt circulation was begun and heating continued until the desired reaction temperature was reached. Oxygen and water were introduced into the oxidation zone which was connected by a U tube to the dehydrogenation zone into which the hydrocarbon was injected by nitrogen pressurization of the feed tank. Flow rates, measured by rotometers, were adjusted to give the desired O_2/hydrocarbon mole ratio (1.0 or 1.6) and 2-s residence time. Nominal residence time was calculated from the unoccupied volume of the dehydrogenation zone divided by the total volume of gas (oxygen, water, and hydrocarbon) injected per second. The molten salt acceptor was LiI containing 2% LiOH.

The product was quenched with water as it emerged from the dehydrogenation zone; the molten salt passed into a sump and was recirculated by means of a centrifugal pump to the oxidation zone. The gaseous and liquid products were separated following the quench.

The run period was continued for a predetermined time period, and all products were collected to provide a material balance which for the two runs of Table V were 87 and 100%, respectively, basis carbon.

The total liquid product was removed from the quench system and the hydrocarbon and water phases separated. The hydrocarbon product was washed twice with 5% $NaHCO_3$ solution and twice with water.

Analyses. The liquid hydrocarbon was analyzed quantitatively by gas chromatography (GC). The *p*-diisopropylbenzene was identified by its known retention time, and the GC peaks corresponding to *p*-isopropylisopropenylbenzene (monoolefin) and *p*-diisopropenylbenzene (diolefin) were trapped and identified by mass spectrometry. When isolated, the diolefin (mp 63–64 °C) was identified by mass spectrometry (mass number 158), and by its ir and NMR spectra.

Nonvolatile residue was determined by GC using an instrument equipped with residue backflush and combustion of hydrocarbon to CO_2.

An integrated sample of the gaseous product collected during the material balance period was analyzed by mass spectrometry.

Product Isolation and Purification. After being washed, the crude product was distilled in a 30-plate Oldershaw column at a head pressure of 20 Torr and a reflux ratio of 4. A total C_{12} fraction was collected and the solid diolefin purified by two recrystallizations from 50% aqueous ethanol. The *p*-diisopropenylbenzene thus obtained contained 0.1–0.2% monoolefin and 10–100 ppm of organic iodide as the only detectable impurities.

Acknowledgment. We thank E. G. Carlson and J. M. Martin, Jr., for the many instrumental analyses necessary for identification of the products reported here.

Registry No. —Iodine, 7553-56-2; ethane, 74-84-0; butane, 106-97-8; LiI, 10377-51-2; PbI_2, 10101-63-0; isopentane, 78-78-4; ethylbenzene, 100-41-4; isopropylbenzene, 98-82-8; propylbenzene, 103-65-1; *p*-diisopropylbenzene, 100-18-5; butylbenzene, 104-51-8; cyclohexane, 110-82-7; methylcyclohexane, 108-87-2; tetralin, 119-64-2; cyclohexene, 110-83-8; toluene, 108-88-3; propene, 115-07-1; isopropenylbenzene, 98-83-9; aniline, 62-53-3; *N*-benzylideneaniline, 538-51-2.

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Polar Effects in Radical Reactions. 6. The Separation of Substituent Effects on Transition States from Substituent Effects on Bond Dissociation Energies. Abstraction of Iodine from Substituted Iodobenzenes by *p*-Nitrophenyl Radicals[1]

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The Hammett equation correlation is reported for the reaction of *p*-nitrophenyl radicals, generated by thermolysis of *p*-nitrophenylazotriphenylmethane at 60 °C, with a series of ten substituted iodobenzenes. Rates of iodine abstraction from the iodobenzenes were measured relative to chlorine abstraction from CCl_4. A plot of log (relative rate) *vs.* σ constants gives meta substituents only, $\rho = 0.0 \pm 0.2$, $s_y = 0.05$ (4 points); para substituents only, $\rho = 0.0 \pm 0.3$, $s_y = 0.01$ (6 points); meta and para substituents, $\rho = 0.1 \pm 0.2$, $s_y = 0.03$ (10 points). Although these zero ρ values could be interpreted as an absence of substituent effects on the rate of this reaction, such an explanation would not be consistent with other data. Instead, these zero ρ values are rationalized in terms of both the effects of substituents on the bond dissociation energy (BDE) of the Ar–I bond of the reactants and the effects of substituents on the stability of the transition state (SETS). For iodobenzenes, positive ρ's are produced by the effects of substituents on BDE, but the perturbation due to SETS for *p*-nitrophenyl radicals is toward negative ρ's. The necessity for considering both of these effects in other reaction systems also is discussed.

Polar effects on free-radical reactions have usually been explained as arising from the contribution of dipolar structures to the stabilities of the transition states of reactions of neutral free radicals.[3a,4a,5] In recent years it has become clear that an extremely useful technique for probing the contribution of these polar effects is the application of the Hammett equation to atom abstraction reactions such as hydrogen abstraction from substituted toluenes by a radical R· (eq 1),[6] in which Ar = C_6H_4X.

$$R\cdot + HCH_2Ar \rightarrow [\text{transition state}] \rightarrow RH + \cdot CH_2Ar \quad (1)$$

The transition state for eq 1 can be represented by the three resonance structures shown in eq 2.

$$[R\cdot + \dot{H}\cdot CH_2Ar \leftrightarrow R^+\dot{H}^-{:}CH_2Ar \leftrightarrow R{:}^-\dot{H}\,{}^+CH_2Ar] \quad (2)$$

In most of the early discussions of polar effects, polar resonance structures were only explicitly written for the transition state.[7] This appears to have led most chemists in more recent years to rationalize Hammett equation correlations of radical reactions solely in terms of the effect of substituents on the stabilities of the structures shown in eq 2.[5-7]

An opposing viewpoint was suggested in 1972 by Zavitsas and Pinto.[8] These authors suggested that polar substituent effects on transition states were unimportant in understanding the relative reactivities of substituted toluenes toward various radicals. Instead, they claimed that these results could be explained by considering only the effects of substituents on eq 3—that is, on the bond dissociation energy (BDE) of the benzylic C–H bond—"without postulating charge separation in the transition state".[8]

$$XC_6H_4CH_2H \rightarrow XC_6H_4CH_2\cdot + H\cdot \quad (3)$$

In our view, it is no more likely that the relative reactivities in Hammett equation studies can be rationalized *only* in terms of substituents effects on BDE than it is that they can be explained *only* in terms of SETS. We suggest that Hammett correlations of both radical and nonradical reactions must be understood in terms of at least two different effects: one, the influence of substituents in the substrate on the BDE of the bond being broken; and, two, the substituent influence (usually by polar contributions) on the absolute free energy of the transition state. One effect depends only on the series of substrates being studied; the other depends on the nature of the reaction. In this paper, we apply this reasoning to understanding Hammett correlations of radical reactions.

Consider the reaction shown in eq 1. Substituents can influence the relative rates of this reaction by (1) affecting transition state stabilities, eq 2, or (2) by affecting BDE's, eq 3.

(1) For convenience, we have coined the acronym SETS (substituent effects on transition states) to indicate the first effect, i.e., electronic (everything except steric) effects of substituents on transition states. Many chemists have only considered SETS in rationalizing Hammett equation studies[9,10] of radical reactions, since it is assumed, because of the greater polarizability of the transition state than the ground state, that substituents have a greater influence on stabilities of transition states of atom abstraction reactions (eq 1) than on BDE (eq 3).[3a]

(2) The BDE of the bond being broken affects the rate of a reaction like eq 1 through its influence on the heat of reaction. The heat of this reaction, ΔH, is given by $D(XC_6H_4CH_2\text{–H}) - D(\text{R–H})$, where the D's indicate the BDE's of the bonds being broken and being made.[3b,4b] Since D(R–H) is unchanged as X is varied, the substituent effect on the BDE of the $XC_6H_4CH_2$–H bond can be a source of the variation in relative rates of eq 1 with change in substituent.

We will discuss several examples from the literature in which consideration of either substituent effects on BDE or SETS *alone* leads to inconsistencies. The point which we wish to make is that these inconsistencies can be resolved by consideration of both SETS and BDE effects.[1d]

On the basis of NMR[11] and isotope effect[12] data, Zavitsas concluded that electron-donating substituents weaken and electron-withdrawing substituents strengthen benzylic C–H bonds in substituted toluenes.[8] Neglecting SETS, Zavitsas reasoned that this ordering of BDE meant that *only* negative ρ's for hydrogen abstraction from toluenes were possible. We have recently shown that SETS cannot be neglected; we obtain positive ρ values for the *tert*-butyl,[1e,13] isopropyl,[13] and undecyl[1d,14] radicals.

A striking example of the inconsistencies that result from consideration of SETS alone can be seen in possible rationalizations of Hammett studies involving thiols and thiyl radicals. Gleicher obtained a ρ of −0.3 for hydrogen abstraction from substituted benzenethiols (ArSH) by *p*-chloro-α-substituted cumyl radicals (X·) (eq 4).[15a]

$$X\cdot + ArSH \rightarrow XH + ArS\cdot \quad (4)$$

This negative ρ was interpreted in terms of the traditional SETS approach to give the description of the transition state shown in eq 5.

$$[X\cdot \dot{H}\cdot SAr \leftrightarrow X^{-}:\dot{H}^{+}SAr] \quad (5)$$

However, in reactions involving benzenethiyl radicals reacting with substituted ethylbenzenes[16] and with substituted α-methylstyrenes,[15b] negative ρ's were obtained and interpreted by the SETS concept as indicating a charge distribution in the transition state as shown in eq 6.

$$PhS\cdot XH \rightarrow [PhS\cdot \dot{H}\cdot X \leftrightarrow PhS^{-}:\dot{H}^{+}X] \rightarrow PhSH + X\cdot \quad (6)$$

Certainly, we would expect the transition states for eq 4 and 6, one of which is the reverse of the other, to have a consistent placement of positive and negative charges. This expectation is not realized in the published descriptions because only SETS were considered; clearly, other effects of substituents on the relative rates of the reactions shown in eq 4–6 must also be taken into account.

Furthermore, it is evident a priori that both SETS and substituent effects on BDE must be considered in rationalizing the ρ values for eq 4 and 6: consideration of SETS alone would predict that one of these reactions should have a positive and one a negative ρ. Since they both are found to have negative ρ's, BDE effects must be more important than SETS in one of the these systems. It appears probable that electronic effects are more easily transmitted through a sulfur atom than a carbon;[17] thus, the effect of substituents on BDE should be relatively more important in eq 4 than in the reaction of thiyl radicals with ethylbenzenes. That is, electron-donating substituents substantially weaken the S–H bond in the ground state of thiols and thereby establish a negative ρ for eq 4 of such magnitude that even SETS of the type which would lead to a positive ρ, eq 5a

$$[X\cdot \dot{H}\cdot SAr \leftrightarrow X^{+}\ \dot{H}^{-}:SAr] \quad (5a)$$

are not sufficient to produce a positive ρ for X· radicals such as α-substituted cumyl radicals that are only modestly nucleophilic. In order to observe a positive ρ for eq 4, a strongly nucleophilic radical would be required.[18]

The effect of electron-donating substituents on X–H compounds in eq 6 would be expected to be less than the effect of these substituents on thiols in eq 4.[17] However, electron-donating substituents do moderately weaken the C–H bond in the toluenes.[11,12] Also, the thiyl radical is probably more electrophilic than the benzyl radical.[16] Thus a negative ρ is observed for eq 6 because both BDE effects and SETS produce a negative ρ. A negative ρ is observed for eq 4 because the perturbation due to SETS, which would lead to a positive ρ, is overwhelmed by substituent effects on BDE, which lead to a negative ρ.

Another reaction which requires consideration of both SETS and substituent effects on BDE is shown in eq 7.

$$Ar'\cdot + Ar\text{-}I \rightarrow Ar'\text{-}I + Ar\cdot \quad (7)$$

Danen[19] has reported a ρ of +0.57 for abstraction of iodine from substituted iodobenzenes when the aryl radical is phenyl (i.e., Ar'· = Ph·). The SETS concept, as usually applied, would view the transition state for this reaction as shown in eq 8. Since ρ is positive, the typical SETS arguments would be that **3** is more important than **2**.

$$Ph\cdot + ArI \rightarrow \underset{\mathbf{1}}{[Ph\cdot \dot{I}\cdot Ar} \leftrightarrow \underset{\mathbf{2}}{Ph^{-}:\dot{I}^{+}Ar} \leftrightarrow \underset{\mathbf{3}}{Ph^{+}\dot{I}^{-}:Ar}]$$

$$\rightarrow PhI + Ar\cdot \quad (8)$$

Danen argued in this way and invoked SETS alone to explain the positive ρ value he observed for this reaction.[19] However, we believe that it is not reasonable to postulate that SETS could produce a linear Hammett plot for a reaction in which the direction of the dipole must vary. Surely structure **2** must be more important than **3** when Ar–I is p-$MeOC_6H_4$–I, and **3** must be more important than **2** for Ar–I equal to p-$NO_2C_6H_4$–I. But if this were true, SETS alone would produce a V-shaped Hammett plot for eq 8.

Thus, the normal SETS view of the transition state for eq 8 predicts a result which is inconsistent with the linear Hammett equation plot which Danen observed. Instead, we propose[20] the description shown in eq 9.[21]

$$[Ph\cdot\ \dot{I}\cdot Ar \longleftrightarrow \overbrace{Ph^{\delta+}\ I^{-\ \delta+}Ar}] \quad (9)$$

The advantages of this description are that it has a symmetrical charge distribution (as it must) when Ar' = Ph and it predicts a linear Hammett correlation. However, this dipolar form predicts a negative ρ value for eq 8; thus, for this reaction SETS alone predict the wrong sign for ρ. The observed positive ρ could be rationalized if the partial negative charges were placed on the Ph and Ar and the partial positive charge on the iodine in eq 9. However, the relative electron affinities of these species (Ph· = 1.2–1.6[22] or 2.3[23] eV and I· = 3.24,[22] 3.063,[24] or 3.41[25] eV) preclude this possibility.

In order to rationalize the positive ρ which is observed for eq 8, BDE effects must also be considered.[1d] We assume that in Ar–I compounds, electron-donating substituents strengthen the C–I bond[26] [perhaps by stabilizing the dipolar resonance structure ($Ar\text{–}I \leftrightarrow Ar^{+}\ ^{-}I$) *more* than they stabilize the dipolar resonance structure of the transition state (eq 9)].[29] Therefore, the BDE may be more susceptible to the perturbing effects of substituents than the transition state, and a positive ρ is observed because the tendency to produce a negative ρ from effects of substituents on the transition state in eq 9 is more than counteracted by these effects on the BDE.

In this paper we will report the results of our study of iodine abstraction from substituted iodobenzenes by p-nitrophenyl radicals ($NO_2Ph\cdot$) and discuss these results in terms of SETS and substituent effects on BDE.

Experimental Section

Chemicals. The liquid iodobenzenes (m-Me-, p-F-, m-F-, m-CF_3-, and p-CF_3-iodobenzenes and iodobenzene itself) were washed with a 10% aqueous solution of sodium thiosulfate to remove any dissolved iodine, dried with anhydrous magnesium sulfate, and vacuum distilled. The solid iodobenzenes (p-MeO-, p-Ph-, and p-Br-iodobenzenes) were recrystallized from ethanol and dried under vacuum. All the iodobenzenes were stored under refrigeration in the dark. MCB Chromatoquality carbon tetrachloride was used as received. p-Nitrophenylazotriphenylmethane (NAT) was prepared by the method of Cohen, Cohen, and Wang.[30] In order to get reasonable yields of N-triphenylmethyl-N'-p-nitrophenylhydrazine the following modification of Cohen's procedure should be noted. The "mud" which formed during reflex of triphenylmethyl chloride and p-nitrophenylhydrazine in ether must be repeatedly washed with hot dichloromethane. These washings were combined with the ether layer and treated according to Cohen.

Procedures for Kinetic Runs. For a single kinetic run for one substituted iodobenzene (ArI), reaction solutions of three or four different ArI to CCl_4 ratios were prepared by adding ArI and NAT to CCl_4. The $[CCl_4]/[ArI]$ ratio varied from 5 to 30; the concentration of NAT in solutions when this ratio was less than 10 was 0.2 M; in the other solutions the concentration of NAT was 0.05 M. After placing the reaction mixtures in sample tubes, degassing by four freeze–pump–thaw cycles, and sealing the tubes, the solutions were heated in an oil bath at 60 °C for 16 h (10 initiator half-lifes[31]). The ratio of p-iodonitrobenzene ($NO_2C_6H_4I$) to p-chloronitrobenzene ($NO_2C_6H_4Cl$) in the reacted solution was determined by VPC from the ratio of their peak areas. All VPC analyses were performed on a Varian 1440 flame ionization gas chromatograph using a 10 ft × 2 mm glass column of 10% OV-1 on 100/120 Chromosorb W AW-DMCS. A Spectro-Physics System I computing integrator was used to measure the relevant peak areas.

Results

Kinetic Analysis. *p*-Nitrophenyl radicals, $NO_2Ph\cdot$, were generated, in a system analogous to Danen's,[19] by thermolysis of *p*-nitrophenylazotriphenylmethane (NAT) at 60 °C for 16 h in a mixture of a substituted iodobenzene (ArI) and carbon tetrachloride (eq 10).

$$NAT \xrightarrow{60\ °C} NO_2Ph\cdot + N_2 + Ph_3C\cdot \quad (10)$$

After escaping from the cage, the $NO_2Ph\cdot$ radicals may either abstract iodine from ArI (eq 11) to produce *p*-iodonitrobenzene ($NO_2C_6H_4I$) or abstract chlorine from CCl_4 (eq 12) to give *p*-iodonitrobenzene ($NO_2C_6H_4Cl$).

$$NO_2Ph\cdot + ArI \xrightarrow{k_I} NO_2C_6H_4I + Ar\cdot \quad (11)$$

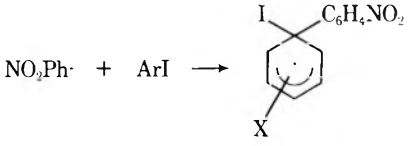
$$NO_2Ph\cdot + CCl_4 \xrightarrow{k_{Cl}} NO_2C_6H_4Cl + \cdot CCl_3 \quad (12)$$

Values of k_I relative to k_{Cl} were determined by measuring by VPC the yields of $NO_2C_6H_4I$ and $NO_2C_6H_4Cl$ produced from various [ArI]/[CCl_4] ratios (eq 13).

$$\frac{k_I}{k_{Cl}} = \frac{[NO_2C_6H_4I][CCl_4]}{[NO_2C_6H_4Cl][ArI]} \quad (13)$$

There are four possible complications which could invalidate our kinetic analysis. (1) $NO_2C_6H_4I$ or (2) $NO_2C_6H_4Cl$ could be formed by reactions other than those shown in eq 11 and 12. (3) $NO_2C_6H_4I$ or (4) $NO_2C_6H_4Cl$ could be consumed in subsequent reactions. These complexities are discussed below.

(1) $NO_2C_6H_4I$ could be produced by nitrophenylation of ArI at the position bearing the iodine atom followed by iodine abstraction from the substituted cyclohexadienyl radical by $NO_2Ph\cdot$ (eq 14).



$$\xrightarrow{NO_2Ph\cdot} NO_2C_6H_4I + NO_2C_6H_4Ar \quad (14)$$

However, reaction 14 was shown to be insignificant in our system since no 4-nitrobiphenyl was found by VPC in a thermolyzed solution of 0.2 M NAT in 0.8 M iodobenzene and 9.3 M CCl_4.[32] Also, decomposition of 0.050 M NAT in 0.50 M *p*-bromoiodobenzene and 9.9 M CCl_4 gave 0.013 M $NO_2C_6H_4Cl$ and 0.027 M $NO_2C_6H_4I$. This accounts for 80% of the $NO_2Ph\cdot$ that could possibly be formed, and the remaining 20% of the radicals may be accounted for as cage products or free-solution combination products such as $NO_2C_6H_4$–CPh_3.[33] Danen also reported that phenylation of ArI was insignificant in his system.[19] Therefore, we conclude that eq 11 is the only important source of $NO_2C_6H_4I$.

(2) Excluding CCl_4, the most likely chlorine donor in our reaction mixture is hexachloroethane, which is formed by the dimerization of trichloromethyl radicals. This chloro compound is not only less reactive than CCl_4,[34] but also is present at such low concentrations (always less than 0.02 M) that abstraction of chlorine from it must be at least 500 times slower than abstraction from CCl_4.

(3) Although $NO_2C_6H_4I$ is an iodine donor, its concentration is so small (generally less than 0.03 M) that the primary fate of the Ar· formed in eq 11 is reaction with CCl_4 to form ArCl rather than re-forming ArI by the reverse of reaction 11. In the kinetic runs with the larger initial NAT concentration, the concentration of $NO_2C_6H_4I$ may be as high as 0.15 M; however, the consistency of the k_I/k_{Cl} values as the concentrations of the substrates and, therefore, the concentration of $NO_2C_6H_4I$, are varied indicates that $NO_2C_6H_4I$ is not consumed in subsequent reactions (see Table I).

(4) Aryl chlorides must be very stable in our reaction system because they should be less reactive than the corresponding aryl bromides which are, in fact, quite stable. We find k_{Br}/k_{Cl} = 0.39 for $NO_2Ph\cdot$ reacting with bromobenzene (4.8 M) and CCl_4 (5.2 M). Therefore, $NO_2C_6H_4Cl$ is stable under our reaction conditions.

We conclude that eq 13 is an accurate expression for the reactivity of ArI relative to CCl_4 toward *p*-nitrophenyl radicals in our kinetic system.

Reactivities of Substituted Iodobenzenes. A Hammett $\sigma\rho$ correlation of our data at 60 °C (Table I and Figure 1) gives meta substituents only, $\rho = 0.0 \pm 0.2$, $s_y = 0.05$, four points; para substituents only, $\rho = 0.0 \pm 0.3$, $s_y = 0.01$, six points; meta and para substituents, $\rho = 0.1 \pm 0.2$, $s_y = 0.03$, ten points.[35] Since the para-substituted iodobenzenes are, in general, *less reactive* than the meta derivatives, the fit of all the points to a single least-squares line is not good. Instead, there appear to be two nearly parallel lines in Figure 1, one for the meta-substituted compounds and one for the para. Danen also noted this difference in reactivity of meta- and para-substituted iodobenzenes in his study of iodine abstraction by phenyl radicals.[19] He suggested that para substituents may decrease the reactivity of ArI either by strengthening the carbon–iodine bond in the ground state or by stabilizing this bond in the "presumed phenylaryliodine intermediate" (Ar–İ–Ar′) more than is accounted for by σ values. We prefer Danen's first proposal which rationalizes the difference as being due entirely to BDE effects.[37] It seems unlikely that Ar–İ–Ar′ is ever formed; eq 7 probably is a one-step reaction. In addition, if this intermediate were involved in eq 7, its formation would probably have a higher activation energy than its subsequent decomposition, and stabilization of Ar–İ–Ar′ by para substituents would enhance the rate of iodine abstraction rather than decrease it.

Discussion

Since the ρ value for the reaction studied here, eq 11, is zero, it might appear tempting to simply propose that substituents have no effect at all on this reaction: that they influence neither transition state stabilities nor BDE's. However, this simple view is not tenable; rather, we propose that this zero ρ value results from a fortuitous balance of SETS and BDE effects.

It is easy to show that SETS cannot be negligible in eq 11. Since the *p*-nitrophenyl radical is more electrophiic than any other aryl radical (Ar·) produced in this study,[33a,38] there should be charge separation in the transition state of this reaction (eq 11). In fact, judging from the known electronic nature of aryl radicals,[33a,38] *more* charge separation would be expected in the *p*-nitrophenyl radical reaction (eq 11) than in the phenyl radical case (eq 8). However, the ρ value for the *p*-nitrophenyl radical is smaller than that for the phenyl radical contrary to the trend expected on the basis of SETS considerations alone.

It also is obvious that BDE effects must be important in eq 11. If substituent effects on BDE are not important for the *p*-nitrophenyl radical reactions, then they should not be significant in the phenyl radical reaction either, but they are.[39]

Therefore, we interpret the zero ρ value for this reaction of *p*-nitrophenyl radical (eq 11) as evidence of the interplay between SETS and substituent effects on BDE which is involved in this system; in contrast, the reaction of the phenyl radical (eq 8) has little contribution from SETS and the observed ρ appears to result from essentially pure BDE effects. Since the *p*-nitrophenyl radical is electrophilic and the phenyl

Table I. Relative Rate Constants (k_I/k_{Cl}) for Iodine Abstraction from Substituted Iodobenzenes (XArI) by the *p*-Nitrophenyl Radical at 60 °C[a]

Registry no.	X	[NAT][b]	$\frac{[CCl_4]}{[XArI]}$	$\frac{A_{p\text{-NPI}}}{A_{p\text{-NPCl}}}$[c,d]	$\frac{k_I}{k_{Cl}}$	$\frac{k_I}{k_{Cl}}$[e]
		0.05	10.0	3.12	35.5	
696-62-8	*p*-MeO	0.05	14.29	2.36	38.3	36 ± 2
		0.05	20.0	1.54	35.0	
		0.2	4.95	9.69	54.6	
624-31-7	*p*-Me	0.05	10.4	4.62	54.7	54.6 ± 0.1
		0.05	20.8	2.31	54.6	
		0.2	6.7	6.58	50.1	
625-95-6	*m*-Me	0.05	13.4	4.01	61.0	60 ± 10
		0.05	26.8	2.43	74.1	
		0.05	5.0	6.84	38.9	
		0.05	10.0	3.52	40.1	
1591-31-7	*p*-Ph	0.05	14.29	2.53	41.2	40.0 ± 0.9
		0.05	20.0	1.76	40.0	
		0.05	11.6	4.33	57.5	
591-50-4	H	0.05	16.6	3.07	58.2	57.3 ± 0.9
		0.05	23.2	2.12	56.3	
		0.05	11.9	3.75	50.6	
352-34-1	*p*-F	0.05	17.0	2.43	46.9	48 ± 2
		0.05	23.8	1.73	46.8	
		0.2	5.0	8.76	49.8	
		0.05	10.0	4.31	49.1	
589-87-7	*p*-Br	0.05	14.29	2.76	44.9	47 ± 2
		0.05	20.0	1.98	45.1	
		0.2	5.9	8.98	60.6	
		0.05	11.8	4.78	64.4	
1121-86-4	*m*-F	0.05	16.9	3.24	62.4	64 ± 1
		0.05	23.6	2.41	65.1	
		0.05	15.1	3.64	62.6	
401-81-0	*m*-CF_3	0.05	21.6	2.42	59.6	61 ± 2
		0.05	30.2	1.78	61.3	
		0.05	15.1	2.82	48.5	
455-13-0	*p*-CF_3	0.05	21.6	2.02	49.7	48 ± 1
		0.05	30.2	1.37	47.2	

[a] Rate constants for iodine abstraction (k_I) were measured relative to rate constants for chlorine abstraction from CCl_4 (k_{Cl}). [b] Molar concentration of *p*-nitrophenylazotriphenylmethane. [c] Ratio of the areas of the *p*-iodonitrobenzene peak ($A_{p\text{-NPI}}$) to the area of the *p*-chloronitrobenzene peak ($A_{p\text{-NPCl}}$) obtained by VPC. [d] This ratio of areas is corrected by a response factor to give the ratio of concentrations used to calculate k_I/k_{Cl} by eq 13. [e] Average k_I/k_{Cl} ± one standard deviation.

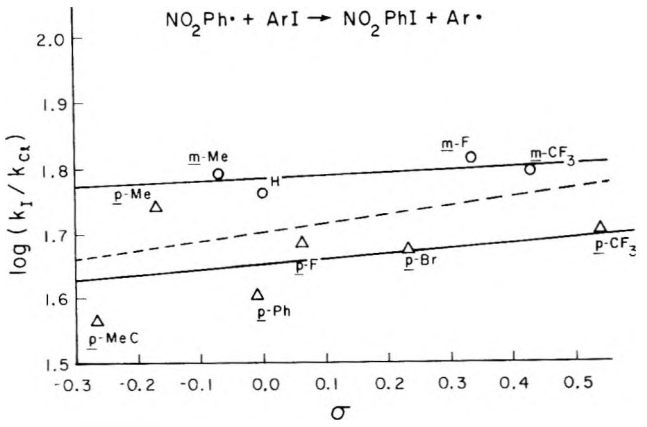


Figure 1. A Hammett equation plot of log (k_I/k_{Cl}) vs. σ for *p*-nitrophenyl radicals reacting at 60 °C with substituted iodobenzenes and CCl_4. Least squares treatment of these data gives $\rho = 0.0 \pm 0.2$ for meta (○) substituents only (upper solid line); $\rho = 0.0 \pm 0.3$ for para (△) substituents only (lower solid line); and $\rho = 0.1 \pm 0.2$ for both meta and para substituents (dashed line).[35]

radial nearly electroneutral relative to the benzyl radical,[33a,38] it is expected that there would be more charge development in the transition state of eq 11 than of eq 8. Therefore, SETS are more important in reaction 11 than in 8.[40] In fact, SETS become nearly as important as substituent effects on BDE, and a ρ of approximately zero results for reaction 11. (BDE effects should be about equal in both the phenyl and the *p*-nitrophenyl radical systems because the substrates, iodobenzenes, are the same, and the radicals are similar in reactivity.[33a,38])

The rationalization of the results of these two Hammett equation studies in terms of free energy *vs.* reaction coordinate diagrams is shown in Figures 2 and 3. In these plots, the curves with *positive slopes* represent the energy of the system Ph· (or NO_2Ph·) + ArI as the Ar–I bond is stretched and broken to form three noninteracting radicals, Ph· (or NO_2Ph·), I·, and Ar·. There is no bond formation along this curve. The curves with *negative slopes* show the free-energy changes which occur as the Ph–I (or NO_2Ph–I) bonds are being formed. These bond-making curves are parallel in Figures 2A and 2B since bond formation is assumed to occur without any interaction with the corresponding Ar· group, and the two bond-breaking curves differ only by the difference in BDE of the $CH_3C_6H_4$–I and BrC_6H_4–I bonds. If resonance contributions are not important, then the activation energies of the two reactions, indicated by arrows a and b in Figure 2, are the energy differences between the initial states and the intersection of the corresponding bond-breaking and bond-making curves. (See the caption for Figure 2 for details.)

Since electron-withdrawing substituents weaken the Ar–I

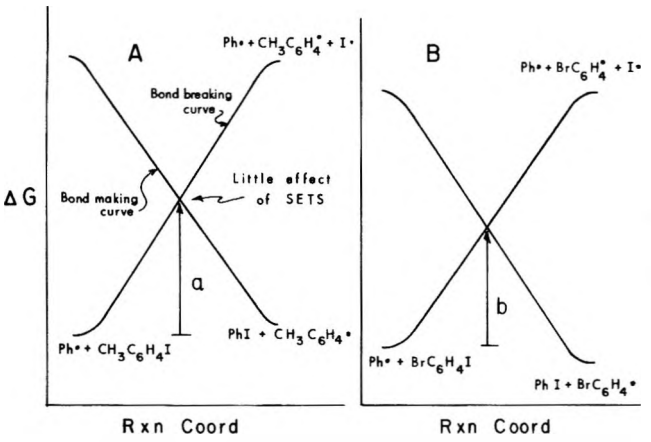


Figure 2. The free energy vs. reaction coordinate curves for iodine abstraction from substituted iodobenzenes by phenyl radicals are shown. The activation energy for abstraction from $CH_3C_6H_4I$, represented by arrow a, is greater than that for abstraction from BrC_6H_4I, arrow b, because electron-withdrawing substituents weaken the Ar–I bond and because there is little resonance contribution to the transition states of these reactions. A positive ρ is predicted.

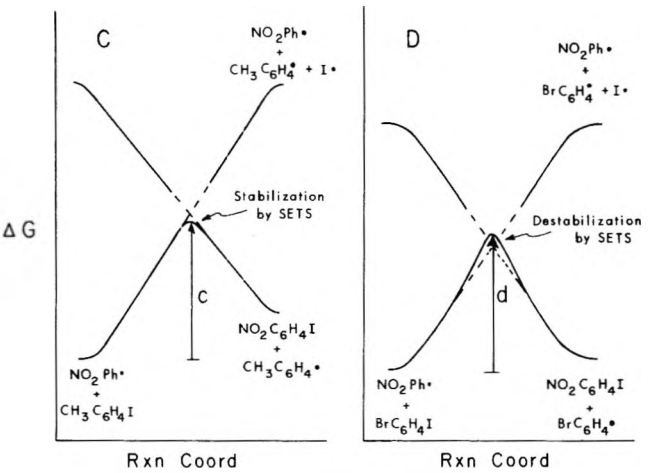


Figure 3. The free energy vs reaction coordinate curves for iodine abstraction from substituted iodobenzenes by *p*-nitrophenyl radicals are shown. In this case, resonance contributions to the transition state stability as well as substituent effects on BDE, are important. Since electron-donating substituents stabilize and electron-withdrawing substituents destabilize the transition state $[NO_2Ph\cdot^{\delta\delta+}\ I\cdot^{\delta-}\ \cdot^{\delta\delta+}Ar]$, the intersections of the bond-breaking and bond-making curves are perturbed as indicated by the solid lines. These resonance effects cause the activation energy for abstraction from $CH_3C_6H_4I$, represented by arrow c, to become approximately equal to that for abstraction from BrC_6H_4I, arrow d. This argument predicts a ρ of about zero.

bond, and, if resonance contributions to the transition state are not important, the activation energy for abstraction of iodine from BrC_6H_4I will be less than that for abstraction from $CH_3C_6H_4I$. This is the case for the phenyl radicals as shown in Figure 2, and the predicted positive ρ is observed. However, resonance contributions (SETS), indicated by the solid lines rounding off the intersections of the curves in Figure 3, are important in the *p*-nitrophenyl radical case. Since SETS stabilize the transition state of the $CH_3C_6H_4I + NO_2Ph\cdot$ reaction system and destabilize that of the $BrC_6H_4I + NO_2Ph\cdot$ system, the activation energies for iodine abstraction from ArI substituted with both electron-withdrawing and electron-donating groups are approximately equal. Therefore, a near-zero ρ is predicted as shown in Figure 3. (See the caption of Figure 3.)

Conclusion

We have stressed in this paper the necessity for considering both substituent effects on transition states (SETS) and substituent effects on bond dissociation energies (BDE) in rationalizing the results of Hammett equation studies. Unfortunately, although the theoretical correctness of this may be widely recognized, in practice it has become common to consider only the effects of substituents on transition states. It is true that in many cases SETS and BDE effects operate in the same direction, and, therefore, consideration of either one alone will "give the right answer", albeit for the wrong reason. However, we have here shown that it is both correct and necessary to consider both types of effects; in the case of the reactions considered here, we have been able to separate SETS and BDE effects and demonstrate the reality of both and the possibility of their mediating different signs of ρ for a given reaction.

Specifically, in the work discussed here, we have shown that BDE effects alone can lead to either negative ρ's (e.g., for hydrogen abstractions from toluenes[8] and benzenethiols[18]) or positive ρ's (e.g., for iodine abstraction from iodobenzenes). However, SETS perturbs the pattern of relative rates which is established by the effects of substituents on BDE. The direction and magnitude of this perturbation depends on the electronic nature of the radical and the substrate, the heat of reaction, and the reaction conditions (e.g., temperature and solvent). These polar transition state effects appear to be well understood. However, consequences of the BDE effects have rarely been considered in radical abstraction reactions. Failure to consider *both* SETS and substituent effects on BDE in rationalizing the results of Hammett equation studies led, at worst, to the inconsistencies in interpretations such as we noted, and at best, to the right answers obtained by partially incorrect reasoning.

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Registry No.—*p*-Nitrophenyl radical, 2395-99-5.

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(35) (a) The results of the least-squares analysis are reported according to the following format:[35b] the slope of the least-squares line and its interval estimator (uncertainty) at the 95% confidence level are $b + (t)(s_b)$,[35c,36] the average standard deviation of the logarithms of the individual k_I/k_{Cl}'s is s_y,[36e] and the number of points is n. (b) W. H. Davis, Jr., and W. A. Pryor, *J. Chem. Educ.*, **53**, 285 (1976). (c) The slope of the least-squares line is b,[36a] and the standard deviation of the slope is s_b.[36b] It may be said with m% confidence that the true value of the slope lies within $(t_{n-2,1-m})(s_b)$ of the calculated slope, b.[36c] The Student's t value for n points and a confidence level of m%, $t_{n-2,1-m}$, can be obtained from a table of the distribution of t (two-tailed tests).[36d]
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(40) If our suggested order of bond dissociation energies is correct, the reactions of the *p*-nitrophenyl radical are more endothermic than are those of phenyl. Therefore, SETS should be more important in the reactions of the *p*-nitrophenyl radical because of this factor as well.

Acylanthranils. 3. The Influence of Ring Substituents on Reactivity and Selectivity in the Reaction of Acylanthranils with Amines

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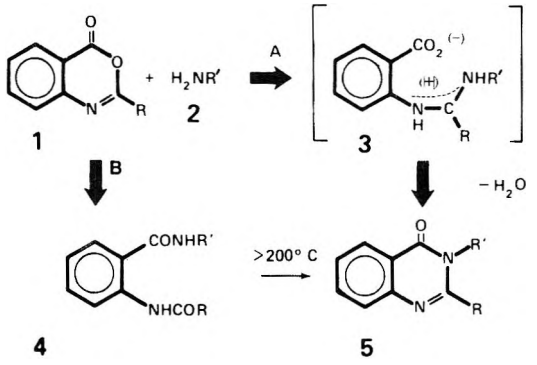
Sixteen acylanthranils were prepared and allowed to react with primary amines to give the corresponding benzamides, **4**, and/or quinazolones, **5**, which confirms the results of other investigators. The product distributions, however, are consistent with our recent suggestion that these products are formed competitively via alternative pathways A and B, as indicated in Scheme I, rather than sequentially **5** from **4** as believed originally. Although ring substituents on the acylanthranil affect markedly the overall *rate* of reaction, they do not necessarily affect *selectivity*. The latter is determined primarily by the electronic and steric factors associated with the substituent R at the 2 position only. As a general rule, the acetylanthranils, which are more reactive, favor pathway A, but the benzoylanthranils, which are less reactive, favor pathway B. Nevertheless the ratio k_A/k_B decreases with increase in bulk of the substituent R at the 2 position because of steric hindrance.

Our reinvestigation[1,2] of the reaction of acylanthranils, **1**, with primary amines, **2**, confirmed the reports of earlier investigators[3,4,5] that *o*-acylamidobenzamides, **4**, and/or the corresponding N-substituted quinazolones, **5**, are isolated as the major products if the reaction is made to occur at about 100 °C or above. We reported,[2] however, that on the one hand N-substituted *N'*-(2-carboxyphenyl)acetamidines, **3**, are almost always produced exclusively as the primary products of the reaction of acetylanthranil, **1b** (R = CH_3), with anilines at room temperature, and that these intermediates are convertible to the corresponding quinazolones by cyclodehydration in solution even at room temperature. On the other

hand, we noted that o-benzamidobenzanilide, **4a**, is produced exclusively[2] when benzoylanthranil, **1a** (R = Ph), is allowed to react with aniline below 150 °C. Since it was shown that the *o*-acylamidobenzamides, **4**, require fusion temperatures of about 250 °C for conversion to the corresponding quinazolones, **5**, it appears that below 150 °C **4** and **5** are produced by alternative pathways A and B as shown in Scheme I, and not

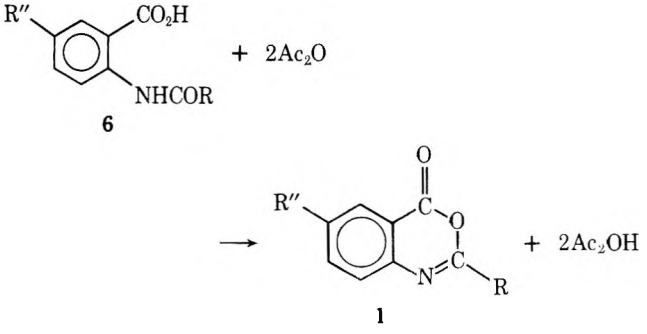
Scheme I



sequentially (**5** from **4**) as suggested by the earlier investigators. Therefore it is now of interest to determine why some acylanthranils follow pathway A exclusively, while others follow pathway B exclusively. Accordingly, the large body of apparently inconsistent results reported by the earlier investigators has been reinterpreted in light of the present realization that acylanthranils react via alternative pathways. Such a reconsideration leads to a more self-consistent pattern that shows how the reactivity and selectivity are dependent upon the electronic and steric factors associated with the molecular structure of the acylanthranil. Exposed areas of uncertainty are clarified herein by new experiments that complement the data already accumulated in the literature.

Results and Discussion

The acylanthranils, **1a–p**, were prepared by us in good yields (i.e., >50%) by cyclodehydration of the corresponding carboxylic acids **6** in acetic anhydride (or thionyl chloride) at reflux for several hours.



The melting point and ir data for this set of 16 acylanthranils are collected in Table I. The more reactive ones, such as acetylanthranil, were allowed to react at room temperature with a given amine, neat or in solution, whereas the less reactive ones, such as benzoylanthranil, required higher temperatures to effect complete reaction within a reasonable time interval as noted in Tables II and IV. The relative reactivities of these acylanthranils were evaluated qualitatively. The corresponding selectivities for reaction via pathways A relative to B, i.e., k_A/k_B = (**3** or **5**)/**4**, were calculated on the basis of the separation and materials balance procedure described previously.[2]

Zentmyer and Wagner[4] reported that the reactivity of acylanthranils varies considerably, as exemplified by acetylanthranil, which is quite sensitive to hydrolysis, and by benzoylanthranil, which is not. Since the former almost always follows pathway A whereas the latter appears to prefer pathway B, one might suspect that selectivity is related to reactivity. The relative rates of attack by a nucleophile at the 2 and 4 positions should be a function of the relative electrophilicities at these alternate sites, which in turn should be a function of the substituents on the acylanthranil, especially at the 2 position.

The results reported by Bogert,[3k] who caused several benzoylanthranils to react with aromatic amines neat at fusion temperature to give the corresponding quinazolones, and those reported by Wagner,[4] who caused another set of benzoylanthranils to react at 100 °C with aniline neat and with ammonia in ethanol at room temperature to give the corresponding o-benzamidobenzamide, are in light of the introduction mutually inconsistent. Although our result with the benzoylanthranil–aniline reaction confirmed the report of Wagner, it was important to show whether benzoylanthranil, **1a**, does indeed follow pathway B as a general rule, and to establish the conditions under which it might also follow pathway A. Accordingly, **1a** was made to react with the simple primary aliphatic amines, *n*-propylamine and *n*-butylamine, in diethyl ether at reflux overnight, with the diamines oxydianiline and hexamethylenediamine, neat and in solution at 140 °C for about 4 h, and with 4,4′-diaminodiphenyl sulfone neat at 250 °C for 4 h.

The results of these experiments are summarized in Tables II and III. They show that the corresponding mono- and bis-*o*-benzamidobenzamides, written symbolically in Table III as BNHR and BNHRNHB, respectively, were isolated in good yield for all reactions made to occur at or below 140 °C. Formation of the mono- and bisquinazolones, written symbolically in Table III as QR and QRQ, occurred only at 250 °C, as evidenced by the reaction with $(p\text{-}NH_2Ph)_2SO_2$ to give a mixture of $(QPh)_2SO_2$, $(BNHPh)_2SO_2$, and $BNHPhSO_2PhQ$ in the approximate ratio of 2/1/1, respectively. These results suggest that the quinazolones isolated by Bogert[3k] were formed sequentially via cyclodehydration of the corresponding o-benzamidebenzamides owing to his fusion temperatures that were above 200 °C, and support the conclusion that benzoylanthranils as a class do indeed react with amines via pathway B exclusively as noted by Wagner. These results also verify that benzoylanthranil, **1a**, is considerably less reactive than acetylanthranil, **1b**, which reacts exothermally with the above amines on contact via pathway A.

Hegarty and Bruice[6] have shown that 2-amino-3,1,4-benzoxazone, **1c** (R = NH_2), reacts slowly with amines to give the corresponding *o*-uramidobenzamides. The qualitative results obtained in our laboratory confirm that **1c** is considerably less reactive than **1b** (R = CH_3) but somewhat more so that **1a** (R = Ph). It can be made to undergo intermolecular condensation, however, at its softening point, about 190 °C, where it does not really melt but is converted instead to a mixture of polymerization products that melts at 285–300 °C.

We prepared trifluoroacetylanthranil, **1d** (R = CF_3), to compare its reactivity and selectivity with those of **1a–c**. We noted that **1d** is considerably more reactive than **1b** as indicated by its sensitivity toward atmospheric moisture to give o-trifluoroacetamidobenzoic acid, and by its ease of reaction with alcohols to give the corresponding ester. In contrast **1b** is quite stable to atmospheric moisture and requires reflux temperature in alkaline alcohol to form the ester.

When **1d** was added to a solution of aniline or *p*-toluidine in benzene, the corresponding trifluoroacetamidines (**4d**) precipitated from solution almost immediately (Tables IV and V). In contrast, the corresponding acetamidine salts from **1b** require a few hours to complete reaction under the same conditions (Table IV). None of the corresponding diamide,

Table I. Cyclodehydration of 2-(RCONH)-5(R′′)PhCO$_2$H (6) to the Corresponding Acylanthranil, 1

R	R′′	Mp of 6, °C	Dehydration agent	1	Mp of 1, °C	Important absorption bands in ir spectrum of 1, μ
Ph	H	180–181	*a*	a	122–123	5.6, 6.1, 7.6, 7.9, 9.4, 9.6, 9.8, 9.9, 13.0, 14.5
CH_3	H	185–186	*a*	b	86–87	5.7, 6.1, 7.4, 8.0, 8.4, 9.5, 10.0, 10.4, 12.9, 14.5
NH_2	H	141–142	*b*	c	*c*	3.0, 5.7, 5.9, 6.2, 7.6, 9.1, 9.8, 10.1, 13.1, 14.5
CF_3	H	185–186	*a*	d*	51–52	5.6, 5.9, 7.4, 8.2, 8.5, 9.0, 10.2, 12.8, 13.2, 14.5
CH_3CH_2	H	118–119	*a*	e	84–85	5.7, 6.0, 6.2, 8.6, 8.8, 9.2, 9.8, 12.8, 14.5
$CH_3(CH_2)_{16}$	H	78–80	*a*	f*	45–46	5.7, 6.1, 6.2, 8.6, 10.0, 10.5, 12.8, 13.9, 14.4
n-$C_8F_{17}SO_2NEtCH_2$	H	184–186	*a*	g*	111–112	5.7, 6.0, 7.2, 8.3, 8.7, 9.4, 9.9, 10.4, 11.0, 13.0, 14.5
p-NO_2Ph	H	234–235	*a*	h	208–210	5.6, 6.2, 6.5, 7.4, 9.4, 10.0, 11.5, 12.8, 13.1, 14.2, 14.5
p-NH_2Ph	H	226–227	*b*	i	221–223	2.9, 3.0, 5.7, 6.2, 6.4, 7.5, 8.0, 8.5, 9.5, 12.0, 13.1, 14.6
p-CH_3CONHPh	H		*d*	j	294–296	3.0, 5.7, 5.9, 6.3, 7.1, 7.6, 8.0, 8.5, 9.5, 11.8, 13.0, 13.6, 14.5
m-NO_2Ph	H	230–232	*a*	k	169–170	5.7, 6.1, 6.2, 6.5, 7.5, 9.5, 9.7, 10.0, 12.9, 13.4, 14.6
m-NH_2Ph	H	227–228	*b*	l	161–163	2.9, 3.0, 5.7, 6.3, 7.5, 7.8, 8.0, 8.2, 9.5, 9.9, 13.0, 13.9, 14.6
Ph	NO_2		*e*	m	168–169	5.7, 6.2, 6.3, 6.5, 7.4, 7.9, 9.2, 9.4, 9.6, 11.7, 12.8, 13.0, 14.2
Ph	NH_2		*f*	n	201–220	2.9, 3.0, 5.7, 6.1, 6.6, 7.3, 8.0, 9.5, 12.0, 12.9, 14.4, 14.7
CH_3	NO_2	215–216	*a*	o	162–163	5.7, 6.1, 6.2, 6.5, 7.3, 7.9, 8.4, 9.2, 9.4, 10.3, 11.5, 12.5, 13.3, 14.4
CH_3	Br	220–221	*a*	p	134–135	5.7, 6.0, 6.8, 8.0, 8.5, 9.5, 10.4, 11.9, 12.8, 14.4, 14.6

[a] Acetic anhydride at reflux. [b] Thionyl chloride in benzene at reflux. [c] 1c softens at 190 °C, but true melting occurs at 285–300 °C. [d] Prepared from 1i by reaction with Ac_2O. [e] 2-Amino-5-nitrobenzoic acid (mp 275–276 °C) converted directly to 1m by reaction with excess benzoyl chloride in pyridine at reflux. [f] Prepared from 1m by reduction with H_2 on Raney nickel in dioxane. * New compounds.

Table II. Reaction of Benzoylanthranil (1a, R = Ph) with Amines

Registry no.	Amine	Reaction conditions: Solvent	Time	Temp, °C	% 1a isolated as: 4	5	k_A/k_B = 5/4
62-53-3	H_2NPh	*a*	1 day	23	93		<1/25
101-80-4	$(p$-$H_2NPh)_2O$	*b*	4 h	Reflux	94		<1/25
		a	1 h	140	53		<1/25
80-08-0	$(p$-$H_2NPh)_2SO_2$	*a*	4 h	250	*e*	*e*	*e*
107-10-8	$H_2N(CH_2)_3H$	*c*	1 day	Reflux	97		<1/25
109-73-9	$H_2N(CH_2)_4H$	*c*	1 day	Reflux	98		<1/25
124-09-4	$H_2N(CH_2)_6NH_2$	*d*	4 h	Reflux	87		<1/25
		a	4 h	140	84		<1/25

[a] Neat. [b] Acetic acid. [c] Diethyl ether. [d] Pyridine. [e] Not determined since conditions known to cause conversion of 4 to 5; only half of product was isolated as the diquinazolone $(QPh)_2SO_2$ mp 364–365 °C. The other half was isolated as mixture of the bisbenzamido and benzamido monoquinazolone derivatives of 4,4′-diaminodiphenylsulfone [$(BNHPh)_2SO_2$ and $BNHPhSO_2PhQ$]. The corresponding characterization data are collected in Table III.

4d, was produced via the alternative route, as indicated by the ir spectrum of the product and its complete solution in dilute $NaHCO_3$.

The ir spectra of the trifluoroacetamidines, **3d**, obtained by reaction of **1d** with aniline and with toluidine, differ somewhat from those of the corresponding hydrocarbon acetamidines, **3b**. The OH absorptions of the former[2] are typical of a carboxylic acid rather than an internal amidine salt as manifested by the latter, which are broad and different in form. In addition the position of the carbonyl absorption for the trifluoroacetamidines are lower in wavelength, changing from about 6.3 μ for the hydrocarbon acetamidines to 5.9 μ for the trifluoroacetamidines which are relatively insoluble in water or in dilute aqueous acid. These observations are in keeping with the expected markedly decreased basicity of the fluoroacetamidines owing to the strong electronegative influence of the CF_3 group.

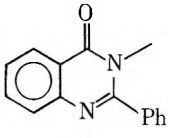
The preparation of formylanthranil, **1q** (R = H), and 6-bromoformylanthranil, **1r** (R = H; R′ = Br), was reported by Wagner[4] and by Bogert.[3f] These acylanthranils were described by them as unstable and extremely sensitive to atmospheric moisture. Reaction with ammonia gave the corresponding quinazolones, **5q** and **5r**, which we now presume were formed via pathway A as indicated in Scheme I. The reported qualitative description of their work suggests that the reactivities of **1q** and **1r** are comparable to that of **1d** and considerably greater than **1b**.

From the foregoing discussion, it is possible to establish

Table III. Characterization Data for Products Obtained by Reaction of 1a with Amines Listed in Table II

Product[a]	Mp, °C	Key ir bands, μ
B-NHPh	286–287	3.0, 6.0, 6.5
$(B\text{-}NHPh)_2O$[b]	300–301	3.0, 6.0, 6.5, 8.1
$(Q\text{-}Ph)_2SO_2$[b]	364–365	5.9, 7.5, 8.6
$B\text{-}NH(CH_2)_3H$	134–135	3.0, 6.0, 6.1, 6.5
$B\text{-}NH(CH_2)_4H$	122–123	3.0, 6.0, 6.1, 6.5
$B\text{-}NH(CH_2)_6NH\text{-}B$[b]	182–183	3.0, 6.0, 6.1, 6.5

[a] B indicates *o*-(PhCONH)PhCO group, Q indicates group



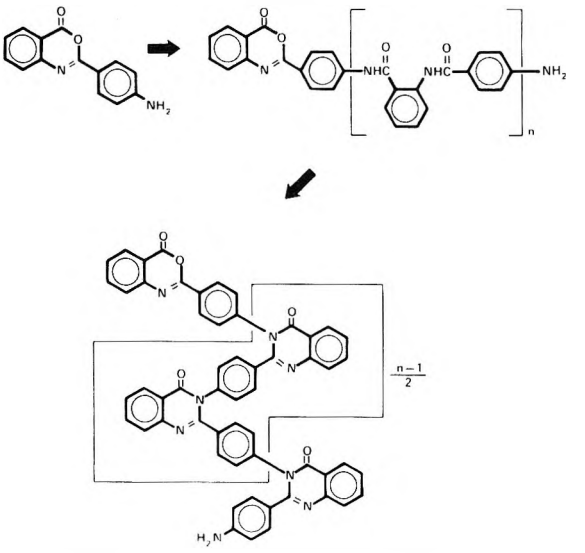
i

i. [b] Satisfactory combustion analytical data for C, H, N (±0.7%) were reported for these compounds. Ed.

qualitatively that the relative reactivities for these five acylanthranils are in the order **d** (R = CF_3) > **q** (R = H) > **b** (R = CH_3) > **c** (R = NH_2) ≃ **a** (R = Ph). This order appears to follow the expected influence on electrophilicity at the 2 position owing to electronic induction and/or resonance contribution of the corresponding R substituent. The position of lowest reactivity for the phenyl group might be ascribed in part to steric hindrance, but not necessarily. A phenyl group is weakly electron withdrawing by induction, but strongly electron contributing when acting in resonance with a >C=N– (or >C=O) group, so that the net effect, like that of NH_2, is to decrease the electrophilicity at the 2 position, thereby favoring pathway B while decreasing the overall rate of reaction. That the more reactive acylanthranils, **1d, 1q** and **1b,** follow pathway A preferentially and the less reactive acylanthranils, **1c** and **1a,** follow pathway B preferentially suggest that the electronic effect might have an important influence on reactive selectivity, at least when R is small.

If the electronic effect were indeed the dominant factor that influences selectivity, then it should be possible to mitigate the extreme converse selectivities manifested by acetylanthranil and benzoylanthranil, by means of appropriate ring substituents that influence the electrophilicity at the 2 and/or 4 positions owing to electronic resonance. The results of Bogert[3] and Wagner,[4] however, show that the corresponding *o*-benzamidobenzamides are obtained universally, when ammonia[3] or aniline[3,4] are caused to react at about 100 °C with *o*- and *p*-toluylanthranils, with *o*- and *p*-chlorobenzoylanthranils, and with *o*-, *m*-, and *p*-nitrobenzoylanthranils. Our results with **1h** (R = *p*-NO_2Ph) and **1k** (R = *m*-NO_2Ph) verified their observations, and showed qualitatively that the reactivities of **1h** and **1m** (R = Ph; R″ = NO_2) were greater than that of **1a** (R = Ph) but less that that of **2b** (R = CH_3) whereas **1k** was about the same as **1a.** The reactivity of *p*-aminobenzoylanthranil, **2i** (R = *p*NH_2Ph), was so low that it was recovered unchanged after 8 days in aniline or in aqueous NaOH at room temperature. Despite their low reactivity the bifunctional acylanthranils, **1i** and **1n,** can be made to undergo intermolecular condensation by fusion just above their melting points for about 10 min to give the corresponding polyamides, as indicated by the sharp bands at 3.0, 6.1, and 6.6 μ in their spectra of the products. Longer times and higher temperatures cause progressive conversion to the corresponding polyquinazolone as indicated by the disappearance of the sharp bands at 3.0, 6.1, and 6.6 μ and the appearance of a sharp band at 5.9 μ in the ir spectra. This conversion is illustrated in Scheme II

Scheme II



using **1i** as the model. Self-condensation of *m*-aminobenzoylanthranil, **1l** (R = *m*-NH_2Ph), is more facile than that of **1i** (or **1m**) and it goes smoothly at 170 °C neat or in solution to give high molecular weight linear polyamide. Again longer reaction times at higher temperature cause progressive cyclodehydration to thermally stable polyquinazolone polymers that melt above 300 °C and are soluble in formic acid or in *m*-cresol. Inherent viscosities in *m*-cresol were in the range of 0.2–0.5.

From these results and the observed relative sensitivity to moisture, it was deduced qualitatively that the relative reactivities of the ring substituted benzoylanthranils listed in

Table IV. Reaction of Acylanthranils 1 with Aniline in Benzene at 23 °C

Acylanthranil, R (R″)	1	Rxn time, days	% isolated as product 4	3	5	Selectivity (3 or 5)/4 k_A/k_B =
Ph	a	1[a]	93			<1/25
CH_3	b	0.2		95		>50/1
CF_3	d	5 min		71		>50/1
CH_3CH_2	e	1	11	Oil	86	9/1
$CH_3(CH_2)_{16}$	f	1	Grease (20)[b]	Oil	78[c]	4/1[b]
$n\text{-}C_8F_{17}SO_2NEtCH_2$	g	7	76	Oil (15)[d]		1/6
CH_3 (6-NO_2)	l	5 min		99		>50/1
CH_3 (6-Br)	m	0.1		95[e]		>50/1
CF_3	d	5 min[f]		92[f]		>50/1

[a] Neat in aniline. [b] Ir indicated that grease was ca. 80% 4f, from which was calculated that 20% 1f units isolated as 4f. [c] 5f was an oil. It was converted quantitatively to its HCl salt (mp 189–191 °C). [d] Ir indicated that this oil was ca. 60% 3g, from which was calculated that 15% 1g was isolated as 3g. Some hydrolysis to *o*-acylamidobenzoic acid occurred during workup. [e] Ir indicated that residue left as product was mostly 3c. Mixture dissolved in dilute aqueous base to give a clear solution from which 5m precipitated overnight. [f] 3d, the reaction product obtained with *p*-toluidine instead of aniline.

Table V. Characterization Data for Products Obtained by Reaction of Aniline with Acylanthranils as Listed in Table IV

1	Product	Mp, °C	Key ir bands, μ
a	4a[a]	286–287	3.0, 6.0, 6.5
b	3b	115–116	See ref 1
d	3d	105–106	3.0–4.0, 5.9, 6.0
e	4e	156–157	3.0, 6.1, 6.5
	5e	125–126	5.9, 6.2
f	5f HCl[a]	189–191	5.9, 6.2
g	4g	108–110	3.0, 5.9, 6.0, 6.5, 8.0, 8.8
l	3l	67–68	3.2, 4.2, 6.2, 6.6
	5l	220–221	5.9, 6.3, 6.5, 7.4
m	5m	186–187	5.9, 6.2
d	3d'[b]	103–104	3.1, 4.1, 5.9, 6.0

[a] See Table III, footnote *a*. [b] 3d' is *N*-(*o*-carboxyphenyl)-*N'*-(*p*-tolyl)acetamidine formed by reaction of 1d with *p*-toluidine in benzene.

Table I are in the order **1b** (R = CH_3) > **m** (R = Ph; R″ = NO_2) ≃ **h** (R = *p*-NO_2Ph) > **k** (R = *m*-NO_2Ph) > **a** (R = Ph) > **l** (R = *m*-NH_2Ph) > **i** (R = *p*-NH_2Ph) ≃ **n** (R = Ph; R″ = NH_2) ≃ **j** (R = *p*-CH_3CONHPh). This order of reactivity parallels the expected influence in electrophilicity at the 2 position owing to the electronic contribution of the ring substituent through resonance and/or induction; electron-withdrawing groups enhance reactivity and electron-donating groups decrease reactivity about as predicted by theory. It is reasonable to assume, therefore, that the same will be true for all the many ring-substituted benzoylanthranils reported by the early investigators. In all those experiments that were carried out below 150 °C the product isolated was the corresponding o-benzamidobenzamide. These consistent results indicate than such reaction of the benzoylanthranil occurs universally via pathway B, despite a reactivity markedly affected by ring substituents. That is to say a significant change in reactivity has virtually no effect on the selectivity of benzoylanthranils.

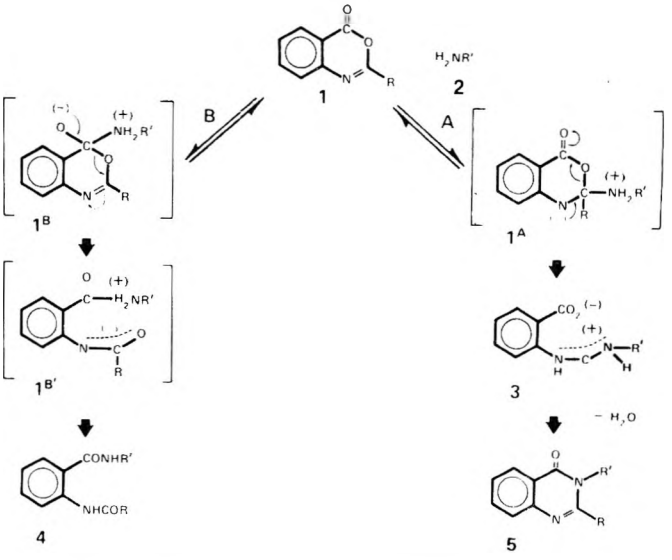
Similarly, the reinterpretation of the data reported for acetylanthranils also indicates a steadfast preference for one pathway exclusive of the other. But in sharp contrast, the acetylanthranils prefer route A. Bogert[3] had prepared the 5-, 6-, and 7-nitroacetylanthranils, 6-bromoacetylanthranil, 6-carboxyacetylanthranil, and the 6- and 7-acetamidoacetylanthranils. These compounds were made to react at about 100 °C with simple aliphatic and aromatic amines. The reported major product, with but one exception, was the corresponding quinazolone, which we now presume was formed via pathway A as shown in Scheme I. The one exception was the reaction of 7-acetamidoacetylanthranil with 2-aminobutane, which gave the corresponding 2,5-di(acetamido)benzamide. To be certain, however, that the ring-substituted quinazolones were indeed formed by cyclodehydration of the acetamidines, **3**, and not the *o*-acetamidobenzamides, **4**, owing to the activating influence of the ring substituents, the acetylanthranils **1o** (R = CH_3; R″ = NO_2) and **1p** (R = CH_3; R″ = Br) were prepared by us (Table I) and allowed to react with aniline in benzene at room temperature. As expected, the corresponding insoluble amidine salts, **3o** and **3p** (Tables IV and V), were isolated in very good yields. These intermediates were then converted almost quantitatively to the corresponding quinazolones **5o** and **5p** by cyclodehydration neat at 120 °C and at room temperature in dilute aqueous base. These results confirm that reaction via pathway A is indeed general for all acetylanthranils.

It was noted in these experiments that reaction of **1o** (R = CH_3; R″ = NO_2) with aniline to give insoluble acetamidine **3o** is complete within 5 min, indicating that the reactivity of **1o** is greater than that of **1b** (R = CH_3) and about comparable to that of **1d** (R = CF_3). The reactivity of **1p** (R = CH_3; R″ = Br) appeared to be somewhat faster than that of **1b**, but less than that of **1o**.

From these qualitative comparisons it was deduced that the relative reactivities for this set of acetylanthranils are in the order **d** (R = CF_3) ≥ **o** (R = CH_3; R″ = NO_2) > **p** (R = CH_3; R″ = Br) > **b** (R = CH_3). Here again it is noticed that the order of reactivity parallels the expected influence on the electrophilicity at the 2 and 4 positions owing to the electronic contribution of the ring substituents through resonance and/or induction. Accordingly, it was logical to assume in the absence of confirmatory experiments that the reactivities of the 6- and 7-acetamidoacetylanthranils prepared by Bogert would be less than that of **1b**. The qualitative description of Bogert's results appears to indicate that the reactivities of these two acetamido substituted acetylanthranils are comparable with that of benzoylanthranil. His results also indicate clearly that the products of reaction at about 100 °C with simple alkylamines and anilines are the corresponding quinazolone despite the reduced reactivity. Again marked changes in reactivity owing to the added electronic influence of ring substituents had no significant effect on the charactersitic selectivity manifested by the parent acylanthanil.

It is concluded, therefore, that the reactivity of the acylanthranil is not the important parameter that determines its selectivity. It is suspected that the relative stability of the corresponding transition states **1A** and **1B** produced by nucleophilic addition of an amine at the 2 and 4 positions, respectively, is an important consideration which at least in part is determined by the electronic character of the R substituent at the 2 position. In our preceding publication,[2] it was suggested that the apparent anomalous preference of acetylanthranil for reaction with anilines via pathway A instead of B, despite an expected electrophilicity of the >C=O group at the 4 position greater than that of the >C=N– group at the 2 position, might be rationalized on the basis that transition states, **1A** and **1B**, are in equilibrium with one another through **1** as shown in Scheme III. Since it is easier to transfer negative

Scheme III



charge to a more electronegative center (i.e., from N to O), **1A** is converted more readily to a stable product **3** (via pathway A) than **1B** which requires transfer of negative charge from O to N in order to cascade to a stable product **4** (via pathway B).

This rationale serves equally well to explain the selectivity noted with **1d** (R = CF_3) and **1q** (R = H), but not that noted

Table VI. Comparison of Reactivity and Selectivity of Acylanthranils at 23 °C and ca. 100 °C as a Function of the Substituent R at the 2 Position

Rel reactivity of 1	b	>	e	>	s	>	f	>	g	≃	a
R	CH_2		Et		*n*-Pr		$H(CH_2)_{17}$		n-$C_8F_{17}SO_2NEtCH_2$		Ph
k_A/k_B = 5/4 at 23 °C	>50		9				~4		~1/6		<1/25
Approximate k_A/k_B at ca. 100 °C calcd from data taken from ref 4			2		1						

with **1a** (R = NH_2) and **1a** (R = Ph) which prefer pathway B. Rationalization of the latter selectivity requires additional considerations that could possibly offset the advantage of facile negative charge transfer from N to O. In the case of **1c** (R = NH_2) the reverse transfer from O to N is perhaps aided by the presence of two amido centers to share the negative charge. This is not true for **1a**, however, which leaves steric hindrance as a possible mitigating factor that raises the energy barrier to formation of **1a**.

If steric hindrance is indeed an important parameter that affects selectivity, then the ratio of reaction via pathway A to that via pathway B [i.e., k_A/k_B = (3 or 5)/4] should decrease with increase in bulk of the R substituent at the 2 position within a set of acylanthranils of about the same electronic character. The data already reported, however, appear to be conflicting and not amenable to clear-cut differentiation between the alternative pathways. Bogert et al.[3p] caused ammonia to react at about 100 °C with 2-R-6-bromo-3,1,4-benzoxazones, where R is H, CH_3, Et, *n*-Pr, *i*-Pr, and *i*-Bu, and they reported only the isolation of the corresponding quinazolones. On the other hand, Zentmyer and Wagner, who caused *n*-propionylanthranil and *n*-butyrylanthranil to react with aniline at about 100 °C, reported[4] the corresponding benzanilides, **4**, as the only products isolated in significant amounts. The yields of isolated products, however, accounted at best for only about 50% of the acylanthranil units made to react with aniline.

To test this "steric" hypothesis the acylanthranils **1b**, **1c**, and **1f** (Table I) were allowed to react with 1 equiv of aniline in benzene at room temperature. The products were separated and the selectivity, k_A/k_B, calculated on the basis of almost total recovery of the acylanthranil units as described previously.[2] The results are summarized in Tables IV and V.

It is noticed that both **4** and **5** were isolated in significant amounts from **1e** and **1f**, and that the selectivity ratio k_A/k_B decreases from >50/1 for **1b** (R = CH_3) to about 4/1 for **1f** [R = $(CH_2)_{17}H$] with the greater change associated with the change from R = CH_3 (**1b**) to R = CH_2CH_3, (**1e**). The distribution of products obtained with **1f** is somewhat uncertain owing to the long aliphatic chain, which made it difficult to separate the products quantitatively; oils and greases were obtained instead of crystalline compounds. The major product, **5f**, was isolated pure as the hydrochloride salt, but the minor product, **4f**, could be isolated only as a smaller neutral fraction that contained unidentified impurities. The amount of **4f** in this fraction was estimated from the ir and NMR spectra. The k_A/k_B ratio of ca. 4/1 for **1f** indicates only that **5f** was still the major product even when *n* is 17, but that the proportion of **4f** to **5f** was only half that realized with **1e** (R = CH_2CH_3; k_A/k_B = 9/1).

The significant shift in selectivity toward pathway B as a function of *n* of the group $(CH_2)_nH$ at the 2 position might also be attributed to the small but monotonic increase in electropositive induction, which is also a function of *n*. To examine this possibility requires simply to compare the corresponding product distribution obtained with an acylanthranil that has a long chain electronegative group attached to the R substituent, which should mitigate the electropositive contribution at the 2 position. Accordingly, *N*-ethyl-*n*-perfluorooctylsulfonamidoacetylanthranil, **1g**, was prepared and allowed to react with aniline as described in the Experimental Section. The results, given in Table IV, show that the selectivity ratio for **1g**, i.e., k_A/k_B = 1/6, is markedly smaller than that realized with **1f**, and that reaction with **1g** decidedly favors pathway B. Despite the mitigating effect of the fluorocarbon sulfonamide group on electropositive induction, the branch at the amide nitrogen atom apparently provides sufficient steric hindrance to an approaching nucleophile so as to enhance the shift toward reaction via pathway B.

It was noted qualitatively that the reactivities of the acetylanthranils **1e**, **1f**, and **1g** toward moisture and amines decrease in that order and are intermediate between **1b** and **1a**. This order of reactivity appears to parallel a decreasing trend in k_A/k_B. A similar decreasing order of reactivity was noted by Zentmyer and Wagner[4] for the acylanthranils **1b**, **1e**, *n*-butyrylanthranil (**1s**), and **1a**. Unfortunately their reported yield data do not permit accurate calculation of selectivity owing to poor materials balance. If one assumes, however, that the unrecovered acylanthranil units were lost as soluble alternative product 3 (or **5**) then the ratio (100% − 4)/4 gives approximate selectivity values at about 100 °C, which appear to parallel qualitatively, though not quantitatively, the order for selectivity values at 23 °C observed by us as indicated in Table VI.

The quantitative discrepancy between our results at 23 °C and those of Zentmyer and Wagner at about 100 °C may be due to the temperature difference, since it was noted by us that the ratio k_A/k_B decreases at higher reaction temperatures as will be discussed in a subsequent publication.

Although the order of reactivity noted in Table VI might be attributed to the combined influence of the electronic character and bulk size of the substituent R at the 2 position, the parallel order for decreasing k_A/k_B can only be attributed to steric hindrance, since a corresponding change in selectivity was not manifested either by amino (or acetamido) substituted acetylanthranils, which were markedly slower than **1b**, nor by nitro substituted benzoylanthranils, which were markedly faster than **1a** as discussed previously.

In summary, it was shown that the wealth of reported information[3] regarding the reaction of acylanthranils with amines to give quinazolones, **5**, and/or benzamides, **4**, which were inconsistent and even conflicting when interpreted on the original assumption that **5** is formed sequentially from **4** by cyclodehydration, now fall into a self-consistent pattern, when reinterpreted in light of the recent suggestion that **5** and **4** are formed competitively via alternative pathways A and B respectively as illustrated in Scheme I. The electronic character and bulk size of the substituent R at the 2 position of the acylanthranil are dominant factors that influence the rate and selectivity of reaction with a given amine, as noted in the relative reactivities toward aniline for the set **1d** (R = CF_3) > **1b** (R = CH_3) > **1a** (R = Ph) and the overwhelming preference of **1d** and **1b** for pathway A, whereas **1a** has the converse preference for pathway B. Selectivity, however, is not a function of reactivity alone, since it is possible to mitigate markedly the reactivity of acetylanthranils and benzoylanthranils by the presence of ring substituents that influence accordingly the electrophilicity at the 2 and/or 4 positions by

resonance and/or induction without affecting the selectivity of the parent acylanthranil. Selectivity appears to be determined by the relative efficiency for conversion of the transition states **1A** and **1B** to stable products **3** and **4**, respectively, as discussed in terms of Scheme III, and the bulk size of the substituent R at the 2 position. The relative reactivity and the selectivity ratio k_A/k_B decrease with increase in bulk of R as indicated by the order in the set of acylanthranils **b** (R = CH_3) > **e** (R = Et) > **f** [R = $(CH_2)_{17}H$] > **g** [R = CH_2NESO_2-$(CF_2)_8F$]. This order of reactivity and selectivity is consistent with progressively greater impediment to approach of a nucleophile to the electrophilic center at the 2 position.

As mentioned earlier, one example, namely, the reported isolation of 2,5-di(acetamido)-*N*-(2-butyl)benzamide as the major product of reaction of 7-(acetamido)acetylanthranil with 2-aminobutane at about 100 °C instead of the expected quinazolone, does not yet fit into the overall pattern as discussed thus far. It is probable, however, that this apparent exception may in fact be the result of steric hindrance on the part of the amine. It is intended, therefore, to investigate the reaction of aliphatic amines with acetylanthranil at room temperature to see how the product distribution is affected in turn by bulky substituent on the amine coreactant.

Experimental Section

A. General Procedure for Preparation of Acylanthranils, 1. This procedure is a variation of those already published.[3,7] In our hands it appeared to be quite general and gave positive results in good yields (i.e., >50%) even with some difficult examples that were reported earlier as negative.

The organic acid precursor, **6**, was converted to the corresponding acyl chloride by treatment with thionyl chloride at reflux temperature for 2 h. The excess reagent was removed under vacuum and the desired product separated from the residue by distillation. The acyl chloride was dissolved in pyridine and then added dropwise to a well-stirred solution of anthranilic acid in pyridine kept at 0 °C. The solvent was removed under vacuum in a rotary film evaporator, and the residue was recrystallized from a suitable solvent to yield the corresponding *o*-acylamidobenzoic acid in the form of white crystals. The acid was converted to the corresponding acylanthranil by treatment with refluxing acetic anhydride (or thionyl chloride) for 2 h. The product, which usually crystallized on cooling, was separated by filtration. The mother liquor was concentrated to about one-fifth its volume to yield a second crop of crystals on cooling. The overall yields from the organic acid to the corresponding acylanthranil were usually above 50%. The results obtained for the preparation of acylanthranils **1a–p** are summarized in Table I. Only the procedures for the fluorocarbon acylanthranils, which are novel compounds, are described in more detail below.

Trifluoroacetylanthranil, 1d. Trifluoroacetyl chloride was prepared by reaction of trifluoroacetic acid with PCl_5. The gas was dried over Drierite and collected at −78 °C. About 0.45 mol of this acyl chloride was recollected in a well-stirred solution of anthranilic acid (0.4 mol) and pyridine (300 ml) kept at 0 °C at atmospheric pressure. The transfer occurred over a period of 1 h. The excess pyridine was removed by evaporation under vacuum. The residue was dissolved in cold, dilute, aqueous NaOH and reprecipitated by addition of cold, dilute HCl to give in about 95% yield *o*-trifluoroacetylanthranilic acid as a white powder (mp 185–186 °C), which was identified by its ir spectrum and partial elementary analysis.

Anal. Calcd for $C_9H_6NO_3F_3$: N, 6.01; neut equiv, 233.2. Found: N, 6.1; neut equiv, 236.

The acid was then converted to the acylanthranil, **1d**, in about 90% yield as described in the general procedure. The product was recrystallized from heptane to give **1d** as off-white crystals (mp 51–52 °C). Trifluoroacetylanthranil was identified by its ir spectrum (Table I) and its partial elementary analysis.

Anal. Calcd for $C_9H_4NO_2F_3$: N, 6.51; neut equiv, 215.1. Found: N, 6.3; neut equiv, 218.

A sample of **1d** was converted to ethyl *o*-(trifluoroacetamido)benzoate (mp 80–81 °C) by reaction with ethanol at room temperature using a trace amount of NaOEt as catalyst. The derivative was characterized by its ir spectrum and its neutralization equivalent in a nonaqueous solvent.

Anal. Calcd for $C_9H_{10}NO_3F_3$: 262.4. Found: 264.

***N*-Ethyl-*n*-perfluorooctylsulfonamidoacetylanthranil, 1g.** *N*-Ethyl-*n*-perfluorooctylsulfonamidoacetic acid (mp 156–157 °C), which was prepared by R. Guenthner of the 3M Co., was converted to the corresponding acyl chloride by reaction with thionyl chloride. After removal of excess thionyl chloride the residue was recrystallized from hexane to give *N*-ethyl-*n*-perfluorooctylsulfonamidoacetyl chloride in the form of tiny, white crystals (mp 66–67 °C). The acyl chloride was made to react with anthranilic acid in toluene kept at reflux temperature for 2 h. The product, which was collected by filtration, was recrystallized from hot benzene to give the expected *o*-acetamidobenzoic acid in the form of white crystals (mp 184–186 °C). The acid was converted to the corresponding acylanthranil by cyclodehydration in hot acetic anhydride. The product was recrystallized from heptane to give *N*-ethyl-*n*-perfluorooctylsulfonamidoacetylanthranil, **1g**, in the form of white crystals (mp 111–112 °C).

The assigned configuration was confirmed by its ir spectrum (Table I).

B. General Procedure for Reaction of Aniline with Acylanthranils. A solution of aniline in benzene was added slowly to a solution of an equivalent amount of the acylanthranil in benzene kept at room temperature. If precipitation began within the working day, reaction was allowed to continue until precipitation appeared to be complete, otherwise it was allowed to occur overnight. The solvent was removed by evaporation under vacuum in a rotary film evaporator and the residue was separated as described previously.[2] The assignment of structures was based on the chemistry of the separation procedure and support as needed by ir, NMR, and elemental analysis. The results are summarized in Table IV and the supporting analytical data are collected in Table V.

C. Reaction of Benzoylanthranil, 1a, with Amines. The general procedure for reaction of acylanthranil with anilines described under B was modified as indicated in Table II to accommodate the much lower reactivity of benzoylanthranil relative to that of acetylanthranil. Reaction of **1e** with 1 equiv of aniline in benzene and with *n*-propylamine or *n*-butylamine in diethyl ether were carried out at reflux temperature for 24 h. Reactions with oxydianiline in acetic acid and with hexamethylenediamine in pyridine were carried out at reflux for 4 h. The fusion reactions with equivalent amounts of oxydianiline, 4,4′-diaminodiphenyl sulfone, and hexamethylenediamine were carried out under nitrogen for 4 h at 140, 250, and 140 °C, respectively. The products were separated and identified essentially as described above under B. The results are summarized in Table II, and the supporting analytical data for the corresponding *o*-benzamidobenzamide products, written symbolically as BNHR, and that for the quinazolone of 4,4′-diaminodiphenyl sulfone, written symbolically as $(QPh)_2SO_2$, are collected in Table III.

Acknowledgment. The authors are indebted to Dr. J. J. McBrady for interpretation of the ir and NMR spectra.

Registry No.—**1a**, 1022-46-4; **1b**, 525-76-8; **1c**, 15607-11-1; **1d**, 16062-71-8; **1e**, 2916-09-8; **1f**, 16062-70-7; **1g**, 16062-73-0; **1h**, 16063-05-1; **1i**, 16063-04-0; **1j**, 60498-31-9; **1k**, 16063-03-9; **1l**, 60498-32-0; **1m**, 16062-68-3; **1n**, 60498-33-1; **1o**, 10073-89-9; **1p**, 19165-25-4; **3b**, 34264-61-4; **3d**, 60498-34-2; **3d′**, 58426-41-8; **3l**, 60498-35-3; **4a**, 18543-23-2; **4e**, 25628-85-7; **4g**, 60498-36-4; **5e**, 5260-41-3; **5f** HCl, 60498-37-5; **5l**, 60498-38-6; **5m**, 22686-82-4; **6a**, 579-93-1; **6b**, 89-52-1; **6c**, 610-68-4; **6d**, 19165-29-8; **6e**, 19165-26-5; **6f**, 19165-27-6; **6g**, 19157-34-7; **6h**, 6307-10-4; **6i**, 60498-39-7; **6j**, 60498-40-0; **6k**, 60498-41-1; **6l**, 60498-42-2; **6m**, 4809-61-4; **6n**, 60498-43-3; **6o**, 3558-18-7; **6p**, 38985-79-4; $(B\text{-}NHPh)_2O$, 60498-44-4; $(Q\text{-}Ph)_2SO_2$, 60498-45-5; $B\text{-}NH(CH_2)_3H$, 26060-09-3; $B\text{-}NH(CH_2)_4H$, 22812-98-2; $B\text{-}NH(CH_2)_3NH\text{-}B$, 60498-46-6.

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Substituent Effects at the Origin of a Free-Radical 1,2-Aryl Migration and in the Related Disproportionation Reaction of 10-Hydro-9-*p*-X-phenyl-9-phenanthryl Radicals

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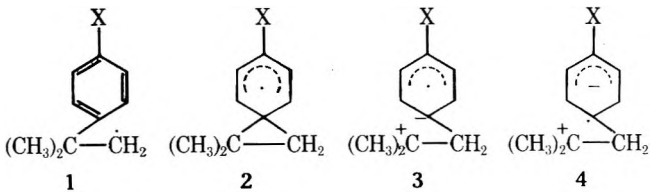
A series of (9-*p*-X-phenyl-9-fluorenyl)acetaldehydes (**5**) (X = H, F, Cl, OCH_3, SCH_3, $SOCH_3$, SO_2CH_3, and CH_3) have been synthesized, characterized, and decarbonylated in the presence and absence of benzyl mercaptan to yield (9-*p*-X-phenyl-9-fluorenyl)carbinyl radicals (U·). In the presence of mercaptan, these radicals rearranged to yield 9,10-dihydro-9-*p*-X-phenylphenanthrenes (**7**) and 9-*p*-X-phenyl phenanthrenes (**6**), and abstracted hydrogen from the mercaptan to yield 9-methyl-9-*p*-X-phenylfluorenes (**8**). The relative percentages of these products were determined by NMR integration, and were used to calculate relative rearrangement rate constants (rel k_R). An excellent linear correlation was found between log rel k_R and Hammett's σ_p ($\rho = 0.39$, $r = 0.988$, s = ±0.05). The methylthio substituted compound showed a strong deviation in the direction of rate enhancement. In the absence of mercaptan the rearranged 10-hydro-9-*p*-X-phenyl-9-phenanthryl radicals (R·) were found to undergo a disproportionation reaction yielding **6** and **7** as the sole products. The relative percentages of these products were used to calculate relative disproportionation rate constants (rel k_D). Separate correlations were obtained between log rel k_D and σ_R or σ_R° for the sulfur-containing substituents and for the non-sulfur-containing substituents. Evidence is presented which indicates that the substituent on the abstracting radical (R·) exerts the controlling influence on the rate of disproportionation.

Free-radical carbon rearrangements in solution have been under investigation since their initial discovery by Urry and Kharasch[1] in 1944. Yet, in spite of three decades of research in this area, until a short time ago little was known concerning the nature of the transition state for vicinal aryl migration, or the effects of substituents upon its stability.

Early work[2-5] implied a gross order of migratory abilities for substituted phenyl groups: *p*-$O_2NC_6H_4$ > *p*-$H_3CC_6H_4$ ≃ C_6H_5 > *p*-$H_3COC_6H_4$. Unfortunately, these results were qualitative, and the systems studied were sufficiently sterically dissimilar to make conclusions drawn from comparison of the results highly tentative.

The first comprehensive and quantitative treatment of substituent effects in free-radical aryl migrations was carried out by Rüchardt and his co-workers,[6-10] who studied the rearrangement of the 2-methyl-2-phenylpropyl (e.g., neophyl) radical as a function of substitution in the migrating aromatic nucleus. Their results showed that electron-withdrawing groups in the migrating ring facilitate the rearrangement process, and that strong electron-withdrawing groups (e.g., *p*-CN or *p*-NO_2) enhance the rate of rearrangement anomalously. To explain these results, they postulated a hybrid rearrangement transition state having polar character due to charge separation (resonance structures **1**–**4** below). Further,



1 **2** **3** **4**

they have suggested that the extent of polar contribution (e.g., forms **3** and **4**) to the migration transition state is substituent dependent, apparently increasing as the extent of electron withdrawal by the substituent increases.

Recently, we reported some preliminary findings[11,12] on the rearrangement of the (9-*p*-X-phenyl-9-fluorenyl)carbinyl radical systems (U·) (X = H, OCH_3, CH_3, or Cl). In this radical, only the phenylene ring of the fluorenyl ring system undergoes rearrangement,[13] thus permitting the unique opportunity to observe substituent effects at the origin of a radical rearrangement. We now wish to report our findings for the rearrangement of this radical (U·) for a spectrum of substituents ranging from electron donating to strongly electron withdrawing[14] and for the disproportionation of the resultant 9,10-dihydro-9-*p*-X-phenyl-9-phenanthryl radicals (R·).

Results and Discussion

The (9-*p*-X-phenyl-9-fluorenyl)acetaldehydes (**5**, X = H, CH_3, Cl, F, OCH_3, or SCH_3)[15] were synthesized from fluorenone and the appropriately substituted phenylmagnesium bromide by a procedure analogous to that described by Nesmeyanov et al.[16] and by Curtin and Hurwitz[4] in an average overall yield of 45%.

The methyl sulfoxide and the methyl sulfone substituted acetaldehydes were obtained by controlled oxidation of the methyl sulfide substituted acetaldehyde, using *m*-chloroperoxybenzoic acid in a procedure adapted from that employed by McIntosh et al.[17] for the oxidation of thiatane derivatives.

The desired (9-*p*-X-phenyl-9-fluorenyl)carbinyl radicals were generated by peroxide-induced decarbonylation of the corresponding aldehydes under identical experimental conditions in the presence of benzyl mercaptan. In each case, 20 mol % of the mercaptan was added to a 0.5 M solution of the aldehyde in purified 1,2-dichlorobenzene. The solution was degassed to remove oxygen, and then it was maintained at 140 ± 0.01 °C with agitation as two quantities, each 20 mol % of di-*tert*-butyl peroxide, were added initially and after 120 min. Each reaction was run for a total of 330 min and the rates of carbon monoxide evolution were monitored by measuring the slopes of various sections of the graphs of volume of gas evolved vs. time for each run.[18] All of the aldehydes were found to undergo decarbonylation to the same extent, and at the same rate, indicating that the rate-determining step is probably the homolysis of the peroxide.

It is notable that the presence of benzyl mercaptan results in a consistent increase in the rate of gas evolution over that observed in similar experiments in which benzyl mercaptan was absent. The effect of mercaptan, as observed earlier by Harris and Waters,[19] is a consequence of aldehydic hydrogen atom abstraction by benzylthiyl radicals in addition to the normally observed hydrogen atom abstraction by *tert*-butoxy radicals. From the average volume of gas evolved it was calculated that approximately 78% decarbonylation had oc-

Table I. Product Percentages [a] Calculated from NMR Integrations

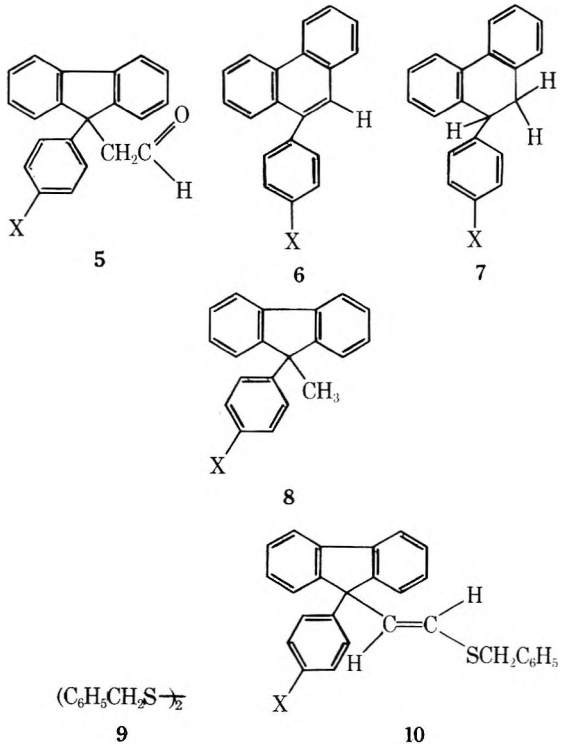
Substituent (X)	% 6 + % 7	% 6 − % 7	% 8	% 6/% 7 Mercaptan present	% 6/% 7 Mercaptan absent
OCH_3	77.0	36	23.0	2.35	2.13
CH_3	80.0	12	20.0	2.08	1.27
H	81.0	8	19.0	1.93	1.17
F	84.0	22	16.0	4.25	1.56
Cl	85.0	20	15.0	1.74	1.50
$SOCH_3$	87.0	20	13.0	3.14	1.50
SCH_3	88.5	38	11.5	4.71	2.23
SO_2CH_3	89.5	10	10.5	1.71	1.22

[a] Each datum is the average of at least two runs. The error is less than 1%.

curred, indicating a chain length of less than or equal to unity.[20-22]

The products from the decarbonylation reaction of the aldehydes were isolated by a combination of column and preparative layer chromatography, and were characterized by standard physical and spectral procedures. In each reaction the products were found to be 9-(*p*-X-phenyl)phenanthrenes (**6**), 9,10-dihydro-9-(*p*-X-phenyl)phenanthrenes (**7**), and 9-methyl-9-(*p*-X-phenyl)fluorenes (**8**) (X = H, CH_3, Cl, F, OCH_3, SCH_3, $SOCH_3$, or SO_2CH_3).

Also obtained, though in low yield, were compounds **9** and **10**. Benzyl disulfide is presumed to arise through dimerization of benzylthiyl radicals. The structure of compound **10** (X = H) was assigned on the basis of elemental analysis, its reaction with bromine in carbon tetrachloride, and its NMR spectrum. This compound most likely arises from a reaction between aldehyde and benzyl mercaptan with subsequent dehydration, a process which has been observed for other aldehydes[23,24] and ketones,[25] but under different reaction conditions. In each instance compounds **9** and **10** together accounted for less than 5% by weight of the overall product mixture. Neither of these compounds was characterized further, since they should be formed in proportionate amounts and to the same extent in each reaction.[26]



The relative percentages (Table I) of the decarbonylation products[27] were determined from the NMR integrations of the characteristic peaks at δ 1.78–1.82 (s, CH_3 of compound **8**), 3.12–3.18 (d, $-CH_2-$ of compound **7**), 3.95–4.01 (t, Ar_2CH- of compound **7**), and 8.67–8.73 (m, for the 4,5 aromatic H's of compound **6**). Each series of compounds showed these NMR peaks as well as those corresponding to the remaining aromatic hydrogens. All other NMR signals were consistent with hydrogen-bearing substituents on the molecules.

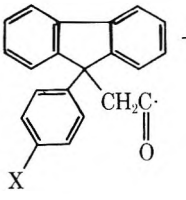
These results are in accord with the reaction mechanism shown in eq 1–13 of Scheme I.

Scheme I

$$(CH_3)_3CO{-}OC(CH_3)_3 \xrightarrow[\Delta]{k_1} 2(CH_3)_3CO\cdot \quad (1)$$

$$PhCH_2SH + (CH_3)_3CO\cdot \xrightarrow{k_2} PhCH_2S\cdot + (CH_3)_3COH \quad (2)$$

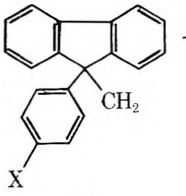
$$5 + (CH_3)_3CO\cdot \xrightarrow{k_3} \text{A}\cdot + (CH_3)_3COH \quad (3)$$



A·

$$5 + PhCH_2S\cdot \xrightarrow{k_4} \text{A}\cdot + PhCH_2SH \quad (4)$$

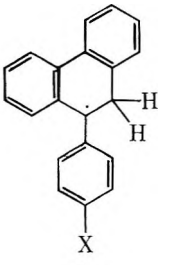
$$\text{A}\cdot \xrightarrow{k_5} \text{U}\cdot + CO \quad (5)$$



U·

$$\text{U}\cdot + PhCH_2SH \xrightarrow{k_A} 8 + PhCH_2S\cdot \quad (6)$$

$$\text{U}\cdot \xrightarrow{k_R} \text{R}\cdot \quad (7)$$



R·

$$\text{R}\cdot + 5 \xrightarrow{k_6} 7 + \text{A}\cdot \quad (8)$$

$$2\text{R} \xrightarrow{k_7} 7 + 6 \quad (9)$$

$$\text{R}\cdot + (CH_3)_3CO\cdot \xrightarrow{k_8} 6 + (CH_3)_3COH \quad (10)$$

$$\text{R}\cdot + PhCH_2SH \xrightarrow{k_9} 7 + PhCH_2S\cdot \quad (11)$$

$$\text{R}\cdot + PhCH_2S\cdot \xrightarrow{k_{10}} 6 + PhCH_2SH \quad (12)$$

$$2PhCH_2S\cdot \xrightarrow{k_{11}} PhCH_2SSCH_2Ph \quad (13)$$

Using the rate constants and mechanism depicted in Scheme I, one can readily derive the expression for the ratio of rearranged (R = % 6 + % 7) to unrearranged (U = % 8) products as shown in eq 14, where k_R and k_A are the rate constants for rearrangement (**7**) and hydrogen atom abstraction (**6**), respectively.

$$R/U = d(R)/d(U) = k_R/k_A\,(PhCH_2SH) \quad (14)$$

In view of the insulation of the substituent (X) from the

Table II. Product Ratios and Relative Rate Constants

Substituent (X)	$(R/U)_X$	Rel k_R	Log rel k_R
OCH_3	3.35	0.785	−0.105
CH_3	4.00	0.938	−0.028
H	4.26	1.000	0.000
F	5.12	1.202	0.080
Cl	5.67	1.329	0.124
$SOCH_3$	6.70	1.570	0.196
SCH_3	7.72	1.818	0.259
SO_2CH_3	8.55	2.010	0.303

radical center, it seems reasonable to assume that the rate constant for hydrogen atom abstraction, k_A, is independent of the substitution on the 9-phenyl moiety. Thus, eq 15 can be readily developed, permitting the calculation of relative rate constants for the rearrangement step.

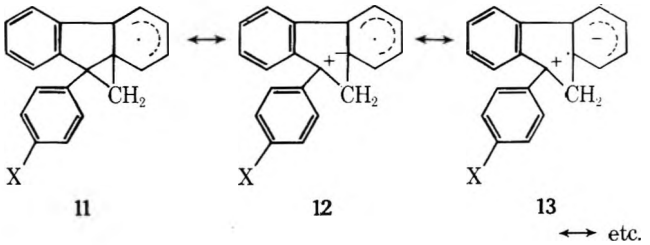
$$\frac{(R/U)_X}{(R/U)_H} = \frac{(k_R)_X/(k_A)_X(PhCH_2SH)}{(k_R)_H/(k_A)_H(PhCH_2SH)} = \frac{(k_R)_X}{(k_R)_H} = \text{rel } k_R \qquad (15)$$

where $(R/U)_X$ = (% **6** + % **7**)/(% **8**) for substituted compounds, $(R/U)_H$ = (% **6** + % **7**)/(% **8**) for unsubstituted compounds, $(k_R)_X$ = rate constant for rearrangement of substituted radical, $(k_R)_H$ = rate constant for rearrangement of the unsubstituted radical, $(k_A)_X$ = rate constant for hydrogen atom abstraction from a substituted radical, $(k_A)_H$ = rate constant for hydrogen atom abstraction from an unsubstituted radical.

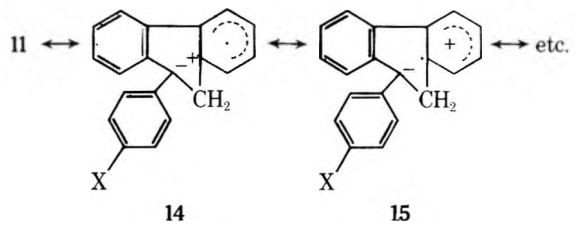
Table II shows the results of applying the product percentage data of Table I to eq 15.

The degree of correlation between the log relative k_R data of Table II and σ_p,[28] σ_m,[28] σ_p^+,[28] σ_I,[29] $\Delta\sigma$,[30] F,[26] R,[28] σ_R,[29] or $\sigma_R°$[29] was evaluated by means of the subprogram "linear regression analysis" of the IBM computer program STATPACK.[31] Bulk correlation was low in each instance. Inspection of the scatter plots indicated that data case X = SCH_3 represented the largest source of deviation. Accordingly, the calculations were repeated with this data case omitted. An excellent linear correlation with Hammett's σ_p was then obtained, in which $\rho = 0.392$, $s = 0.027$, and $r = 0.988$[32] (Figure 1, X = SCH_3 included for reference).

Assuming that the rearrangement is an isoentropic reaction, based on these results, it can be argued that the transition state for the rearrangement is essentially nonpolar in character. If the transition state for rearrangement of the (9-phenyl-9-fluorenyl)carbinyl radical were a hybrid having polar contributions similar to those suggested by Ruchardt et al. for the neophyl radical (cf. **3** and **4**), then canonical structures **11**, **12**, **13**, etc., would be appropriate. Our observation that electron-withdrawing substituents facilitate the rearrangement process clearly militates against hybrids such as **12** and **13** which show development of partial positive character at the migration origin.



Alternatively, one might suggest the rearrangement transition state to be a polar hybrid with the charges reversed from those shown in **12** and **13** as shown in **14** and **15**. Such a hybridization scheme would place partial negative charge where it could most effectively be stabilized by the electron-withdrawing groups.



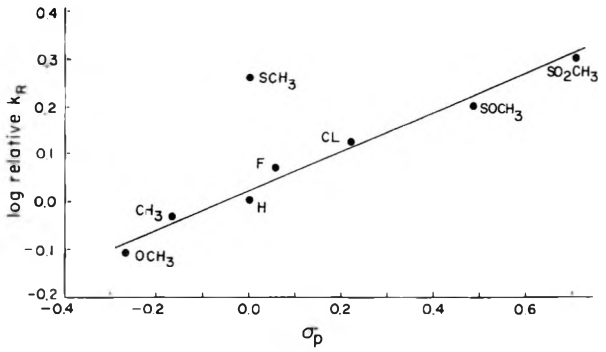


Figure 1. Hammett correlation of log rel k_R vs. σ_p for the rearrangement of the (9-*p*-X-phenyl-9-fluorenyl)carbinyl radical.

Curtin and Kauer[5] have examined the related rearrangement of the 2,2-diphenyl-2-(*p*-nitrophenyl)ethyl radical and estimated that the *p*-nitrophenyl moiety displays a migratory aptitude at least eightfold greater than that of the unsubstituted phenyl group. In the present work if charge separation developed as indicated in **14** and **15**, then partial negative charge would be placed at the migration origin and partial positive charge on the migrating ring. If this were the case, however, in the Curtin and Kauer experiment the unsubstituted phenyl group should have shown a migratory aptitude greater than that of the *p*-nitrophenyl group. The similarity of this rearrangement to that of (9-*p*-X-phenyl-9-fluorenyl)-carbinyl radical would lead one to conclude that structures with this type of polarization probably do not contribute to the transition state of either reaction.

Even if an isokinetic relationship were to exist for this rearrangement, it seems unlikely that ρ would vary far from zero. The small magnitude of the reaction constant is more in keeping with the general trend observed for nonpolar reactions.[33]

The rather striking deviation of the *p*-methylthio substituted radical from the Hammett correlation (Figure 1) indicates a greater participation of this group in stabilizing the rearrangement transition state than is accountable for in terms of inductive influence alone and must also involve electron-pair conjugation of the sulfur atom with radical center. This explanation is compatible with the results of a wide variety of reactions involving this group.[34] The importance of this type of resonance interaction has also been implicated for other substituents[35,36] such as the nitro and cyano groups.

On the basis of the results obtained in the present study and the considerations mentioned above, we conclude that the transition state for the reaction involving substituent effects at the origin of a free-radical aryl migration is essentially radical in character and that polar effects are negligible.

In order to gain further insight into the nature of this rearrangement the decarbonylation reactions were also carried out in the absence of benzyl mercaptan with some interesting results. Under these conditions the intermediate benzyl rad-

icals (R·) were found to undergo disproportionation, allowing the first observations of substituent effects in such a reaction.[37,38]

Column chromatography on neutral alumina separated the mixture of products **6** and **7** from aldehyde **5** and the products of the reaction of **5** on the absorbent surface.[26] None of the unrearranged product, **8**, could be detected. Relative percentages of products were determined as previously described by NMR and these data were cross checked, when possible, by comparing the averaged NMR integrations for the hydrogen bearing substituents on **6** and **7** and were, in each instance, found to be in agreement with the product percentage data obtained from the skeletal framework hydrogens. These data are shown in Table I.

The products **6** and **7** were then separated by multiple development preparative thin layer chromatography, or chemically converted into previously characterized mixtures, and then separated.

In the presence of oxygen[11] only 9-phenylphenanthrene was observed as a product from the decarbonylation reaction of **5** (X = H). Most likely under these conditions disproportionation is not competitive with abstraction by oxygen of a hydrogen atom α to the radical center in the rearranged radical R·. In each instance it was observed that more of **6** than **7** was formed. If these reactions were chain processes, the expected result would have been the formation of more **7** and less of **6**. On the other hand, if all **7** were formed from the disproportionation reaction, an equal amount of **6** would have been anticipated. Clearly there must be an additional source of **6**.[39]

A logical explanation for this excess is that exclusion of oxygen permits a competition to develop between disproportionation reactions of R· to form **6** and **7**, and H-atom abstraction reactions of R· with *tert*-butoxy radical to form additional amounts of **6** (eq 16). Indeed, Trecker and Foote[40] reported a similar reaction

$$\text{R}\cdot + t\text{-BuO}\cdot \xrightarrow{k_E} \mathbf{6} + t\text{-BuOH} \qquad (16)$$

of 2-carbomethoxy-2-propyl radical with *tert*-butoxy radical and calculated that the reaction is thermodynamically favorable. It is obvious from the higher ratio of % **6**/% **7** obtained in the presence of mercaptan (Table I) that benzylthiyl radical also participates in this type of reaction.

While **7** may be formed in two separate reactions, propagation (eq 17) and disproportionation (eq 18), based on the amount of peroxide required for the decarbonylation, the rate data, and the product ratios, it seems likely that little or no chain propagation is occurring.

$$\text{R}\cdot + \mathbf{5} \rightarrow \mathbf{7} + \text{A}\cdot \qquad (17)$$

$$\text{R}\cdot + \text{R}\cdot \rightarrow \mathbf{6} + \mathbf{7} \qquad (18)$$

These results are consistent with the mechanism, K_1, K_3, K_5, K_D (eq 19), and K_E (eq 20). Other, less probable reactions to form **6** and **7** have been excluded from the mechanism.

$$\text{R}\cdot + \text{R}\cdot \xrightarrow{k_D} \mathbf{6} + \mathbf{7} \qquad (19)$$

$$\text{R}\cdot + \text{RO}\cdot \xrightarrow{k_E} \mathbf{6} + \text{ROH} \qquad (20)$$

Accordingly, it seems reasonable to assume that essentially all of **7** is formed in the disproportionation reaction. Since there should also be an equivalent amount of **6** formed in this reaction, the excess of **6** over **7** can be calculated as the difference between the total amount of **6** formed in all reactions and the amount of **6** formed in the disproportionation reaction. The results of these calculations are shown in Table I under column % **6** − % **7**.

Table III. Product Ratios and Relative Rate Constants

Substituent	(DH)/(P_E)	Rel k_D	Log rel k_D
H	5.750	1.000	0.000
SO_2CH_3	4.500	0.783	−0.106
CH_3	3.667	0.638	−0.195
Cl	2.000	0.348	−0.458
$SOCH_3$	2.000	0.348	−0.458
F	1.770	0.304	−0.517
OCH_3	0.889	0.155	−0.810
SCH_3	0.815	0.142	−0.851

It is clear from these data that the substituents have a definite effect on the relative amounts of products formed. The exothermicity of the H-atom exchange reaction would be expected to be high and by the Hammond principle[41,42] the transition state for such a reaction would be expected to occur early along the reaction coordinate. Thus, the H-atom exchange reaction should involve little C–H bond breaking in the transition state, which will bear a close resemblance to the starting radical R·. The rate constant for hydrogen atom exchange, k_E, should be essentially independent of the substituent X, while the stability of radical R· does affect the abstraction reaction and is substituent dependent. Hence, while k_E is independent of the substituent X, k_D is not. The different distribution of products is, therefore, considered to be the result of a substituent effect in the disproportionation step.

In the present study disproportionation occurs to the exclusion of dimerization, a fact which is probably due to steric hindrance to dimerization and to the relative stabilities of the rearranged radicals. This system, therefore, provides a unique opportunity to examine substituent effects on a disproportionation reaction without competition from a dimerization reaction, and without the complication of a substituent dependent hydrogen atom exchange reaction.

An equation (21) can be developed which relates product ratios to the rate constants for disproportionation and hydrogen atom exchange. Comparison of eq 21 for a substituent X against the standard (X = hydrogen) yields eq 22.

$$(\text{DH})/(P_E) = \text{d}(\text{DH})/\text{d}(P_E) = k_D\,(\text{R}\cdot)/k_E\,(\text{RO}\cdot) \qquad (21)$$

(DH) = total amount of **7**
(P_E) = amount of **6** formed in eq 16 (i.e., % **6** − % **7**)
(RO·) = concentration of *tert*-butoxy radicals
(R·) = concentration of R·
k_D = rate constant for the disproportionation
k_E = rate constant for the hydrogen atom exchange

$$\frac{[(\text{DH})/(P_E)]_X}{[(\text{DH})/(P_E)]_H} = \frac{(k_D)_X}{(k_D)_H} = \text{rel } k_D \qquad (22)$$

$[(\text{DH})/(P_E)]_X$ = product ratio for substituted case
$[(\text{DH})/(P_E)]_H$ = product ratio for hydrogen substituted case
$(k_D)_X$ = rate constant for disproportionation of the substituted radical
$(k_D)_H$ = rate constant for disproportionation of the hydrogen substituted radical

The results of applying the data from Table I to eq 22 are shown in Table III. It is noteworthy that all of the substituents studied are rate retarding relative to the hydrogen substituted standard, a behavior which parallels that observed for the relative stabilities of benzyl and benzyl-type radicals.

The degree of correlation between the log rel k_D data of Table III and a variety of substituent constants[28-30] was evaluated by means of the subprogram "linear regression analysis" of the IBM computer program STATPACK.[31] Linear correlations were obtained between log rel k_D and Tafts[29] σ_R or σ_R° constants in two sets (Table IV). One set (A) is comprised of the non-sulfur-containing substituents (X = H, F, Cl, OCH_3, CH_3), while the other set (B) is comprised of the substituents containing sulfur (X = SCH_3, $SOCH_3$, SO_2CH_3). Plots of data for sets A and B (log rel k_D) against σ_R° are shown in Figure 4. It is both unusual and interesting that two separate correlations were observed with each of the substituent parameters. It is not surprising, however, that the observed substituent effect on the rate of

Table IV. Correlation Data for the Disproportionation Reaction

Parameter	Set A vs. σ_R	Set B vs. σ_R	Set A vs. $\sigma_R°$	Set B vs. $\sigma_R°$
Intercept	−0.060	−0.368	−0.010	−0.413
Regression coefficient (ρ)	1.206	1.586	1.718	2.276
Correlation coefficient (r)	0.966	0.975	0.988	0.994
Standard error (s)	0.093	0.117	0.059	0.059

the radical disproportionation reaction follows an order similar to those observed for benzyl-type radical stabilizations[43,44] since the disproportionation step involves a benzyl-type radical.

Most reactions which correlate with Hammett's σ values involve a ground state reactant whose potential energy is affected very little (or not at all) by the substituent; thus the major influence of the substituent is in its ability to stabilize the transition state of the reaction. This disproportionation reaction, however, involves as a reactant a benzyl-type radical the stability of which should be substituent dependent.

The effects of the two substituents in the transition state of the disproportionation reaction must be considered separately. In the hydrogen exchange reaction (eq 20), the substituent on the hydrogen donor radical will have nearly the same effect in the transition state as it does in the initial radical R·. Therefore the substituent on the abstracting radical clearly exerts the controlling influence in this reaction. In the transition state the sp^2 character of the abstracting benzylic-type carbon atom is decreased and the stabilizing effect of the substituent is, consequently, diminished. The overall effect is a lesser stabilization of the transition state relative to the ground state. Thus, the greater the benzyl radical stability the slower the rate of the disproportionation reaction. The present results accordingly reflect the effects of substituents on a reaction step in which the energy barrier is more strongly influenced by the raising or lowering of the energy of the initial state than it is by energy changes in the transition state.

The magnitude of the reaction constants led us to consider the possibility of charge separation in the transition state of this reaction. However, since the reaction constant is merely a measure of the sensitivity of the reaction center to variations in the substituent, other things being equal, it did not seen reasonable to base the assignment of polar character to the transition state solely on the magnitude of ρ_R or $\rho_R°$. This reaction is particularly sensitive to the stability of the benzyl-type initial radical, which is, in turn, strongly dependent on the substituent. Then too, as was mentioned earlier, the transition state should bear a closer resemblance to the starting radical than to products. Though a definite conclusion cannot be reached at this time, these factors tend to support a mechanism that is radical in character and a reaction which has a substantial ρ constant.

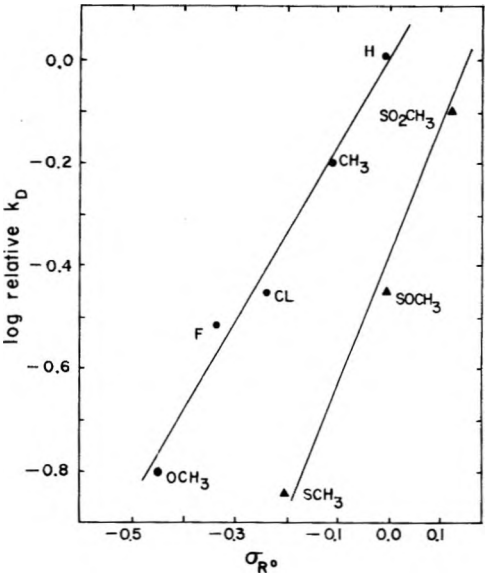


Figure 4. Hammett-type correlation of log rel k_D vs. $\sigma_R°$ for the disproportionation of the 10-hydro-9-*p*-X-phenyl-9-phenanthryl radical.

Experimental Section

All melting points (corrected) were determined on a Thomas-Hoover capillary melting point apparatus. The nuclear magnetic resonance (NMR) spectra were recorded on a Japan Electron Optics Laboratory, high-resolution, C60HL NMR spectrometer, or on a Varian A-60 spectrometer using tetramethylsilane as the internal reference and $CDCl_3$ as the solvent. Mass spectra were recorded on a C. E. C. Du Pont type 490-B single focusing mass spectrometer, using a mass marker and perfluorokerosene for reference. Infrared spectra were determined on a Perkin-Elmer 700, a Beckman IR-8, or a Baird-Atomic KM-1 spectrometer (with polystyrene film reference), employing potassium bromide wafers for solids and matched sodium chloride liquid cells or sodium chloride plates (Wilk's Scientific Co.) for solutions and neat liquids. The combustion analyses were performed by Micro Analysis, Inc., Wilmington, Del.

Thin layer chromatography was performed on either Polygram Sil G/UV_{254} or Polygram Sil N-HR/UV_{254}, 20 × 20 cm × 0.25 mm precoated, plastic TLC plates (Machery-Nagel and Co., through Brinkman Instruments, Inc.) Preparative thin layer chromatography was performed on either 125–1000 μ gradient, glass TL plates (Kontes' Glass Co.), or on normal glass plates spread to the desired thickness with a Desaga spreader (Brinkman Instruments, Inc.), using an aqueous slurry of silica gel 60 PF-254 (E. M. Reagents, for preparative layer chromatography). Dry column chromatography was performed with 35 mm i.d. Nylon tubing, using Woelm silica gel, dry column grade (activity III/30 mm), containing 0.5% inorganic (uv_{254}) fluorescent indicator. Both TLC plates and dry columns were visualized with a UVSL-25, multiband, Mineralight ultraviolet lamp (short–long wave, from Ultraviolet Products, Inc., San Gabriel, Calif.); all thin layer plates were visualized, additionally, in a glass chamber saturated with iodine.

Column chromatography was performed in 10 mm (qualitative), or 22 mm (preparative) i.d. glass columns (Kontes' Glass Co.). The adsorbents used were silica gel, 0.05–0.2 mm (70–325 mesh ASTM for column chromatography, E. M. Reagents), or alumina (aluminum oxide, Woelm, neutral, activity grade I).

All gas chromatography was conducted on a Perkin-Elmer 820 gas chromatograph, employing dual 5 ft × 0.5 in. columns of 15% Dexsil 300 GC on 90–100 mesh Anakrom Q, DMCS (Analabs, Inc., North Haven, Conn.), or on a 20 × 0.25 in. column containing molecular sieve 5A. All spectral data were consistent with the assigned structures.

Materials. Technical grade fluorenone was purified by distillation [bp 341.5 °C (760 mm)], followed by recrystallization from hexane (mp 82–84 °C) prior to use; 98+% fluorenone (mp 82–84 °C), Aldrich Chemical Co., Inc.) was employed without further purification. Bromobenzene, *p*-bromothioanisole, 4-bromotoluene, 4-bromofluorobenzene, *p*-bromoanisole, and *p*-bromochlorobenzene were obtained from Aldrich Chemical Co., Inc.; each was distilled prior to use. Hydrogen chloride gas was obtained from the Matheson Coleman and Bell Co. Ether was dried over sodium metal prior to use, and benzene was distilled (bp 80 °C), then dried over metallic sodium prior to use. Mercuric acetate (Fischer Scientific Co.) and *m*-chloroperoxybenzoic acid (mp 92–94 °C dec), 85% (Aldrich Chemical Co., Inc.) were used without further purification. Vinyl acetate (Eastman Kodak Co.) with 0.2% diphenylamine inhibitor was distilled (bp 72–73 °C) immediately prior to use.

Preparation of 9-*p*-X-Phenyl-9-fluorenols (X = H, CH_3, Cl, OCH_3, F, or SCH_3). The 9-*p*-X-phenyl-9-fluorenols (X = H, CH_3, Cl, OCH_3, F, or SCH_3)[45] were prepared from fluorenone and the appropriately substituted *p*-X-bromobenzenes by a Grignard reaction according to a procedure similar to one described by Curtin and Hurwitz.[4]

9-Phenyl-9-fluorenol was obtained in 80% yield, mp 108–109 °C (lit.[46] 108–109 °C) on recrystallization from benzene–petroleum ether (bp 30–60 °C).

9-*p*-Methylphenyl-9-fluorenol was obtained in 86% yield, mp 73–79 °C (lit.[47,48] 86–87 °C).

9-*p*-Chlorophenyl-9-fluorenol was obtained in 84% yield, mp 81–85 °C (lit.[48] 91–92 °C).

9-*p*-Methoxyphenyl-9-fluorenol was obtained in 64% yield, mp 76–81 °C (lit.[49] 87–88 °C).

9-*p*-Fluorophenyl-9-fluorenol was obtained in 69% yield: mp 100.5–102 °C; ir 3355, 3050, 1601, and 1195 cm^{-1}; NMR δ 2.55 (s, –OH, broad, 1), 7.12 (m, aryl, 10), and 7.61 (m, aryl, 2).

Anal. Calcd for $C_{19}H_{13}FO$: C, 82.54; H, 4.42; F, 6.79. Found: C, 82.67; H, 4.32; F, 6.71.

9-*p*-Methylthiophenyl-9-fluorenol was obtained in 80% yield: mp 60.5–62 °C; ir (KBr) 3420, 3050, 1601, and 1185 cm^{-1}; NMR δ 2.40 (s, $-SCH_3$, 3), 2.60 (s, –OH, broad, 1), 7.27 (m, aryl, 2).

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.91; H, 5.30; S, 10.53. Found: C, 78.68; H, 5.41; S, 10.32.

Preparation of 9-Chloro-9-*p*-X-phenylfluorenes (X = H, CH_3, Cl, OCH_3, F, or SCH_3). The 9-chloro-9-*p*-X-phenylfluorenes (X = H, CH_3, Cl, OCH_3, F, or SCH_3) were prepared from the corresponding 9-*p*-X-phenyl-9-fluorenols by a procedure similar to one described by Curtin and Hurwitz.[4]

9-Chloro-9-phenylfluorene was obtained in 95% yield, mp 73–75 °C (lit.[50] 78–79 °C) on recrystallization from petroleum ether (bp 80–110 °C).

9-Chloro-9-*p*-methylphenylfluorene was obtained in 63% yield, mp 64–68 °C (lit.[51] 96–97 °C).

9-Chloro-9-*p*-chlorophenylfluorene was obtained in 63% yield, mp 74–76 °C (lit.[48] 79.5–80.5 °C).

9-Chloro-9-*p*-methoxyphenylfluorene was obtained in 85% yield, mp 148–150 °C (lit.[52] 149–151 °C).

9-Chloro-9-*p*-fluorophenylfluorene was obtained in 80% yield: mp 120.5–121 °C after recrystallization from dichloromethane–petroleum ether; ir 3055, 1600, and 1185 cm^{-1}; NMR aryl complex multiplets between 6.95 and 7.88 (aryl, 12).

Anal. Calcd for $C_{19}H_{12}ClF$: C, 77.49; H, 4.20; F, 6.73. Found: C, 77.42; H, 4.11; F, 6.45.

9-Chloro-9-*p*-methylthiophenylfluorene was obtained in 94% yield: mp 100–100.5 °C; ir (KBr) 3050, 2940, 1601, and 1190 cm^{-1}; NMR δ 2.48 (s, SCH_3, 3), 7.30 (m, aryl, 10), and 7.69 (m, aryl 2).

Anal. Calcd for $C_{20}H_{15}ClS$: C, 74.41; H, 4.68; S, 9.93. Found: C, 74.45; H, 4.65; S, 9.70.

Preparation of Chloromercuriacetaldehyde. The procedure employed was that of Curtin and Hurwitz,[4] which is a modification of that used by Nesmeyanov.[16] The chloromercuriacetaldehyde was obtained in 65% yiel, mp 129–132 °C dec (lit.[4] 129–130 °C).

Preparation of (9-*p*-X-Phenyl-9-fluorenyl)acetaldehydes (X = H, Cl, F, CH_3, OCH_3, SCH_3, $SOCH_3$, SO_2CH_3). The aldehydes were prepared by the method of Curtin and Hurwitz[4] as modified by Vittimberga.[11] In a typical procedure 0.12 mol of 9-chloro-9-*p*-X-phenylfluorene was placed in a 500-ml three-necked flask equipped with mechanical stirrer, glass stopper, and reflux condenser fitted with anhydrous calcium chloride drying tube. After complete dissolution of the solid in 200 ml of anhydrous benzene, 34.9 g (0. 25 mol) of chloromercuriacetaldehyde was added and the mixture was stirred at ambient temperature for 18 h. The mixture was then heated at reflux for 2 h on a steam bath, cooled to room temperature, and filtered to remove insoluble mercury salts.

The benzene solution was then washed repeatedly with 10% aqueous sodium carbonate solution until all red-brown mercury salts, precipitated by the washings, were removed (usually 4 × 150 ml of 10% aqueous sodium carbonate). Following this, the benzene layer was washed several times with water and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the benzene was evaporated in vacuo to yield a solid (X = Cl, CH_3, OCH_3, or SCH_3), or a viscous amber liquid (X = H or F), which yielded an amorphous solid on standing overnight. Recrystallization from benzene–petroleum ether gave pure aldehyde in the cases of X = Cl, CH_3, OCH_3, or SCH_3, but failed in the cases of the hydrogen and fluoro-substituted compounds.

The aldehydes (X = H or F) were obtained in pure form by conversion to their respective diethyl acetals, followed by reconversion (after purification) to the aldehyde form by a procedure adapted from Vogel.[53] To accomplish this, the aldehydes were heated at reflux for 15 min in an excess of absolute ethyl alcohol, followed by cooling to crystallize the acetals. The purified acetals were then reconverted to their respective aldehydes by heating at reflux for 2 h in an acidic dioxane solution. The aldehydes were extracted from the crude reaction mixtures with diethyl ether, and, after drying, the drying agent and solvent were removed as usual. The residual powdered aldehydes were then recrystallized to yield pure aldehydes.

(Phenyl-9-fluorenyl)acetaldehyde was obtained in 80% yield, mp 114.5–115 °C (lit.[11] 114–115 °C).

(9-*p*-Methylphenyl-9-fluorenyl)acetaldehyde was obtained in 76% yield: mp 112–113 °C; ir (KBr) 1715, 1447, 807, 750, 733, and 680 cm^{-1}; NMR δ 2.22 (s, $-CH_3$, 3), 3.27 (d, $-CH_2-$, 2, J = 2.5 Hz), 7.17 (m, aryl, 10), 7.68 (m, aryl, 2), and 8.91 (t, –CHO, 1, J = 2.5 Hz).

Anal. Calcd for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.41; H, 5.98.

(9-*p*-Chlorophenyl-9-fluorenyl)acetaldehyde was obtained in 91% yield: mp 109–110 °C; ir (KBr) 1718, 1486, 1445, 1087, 1006, 752, 730, and 674 cm^{-1}; NMR δ 323 (d, $-CH_2-$, 2, J = 2.5 Hz), 7.15 (m, aryl, 10), 7.69 (m, aryl, 2), and 8.85 (t, –CHO, 1, J = 2.5 Hz).

Anal. Calcd for $C_{21}H_{15}OCl$: C, 79.12; H, 4.74; Cl, 11.12. Found: C, 78.98; H, 4.99; Cl, 10.89.

(9-*p*-Methoxyphenyl-9-fluorenyl)acetaldehyde was obtained in 92% yield: mp 133–134 °C; ir (KBr) 1712, 1447, 1253, 1186, 1030, 828, 755, and 739 cm^{-1}; NMR δ 3.22 (d, $-CH_2-$, 2, J = 2.5 Hz), 3.63 (s, $-OCH_3$, 3), 6.64 (d, aryl, 2, J = 9 Hz), 6.97 (d, aryl, 2, J = 9 Hz), 7.27 (m, aryl, 6), 7.73 (m, aryl, 2), and 8.99 (t, –CHO, 1, J = 2.5 Hz).

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.82. Found: C, 84.04; H, 5.55.

(9-*p*-Fluorophenyl-9-fluorenyl)acetaldehyde was obtained in 88% yield: mp 99.5–100.5 °C on recrystallization from diethyl ether–petroleum ether (bp 30–60 °C); ir (KBr) 3055, 2950, 2850, 2755, 1715, 1601, and 1195 cm^{-1}; NMR δ 3.32 (d, $-CH_2-$, 2, J = 2.5 Hz), 7.03 (m, aryl, 4), 7.33 (m, aryl, 6), 7.76 (m, aryl, 2), and 8.70 (t, –CHO, 1, J = 2.5 Hz).

Anal. Calcd for $C_{21}H_{15}FO$: C, 83.43; H, 5.00; F. 6.28. Found: C, 83.19; H, 4.90; F, 6.34.

(9-*p*-Methylthiophenyl-9-fluorenyl)acetaldehyde was obtained in 62% yield: mp 99–100 °C (benzene–petroleum ether); ir (KBr) 3055, 2955, 2855, 2760, 1715, 1600, and 1185 cm^{-1}; NMR δ 2.24 (s, $-SCH_3$, 3), 3.24 (d, $-CH_2-$, 2, J = 2.5 Hz), 6.92 (m, aryl, 4), 7.27 (m, aryl, 6), and 7.63 (m, aryl, 2), and 8.75 (t, –CHO, 1, J = 2.5 Hz).

Anal. Calcd for $C_{22}H_{18}OS$: C, 79.97; H, 5.48; S, 9.70. Found: C, 79.79; H, 5.27; S, 9.66.

Preparation of (9-*p*-Methylsulfinylphenyl-9-fluorenyl)acetaldehyde (X = $SOCH_3$). This aldehyde was prepared by adaption of the method of McIntosh, Goodbrand, and Masse[17] for the oxidation of thiatane derivatives. (9-*p*-Methylthiophenyl-9-fluorenyl)acetaldehyde (9.90 g, 3 × 10^{-2} mol) was dissolved in 50 ml of dichloromethane at 0 °C in a 500-ml three-necked flask equipped with magnetic stirrer, pressure-equalizing dropping funnel, condenser fitted with anhydrous calcium chloride drying tube, and thermometer. At 0 °C, 6.72 g (3.3 × 10^{-2} mol) of *m*-chloroperoxybenzoic acid was dissolved in 150 ml of dichloromethane. This ice-cold solution was charged into the dropping funnel and added to the aldehyde solution over a 15-min period at a rate such as to maintain the temperature of the mixture between 0 and 5 °C. The mixture was then stirred at 0 °C for 3 h.

The solution was diluted with 100 ml of cold dichloromethane and extracted with 4 × 250 ml of 10% aqueous sodium carbonate and 2 × 250 ml of distilled water. After drying over anhydrous sodium sulfate, the solution was filtered and solvent was removed in vacuo to give an amber-colored solid (X = $SOCH_3$).

(9-*p*-Methylsulfinylphenyl-9-fluorenyl)acetaldehyde was obained in 87% yield: mp 160–160.5 °C (benzene); ir (KBr) 3050, 2940, 2850, 2750, 1715, 1600, 1190, and 1070 cm^{-1}; NMR δ 2.60 (s, $-SOCH_3$, 3), 3.37 (d, $-CH_2-$, 2, J = 2.5 Hz), 7.30 (m, aryl, 10), 7.73 (m, aryl, 2), and 8.83 (t, –CHO, 1, J = 2.5 Hz).

Anal. Calcd for $C_{22}H_{18}O_2S$: C, 76.27; H, 5.24; S, 9.26. Found: C, 76.47; H, 4.97; S, 9.20.

Preparation of (9-*p*-Methylsulfonylphenyl-9-fluorenyl)-acetaldehyde (X = SO_2CH_3). The aldehyde (X = SO_2CH_3) was also prepared by an adaptation of the methods employed by McIntosh and co-workers[17] for the oxidations of thiatane derivatives. (9-*p*-methylthiophenyl-9-fluorenyl)acetaldehyde (15.000 g, 4.54 × 10^{-2} mol) was dissolved in 100 ml of dichloromethane at 0 °C in a 500-ml three-necked flask equipped with magnetic stirrer, dropping funnel, thermometer, and reflux condenser fitted with anhydrous calcium chloride drying tube. At 0 °C, 20.760 g (1.21 × 10^{-1} mol) of *m*-chloroperoxybenzoic acid was dissolved in 200 ml of dichloromethane. The latter ice-cold solution was charged into the dropping funnel, and added to the aldehyde solution over a period of 30 min, at a rate such as to maintain the solution temperature between 0 and 5 °C. The mixture was then stirred at 0 °C for 3 h and, finally, at ambient temperature for 3 h.

After dilution with 200 ml of dichloromethane, the reaction mixture was extracted with 4 × 250 ml of 10% aqueous sodium carbonate solution and 2 × 250 ml of distilled water. The dichloromethane solution was dried over anhydrous sodium sulfate. Subsequently, the drying agent was removed by filtration and the solvent by evaporation under vacuum leaving a thick amber colored oil as residue, which crystallized on standing overnight.

(9-*p*-Methylsulfonylphenyl-9-fluorenyl)acetaldehyde (X = SO_2CH_3) was obtained in 66.5% yield: mp 161.5–162 °C (benzene–petroleum ether); ir (KBr) 3055, 2940, 2920, 2840, 2750, 1712, 1600, 1320, and 1160 cm^{-1}; NMR δ 2.83 (s, $-SO_2CH_3$, 3), 3.32 (d, $-CH_2-$, 2, J = 2.5 Hz), 7.13 (m, aryl, 10), 7.58 (m, aryl, 2), and 8.79 (t, –CHO, 1, J = 2.5 Hz).

Anal. Calcd for $C_{22}H_{18}O_3S$: C, 72.91; H, 5.01; S, 8.85. Found: C, 73.15; H, 5.14; S, 8.85.

Materials, Equipment, and Procedure Used in the Decarbonylations. *o*-Dichlorobenzene (Matheson Coleman and Bell) was purified by successive washing with concentrated sulfuric acid, 10% sodium carbonate solution, and distilled water. Drying over anhydrous calcium chloride and distillation gave pure *o*-dichlorobenzene (bp 178.5–179 °C). Di-*tert*-butyl peroxide (K & K Laboratories, Inc.) was distilled before use, bp 55–56 °C (120 mm). Benzyl mercaptan (Aldrich Chemical Co., Inc.) was used without further purification.

For the decarbonylations, the reaction vessel used was a 50-ml Claisen distilling flask with the side arm removed. One neck of the flask was fitted with a rubber serum stopper (through which the peroxide was injected), and the other neck, immediately prior to immersion of the flask in the oil bath, was connected to the gas measuring system by means of Latex rubber tubing.

The constant temperature bath, shaking apparatus, and gas measuring system are shown in Figure 2 (see paragraph at end of paper regarding supplementary material). The glass, constant temperature bath (Lab-Line Instruments, Inc.; 800 W), containing hydrogenated cottonseed oil (Arthur H. Thomas Co.) was maintained at 140 ± 0.1 °C with a Lux Scientific Corp. vertical relay, and a Jumo contact thermometer.

In the standard decarbonylation reaction procedure, 12 ml of a 0.5 M solution of the aldehyde in *o*-dichlorobenzene was pipetted into the reaction vessel; the solution was degassed through five successive freeze–vacuum–thaw cycles, and then dry nitrogen was introduced in order to provide an inert atmosphere. When the decarbonylations were conducted in the presence of benzyl mercaptan, 0.14 ml (0.0012 mol, 20 mol %) of this compound was introduced prior to the degassing procedure. The reaction vessel was then quickly attached to the gas measuring system (prepurged with dry nitrogen gas).

The reaction vessel (Figure 3) (see paragraph at end of paper regarding supplementary material) was supported at H by means of a swivel clamp so that the flask was immersed in the oil bath up to the mark M, and attached at point J to a shaker arm K, so that the vessel could be rocked back and forth at 80 swings per minute through an arc of 6 in. After immersion in the oil bath, all connections were tightly secured and the mixture was equilibrated for 10 min. The expansion gas escaping from the reaction vessel during this time (at L) was passed through a water-cooled spiral condenser, and allowed to escape at C after having entered at A. Following the equilibration period, 0.225 ml (0.0212 mol, 20 mol %) of di-*tert*-butyl peroxide was injected through serum cap I into the reaction vessel, and the shaker was started. The decarbonylation gas was allowed to enter buret E through port A with stopcock B open to the reaction vessel, buret E, and leveler G, with the stopcock D open to B but closed to C. When a reading was to be made, stopcock B was closed to A and left open to E and G. Water was quickly drained from buret F so that the water level in leveler G was quickly adjusted. The gas volume was read; and then stopcock B was reopened to the reaction vessel. After 120 min of reaction time, the shaker was halted, an additional 0.225 ml of di-*tert*-butyl peroxide was injected through I, and the shaker was restarted. The decarbonylation reaction was carried out for a total of 330 min. At the end of each run, the reaction solution was quenched by immediately cooling the reaction vessel in ice, and retained for the product analysis.

Isolation of the Products from the Decarbonylation Reactions. In a typical isolation procedure (X = H, CH_2Cl, OCH_3, F, or SCH_3), the reaction solution was concentrated in vacuo to remove the *o*-dichlorobenzene and the resulting residue was chromatographed on a 22 × 350 mm column containing 120 g of alumina (Woelm, neutral, activity I). Elution with mixtures of petroleum ether–benzene–ether–methanol in increasing polarity (average flow rate 40 ml/6 min) separated the products from unreacted aldehyde. In each case, the course of chromatography was monitored by analytical, simultaneous TLC run side by side on a Polygram Sil G/UV_{254} precoated plastic TLC plate, using benzene–petroleum ether (3:1) as the developer, and visualizing with uv light and iodine. The yellow oils obtained in these chromatographic fractions have been found to be the result of an oxidation–reduction reaction of the aldehyde on the absorbent surface.[26] After combination of the product aromatic hydrocarbon containing fractions, the NMR spectrum ($CDCl_3$) of the product mixture was recorded. From knowledge of the chemical shifts and numerous integrations, the percentages of the components in the product mixtures were calculated.

In the cases of the decarbonylation of the methylsulfinyl and methylsulfonyl substituted aldehydes (X = $SOCH_3$ or SO_2CH_3) the same general procedure was followed; however, silica gel 0.05–0.20 mm (70–325 mesh ASTM, E. M. Reagents) was used as the absorbent in place of alumina, and elution was carried out with mixtures of petroleum ether, ether, and methanol in increasing polarity. Again, the course of the chromatography was monitored by TLC; appropriate fractions were combined, and numerous integrations of the NMR spectra ($CDCl_3$) permitted calculation of the respective percentages of products of the decarbonylation reactions. Fractional recrystallization proved ineffective toward the separation and isolation of the components of these product mixtures. Attempts were made to separate the mixture components using a Perkin-Elmer 820 gas chromatograph employing matched 5 ft × 0.25 in. columns of 15% Dexsil 300 GC on 90–100 mesh Anakrom Q DMCS (Analabs). Separation of product mixtures was effected in the cases of the aldehydes where X = H, F, and CH_3SO_2. However, none of the products could be isolated by this method.

Unless otherwise stated, small samples of 8 were obtained by column chromatography on neutral alumina. Separation of 6 and 7 was effected by techniques of preparative thin layer chromatography on silica gel. In both methods mixtures of petroleum ether and benzene were used as eluents. Bands were carefully scraped from the plate and the organic compounds were then recovered by extraction with chloroform. Drying and evaporation of the solvent left a residue which was further purified by recrystallization from an appropriate solvent system.

Attempts to transfer these procedures to dry column chromatography using Woelm dry column grade silica gel (activity III, 30 mm) in 35-mm i.d. Nylon tubing, and the developer which gae a separation in PLC, failed to provide a useful separation of the mixture components. This method was therefore abandoned. Separation of products was made by chromatography as usual and relative percent yields determined by NMR.

Thermal Stability of (9-Phenyl-9-fluorenyl)acetaldehydes. The decarbonylation procedure was carried out as previously described, but without di-*tert*-butyl peroxide. After 330 min of heating, the *o*-dichlorobenzene was removed in vacuo. The NMR spectrum ($CDCl_3$) of the resulting paste was identical with that of starting material. Column chromatography of this residue on neutral alumina yielded only the starting aldehyde, and a yellow oil resulting from the reaction of the aldehyde on the alumina surface.[26] Similar results were obtained with 3 ml of 0.5 M solutions of the other aldehydes used in this study.

Product Stability under Reaction Conditions. A mixture consisting of 25% (by mole) 7 (X = H), 25% 8 (X = H), and 50% 6 (X = H) and weighing 240 mg was dissolved in 5 ml of *o*-dichlorobenzene. The solution was degassed, 0.04 ml (2.1×10^{-4} mol) of di-*tert*-butyl peroxide was added, and the mixture was heated at 140 °C for 330 min. The percentages of 6, 7, and 8 (X = H) redetermined by integration of the NMR spectrum, after removal of solvent, and also after column chromatography on neutral alumina, were found to be unchanged. Repetition of this experiment in the presence of 0.07 ml (1.2×10^{-4} mol) of benzyl mercaptan also showed the product percentages to be unaffected by the reaction conditions, or chromatographic workup.

Calculation of Percentages from NMR Spectra. Accuracy Test. A mixture of 6 (x , och_3) and 7 (X = OCH_3) was prepared gravimetrically from pure samples so that the percentages were 46.7 and 53.3%, respectively. The mixture was dissolved in deuteriochloroform, the NMR spectrum recorded, and the product percentages calculated from the averaged integrations. The average value for the percentage of 7 (X = OCH_3) was 53.8% so that the error is assumed to be not more than ±1%. Similar results were obtained with X = H.

Decarbonylations in the Presence of Benzyl Mercaptan. Products from the Decarbonylation of 5 (X = H). The hydrocarbon mixture consisted of 53% 9-phenylphenanthrene (6, X = H), 28% 9,10-dihydrophenylphenanthrene (7, X = H), and 19% 9-methyl-9-phenylphenanthrene (8, X = H).

9-Phenylphenanthrene was recrystallized from petroleum ether (bp 30–60 °C), mp 104–105 °C (lit.[11] mp 104–105 °C).

9,10-Dihydro-9-phenylphenanthrene was recrystallized from petroleum ether (bp 30–60 °C), mp 78.5–80 °C (lit.[54] mp 79–80 °C).

9-Methyl-9-phenylfluorene was recrystallized from petroleum ether, mp 84.5–85 °C (lit.[55] mp 84–85 °C).

Products from the Decarbonylation of 5 (X = CH_3). The hydrocarbon mixture consisted of 54% 9-*p*-methylphenylphenanthrene (6 X = CH_3), 26% 9,10-dihydro-9-*p*-methyphenylphenanthrene (7, X = CH_3), and 29% 9-methyl-9-*p*-methylphenylfluorene (8, X =

CH_3). Samples of compounds **6** and **7** were obtained by preparative layer chromatography. The sulfur containing compounds **9** and **10** (X = CH_3)[56] were isolated by thin layer chromatography on silica gel using petroleum ether–benzene (10:1) as the solvent. These products were then characterized as dibenzyl disulfide, **9**, and *trans*-1-(9-*p*-methylphenyl-9-fluorenyl)-4-phenyl-3-thia-1-butene (**10**, X = CH_3).

9-*p*-Methylphenylphenanthrene was recrystallized from petroleum ether, mp 91.5–92.5 °C (lit.[57] mp 90–91 °C).

9,10-Dihydro-9-*p*-methylphenylphenanthrene was recrystallized from petroleum ether: mp 78–79.5 °C; ir (KBr) 1443, 812, 766 and 746 cm^{-1}; NMR δ 2.26 (s, $-CH_3$, 3), 3.12 (d, $-CH_2$, 2, J = 7.5 Hz), 4.12 (t, $-CHAr_2$, 1, J = 7.5 Hz), 7.14 (m, aryl, 10), and 7.80 (m, aryl, 2).

Anal. Calcd for $C_{21}H_{18}$: C, 93.27; H. 6.71. Found: C, 93.08; H, 6.61.

9-Methyl-9-*p*-methylphenylfluorene was recrystallized from ethanol: mp 57.5–58.5 °C; ir (KBr) 1443, 1018, 800, 768, 746, and 733 cm^{-1}; NMR δ 1.78 (s, $-CH_3$, 3), 2.20 (s, $ArCH_3$, 3), 6.85 (m, aryl, 4), 7.15 (m, aryl, 6), and 7.62 (m, aryl, 2).

Anal. Calcd for $C_{21}H_{18}$: C, 93.29; H, 6.71. Found: C, 93.44; H, 6.75.

Dibenzyl disulfide was obtained as a viscous liquid (lit.[58] mp 69–70 °C). The infrared spectrum (film), almost identical with that of a pure sample, showed major absorptions at 1493, 1453, 763, and 695 cm^{-1}. The NMR spectrum showed bands at δ 3.51 (s, $-CH_2-$, 4) and 7.18 (s, aryl, 10).

trans-1-(9-*p*-Methylphenyl-9-fluorenyl)-4-phenyl-3-thia-1-butene was obtained as a viscous liquid which would not crystallize: ir (film) 3049, 3030, 1508, 1493, 1449, 945, 823, 749, and 698 cm^{-1}; NMR δ 2.16 (s, $-CH_3$, 3), 3.60 (s, $-CH_2$, 2), 5.67 (d, $-CH{=}CH$, 1, J = 15 Hz), 6.16 (d, $-CH{=}CH$, 1, J = 15 Hz), 6.75 (s, aryl, 5), 7.07 (m, aryl, 10), and 7.55 (m, aryl, 2).

Anal. Calcd for $C_{29}H_{24}S$: C, 86.10; H, 5.98; S, 7.92. Found: C, 86.05; H, 5.78; S, 8.07.

Products from the Decarbonylation of 5 (X = Cl). The hydrocarbon mixture consisted of 54% 9-*p*-chlorophenylphenanthrene (**6**, X = Cl), 31% 9,10-dihydro-9-*p*-chlorophenylphenanthrene (**7**, X = Cl), and 15% 9-methyl-9-*p*-chlorophenylfluorene (**8**, X = Cl).

9-*p*-Chlorophenylphenanthrene was recrystallized from petroleum ether: mp 131–133 °C; ir (KBr) 1488, 1087, 1013, 833, 822, 769, 750 and 727 cm^{-1}; NMR δ 7.67 (m, aryl, 11) and 8.71 (m, aryl, 2).

Anal. Calcd for $C_{20}H_{13}Cl$: C, 83.19; H, 4.54; Cl, 12.28. Found: C, 83.30; H, 4.28; Cl, 12.43.

9,10-Dihydro-9-*p*-chlorophenylphenanthrene was recrystllized from petroleum ether: mp 108–109.5 °C; ir (KBr) 1488, 1087, 1012, 836, 818, 776, 752, 739, and 724 cm^{-1}; NMR δ 3.13 (d, $-CH_2-$, 2, J = 7.5 Hz), 4.15 (t, $-CHAr_2$, 1, J = 7.5 Hz), 7.16 (m, aryl, 10), and 7.84 (m, aryl, 2).

Anal. Calcd for $C_{20}H_{15}Cl$: C, 82.61; H, 5.20; Cl, 12.19. Found: C, 82.64; H, 4.98; Cl, 12.28.

9-Methyl-9-*p*-chlorophenylfluorene was recrystallized from petroleum ether: mp 111–113 °C; ir (KBr) 1488, 1443, 1089, 1011, 766, 758, and 736 cm^{-1}; NMR δ 1.80 (s, $-CH_3$, 3), 7.15 (m, aryl, 10), and 7.64 (m, aryl, 2).

Anal. Calcd for $C_{20}H_{15}Cl$: C, 82.61; H, 5.20; Cl, 12.19. Found: C, 82.62; H, 5.37; Cl, 12.08.

Products from the Decarbonylation of 5 (X = OCH_3). The hydrocarbon mixture consisted of 54% of 9-*p*-methoxyphenylphenanthrene (**6**, X = OCH_3), 23% of 9,10-dihydro-9-*p*-methoxyphenylphenanthrene (**7**, X = OCH_3), and 23% of 9-methyl-9-*p*-methoxyphenylfluorine (**8**, X = OCH_3).

9-*p*-Methoxyphenylphenanthrene was recrystallized from petroleum ether–benzene, mp 156–157.5 °C (lit.[59] mp 155.5–156 °C).

9,10-Dihydro-9-*p*-methoxyphenylphenanthrene was recrystallized from petroleum ether: mp 106–107 °C; ir (KBr) 1511, 1449, 1247, 1176, 1031, 870, 824, 767, and 752 cm^{-1}; NMR δ 3.14 (d, $-CH_2-$, 2, J = 7.5 Hz), 3.72 (s, $-OCH_3$, 3), 4.12 (t, $CHAr_2$, 1, J = 7.5 Hz), 7.09 (m, aryl, 10), and 7.82 (m, aryl, 2).

Anal. Calcd for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 87.94; H, 6.18.

9-Methyl-9-*p*-methoxyphenylfluorene was recrystallized from petroleum ether: mp 138–140 °C; ir (KBr) 1504, 1439, 1247, 1179, 1031, 766, 749, and 736 cm^{-1}; NMR δ 1.81 (s, $-CH_3$, 3), 3.69 (s, $-OCH_3$, 3), 6.70 (d, aryl, 2, J = 8.5 Hz), 7.05 (d, aryl, 2, J = 8.5 Hz), 7.18 (m, aryl, 6), and 7.71 (m, aryl, 2).

Anal. Calcd for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 88.01; H, 6.35.

Products from the Decarbonylation of 5 (X = F). The hydrocarbon mixture consisted of 68% 9-*p*-fluorophenylphenanthrene (**6**, X = F), 16% 9,10-dihydro-9-*p*-fluorophenylphenanthrene (**7**, X = F), and 16% 9-methyl-9-*p*-fluorophenylfluorene (**8**, X = F).

9-*p*-Fluorophenylphenanthrene was recrystallized from absolute methanol: mp 148.5–149 °C; ir ($CHCl_3$) 3140, 1605, 1510, 1440, and 1220 cm^{-1}; NMR δ 7.65 (m, aryl, 11) and 8.73 (m, aryl, 2).

Anal. Calcd for $C_{20}H_{13}F$: C, 88.21; H, 4.81; F. 6.98. Found: C, 88.12; H, 4.68; F, 7.20.

9,10-Dihydro-9-*p*-fluorophenylphenanthrene was recrystallized from absolute methanol: mp 89.5–90 °C; ir ($CHCl_3$) 3145, 2955, 2880, 1600, and 1450 cm^{-1}; NMR δ 3.09 (d, $-CH_2-$, 2, J = 7.5 Hz), 4.09 (t, $-CHAr_2$, 1, J = 7.5 Hz), 6.98 (m, aryl, 10), and 7.69 (m, aryl, 2).

Anal. Calcd for Cinfc20$H_{15}F$: C, 87.56; H, 5.51; F, 6.93. Found: C, 87.42; H, 5.37; F. 7.21.

9-Methyl-9-*p*-fluorophenylfluorene was recrystallized from petroleum ether (bp 30–60 °C): mp 113–113.5 °C; ir (KBr) 3050, 2940, 1600, and 1460 cm^{-1}; NMR δ 1.80 (s, $-CH_3$, 3), 6.97 (m, aryl, 10), and 7.59 (m, aryl, 2).

Anal. Calcd for $C_{20}H_{15}F$: C, 87.56; H, 5.51; F, 6.93. Found: C, 87.58; H, 5.51; F, 6.77.

Products from the Decarbonylation of 5 (X = SCH_3). The hydrocarbon mixture consisted of 73% 9-*p*-methylthiophenylphenanthrene (**6**, X = SCH_3), 15.5% 9,10-dihydro-9-*p*-methylthiophenylphenanthrene (**7**, X = SCH_3), and 11.5% 9-methyl-9-*p*-methylthiophenylfluorene (**8**, X = SCH_3).

9-*p*-Methylthiophenylphenanthrene was recrystallized from absolute methanol: mp 139.5–140.5 °C; ir ($CHCl_3$) 3050, 3020, 2940, 1600, 1500, 1460, 1440, and 1210 cm^{-1}; NMR δ 2.49 (s, $-SCH_3$, 3), 7.45 (m, aryl, 11), and 8.67 (m, aryl, 2).

Anal. Calcd for $C_{21}H_{16}S$: C, 83.96; H, 5.37; S, 10.67. Found: C, 83.86; H, 5.44; S, 10.67.

9,10-Dihydro-9-*p*-methylthiophenylphenanthrene was recrystallized from absolute methanol: mp 99.5–100.5 °C; ir ($CHCl_3$) 3050, 3020, 2950, 2880, 1600, 1500, 1440, and 1230 cm^{-1}; NMR δ 2.33 (s, $-SCH_3$, 3), 3.07 (d, $-CH_2-$, 2, J = 7.5 Hz), 3.93 (t, $-CHAr_2$, 1, J = 7.5 Hz), 6.93 (m, aryl, 10), and 7.56 (m, aryl, 2).

Anal. Calcd for $C_{21}H_{18}S$: C, 83.40; H, 6.00; S, 10.60. Found: C, 83.19; H, 5.56; S, 10.26.

9-Methyl-9-*p*-methylthiophenylfluorene was recrystallized from petroleum ether: mp 101–103 °C dec; ir ($CHCl_3$) 3055, 3025, 2950, 2880, 1600, 1500, and 1450 cm^{-1}; NMR δ 1.77 (s, $-CH_3$, 3), 2.33 (s, $-SCH_3$, 3), 7.13 (m, aryl, 10), and 7.63 (m, aryl, 2). The amount of pure material available was insufficient for combustion analysis; however, mass spectrometry showed a parent peak at *m/e* 302. Other fragmentation peaks consistent with the assigned structure were also observed.

Products from Decarbonylation of 5 (X = $SOCH_3$). The hydrocarbon mixture consisted of 66% 9-*p*-methylsulfinylphenylphenanthrene (**6**, X = $SOCH_3$), 21% 9,10-dihydro-9-*p*-methylsulfinylphenylphenanthrene (**7**, X = $SOCH_3$), and 13% 9-methyl-9-*p*-methylsulfinylphenylfluorene (**8**, X = $SOCH_3$). Repeated efforts to separate the hydrocarbon mixture into pure **6**, **7**, and **8** by preparative thin layer, or dry column, or normal column chromatography on Florisil, on silica gel, or on alumina failed to give homogeneous samples. However, a small sample of **6** could be isolated by preparative thin layer chromatography.

9-*p*-Methylsulfinylphenylphenanthrene was recrystallized twice from petroleum ether, followed by twice from methanol: mp 124–125 °C; ir ($CHCl_3$) 3055, 2905, 1600, 1400, 1450, and 1075 cm^{-1}; NMR δ 2.73 (s, $-SOCH_3$, 3), 7.56 (m, aryl, 11), and 8.63 (m, aryl, 2).

Anal. Calcd for $C_{21}H_{16}SO$: C, 79.71; H, 5.10; S, 10.13. Found: C, 79.43; H, 5.28; S, 10.02.

It was possible to further demonstrate the identity of the mixture by reduction with lithium aluminum hydride using an adaptation of the general procedure of Djerassi and co-workers.[60] In a 50-ml flask fitted with reflux condenser and anhydrous calcium chloride drying tube were placed 80 mg (2.07 mmol) of lithium aluminum hydride and 4 ml of dry tetrahydrofuran. To this was added, portionwise over 10 min, a solution of 200 mg of the hydrocarbon mixture in 10 ml of dry tetrahydrofuran. The mixture was heated at reflux for 2 h, cooled to room temperature, and quenched by careful titration with distilled water. The resultant paste was diluted with 30 ml of diethyl ether, filtered, and washed with 20 ml of ether. The combined ether layers were extracted with 3 × 60 ml of distilled water and dried over anhydrous sodium sulfate. Removal of the drying agent by filtration, followed by evaporation of the solvent in vacuo, gave 193 mg of white amorphous solid.

The infrared spectrum of the starting mixture showed a strong sulfoxide SO band at 1060 cm^{-1}, which was absent in the infrared spectrum ($CHCl_3$ solution) of the reduced mixture. The NMR spectrum of the starting mixture showed signals at δ 1.81 (s, CH_3), 2.58 (s, $SOCH_3$), 2.73 (s, $SOCH_3$), 3.11 (d, $-CH_2-$, J = 7.5 Hz), 4.09 (t, $-CHAr_2$,

J = 7.5 Hz), 7.05 (m, aryl), 7.57 (m, aryl), and 8.67 (m, aryl), indicating a mixture consisting of 66% **6**, 21% **7**, and 13% **8** (X = $SOCH_3$). The NMR spectrum ($CDCl_3$) of the mixture after treatment with lithium aluminum hydride and workup showed signals at δ 1.74 (s, $-CH_3$), 2.35 (s, $-SCH_3$), 2.47 (s, $-SCH_3$), 3.10 (d, $-CH_2-$, J = 7.5 Hz), 4.13 (t, $-CHAr_2$, J = 7.5 Hz), 7.09 (m, aryl), 7.74 (m, aryl), and 8.59 (m, aryl), indicating a mixture consisting of 67% **6**, 20% **7**, and 13% **8** (X = SCH_3). The character of the reduced mixture was further confirmed by chromatographic separation in the manner described above for the decarbonylation of **5** (X = SCH_3).

Products from the Decarbonylation of 5 (X = SO_2CH_3). The hydrocarbon mixture consisted of 56.5% 9-*p*-methylsulfonylphenylphenanthrene (**6**, X = SO_2CH_3), 33% 9,10-dihydro-9-*p*-methylsulfonylphenylphenanthrene (**7**, X = SO_2CH_3), and 10.5% 9-methyl-9-*p*-methylsulfonylphenylphenanthrene (**8**, X = SO_2CH_3). Attempts to isolate **6**, **7**, and **8** by means of preparative thin layer chromatography, dry column chromatography, or normal column chromatography on silica gel, Florisil, or neutral alumina all failed to yield homogeneous samples. The NMR spectrum displayed signals at δ 1.79 (s, $-CH_3$, **8**), 2.92 (s, $-SO_2CH_3$, **7** and **8**), 3.04 (s, $-SO_2CH_3$, **6**), 3.13 (d, partially overlapped by the singlet at 3.04, $-CH_2-$, **7**), 4.09 (t, $-CHAr_2$, J = 7.5 Hz, **7**), 7.15 (m, aryl), 7.91 (m, aryl), and 8.62 (m, aryl, **6**) in agreement with a mixture of **6**, **7**, and **8** (X = SO_2CH_3).

Decarbonylation of **5** (X = SO_2CH_3) in the absence of benzyl mercaptan led to a mixture of **6** and **7**, and no **8**. Samples **6** and **7** were separable from this mixture by means of preparative thin layer chromatography on silica gel [20 mg of mixture per 1000-μ plate, 16 successive developments with benzene–chloroform (5:1) each].

9-*p*-Methylsulfonylphenylphenanthrene was recrystallized from absolute methanol: mp 163.5–164.5 °C; ir ($CHCl_3$) 3050, 2950, 1600, 1500, 1470, 1320, and 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.07 (s, $-SO_2CH_3$, 3), 7.64 (m, aryl, 11), and 8.67 (m, aryl, 2).

Anal. Calcd for $C_{21}H_{16}SO_2$: C, 75.88; H, 4.85; S, 9.65; O, 9.62. Found: C, 75.59; H, 4.71; S, 9.68; O, 9.85.

9,10-Dihydro-9-*p*-methylsulfonylphenylphenanthrene was recrystallized from absolute methanol: mp 127.5–129.5 °C; ir 3050, 3020, 2950, 2900, 1600, 1315, and 1160 cm^{-1}; NMR δ 2.92 (s, $-SO_2CH_3$, 3), 3.17 (d, $-CH_2-$, 2, J = 7.5 Hz), 4.13 (t, $-CHAr_2$, 1, J = 7.5 Hz), 7.05 (m, aryl, 10), and 7.71 (m, aryl, 2). The amount of material available was insufficient for a combustion analysis; however, mass spectrometry showed a parent peak at m/e 334. Other fragmentation peaks consistent with the assigned structure were also observed.

Registry No.—**5** (X = H), 5043-46-9; **5** (X = CH_3), 31462-50-7; **5** (X = Cl), 60253-20-5; **5** (X = OCH_3), 31462-49-4; **5** (X = F), 60253-21-6; **5** (X = SCH_3), 60253-22-7; **5** (X = $SOCH_3$), 60253-23-8; **5** (X = SO_2CH_3), 60253-24-9; **6** (X = H), 844-20-2; **6** (X = CH_3), 37842-68-5; **6** (X = Cl), 37842-69-6; **6** (X = OCH_3), 37842-67-4; **6** (X = F), 60253-25-0; **6** (X = SCH_3), 60253-26-1; **6** (X = $SOCH_3$), 60253-27-2; **6** (X = SO_2CH_3), 60253-28-3; **7** (X = H), 5235-80-3: **7** (X = CH_3), 37842-71-0; **7** (X = Cl), 37842-72-1; **7** (X = OCH_3), 37842-70-9; **7** (X = F), 60253-01-2; **7** (X = SCH_3), 60253-02-3; **7** (X = $SOCH_3$), 60253-03-4; **7** (X = SO_2CH_3), 60253-04-5; **8** (X = H), 56849-83-3; **8** (X = CH_3), 60253-05-6; **8** (X = Cl), 60253-06-7; **8** (X = OCH_3), 60253-07-8; **8** (X = F), 60253-08-9; **8** (X = SCH_3), 60253-09-0; **8** (X = $SOCH_3$), 60253-10-3; **8** (X = SO_2CH_3), 60253-11-4; **9**, 150-60-7; **10** (X = CH_3), 60253-12-5; U· (R = H), 60253-13-6; U· (R = CH_3), 60253-14-7; U· (R = Cl), 60253-15-8; U· (R = OCH_3), 60253-16-9; U· (R = F), 60253-17-0; U· (R = SCH_3), 60253-18-1; U· (R = $SOCH_3$), 60253-19-2; U· (R = SO_2CH_3), 60252-86-0; R· (X = H), 60252-87-1; R· (X = CH_3), 60252-88-2; R· (X = Cl), 60252-89-3; R· (X = OCH_3), 60252-90-6; R· (X = F), 60252-91-7; R· (X = SCH_3), 60252-92-8; R· (X = $SOCH_3$), 60252-93-9; R· (X = SO_2CH_3), 60252-94-0; bromobenzene, 108-86-1; *p*-bromothioanisole, 104-95-0; *p*-bromochlorobenzene, 106-39-8; 4-bromotoluene, 106-38-7; 4-bromofluorobenzene, 460-00-4; *p*-bromoanisole, 104-92-7; 9-phenyl-9-fluorenol, 25603-67-2; 9-*p*-methylphenyl-9-fluorenol, 57028-28-1; 9-*p*-chlorophenyl-9-fluorenol, 60252-95-1; 9-*p*-methoxyphenyl-9-fluorenol, 57028-27-0; 9-*p*-fluorophenyl-9-fluorenol, 2284-44-8; 9-*p*-methylthiophenyl-9-fluorenol, 60252-96-2; 9-chloro-9-phenylfluorene, 25022-99-5; 9-chloro-9-*p*-methylphenylfluorene, 60252-97-3; 9-chloro-9-*p*-chlorophenylfluorene, 60252-98-4; 9-chloro-9-*p*-methoxyphenylfluorene, 60252-99-5; 9-chloro-9-*p*-fluorophenylfluorene, 1994-55-4; 9-chloro-9-*p*-methylthiophenylfluorene, 60253-00-1; chloromercuriacetaldehyde, 5321-77-7; benzyl mercaptan, 100-53-8.

Supplementary Material Available. Figure 2, showing the gas collecting and measuring apparatus, and Figure 3, showing the reaction vessel (2 pages). Ordering information is given on any current masthead page.

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1-Ethynylcyclopropyl Tosylate Solvolysis. 2.[1] *p*-Aryl Substituent Effect upon Rate and Product Distribution

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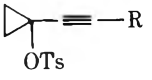
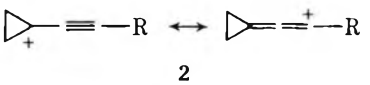
1-*p*-Tolylethynylcyclopropyl tosylate (**4**) and 1-*p*-anisylethynylcyclopropyl tosylate (**5**) have been prepared. Their rates of reaction and the resulting products of solvolysis in various solvents were compared with those of 1-phenylethynylcyclopropyl tosylate (**3**). The relative rates (k_{rel}) in 50% ethanol (70 °C) are **3**, k_{rel} = 1; **4**, k_{rel} = 7.5; and **5**, k_{rel} = 152. The rate enhancements over the parent system **3** due to *p*-methyl (**4**) and *p*-methoxy substitution (**5**), the solvent effects (m = 0.583–0.505), and the ρ value (−2.98) are clearly consistent with a SN'i ionization process involving anchimeric assistance of the triple bond (k_Δ), and leading to the mesomeric cation **11**, which is highly stabilized by further delocalization of the positive charge through the adjacent aryl ring. A cyclopropyl tosylate solvolysis, involving no ring opening at all, is reported.

In a previous solvolytic investigation, we reported the behavior of a variety of substituted 1-ethynylcyclopropyl tosylates **1**.[1]



1

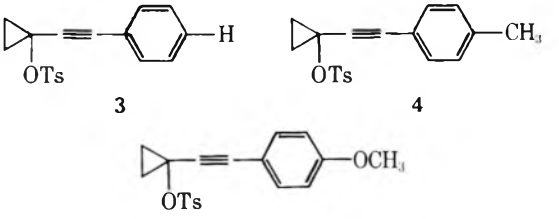
The solvolytic reactions of simple cyclopropyl derivatives usually afford, in the absence of steric[2] or direct conjugative interaction,[3] only allyl products[4] through concerted ionization and disrotatory ring opening.[5] On the other hand, it has been shown that the resonance-stabilized cation **2** does not undergo such a ring opening.



2

However, the formation of **2** as an intermediate in the solvolysis of 1-ethynylcyclopropyl tosylates **1** appeared to be strongly dependent upon the nature of the substituent R, as evidenced from product distribution and kinetic data. Thus, for instance, the products of aqueous ethanolysis of **1** (R = CH_3) were only allylic derivatives from opening of the cyclopropane ring while unrearranged cyclopropanols (or derivatives) were obtained from **1** (R = cyclopropyl) in high yield.[1] Therefore, the stabilization of the positive charge of **2**, by delocalization over the three carbons of the mesomeric propargyl allenyl system, entails a powerful electron-releasing substituent at the allenyl end.

We report here the solvolysis reactions of the 1-*p*-arylethynyl 1-tosyloxy cyclopropanes **3**, **4**, and **5** in order to determine the increase in the stabilization of the intermediate mesomeric

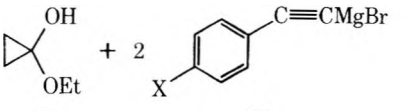


3 **4**

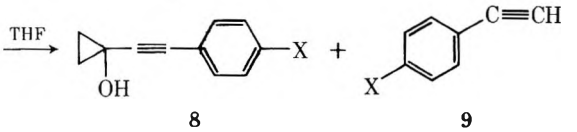
5

cations induced by the increased electron-releasing effect of the para substituents H, CH_3, OCH_3.

Syntheses. The reaction of the hemiketal of cyclopropanone **6**[6] with 2 equiv of the acetylenic magnesium bromides **7** provides the 1-*p*-arylethynylcyclopropanols **8** in high yield.



6 **7**



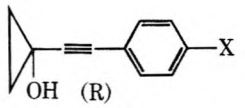
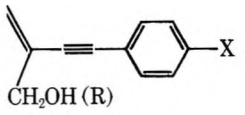
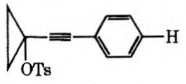
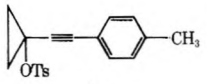
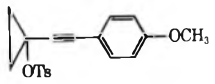
8 **9**

75–86%

X = H, CH_3, OCH_3

The hemiketal **6** is now readily available from ethyl 3-chloropropanoic ester;[7] the para arylacetylenic compounds which give the Grignard reagents **7** by exchange with ethylmagnesium bromide[7] were prepared from the suitable para-

Table I. Solvolysis Products (%) of 1-Arylethynylcyclopropyl Tosylates[a]

	Solvent	Reaction time, h	 8	 10
 3	EtOH–H_2O (50:50)	40	85[b]	15[b]
	Acetone–H_2O (60:40)	48	73.5	26.5
	Trifluoroethanol	8	52[c]	48[c]
 4	EtOH–H_2O (50:50)	40	95[b]	5[b]
	Acetone–H_2O (60:40)	48	82.5	17.5
	Trifluoroethanol	8	65[c]	35[c]
 5	EtOH–H_2O (50:50)	40	100[b]	0
	Acetone–H_2O (60:40)	48	92.5	7.5
	Trifluoroethanol	8	94[c]	6[c]

[a] Temperature 70 °C, buffered with 1.1 equiv of triethylamine. [b] As a mixture of the alcohol and its ethyl ether. [c] As tri fluoroethyl ether.

Table II. Solvolysis Rates of the 1-Arylethynylcyclopropyl Tosylates

	Solvent[a]	Temp, °C	$k \times 10^4$, s^{-1}[b]	Rel rate, 50E, 70 °C	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	m
3, X = H	50E	70	0.838 ± 0.017	1	19.67 ± 0.01	−20.10 ± 0.01	0.583
	50E	75	1.320 ± 0.006				
	80E	70	0.090 ± 0.003				
4, X = CH_3	50E	50	0.481 ± 0.019				
	50E	70	6.266 ± 0.025	7.47	23.27 ± 0.01	−6.45 ± 0.01	0.540
	50E	75	16.79 ± 0.17				
	80E	70	0.80 ± 0.01				
	80E	75	1.02 ± 0.02				
5, X = OCH_3	50E	50	19.84 ± 0.52				
	50E	60	39.23 ± 0.06				
	50E	70	127.30 ± 0.01	151.55	19.89 ± 0.01	−9.51 ± 0.01	0.505
	80E	70	18.58 ± 0.01				

[a] 50E refers to 50% aqueous ethanol, v/v before mixing. [b] The errors reported were determined by means of a least-squares computer program.

substituted benzaldehyde following a reported procedure.[8] The tosylates **3**, **4**, and **5** were then readily obtained from the cyclopropanols **8** by usual procedures.

Results and Discussion

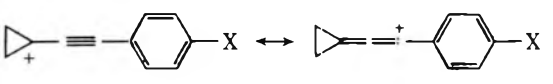
The 1-*p*-arylethynyl-1-tosyloxycyclopropanes **3**, **4**, and **5** were solvolyzed in solvents of different ionizing power and nucleophilicity, buffered with 1.1 equiv of triethylamine in order to avoid any acid-catalyzed rearrangement of the products.[9]

The temperature of the reaction was chosen low enough, i.e., 70 °C, to avoid the subsequent homoketonization of the cyclopropanols.[1,10] For each run, the products were separated by gas chromatography and their structures unequivocally proven by ir, NMR, and mass spectroscopy.

The cyclopropyl tosylates **3**, **4**, and **5**, as shown by the product distribution, listed in Table I, solvolyze with the formation of a mixture of the unrearranged cyclopropanols (or ethyl ethers) **8** and of the open ring allylic derivatives **10**, solely. As expected, the amount of unrearranged products **8** is clearly dependent upon the electron-donating power of the para substituent X of the phenyl ring. Moreover, the higher the ionizing power and the lower the nucleophilicity of the solvent, the more marked is the *p*-phenyl substituent effect; thus, for instance, the aqueous ethanolysis of the tosylates **3** (X = H) and **5** (X = OCH_3) afforded 85 and 100% of unrearranged cyclopropanols **8**, while in trifluoroethanol the corresponding values were 52 and 94%, respectively.

The solvolysis rates of the tosylates **3–5** in aqueous ethanol, measured by automatic continuous titration at pH 7.0, are presented in Table II. They increase too with X: the tosylates **4** (X = CH_3) and **5** (X = OCH_3) reacted 7.5 and 151.5 times faster than the parent tosylate **3** (X = H), respectively.

The effect of an electron-releasing group X on the solvolysis reaction is therefore noticeable. If the rate data for the cyclopropyl tosylates **3**, **4**, and **5** are plotted vs. Brown σ_p^+ substituent constants a ρ value of −2.98 is obtained, for the solvolysis in 80% aqueous ethanol. This result is highly consistent with an intermediate mesomeric carbenium ion **11**, in which

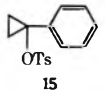
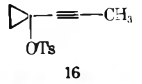
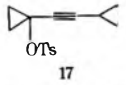
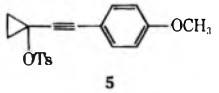


11

substantial delocalization of the positive charge through the 3 carbon unit exists.

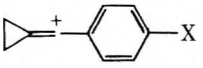
It must be noted that the substituent effect on the solvolysis rates of triarylchloroallenes[11] (80% aqueous acetone) and of 1-arylcyclopropyl tosylates[12] (acetic acid) corresponds to ρ values of −2.0 and −4.31, respectively.

Table III. Comparison of the Solvolysis Rate and Product Distribution of Some *tert*-1-Tosyloxycyclopropane Derivatives[a]

	$k \times 10^4$, s^{-1}	Rate ratios	Unrearranged product,[c] %	Ref
 13	0.18	1	0	9
 14	2915	16.10^3	68.5	9
 15	0.53[b]		0	12
 16	0.14	1	0	1
 17	18.81	133	90	1
 5	127.3	909	100	This work

[a] In 50% aqueous ethanol at 70.0 °C. [b] In acetic acid at 70.5 °C. [c] The counterpart is the product from ring opening, i.e., the allylic derivatives.

We have recently reported the generation of the vinyl cations **12** from the solvolytic reaction of the corresponding (1-bromo-1-*p*-arylmethylene)cyclopropanes.[13]



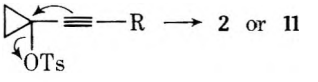
12

The enhancement of the rate of solvolysis by varying X under the same conditions correspond to a ρ value of -2.8.

These highly comparable data represent further convincing evidence that the solvolysis of *p*-aryl substituted ethynyl cyclopropyl tosylates **3–5** does indeed proceed through a resonance-stabilized vinyl cation **11**. Such a similarity of substituents effects in the generation of the vinyl cations **12** and in the generation of the mesomeric cations **11** confirms our previous findings.[1]

The activation parameters calculated from the temperature dependence of the solvolysis rates listed in Table II are consistent with the data reported on such vinyl cations; thus, for example, solvolysis of triphenylchloroallene (80% aqueous acetone) gives $\Delta H^{\ddagger} = 20.1$ kcal/mol and $\Delta S^{\ddagger} = -10.9$ eu,[11] solvolysis of 2,2-diphenyl-1-anisyliodoethylene (70% aqueous DMF) gives $\Delta H^{\ddagger} = 23.5$ kcal/mol and $\Delta S^{\ddagger} = -16.3$ eu,[14] solvolysis of 3,4-dimethyl 2-bromo-1,3-butadiene (80% aqueous ethanol) involving a mesomeric vinyl cation as intermediate gives $\Delta H^{\ddagger} = 25.6$ kcal/mol and $\Delta S^{\ddagger} = -17.2$ eu.[15]

The *m* values listed in Table II, which are a measure of the sensitivity of the substrate to changes in solvent ionizing power *Y*,[16] are lower than would be expected for anchimerically and nucleophilically unassisted solvolysis (k_c, $m \sim 1$),[17] but they fall in the range normally found for k_s and k_Δ processes.[18] From the low propensity of the parent cyclopropyl substrate to changes in solvent nucleophilicity, Schleyer et al. have reported that the solvolyses of cyclopropyl derivatives are not k_s processes; i.e., there is no specific back-side nucleophilic involvement of solvent in the transition state, but mainly k_Δ processes ($m = 0.508$) where the electrons from the breaking cyclopropane bond take the place of the attacking nucleophile.[19] In the absence of ring opening here, the anchimeric assistance is likely provided by the electrons of the adjacent triple bond moving toward the back side of the C–tosylate bond; thus, the solvolysis of the 1-ethynylcyclopropyl tosylates **1** can be regarded more likely as a SN'i ionization process.



1

In the study of neighboring group effects, it has been postulated that the more stable the carbenium ion center, the less demand that center will make upon a neighboring group for additional stabilization through π or σ participation.[20] This postulate seems to be valid too for the mesomeric cation **11**. Indeed, increasing the electron supply at the cationic center by varying the substituent X on the aryl group increases the anchimeric assistance of the triple bond (see the decreasing values of *m*, Table II) and reduces the ring opening of the cyclopropyl moiety into allyl derivatives, while, for instance, the tosylate **1** (R = CH_3) solvolysis entailed high carbon–carbon bond participation from the cyclopropane ring and afforded only the ring open derivatives.[1]

In Table III are gathered the kinetic data and product distribution for the solvolysis of various tertiary substituted 1-tosyloxycyclopropanes. An increase in the solvolysis rates, implying an increase in the stabilization of the intermediate cation, is therefore clearly observed when a more powerful electron-releasing group is successively substituted at the electron deficiency. Thus changing from an isopropyl **13** to a cyclopropyl **14** provides a rate enhancement of 16.10^3 and affords, at most, 68.5% of unrearranged cyclopropyl derivatives;[9] while changing from a methyl **16** to a cyclopropyl **17** or to a *p*-anisyl **5** provides rate increases of 133 and 909 only, but a higher proportion of unrearranged products, 90 and 100%, respectively. The present result, which is the first example of a cyclopropyl tosylate solvolysis via cationic intermediate involving no ring opening *at all*, provides a particularly straightforward demonstration of the stabilizing effect of a suitably substituted triple bond.

The lack of carbonyl or (and) allenic absorptions in the ir and of vinylic or (and) dimethylenallenic absorptions in the NMR spectra of the crude solvolytic products confirms our

previous findings that the mesomeric cations such as 11 react exclusively at the propargyl position.[1] This result is not at all a point of controversy; as a matter of fact, several alkynyl carbenium ions for which spectroscopic data indicate a strong contribution from the allenyl cation form have the same behavior,[11,21-24] unless the propargyl position is sterically hindered.[24]

A more detailed description of the charge distribution in the mesomeric cation 2 on the basis of ^{13}C NMR chemical shifts is under investigation.

Experimental Section

The preparation and description of 1-(phenylethynyl)cyclopropanol 8 (X = H) and of 1-(phenylethynyl)-1-tosyloxycyclopropane 3 have been previously reported.[1]

p-Tolylacetylene 9 (X = CH_3) was prepared using the procedure of Corey and Fuchs[8] by adding 16.8 g (140 mmol) of freshly distillated *p*-tolualdehyde to a reagent prepared from interaction of 18.35 g (281 mmol) of zinc dust, 73.7 g (281 mmol) of triphenylphosphine, and 93.2 g (281 mmol) of carbon tetrabromide in 500 ml of methylene chloride at room temperature for 30 h.

After a reaction time of 2 h at room temperature, 2000 ml of pentane was added to the reaction mixture, and the insoluble material removed by filtration. The insoluble fraction was reworked by several cycles of methylene chloride extraction and pentane precipitation to remove all of the olefinic product.

The solvents were removed by rotary evaporation and distillation of the residue at reduced pressure gave 32.7 g (85%) of 1,1-dibromo-2-*p*-tolylethylene: bp 85 °C (0.05 mm); NMR (CCl_4) δ 2.30 (s, 3 H), 7.35 (s, 1 H) and 7.0–7.45 (q, 4 H).

A solution of 32.7 g (118 mmol) of the dibromo olefin in 250 ml of tetrahydrofuran at −78 °C was treated with 237 mmol (103 ml of a 2.3 N hexane solution) of *n*-butyllithium. The reacting mixture was allowed to stir overnight at −78 °C and then for 1 h at 25 °C. The mixture was poured on crushed ice containing 118 mmol of hydrochloric acid. The organic layer was washed with water and dried over $MgSO_4$ and the solvent removed by distillation. Fractional distillation of the crude material yielded 9.6 g (68%) of *p*-tolylacetylene: bp 54 °C (10 mm) [lit.[25] bp 65–67 °C (18 mm)]; ir (neat) 3280 (ν ≡C–H) and 2100 cm^{-1} (ν C≡C); NMR (CCl_4) δ 2.30 (s, 3 H), 2.85 (s, 1 H), and 6.95–7.35 ppm (q, 4 H).

1-(p-Tolylethynyl)cyclopropanol 8 (X = CH_3) was prepared using the reported procedure.[1] To 70 mmol of ethylmagnesium bromide prepared from 1.7 g of magnesium and 8.65 g of ethyl bromide in 50 ml of anhydrous tetrahydrofuran was added a solution of 8.4 g (70 mmol) of *p*-tolylacetylene in 20 ml of tetrahydrofuran. The mixture was refluxed for 2 h. To the cold *p*-tolylacetylenemagnesium bromide was added with stirring 3.57 g (35 mmol) of 1-ethoxycyclopropanol[1] and the reacting mixture was refluxed for 4 h. The cold mixture was poured on a mixture of crushed ice and 70 ml of H_2SO_4 (1 N) and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated to yield a light yellow oil. Thin layer chromatography, ir, and NMR spectra showed two compounds in equal amount. The first was readily removed by distillation [bp 54 °C (10 mm)] and identified as the starting *p*-tolylacetylene. The residue was 4.5 g (75%) of practically pure 1-(*p*-tolylethynyl)cyclopropanol 8 (X = CH_3): ir (neat) 3080 (ν C–H) and 2210 cm^{-1} (ν C≡C); NMR (CCl_4) δ 1.08 (m, 4 H), 2.32 (s, 3 H), 3.50 (m, 1 H), and 6.95–7.35 ppm (m, 4 H); MS M^+ *m/e* (rel intensity) 172 (62.5), 157 (12.5), 143 (100), 129 (29), 128 (17.5), 115 (41), 92 (35), 58 (72.5).

p-Anisylacetylene 9 (X = OCH_3) was prepared by the procedure of Corey and Fuchs[8] using 20.9 g (320 mmol) of zinc dust, 84 g (320 mmol) of triphenylphosphine, 106.2 g (320 mmol) of carbon tetrabromide, and 21.7 g (159 mmol) of freshly distillated *p*-anisaldehyde yielding 36 g (80%) of 1,1-dibromo-2-*p*-anisylethylene: bp 114 °C (0.025 mm); NMR (CCl_4) δ 3.75 (s, 3 H), 7.45 (s, 1 H), and 6.70–7.50 ppm (q, 4 H). Treatment with 2 equiv of *n*-BuLi as described above for *p*-tolylacetylene yielded 12.16 g (75%) of *p*-anisylacetylene: bp 85–86 °C (10 mm) [lit.[26] 86–87 °C (17 mm)]; ir (neat) 3280 (ν ≡C–H) and 2100 cm^{-1} (ν C≡C); NMR (CCl_4) δ 2.85 (s, 1 H), 3.78 (s, 3 H), and 6.80–7.45 ppm (q, 4 H).

1-(p-Anisylethynyl)cyclopropanol 8 (X = OCH_3) was prepared analogously to 8 (X = CH_3) by the reaction of the *p*-anisylacetylenemagnesium bromide [obtained from 18.22 g (138 mmol) of *p*-anisylacetylene and 138 mmol of ethylmagnesium bromide] with 7.04 g (69 mmol) of 1-ethoxycyclopropanol.[1] After the usual workup a mixture of two compounds in equal amount was obtained. The first, liquid, was simply removed by filtration under vacuum through a glass-sintered funnel and identified as the starting *p*-anisylacetylene. The solid residue was 11.15 g (86%) of practically pure 1-(*p*-anisylethynyl)cyclopropanol 8 (X = OCH_3), recrystallizable from ethyl acetate, mp (ethyl acetate) 91.8 °C.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.42; O, 16.99. Found: C, 76.47; H, 6.36.

Ir (CCl_4) 3590 (ν O–H), 3090 (ν C–H), and 2290 cm^{-1} (ν C≡C); NMR (CCl_4) δ 1.04 (m, 4 H), 3.75 (s, 3 H) and 6.65–7.30 ppm (q, 4 H); MS M^+ *m/e* (rel intensity) 188 (71.5), 173 (15.5), 159 (100), 145 (17), 144 (17), 127 (12), 117 (17), 115 (17), 108 (65), 55 (64).

1-(p-Tolylethynyl)-1-tosyloxycyclopropane 4. The tosylate 4 was obtained by conventional means through the reaction of the cyclopropanol 8 (X = CH_3) with 1.1 equiv of tosyl chloride in pyridine (dried over molecular sieves) at 0 °C for 48 h. Two recrystallizations from pentane gave the pure 1-(*p*-tolylethynyl)-1-tosyloxycyclopropane 4: mp 83.2 °C; NMR (CCl_4) δ 1.20–1.65 (m, 4 H), 2.32 (s, 6 H), 6.98 (s, 4 H), and 7.10–7.90 ppm (q, 4 H).

Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.91; H, 5.55; O, 14.70; S, 9.82. Found: C, 70.08; H, 5.57; S, 9.52.

1-(p-Anisylethynyl)-1-tosyloxycyclopropane 5. The tosylate 5 was obtained from cyclopropanol 8 (X = OCH_3) and 1.1 equiv of tosyl chloride in pyridine. Two recrystallizations from pentane gave the pure 1-(*p*-anisylethynyl)-1-tosyloxycyclopropane 5: mp 65.0 °C; NMR (CCl_4) δ 1.20–1.60 (m, 4 H), 2.32 (s, 3 H), 3.78 (s, 3 H), 6.60–7.10 (q, 4 H), and 7.10–7.90 ppm (q, 4 H).

Anal. Calcd for $C_{19}H_{18}O_4S$: C, 66.65; H, 5.30; O, 18.69; S, 9.36. Found: C, 66.54; H, 5.36; S, 9.28.

Description of a Typical Comparative Product Analysis. The tosylates 3, 4, and 5 (150 mg, ~0.5 mmol) were dissolved in 2.5 ml of EtOH–H_2O (50:50) mixture containing 1.1 equiv of triethylamine as buffer, respectively. The three solvolysis mixtures were heated in sealed tubes at 70 °C for 40 h. After cooling the tubes were opened and the solvents removed on a rotary evaporator. The residues mixed with concentrated aqueous NaCl solutions were extracted with pentane three times each. The pentane extracts were dried over $MgSO_4$ and concentrated on a rotary evaporator.

The three crude solvolysis mixtures were worked up by gas chromatography and the products of each solvolysis were identified comparatively by combined GC and MS analysis and from their ir and NMR spectra.

The other solvolysis reactions were run in the same way, under the conditions reported in Table I.

1-Ethoxy-1-(phenylethynyl)cyclopropane 8 (X = H; R = CH_2CH_3) has been described.[1]

1-(2′,2′,2′-Trifluoroethoxy)-1-(phenylethynyl)cyclopropane 8 (X = H; R = CH_2CF_3): NMR (CCl_4) δ 1.15 (m, 4 H), 3.60–4.05 (q, 2 H, *J* = 8.7 Hz) and 7.30 ppm (m, 5 H); ir (neat) ν C≡C 2220 cm^{-1}; MS M^+ *m/e* (rel intensity) 240 (45), 171 (45), 157 (39), 141 (68), 129 (100), 128 (58), 127 (27), 115 (54).

2-Methylene-4-phenyl-2-butyn-1-ol 10 (X = H) has been described.[1]

1-Ethoxy-3-methylene-4-phenyl-3-butyne 10 (X = H; R = CH_2CH_3) has been described.[1]

1-(2′,2′,2′-Trifluoroethyl)-2-methylene-4-phenyl-3-butyne 10 (X = H; R = CH_2CF_3): NMR (CCl_4) δ 3.60–4.05 (q, 2 H, *J* = 8.7 Hz), 4.15 (m, 2 H), 5.55 (m, 2 H) and 7.30 ppm (m, 5 H); ir (neat) ν C≡C 2220 cm^{-1}; MS M^+ *m/e* (rel intensity) 240 (56), 171 (9), 157 (7.5), 142 (27), 141 (32), 127 (100), 115 (12), 77 (30).

1-Ethoxy-1-(p-tolylethynyl)cyclopropane 8 (X = CH_3; R = CH_2CH_3): NMR (CCl_4) δ 1.08 (m, 4 H), 1.10–1.32 (t, 3 H, *J* = 7 Hz), 2.32 (s, 3 H), 3.50–3.85 (q, 2 H, *J* = 7 Hz), and 6.95–7.35 ppm (q, 4 H); ir (neat) ν C≡C 2190 cm^{-1}; MS M^+ *m/e* (rel intensity) 200 (5), 185 (6), 172 (31.5), 157 (46), 143 (100), 129 (58), 115 (37), 89 (21).

1-(2′,2′,2′-Trifluoroethoxy)-1-(p-tolylethynyl)cyclopropane 8 (X = CH_3; R = CH_2CF_3): NMR (CCl_4) δ 1.20 (m, 4 H), 2.35 (s, 3 H), 3.60–4.05 (q, 2 H, *J* = 8.7 Hz), and 7.0–7.35 ppm (q, 4 H); ir (neat) ν C≡C 2190 cm^{-1}; MS M^+ *m/e* (rel intensity) 254 (31.5), 185 (70), 171 (42.5), 157 (31.5), 155 (30), 143 (100), 128 (65), 115 (37).

2-Methylene-4-p-tolyl-3-butyn-1-ol 10 (X = CH_3): NMR (CCl_4) δ 2.35 (s, 3 H), 3.50 (m, 1 H), 4.20 (m, 2 H), 5.50–5.60 (m, 2 H), and 6.95–7.35 (q, 4 H); ir (neat) ν C≡C 2190 cm^{-1}; MS M^+ *m/e* (rel intensity) 172 (20), (157) (5), 143 (100), 129 (11), 115 (15), 89 (10).

1-Ethoxy-2-methylene-4-p-tolyl-3-butyne 10 (X = CH_3; R = CH_2CH_3): NMR (CCl_4) δ 1.10–1.32 (t, 3 H, *J* = 7 Hz), 2.30 (s, 3 H), 3.50–3.85 (q, 2 H, *J* = 7 Hz), 4.15 (m, 2 H), 5.50 (m, 2 H) and 6.95–7.35 ppm (q, 4 H); ir (neat) ν C≡C 2190 cm^{-1}; MS M^+ *m/e* (rel intensity) 200 (4), 185 (9), 172 (37), 171 (100), 141 (56).

1-(2′,2′,2′-Trifluoroethyl)-2-methylene-4-p-tolyl-3-butyne 10 (X = CH_3; R = CH_2CF_3): NMR (CCl_4) δ 2.35 (s, 3 H), 3.60–4.05 (q, 2 H, *J* = 8.7 Hz), 4.20 (m, 2 H), 5.55 (m, 2 H), and 6.95–7.30 ppm

(q, 4 H); ir (neat) ν C≡C 2190 cm^{-1}; MS M$^+$ *m/e* (rel intensity) 254 (72), 185 (16), 156 (28), 141 (100), 128 (15), 115 (36).

1-Ethoxy-1-(*p*-anisylethynyl)cyclopropane 8 (X = OCH$_3$; R = CH$_2$CH$_3$): NMR (CCl_4) δ 1.02 (m, 4 H), 1.05–1.30 (t, 3 H, J = 7 Hz), 3.50–3.85 (q, 2 H, J = 7 Hz), 3.75 (s, 3 H), and 6.65–7.35 ppm (q, 4 H); ir (neat) ν C≡C 2185 cm^{-1} (very strong); MS M$^+$ *m/e* (rel intensity) 216 (3), 201 (6.5), 188 (41), 172 (20), 159 (100), 144 (35), 116 (20), 115 (15), 88 (20).

1-(2′,2′,2′-Trifluoroethoxy)-1-(*p*-anisylethynyl)cyclopropane 8 (X = OCH$_3$; R = CH$_2$CF$_3$): NMR (CCl_4) δ 1.10–1.20 (m, 4 H), 3.75 (s, 3 H), 3.80–4.20 (q, 2 H, J = 8.7 Hz), and 6.70–7.30 ppm (q, 4 H); ir (neat) ν C≡C 2190 cm^{-1}; MS M$^+$ *m/e* (rel intensity) 270 (24.5), 201 (100), 187 (47), 173 (30), 171 (27), 159 (89), 145 (36), 144 (32), 128 (38), 116 (28), 115 (24.5), 57 (32), 55 (45).

2-Methylene-4-*p*-anisyl-3-butyn-1-ol 10 (X = OCH$_3$): NMR (CCl_4) δ 3.75 (s, 3 H), 4.20 (m, 2 H), 5.50 (m, 2 H), and 6.70–7.40 ppm (q, 4 H); ir (neat) ν C≡C 2185 cm^{-1}; MS M$^+$ *m/e* (rel intensity) 188 (7.5), 159 (100), 144 (4), 116 (3), 57 (4), 55 (2.8).

1-(2′,2′,2′-Trifluoroethoxy)-2-methylene-4-*p*-anisyl-3-butyne 10 (X = OCH$_3$; R = CH$_2$CF$_3$): NMR (CCl_4) δ 3.75 (s, 3 H), 3.80–4.20 (q, 2 H, J = 8.7 Hz), 4.15 (m, 2 H), 5.55 (m, 2 H), and 6.70–7.40 ppm (q, 4 H); ir (neat) ν C≡C 2180 cm^{-1}; MS M$^+$ *m/e* (rel intensity) 270 (70), 172 (25.5), 157 (100), 135 (25.5), 57 (60), 55 (29.5).

Kinetic procedures have been described in the preceding report.[1]

Acknowledgment. The author is grateful to Professor J. M. Conia for his interest and constant encouragement throughout this work.

Registry No.—**3,** 57951-60-7; **4,** 60512-41-6; **5,** 60512-42-7; **6,** 13837-45-1; **8** (X = CH$_3$), 60512-43-8; **8** (X = OCH$_3$), 60512-44-9; **8** (X = H; R = CH$_2$CF$_3$), 60512-45-0; **8** (X = CH$_3$; R = CH$_2$CH$_3$), 60512-46-1; **8** (X = CH$_3$; R = CH$_2$CF$_3$), 60512-47-2; **8** (X = OCH$_3$; R = CH$_2$CH$_3$), 60512-48-3; **8** (X = OCH$_3$; R = CH$_2$CF$_3$), 60512-49-4; **9** (X = CH$_3$), 766-97-2; **9** (X = OCH$_3$), 768-60-5; **10** (X = H; R = CH$_2$CF$_3$), 60512-50-7; **10** (X = CH$_3$), 60512-51-8; **10** (X = CH$_3$; R = CH$_2$CH$_3$), 60512-52-9; **10** (X = CH$_3$; R = CH$_2$CF$_3$), 60512-53-0; **10** (X = OCH$_3$), 60512-54-1; **10** (X = OCH$_3$; R = CH$_2$CF$_3$), 60512-55-2; 1,1-dibromo-2-*p*-tolylethylene, 60512-56-3; 1,1-dibromo-2-*p*-anisylethylene, 60512-57-4; tosyl chloride, 98-59-9.

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Oxyfunctionalization of Hydrocarbons.[1a] 5. Protolytic Cleavage–Rearrangement Reactions of Tertiary Alkyl (Arylalkyl) Peroxy Esters in Superacids

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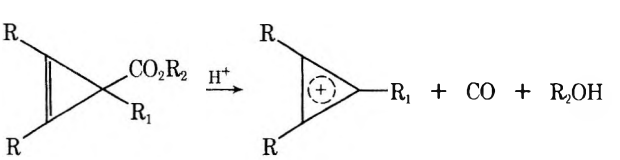
In continuation of our work on superacid induced cleavage–rearrangement reactions of hydroperoxides,[2a] we have undertaken a study of the superacid induced cleavage–rearrangement reactions of peroxy esters. Studies included those of *tert*-alkyl peroxyacetates, as well as various other *tert*-butyl peroxy esters. Particularly, *tert*-butyl peracetate was found to be unique in that both O–O and C–O cleavage products were observed, depending upon conditions. The yield of O–O and C–O cleavage products from various peroxy esters is discussed in terms of the inactivation (via protonation) of peroxy acid and the relative migratory aptitude of alkyl groups. The direct observation of the reaction intermediates, including the dimethylphenoxycarbenium ion **24** in the reactions of cumyl peroxy esters, is discussed.

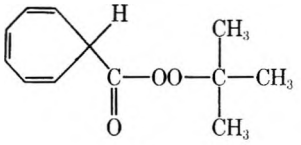
Unlike the related acid-catalyzed cleavage–rearrangement reaction of hydroperoxides (**1**)[2] those of peroxy esters are considerably less studied.

Protolysis of peroxy esters has been employed as a means of preparation of stable carbenium ions. Thus Farnum et al., upon decarboxylation of the peroxy ester, obtained the corresponding cyclopropenium ion **2**.[3]

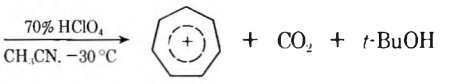


1 **2**

Similarly Rüchardt and Schwarzer obtained the tropylium ion **4** from the peroxy ester **3**.[4]

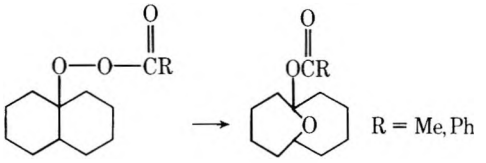


3



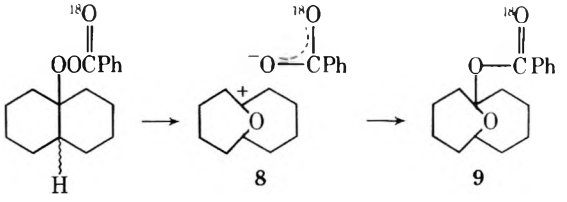
4

Ionic cleavage–rearrangement reactions of peroxy esters have also been known for some time. Criegee,[5] in 1944, observed that the acetate and benzoate esters of *trans*-9-decalyl hydroperoxide **5** rearranged on standing to give isomeric esters of type **6**.



5 **6**

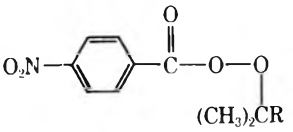
It was shown subsequently that the Criegee rearrangement, which competes effectively with homolytic decomposition, is facilitated by polar solvents,[6,7] added salt,[8] and with increased electron-withdrawing power of R.[6] Furthermore, the rearrangement was shown to proceed intramolecularly since incorporation of the *p*-nitrobenzoate or *p*-bromobenzoate group into the product, when *trans*-9-decalyl perbenzoate was decomposed in the presence of added lithium *p*-nitrobenzoate[7] or sodium *p*-bromobenzoate,[8] did not occur. That the oxygens in the carboxylate group are nonequivalent during the rearrangement of **7** was shown by the almost complete retention of an ^{18}O label in the carbonyl group of **9**.[9]



7 **8** **9**

These results were interpreted in terms of a highly structured tight ion-pair intermediate **8**, which collapsed to the product before equilibration of the oxygens of the carboxylate anion.[10]

The most detailed investigation to date of the Criegee rearrangement is that of Winstein and Hedaya,[11] who solvolyzed



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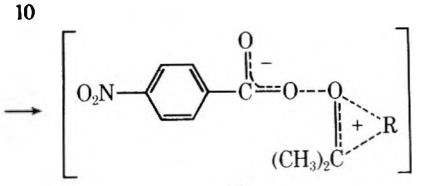

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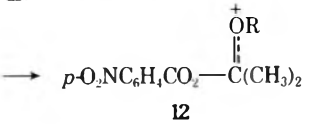
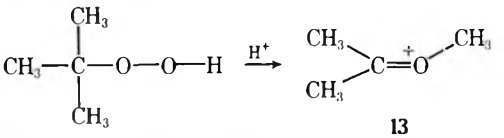


12

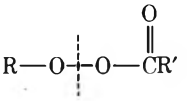
a series of 2-substituted 2-propyl *p*-nitroperbenzoates **10**. Steric acceleration was found to be negligible and they concluded that the relative rate order R = CH_3 < CH_2CH_2Ph < CH_2CH_3 < $CH(CH_3)_2$ < CH_2Ph < $CH_2C_6H_4OCH_3$-*m* < $CH_2C_6H_4OCH_3$-*p* < 4-camphyl < C_6H_5 < $C(CH_3)_3$ is best described in terms of a nonclassical type bridged transition state **11** which collapsed to an α-alkoxy carbenium ion **12**.

We have shown previously[2a] that for the acid-induced cleavage–rearrangement reaction of *tert*-alkyl hydroperoxides in superacid media intermediates analogous to **12** could be observed by NMR spectroscopy, e.g., **13**.



13

Furthermore, it was found that by using the corresponding peracetate the intermediates showed little or no further reaction and were conveniently observed. Among the hydroperoxides studied *tert*-butyl hydroperoxide was found to be unique in that it gave products from both O–O and C–O cleavage. We decided, therefore, to further study the reactions of peroxy esters in superacids, with particular emphasis on the effect of varying the nature of the alkyl (a) and acyloxy (b) groups.



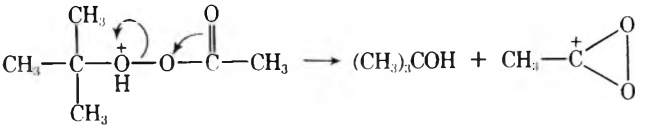
(a) (b)

Results and Discussion

The preparation of the peroxy esters used in this study is described in the Experimental Section. The esters were characterized and their purity checked by both ^1H and ^{13}C NMR spectroscopy. ^{13}C NMR parameters for the *tert*-butyl peroxy esters studied are given in Table I.

***tert*-Butyl Peracetate (14).** The ^1H NMR and ^{13}C NMR spectra of the resultant solution from the reaction of **14** with a fivefold excess of magic acid in SO_2ClF at −78 °C showed the dimethylmethoxycarbenium ion **13** and protonated acetic acid in 60% yield, together with 40% of the trimethylcarbenium ion **15** and peracetic acid. The former products are the result of O–O cleavage, route a of Scheme I, while the latter are the result of C–O cleavage, route b of Scheme I.

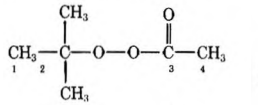
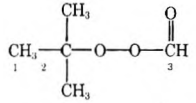
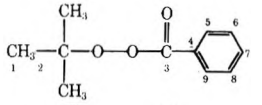
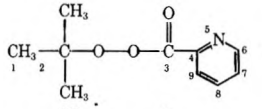
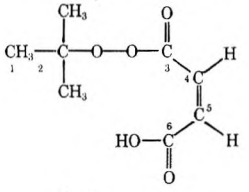
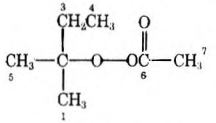
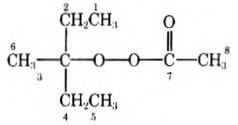
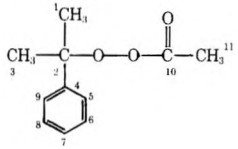
Ion **13** showed no sign of solvolytic cleavage under the conditions employed. The third alternative cleavage path for b, namely, cleavage to the acetyloxy cation, the cyclic form of which could be significantly stabilized,[12] was not indicated by the experimental data.



Treatment of **14** with a twofold excess of magic acid resulted in exclusive reaction via route a, as found previously for *tert*-butyl hydroperoxide.[2a] Furthermore, reaction products of **14** with an equimolar amount of magic acid, in SO_2ClF at −78 °C, gave the ion **13** and acetic acid together with a third species, which on the basis of its ^{13}C NMR data is regarded as protonated *tert*-butyl peracetate **16**, the expected primary protonation product.

These results may be explained by the reasoning used in the case of the *tert*-butyl hydroperoxide/magic acid systems, that an excess of magic acid is required to deactivate peracetic acid to act as a nucleophile, thus enabling direct observation of

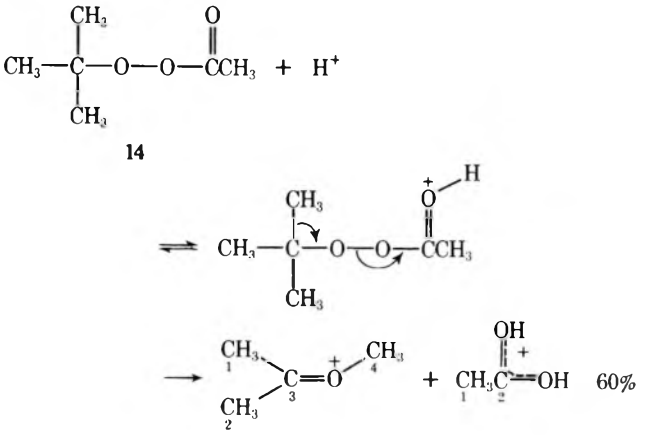
Table I. ^{13}C NMR Chemical Shifts for Peroxy Esters Studied

Registry no.	Compd	Chemical shift[a] 1	2	3	4	5	6	7	8	9	10	11
107-71-1	 [b]	25.3 26.14	83.21 83.16	168.16 168.21	16.75 17.61							
819-50-1		25.36	84.23	161.39								
614-45-9		27.68	85.29	165.73	134.9	130.52	130.17	134.9	130.17	130.52		
60512-72-3	 [b]	23.48	83.39	161.83	144.7		148.19	124.65	137.24	127.26		
1931-62-0		26.29	84.24	163.91	132.92		165.56					
690-83-5		23.77	85.36	31.60	8.23	23.77	168.03	17.63				
60512-73-4		7.19	29.27	87.65	29.27	7.19	20.94	167.7	17.71			
34236-39-0		26.36	85.63	26.36	144.0	128.15	125.1	127.35	125.1	128.15	167.35	17.80

[a] $CDCl_3$, internal ambient temperature unless otherwise stated. [b] SO_2ClF, external Me_4Si, −40 °C.

Scheme I

route a

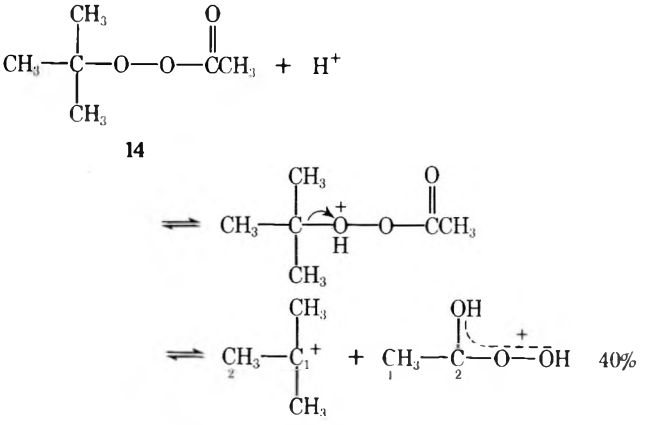


14

13

^{13}C NMR: 1, 26.83; 2, 32.1; 3, 245.48; 4, 68.87
^{1}H NMR: 1, 2, 3.40; 4, 5.23
^{13}C NMR: 1, 20.08; 2, 144.68
^{1}H NMR: 1, 3.27; 2, 13.07, 12.27

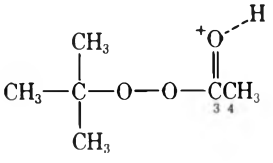
route b



14

15

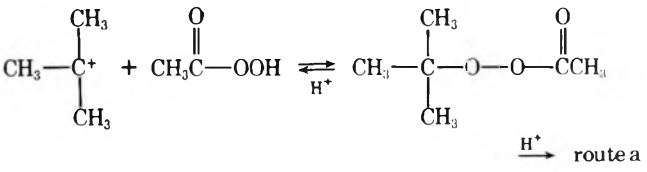
^{13}C NMR: 1, 335.7; 2, 47.78
^{1}H NMR: 2, 4.30
^{13}C NMR: 1, 16.90; 2, 192.30
^{1}H NMR: 1, 3.27; 2, 13.57, 13.33



16

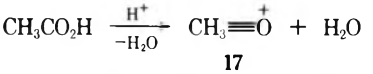
^{13}C NMR: 1, 24.94; 2, 86.66; 3, 177.28; 4, 17.19 [$\delta_{^{13}C}$ (Me_4Si)]

C–O cleavage. At lower acid concentrations the peroxy ester readily re-forms and can then react via O–O cleavage.



Indeed the rearrangement reaction of peroxy esters is so facile that alkylation of peroxy acids cannot be used as a method of preparation of peroxy esters.[13]

The equilibrium character of the solution obtained from the reaction of *tert*-butyl peracetate with a fivefold excess of magic acid was proven by gently warming the solution to −10 °C in the NMR probe. This shifted the equilibrium to the right, resulting in loss of the trimethylcarbenium ion with subsequent increase in the amount of carboxonium ion **13** and acetic acid in solution. After ~30 min at −10 °C no trace of the trimethylcarbenium ion remained, and at this temperature acetic acid was dehydrated to yield the acetylium ion **17**.[14]



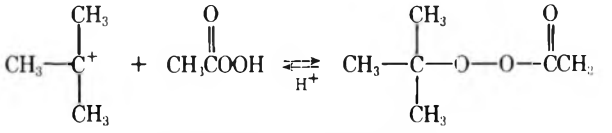
17

Our success in trapping products from both C–O and O–O heterolysis in the reaction of **14** with a fivefold excess of magic acid led us to examine the reaction of other peroxy esters under similar conditions to check if this pathway was characteristic only of the *tert*-butyl system as found previously for a series of *tert*-alkyl hydroperoxides.[2a]

Our attention was first turned to variation of the acyloxy group in *tert*-butylperoxy esters. Reactions of these peroxy esters with a fivefold excess of magic acid are summarized in Table II.

It is apparent that the nature of the acyl group played a considerable part in determining the course of the reactions. As seen from Table II, there is an increase in the percentage of reaction via O–O cleavage.

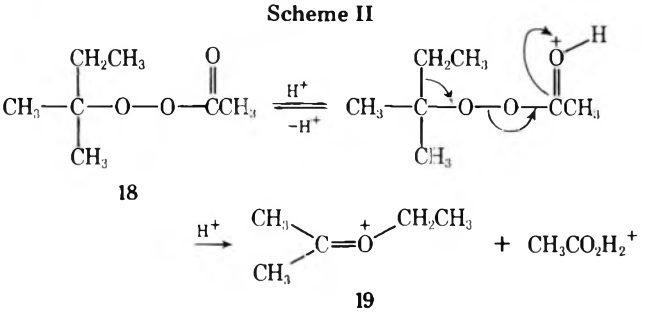
This can be interpreted in terms of the relative ease of deactivation of the peroxy acid as a nucleophile. The more acidic the peroxy acid, the less readily it will be protonated. Thus for the least acidic of the three studied systems, peroxyacetic acid, trapping of the C–O cleavage reaction is facilitated since the reaction of the formed carbenium ion with peroxy acid will be inhibited.



Though the basicities of these peroxy acids were not known, the order of basic strengths would be expected to correspond to those of model compounds with the same RC=O groups. Of the related carboxylic acids [RC(=O)OH], acetic acid (R = CH_3) is more basic (pK_b = −6.10) than benzoic acid (R = Ph, pK_b = −7.26).[15] Of the related ketones, RC(=O)CH_3 and RC(=O)Ph, the order of basic strengths is R = CH_3 > Ph > H.[16a,b] Based on extrapolations, the order of base strength of the peroxy acids would be peracetic > perbenzoic > performic acid. The latter two peroxy acids would be increasingly less capable of deactivation on the carbonyl oxygen of the COOOH group.

Next our attention was directed to the variation of the alkyl group of the *tert*-alkyl peracetates. Addition of *tert*-amyl peracetate **18** to a fivefold excess of magic acid, in SO_2ClF at −78 °C, yielded exclusively the dimethylethoxycarbenium ion **19** and acetic acid, the expected products from O–O cleavage. No trace of C–O cleavage products, i.e., the dimethylethylcarbenium ion and peracetic acid, was found. Furthermore, the ethyl group migrated to the total exclusion of methyl migration, Scheme II.

Scheme II



18

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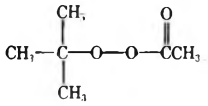
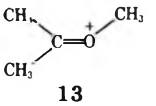
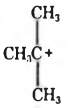
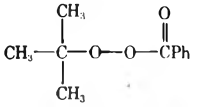
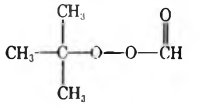
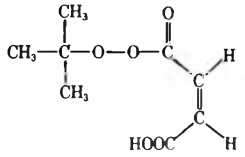
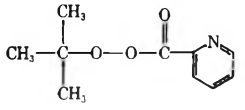
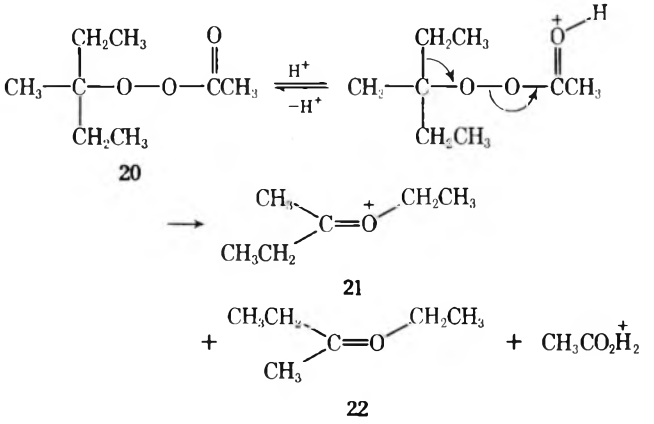
Table II. Reactions of *tert*-Butyl Peroxy Esters with Magic Acid[a]

Peroxy ester	% O–O[b] cleavage	% C–O[b] cleavage	Observed products[c]		
	60	40	 13	 15	Acetic acid Peracetic acid
	85	15	13	15	Benzoic acid Perbenzoic acid[d]
	>95	<5	13	15	Formic acid[e]
	>95	<5	13	15	Maleic acid[f] Fumaric acid
	100	0	13		α-Picolinic acid[g]

[a] All reactions carried out in fivefold excess of magic acid to peroxy esters in SO_2ClF at −78 °C. [b] Yields determined by integration of the ^1H NMR spectra. [c] Product was analyzed using ^1H and ^{13}C NMR. [d] Carbonyl and C_{ipso} could be distinguished from those of benzoic acid: benzoic acid, C=O 182.54, C_i 119.64 ppm; perbenzoic acid, C=O 181.55, C_i 116.76 ppm. [e] Only one C=O absorption was detected in ^{13}C NMR. If peroxyformic acid were present two carbonyl signals would be expected.[14b] [f] Showed two C=O absorptions in ^{13}C NMR due to the two isomeric acids. [g] Only one C=O absorption was detected in the ^{13}C NMR spectrum.

Similar treatment of 3-methylpentyl 3-peracetate **20** also gives exclusive O–O cleavage (Scheme III). **21** is regarded as the major isomer.[2a]

Scheme III

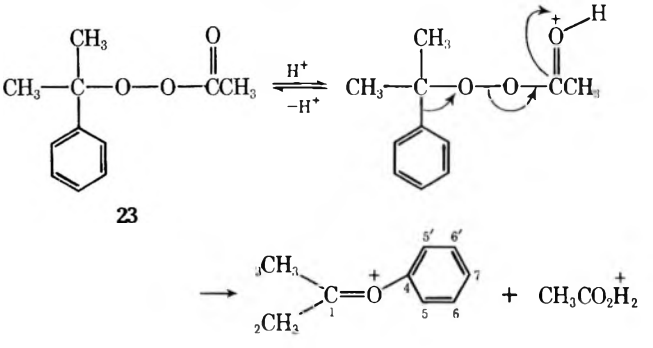


We were also unable to detect any evidence for C–O cleavage on treating cumyl peracetate **23** with a fivefold excess of magic acid. However, the blood-red solution produced in the above reaction showed (by NMR) the carboxonium ion **24** which we believe to be the first direct observation of this significant intermediate (Scheme IV), which is of course also the key to the cumene hydroperoxide rearrangement.

Previous attempts using cumyl hydroperoxide **25** failed to yield observable **24** upon treatment with magic acid.[14b] The dark green solution so obtained contained the decomposition products of **24**, namely phenol and acetone, indicating that **24** is easily susceptible to hydrolysis (Scheme V). Indeed both phenol and acetone were also observed as minor products from the decomposition of **23**.

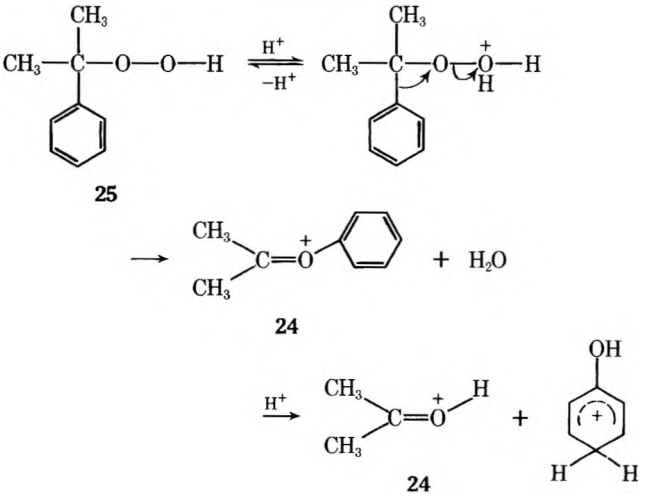
For the related reactions of *tert*-alkyl hydroperoxides,[2a] we

Scheme IV

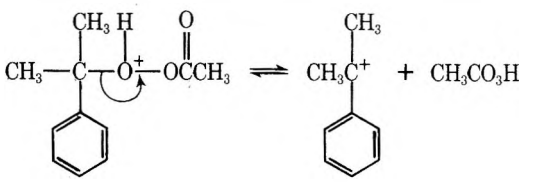


^{13}C NMR: 1, 248.27; 2, 32.22; 3, 29.10; 4, 154.16; 5,5′, 118.03; 6,6′, 131.95; 7, 131.14 [$\delta_{^{13}C}$ (Me_4Si)]

Scheme V



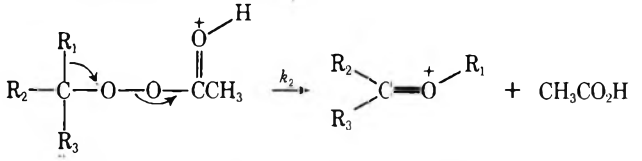
attributed the singular behavior of the *tert*-butyl system to the relative stability of the trimethylcarbenium ion **15**. This, however, cannot be the main factor since the dimethylphenylcarbenium ion **26** which would result from C–O cleavage of cumyl peracetate is a more stable species than **15**.[14b]



26

We therefore now consider that the important feature of these reactions is the relative migratory aptitude of the migrating alkyl (aryl) group.

In all systems studied in which an alkyl (aryl) group migrates to oxygen the methyl group has been found to have the lowest migratory aptitude.[2] For the peroxyacetates investigated in the present study the observed order of relative migratory aptitude is phenyl > ethyl > methyl, in good accord with the observations of Hedaya and Winstein in solvolytic systems.[11] Thus, in the reactions of



the increase in k is on the order of $R_1R_2R_3 = Et_2Me > EtMe_2 > Me_3$ and $R_1R_2R_3 = PhMe_2 > Me_3$. This relative migratory aptitud is one of the factors which determine the ratio of O–O and C–O cleavage, as well as the basicity of peroxy acids produced by the reaction.

In conclusion the protolytic cleavage–rearrangement reactions of peroxy esters in superacidic media are clearly related to the analogous reaction of hydroperoxides,[2a] and, as with the hydroperoxides, only the *tert*-butyl systems were found to give both O–O and C–O cleavage products. Our studies allowed the direct observation of the carboxonium ion intermediates key to both processes.

Experimental Section

Preparation of Peroxy Esters. Cumyl peracetate was prepared according to the method of Yablokov, Shushunov, and Kolyaskipa.[17] ***tert*-Butyl, *tert*-amyl,** and **3-methylpentyl 3-peracetate** were prepared analogously. This method gave good yields, ca. 70%, of high purity (>95%) peroxy ester. ***tert*-Butyl performate** was prepared according to the method of Rüchardt and Hecht.[18] Double distillation failed to remove the *tert*-butyl hydroperoxide impurity which was present to the extent of ~15%. ***tert*-Butyl perpicolinate,** 95%, was prepared by treating the 1,4-diazobicyclo[2.2.2]octane (Dabco) salt of *tert*-butyl hydroperoxide with 2-picolyl chloride hydrochloride. ***tert*-Butyl perbenzoate,** 99%, and ***tert*-butyl permaleate,** 98%, were obtained from Lucidol Corp., Buffalo, N.Y.

General Procedure for Reactions of Peroxy Esters with Magic Acid. To a vigorously stirred (vortex mixer) solution of a 5-mol excess of magic acid (1:1 FSO_3H–SbF_5) in SO_2ClF at dry ice–acetone temperature (ca. −78 °C) an SO_2ClF solution of the peroxy ester (ca. 0.5 g) was added slowly in small portions. The resulting solution was then transferred at the same temperature into the precooled NMR probe for study.

NMR Spectroscopic Study. ^1H NMR spectra were obtained in a Varian Associates Model A56/60-A spectrometer equipped with a variable temperature probe. ^{13}C NMR spectra were obtained on a Varian Associates Model XL-100 spectrometer equipped with a broad band decoupler and variable temperature probe. Operational parameters were as described previously.

Acknowledgment. Support of our work by the National Institutes of Health and the National Science Foundation is gratefully acknowledged.

Registry No.—Magic acid, 23854-38-8; *tert*-butyl hydroperoxide Dabco salt, 60512-74-5; picolinic acid chloride HCl, 39901-94-5.

References and Notes

(1) (a) Part 4: G. A. Olah, N. Yoneda, and D. G. Parker, *J. Am. Chem. Soc.*, in press. (b) Postdoctoral Fellows.
(2) (a) G. A. Olah, D. G. Parker, N. Yoneda, and F. Pelizza, *J. Am. Chem. Soc.*, **98**, 2245 (1976); (b) N. C. Deno, W. E. Billups, K. E. Kramer, and R. R. Lastomirsky, *J. Org. Chem.*, **35**, 3080 (1970); (c) D. Swern, "Organic Peroxides", Vo . II, Wiley, New York, N.Y., 1971, p 65; (d) J. B. Lee and B. C. Off, *Q. Rev., Chem. Soc.*, **21**, 429 (1967); (e) A. G. Davies, "Organic Peroxides", Butterworths, London, 1961; (f) B. C. Hawkins, "Organic Peroxides", Van Nostrand, Princeton, N.J., 1961.
(3) D. G. Farnum, G. Mehta, and R. G. Silberman, *J. Am. Chem. Soc.*, **89**, 5048 (1967).
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(6) R. Criegee, *Justus Liebigs Ann. Chem.*, **560**, 127 (1948).
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A Convenient and Efficient Preparation of Aromatic α-Hydroperoxy Acids via Oxygenation of α-Lithio Enolates, Prepared by Direct α-Lithiation of Arylacetic Acids[1]

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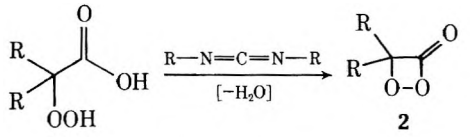
Direct α-lithiation of aromatic acetic acids by *n*-butyllithium in THF at −40 °C affords essentially quantitatively lithium α-lithiocarboxylates. The method can be employed as a convenient titration of alkyllithiums. α-Deuteration and bistrimethylsilylation of the α-lithiocarboxylates takes place essentially quantitatively. These are reliable electrophiles for the quantitative determination of the α-lithiocarboxylates. Direct oxygenation at room temperature affords good yields of the respective α-hydroxy acids, while reaction with molecular oxygen at dry ice temperature by inverse addition is an excellent method for the preparation of α-hydroperoxy acids derived from arylacetic acids.

α-Hydroperoxy acids **1**, which on cyclodehydration serve as precursors to α-peroxylactones **2** (eq 1),[3] are extremely



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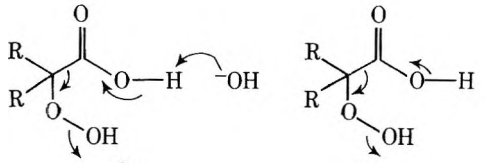
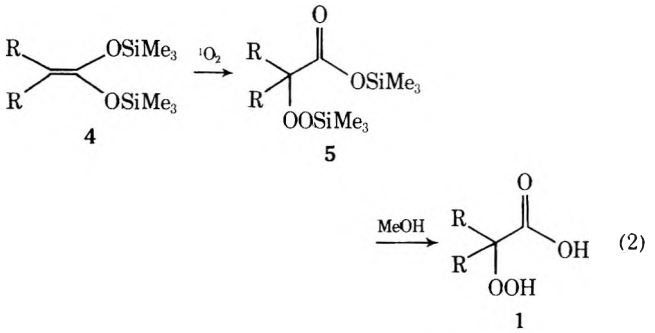


base- and acid-sensitive compounds in view of the facile Grob-type fragmentations[4] depicted in the respective transition states **3a** and **3b**. Since these decarboxylations efficiently destroy the α-hydroperoxy acids **1**, it was essential to circumvent this problem by working under neutral conditions. We took advantage of the oxygenophilic propensity of the trimethylsilyl group and prepared a number of α-hydroperoxy acids **1** by singlet oxygenation of ketene bis(trimethylsilyl) acetals **4** and subsequent desilylation of the peroxy ester **5** with methanol (eq 2). Analogous silatropic shifts have been ob-



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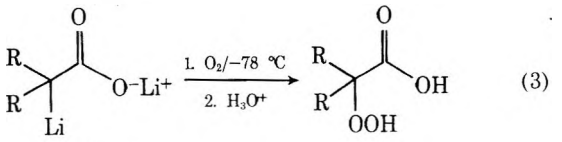
served in the singlet oxygenation of trimethylsilyl enol ethers.[5]

This novel α-hydroperoxylation lacks unfortunately generality since the classical prototropics shifts (ene reaction) compete with the silatropic shift when R is a nontertiary alkyl group[6] in the ketene acetal **4**. When R is an aromatic group, the classical [2 + 4] cycloaddition of the styryl unit with singlet oxygen competes.[7]

Recently, we and others[8] have shown that α-lithio enolates can be directly oxygenated to afford α-hydroperoxy acids **1** after acidification (eq 3). Unfortunately, this most direct α-



(3)

oxygenation is limited to nonaromatic substrates since an attempt to α-oxygenate α-lithio-α-phenylacetate gave only decomposition and reduction products.[8b] To suppress the Grob fragmentation process, since benzaldehyde was the major product, we did not use hexamethylphosphoramide (HMPA) and pumped off the diisopropylamine prior to α-oxygenation. While this process gave significantly improved results for the lower α-alkyl- and α,α-dialkylacetic acids, only poor yields of impure α-hydroperoxy acids could be realized for phenylacetic acid.[9] It was clear to us that even traces of amines exerted detrimental effects in the preparation of α-hydroperoxy acids derived from arylacetic acids via α-lithiation with lithium diisopropylamide (LDA).

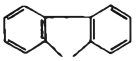
Although aliphatic carboxylates form ketones on treatment with alkyllithiums,[10] Ivanov and colleagues demonstrated[11] that arylacetates can be α-lithiated with alkyllithiums directly; however, generally the yields were poor (19–35%). It was not clear whether the metalation process worked poorly or whether the titration of the α-lithioacetates with electrophiles was inefficient. Since it was critical for the α-oxygenation process that the α-lithio enolates were formed in high purity and high yield, in order not to encumber the purification of the labile α-hydroperoxy acids **1**, we undertook the present investigation on the α-lithiation of arylacetic acids, and for comparison alkylacetic acids, with *n*-butyllithium.[12] Electrophilic substitution with deuterium oxide, trimethylsilyl chloride, benzophenone, and molecular oxygen was used for diagnosing the efficiency of α-lithioacetate formation. In the latter case, inverse addition at low temperature should afford α-hydroperoxy acids,[8] while normal addition at room temperature should lead to α-hydroxy acids.[13]

Experimental Section

All commercially available solvents, starting materials, and authentic samples for product comparison were rigorously purified according to literature procedures. Boiling points and melting points are uncorrected; the latter were determined on a Thomas-Hoover melting apparatus. The infrared spectra were measured on a Perkin-Elmer Model 237B Infracord. The NMR spectra were taken on a Varian T60 or Hitachi Perkin-Elmer R-24B spectrometer.

α-Lithiation. A 100-ml round-bottom flask with side arm, provided with a spinbar, was attached to a nitrogen manifold and protected with a rubber septum. After flame drying under a nitrogen atmosphere, by means of a calibrated syringe 1.4 mmol of the carboxylic acid in 30 ml of anhydrous THF was introduced through the serum

Table I. Yields of Electrophilic Substitution Products of Lithium α-Lithiocarboxylate (6) in THF

System	R_1	R_2	7 % yield[a]	7 % D[b]	8 % yield	4 % yield	9 % yield	1 % yield	1 % perox[d]
a	Ph	H	83	95	81	80	86	82	96
b	Ph	Ph	85	100	0[c]	77	75	67	95
c			87	95	0[c]	95[b]	70	66	92
d	*t*-Bu	H	77	58	14	32[b]			
e	Me	Me	69	50	28[b]	18[b]			

[a] Calculated on the basis of recovered acid. [b] Determined by NMR. [c] Not even traces of β-hydroxy acids could be detected by TLC. [d] Determined by iodometry; recrystallized pure product ca. 30%.

cap. The contents were cooled to −60 °C by means of a dry ice/acetone bath and while stirring magnetically a stoichiometric amount of standardized *n*-butyllithium in *n*-hexane (1.8–2.4 M) was injected dropwise by means of a calibrated syringe (ca. 5 min) to prepare the lithium carboxylate. After 60 min the reaction mixture was warmed to −40 °C and the second mole of *n*-BuLi was added dropwise from the same syringe. During this stage the pale yellow lithium carboxylate solution turned an intense dark red color, indicating that the α-lithiocarboxylate had formed. The reaction mixture was stirred for an additional 100 min at −40 °C to complete the α-lithiation and used for the electrophilic substitution reaction described below.

α-Deuteration. To the above prepared lithium α-lithiocarboxylate solution in THF was added dropwise, while stirring magnetically and cooling at −40 °C, about a 200 molar excess of deuterium oxide (99.8% deuterium) by means of a syringe. The α-lithiocarboxylate color immediately disappeared. After 60 min of stirring at −20 °C (a control experiment showed that hydrogen–deuterium exchange at the α position was negligible!), the solvent and excess D_2O was rotoevaporated (ca. 10 °C, 2 mm) and the residue acidified with 10% aqueous HCl, extracted with 4 × 5 ml of ether, and dried over $MgSO_4$. Rotoevaporation (ca. 30 °C, 25 mm) of the ether and NMR analysis of the crude α-deuterated acid **7** for residual α hydrogens gave the percent deuteration summarized in Table I. Fractional distillation or recrystallization was not necessary since the recovered acid was pure by NMR.

α-Diphenylhydroxymethylation. To the above prepared α-lithiocarboxylate solution in THF was added dropwise, while stirring magnetically and cooling at −40 °C by means of a dry ice/acetone bath, stoichiometric amounts of benzophenone in 10 ml of anhydrous THF by means of a syringe and the solution was stirred for 10 h at room temperature (ca. 30 °C). The THF was rotoevaported (ca. 30 °C at 20 mm), the residue hydrolyzed with 10% HCl and extracted with 4 × 5 ml of CH_2Cl_2, and the combined extracts dried over $MgSO_4$, and rotoevaporation (ca. 30 °C 25 mm) of the solvent afforded the crude α-hydroxy acid **8**. Final purification by recrystallization or fractional distillation at reduced pressure gave the pure β-hydroxy acids **8**, confirmed by the reported physical constants and ir and NMR spectral data. The results are summarized in Table I.

O,O-Bistrimethylsilylation. To the above prepared α-lithiocarboxylate solution in THF was added dropwise, while stirring magnetically and cooling at −40 °C by means of a dry ice/acetone bath, a 10% molar excess of trimethylsilyl chloride by means of a syringe and the solution was stirred at −40 °C for 2 h. The THF was rotoevaporated (ca. 30 °C, 20 mm) and the residue molecularly distilled at 0.01 mmHg to afford the pure ketene acetal **4** (Table I).

α-Hydroxylation. Through the above prepared α-lithiocarboxylate solution in THF was bubbled a fast stream of dry oxygen gas by means of a stainless steel capillary (12 G), while stirring magnetically at ca. 20 °C. The α-oxycarboxylate precipitated from the reaction mixture. The THF was rotoevaporated (ca. 30 °C, 20 mm) and the residue hydrolyzed with 10% aqueous HCl. Extraction with 4 × 5 ml of ether, drying of the combined ether extracts with anhydrous $MgSO_4$, rotoevaporation (ca. 30 °C, 25 mm) of the ether, and recrystallization gave the pure α-hydroxy acid, confirmed by the reported physical constants and ir and NMR data (Table I).

α-Hydroperoxylation. Into a 100-ml round-bottom flask with side arm, provided with a magnetic stirrer, attached to the nitrogen manifold and protected with a rubber septum, were placed 50 ml of anhydrous THF, cooled to −78 °C by means of a dry ice/acetone bath, and saturated with dry oxygen gas by means of a 12G stainless steel capillary. With magnetic stirring, continuous bubbling of oxygen, and cooling at −70 °C, by means of a 12G stainless steel capillary syphon the above prepared α-lithiocarboxylate solution was added dropwise over a period of 110 min. After 30 min of stirring at −78 °C, the reaction mixture was hydrolyzed (controlling the temperature rigorously) by adding 10% aqueous HCl dropwise by means of a syringe. The reaction mixture was allowed to warm up to 5 °C, transferred to a separatory funnel, diluted with two volumes of ice, and extracted with 6 × 10 ml of ether, keeping the temperature below 10 °C by adding ice. The combined ether extracts were dried over $MgSO_4$ in the refrigerator, and the ether rotoevaporated (10°C, 10 mm) until solidified α-hydroperoxy acid **1** remained. The last traces of solvents (THF) were removed at 10 °C (0.1 mm). The peroxide content was determined by iodometric titration and the pure α-hydroperoxy acid obtained by recrystallization. The results are summarized in Table I and the experimental data for each system described below.

α-Hydroperoxyphenylacetic acid (1a) was obtained in 82% yield of crude product (by iodometry) and three times recrystallized from ether/benzene, mp 96–97 °C dec, 96% iodometric titer. The spectral data follow: ir (KBr) 3500–2800 (–OOH and $-CO_2H$), 1725 (C=O), 700 cm^{-1} (monosubstituted aromatic); NMR (60 MHz, $CDCl_3$) δ (Me_4Si) 5.53 (1 H, s, α-H), 6.82 (2 H, s, –OOH and $-CO_2H$, broad), and 7.44 (5 H, m, C_6H_5, broad).

α-Hydroperoxydiphenylacetic acid (1b) was obtained in 67% yield of crude product (by iodometry) and three times recrystallized from ether–benzene, mp 100–102 °C dec, 95% iodometric titer. The spectral data follow: ir (KBr) 3500–2800 (–OOH and $-CO_2H$), 1725 (C=O), 700 cm^{-1} (monosubstituted aromatic); NMR (60 MHz, $CDCl_3$) δ (Me_4Si) 7.40 (10 H, m, C_6H_5, broad).

9-Hydroperoxy-9-fluorenecarboxylic acid (1c) was obtained in 66% yield of crude product (by iodometry), and recrystallized three times from ether–benzene, mp 126–128 °C dec, 92% iodometric titer. The spectral data follow: ir (KBr) 3500–2800 (–OOH and $-CO_2H$) and 1720 cm^{-1} (C=O); NMR (60 MHz, CD_3COCD_3) δ (Me_4Si) 6.00 (2 H, s, –OOH and $-CO_2H$, broad) and 7.40 (8 H, m, aromatic CH, broad).

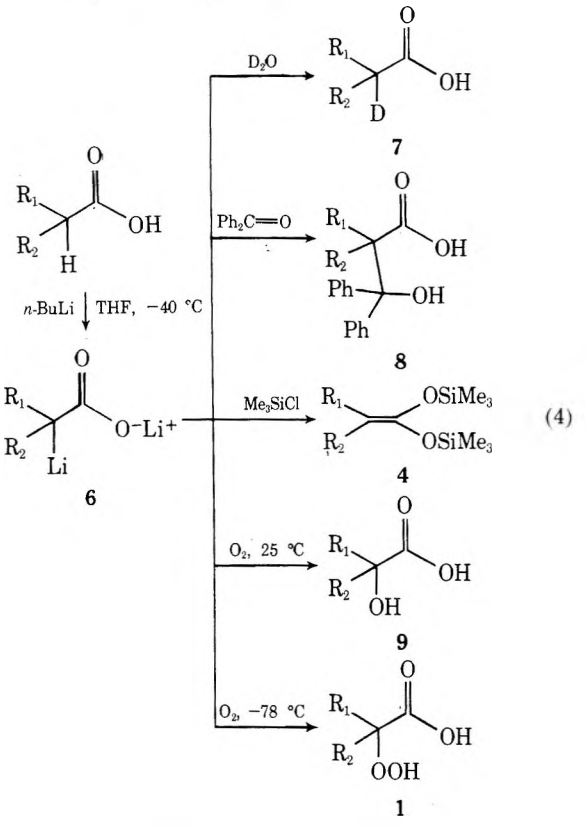
Discussion

The results of Table I clearly reveal that essentially quantitative α-lithiation of arylacetic acids with *n*-BuLi is feasible. In fact, we have used this process as a convenient method for titration of alkyllithiums. However, the end point is not sharp and the titer is at best within 5% reliable.[12]

For nonaromatic acids only fair results are obtained. Even under the optimized conditions of Table I, due to the reduced acidity of the α hydrogen, substantial carbonyl attack by the alkyllithium takes place, affording the respective alkyl ketones. For example, at lower temperatures (−78 °C) very little reaction, i.e., neither α-lithiation nor carbonyl addition, was observed since the acid was recovered unchanged in high yield. At higher temperatures (0 °C) an increased amount of carbonyl addition was observed. The use of *tert*-butyllithium did

not improve the yield of α-lithiation; on the contrary, more carbonyl addition took place.

The various electrophilic substitution processes are summarized in eq 4. Deuterium oxide and trimethylsilyl chloride



(4)

are excellent electrophiles for titrating the α-lithiocarboxylates. On the basis of NMR data, essentially quantitative deuteration and trimethylsilylation takes place. Since both are hard electrophiles, the attack takes place on oxygen rather than carbon and steric factors are minimized. For example, the significance of steric factors is dramatically exposed in the reaction of the α-lithiocarboxylates with benzophenone. Not even traces of the α-hydroxy acids **8b** and **8c** could be detected and only low yields of **8d** and **8e** could be isolated. Hydroxymethylation with ketones or aldehydes is not recommended for the titration of α-lithiocarboxylates.

Molecular oxygen, a soft electrophile, as expected affords high yields of the desired α-hydroxy and α-hydroperoxy acids, depending on the reaction conditions. Since the oxygen molecule is a relatively small electrophile, α-attack is unobstructed. Although this direct α-peroxylation of α-lithiocarboxylates is a convenient and efficient preparation of α-hydroperoxy acids derived from arylacetic acids, great care must be exercised in their isolation in view of their labile nature toward thermal, acid-, and base-catalyzed decarboxylation. Presently we are extending this method to other hitherto unavailable α-hydroperoxy acids which are of interest in biological oxidations.

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Registry No.—**1a**, 60538-67-2; **1b**, 60538-68-3; **1c**, 60538-69-4; **6a**, 60538-70-7; **6b**, 60538-71-8; **6c**, 60538-72-9; benzeneacetic acid, 103-82-2; α-phenylbenzeneacetic acid, 117-34-0; 9*H*-fluorene-9-carboxylic acid, 1989-33-9; *n*-butyllithium, 109-72-8.

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Chemiluminescence from Base-Catalyzed Decomposition of α-Hydroperoxy Esters. Dioxetanone Mechanism[1]

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Chemiluminescence (CL) was observed from the methoxide-catalyzed decomposition of six α-hydroperoxy esters **4a–f** in the presence of fluorescein in MeOH. The quantum yields (Φ) of the CL were in the range of 5×10^{-6} to 3×10^{-4} and increased linearly with increasing concentration of fluorescein. Although the decomposition of 4 was dramatically accelerated by addition of water, the CL intensity remained constant, and hence Φ was significantly reduced. This suggests that the major reaction is the hydrolytic decomposition and the CL comes from a minor reaction involving no HO^- ion. The efficiency of fluorescers was in the order of fluorescein ≃ eosin ≫ diphenylanthracene > dibromoanthracene. These results were discussed in connection with a mechanism of CL involving a charge-transfer complex between dioxetanone (**3**) and fluorescers. This mechanism differs from the reported CL from the spontaneous decomposition of 3 producing a triplet ketone.

1,2-Dioxetanes (**1**)[2] and 1,2-dioxetanedione (**2**)[3] are well known as intermediates or potent starting materials for chemiluminescence. 1,2-Dioxetanones (**3**) were synthesized[4b] from α-hydroperoxy acids and shown to be luminescent.[4-6]

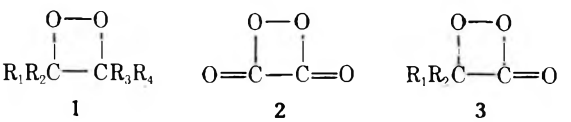

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Table I. Chemiluminescence from Base-Catalyzed Decomposition of α-Hydroperoxy Esters (4) at 40 °C [a]

Peroxide (R_2)	Solvent[b]	$10^5 k_{obsd}$,[c] s^{-1}	Fluorescer[d]	Rel I[e]	$10^6 \Phi_{obsd}$	$10^6 \Phi$[f]
		A. Effect of Fluorescers				
4a (Ph)	MeOH	5.72	Fl	20	4.2	280
	MeOH	5.72	Eosin	6.0	1.25	320
	MeOH	5.72	DPA	<0.1	<0.02	<0.02
	MeOH	5.72	DBA	0.0	0.00	0.00
4c (*i*-Pr)	MeOH	4.5	Fl	8.7	2.3	160
	MeOH	4.5	DPA	~0.7	~0.07	~0.08
	MeOH	4.5	DBA	0.0	0.00	0.00
		B. Effect of Solvents and Temperature				
4a (Ph)	MeOH	5.72	Fl	20	4.2	280
	90% MeOH	103[g]	Fl	20	0.23	15.5
	50% MeOH	612	Fl	~20	~0.039	~2.7
	MeOH (25 °C)	0.54	Fl	~2.0	~4.4	~300
4c (*i*-Pr)	MeOH	4.5	Fl	8.7	2.3	160
	50% MeOH	47.4	Fl	20.6	0.52	35
		C. Effect of Substituents				
4a (Ph)	MeOH	5.72	Fl	20	4.2	280
4c (*i*-Pr)	MeOH	4.5	Fl	8.7	2.3	160
4b (Ph)	MeOH	4.8	Fl	4.7	1.2	80
4f ($PhCH_2$)	MeOH	4.8	Fl	1.1	0.3	20
4d (Et)	MeOH	2.9	Fl	0.5	0.19	13
4e (Me)	MeOH	11.8	Fl	0.7	0.07	5

[a] Reaction with 0.01 M 4 and 0.25 M MeONa. [b] MeOH is pure MeOH and percent is volume percent of aqueous MeOH. [c] Rate constants of overall decomposition determined by iodometry. [d] Fluorescer of 0.0025 M concentration; Fl = fluorescein, DPA = diphenylanthracene, and DBA = dibromoanthracene. [e] Initial relative intensity of chemiluminescence. [f] $\Phi = \Phi_{obsd}/\Phi_F^A$; $\Phi_F^A = 0.0147$ with 0.0025 M Fl, 0.0039 with 0.0025 M eosin, and 0.85 with 0.0025 M DPA. [g] Rate constant from the CL decay was 1.1×10^{-3} s^{-1}, which is close to that by iodometry.

The decomposition of **3** is also interesting in relation to the chemi- and bioluminescence of luciferins.[7] Here we wish to report chemiluminescence from the base-catalyzed decomposition of simple α-hydroperoxy esters (**4**), where the luminescence is probably via a complex composed of **3** and an added fluorescer.

$R_1R_2CCO_2R_3$ (OOH) — **4**

	R_1	R_2	R_3
a	Ph	Ph	Me
b	Ph	Ph	Et
c	Ph	*i*-Pr	Me
d	Ph	Et	Me
e	Ph	Me	Me
f	Ph	$PhCH_2$	Me

(Ph = C_6H_5)

Results

α-Hydroperoxy esters (**4**) decompose gradually on addition of sodium methoxide in MeOH to give ketones and the pseudo-first-order rate constants k_{obsd} were determined by iodometry.

$$v = k_{obsd}[4]_s \quad (1)$$

Here, $[\ ]_s$ denotes stoichiometric concentration. The validity of eq 1 was confirmed for the case of **4a**; the k_{obsd} values were constant up to 80% conversion and at various initial concentrations of 0.005, 0.01, and 0.02 M. The rate constant of decomposition was not altered by addition of EDTA.

The addition of water to the MeOH solution greatly increased the rate (Table IB). This hydrolytic decomposition is known to proceed via hydrolysis of α-peroxy esters leading eventually to ketones and carbon dioxide.[8]

Effect of Fluorescers. Although the reaction of **4** with MeONa is nonluminescent, the addition of fluorescers led to chemiluminescence (CL) as shown in Table IA. The CL with xanthene dyes (fluorescein and eosin) was considerably strong, while the CL with diphenylanthracene (DPA) and dibromoanthracene (DBA) were weak or undetectable. Bubbling of nitrogen had no effect.

Quantum yield of the CL was calculated according to eq 2 and 3 (reaction volume is always 3 ml in a quartz cell 1 cm long):

$$\Phi_{obsd} = \frac{I}{k_{obsd}[4]_s \times 6 \times 10^{23}} \quad (2)$$

$$\Phi = \Phi_{obsd}/\Phi_F^A \quad (3)$$

Here, I is the number of photons produced per second and Φ_F^A is the apparent fluorescence quantum yield of a fluorescer at the experimental concentrations (see the Experimental Section for details). The Φ value thus obtained is ca. 3×10^{-4} (i.e., 0.03%) for the case of **4a** and fluorescein or eosin at 40 °C (Table IA and B).

The relative intensity of the CL (rel I) from **4a** with 0.025 M fluorescein (Fl) is proportional to $[4a]_s$ at the concentrations of 5–20 mM. On the other hand, rel I increased with increasing [Fl] up to ca. 2 mM and then decreased. But the resulting Φ increased with increasing [Fl] after correcting the fluorescence efficiency of Fl according to eq 3 (Table II).

The use of eq 2 was justified by the proportionality of rel I vs. [4] and also by the identity of the rate constant from rel I with that from iodometry (see Table IB).

Effect of Solvents and Substituents. The decomposition rate (k_{obsd}) of **4** in aqueous MeOH is much faster than that in MeOH, while the CL intensity remains constant (Table IB). This leads to a considerable decrease in the Φ value in aqueous MeOH. The decay curve of rel I in aqueous MeOH was identical with the one by iodometry.

Similar luminescence is observed for other α-hydroperoxy esters. Although the overall decomposition rate constants

Table II. Effect of [Fl] on the CL of 4a in MeOH at 40 °C [a]

[Fl], 10^3 M	$\Phi_F{}^A$ [b]	Rel I[c]	$10^6\ \Phi_{obsd}$	$10^4\ \Phi$[d]
0.322	0.45	4.30	0.90	0.020
0.625	0.101	7.85	1.64	0.162
0.910	0.027	10.5	2.20	0.81
1.18	0.026	12.7	2.65	1.02
1.43	0.023	14.5	3.02	1.32
2.00	0.0175	16.3	3.40	1.95
2.50	0.0147	19.6	4.10	2.8
5.0	~0.011	20.0	4.17	~3.8
12.5		12.4	2.58	

[a] Reaction with [4a] = 0.01 M, [MeONa] = 0.25 M, and Fl = fluorescein. [b] Fluorescence yield of fluorescein at the concentration indicated. [c] Relative intensity of the initial CL. [d] $\Phi = \Phi_{obsd}/\Phi_F{}^A$.

(k_{obsd}) are of the same order, the quantum yields are in the range of 10^{-4}-10^{-6}, the order being **4a** > **4c** > **4b** > **4f** > **4d** > **4e** (Table IC).

Effect of [MeONa]. The CI was affected by base concentrations; the rel I of **4a** increased and then decreased with increasing [MeONa], resulting in a maximum intensity at ca. 50 mM MeONa (Table III). This relationship is in contrast with that for α-hydroperoxy ketones, which has no maximum.[9,10]

Discussion

Hydrolysis and a Dioxetanone Mechanism. The base-catalyzed decomposition of α-peroxy esters to ketones and carbon dioxide in aqueous solution proceeds via the hydrolysis of the esters,[8] and the reaction with alkoxide ion in alcohol–benzene exhibits a preliminary transesterification without the decomposition of the peroxy group.[11] The latter fact together with the facile decomposition in aqueous MeOH suggests that the base-catalyzed decomposition of **4** proceeds predominantly via the hydrolyzed α-peroxy acid (**5**) (eq 7). Since methanol contains a trace amount of water, the decomposition in MeOH also proceeds mainly via eq 7.

No luminescence was observed with α-alkylperoxy esters.[8a] In contrast, the observation of CL from α-hydroperoxy esters suggests an intervention of a dioxetane intermediate. In spite of the acceleration in the decomposition of **4** by the addition of water, i.e., HO^-, the initial CL intensity remains constant. This indicates that the luminescence (eq 5 and 6) is competitive with the nonluminescent decomposition via hydrolysis (eq 7). These facts and the appearance of a maximum in the plot of rel I vs. [MeONa] (curve A in Figure 1) can be explained by the following sequences and considerations.

$$\underset{\text{OOH}}{\underset{|}{R_1R_2CCO_2Me}} + MeO^- \overset{K_4}{\rightleftharpoons} \underset{\text{OO}^-}{\underset{|}{R_1R_2CCO_2Me}} + MeOH \quad (4)$$

4 **4A**

$$\underset{\text{OO}^-}{\underset{|}{R_1R_2CCO_2Me}} \overset{k_5}{\underset{k_{-5}}{\rightleftharpoons}} \underset{\text{O—O}}{\underset{|}{R_1R_2C—C=O}} + MeO^- \quad (5)$$

4A **3**

$$3 + Fl \xrightarrow{k_6} R_1R_2C{=}O + CO_2 + Fl^* \text{ (CL)} \quad (6)$$

$$4 + HO^- \xrightarrow{k_7} \underset{\text{OOH}}{\underset{|}{R_1R_2CCO_2^-}}$$

5

$$\longrightarrow R_1R_2C{=}O + CO_2 + HO^- \text{ (no CL)} \quad (7)$$

Table III. Effect of [MeONa] on the CL of 4a in MeOH at 40 °C [a]

[MeONa], M	Rel I[b]	[MeONa], M	Rel I[b]
0.0084	10.1	0.054	25.7
0.0140	17.7	0.125	23.4
0.0196	22.3	0.250	20.4
0.028	23.8	0.500	10.6

[a] Reaction with 0.005 M **4a** and 0.0025 M fluorescein. [b] Relative intensity of the initial CL.

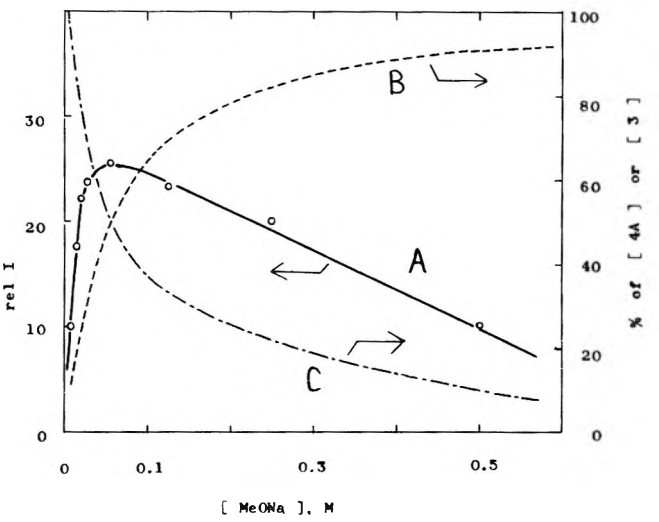

Figure 1. Effect of [MeONa] on the CL from the basic decomposition of **4a** (see Table III for the conditions); A, initial rel I vs. [MeONa]; B, % of [4A] vs. $[4]_s$; C, % of [3] vs. $[3]_0$ at [MeONa] = 0 (see text, eq 9 and 10).

From a steady-state assumption of dioxetanone **3** the concentration of **3** is expressed as

$$[3] = \frac{k_5[4A]}{k_{-5}[MeO^-] + k_6[Fl]} = \frac{k_5K_4[MeO^-][4]_s}{(k_{-5}[MeO^-] + k_6[Fl])(K_4[MeO^-] + 1)} \quad (8)$$

Here, $K_4[4][MeO^-] = [4A]$ and the K_4 value is 18 M^{-1} in MeOH and 26 M^{-1} in 75% MeOH at 20 °C.[12] If $k_{-5}[MeO^-] \ll k_6[Fl]$ at low $[MeO^-]$ (i.e., equilibrium 5 is not established),

$$[3] = \frac{k_5K_4[MeO^-][4]_s}{k_6[Fl](K_4[MeO^-] + 1)} \quad (9)$$

Since the CL intensity is proportional to [3] (i.e., rel I $\propto k_6[3]$), eq 9 can explain the increasing CL at lower $[MeO^-]$ (i.e., curve B in Figure 1). If $k_{-5}[MeO^-] \gg k_6[Fl]$ at higher $[MeO^-]$,

$$[3] = \frac{K_4K_5[4]_s}{K_4[MeO^-] + 1} \quad (10)$$

The observed decrease of rel I at higher concentrations of base (curve C in Figure 1) can be explained by eq 10, where K_4 = 18 M^{-1} [12] and $K_5 = k_5/k_{-5}$.

The observed maximum in Figure 1 can thus be explained by eq 9 at lower base concentrations and by eq 10 at higher ones. A quantitative treatment is, however, impossible because of unknown values of k_5 and k_{-5}.[13]

The effect of substituents on Φ shows the order **4a** > **4c** > **4f** > **4d** > **4e**, which seems to reflect the bulkiness (e.g., Taft's E_s value) of R_2 group; i.e., E_s values being in the order Ph > *i*-Pr > $PhCH_2$ > Et > Me. The order in Φ can be explained by the competition between the major hydrolytic decomposition (eq 7) and the CL one (eq 5 + eq 6). That is, the intramolecular

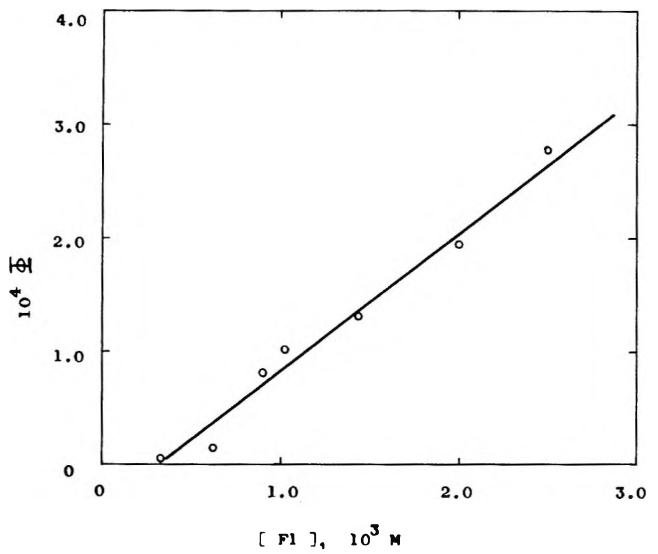

Figure 2. Dependence of the CL yields (Φ) on [Fl] from the basic decomposition of **4a** (see Table II for the reaction conditions; Fl = fluorescein).

C=O addition (k_5) is probably less sensitive to the steric hindrance than the intermolecular one (k_{-5} and/or k_7).[14] Thus the CL yields are higher for hydroperoxy esters bearing larger groups. A more quantitative argument is, however, is impossible at present because of the unknown values of k_5, k_{-5}, k_6, and the quantum yield for eq 6.

Chemiluminescence Precursor. The thermolysis of tetramethyldioxetane (**1**, $R_1 = R_2 = R_3 = R_4 = Me$)[2c] and dimethyldioxetanone (**3**, $R_1 = R_2 = Me$)[4c,5] yields mostly triplet acetone (over 95%), the overall Φ being 0.2 for the dioxetanone. The CL from the base-catalyzed decomposition of α-hydroperoxy ketones shows also a predominant formation of triplet acetone, the CL intensity with various fluorescers being in the order of DBA ≫ DPA ~ fluorescein;[10] the high efficiency of DBA suggests the formation of a triplet ketone.[5]

On the other hand, the present case of α-hydroperoxy esters showed the reverse order of fluorescein ≃ eosin ≫ DPA > DBA and the Φ values are 10^3–10^4 times less than the neutral thermolysis of **3**. No observation of the CL with DBA suggests that no triplet ketone (^{T}C=O) is formed. This indicates also no formation of singlet ketone (^{S}C=O), if any, for the present case of aromatic ketones, since the intersystem crossing from ^{S}C=O to ^{T}C=O is fast and efficient.[15]

When an energy transfer from a short-lived precursor to a fluorescer is concerned, a linear relationship is usually observed between $1/\Phi$ and $1/[Fl]$.[16] But, for the present case of **4a** and fluorescein, the plot of $1/\Phi$ vs. $1/[Fl]$ is not linear and a linear relationship is observed between Φ and [Fl] (Figure 2). The failure of the plot in Figure 2 to pass through 0.0 may be allowed in view of the experimental error (±20%) in Φ values. The relation in Figure 2 is explicable by assuming a charge-transfer (C-T) complex between dioxetanone **3** and fluorescer (Fl).[3]

$$3 + Fl \rightleftarrows \text{C-T complex} \rightarrow R_1R_2C{=}O + CO_2 + Fl^* \quad (11)$$

Thus, the rate of formation of Fl* (i.e., rel I) is proportional to the product of [3] and [Fl] as is the case.

The assumption of the C-T complex (eq 11) seems to explain the effective luminescence with the xanthene dyes. That is, the ionization potential (IP) of aromatics is correlated with σ^+ to give a negative ρ value,[17a] and hence the IP of xanthene dyes with a strongly electron-donating group ($-O^-$) is considerably low.[17b] A similar C-T complex mechanism has been suggested for the luminescence from dioxetanedione **2**[3] and dioxetanone **3**.[4a] Since such a complex was not detected for the case of dioxetane **1**,[18] the attachment of the electron-attracting carbonyl group seems to be necessary for the formation of the C-T complex as is the case of **2** and **3**. In conclusion, the present CL can well be rationalized by the sequences of eq 4, 5, and 11.

A reason follows for the operation of the C-T complex mechanism, while dioxetanones have an energy transfer mechanism via triplet ketone formed in the high yield by the thermolysis of **3** at room temperature.[4,5] Although the lifetimes of dioxetanones are several minutes or longer in neutral solvents,[4,6] the steady-state concentration of **3** under the basic condition is probably reduced by its facile reverse reaction with MeO^- (k_{-6} in eq 5). This makes the C-T mechanism (eq 4, 5, and 11) an only effective CL scheme and reduces the spontaneous decomposition of **3** to produce ^{T}C=O, which is contrary to the reported case.[5]

Experimental Section[19]

Materials. Starting esters, $R_1R_2CHCO_2Me$, were rectified after the reaction of methyl phenylacetate, alkyl halide, and *t*-BuOK (molar ratio of 1:1:1.2) in *t*-BuOH-DMF (1:5) under nitrogen (30 min at room temperature). Alkyl halides, MeI, EtBr, *i*-PrBr, and $PhCH_2Cl$, gave 60–90% yields of the esters, boiling points being 118–121 °C (25 mm) [lit.[20] 115 °C (24 mm)], 110–112 °C (12 mm) (lit.[21] 225–226 °C), 113–116 °C (14 mm),[22] and 147–150 °C (1.5 mm) [lit.[24] 123–124 °C (0.2 mm)], respectively.

α-Hydroperoxy esters, **4a** and **4b**, are reported previously.[11] The other peroxides, **4c–f**, were synthesized by method I in the previous report[11] in 30–70% yields. Peroxide **4f** was recrystallized from benzene–petroleum ether (2:1), melting point 107–108 °C (lit.[8b] 109 °C). Liquid peroxides, **4c–e**, were purified by passing through a column of Florisil using *n*-hexane–dichloromethane as an eluent.

Iodometry[11] showed over 95% purity of the peroxides. The structures of α-hydroperoxy esters were supported by the following NMR spectra (δ, CCl_4): for **4e** (R_2 = Me), 1.83 (s, 3 H), 3.06 (s, 3 H), 7.1–7.4 (m, 5 H), 9.28 (s, 1 H); for **4d** (R_2 = Et), 0.80 (t, 3 H, J = 7.5 Hz), 2.21 and 2.26 (two q, 2 H, J = 7.5 Hz), 3.65 (s, 3 H), 7.1–7.4 (m, 5 H), 8.63 (broad s, 1 H); for **4c** (R_2 = *i*-Pr), 0.80 and 0.95 (two d, 6 H, J = 6 Hz), 2.34 (septet, 1 H, J = 6 Hz), 7.1–7.6 (m, 5 H), 9.61 (s, 1 H). A characteristic downfield shift (δ 7–10) of the hydroperoxy proton has already been mentioned.[11]

Chemiluminescence. The CL was monitored by a Hitachi MPF-2A fluresecence spectrophotometer using a 4-ml quartz cell (1-cm path length). Usually, the decomposition of **4** was moderate at 40 °C and then the CL intensity was practically constant for several minutes. When the decomposition was fast as was the case in aqueous MeOH, the initial I at time zero was determined from the plot of I vs. time. Reproducibility of the CL intensity was adequate (within ±20%) and the CL spectrum with fluorescein (E_{max} = 540 nm) recorded with slit width of 40 nm was identical with the fluorescence spectrum of the fluorescer under the same conditions.

The quantum yield was measured according to the literature method[25] using DPA and fluorescein. The incident light from Xe arc was determined by the ferrioxalate actinometry.[26] The quantum yield Φ was calculated from eq 2 and 3 using 3 ml of solution for all determinations.

Products. The methoxide-catalyzed decomposition of **4** in MeOH afforded 60–95% yields of ketones ($R_1R_2C{=}O$) by GLC analysis. Since further reactions (e.g., autoxidation) of the ketones produced also occurred, the yields were significantly lowered except for the case of benzophenone. Carbon dioxide was not determined since its formation is already reported.[8b]

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Registry No.—**4a**, 57272-44-3; **4b**, 25818-61-5; **4c**, 60538-63-8; **4d**, 60538-64-9; **4e**, 60538-65-0; **4f**, 60538-66-1.

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Steric Effects in Homogeneous Gas-Phase Reactions. Pyrolysis of Isopropyl Esters

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Absolute reaction rate constants have been determined in the pyrolysis of 18 isopropyl alkanoates to acids and propene in a very carefully deactivated stainless steel static reactor. Trisubstitution by alkyl groups at the α position of the acid moiety showed a small, but readily measurable, rate of acceleration. Substitution at the β position had no effect on the rate of pyrolysis. This rate acceleration was reflected in the entropy of activation. α-Phenyl and α-chloro substituents influence pyrolysis rates more than α-alkyl substituents and at least with the chloro substituent the effects are a combination of both steric and electronic.

The pyrolysis of esters, when studied in a very carefully deactivated reactor, has been demonstrated to be a homogeneous, first order, unimolecular reaction proceeding through a converted cyclic transition with a degree of charge separation between the oxygen and carbon. Removal of the β hydrogen is also part of the rate-determining step. The mechanism which has been proposed[2] explained all available data excepting some rearrangements which likely were not gas-phase reactions but surface-catalyzed reactions. Refinements to this mechanism have been presented by others.[3] There are, no doubt, many studies on ester pyrolysis which were thought to be gas-phase reactions but were carried out in unseasoned reactors, e.g., dropping the ester through a clean glass tube, which most likely were not homogeneous gas-phase reactions but rather were surface-catalyzed reactions resulting in different product ratios, rearrangements, and faster reaction rates than are found under strictly gas-phase reactions conditions.

There have been many studies dealing with the electron influences on the rate of pyrolysis,[4a] but only a very few which have dealt specifically with steric influences on pyrolysis rates. Studies of steric effects in the acid moiety are very limited. Tinkelenberg et al. included some steric effect studies in their paper on the polar nature of β-elimination reactions.[4b] Effects of electronic changes in the acid portion are known to be not nearly as influential as they are in the alkyl portion. This paper reports a study of changes in steric effects in the acid portion on the ease of ester pyrolysis and a report of some electronic effects studies.

Steric effects in unimolecular homogeneous gas-phase pyrolysis of esters are not expected to be pronounced and certainly not as great as found in bimolecular reactions such as found in mineral acid catalyzed esterification of carboxylic acids. However, a measure of the effects, if present, would reveal some interesting aspects about gas-phase pyrolysis mechanisms and the nature of steric interactions as well. In homogeneous gas-phase reactions, all solvent effects are excluded.

The absolute rate constants have been determined for 18 isopropyl esters in which the extent of substitutions at the α and β positions have been varied. The electronic effects by different alkyl groups are very similar. Therefore, any change in rate will reflect steric interactions. Although the high temperatures used in pyrolysis of esters (~378 °C) minimize substituent effects, small effects are readily detectable within experimental error when studies are made in a carefully deactivated reactor. Activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) were determined for the two esters (VII and VIII, Table I)

Table I. Synthetic and Pyrolysis Kinetic Data for Isopropyl Carboxylates

Registry no.	Isopropyl ester	Formula	Bp, °C (mm)	n^{20}D	Purity, %	Yield, %	$k \times 10^3$ at 651 K	$k_{alkanoate}/k_{acetate}$
108-21-4	I acetate[a]	$CH_3COOCH(CH_3)_2$	85 (640)	1.3783	98.1	30	5.93 ± 0.17	1.00
637-78-5	II propionate[b]	$CH_3CH_2COOCH(CH_3)_2$	108 (640)	1.3865	98.3	40	6.10 ± 0.20	1.03
638-11-9	III butyrate[c]	$CH_3(CH_2)_2COOCH(CH_3)_2$	125 (640)	1.3930	99.6	55	5.93 ± 0.27	1.00
18362-97-5	IV valerate[d]	$CH_3(CH_2)_3COOCH(CH_3)_2$	147.5 (640)	1.4002	97.3	7.2	5.97 ± 0.07	1.01
2311-46-8	V caproate[e]	$CH_3(CH_2)_4COOCH(CH_3)_2$	177 (640)	1.4072	96.3	18	6.03 ± 0.27	1.02
617-50-5	VI isobutyrate[f]	$(CH_3)_2CHCOOCH(CH_3)_2$	120.8 (640)	1.3873	98.6	62	6.80 ± 0.20	1.15
5129-36-2	VII pivalate (trimethylacetate)[g]	$(CH_3)_3CCOOCH(CH_3)_2$	125 (640)	1.3882	98.7	21	7.68 ± 0.32	1.30 (1.40)[h]
60498-66-0	VIII β,β-dimethylbutyrate (*tert*-butylacetate)[i]	$(CH_3)_3CCH_2COOCH(CH_3)_2$	147 (640)	1.4025	98.2	61	5.95 ± 0.19	1.01
5129-47-5	IX α-ethylbutyrate[j]	$CH_3—CH_2CH(CH_2CH_3)COOCH(CH_3)_2$	163 (640)	1.4033	96.8	30	6.97 ± 0.17	1.18
6639-15-2	X α-methylvalerate[k]	$CH_3(CH_2)_2CH(CH_3)COOCH(CH_3)_2$	171 (640)	1.4021	97.3	29	6.88 ± 0.24	1.16
60498-67-1	XI α-propylvalerate[l]	$CH_3(CH_2)_2CH(CH_2CH_2CH_3)COOCH(CH_3)_2$	32 (0.1)	1.4109	97.5	14	6.89 ± 0.30	1.16
4861-85-2	XII phenylacetate[m]	$PhCH_2COOCH(CH_3)_2$	65 (0.3)	1.4875	99.4	29	8.13 ± 0.13	1.37
60498-68-2	XIII diphenylacetate[n]	$Ph_2CHCOOCH(CH_3)_2$	132 (0.3) (mp) 42–43		>99	52	11.2 ± 0.07	1.88
22767-95-9	XIV hydrocinnamate (β-phenylpropionate)[o]	$PhCH_2CH_2COOCH(CH_3)_2$	87 (3)	1.4868	99.3	69	7.37 ± 0.07	1.24
18060-77-0	XV crotonate[p]	$CH_3CH{=}CHCOOCH(CH_3)_2$	140 (640)	1.4221	98.7	9	7.1 ± 0.20	1.20
60512-85-8	XVI *trans*-cinnamate[q]	$PhCH{=}CHCOOCH(CH_3)_2$	98 (0.6)	1.5450	98.1	51	8.13 ± 0.37	1.37
105-48-6	XVII chloroacetate[r]	$ClCH_2COOCH(CH_3)_2$	142 (640)	1.4193	98.9		10.6 ± 0.40	1.79
17640-21-0	XVIII methoxyacetate[s]	$CH_3OCH_2COOCH(CH_3)_2$	152 (640)	1.4010	95.4	55	6.87 ± 0.27[t]	1.16

[a] Bp 88–91 °C (734 mm), n^{20} 1.3773: "Handbook of Chemistry and Physics", 52d ed, R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1971, p C-81. [b] Bp 109–110 °C (760 mm); n^{20} 1.3872: *ibid.*, p C-446. [c] Bp 130–131 °C (760 mm), n^{20} 1.3936: *ibid.*, p C-216. [d] Bp 153.5 °C (760 mm), n^{20} 1.4061: *ibid.*, p C-411. [e] Bp 109.4 °C (100 mm): C. W. Bonhorst, P. M. Althouse, and H. O. Triebold, *Ind. Eng. Chem.*, **40**, 2379 (1948). [f] Bp 118–121 °C (727 mm): Pribran and Handl, *Monatsh. Chem.*, **3**, 691 (1881); *Beilstein*, 4th ed, **2**, 291 (1920). [g] Bp 127.7 °C (760 mm), n^{18} 1.3893: L. Kahovec and K. W. F. Kohlrausch, *Monatsh. Chem.*, **74**, 116 (1943); Beilstein, 4th ed, III, **2**, 711 (1960). [h] A. Tinkelenberg, E. C. Kooyman, and R. Louw, ref 4b. [i] Bp 94–95 °C (110–112 mm): F. C. Whitmore and A. H. Homeyer, *Chem. Abstr.*, **30**, 7125[9] (1936); U.S. Patent 2 052 995. [j] Bp 161–162 °C (not listed), n^{20} 1.4031: M. B. Ordyan, Ya. T. Eidus, M. A. Kanevskaya, and L. I. Shokina, *Arm. Kim. Zh.*, **19**, 280 (1966); *Chem. Abstr.*, **66**, 18533y (1967). [k] Not found in literature. [l] Not found in the literature. [m] n^{20} 1.4950: J. E. Baldwin and L. E. Walker, *J. Am. Chem. Soc.*, **88**, 3769 (1966). [n] Bp 115 °C (0.1 mm), mp 42–44 °C: A. B. H. Funcke *et al.*, *Arzneim.-Forsch.*, **4**, 492 (1954); *Chem. Abstr.*, **49**, 10888c (1954). [o] Bp 126 °C (11 mm): P. Walden and R. Swinne, *Z. Phys. Chem. (Leipzig)*, **79**, 726 (1912); Beilstein, I, **9**, 198 (1932). [p] Bp 145–146.5 °C (not listed): O. Bruner and P. Hanke, *Monatsh. Chem.*, **83**, 1485 (1952); *Chem. Abstr.*, **48**, 573*i* (1954). [q] Bp 268–270 °C (not listed): D. Vorlander and R. Walter, *Z. Phys. Chem. (Leipzig)*, **118**, 12 (1925); Beilstein, 4th ed, II, **9**, 387 (1949). [r] Bp 149 °C (760 mm): Steinlen, *Chem. Zentralbl.*, **68**, 659 (1867); Beilstein, 4th ed, **2**, 198 (1920). [s] Bp 148 °C (not listed), n^{20} 1.4001: M. H. Palamaa and V. Jaakkola, *Chem. Ber.*, **67**, 947 (1934). [t] The maximum deviation from the average.

which show how methyl substituents at the α position alter activation parameters compared to methyl substituents at the β position.

Experimental Section

Materials. The isopropyl esters were synthesized from commercially available acids by two different methods. Method I[5] was a simple esterification using dry hydrogen chloride gas (3–4 N solution) in a 3 molar excess of 2-propanol. Refluxing was continued from 2 to 5 days. The mixture was taken up in chloroform and then extracted with a saturated aqueous solution of sodium bicarbonate to remove the organic and inorganic acids. The crude ester–chloroform solution was dried overnight ($MgSO_4$) and the volatile solvent removed on a rotary evaporator. The esters were distilled through a 24-in. spinning band column and the purity determined by a Hewlett-Packard 5830A digital computer controlled flame ionization gas chromatograph (20 in. 10% UC-W982 0.125 in. stainless steel column). Characterization was by refractive index, NMR, and mass spectral analysis. Esters I–VII, IX, and XII–XVIII were prepared by method I. Owing to the expense and small working quantities of the other acids, the following method was used to prepare esters VIII, X, and XI.[6] Millimolar quantities of the acids were dissolved in 11 molar excess of benzene, a four times excess of trifluoroacetic anhydride, and a 10 molar excess of 2-propanol. After refluxing overnight, the solution was washed with 10% sodium hydroxide solution, dried over magnesium sulfate and fractionally distilled. The yield, in every case, was sacrificed for purity. The data on the esters are reported in Table I.

Kinetics. Kinetic data were obtained by monitoring pressure changes in a constant-volume static reactor which has been previously described.[7] The reaction temperature (651.0 K) was determined by in situ thermocouples calibrated against a platinum resistance thermometer. Thermolyses were carried out at initial reactant pressures in the range of 250–400 Torr. With selected esters cyclohexene was added to check for radical reactions. Reaction rates were invariant with initial pressure and/or additive. The reaction chamber was well seasoned by the thermolysis of multiple injections of 3-butenoic acid at 680 K.[8] The absence of surface catalysis was ascertained by the thermolysis of 1-phenylethyl acetate which gave first-order kinetics of high precision (±1–2%) in agreement with reported values.[9] The rate constants, standard deviations, and correlation coefficients were computer calculated. The reaction rate constants for each of the esters are shown in Table I. At least three rate determinations were made on each ester. The maximum deviation from the average never exceeded 4.4%. The reaction proceeded to 80% completion without any complications or subsequent decompositions. The products were the acid and propene.

Discussion

There is no observable effect on the rate of pyrolysis with increasing chain length within experimental error. The relative rate constants ($k_{carboxylate}/k_{acetate}$) from acetate through caproate are 1.00:1.03:1.00:1.01:1.02, respectively. These results demonstrate that one alkyl substituent at the α or β position, regardless of its size within the range studied, has no effect, sterically or electronically, on the rate of pyrolysis. This is a surprising result as it is generally considered that larger molecules fragment more readily than smaller ones.[10]

The second and third methyl substituent at the α position, however, shows a steric acceleration effect. The relative rates in the pyrolysis of isopropyl esters are acetate (I):propionoate (II):isobutryrate (VI):pivalate (trimethylacetate) (VII) 1.00:1.03:1.15:1.30. These are not marked effects but are beyond experimental error. Cross and Stimson did not observe any difference in the rate of pyrolysis between ethyl acetate and ethyl trimethylacetate.[11] Substituent effect in primary esters are less pronounced than in secondary and tertiary esters, and therefore they are more difficult to detect.

The lack of any influence by alkyl branching at the β position in the pyrolysis of isopropyl carboxylates is forcibly demonstrated by the tabulated results given in Table II. If isopropyl isobutyrate is selected as a logical standard it is clearly evident that substitution by one or two methyl or ethyl substituents at the β position has absolutely no influence on the rate of ester pyrolysis. This is further emphasized by comparing the results when three methyl substituents are examined at these two positions.

Table II. Effect of Alkyl Branching at the β Position in Alkanoate Pyrolysis[a] R-$COOCH(CH_3)_2$

R	$K \times 10^3$	Maximum deviation	Average deviation	Ratio
H_3C>CH, H_3C	6.80	±0.20	±0.10	1.00
CH_3CH_2>CH, CH_3CH_2	6.97	±0.17	±0.11	1.03
CH_3>CH, $CH_3(CH_2)_2$	6.88	±0.24	±0.18	1.01
$CH_3(CH_2)_2$>CH, $CH_3(CH_2)_2$	6.89	±0.30	±0.22	1.01

[a] 651 ± 0.1 K.

Placing three methyl substituents at the α position has perceptibly more effect on the rate of pyrolysis than three methyl substituents at the β position. Isopropyl pivalate (isopropyl trimethylacetate) (VII) pyrolyzed 1.3 times faster than isopropyl β,β-dimethylbutyrate (isopropyl *tert*-butylacetate) (VIII). Tinkelenberg et al. reported 1.4 for the ratio of cyclohexyl trimethylacetate/cyclohexyl acetate. These comparisons of effects of the α and β position demonstrate that steric effects in ester thermolysis are greater at the α position than at the β position.

Likewise, a phenyl substituent increases the rate of pyrolysis more at the α position than at the β position. The ratios for the isopropyl ester are acetate (I):β-phenylpropionoate (XIV):phenylacetate (XII):diphenylacetate (XIII) 1.0:1.24:1.37:1.88. The effect is primarily steric since the phenyl substituent causes only a minor electronic effect being electromerically insulated from the reaction site by a methylene group. Electronic changes in the acid portion of the ester are known to cause only a minor influence on ester pyrolysis.[12] The effect of a C=C double bond on ester pyrolysis was studied by comparing the absolute reaction rate constants in the pyrolysis of isopropyl esters of *n*-butyric acid (III), *trans*-crotonic acid (XV), and *trans*-cinnamic acid (XVI). Their relative rates are 1.00:1.20:1.37, respectively. Again the effect is not large but well beyond experimental error and clearly shows that unsaturation increases the rate. Here electronic effects could be relayed to the active site and would be expected to have an effect. Kairaitis and Stimson[13] reported a similar result. Their data, taken at 410.4 °C (683.5 K), for ethyl butyrate (1.61×10^{-3}) and ethyl *trans*-crotonate (1.83×10^{-3}) gave a ratio of 1.14. Primary esters are not expected to show as large a substituent effect as secondary esters.

α-Chloro substituents are more effective on the rate of pyrolysis of esters than are α-alkyl or α-aryl substituents. The rate of pyrolysis of isopropyl chloroacetate (XVII) was 1.79 times faster than the rate for isopropyl acetate (I). Similar results are reported for *tert*-butyl esters although it is difficult to place a number on the extent of influence. Several values have been reported for the rate constant in the pyrolysis of *tert*-butyl acetate.[14] When the reported values, obtained at different temperatures, were recalculated to 650 K, they ranged from 243×10^{-3} to 615×10^{-3}. Using Emovon and Maccoll's[15] values for *tert*-butyl acetate (496×10^{-3}), and Emovon's values[16] for *tert*-butyl α-chloracetate (1925×10^{-3}) and *tert*-butyl α,α-dichloroacetate (4430×10^{-3}) the relative rates are 1.00:3.9:9.0, respectively. Substituent effects are expected to be greater with tertiary esters than with secondary and primary esters and indeed they are. With chloro substit-

uents at the α position, electronic and steric effects are combined to magnify the substituent influence. An α-methoxy substituent and α-unsaturation have greater acceleration effects on pyrolysis than do α-alkyl substituents but not as great an effect as α-phenyl and α-chloro substituents.

Kooyman et al.[4b] reported a ratio of cyclohexyl trifluoroacetate/cyclohexyl acetate of 19. This very strong effect at the α position of the acid is very significant and most likely is polar rather than steric. The data for isopropyl trichloroacetate are not available but it would appear from the increased rates due to one α-chloro substituent that three chloro substituents would cause an effect even greater than three fluoro substituents because of the combination of both steric and electronic effects.

In summary, therefore, these results demonstrate that substituent effects are more important at the α than at the β position in the acid moiety of esters on their pyrolysis. Multiple branching at the α position by alkyl groups causes a greater steric acceleration effect (compound VII) than similar substitution at the β position (compound VIII).

It is now clear that in pyrolysis, electron-withdrawing groups or electron-releasing groups in the acid moiety at the α position cause rate accelerations.

This suggests that the effects by α-aryl and α-aryl are more than electronic. We proposed that steric effect raise the ground state of the ester effectively reducing the activation free energy. Further evidence to support this concept was found by comparing the activation parameters of the isopropyl esters of trimethyl acetate (VII) and *tert*-butyl acetate (VIII). The entropy of activation ($\Delta S^{\ddagger}$) for VII, where the three methyl groups are located at the α position, showed a less negative value than β-methyl substituent. $\Delta S^{\ddagger}$ for VII was −0.25, while $\Delta S^{\ddagger}$ for VIII was −4.7. The rate ratio for the pyrolysis of these two esters was 1.3. From this we conclude that the more sterically hindered ester (VII) is held in a favorably conformation leading to the cyclic transition state. This supports the well-accepted mechanistic concept.[2] The enthalpies of activation for VII and VIII were found to be 45.0 and 42.5 kcal/mol, respectively. Wigfield and Phelps reported recently[17] that the major component of the free energy barrier in the sodium borohydride reduction of hindered ketones, which alters reactivity, is entropy.

Although ester pyrolysis and ester formation are very different processes, it is interested to compare the two reactions sterically. Newman[18] proposed that steric effects at the β carbon in acid esterification was greater than at the α carbon. However, Sniegoski[19] has challenged Newman's interpretation of the data.

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Electrocyclic Synthesis of 5,6- and 7,8-Dihydroquinolines and 5,6- and 7,8-Dihydroisoquinolines

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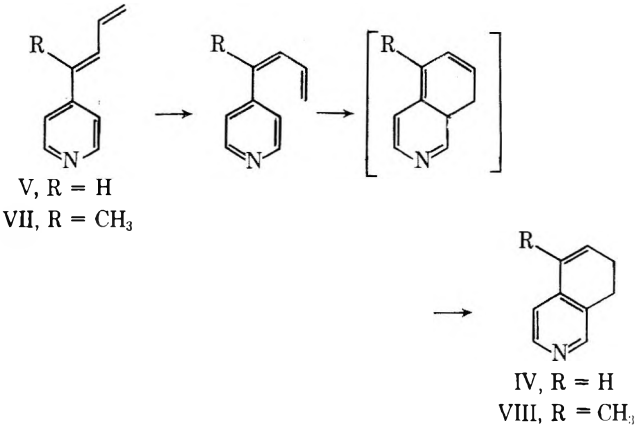
The gas-phase pyrolysis of a number of 1-(ω-pyridinyl)-1,3-butadienes (650 °C, 1 mm, and a contact time ~0.1 s) has been studied. The following results were obtained: 1-(α-pyridinyl)-1,3-butadiene yields 5,6-dihydroquinoline, 1-(β-pyridinyl)-1,3-butadiene yields 5,6-dihydroisoquinoline (35%) and 7,8-dihydroquinoline (65%), and 1-(γ-pyridinyl)-1,3-butadiene yields 7,8-dihydroisoquinoline. Analogous results were obtained on pyrolysis of 1-methyl-1-(ω-pyridinyl)-1,3-butadienes and 1-(6′-methyl-2′-pyridinyl)-1,3-butadiene. The structures of these 5,6- and 7,8-dihydroquinoline and 5,6- and 7,8-dihydroisoquinoline isomers were determined by spectral methods, dehydrogenation to the parent aromatic heterocycle, and in the case of 5,6- and 7,8-dihydroquinoline by use of Eu(fod)$_3$ NMR shift reagent. The mechanism of this reaction is discussed.

We should like to report a general synthesis of 5,6- and 7,8-dihydroquinolines (I, II) and 5,6- and 7,8-dihydroisoquinolines (III, IV) based on joining onto a pyridine ring a specific partially reduced aromatic ring. The critical ring closure reaction onto the pyridine nucleus is an electrocyclic reaction.[1] A communication reporting this reaction appeared 5 years ago.[2] The inaccessibility of I, II, III, and IV isomers convinced us that a detailed study to improve regioselectivity and yields and to determine the scope of this reaction was warranted.

The synthesis is based on the gas-phase pyrolysis of the appropriate 1-(ω-pyridinyl)-1,3-butadiene. Pyrolysis of 1-(γ-pyridinyl)-1,3-butadiene (V)[3] in the gas phase at 650 °C

and 1 mm pressure in a flow system with a contact time of about 0.1 s yields IV. No isoquinoline or quinoline as previously reported[2] were observed. This difference probably results from the lower temperature used. This result can be rationalized by the following reaction sequence. *cis*-V undergoes a disrotatory electrocyclic reaction to yield 8,9-dihydroisoquinoline. This step is related to the thermally allowed disrotatory reaction converting a conjugated triene into a 1,3-cyclohexadiene.[1,4-6] In the case of *cis*-V, the triene undergoing reaction is composed of the two double bonds of the 1,3-butadiene and two π electrons from the pyridine ring. Analogous examples in which a benzene ring contributes two π electrons to a triene system in thermally allowed electrocyclic reactions have been reported.[7-9] Clearly, this involves disruption of the aromatic 6-π-electron system of the pyridine ring. The high temperature required for the reaction may reflect the loss of resonance energy in the transition state. This is followed rapidly by a symmetry allowed 1,5-suprafacial sigmatropic hydrogen rearrangement leading to restoration of the aromatic pyridine nucleus.[10] Since only *cis*-V has the proper geometry to undergo electrocyclic reaction, the first step in the case of *trans*-V must be an isomerization of trans to cis.



V, R = H
VII, R = CH_3

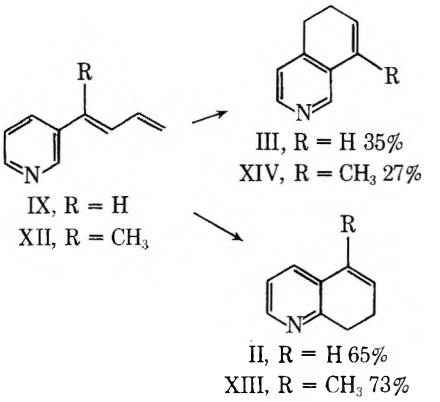
IV, R = H
VIII, R = CH_3

The starting 1-(ω-pyridinyl)-1,3-butadienes were prepared by a Wittig reaction of allylidenetriphenylphosphorane with ω-pyridinyl carboxaldehydes, albeit in low yield (~25%). 1-(α-, β-, and γ-pyridinyl)-1,3-butadienes are known but their spectral properties have not been reported.[3]

Cis and trans geometric isomers of both 1-(β-pyridinyl)-1,3-butadiene (IX) and V were obtained. In both, the cis was the predominant. Stereochemistry was assigned on the basis of uv spectra on the assumption that the *trans*-V or IX would absorb at longer wavelength and that ϵ would be greater than that of the corresponding cis isomer by analogy to the uv of *cis*- and *trans*-1-phenyl-1,3-butadiene.[11] Only a single geometric isomer of 1-(α-pyridinyl)-1,3-butadiene (X) was isolated. Its uv spectra was significantly different from those of either V or IX. It had considerable fine structure and the lowest energy absorption was shifted to longer wavelength.

1-Methyl-1-(ω-pyridinyl)-1,3-butadienes were prepared in three steps. Addition of allyl Grignard reagent to ω-acetylpyridine yields an alcohol which was converted to the corresponding chloride by treatment with $SOCl_2$. The chloride was dehydrohalogenated with KOH/CH_3OH to yield a mixture of the desired 1-methyl-1-(ω-pyridinyl)-1,3-butadiene and 2-(ω-pyridinyl)-1,4-pentadiene. The desired conjugated isomer was always predominant. Only a single geometric isomer of the three 1-methyl-1-(ω-pyridinyl)-1,3-butadienes was ever isolated. No attempt was made to determine if it was the *E* or *Z* isomer. Pyrolyses were carried out on mixtures of these isomers. Control experiments showed that 2-(ω-pyridinyl)-1,4-pentadienes were unchanged on pyrolysis. 1-(6′-Methyl-2′-pyridinyl)-1,3-butadiene (XI) was prepared in an analogous manner by addition of allyl Grignard reagent to 6-methyl-2-pyridinecarboxaldehyde in 59% overall yield.

Pyrolysis of IX[3] yields a mixture of III and II in a ratio of 1:2, in addition to small amounts of recovered IX. Neither quinoline nor isoquinoline were ever observed. Pyrolysis of 1-methyl-(β-pyridinyl)-1,3-butadiene (XII) yields a mixture of 5-methyl-7,8-dihydroquinoline (XIII) and 8-methyl-5,6-dihydroisoquinoline (XIV) (~3:1).

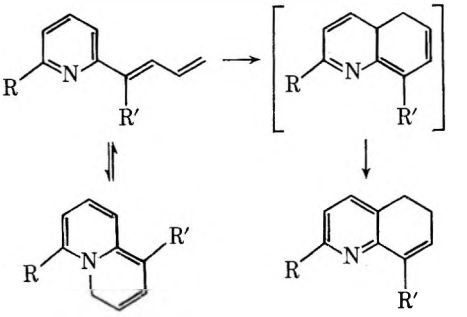


IX, R = H
XII, R = CH_3

III, R = H 35%
XIV, R = CH_3 27%

II, R = H 65%
XIII, R = CH_3 73%

Pyrolysis of X[3] yields I and small amounts of recovered X. Neither quinoline nor 4-quinolizine were ever observed. This selectivity may not reflect high regioselectivity in the electrocyclic reaction, but rather the instability of the 4-quinolizine ring system. 4-Quinolizine is expected to open to yield X on the basis of previous work.[12] Likewise, pyrolysis of XI yields 2-methyl-5,6-dihydroquinoline (XV) and small amounts of recovered XI. Neither 2-methylquinoline nor 6-methyl-4-quinolizine were observed. Pyrolysis of 1-methyl-1-(α-pyridinyl)-1,3-butadiene (XVI) yields 8-methyl-5,6-dihydroquinoline (XVII). Neither 8-methylquinoline nor 1-methyl-4-quinolizine were observed.



X, R = H; R′ = H
XVI, R = H; R′ = CH_3
XI, R = CH_3; R′ = H

I, R = H; R′ = H
XVII, R = H; R′ = CH_3
XV, R = CH_3; R′ = H

The I, II, III, and IV isomers are new compounds. Their structures were determined by spectral methods (ir, NMR, uv). In addition, a pure sample of each dihydro isomer was dehydrogenated by oxidation with 2,3-dichloro-5,6-dicyanoquinone (DDQ) in dimethoxyethane at 50 °C.[13] The identity of the parent aromatic heterocycle obtained was determined by GLC and NMR spectra. These results were consistent. Finally, the structures of I and II obtained respectively from the pyrolysis of X and IX were confirmed by use of $Eu(fod)_3$ NMR shift reagent. $Eu(fod)_3$ behaves as a Lewis acid and thus is expected to coordinate to the nitrogen of these dihydroquinoline isomers.[14,15] The effect of $Eu(fod)_3$ on the chemical shift of a particular proton in the substrate is related to the concentration of $Eu(fod)_3$ as well as to the distance and geometry of the proton from the Eu^{3+} ion.[15] Those protons which are closest to the Eu^{3+} ion shift the most.[15] On this basis, we expect major downfield shifts for the aromatic proton

at C-2 and for the vinylic proton at C-8 in I. On the other hand, we expect major downfield shifts of the aromatic proton at C-2 and the benzylic protons at C-8 in II. Results consistent with these expectations were obtained. For supporting data—spectra, as well as plots of the chemical shifts of each proton vs. the sum of all the chemical shifts of these protons observed at various concentrations of $Eu(fod)_3$[16]—see supplementary material in the microfilm edition.

Experimental Section

All reactions were carried out under an atmosphere of prepurified nitrogen. Ir spectra were determined as neat liquids on a Perkin-Elmer 337 spectrometer. They were calibrated against known peaks in a polystyrene film. NMR spectra were recorded on a Varian XL-100 spectrometer. Spectra were taken using 10% solutions in $CDCl_3$ with an internal standard of Me_4Si. Samples of all compounds for spectral and elemental analysis were purified by preparative vapor phase chromatography on a Hewlett-Packard F & M 700 using a 20% FFAP (Varian) on 60/80 mesh Chromosorb P, which had been modified by addition of 10% powdered KOH, 10 ft × 0.25 in. column at a temperature of 165 °C. Ultraviolet spectra were obtained in spectrograde cyclohexane on a Beckman Acta M spectrometer. Melting points were taken on a Hoover-Thomas apparatus and are uncorrected. Picrate derivatives were prepared by standard procedures and were recrystallized from 95% ethanol. Microanalysis was performed by Elek Microanalytical Laboratories, Torrance, Calif.

1-(α-Pyridinyl)-1,3-butadiene (X). In a 500-ml three-necked round-bottom flask equipped with a pressure-equalizing addition funnel, a reflux condenser, and a rubber septum were placed 39.1 g (103 mmol) of allyltriphenylphosphonium bromide (Aldrich), 200 ml of anhydrous ether, and a Teflon-covered magnetic stirring bar. *n*-Butyllithium (Alfa) in hexane (1.9 M, 52 ml) was added by syringe. The solution was refluxed for 1 h. α-Pyridinecarboxaldehyde (Aldrich), 9.5 g (89 mmol), was added dropwise to the stirred solution of ylide. After 3 h, the mixture was filtered to remove triphenylphosphine oxide. Volatile solvents were removed from the filtrate by evaporation under reduced pressure. The volatile product was separated from the nonvolatile residue by bulb to bulb distillation at 60 °C (0.1 mm) to yield 4.5 g (34 mmol, 39%) of X. Only a single isomer of X was ever isolated: ^1H NMR δ 8.6 (d, 1 H, J = 6 Hz), 7.6 (m, 2 H), 7.2 (m, 2 H), 6.5 (m, 2 H), 5.4 (dd, 2 H, J = 14 and 8 Hz); ir C=C 1626 cm^{-1}; uv λ 2620 Å, ε 3.05 × 10^4, λ 2740 Å, ε 2.77 × 10^4, λ 2930 Å, ε 2.26 × 10^4, λ 3020 Å, ε 2.26 × 10^4, λ 3150 Å, ε 1.24 × 10^4; mp (picrate) 145.5 °C (lit. mp 146.5–147 °C).[12]

1-(β-Pyridinyl)-1,3-butadiene (IX) was prepared as above from β-pyridinecarboxaldehyde (Aldrich) in 29% yield. It was separated into cis and trans geometric isomers in a ratio of 64/36 by preparative GLC. The cis isomer had the shorter retention time.

***cis*-IX:** ^1H NMR δ 8.6 (s, 1 H), 8.5 (d, 1 H, J = 6 Hz), 7.65 (d, 1 H, J = 8 Hz), 7.3 (dd, 1 H, J = 8 and 6 Hz), 6.8 (m, 1 H), 6.4 (m, 2 H), 5.4 (dd, 2 H, J = 16 and 10 Hz); ir C=C 1600 cm^{-1}; uv λ 2600 Å, ε 3.19 × 10^4; mp (picrate) 134 °C (lit. mp 138 °C).[3]

***trans*-IX:** ^1H NMR δ 8.65 (s, 1 H), 8.5 (d, 1 H, J = 5 Hz), 7.77 (d, 1 H, J = 9 Hz), 7.3 (dd, 1 H, J = 9 and 5 Hz), 7.0–6.3 (m, 3 H), 5.3 (dd, 2 H, J = 18 and 10 Hz); ir C=C 1600 cm^{-1}; uv λ 2675 Å, ε 4.17 × 10^4; mp (picrate) 115 °C.

1-(γ-Pyridinyl)-1,3-butadiene (V)[3] was prepared as above from γ-pyridinecarboxaldehyde (Aldrich) in 21% yield. It was separated into cis and trans geometric isomers in a ratio of 60:40 by GLC.

***cis*-V:** ^1H NMR δ 8.6 (d, 2 H, J = 8 Hz), 7.2 (d, 2 H, J = 9 Hz), 6.9 (m, 1 H), 6.5 (m, 2 H), 5.4 (dd, 2 H, J = 16 and 8 Hz); ir C=C 1600 cm^{-1}; uv λ 2650 Å, ε 2.29 × 10^4.

***trans*-V:** ^1H NMR δ 8.5 (d, 2 H, J = 5 Hz), 7.3 (d, 2 H, J = 5 Hz), 7.1–6.3 (m, 3 H), 5.5 (dd, 2 H, J = 16 and 10 Hz); ir C=C 1610 cm^{-1}; uv λ 2700 Å, ε 3.61 × 10^4; mp (picrate) 131 °C.

1-Methyl-1-(α-pyridinyl)-1,3-butadiene (XVI) was prepared in three steps from 2-acetylpyridine. Intermediate products were neither purified nor characterized. The following apparatus was used for each step: a 250-ml three-necked round-bottom flask equipped with a reflux condenser, a pressure-equalizing addition funnel, a rubber septum, and a Teflon-coated magnetic stirring bar. 2-Acetylpyridine (Reilly), 4.2 g (35 mmol), and 50 ml of anhydrous ether were placed in the flask. Allylmagnesium chloride (Alfa), 1.9 M in THF, 28 ml (70 mmol), was added dropwise to the stirred, cooled (0 °C) solution of 2-acetylpyridine. After 3 h 50 ml of a saturated NH_4Cl solution was added. The organic and aqueous layers were separated. The aqueous layer was extracted with 2 × 50 ml of ether. The combined ether extracts were dried over anhydrous $MgSO_4$ and filtered, and the volatile solvents removed by evaporation under reduced pressure to yield 2-(α-pyridinyl)-2-hydroxy-4-pentene. Thionyl chloride, 5 ml (70 mmol), was placed in the flask. The above alcohol, 5.2 g (35 mmol), dissolved in 20 ml of $CHCl_3$ was added dropwise to the cooled (0 °C) solution of $SOCl_2$. After the addition was complete, the flask was heated at 80 °C for 15 min until the evolution of SO_2 had subsided. The solution was cooled and made basic by addition of concentrated K_2CO_3. The layers were separated and the aqueous phase extracted with 3 × 50 ml of ether. The ether extracts were combined, dried over anhydrous $MgSO_4$, and filtered, and the volatile solvents removed by evaporation under reduced pressure to yield 2-(α-pyridinyl)-2-chloro-4-pentene. Ten grams of KOH and 50 ml of CH_3OH were placed in the flask. The above chloride, 5.8 g (35 mmol), dissolved in 10 ml of CH_3OH was added to the refluxing solution of KOH/CH_3OH. After 4 h, the reaction mixture was cooled and extracted with 3 × 100 ml of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over anhydrous $MgSO_4$ and filtered, and the volatile solvents removed by evaporation under reduced pressure. The volatile products were separated from nonvolatiles by bulb to bulb distillation at 75 °C (0.1 mm) to yield 2.6 g (51%) of a mixture of XVI and 2-(α-pyridinyl)-1,4-pentadiene in a ratio of 66:34. The XVI had the longer retention time.

XVI: ^1H NMR δ 8.6 (d, 1 H, J = 5 Hz), 7.6 (m, 2 H), 7.2–6.6 (m, 3 H), 5.4 (dd, 2 H, J = 16 and 10 Hz), 2.25 (d, 3 H, J = 1 Hz); ir C=C 1600 cm^{-1}; uv λ 2780 Å, ε 2.1 × 10^4, λ 2920 Å, ε 1.95 × 10^4, λ 3020 Å, ε 1.6 × 10^4, λ 3170 Å, ε 4.5 × 10^3; mp (picrate) 152.5 °C. Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64. Found: C, 82.95; H, 7.55.

1-Methyl-1-(β-pyridinyl)-1,3-butadiene (XII) was prepared as above from 3-acetylpyridine, 4.1 g (34 mmol) (Aldrich), to yield 1.9 g (13 mmol, 39%) of a mixture of XII and 2-(β-pyridinyl)-1,4-pentadiene in a ratio of 73:27. They were separated by preparative GLC. XII had a longer retention time.

XII: ^1H NMR δ 8.6 (s, 1 H), 8.4 (d, 1 H, J = 5 Hz), 7.7 (d, 1 H, J = 5 Hz), 7.2 (dd, 1 H, J = 8 and 5 Hz), 6.5 (m, 2 H), 6.3 (dd, 2 H, J = 15 and 8 Hz), 2.2 (s, 3 H); ir C=C 1630 cm^{-1}; uv λ 2700 Å, ε 2.05 × 10^4; mp (picrate) 154 °C. Anal. Calcd for $C_{16}H_{14}N_4O_7$ (picrate): C, 51.34; H, 3.77. Found: C, 50.97; H, 4.07.

1-Methyl-1-(γ-pyridinyl)-1,3-butadiene (VII) was prepared as above from 4-acetylpyridine (Reilly), 4.0 g (33 mmol), to yield 2.5 g (18 mmol, 52%) of a mixture of VII and 2-(γ-pyridinyl)-1,4-pentadiene in a ratio of 61:39. They were separated by preparative GLC. VII had a longer retention time.

VII: ^1H NMR δ 8.55 (d, 2 H, J = 6 Hz), 7.30 (d, 2 H, J = 6 Hz), 6.7 (m, 2 H), 5.4 (dd, 2 H, J = 14 and 7 Hz), 2.2 (s, 3 H); ir C=C 1595 cm^{-1}; uv λ 2750 Å, ε 1.97 × 10^4; mp (picrate) 155 °C. Anal. Calcd for $C_{16}H_{14}N_4O_7$ (picrate): C, 51.34; H, 3.77. Found: C, 51.13; H, 3.91.

1-(6′-Methyl-2′-pyridinyl)-1,3-butadiene (XI) was prepared as above from 6-methyl-2-pyridinecarboxaldehyde (Aldrich), 5.5 g (44 mmol), to yield 3.9 g (27 mmol, 59%) of XI: ^1H NMR δ 7.6 (dd, 1 H, J = 14 and 8 Hz), 7.2 (m, 3 H), 6.6 (m, 2 H, upon irradiation at 5.4, the multiplet collapsed to a doublet with J = 17 Hz), 5.4 (dd, 2 H, J = 20 and 10 Hz), 2.6 (s, 3 H); ir C=C 1600 cm^{-1}; uv λ 2620 Å, ε 1.75 × 10^4, λ 2700 Å, ε 1.63 × 10^4, λ 2950 Å, ε 1.31 × 10^4, λ 3050 Å, ε 1.38 × 10^4, λ 3180 Å, ε 8.14 × 10^3; mp (picrate) 136 °C. Anal. Calcd for $C_{16}H_{14}N_4O_7$ (picrate): C, 51.34; H, 3.77. Found: C, 51.36; H, 3.91.

Pyrolysis of 1-(ω-Pyridinyl)-1,3-butadiene. The pyrolysis was performed using a 30-cm vertical tube oven. The diameter of the heated zone was 3.5 cm. The pyrolysis tube was made from a quartz tube (9 mm o.d., 8 mm i.d.), 250 cm long. It was wrapped in the form of a helical spiral of 30 turns. The height of the spiral was 30 cm. A 10-ml round-bottom flask containing a Teflon-covered magnetic stirring bar and the 1-(ω-pyridinyl)-1,3-butadiene to be pyrolyzed was connected to the bottom of the pyrolysis tube. The top of the pyrolysis tube was attached to a cold finger condenser which was cooled with liquid nitrogen. The outlet of the condenser was connected to a vacuum pump. The pyrolysis tube was heated to around 650 °C. The temperature was determined by use of a Leeds and Northrup potentiometer and an iron–constantan thermocouple. The 1-(ω-pyridinyl)-1,3-butadiene was distilled under vacuum into the pyrolysis tube by heating the 10-ml round-bottom flask to 75–90 °C with an oil bath. Under these conditions, about 1 g of 1-(ω-pyridinyl)-1,3-butadiene passed through the pyrolysis tube in 20 min. Thus the contact time is approximately 0.1 s. After completion of the pyrolysis, the cold finger condenser, with the pyrolysate frozen onto it, was disconnected from the pyrolysis tube and connected to a 10-ml round-bottom flask flushed with nitrogen. The coolant was allowed to evaporate and the product dripped off the condenser into the round-bottom flask.

X, 1.3 g (10.0 mmol), was pyrolyzed at 650 °C over a period of 21 min at a pressure of 0.1 mm. The product, 1.24 g, was analyzed by

GLC. In addition to recovered starting material, 0.44 g (3.3 mmol), there was isolated I, 0.8 g (6.1 mmol, 88% yield based on recovery starting material).

5,6-Dihydroquinoline (I): ^{1}H NMR δ 8.3 (d, 1 H, J = 7 Hz), 7.3 (d, 1 H, J = 7 Hz), 6.9 (dd, 1 H, J = 8 and 5 Hz), 6.6 (d, 1 H, J = 10 Hz), 6.3 (td, 1 H, J = 10 and 5 Hz), 2.8 (t, 2 H, J = 8 Hz), 2.4 (br m, 2 H); ir C=C 1640 cm^{-1}; uv λ 2890 Å, ϵ 7.9 × 10^3, λ 2570 Å, ϵ 6.55 × 10^3; mp (picrate) 179 °C. Anal. Calcd for $C_{15}H_{12}N_4O_7$ (picrate): C, 50.01; H, 3.36. Found: C, 50.01; H, 3.55.

IX, 1.5 g (11.4 mmol), was pyrolyzed at 648 °C over a period of 30 min at a pressure of 1 mm. The products, 1.2 g (9.2 mmol). were analyzed by GLC. There was no recovered starting material. II, 0.78 g (6 mmol), 52% yield, and III, 0.42 g (3.2 mmol), in 28% yield were obtained. II had the shorter retention time.

7,8-Dihydroquinoline (II): ^{1}H NMR δ 8.3 (d, 1 H, J = 6 Hz), 7.3 (d, 1 H, J = 7 Hz), 7.1 (dd, 1 H, J = 8 and 5 Hz), 6.42 (d, 1 H, J = 10 Hz), 6.1 (td, 1 H, J = 10 and 4 Hz), 3.0 (t, 2 H, J = 9 Hz), 2.5 (br m, 2 H); ir C=C 1640 cm^{-1}; uv λ 2570 Å, ϵ 1.11 × 10^4; mp (picrate) 176 °C. Anal. Calcd for $C_{15}H_{12}N_4O_7$ (picrate): C, 50.01; H, 3.36. Found: C, 50.00; H, 3.56.

5,6-Dihydroisoquinoline (III): ^{1}H NMR δ 8.3 (br s, 2 H), 7.1 (d, 1 H, J = 6 Hz), 6.58 (d, 1 H, J = 10 Hz), 6.2 (td, 1 H, J = 10 and 4 Hz), 2.9 (t, 2 H, J = 10 Hz), 2.5 (br s, 2 H); ir C=C 1580 cm^{-1}; uv λ 2550 Å, ϵ 2.0 × 10^4; mp (picrate) 150 °C. Anal. Calcd for $C_{15}H_{12}N_4O_7$ (picrate): C, 50.01; H, 3.36. Found: C, 50.21; H, 3.39.

V, 1.3 g (9.2 mmol), was pyrolyzed at 649 °C at a pressure of 0.8 mm over 27 min. The products, 0.9 g (7.1 mmol), were analyzed by GLC. Recovered starting material, 0.2 g (1.7 mmol), was isolated in a trans to cis ratio 3:1. The ratio of starting material prior to pyrolysis was 2:3 trans to cis. Cis reacts faster than trans, but some trans has reacted. In addition, there was isolated IV, 0.7 g (5.4 mmol), 70% corrected yield.

7,8-Dihydroisoquinoline (IV): ^{1}H NMR δ 8.4 (d, 1 H, J = 6 Hz), 8.38 (s, 1 H), 6.90 (d, 1 H, J = 6 Hz), 6.47 (d, 1 H, J = 10 Hz), 6.37 (td, 1 H, J = 10 and 5 Hz), 2.8 (t, 2 H, J = 8 Hz), 2.4 (br m, 2 H); ir C=C 1650 cm^{-1}; uv λ 2590 Å, ϵ 7.1 × 10^3; mp (picrate) 184 °C (lit. mp 184–185 °C).[2] Anal. Calcd for $C_{15}H_{12}N_4O_7$ (picrate): C, 50.01; H, 3.36. Found: C, 50.09; H, 3.55.

XI, 1.0 g (6.9 mmol), was pyrolyzed at 648 °C and 0.12 mm over 25 min. The products, 0.9 g (5.5 mmol), were analyzed by GLC. In addition to recovered starting material, 0.26 g (1.8 mmol), there was isolated XV, 0.54 g (3.7 mmol), 73% corrected yield.

2-Methyl-5,6-dihydroquinoline (XV): ^{1}H NMR δ 7.3 (d, 1 H, J = 7 Hz), 6.9 (d, 1 H, J = 7 Hz), 6.6 (d, 1 H, J = 10 Hz), 6.3 (td, 1 H, J = 10 and 4 Hz), 2.8 (t, 2 H, J = 9 Hz), 2.5 (s, 3 H), 2.4 (br m, 2 H); ir C=C 1650 cm^{-1}; uv λ 2400 Å, ϵ 4.53 × 10^3, λ 2580 Å, ϵ 5.1 × 10^3, λ 2940 Å, ϵ 7.3 × 10^3, λ 3150 Å, ϵ 5.78 × 10^3; mp (picrate) 144 °C. Anal. Calcd for $C_{16}H_{14}N_4O_7$ (picrate): C, 51.34; H, 3.77. Found: C, 51.39; H, 3.94.

Pyrolyses of 1-methyl-1-(ω-pyridinyl)-1,3-butadienes were carried out as previously described on mixtures of 1-methyl-1-(ω-pyridinyl)-1,3-butadiene and the isomeric 2-(ω-pyridinyl)-1,4-pentadiene. It was shown by control experiments that the 2-(ω-pyridinyl)-1,4-pentadienes were stable under the pyrolysis conditions. The yields of products are based on the amount of reactive 1-methyl-1-(ω-pyridinyl)-1,3-butadiene consumed in the pyrolysis reaction.

XVI, 0.75 g (5.2 mmol), was pyrolyzed at 654 °C at a pressure of 0.1 mm over 19 min. The products were analyzed by GLC. No starting material was recovered. XVII, 0.55 g (3.9 mmol), 72% yield, was isolated.

8-Methyl-5,6-dihydroquinoline (XVII): ^{1}H NMR δ 8.39 (d, 1 H, J = 6 Hz), 7.3 (t, 1 H, J = 6 Hz), 7.0 (dd, 1 H, J = 8 and 5 Hz), 6.1 (br s, 1 H), 2.8 (t, 2 H, J = 8 Hz), 2.3 (br m, 2 H), 2.18 (d, 3 H, J = 1 Hz); ir C=C 1665 cm^{-1}; uv λ 2620 Å, ϵ 5.7 × 10^3, λ 2900 Å, ϵ 8.04 × 10^3, λ 3000 Å, ϵ 6.5 × 10^3; mp (picrate) 132 °C. Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64. Found: C, 82.87; H, 7.50.

XII, 0.84 g (5.8 mmol), was pyrolyzed at 652 °C at a pressure of 0.1 mm over 19 min. The products were analyzed by GLC. No starting material was recovered. The products were isolated: XIII, 0.49 g (3.3 mmol), 57%, and XIV, 0.17 g (1.2 mmol), 21%.

5-Methyl-7,8-dihydroquinoline (XIII): ^{1}H NMR δ 8.25 (d, 1 H, J = 6 Hz), 7.4 (d, 1 H, J = 8 Hz), 7.05 (dd, 1 H, J = 8 and 6 Hz), 6.8 (br s, 1 H), 2.92 (t, 2 H, J = 8 Hz), 2.4 (br m, 2 H), 2.0 (d, 3 H, J = 1 Hz); ir C=C 1650 cm^{-1}; uv λ 2600 Å, ϵ 9.4 × 10^3, λ 2860 Å, ϵ 7.65 × 10^3, λ 2980 Å, ϵ 4.87 × 10^3; mp (picrate) 175.5 °C. Anal. Calcd for $C_{16}H_{14}N_4O_7$ (picrate): C, 51.34; H, 3.77. Found: C, 51.42; H, 3.99.

8-Methyl-5,6-dihydroisoquinoline (XIV): ^{1}H NMR δ 8.4 (s, 1 H), 8.36 (d, 1 H, J = 6 Hz), 7.01 (d, 1 H, J = 6 Hz), 6.9 (br s, 1 H), 2.78 (t, 2 H, J = 8 Hz), 2.3 (br m, 2 H), 2.1 (d, 3 H, J = 2 Hz); ir C=C 1650 cm^{-1}; uv λ 2570 Å, ϵ 6.05 × 10^3; mp (picrate) 161 °C. Anal. Calcd for $C_{16}H_{14}N_4O_7$ (picrate): C, 51.34; H, 3.77. Found: C, 51.17; H, 4.11.

VII, 0.74 g (5.1 mmol), was pyrolyzed at 643 °C at a pressure of 0.1 mm over 24 min. The products were analyzed by GLC. In addition to recovered starting material, 0.1 g (0.7 mmol), there was isolated VIII (0.4 g, 2.8 mmol), 59% corrected yield.

5-Methyl-7,8-dihydroisoquinoline (VIII): ^{1}H NMR δ 8.4 (d, 1 H, J = 6 Hz), 8.37 (s, 1 H), 7.0 (d, 1 H, J = 6 Hz), 6.02 (br s, 1 H), 2.75 (t, 2 H, J = 8 Hz), 2.3 (br m, 2 H), 2.1 (d, 3 H, J = 2 Hz); ir C=C 1640 cm^{-1}; uv λ 2610 Å, ϵ 9.12 × 10^3; mp (picrate) 184 °C. Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64. Found: C, 82.59; H, 7.54.

Dehydrogenation of Dihydroquinolines and Dihydroisoquinolines. A solution of 50 mg of the dihydroquinoline or dihydroisoquinoline and 5 ml of dry dimethoxyethane was treated with 90 mg of DDQ (Eastman), and heated at 50 °C for 24 h.[13] After an acid–base workup, product analysis was carried out by GLC. Retention times were identical with those of known samples of quinolines or isoquinolines. NMR spectra were also consistent.

Eu(fod)$_3$ Shift Experiments. Eu(fod)$_3$ was obtained from Bio-Rad Laboratories and was dried in a vacuum desiccator over phosphorus pentoxide prior to use. In a typical experiment, 50 μl of a 0.59 M solution of Eu(fod)$_3$ in $CDCl_3$ was syringed into a 5-mm NMR tube containing 50 mg of the dihydroquinoline in 0.4 ml of $CDCl_3$/1% Me_4Si. A spectrum was then taken of this new solution. This procedure was repeated until 200 μl of shift reagent solution had been added.

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Registry No.—I, 24334-23-4; I picrate, 54087-12-6; II, 37624-11-6; II picrate, 54086-93-0; III, 60498-99-9; III picrate, 60499-00-5; IV, 24334-24-5; IV picrate, 54087-13-7; *cis*-V, 60499-01-6; *trans*-V, 60499-02-7; *trans*-V picrate, 60499-03-8; VII, 60499-04-9; VII picrate, 60499-05-0; VIII, 60499-06-1; VIII picrate, 60499-07-2; *cis*-IX, 60499-08-3; *trans*-IX, 60499-09-04; *trans*-IX picrate, 60499-10-7; X 3054-98-6; XI, 10497-82-2; XI picrate, 10530-42-4; XII, 60499-11-8; XII picrate, 60499-12-9; XIII, 60499-13-0; XIII picrate, 60499-14-1; XIV, 60499-15-2; XIV picrate, 60499-16-3; XV, 60499-17-4; XV picrate, 60499-18-5; XVI, 60499-19-6; XVI picrate, 60499-20-9; XVII, 60499-21-0; XVII picrate, 60499-22-1; allyltriphenylphosphonium bromide, 1560-54-9; α-pyridinecarboxaldehyde, 1121-60-4; β-pyridinecarboxaldehyde, 500-22-1; γ-pyridinecarboxaldehyde, 872-85-5; 2-acetylpyridine, 1122-62-9; allyl chloride, 107-05-1; 2-(α-pyridinyl)-2-hydroxy-4-pentene, 60499-23-2; 2-(α-pyridinyl)-2-chloro-4-pentene, 60499-24-3; 3-acetylpyridine, 350-03-8; 4-acetylpyridine, 1122-54-9; 6-methyl-2-pyridinecarboxaldehyde, 1122-72-1.

Supplementary Material Available. NMR spectra of dihydroquinolines and plots of δ_i vs. $\Sigma\delta$ with Eu(fod)$_3$ (4 pages). Ordering information is given on any current masthead page.

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Conformational Analysis. 33.[1] Carbon-13 Nuclear Magnetic Resonance Spectra of Saturated Heterocycles. 5.[2] *cis*-Decahydroquinolines

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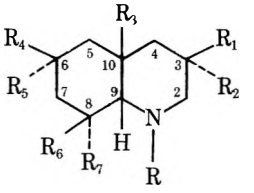
The ^{13}C NMR spectra of *cis*-decahydroquinoline, its two epimeric 3-, 6-, and 8-methyl, as well as its 10-methyl, 3α,10-, 3β,10-, and 8α,10-dimethyl homologues and the corresponding *N*-methyl compounds were recorded. Configurational and conformational assignments have been made on the basis of ^{13}C and ^{1}H NMR spectra. The parent, 10-methyl, 6β-methyl, and 8β-methyl compounds are conformationally heterogeneous; conformational equilibria were determined by low-temperature ^{13}C NMR spectroscopy. Signals in the ^{13}C spectra were assigned on the basis of those of the parent compounds[3a-c] with the help of parameters previously established[2] in the *trans*-decahydroquinoline series. The previously reported[2] upfield shift due, formally, to an antiperiplanar lone pair on nitrogen bearing alkyl [*anti*-:N(Me)-C–C] as well as the downfield shift caused by steric compression of syn-axial methyl groups were confirmed. Groups to which syn-axial substituents are attached are also shifted downfield. Shift parameters of the type introduced by Grant and co-workers[2,4,5] are tabulated for the *cis*-decahydroquinoline series. The ^{13}C spectra of $\Delta^{1,9}$-octahydroquinoline and several of its methyl homologues have been recorded. Conformational equilibria in variously substituted *cis*-decahydroquinolines are discussed.

In a previous paper[2] we have discussed the ^{13}C NMR spectra of a number of methyl-substituted *trans*-decahydroquinolines. Here we report the spectra of 11 *cis*-decahydroquinolines, **1–11** (R = H), and of the corresponding *N*-methyl homologues **1m–11m** (R = CH_3). The spectra of the parent compounds **1** and **1m** have already been published by Booth and Griffiths[3] and are included for completeness only; the remaining spectra are new.[3d]



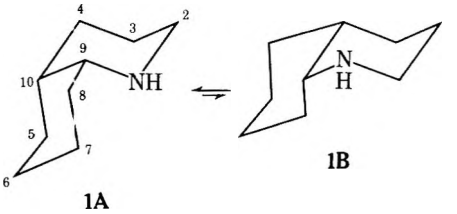
1–11, R = H
1m–11m, R = CH_3

1, R_1–R_7 = H
2, R_1, R_2, R_4–R_7 = H; R_3 = CH_3 (10-CH_3)
3, R_1, R_3–R_7 = H; R_2 = CH_3 (3α-CH_3)
4, R_2–R_7 = H; R_1 = CH_3 (3β-CH_3)
5, R_1–R_4, R_6, R_7 = H; R_5 = CH_3 (6α-CH_3)
6, R_1–R_3, R_5–R_7 = H; R_4 = CH_3 (6β-CH_3)
7, R_1–R_6 = H; R_7 = CH_3 (8α-CH_3)
8, R_1–R_5, R_7 = H; R_6 = CH_3 (8β-CH_3)
9, R_1, R_2, R_4–R_6 = H; R_3 = R_7 = CH_3 (8α, 10-di-CH_3)
10, R_1, R_4–R_7 = H; R_2 = R_3 = CH_3 (3α, 10-di-CH_3)
11, R_2, R_4–R_7 = H; R_1 = R_3 = CH_3 (3β, 10-di-CH_3)

In Table I are summarized all pertinent chemical shifts for compounds **1–11**, in Table II those for **1m–11m**. The spectra were first recorded at 30 °C but because a number of signals for the conformationally heterogeneous compounds **1, 2, 6,** and **8** and their *N*-methyl analogues **1m, 2m, 6m,** and **8m** were exchange-broadened at that temperature, their spectra were also recorded at 55 °C or (in the case of **1**) 65 °C. At these temperatures exchange was fast enough to lead to sharpening of all the signals. At low temperatures (−68 °C) the spectra of the eight conformationally heterogeneous compounds decoalesced into two sets of lines in each case (Tables I and II) which could be assigned to the two contributing conformations. The spectra of the other 14 compounds did not change appreciably upon cooling (except for a slight temperature dependence of the chemical shifts); these compounds are presumably conformationally homogeneous.

In the sequel we shall discuss the spectral assignments for each of the compounds studied, the salient features of the ^{13}C NMR spectra, and, for the conformationally heterogeneous compounds, the position of equilibrium and rationale therefor.

^{13}C Spectra. Except for closely coincident signals (shown in parentheses in Tables I and II to denote that they may have to be interchanged) assignments were made relatively easily by a combination of off-resonance decoupling, analogy with *cis*-decalins,[4] analogies with the *trans*-decahydroquinolines,[2] known[5] effects of methyl substituents in six-membered rings, and, above all, on the basis of the earlier assignment[3] of the parent compounds **1** and **1m** which was confirmed in the present study. Individual compounds will be discussed below; in all cases the carbons next to nitrogen (C-2, C-9, and, where pertinent, NCH_3) displayed signals at lowest field and were distinguished from each other by off-resonance decoupling. At next lowest field was usually found C-10, except in those cases where C-4 and C-5 were downfield shifted by the β_e effect[5] of an appropriately located equatorial methyl group; in all cases the assignment of C-10 was confirmed by off-resonance decoupling which also served to identify signals of *C*-methyl groups, if any.



1A **1B**

1mA, 1mB,
NCH_3 instead of NH

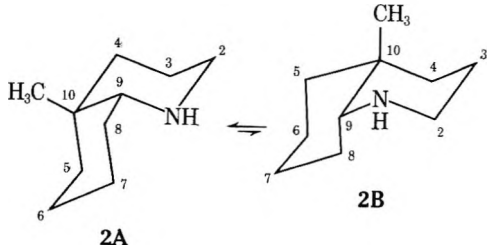
The spectral assignments for this conformer mixture have been made previously.[3a] Our signals agree with those reported, though only moderately well, deviations of 0.5 ppm being common, probably because of the broadness of the lines. At low temperature (Table I) two sets of sharp lines are seen whose shifts are in excellent agreement with those reported[3a,c] (generally within 0.1 ppm). The major set of low-temperature signals is assigned to conformer **1A**, which predominates in a ratio of 90:10 (lit.[3a] 93.5:6.5 at −74 °C). Similar arguments apply to **1m**, which has also been studied previously.[3b] In concordance with the earlier study[3b] we find a diminished percentage of **1mA** (71%, nearly identical with the percentage reported[3b] at −50 °C) compared to **1A**. With one or two exceptions, our signal positions both at 55 and −68 °C agree with

Table I. ^{13}C Chemical Shifts[a] for *cis*-Decahydroquinolines

Compd[b]	Temp[c]	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9[d]	C-10[d]	CH_3
Parent, 1	30	46.58	22.73	29.82	26.57	25.56	21.64	31.87	55.03	35.85	
Parent, 1	65	46.76	23.07	30.09	26.87	25.79	21.85	32.18	55.39	36.30	
Parent, 1A[e]	−68	47.73	21.18	30.60	24.98	26.32	20.34	32.75	54.79	35.13	
Parent, 1B[e]	−68	39.74	*f*	23.97	31.66	*f*	*f*	*f*	53.87	35.60	
10-CH_3, 2	30	46.46	(23.10)	38.21	31.29	(21.87)	21.16	28.31	60.12	32.27	26.52
10-CH_3, 2	55	46.69	(23.32)	38.50	31.62	(22.13)	21.36	28.66	60.48	32.50	26.63
10-CH_3, 2A[g]	−68	47.25	(22.48)	39.19	28.94	(21.42)	19.93	28.01	59.66	31.99	26.22
10-CH_3, 2B[g]	−68	*f*	*f*	*f*	40.26	*f*	25.90	*f*	58.58	32.36	27.30
3α-CH_3, 3(B)	30	47.78	33.38	33.54	31.74	20.65	(26.09)	(25.88)	53.80	36.45	19.78
3β-CH_3, 4(A)	30	55.53	26.59	40.07	26.15	26.59	20.66	32.63	54.69	36.05	19.65
6α-CH_3, 5(A)	30	48.11	21.62	30.85	34.25	33.16	29.29	33.16	54.62	35.75	22.76
6β-CH_3, 6	30	41.69	(26.44)	(26.44)	38.93	26.76	32.97	(26.13)	54.55	35.11	21.57
6β-CH_3, 6	55	41.97	(26.58)	(26.72)	38.93	26.93	32.99	(26.34)	54.76	35.20	21.49
6β-CH_3, 6A[h]	−68	47.50	20.92	(30.08)	(32.42)	*f*	(28.37)	*f*	54.79	(30.08)	17.90
6β-CH_3, 6B[h]	−68	39.53	27.23	24.80	40.45	26.17	34.35	25.17	53.65	35.91	22.60
8α-CH_3, 7(A)	30	48.17	22.05	31.14	24.80	26.52	28.48	36.65	60.44	37.22	18.65
8β-CH_3, 8	30	43.31	25.10	27.81	29.47	21.16	31.49	30.65	61.17	34.10	18.37
8β-CH_3, 8	55	43.50	25.20	28.00	29.54	21.24	31.55	30.95	61.39	34.28	18.38
8β-CH_3, 8A[i]	−68	47.84	21.49	(30.38)	25.16	20.44	26.18	34.85	60.41	(30.08)	17.54
8β-CH_3, 8B[i]	−68	38.98	26.75	24.77	32.05	21.04	34.53	26.63	60.64	35.65	18.85
8α,10-Dimethyl, 9(A)	30	47.89	(22.86)	40.22	28.99	(22.08)	28.28	30.75	65.62	33.36	18.98 (8)
											26.14 (10)
3α,10-Dimethyl, 10(B)	30	47.55	28.27	38.16	40.74	21.72	(26.38)	(26.69)	58.87	33.50	19.98 (3)
											28.39 (10)
3β,10-Dimethyl, 11(A)	30	55.41	28.03	49.39	30.43	21.97	20.27	28.33	59.84	32.85	19.56 (3)
											26.29 (10)

[a] In $CDCl_3$, from internal Me_4Si, ppm. Parentheses indicate that assignments are not unambiguous. [b] *cis*-Decahydroquinoline. For conformations A and B see formula schemes in text. "α" means "substituent is on the opposite side as the hydrogen at C-10," "β" means "on the same side of the ring as this hydrogen." [c] °C. Only when compounds were found to be conformationally inhomogeneous at room temperature, were low and high temperature ^{13}C NMR spectra recorded. [d] 9 and 10 are used rather than 8a and 4a to allow exclusive use of "a" for "axial." [e] 90% 1A; 10% 1B. [f] Not observed because either overlaid by a signal of the major component or too small to be discerned. [g] 94% 2A; 6% 2B. [h] 11% 6A; 89% 6B. [i] 41.5% 8A; 58.5% 8B.

those reported[3b] to within 0.2 ppm (average deviation 0.1 ppm).



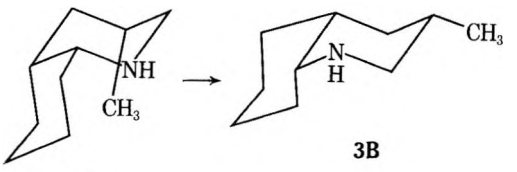
2A 2B

2mA, 2mB, NCH_3 instead of NH

Since compound 2[3d] is conformationally heterogeneous, assignments in the low-temperature spectrum of **2A** are discussed first. Signals for C-2 and C-7 are essentially unchanged from the parent compound **1A**. C-4 is shifted nearly 9 ppm downfield by the β_e effect of the methyl substituent, C-5 is shifted 4 ppm downfield by a β_a effect. Signals for C-6 and C-8 are shifted upfield by the axial methyl group (steric shift) by 4.5–5 ppm. In the minor isomer **2B** only CH_3, C-5, C-7, C-9, and C-10 were seen. Integration indicates 94% of the major isomer and 6% of the minor. The room temperature spectrum can be assigned by its general similarity with that of the major conformer. The steric compression effect of the axial methyl group shifts from the cyclohexane ring (C-6, C-8) to the piperidine ring (C-3) as one passes from **2A** to **2B**, whereas that of the axial methylene and NH groups of the ring junctions passes from C-3, C-5, and C-7 to C-2, C-4, C-6, and C-8. The effects at C-3, C-6, and C-8 should roughly compensate each other, but C-4 and C-2 should move upfield in **2B** and therefore in the mixture **2** whereas C-5 and C-7 should move downfield; these changes are indeed observed. (The upfield shift for C-4 is enhanced by a change from the larger downfield shifting β_e to the smaller β_a whereas the downfield shift of C-5 is enhanced by the opposite change as one proceeds from **2A** to **2B**.)

The assignments in the *N*-methyl analogues **2mA** and the conformer mixture **2m** were made analogously by comparison with **1mA** and **1m**. In this case, most of the signals for the minor isomer **2mB** were recorded and the predicted effects on C-2, C-4, C-5, and C-7 (vide supra) as one passes from **2mA** to **2mB** can be individually verified. C-8 in **2mB** is 7.5 ppm upfield from C-8 in **2mA** and the conformer mixture at 55 °C also shows a substantial upfield shift of C-8 compared to its position in the major iscmer **2mA**. Part of this shift is no doubt due to the change of the Me–N–C(9)–C(8) segment from the e,e to the e,a conformation.[5] However, this conformational change may be insufficient to account for the total effect; we shall return to this point later.

The ratio of **2mA** to **2mB**, obtained by integration of several peaks belonging to each conformer, is 77:23 at −68 °C.



3A 3B

3mA, 3mB, NCH_3 instead of NH

Compound **3** displays a sharp spectrum at room temperature, indicating conformational homogeneity; conformer **3A** should be greatly destabilized by a CH_3/CH_2 syn-axial interaction. Thus **3** exists entirely as **3B**. Its signals correspond closely to those in **1B** where comparison[3a] is possible except for C-3 and C-2, C-4 which are affected by α_e and β_e effects, respectively. C-6, C-7, and C-8 were not seen in **1B**; the assignment of C-6 is unequivocal[3b] but C-7 and C-8 are too close

Table II. ^{13}C Chemical Shifts[a] for *N*-Methyl-*cis*-decahydroquinolines, and Shift Effects[b] upon Introduction of Equatorial or Axial *N*-Methyl Groups

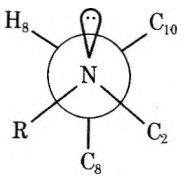
Compd[c]	Temp[d]	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	CCH_3	NCH_3
N-CH_3, **1m**	+30	55.8[e]	23.35	28.44	28.44	25.01	21.86	25.9[e]	62.89	36.94		42.91
N-CH_3, **1m**	+55	55.17	23.46	28.91	28.56	25.18	22.00	25.73	63.00	37.13		42.87
N-CH_3, **1mA**[f]	−68	58.38	21.71	30.83	26.41	26.13	19.65	29.39	63.42	36.47		43.22
(Effect of N-Me		+10.65	+0.53	+0.23	+1.43	−0.19	−0.69	−3.36	+8.63	+1.34)		
N-CH_3, **1mB**[f]	−68	47.47	25.39	22.88	31.67	20.94	*g*	15.65	60.69	36.14		42.53
(Effect of N-Me		+7.73		−1.09	+0.01				+6.82	+0.54)		
N,10-Dimethyl, **2m**	+30	55.3[e]	22.01	36.5[e]	34.3[e]	22.18	21.83	21.53	68.18	33.49	27.27	43.32
N,10-Dimethyl, **2m**	+55	54.75	22.14	36.00	34.61	22.30	21.91	21.31	68.18	33.62	27.33	43.27
N,10-Dimethyl, **2mA**[h]	−68	58.15	(21.66)	39.52	29.86	(21.51)	19.20	23.23	68.66	32.84	26.58	43.47
(Effect of N-Me		+10.90	−0.82	+0.33	+0.92	+0.09	−0.73	−4.78	+9.00	+0.85	+0.36)	
N,10-Dimethyl, **2mB**[h]	−68	47.37	*g*	27.95	40.64	*g*	25.39	15.70	65.85	33.61	26.83	42.88
(Effect of N-Me					+0.38		−0.51		+7.27	+1.25	−0.47)	
N,3α-Dimethyl, **3m(B)**	+30	55.75	31.46	32.59	31.81	21.10	25.63	16.55	60.53	35.96	19.71	42.31
(Effect of N-Me		+7.97	−1.92	−0.95	+0.07	+0.45	−0.46	−9.33	+6.73	−0.49	−0.07)	
N,3β-Dimethyl, **4m(A)**	+30	66.23	26.73	40.09	27.40	26.79	19.85	29.29	63.20	37.55	19.97	43.04
(Effect of N-Me		+10.70	+0.14	+0.02	+1.25	+0.20	−0.81	−3.34	+8.51	+1.50	+0.32)	
N,6α-Dimethyl, **5m(A)**	+30	58.58	21.99	31.07	35.48	33.41	28.52	29.64	63.09	37.16	22.63	43.07
(Effect of N-Me		+10.47	+0.37	+0.22	+1.23	+0.25	−0.77	−3.52	+8.47	+1.41	−0.13)	
N,6β-Dimethyl, **6m**	+30	48.74	25.64	24.81	40.17	27.08	33.56	16.82	61.27	35.94	22.23	42.68
N,6β-Dimethyl, **6m**	+55	49.21	25.60	25.26	40.17	27.26	33.56	17.41	61.58	35.88	22.11	42.73
N,6β-Dimethyl, **6mB**[i]	−68	47.32	25.89	23.56	40.28	26.66	33.71	15.30	60.32	36.24	22.60	42.51
(Effect of N-Me		+7.79	−1.34	−1.24	−0.17	+0.49	−0.64	−9.87	+6.67	+0.33	0.00)	
N,8α-Dimethyl, **7m(A)**	+30	59.56	21.64	30.85	26.61	26.40	28.42	39.98	68.80	39.80	23.24	45.31
(Effect of N-Me		+11.39	−0.41	−0.29	+1.81	−0.12	−0.06	+3.33	+8.36	+2.58	+4.59)	
N,8β-Dimethyl, **8m**	+30	56[e]	21.29	29.74	28.19	20.54	28.5[e]	30.43	69.16	28.75	18.13	43.16
N,8β-Dimethyl, **8m**	+55	55.47	21.43	29.68	28.49	20.71	28.71	30.25	69.23	28.94	18.26	43.15
N,8β-Dimethyl, **8mA**[j]	−68	58.66	21.28	30.48	26.17	19.79	24.85	29.56	70.00	28.08	17.39	43.38
(Effect of N-Me		+10.82	−0.21	+0.10	−1.01	−0.65	−1.33	−5.29	+9.59	−2.00	−0.15)	
N,8β-Dimethyl, **8mB**[j]	−68	45.66	(20.71)	*g*	31.74	(20.71)	35.57	(27.36)	67.41	(28.32)	19.45	41.71
(Effect of N-Me		+6.68	−6.04		−0.31	−0.33	+1.04	+0.73	+6.77	−7.33	+0.60)	
N,8α,10-Trimethyl, **9m(A)**	+30	59.38	22.11	39.75	30.81	22.48	28.26	31.98	73.93	35.39	23.42 (8)	45.38
(Effect of N-Me		+11.49	−0.75	−0.75	+1.82	+0.40	−0.02	+1.18	+8.31	+2.03	+4.44 27.42 (10) +1.28	
N,3α,10-Trimethyl, **10m(B)**	+30	55.75	27.43	37.31	41.09	21.72	25.79	16.10	65.75	34.48	19.97 (3)	42.74
(Effect of N-Me		+8.20	−0.84	−0.85	+0.35	±0.0	−0.59	−10.59	+6.88	+0.98	−0.01 29.06 (10) +0.67	
N,3β,10-Trimethyl, **11m(A)**	+30	66.28	26.63	49.48	31.45	22.11	19.53	23.74	68.51	33.83	19.75 (3)	43.33
(Effect of N-Me		+10.87	−1.40	+0.09	+1.02	+0.32	−0.74	−4.59	+8.67	+0.98	+0.19 26.63 (10) +0.34	

[a] See footnote *a*, Table I. [b] Data in parentheses; calculated for pairs of conformationally homogeneous compounds. $\delta_{mA} - \delta_A$, or $\delta_{mB} - \delta_B$; a plus sign indicates that the signal is downfield shifted upon introduction of the NCH_3 group. Position of NCH_3 is not definite in **1mB**, **3mB**, and **6mB** (see Discussion). [c] See footnote *b*, Table I. [d] See footnote *c*, Table I. [e] Signal was extremely broad. [f] 71% **1mA**, 29% **1mB**. [g] See footnote *f*, Table I. [h] 77% **2mA**, 23% **2mB**. [i] >95% **6mB**; only the signal for C-9 (63.59) of **6mA** could be observed. [j] 89.5% **8mA**, 10.5% **8mB**.

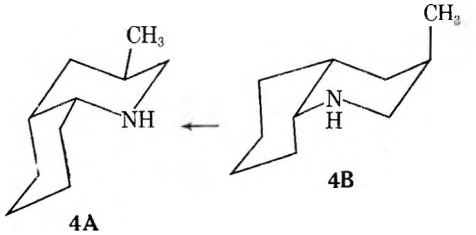
for unambiguous assignment, since C-7, which is 1.4 ppm downfield of C-8 in *cis*-decalin (low-temperature spectrum),[4] is shifted upfield[2] by replacement of the $CH_2\gamma$ group by NH. The equatorial methyl group in **3B** is shifted upfield from its normal[5] position by the anti-periplanar nitrogen.[6]

Compound **3m** is similarly conformationally homogeneous. Accordingly, all its signals correspond closely to those[3b] of **1mB** save those at C-3 (α_e effect) and C-2 and C-4 (β_e effect). C-8 is found at very high field similarly as in **1mB** and **2mB**. Comparison of C-8 in **3mB** with C-8 in **3B** (a corresponding comparison could not be made for **1** or **2**) indicates a −9.3 ppm (upfield) shift in the *N*-methyl compound. In the carbocyclic analogues, the computed[5b] upfield shift (combination of gauche and buttress effects) is −6.8 ppm and the observed[4] shift from *cis*-decalin to 1β-methyl-*cis*-decalin is −6.5 ppm. We have reported elsewhere[7a] that enhanced upfield shifts occur when there is a combination of an anti-periplanar lone pair and a methyl group on amine nitrogen (Chart I). It is not clear whether the effect is actually caused by the lone pair or whether it is simply an enhanced compression effect. However, the latter alternative is unlikely because the effect does not operate in reverse: the upfield shift of an axial *N*-methyl group[2] by introduction of an equatorial methyl gauche to it[7a,c] is only −7.7 ppm.

Chart I



C-8 is shifted upfield when R = CH_3 but not when R = H

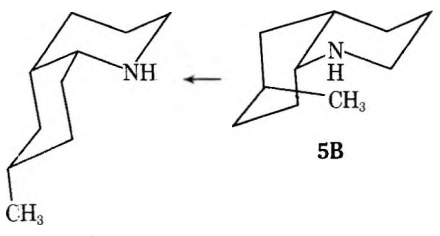


4A **4B**

4mA, 4mB,
NCH_3 instead of NH

The signals in **4**[3d] are sharp at room temperature, pointing to conformational homogeneity. In this case the intrinsic preference for the **A** isomer (cf. discussion of **1** above) is reinforced by the fact that **4B** would have an axial methyl group. The signals for C-2, C-3, and C-4 in **4A** are shifted downfield from those in **1A** by the expected α_e and β_e effects. The equatorial methyl group is shifted upfield by the anti-periplanar nitrogen[6] as discussed above for **3B**.

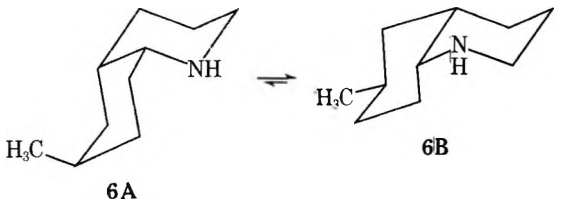
Compound **4m** similarly exists in conformation **4mA** with the expected downfield shifts, relative to **1mA** at C-2, C-3, and C-4. The complete coincidence of C-8 with that in **1mA** confirms the absence of the **4mB** isomer in which, as discussed above, C-8 would have shifted strongly upfield.



5A **5B**

5mA, 5mB,
NCH_3 instead of NH

Compound **5** also shows a sharp ^{13}C spectrum at room temperature: conformer **5B** with its methyl group syn-axial to C-4 is not viable. Comparison of **5A** (= **5**) with **1A** discloses essentially unchanged shifts in the piperidine ring; in the cyclohexane ring C-6, C-5, and C-7 experience the expected downfield α_e and β_e shifts of the methyl substituent which, itself, displays the normal shift. The situation in **5m** (= **5mA**) is entirely analogous.

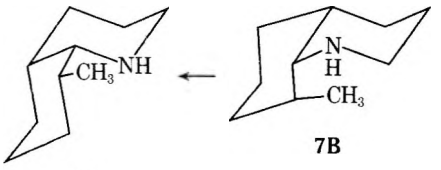


6A **6B**

6mA, 6mB,
NCH_3 instead of NH

Compound **6**, the diastereomer of **5**, is conformationally heterogeneous as indicated by its broad spectrum at room temperature which sharpens only on warming to 55 °C. At −68 °C two spectra are seen, that of the major isomer **6B** (89%) and that of the minor isomer **6A** (11%). Assignments in the minor isomer are based on comparison with **1A** with little shift occurring at C-2, C-3, C-4, and C-9. The remaining assignments are uncertain because two of the expected signals were not seen and off-resonance decoupling could not be performed on the rest, which are all expected to fall in the same region of the spectrum. The position of the axial methyl group is normal. Assignment of the signals in **6B** is straightforward through comparison with **1B**[3a] and **3B** taking into account the α_e and β_e effects of the methyl substituent at C-6,5,7. We note, however, that the position of C-3 in **6B** (27.23 ppm) is 2.2 ppm upfield from that published[3a] for **1B** (29.4 ppm). A similar discrepancy is found between **8B** (see below: C-3 at 26.75 ppm) and **1B**; we have already indicated[3c] that we could not find a resonance for **1B** at the position reported. (We do find a weak signal in the low-temperature spectrum of **1** at ca. 27.1 ppm but this signal may be caused by *trans*-decahydroquinoline impurity which, at room temperature, displays C-3 at 27.29 ppm.[2]) In the conformer mixture **6** at 55 °C, assignments are based on similarity of signal positions with those in the major conformer **6B**; C-4, C-8, and C-3 are, however, too close to each other for individual assignment.

The situation in **6m** is similar to that in **6** except that the minor conformer is reduced to less than 5% and only one of its carbons (C-9, at 63.59 ppm) could be seen. The peaks of the major conformer (and hence of the conformer mixture **6m**) are readily assigned by comparison with **1mB**.



7A **7B**

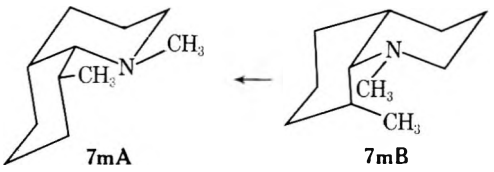
Conformation **7B**, with the methyl group syn-axial to C-2 and C-4, will not contribute and therefore **7** displays a sharp spectrum at room temperature. Assignments of peaks, by comparison with the parent compound **1A**, is straightforward. C-2, C-3, C-4, C-5, and C-6 are little affected by the methyl substituent. The relatively large downfield shift of C-10 comes from the $\beta_g\gamma_t$ effect[4] (corresponding to the $\beta_a\gamma_e$ effect[5b] in monocyclic systems) introduced by the combination of N-1 (β_g) and Me-8 (γ_t). C-8 shifts downfield by only ca. 3.9 ppm (Table III), considerably less than the α carbon in the other

Table III. Effects[a] of Methyl Substitution on ^{13}C Chemical Shifts in *cis*-Decahydroquinolines[b]

Effect[c,d]	Ring atom	Value Found	Value Calcd[c]	Compd[b]
α_e	3	(+5.4)	+6.0	4(A)
α_e	3	(+6.2[e])	+6.0	3(B)
α_e	6	(+6.8)	+6.0	5(A)
α_e	6	(+5.5[f])	+6.0	6B
α_e	3	(+5.6[g])	+6.0	11(A)
$\alpha_e + \alpha_e\beta_a$	8	(+3.9)	+3.1	7(A)
$\alpha_e + \alpha_e\beta_a$	8	(+2.7[g])	+3.1	9(A)
$\alpha_e + \alpha_e\beta_e$	8	(+0.8[f])	+3.5	8B
β_e	2	(+7.8)	+9.0	4(A)
β_e	2	(+8.0)	+9.0	3(B)
β_e	4	(+9.5)	+9.0	4(A)
β_e	4	(+9.6)	+9.0	3(B)
β_e	5	(+9.3)	+9.0	5(A)
β_e	5	+8.8	+9.0	6B
β_e	7	(+9.0)	+9.0	5(A)
β_e	7	(+8.3[f])	+9.0	6B
β_e	7	(+8.4[f])	+9.0	8B
β_e	2	(+8.2[g])	+9.0	11(A)
β_e	4	(+10.2[g])	+9.0	11(A)
$\beta_e + \beta_e\gamma_a$	7	(+8.1)	+8.2	7(A)
$\beta_e + \beta_e\gamma_a$	7	(+8.4[g])	+8.2	9(A)
$\beta_e + \alpha_a\beta_e$	9	(+5.7)	+5.6	7(A)
$\beta_e + \alpha_a\beta_e$	9	(+6.0[g])	+5.6	9(A)
$\beta_e + \alpha_e\beta_e$	9	+6.8	+6.5	8B
$\beta_e + G_\beta$	4	+8.6	+7.7	2A
$\beta_e + G_\beta$	4	+9.1[h]	+7.7	9(A)
$\beta_e + G_\beta$	4	+9.3[i]	+7.7	11(A)
$\beta_e + G_\beta$	5	+8.6	+7.7	2B
$\beta_e + G_\beta$	5	+9.0[j]	+7.7	10(B)
α_a	8	+2.1	+1.4	8A
$\alpha + Q\text{-}T + 2V_g$	10	−3.1	−3.2[k]	2A
$\alpha + Q\text{-}T + 2V_g$	10	−3.2	−3.2[k]	2B
$\alpha + Q\text{-}T + 2V_g$	10	−3.9[h]	−3.2[k]	9(A)
$\alpha + Q\text{-}T + 2V_g$	10	−3.0[j]	−3.2[k]	10(B)
$\alpha + Q\text{-}T + 2V_g$	10	−3.2[i]	−3.2[k]	11(A)
β_a	7	+5.8	+5.4	8A
β_a	9	+5.6	+5.4	8A
$\beta_a + G_\beta$	4	+4.6[j]	+4.1	10(B)
$\beta_a + G_\beta$	5	+4.0	+4.1	2A
$\beta_a + G_\beta$	5	+4.2[h]	+4.1	9(A)
$\beta_a + G_\beta$	5	+4.3[i]	+4.1	11(A)
$\beta_a + G_\beta$	9	+4.9	+4.1	2A
$\beta_a + G_\beta$	9	+4.7	+4.1	2B
$\beta_a + G_\beta$	9	+5.2[h]	+4.1	9(A)
$\beta_a + g_\beta$	9	+5.1[j]	+4.1	10(B)
$\beta_a + G_\beta$	9	+5.2[i]	+4.1	11(A)
γ_a	6	−5.9	−6.4	8A
$\gamma_a + G_\gamma$	3	−5.1[j]	−4.4	10(B)
$\gamma_a + G_\gamma$	6	−4.9	−4.4	2A
$\gamma_a + G_\gamma$	6	−4.4[h]	−4.4	9(A)
$\gamma_a + G_\gamma$	6	−4.6[i]	−4.4	11(A)
$\gamma_a + G_\gamma$	8	−4.7	−4.4	2A
$\gamma_a + G_\gamma$	8	−5.9[h]	−4.4	9(A)

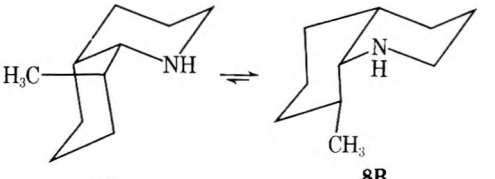
[a] Reference: **1A** or **1B** unless otherwise indicated. Where room temperature signals (of **3**, **4**, **5**, **7**, and **9**) are compared with the signals at −68 °C in **1A**, **1B** (or in other low temperature spectra as indicated), the effects are placed in parentheses. Disregard of the temperature change leads to inaccuracies of 0.1–0.9 ppm (see text). [b] Similar results are obtained on comparison of NCH_3 compounds (**mA** vs. **1mA**, and **mB** vs. **1mB**), except for **7mA** and **9mA** [syn-axial $CH_3(1)/CH_3(8)$] and **8mB** [axial $CH_3(1)$ compared to equatorial in **1mB**]. [c] Parameters of Table IV, ref 5b, were used if not otherwise indicated. [d] $\delta_A - \delta_{1A}$, or $\delta_B - \delta_{1B}$, if not otherwise indicated. A positive sign indicates that the signal is downfield in the methyl substituted compound. [e] Corresponding signal was not seen in **1B**; the signal in **6B** (−68 °C) was used instead. [f] Corresponding signal was not seen in **1B**; the signal in **3**(B) (30 °C) was used instead. [g] Compared with **2A**. [h] Compared with **7(A)**. [i] Compared with **4(A)**. [j] Compared with **3(B)**. [k] Since no comparable parameters are given in ref 5b, the values from ref 4 are used.

methyl derivatives, because the usual α_e effect is, in the present situation, complemented by an $\alpha_e\beta_a$ effect (Me-8, N-1).[2,5b] Similarly, the β_e effect is ca. 8.2 ppm (see Table III) at C-7 but the downfield shift at C-9, where an $\alpha_a\beta_e$ effect (of N-1 and Me-8) contributes,[5b] is much smaller. The *C*-methyl group, though equatorial, resonates at relatively high field because of gauche interaction with N-1.[6]



7mA **7mB**

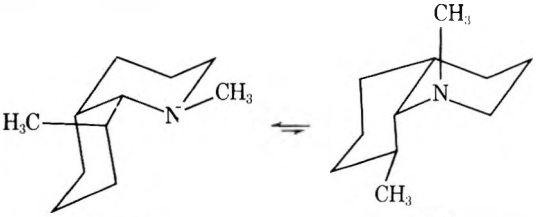
The conformational situation in **7m** is more complex. The syn-axial N-Me/C-Me interaction in **7mA** cannot be relieved by making the *N*-methyl group axial, since even more serious congestion would result. Conformer **7mB** is excluded for the reasons mentioned for **7B**; thus **7m** seems to exist entirely in conformation **7mA** (compare signals at C-3, C-4, C-5, and C-6 with **1mA**). The distortion which no doubt occurs in this rather strained species reflects itself in downfield shifts at C-2 and C-10 (ca. 1.2 and 3.3 ppm relative to **1mA**—the corresponding shift differences of **7A** vs. **1A** are ca. 0.4 and—vide supra—2.1 ppm; in contrast, the shift differences at C-7 and C-9 are similar for **7** and **7m**). Most notable is the mutual downfield shifting of the methyl groups in **7mA**: C-Me from 18.65 ppm in **7** to 23.24 ppm in **7m**; N-Me from 43.22 ppm in **1mA** to 45.31 ppm in **7mA**. This effect is similar to that seen by Stothers and co-workers for Me syn-axial to OH.[9] Also remarkable is the large downfield shift of C-8 relative to **1mA** (10.6 ppm) and to **7A** (3.3 ppm—the γ-gauche upfield shift of the N-Me group is evidently overwhelmed); similar downfield shifts are seen in other systems[2,9] for ring carbons which bear syn-axial substituents.



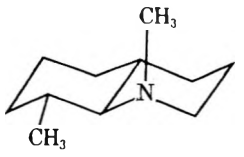
8A **8B**

Of the compounds studied, **8** is the conformationally most heterogeneous. At room temperature, most of its signals were quite broad, though a sharp spectrum was obtained at 55 °C. At −68 °C the spectrum was resolved into that of a major conformer **8B** (59%) and of a minor one, **8A** (41%) whose signal assignments rest on those of **1A**, and of **1B** and **3B**, respectively. The signals of **8A** remote from the methyl group agree well with those of **1A** and the shifts engendered by the methyl are satisfactorily explained in terms of the usual α_a, β_a, and γ_a effects. Agreement of **8B** with **1B** and **3B** is less good, possibly due to a shifting of the NH from the normal[10] equatorial to the axial position caused by Me-8. Particularly to be noted is the anomalously small $\alpha_e + \alpha_e\beta_e$ effect of the methyl group (itself normal in shift) on C-8 of only 0.75 ppm.

The signals of the conformer mixture at 55 °C are readily assigned from those of the two components and knowledge of their relative proportions.

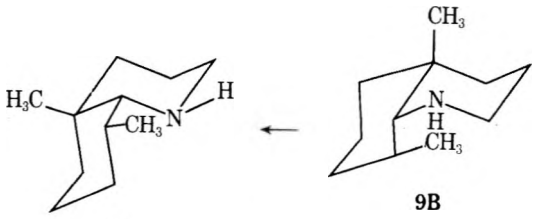


8mA **8mB**



12

In the *N*-methyl derivatives **8m** the conformational proportions are reversed from those of the corresponding NH compounds **8**. Conformer **8mA** now clearly predominates (89.5%) with **8mB** contributing but 10.5%. The signals of **8mA** are readily assigned from those of **1mA** with reasonable agreement after application of the usual α_a, β_a, and γ_a shifts. However, the signals of **8mB** are not comparable to those of **1mB**[3b] because model considerations indicate that the N-Me group in **8mB** is sterically prevented from occupying its normal[7b] equatorial position. Shifting it to the axial position will bring about changes at C-2, C-3, C-9, and C-10, as well as at C-8 which is now no longer anti-periplanar to the lone pair and thus no longer experiences the upfield shifting effect from either that cause or that of a buttressing gauche substituent (vide supra). Nevertheless, the assignment of the low-field signals to C-2 and C-9 is straightforward. The position of C-3 can be estimated by its similarity with C-3 in the trans analogue **12**;[2] C-4 is not much affected by the position of the *N*-methyl group and should be close to its normal position (**1mB**, **6mB**) of 25.5 ppm; both signals are overlaid by signals of the major conformer **8mA**. C-5 and C-6 are assigned from the spectrum of **1mB**, C-7 from the spectrum of **12**. C-10 is expected at 28 ppm (correcting the value of 35.65 in **8B** by a γ_a effect[2] of −7.5 ppm). C-8 might be expected at 26.6 ppm, its shift in **8B**; signals are found at 28.32 and 27.36 ppm. Both the signals of C-8 and of NCH_3 are at lower field than predicted: in **12**, NCH_3 resonates at 33.23, and correction for the gauche and buttressing effects[5b] of C-8 6.77 ppm) which are absent in **8mB** brings the expected value to 40 ppm. It would appear from the literature[11] that the 1,2-anti-periplanar arrangement of two groups causes an additional downfield shift of about 1.5 ppm which may account for the lower than expected field position of the signals for C-8 and N-Me. Me-8 in **8mB** agrees well in shift with 8-Me in **12**.

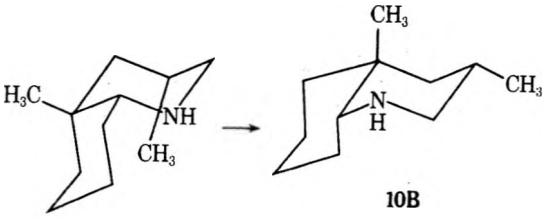


9A **9B**

9mA, 9mB,
NCH_3 instead of NH

Compound **9** shows the sharp spectrum of a conformationally homogeneous species (**9A**): **9B** suffers from the same methyl–methylene syn-axial interactions as **7B**. Assignment of signals in **9A** is straightforward on the basis of the analogy with **2A** and **7A**. As in **2A**, C-3 and C-6 are too close to each other for unequivocal assignment.

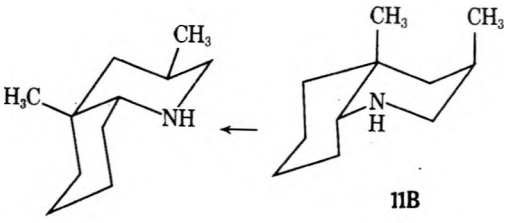
The spectrum of **9m** similarly points to conformational homogeneity in the form **9mA**. C-8, C-10, and the methyl groups can be assigned easily from the off-resonance decoupled spectrum, the rest of the signals by analogy with **7m(A)** and **2mA**.



10A **10B**

10mA, 10mB,
NCH_3 instead of NH

The 3α,10-dimethyl-*cis*-decahydroquinoline (**10**) exists exclusively in conformation **10B** because of a CH_3/C-5 syn-axial interaction in the **A** conformation. Assignment of signals is facile by comparison with **3** and use of parameters for methyl substitution,[2] except for C-7 and C-8, which are too close for unambiguous assignment. Compound **10m** is also conformationally homogeneous (**10mB**); in this compound the NCH_3 group must be exclusively in the equatorial position through the biasing influence of the CH_3-10 group, as in **2mB**. Again C-8 resonates at very high field.



11A **11B**

11 mA, 11mB,
NCH_3 instead of NH

Compound **11**, finally, exists in conformation **A** whose natural predominance is further enhanced by the CH_3/CH_3 syn-axial interactions in **B**. The same is true for **11m** (= **11mA**). Assignment of signals is unambiguous by comparison with **4(A)**, **2A** and **4m(A)** and **2mA**, respectively.

The various shift parameters which may be derived from the observed shifts in the *cis*-decahydroquinoline series are collected in Table III. Because of temperature dependence of ^{13}C shifts (found, in some *trans*-decahydroquinolines, to range from 0.1 to 0.9 ppm over a 100 °C temperature range, with a

Table IV. Conformational Equilibria in Mobile *cis*-Decahydroquinolines[a]

	R = H			R = CH_3 (m series)		
Compd	A, %	B, %	$\Delta G°_{205}$, kcal/mol	A, %	B, %	$\Delta G°_{205}$, kcal/mol
1	90 ± 1[b]	10 ± 1[b]	0.90 ± 0.05[b]	71 ± 2[c]	29 ± 2[c]	0.36 ± 0.04
2	94.5 ± 1	5.5 ± 1	1.16 ± 0.08	77 ± 1	23 ± 1	0.49 ± 0.03
6	11 ± 1	89 ± 1	−0.85 ± 0.04	<5	>95	<−1.2
8	41 ± 2	59 ± 2	−0.15 ± 0.04	89.5 ± 1.5	10.5 ± 1.5	0.87 ± 0.07

[a] In $CDCl_3$ at −68 °C (205 K). For enumeration of signals used in integration, see Experimental Section. [b] Lit.[3a] 93.5% **A**, 6.5% **B** at −74 °C, $\Delta G°$ = 1.05 kcal/mol. [c] Lit.[3b] 70% **A**, 30% **B** at −50 °C, $\Delta G°$ = 0.38 kcal/mol.

mean of 0.46 ppm) some of these parameters, where room temperature data are compared with the low temperature values of the parent compounds **1A** and **1B**, are of low accuracy. Such values are marked as such in Table III and are included only for the sake of completeness. For the same reason, standard deviations are not indicated in the table.

The most salient aspect of the data in Table III is the generally very close agreement of the parameters in the *cis*-decahydroquinoline series with the Grant parameters[4,5] in cyclohexane. This feature had been previously observed in *trans*-decahydroquinolines.[2]

Conformational Analysis. In Table IV are shown the percentages of the two conformers (**A** and **B**) for **1, 2, 6,** and **8** and their *N*-methyl derivatives **1m, 2m, 6m,** and **8m,** along with the corresponding free-energy differences, at −68 °C, for the equilibrium **A** ⇌ **B** (cf. the earlier diagrams). These percentages were obtained by integration of the C-13 signals in the low-temperature spectra. While it is known that there are pitfalls in the procedure—unequal NOE effects and relaxation times may cause the signals not to be proportional in area to the number of nuclei—in the present instance the chances for systematic error are reduced because except in the case of **6m,** several different sets of signals belonging to the two conformers were integrated (see Experimental Section). In addition, Booth and Griffiths[3b] have cited evidence relating to T_1 measurements in *cis*-decahydroquinolines which suggests that at least the CH_2 groups should provide reliable integrals in a mixture of isomers or conformers.

The position of equilibrium for **1** and **1m** has been determined previously[3a] and interpreted[3b] in a straightforward way. In **1A** two of the butane-gauche interactions of *cis*-decalin are replaced by the less unfavorable[12] propylamine-gauche interactions. In **1B** one of the butane-gauche interactions is replaced by a *more* unfavorable C–N–C–C gauche interaction (more unfavorable because the C–N distance is shorter than C–C). Quantitatively speaking one may compare the situation in **1A** to that in axial *N*-methylcyclohexylamine, which is[13] about 1 kcal/mol less stable than the equatorial isomer, the difference between its conformational equilibrium and that of methylcyclohexane ($-\Delta G_{Me}$ = 1.7 kcal/mol) being 0.7 kcal/mol. (Complete agreement between this figure and the 0.90 kcal/mol difference between **1A** and **1B** cannot be expected, for whereas the conformational situation in **1A** is similar to that in the axial conformation of *N*-methylcyclohexylamine, the equatorial conformer of this amine has possibilities of rotational isomerism which do not exist in **1B.** The qualitative conclusion—that **1B** should be disfavored by more than 0.7 kcal/mol—is indeed borne out.)

Compared to the **1A** ⇌ **1B** case, the equilibrium in **1mA** ⇌ **1mB** is shifted substantially toward the **B** isomer. This has been explained[3b] as being due to a $CH_2(8)/CH_3(N)$ compression in **1mA** which is clearly seen in a Dreiding model. Another way of interpreting this interaction is to say that in a saturated heterocyclic six-membered ring, the region around the heteroatom is usually puckered (torsional angle $\tau > 60°$). One result of this puckering is to bring the equatorial/equatorial (e,e) vicinal groups closer together than the equatorial/axial (e,a) ones, contrary to what happens in cyclohexane[14] where $\tau_{e,e}$ (≈65°) > $\tau_{e,a}$ (≈55°).

We note that ΔG in **1m** is similar to the value determined previously[15] by an indirect method in solvent methanol (0.47 kcal/mol) but quite different from the value[15] in glyme, 1.3 kcal/mol.

The N-Me(a) ⇌ N-Me(e) equilibrium in **1m** requires mention. Axial *N*-methyl cannot contribute in **1mA** because of the syn-axial interactions with C-5 and C-7. However, **1mB** (and, thus, also **3mB** and **6mB**) may exist in part with axial *N*-methyl. In **2mB** and **10mB** the NCH_3 must be purely equatorial (N-Me/10-Me syn-axial interactions in the N-Me axial form), in **8mB** purely axial (N-Me/8-Me syn-axial interaction in the equatorial form). In **1mB** the axial NCH_3 conformation has two Me/H syn-axial interactions whereas the conformation with equatorial N-Me has only one; the difference thus amounts to one syn-axial N-Me/H. The magnitude of this interaction has been variously estimated as ½ × 1.8 = 0.9 kcal/mol[7b] or ½ × 3.0 = 1.5 kcal/mol.[8b] The former value would indicate the presence of 18% of the N-Me(a) conformation at 30 °C and 10% at −68 °C; the latter 7.5% at 30 °C and 2.5% at −68 °C. Accurate experimental information is, unfortunately, hard to come by: the axial N-Me in **8mB** and the equatorial ones in **2mB** and **10mB** (Table II) are too close in shift to permit reliable interpolation for the cases of **1mB, 3mB,** and **6mB.** One can use the shift changes of C-3, C-10, and C-8 upon addition of an *N*-methyl group as an indicator, if the signals can be seen in both NH and NCH_3 derivatives of equatorially biased (**2mB, 10mB**), axially biased (**8mB**), and "mobile" (**1mB, 3mB, 6mB**) compounds (Table II). The changes at C-8 are most telling, since this C atom is shifted strongly upfield by equatorial N-methylation (**10B** → **10mB:** −10.6 ppm), but downfield by axial N-methylation (**8B** → **8mB:** +0.7 ppm). Use of the corresponding shift differences at 30 °C (**3B** → **3mB:** −9.3 ppm) and at −68 °C (**6B** → **6mB:** −9.9 ppm) allows estimation of the conformational population in the "mobile" systems. The results are 11.5% NCH_3 axial at 30 °C (K = 7.7; $\Delta G°$ = 1.2 kcal/mol) and 6% NCH_3 axial at −68 °C (K = 15.1; $\Delta G°$ = 1.1 kcal/mol). This suggests that the NCH_3 axial conformation may be disregarded even in the **mB** series (except in the case of **8mB,** vide supra) and that the N-Me/H syn-axial interaction is higher than we have reported previously.[7b] In an investigation independent of ours[7b] and Robinson's,[8a,b] $-\Delta G°$ for N-Me was indeed found to be ≥2.7 kcal/mol.[8c]

The conformational equilibria in **2**[3d] and **2m** are surprising. One might have expected that the methyl group at C-10 finds itself in a less favorable environment in conformation **A** (methyl syn-axial to two hydrogen atoms in the cyclohexane ring) than in conformation **B** (methyl syn-axial to one hydrogen and one lone pair in the piperidine ring—a situation found more favorable for the methylene group in **1B** as compared to **1A**). If that were so, equilibrium in **2** and **2m** should have been shifted toward conformer **B** compared to **1** and **1m** contrary to what is observed: both the equilibria between **2A** and **2B** and between **2mA** and **2mB** are actually slightly shifted toward the **A** side compared to the **1A** ⇌ **1B** and **1mA** ⇌ **1mB** equilibria. The best rationalization we can suggest is one based on a reflex effect:[16] the very close approach of H_a-8 and H_a-2 in **1B** (which, as implied earlier,[3b] is partially responsible for the lesser stability of the **B** form) leads to a substantial bending apart of C-8 and C-2 which, in turn, forces together Me_a-10 and H_a-3 in the **B** conformer, thus enhancing their interactions. This effect is reciprocal, of course, and another way of expressing it is to say that Me-10 in the **B** conformer prevents minimization of the strain caused by the C-2/C-8 compression (Scheme I). An additional possibility is that the 10-methyl group in the **B** conformer prevents the NR group from occupying the axial position and thus destabilizes **B** through loss of entropy of mixing. This effect, while plausible for **2,** is not likely to be important for **2m,** for the reasons discussed above.

Scheme I

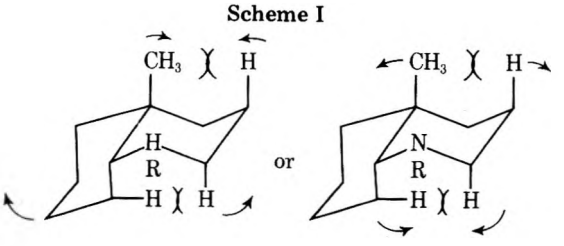


Table V. Pertinent ^{1}H Chemical Shifts[a] of *cis*-Decahydroquinolines (1–11) and *N*-Methyl-*cis*-decahydroquinolines (1m–11m)[b]

Registry no.	Substance[c]	H_{2e}	H_{2a}	H_9	NCH_3	CCH_3
10343-99-4	Parent, 1	3.02 (d, 11 of m)	2.64 (t, 12 of d, 3)	2.82 (s, ½-width 8)		
45846-78-4	10-CH_3, 2	3.04 (d, 12 of m)	2.58_5 (d, 12 of d, 10 of d, 3)	2.41 (t, 3)		0.94 (s)
60490-03-1	3α-CH_3, 3(B)	2.68 (d, 12 of d, 4)	2.37_5 (d, 12 of d, 10)	2.84 (d, 12 of t, 4)		0.85 (d, 6)
60166-53-2	3β-CH_3, 4(A)	3.04_5 (d, 11 of d, 4 of d, 2)	2.25 (t, 11)	2.78 (s, ½-width 7)		0.78 (d, 6)
60490-04-2	6α-CH_3, 5(A)	3.10 (d, 11 of m)	2.65 (t, 11 of d, 3.5)	2.81 (s, ½-width 7)		0.92 (d, 6)
60490-05-3	6β-CH_3, 6	2.80 Multiplet, not resolved				0.86_5 (d, 6.3)
60490-06-4	8α-CH_3, 7(A)	3.11 (d, 12 of m)	2.57 (t, 12 of d, 4)	2.63 (s, overlaid with H_{2a})		0.91 (d, 6.5)
60490-07-5	8β-CH_3, 8	2.75 Multiplet, not resolved		2.43 (d, 6.5 of d, 3.5)		0.94_5 (d, 7)
60490-08-6	8α,10-Dimethyl, 9(A)	3.14 (d, 11 of m)	2.53 (t, 11 of d, 3)	2.24 (d, 3)		0.88 (d, 6.5)[d] 0.92 (s)[e]
60490-09-7	3α,10-Dimethyl, 10(B)	2.69 (d, 12.5 of d, 5)	2.37 (d, 12.5 of d, 11)	2.38 (d, 12 of d, 3.5)		0.79 (d, 6)[f] 1.08 (s)[e]
60490-10-0	3β,10-Dimethyl, 11(A)	3.01_5 (d, 11 of d, 4 of d, 2)	2.16 (t, 11)	2.34 (s, ½-width 7)		0.76 (d, 6.5)[f] 0.92 (s)[e]
16726-25-3	*N*-Methyl, 1m	2.67 (broad m)	Not resolved		2.20	
60490-11-1	*N*,10-Dimethyl, 2m	2.70 (broad m)	Not resolved		2.22	1.00 (s)
60490-12-2	*N*,3α-Dimethyl, 3m(B)	2.45 (d, 10.5 of d, 4)	2.05_5 (t, 10.5)	2.71_5 (d, 10.5 of t, 4)	2.37	0.88 (d, 6)
60490-13-3	*N*,3β-Dimethyl, 4m(A)	2.80 (d, 10.5 of d, 3.5 of d, 2)	1.60 (t, 10.5)	Not resolved	2.16_5	0.79_5 (d, 6)
60490-14-4	*N*,6α-Dimethyl, 5m(A)	2.87 (d, 9 of m)	Not resolved	1.93 (s, ½-width 7)	2.16	0.93 (d, 6)
60490-15-5	*N*,6β-Dimethyl, 6m	2.40 Overlaid with NCH_3, not resolved		2.65 (d, 11 of t, 4)	2.35	0.84 (d, 6)
60490-16-6	*N*,8α-Dimethyl, 7m(A)	2.74 (d, 11 of m)	Not resolved	1.97 (s, ½-width 6)	2.22_5	1.12_5 (d, 6.5)
60490-17-7	*N*,8β-Dimethyl, 8m	2.89 (d, 10 of m)	Not resolved		2.28	0.97_5 (d, 7)
60490-18-8	*N*,8α,10-Trimethyl, 9m(A)	2.78_5 (d, 11 of m)	2.18 (t, 11 of d, 3)	1.68 (d, 3)	2.28_5	1.11 (d, 7)[d] 0.95 (s)[e]
60490-19-9	*N*,3α,10-Trimethyl, 10m(B)	Not resolved			2.31_5	0.84 (d, 6)[f] 1.12_5 (s)[e]
60490-20-2	*N*,3β,10-Trimethyl, 11m(A)	2.78 (d, 10.5 of d, 3.5 of d, 2)	1.60_5 (d, 11.5 of d, 10.5)	Not resolved	2.17_5	0.77_5 (d, 6.5)[f] 0.95 (s)[e]

[a] In $CDCl_3$, ppm, from Me_4Si; the reported shift values are centers of groups of signals in the spectra. [b] The parenthesized data are multiplicity and coupling constants (in hertz). [c] Substituted *cis*-decahydroquinoline. [d] CH_3-8. [e] CH_3-10. [f] CH_3-3.

Conformational equilibria in **6** and **6m** are readily accounted for by assuming additivity of ΔG in the equilibria for **1** or **1m** with ΔG for the methyl group at C-6 (−1.7 kcal/mol[17]). The calculated ΔG for **6** is then 0.90 − 1.7 = −0.80 kcal/mol vs. −0.85 found; the corresponding value for **6m** is 0.37 − 1.7 = −1.33 kcal/mol, too negative for accurate experimental determination by low-temperature ^{13}C NMR (which, however, supports $\Delta G < -1.2$ kcal/mol).

The equilibrium for **8** allows one to calculate the CH_3–C–C–N gauche interaction. Conformer **8A** is destabilized compared to **1A** by 1.7 kcal/mol (two CH_3/H syn-axial interactions). If this were all, ΔG for **8** should be −0.80 kcal/mol, as calculated for **6** above, or −0.85 kcal/mol, as observed. The experimental value, −0.15 kcal/mol, indicates an offsetting interaction of 0.65–0.70 kcal/mol in **8B** ascribable to gauche Me–C–C–N. The small difference (0.15 kcal/mol) between this figure and the butane-gauche (CH_3–C–C–C) interaction (0.85 kcal/mol in cyclic compounds) contrasts with that (½ × 0.90 = 0.45 kcal/mol) found in **1** (vide supra). This may be because in **8B** the gauche interaction is either of the Me–C–C–NH (rather than Me–C–C–N:) type or else the hydrogen on nitrogen in **8B** must be forced into the less favorable[10] axial position.

The situation in **8m** is substantially different because the N-Me group in **8mB** is forced, by Me-8 to become axial (or else there would be a very severe Me/Me syn-axial interaction). This increases the number of N-Me/H syn-axial interactions from one (with H_e-8) to two (with H_a-3 and H_a-10). The calculated ΔG for **8mA** ⇌ **8mB**, starting with the value of 0.37 kcal/mol for **1m** and adding the increments discussed in the previous paragraph plus the new increment of 0.9[7b] or 1.5[8b] kcal/mol, is 0.37 − 1.7 + 0.7 + 0.9 (or 1.5) = 0.27 or 0.87 kcal/mol, compared to the experimentally found +0.87. Once again the larger value for the N-Me(a)/H syn-axial interaction gives the better agreement with experiment.

Compounds **3(B)**, **5(A)**, **7(A)**, **9(A)**, **10(B)**, and **11(A)** and the corresponding methyl derivatives **3m(B)**, **5m(A)**, **7m(A)**, **9m(A)**, **10m**, and **11m** are conformationally homogeneous because the alternative conformers (**3A, 5B, 7B, 9B, 10A, 11B, 3mA, 5mB, 7mB, 9mB, 10mA, 11mB**) would have severe methyl/methylene syn-axial interaction (see also the earlier discussion regarding **9mB**). Compounds **4** and **4m** exist as the **A** conformers because the intrinsic preference for the **A** conformation is, in these cases, reinforced by the presence of the axial methyl groups in **4B** and **4mB**.

Synthesis, Configurational Assignments, and ^{1}H NMR Spectra. The compounds investigated were prepared by hydrogenating either the parent quinoline or 5,6,7,8-tetrahydroquinoline[18] over platinum in concentrated hydrochloric acid at elevated temperature and 50 psi pressure of hydrogen, or by hydrogenating the corresponding $\Delta^{1,9}$-octahydroquinoline[19] over Raney nickel in ethanol, at room temperature and 50 psi pressure of hydrogen.

Both methods have advantages and drawbacks. While hydrogenation of quinolines in strongly acidic medium proceeds quite readily to the 5,6,7,8-tetrahydro stage even at room temperature,[18] further reduction to the decahydro stage is extremely slow, especially in hydrochloric acid. Use of different acids (e.g., 12 N H_2SO_4) shortens the reaction time somewhat, but also increases the amount of trans fused decahydro product, whereas in hydrochloric acid one obtains very high proportions of *cis*-decahydroquinolines.[20] Hydrogenation at ~70 °C and use of increased amounts of catalyst cuts the reaction time to a reasonable length.

Hydrogenation of $\Delta^{1,9}$-octahydroquinolines proceeds readily with a variety of catalysts, but leads to mixtures with varying proportions of trans products. In contrast to quinoline reduction, use of an acid medium seems to increase the amounts of trans products formed; in strongly acidic medium (concentrated HCl) hydrogenation times again become very long, without leading to an increase in the yield of cis-fused product. The highest proportions of cis-decahydroquinolines were obtained with Raney nickel in anhydrous ethanol. While some *trans*-decahydroquinolines are always formed (more so in 95% than in absolute ethanol), this method has the advantage of short reaction times; moreover, it permits the synthesis of 10-methyl substituted *cis*-decahydroquinolines.[21]

The structure of the *cis*-decahydroquinolines follows, in the first instance, from that of their quinoline or octahydroquinoline precursors. Trans isomers, if any, formed as by-products were removed by preparative gas chromatography; the epimeric cis compounds were similarly separated. Since the trans isomers were readily identified by comparison with earlier prepared[19] samples, this left only the problem of assignment of the two cis epimers in the case of the 3- (**3, 4**), 6- (**5, 6**), 8-methyl (**7, 8**), and 3,10-dimethyl (**10, 11**) homologues. The strongest evidence for configurational and conformational assignment rests on the ^{13}C NMR spectra, which have already been discussed in detail. The ^{1}H NMR spectra tabulated in Table V were generally less definitive than in the conformationally homogeneous trans series;[19] however, the **B** conformation in the case of **3, 3m,** and **10** was characterized by the large coupling constant for H_9 ($J_{H_9/H_{8a}}$). Compound **8,** which exists as a conformational mixture, showed an intermediate coupling constant for H_9 whereas those compounds existing in the **A** conformation (notably **4, 5, 11, 5m, 7m**) displayed H_9 as a relatively narrow unresolved multiplet, except in the case of **9A** and **9mA** where the expected doublet ($J_{e,a}$ = 3 Hz) is resolved. In the case of the equatorial *N*-methyl compounds (i.e., excluding **8mB**) H_{2a} is anti axial to the lone pair on the nitrogen of the N-Me group, a situation which causes a strong upfield shift.[19] Unfortunately the signal is resolved only in **4m** and **11m,** where indeed it is at very high field (1.60 ppm) and shows a large apparent triplet splitting (combination of J_{gem} ≈ and approximately equal J_{aa}). The same triplet is seen in **3m,** still much upfield from H_{2e}, but not at quite as high field as in **4m** because of the countervailing downfield shift by the syn-axial C-8 in the **3mB** conformation. Characteristic coupling constants are also seen for H_{2a} in **5, 7, 9, 9m, 10,** and **11,** and for H_{2e} in **3, 4, 5, 9, 10,** and **11** and **3m, 4m, 5m,** and **11m.** Finally, **7mA** and **9mA,** earlier mentioned as having a C-Me/N-Me syn-axial interaction, display the CH_3-8 protons at unusually low field (1.1, 1.12 ppm).

In summary, we feel that the combination of arguments based on conformational analysis, ^{13}C, and (to a lesser extent) ^{1}H chemical shifts leaves no doubt on the assignment of the epimers **3/4, 5/6, 7/8,** and **10/11.**

Octahydroquinolines. In Table VI are summarized the C-13 spectra of several $\Delta^{1,9}$-octahydroquinolines prepared in the course of this investigation. Signal assignments for the parent compound are supported by the spectra of the *8,8,10-d_3* analogues prepared by exchange with NaOEt/EtOD. The remaining assignments were made on a parametric basis.

Experimental Section

Melting points were determined on an Electrothermal variable temperature heating block. Analytical gas–liquid chromatography was carried out with a Hewlett-Packard 5750 research chromatograph, equipped with a thermal conductivity detector, on 0.125-in. columns. Columns used were a 12-ft, aluminum, 20% Carbowax 20M + 10% KOH on Chromosorb W, 80/100 mesh; a 20-ft, aluminum, 20% QF-1 on Chromosorb W, 80/100 mesh; and a 10-ft, stainless steel, 30% SE-30 on Chromosorb W, 60/80 mesh, at temperatures between 100 and 200 °C. A Varian Aerograph Series 2700 and a Varian Aerograph Model 960, with 0.375-in. aluminum columns with matching phase on Chromosorb A were used for preparative VPC.

NMR spectra were recorded on a Varian XL-100 pulsed Fourier transform nuclear magnetic resonance spectrometer. ^{1}H NMR spectra

Table VI. ^{13}C Chemical Shifts[a] of $\Delta^{1,9}$-Octahydroquinolines

Compd[b]	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	CH_3
Parent[c]	49.64	21.42	27.54	35.04	26.01	28.02	39.34	173.21	38.72	
Parent[c,d]	47.54	19.99	28.74	36.16	25.50	25.87	38.30	199.46	41.58	
6-CH_3	49.72	21.45	27.97	43.44	32.34	35.74	38.79	172.82	37.81	21.80
8α-CH_3[e]	49.92	21.22	28.14	35.76	25.99	36.90	41.69	174.90	38.94	16.85
8β-CH_3[e]	49.56	21.58	28.06	35.18	20.44	33.01	41.61	176.98	34.21	18.41
10-CH_3	49.98	19.43	36.95	41.93	21.85	27.97	36.02	175.97	36.73	24.45
8,10-Dimethyl	50.41	19.47	37.56	42.28	21.85	37.21	36.98	177.36	36.79	17.44 (8) 25.14 (10)
3α,10-Dimethyl[f]	57.96	25.53	45.69	42.20	21.65	27.80	35.67	175.17	38.07	19.46 (3) 25.66 (10)
3β,10-Dimethyl[f]	57.54	24.38	46.24	41.07	22.14	28.69	35.67	177.26	36.67	19.11 (3) 24.64 (10)

[a] In parts per million, from internal Me_4Si. Solvent $CDCl_3$, if not otherwise indicated. [b] $\Delta^{1,9}$-Octahydroquinoline. [c] Shifts of $\Delta^{1,9}$-octahydroquinoline in $CDCl_3$ and CF_3COOH are slightly different from values reported earlier[17] because of using 25.16 MHz rather than 25.2 for calculation of parts per million. [d] In CF_3COOH; lock signal in this case was F. [e] Mixture of isomers; from integration of corresponding signals ratio was determined as 75% 8α-CH_3 and 25% 8β-CH_3. [f] Assignment of structures was made by comparison with matching decahydro compounds (Table I); see Experimental Section.

were recorded in the cw mode, in 5-mm o.d. tubes. ^{13}C NMR spectra were measured at 25.16 MHz, in the pulsed mode, in 10-mm o.d. tubes. Solvent in both cases was $CDCl_3$, with 2–5% Me_4Si admixed as internal reference; the deuterium of the solvent provided the internal lock signal. Integration of corresponding signals in the low-temperature ^{13}C spectra was effected by counting squares of the signal areas, and by multiplying signal height with half width, after expanding electronically as much as resolution and noise level permitted. The following signals (numbers refer to position of carbon atoms) were integrated and gave (parenthesized) percentages (only one conformer of each pair is reported): **1A,** 2 (91), 4 (89), 9 (90); **1mA,** 2 (73), 4 (72), 8 (72), 9 (72), NCH_3 (68); **2A,** 5 (95), 7 (95), 9 (94), 10 (94), CH_3 (95); **2mA,** 2 (76), 4 (76), 5 (77), 7 (77), 8 (79), 9 (78), NCH_3 (76); **6A,** 2 (11), 3 (11), 7 (12), 9 (12), CH_3 (8); **8A,** 2 (41), 5 (43), 6 (41), 7 (40), 9 (41), CH_3 (39); **8mA,** 2 (90), 3 (89), 9 (91), 10 (89), CCH_3 (90), NCH_3 (88).

Microanalyses were carried out by Galbraith Laboratories, Inc.

Starting Materials. The synthesis of the various quinolines, 5,6,7,8-tetrahydroquinolines,[18] and $\Delta^{1,9}$-octahydroquinolines[19] has been described elsewhere in detail. Quinolines obtained commercially were purified previous to hydrogenation by heating with Raney nickel in ethanol and distillation.[18,20]

trans-Decahydroquinolines, formed as by-products in the hydrogenations, were identified by VPC comparison with the authentic samples[19] on the columns described above.

3,10-Dimethyl-$\Delta^{1,9}$-octahydroquinolines were prepared in a way analogous to the synthesis of 10-methyl-[19,21] and 8,10-dimethyl-$\Delta^{1,9}$-octahydroquinoline.[19]

2-(2′-Cyanopropyl)-2-methylcyclohexanones (13). 2-Methylcyclohexanone was washed with dilute alkali and water, dried over $MgSO_4$, and distilled. To 260 g (2.32 mol) of the ketone and 7 g of Triton B. 39.3 g (0.58 mol) of freshly distilled methacrylonitrile was added dropwise with stirring. The reaction vessel was cooled intermittently to keep the temperature below 35 °C. After addition was complete the mixture was stirred at room temperature overnight, diluted with ether, neutralized with dilute HCl, washed with a saturated solution of NaCl, and dried over $MgSO_4$. The ether was evaporated at reduced pressure and the residue distilled to give unreacted 2-methylcyclohexanone and **13,** bp 119 °C (0.5 mm), yield 77.3 g (74%). Gas chromatography (SE-30) shows ~8% by-product, presumably 2-(2′-cyanopropyl)-6-methylcyclohexanone.

2-(2′-Cyanopropyl)-2-methyl-1,1-ethylenedioxycyclohexanes (14). A solution of **13** (72 g, 0.4 mol), ethylene glycol (30 g), and 0.5 g of toluenesulfonic acid in 250 ml of benzene was heated to reflux and the water formed was separated with a Dean-Stark trap. After 48 h the solvent was evaporated and the residue dissolved in ether and washed three times with water. The ether solution was dried, the ether removed at reduced pressure, and the residue distilled, bp 114 °C (0.5 mm), yield 89.2 g (92%).

2-(2′-Methyl-3′-aminopropyl)-2-methyl-1,1-ethylenedioxycyclohexanes (15). A solution of 80.6 g (0.36 mol) of **14** in 200 ml of anhydrous ether was slowly added to 14.6 g of $LiAlH_4$ in 1 l. of anhydrous ether and the mixture heated to reflux overnight. The excess $LiAlH_4$ was carefully decomposed with water, the ether layer separated, and the residue washed repeatedly with ether. The combined ether phases were concentrated without drying and the products (**15**) were used without purification.

3α,10- and 3β,10-Dimethyl-$\Delta^{1,9}$-octahydroquinoline (16α, 16β). Compounds **15** were dissolved in 200 ml of 2 N HCl and the solution was heated to reflux for 1 h, cooled, made strongly basic with a 50% solution of NaOH, and extracted repeatedly with petroleum ether. The extract was dried, the solvent and then the residue distilled, bp 106–110 °C (12 mm), yield 49.5 g (83% from **14**). Gas chromatography (Carbowax–KOH) shows two strongly overlapping peaks of **16α** and **16β** (together 93%) and ~7% by-product (presumably 3,8-dimethyl-$\Delta^{1,9}$-octahydroquinolines) Picrate, mp 117–122 °C.

Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.62. Found: C, 51.60; H, 5.80.

NMR: ^{13}C see Table VI. Assignment of signals was possible by comparison with the spectrum of material recovered after hydrogenation (see below), which proved to be a pure isomer. Assignment of configurations was made on the basis of comparison with the corresponding 3,10-dimethyl-*cis*-decahydroquinolines **10** and **11,** but is only tentative.

^1H of **16α** (recovered after hydrogenation): CH_3(3) 0.89 ppm (d, 6.5 Hz); CH_3(10) 1.17 ppm; H_{2a} 2.90 ppm (d, J = 17 Hz, of d, J = 10 Hz, of d, J = 3 Hz); H_{2e} 3.70 ppm (d, J = 17 Hz, of m).

16β (from spectrum of mixture): CH_3(3), CH_3(10) as **16α**; H_{2a} 2.83 ppm; H_{2e} 3.66 ppm. Overlap with the signals of **16α** prevented a more detailed analysis.

Reduction of 16α and 16β with Sodium–Ethanol. A solution of 6.6 g of **16α** + **16β** in 80 ml of anhydrous ethanol was reduced with 20 g of sodium as previously reported.[19] The mixture of products was separated by preparative gas chromatography (Carbowax–KOH). Products in order of increasing retention times were as follows.

3β,10-Dimethyl-*cis*-decahydroquinoline (11), 46%. Picrate, mp 180–182 °C.

Anal. Calcd for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.10. Found: C, 51.70; H, 6.00.

NCH_3 derivative: picrate, mp 147–148 °C.

3α,10-Dimethyl-*trans*-decahydroquinoline (17), 51%, mp 28–29 °C. Picrate, mp 193 °C.

Anal. Calcd for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.10. Found: C, 51.55; H, 6.14.

^1H NMR CH_3(3) 0.77 ppm (d, J = 6.5 Hz); CH_3(10) 0.92 ppm (s); H_9 2.13 ppm; H_{2a} 2.22$_5$ ppm (t, J = 11.5 Hz); H_{2e} 3.02 ppm (d, J = 11.5 Hz, of d, J = 4 Hz, of d, J = 2 Hz).

NCH_3 derivative: picrate, mp 212–213 °C.

3β,10-Dimethyl-*trans*-decahydroquinoline (18), 3%. No derivatives of **18** were prepared because of the extremely small amount of isolated material.

^1H NMR CH_3(3) 1.14 ppm (d, J = 7.2 Hz); CH_3(10) 1.00 ppm (s); H_9 2.17$_5$ ppm; H_{2e}, H_{2a} 2.87 ppm (AB near degenerate).

Hydrogenation of 16α and 16β. The mixture of **16α** + **16β** was hydrogenated over Raney nickel in anhydrous ethanol in the manner described below. Products were **11** (41%), **18** (4.5%), and and **3α,10-dimethyl-*cis*-decahydroquinoline (10),** 30.5%, which could not be separated from 10% of **17.** Picrate of the mixture: mp 155–158 °C.

Anal. Calcd for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.10. Found: C, 51.66; H, 6.18.

Table VII. Hydrogenations[a] of Quinolines, Tetrahydroquinolines, and $\Delta^{1,9}$-Octahydroquinolines[b]

Registry no.	Substance reduced (catalyst, temp)	Solvent (redn time[c])	%	Product[d]
91-22-5	Quinoline	HCl concd	90	*cis*-[e]
	(Pt, ~70 °C)	(72 h)	8	*trans*-[f]
			2	$\Delta^{1,9}$-Octahydro-
	Quinoline	H_2SO_4 12 N	60	*cis*-[e]
	(Pt, R.T.)	(20 h)	40	*trans*-[f]
1074-06-2	$\Delta^{1,9}$-Octahydroquinoline	C_2H_5OH, anhyd	78	*cis*-[e]
	(Raney nickel, R.T.)	(12 h)	22	*trans*-[f]
	$\Delta^{1,9}$-Octahydroquinoline	C_2H_5OH, anhyd	65	*cis*-[e]
	[Pd (5%) on C, R.T.]	(12 h)	35	*trans*-[f]
	$\Delta^{1,9}$-Octahydroquinoline	CH_3COOH (5% HCl)	50	*cis*-[e]
	(Pt, R.T., 1 atm)	(7 h)	50	*trans*-[f]
611-32-5	8-Methylquinoline	HCl concd	<1	8α-Methyl-*trans*-[f]
	(Pt, ~70 °C)	(100 h)	66	8α-Methyl-*cis*-[g]
			19[i,j]	8β-Methyl-*trans*-[f] + 8β-Methyl-*cis*-[h]
			14	8-Methyl-$\Delta^{1,9}$-octahydro
	8-Methylquinoline	CH_3COOH–HCl[k]	18	8α-Methyl-*trans*-[f]
	(Pt, ~70 °C)	(24 h)	44	8α-Methyl-*cis*-[g]
			23[l]	8β-Methyl-*trans*-[f] + 8β-Methyl-*cis*-[h] (little)
			15	8-Methyl-$\Delta^{1,9}$-octahydro
52761-53-2	8-Methyl-$\Delta^{1,9}$-octa-	HCl concd	29	Starting material
	hydroquinoline	(24 h[l])	29	8α-Methyl-*trans*-[f]
	(Pt, ~70 °C[l])		44	8α-Methyl-*cis*-[g]
			27	8β-Methyl-*trans*-[f]
	8-Methyl-$\Delta^{1,9}$-octa-	C_2H_5OH, anhyd	5	8α-Methyl-*trans*-[f]
	hydroquinoline	(12 h)	75	8α-Methyl-*cis*-[g]
	(Raney nickel, R.T.)		25[l]	8β-Methyl-*trans*-[f] + 8β-Methyl-*cis*-[h] (little)
91-62-3	6-Methylquinoline	HCl concd	26	6β-Methyl-*cis*-[m]
	(Pt, ~70 °C)	(24 h)	4	6α-Methyl-*trans*-[f]
			70	6α-Methyl-*cis*-[n]
52601-67-9	6-Methyl-$\Delta^{1,9}$-octa-	C_2H_5OH, anhyd	45	6α-Methyl-*trans*-[f]
	hydroquinoline	(12 h)	55	6α-Methyl-*cis*-[n]
	(Raney nickel, R.T.)			
612-58-8	3-Methylquinoline	HCl concd	91.5	3α-Methyl-*cis*-[o]
	(Pt, ~70 °C)	(24 h)	8.5	3β-Methyl-*cis*-[h]
28712-62-1	3-Methyl-5,6,7,8-	HCl concd	90	3α-Methyl-*cis*-[o]
	tetrahydroquinoline	(24 h)	10	3β-Methyl-*cis*-[h]
	(Pt, ~70 °C)			
37442-12-9	10-Methyl-$\Delta^{1,9}$-octa-	C_2H_5OH, anhyd[p]	85	10-Methyl-*cis*-[q]
	hydroquinoline	(12 h)	15	10-Methyl-*trans*-[f]
	(Raney nickel, R.T.)			
55905-40-3	8,10-Dimethyl-$\Delta^{1,9}$-	C_2H_5OH, anhyd	86	8α,10-Dimethyl-*cis*-[r]
	octahydroquinoline	(12 h)	14	8α,10-Dimethyl-*trans*-[f]
	(Raney nickel, R.T.)			
60490-22-4	3,10-Dimethyl-$\Delta^{1,9}$-	C_2H_5OH, anhyd	41	3β,10-Dimethyl-*cis*-[s]
	octahydroquinoline[s]	(100 h)	30.5	3α,10-Dimethyl-*cis*-[s]
	(Raney nickel, R.T.)		10	3α,10-Dimethyl-*trans*-[s]
			4.5	3β,10-Dimethyl-*trans*-[s]
			14	3α,10-Dimethyl-$\Delta^{1,9}$-octahydroquinoline[s]

[a] At 50 psi pressure of hydrogen, if not otherwise indicated. [b] For starting materials see ref 19. [c] Hydrogenations were continued for additional 3–8 h after noticeable hydrogen uptake had ceased. [d] Determined by VPC and listed in order of increasing retention times; products are decahydroquinolines if not otherwise indicated. [e] Picrate, mp 144–145 °C (lit.[20] 144–144.5 °C). [f] For identification of trans compounds see ref 19. [g] Picrate, mp 147 °C. Anal. Calcd for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80. Found: C, 50.17; H, 5.80. NCH_3 derivative: picrate, mp 201–202 °C. [h] Because of the extremely small amounts of pure compound isolated, no derivatives were prepared. [i] Considerable overlapping of signals in VPC on all columns available prevented determination of exact ratio. [j] Integration of NMR signals gave the relative ratio of 8β-methyl-*trans*:8β-methyl-*cis* of 30:70. [k] 42.5% CH_3COOH, 42.5% H_2O, 15% HCl concd. [l] After hydrogenation at R.T. for 24 h, only 24% of the starting material had reacted. The experiment was continued at elevated temperature for an additional 24 h. [m] Picrate, mp 136–137 °C. Anal. Calcd for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80. Found: C, 50.19; H, 5.69. NCH_3 derivative: picrate, mp 185–186 °C. [n] Hydrochloride, mp 266–268 °C (lit.[22] 263–264 °C for 6-methyl-*cis*-decahydroquinoline of otherwise unspecified configuration). Picrate, mp 175–176 °C. NCH_3 derivative: picrate, mp 191–192 °C. [o] Picrate, mp 155.5–156.5 °C. Anal. Calcd for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80. Found: C, 50.55; H, 5.81. NCH_3 derivative: picrate, mp 136–137 °C. [p] An identical isomer ratio was found after 48-hr hydrogenation time. Use of 96% aqueous ethanol gave ~60% cis, ~40% trans after 48 h hydrogenation. Picrate, mp 193 °C (lit.[21] 190–192 °C). NCH_3 derivative: picrate, mp 227–228 °C. [r] Picrate, mp 205–207 °C. Anal. Calcd for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.10. Found: C, 51.66; H, 6.06. NCH_3 derivative: picrate, mp 217–218 °C. [s] See text.

NCH_3 derivative: picrate, mp 162–168 °C.

3α,10-Dimethyl-$\Delta^{1,9}$-octahydroquinoline (16α), pure by ^{13}C spectrum, 14%. Picrate: mp 126–127 °C.

Configuration of products **10**, **11**, **17**, and **18** was assigned by comparison of their ^{13}C and ^{1}H spectra with known spectra[2,19] of 3- and 10-methyldecahydroquinolines (see also Discussion).

Hydrogenations. These were carried out in a Parr low-pressure shaker type hydrogenation apparatus at 50 psi pressure of hydrogen. A wrap-around bottle heater was used where elevated temperatures were required.

Fifty millimoles of starting material was dissolved in a 500-ml Parr bottle in 50 ml of ice-cold acid (see Table VII) or in anhydrous ethanol; 2.5 g of platinum[23] or 5 g of Raney nickel[24] or 1.5 g of palladium (5%) on C was added, the bottle connected to the hydrogenator, the air removed, and the bottle heated to the required temperature. Hydrogenation was continued for 3–8 h after detectable hydrogen uptake had ceased. The solution was brought to room temperature and the catalyst was filtered off.

Acidic solutions were chilled in ice, made strongly basic with 50% NaOH solutions, and extracted repeatedly with petroleum ether. The combined extracts were dried over Na_2SO_4, the solvent was distilled off, and the residue was purified by total distillation at reduced pressure (without fractionation) by means of a Kugelrohr unit, using bulbs with ground glass joints. The distilled products were checked by VPC, using the columns described above. Compositions given in Table VI were determined this way.

Solutions in ethanol were worked up by distilling off the solvent, followed by total distillation of the residue and determination of the composition by VPC as described above.

Products were isolated by preparative VPC on the columns described above, and identified by their ^{1}H (Table V) and ^{13}C (Tables I and II) NMR spectra. *N*-Methyl derivatives were prepared by the usual Clark–Eschweiler procedure using HCOOH and HCHO; the melting points of the picrates of the NH precursors and of the *N*-methyl derivatives are listed in Table VII.

Compounds **1** and **1m** have been described previously.[3,20] The configuration of 2[3d] had been deduced[21] from the analogy of its formation to the formation of *cis*-decahydroquinoline upon hydrogenation of the corresponding $\Delta^{1,9}$-octahydroquinoline. Compound **5** proved to be identical with a 6-methyl-*cis*-decahydroquinoline previously described[22] without specification of configuration of the methyl group. The remaining NH and NCH_3 *cis*-decahydroquinolines (with the exception of 4[3d]) are new.

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Registry No.—**2m** picrate, 60490-21-3; **3** picrate, 60490-23-5; **3m** picrate, 60490-24-6; **5** HCl, 60490-25-7; **5** picrate, 60490-26-8; **5m** picrate, 60490-27-9; **6** picrate, 60490-28-0; **6m** picrate, 60490-29-1; **9** picrate, 60490-30-4; **9m** picrate, 60490-31-5; **10** picrate, 60490-32-6; **11** picrate, 60490-33-7; **13** (*R**,*R**), 60490-34-8; **13** (*R**,*S**), 60490-35-9; **14** (*R**,*R**), 60490-36-0; **14** (*R**,*S**), 60490-37-1; **15** (*R**,*R**), 60490-38-2; **15** (*R**,*S**), 60490-39-3; **16α**, 60490-40-6; **16α** picrate, 60490-41-7; **16β**, 60490-42-8; **16β** picrate, 60490-43-9; **17** picrate, 60490-45-1; **17** (NCH_3) picrate, 60490-47-3; **18**, 60490-48-4; 2-methylcyclohexanone, 583-60-8; methacrylonitrite, 126-98-7.

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Long-Range Proton Electron Spin Resonance Splittings in Anion Radicals of Bicyclo[2.2.1]hept-5-ene-2,3-diones[1]

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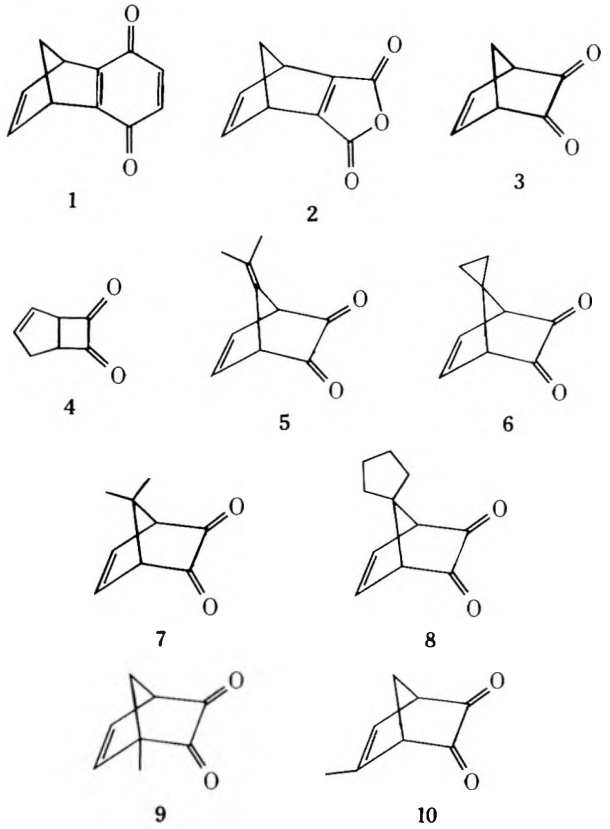
A variety of bicyclo[2.2.1]hept-5-ene-2,3-diones were prepared by hydrolysis of their cyclopentadiene-dichlorovinylene carbonate Diels–Alder adducts. Electrolytic reduction of these diketones in Me_2SO with tetra-*n*-butylammonium perchlorate as supporting electrolyte produced their anion radicals, which were examined with electron spin resonance spectroscopy. Long-range hyperfine splittings are reported and mechanisms for these interactions are discussed.

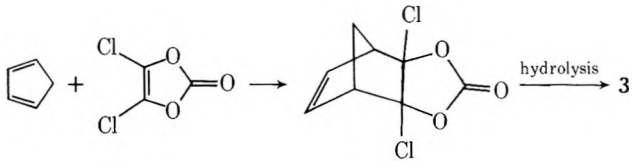
Many examples of long-range ESR splittings by nuclei separated by three or more bonds from the center containing the unpaired electron have been reported in the literature. An excellent review has been recently published which describes these splittings in semidiones, semiquinones, semifuraquinones, nitroxides, iminoxy radicals, and aliphatic radicals.[2] Some of the larger splittings have been observed in anion radicals with rigid bicyclic structures.[2] In the bicyclo[2.2.1]-heptene skeleton both the semiquinone ($1\cdot^-$)[3] and semifuraquinone ($2\cdot^-$)[4] have been examined. Although an earlier attempt to prepare the semidione ($3\cdot^-$) was unsuccessful,[5] later work revealed that a mixture of $3\cdot^-$ and $4\cdot^-$ could be obtained



by reacting esters or silyl ethers of *endo*-3-hydroxy-2-norbornenone with base and Me_2SO.[6] We reported in a preliminary communication[1] about the same time that $3\cdot^-$ could be prepared in the absence of $4\cdot^-$ by electrolytic reduction of the diketone **3**. In this paper we report in detail long-range splittings in $3\cdot^-$ and its derivatives, $5\cdot^-$–$10\cdot^-$.

Synthesis of Bicyclo[2.2.1]hept-5-ene-2,3-diones and Their Anion Radicals. The method for synthesizing compounds **5**–**10** was based on a report in the literature[7] for the synthesis of **3** which is given in Scheme I. The conditions required to prepare the Diels–Alder adducts did vary somewhat. Dimethylfulvene and spiro[4.2]hepta-2,4-diene were heated with an excess of dichlorovinylene carbonate at 115 °C for 1 h resulting in a mixture of endo and exo adducts from each diene. Reaction of spiro[4.4]nona-2,4-diene and 5,5-dimethylcyclopenta-1,3-diene with the carbonate required a reaction period of ~21 h at 130–145 °C and only one isomer in significant yield (presumably the endo one) was formed from each diene. In the preparation of **9** and **10**, a solution of methylcyclopentadiene dimer and the carbonate was simply heated to reflux for 1 h. The reaction mixture consisted of the exo and endo adducts of 1-methylcyclopenta-1,3-diene and 2-methylcyclopenta-1,3-diene. Unfortunately, there was no evidence for the formation of the exo and endo adducts from 5-methylcyclopenta-1,3-diene.

Scheme I



The diketones **5**–**10** were prepared from their corresponding Diels–Alder adducts by hydrolysis under acid or base conditions. Acid hydrolysis was accomplished by heating the adduct in 50% aqueous dioxane at 85–90 °C for a period of at least 1 h, whereas base hydrolysis was effected by reaction with alcoholic KOH at room temperature.

The anion radicals of **3** and **5**–**10** were obtained by electrolytic reduction of their diketones or carbonate precursors in Me_2SO or DMF at room temperature using tetra-*n*-butylammonium perchlorate as supporting electrolyte. The ESR spectrum for each of these anion radicals gives no evidence for a second radical specie. Thus, rearrangements to the bicyclo[3.2.0]heptene skeleton (e.g., $3\cdot^- \rightarrow 4\cdot^-$) do not occur under these conditions. Substitution at the syn and anti C-7 positions enhances the stability of these anion radicals considerably. When the current was terminated, $3\cdot^-$ and $5\cdot^-$ were undetectable by ESR spectroscopy after several minutes whereas $7\cdot^-$ and $8\cdot^-$ decayed with half-lives of 15–30 min.

Assignment of Hfsc's to Anion Radicals of Bicyclo[2.2.1]hept-5-ene-2,3-diones. Electrolytic reduction of **3** and **5**–**10** in the cavity of an ESR spectrometer produced ESR spectra for their anion radicals. All of the anion radicals except $7\cdot^-$ gave well-resolved spectra which were simulated giving the hfsc's in Table I. Generation of $7\cdot^-$ from **7** or its carbonate precursor at room temperature or below gave a ten-line multiplet with a line width of 0.40 G. Presumably the broadening is caused by a small methyl splitting which is below the resolution limit of our spectrometer (<0.10 G).

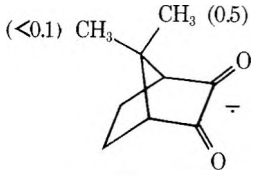
The assignment of the 1.04 and 0.70 G coupling in $3\cdot^-$ to the bridgehead and vinyl positions, respectively, follows from an

Table I. Hyperfine Splitting Constants for Anion Radicals of Bicyclo[2.2.1]hept-5-ene-2,3-diones in Me_2SO at 25 °C

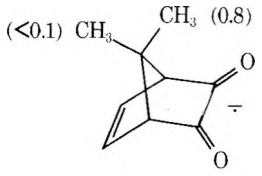
Registry no.	Anion radical	a^H, G C-1,4	C-5,6	C-7s	C-7a	Other
53602-58-7	**3**·⁻	1.04	0.70	2.14	8.08	
53602-59-8	**5**·⁻	0.89	0.56			1.63 (2 CH_3)
53531-36-5	**6**·⁻	0.95	0.68			0.20 (CH_2)
60526-36-5	**7**·⁻	0.96	0.72			0.78 (CH_3)
60526-37-6	**8**·⁻	0.96	0.70			0.21 (CH_2), 0.41 (CH_2)
55689-06-0	**9**·⁻	1.01 (1)	0.66, 0.74	2.07	7.69	0.16 (CH_3)
55689-07-1	**10**·⁻	0.97	0.85 (1)	1.81	7.86	0.59 (CH_3)

examination of the hfsc's for **9**·⁻ and **10**·⁻. The very large 8.08 coupling is assigned to the anti-7 position based on the large W-plan couplings that have been observed in bicyclic semidiones[6,8] and from an INDO calculation for **3**·⁻.[6] A long-range interaction of one methyl group (0.78 G) is observed in **7**·⁻.

In the saturated semidione **11**, a splitting for only one methyl group is also observed (0.53 G) and has been experi-



11

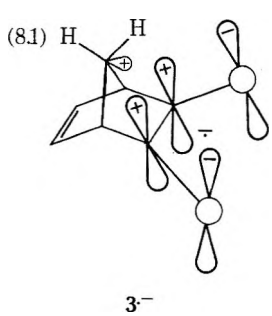


7·⁻

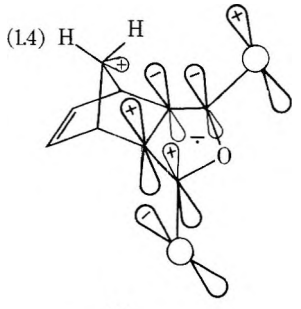
mentally determined to be the *syn*-methyl.[6] If a through space interaction is occurring between the *syn*-methyl group and the spin label as has been previously suggested,[6] it seems reasonable to assign the 0.78 G splitting in **7**·⁻ to the *syn*-methyl in view of its proximity to the spin label. A similar argument could also be used, although with less certainty, to assign the 0.20 and 0.41 G splittings in **6**·⁻ and **8**·⁻, respectively, to the *syn*-methylene groups.

Mechanisms for Long-Range Couplings in Anion Radicals of Bicyclo[2.2.1]hept-5-ene-2,3-diones. One approach to studying long-range interactions is to consider the spin label and interacting σ or π moieties as localized molecular orbitals.[2,9] If the highest occupied π molecular orbital (HOMO) of the spin label is symmetric with respect to a plane perpendicular to the spin label and bisecting the σ or π moiety, the interaction between the hydrogen(s) in the σ or π moiety with the unpaired electron in the spin label will be significantly greater than for spin labels whose HOMO is antisymmetric. The semidione and semifuraquinone spin labels can be used to study this effect since their HOMO's are symmetric and antisymmetric, with respect to this plane, respectively, and both spin labels have similar spin densities at C_{α}.[10]

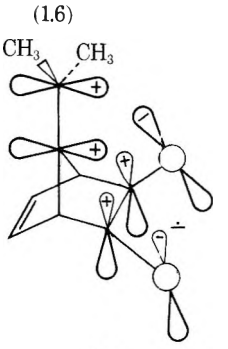
The a_{7a}^H splitting in semidione **3**·⁻ (8.1 G) is considerably greater than in semifuraquinone **12** (1.4 G). This large difference arises because a spin delocalization interaction (homohyperconjugation) in **3**·⁻ between the C–H moiety and spin label is possible a as result of their HOMO's having the same symmetry. This interaction is not possible in **12** since the HOMO's of the C–H moiety and semifuraquinone spin label have opposite symmetries. A striking illustration of this effect can also be seen in comparison between **5**·⁻ and **13** where



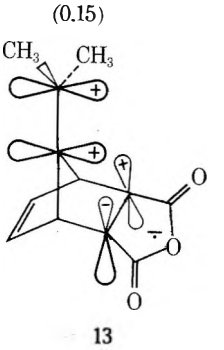
3·⁻



12



5·⁻

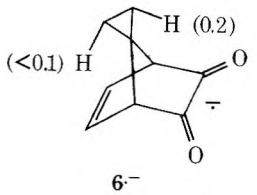


13

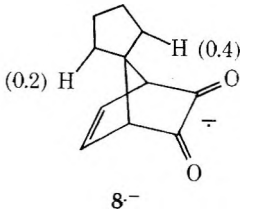
methyl splittings of 1.63 and 0.15 G are obtained, respectively. The HOMO's of the ethylenic moiety and the spin label in **5**·⁻ are symmetric with respect to the plane bisecting the spin label but are of opposite symmetry in **13**. The proximity of the ethylenic and semidione orbitals in **5**·⁻ promotes spin delocalization through a homohyperconjugative mechanism.

Although spin delocalization to the 7-anti hydrogen (H-7a) in **3**·⁻ appears to be the predominant interaction, spin polarization contributions to both H-7a and H-7s cannot be neglected as has previously been discussed.[6] This is evident in **12** where the hydrogens of the methylene bridge lie in the nodal plane but have significant splittings of 1.4 (H-7a) and 0.8 G (H-7s).

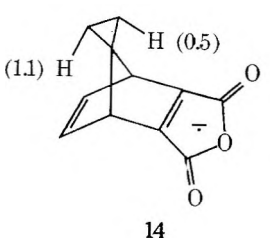
If the assignments for the methyl and methylene splittings in semidiones **6**·⁻–**8**·⁻ are correct, it is likely that the larger splittings for the syn hydrogens result from a through space interaction. This is apparently not the case for semifuraquinones **14** and **15**, where the larger splittings occur for the anti hydrogens.[10] Irregardless of how the assignments are made for **6**·⁻ and **8**·⁻, it is clear that the hfsc's for the bridging hy-



6·⁻



8·⁻



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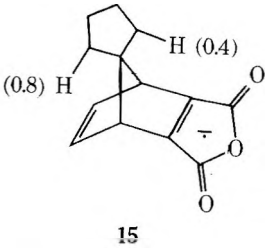

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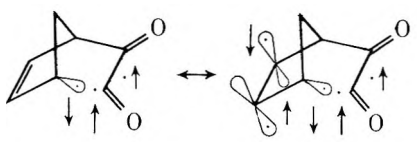
drogens are larger in the semifuraquinones than in the corresponding semidiones. This could be the result of spin polarization and delocalization contributions that are opposite in sign giving partial cancellation in the semidiones.

INDO calculations by Russell and co-workers[6] have been made on $2\cdot^-$ and $3\cdot^-$ and vinyl hydrogen (H_v) splittings of +1.56 and −0.52 G, respectively, were obtained. These values compare with experimental splittings of 0.8 and 0.7 G where the signs of the couplings constants have not been determined. These authors concluded that the −0.5 G coupling (calculated) in $3\cdot^-$ is the net effect of a −2.0 G spin delocalization contribution (e.g., 1,3-π overlap) and a +1.5 G spin polarization contribution (e.g., structures **16** and **17**). If the major contribution of spin density to the vinyl carbon by spin polarization occurs via **16** and **17**, a vinyl methyl coupling similar in magnitude to the H_v coupling but opposite in sign would be expected. Interestingly, the methyl splitting in $10\cdot^-$ (0.60 G) is about the same as the H_v splitting (0.85 G).



16 17

Experimental Section

ESR Spectra. Spectra were recorded on a Varian Associates V-4502 spectrometer. Electroreductions were carried out at the surface of a mercury pool in Me_2SO or DMF (both distilled from CaH_2) using a standard electrolytic cel.

Bicyclo[2.2.1]hept-5-ene-2,3-dione (3) was prepared by the method of Scharf and co-workers, mp 42–43 °C (lit.[11] mp 43 °C).

7-(1-Methylethylidene)bicyclo[2.2.1]hept-5-ene-2,3-dione (5). Dichlorovinylene carbonate[7] (10 g) was introduced into a three-neck round-bottomed flask fitted with a septum for N_2 inlet, a condensor, and a dropping funnel. After the system was purged with N_2 for 15 min, the flask was immersed into a mineral oil bath at 115 °C. With stirring dimethylfulvene (1.1 g) was added to the carbonate over 5 min and the resulting solution was heated at 115 °C for an additional 1 h. Removal of excess carbonate gave a solid which was dissolved in ether and partially decolorized with charcoal. Filtration and removal of solvent gave 1.38 g of an off-white solid consisting of the endo and exo Diels–Alder adducts. Without further purification these adducts were dissolved in 50 ml of H_2O–dioxane (1:1) and heated to 85 °C for 2 h. The aqueous solution was extracted with CH_2Cl_2 until colorless and the combined extracts were washed with H_2O and dried over $MgSO_4$. Removal of the methylene chloride gave a red solid which was sublimed (60–70 °C, 0.1 mm) and recrystallized from ligroin (bp 63–73 °C) to give 0.41 g of **5** (26% from dimethylfulvene) as red crystals: mp 101–102 °C; ^{1}H NMR ($CDCl_3$) δ 6.61 (t, 1, J = 2.0 Hz), 3.88 (t, 1, J = 2.0 Hz), 1.77 (s, 3).

***exo*- and *endo*-7-Spirocyclopropane-2,3-dichlorobicyclo[2.2.1]hept-5-ene-2,3-diol Carbonate. Precursors to 6.** A solution of spiro[4.2]hepta-2,4-diene (2.0 g) and dichlorovinylene carbonate (15.0 g) was heated in a sealed tube at 115 °C for 1 h. Removal of excess carbonate under reduced pressure gave a deeply colored residue which was chromatographed on silica gel and eluted with benzene. The light yellow benzene solution was decolorized with charcoal. Removal of the benzene gave a colorless solid which was recrystallized from ligroin giving initially 1.25 g of a colorless single isomer: mp 137–140 °C; ir (KBr) 1825 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.47 (t, 2, J = 2.0 Hz), 2.98 (t, 2, J = 2.0 Hz), 1.18–0.40 (A_2B_2, 4).

Anal. Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26. Found: C, 48.73; H, 3.19.

A second crop of crystals (0.30 g) consisted of a mixture of the exo and endo isomers.

7-Spirocyclopropanebicyclo[2.2.1]hept-5-ene-2,3-dione (6). A solution of the carbonate precursors to **6** (0.5 g) in 50 ml of 50% aqueous dioxane was heated at 80–85 °C for 2 h. The solution was extracted with CH_2Cl_2 (4 × 10 ml) and the extracts were combined, washed with H_2O, and dried over $MgSO_4$. Removal of the methylene chloride gave a yellow oil that solidified on standing. Recrystallization from ligroin gave 0.23 g (77%) of yellow crystals: mp 67–68 °C; ir (melt) 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.54 (t, 2, J = 2.0 Hz), 2.82 (t, 2, J = 2.0 Hz), 0.80 (s, 4).

Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.90; H, 5.32.

7,7-Dimethyl-2,3-dichlorobicyclo[2.2.1]hept-5-ene-2,3-diol Carbonate. Precursor to 7. A solution of 5,5-dimethyl-1,3-cyclopentadiene (1.25 g) and dichlorovinylene carbonate (10.30 g) was heated in a sealed tube at 145 °C for 20 h. Removal of carbonate and unreacted diene gave a colored residue which was chromatographed several times on silica gel and eluted with benzene–cyclohexane (3:1) to give light yellow crystals of only one isomer, presumably the endo one. Recrystallization from ligroin gave colorless crystals in poor yield (<10%): mp 112–113 °C; ir (Nujol) 1830 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.28 (t, 2, J = 2.0 Hz), 3.1 (t, 2, J = 2.0 Hz), 1.46 (s, 3), 1.12 (s, 3).

Anal. Calcd for $C_{10}H_{10}Cl_2O_3$: C, 48.24; H, 4.02. Found: C, 48.38; H, 4.11.

7,7-Dimethylbicyclo[2.2.1]hept-5-ene-2,3-dione (7). To a solution of the carbonate precursor (0.20 g) in 10 ml of 95% ethanol at 25 °C was slowly added 14.04 ml of a 0.23 M alcoholic NaOH solution with stirring. The resulting yellow solution was diluted with 50 ml of water and extracted with CH_2Cl_2 until the aqueous layer was colorless (5 × 15 ml). The CH_2Cl_2 extracts were combined and dried over $MgSO_4$. Removal of the methylene chloride gave a yellow solid that was recrystallized from ligroin to give 0.115 g (95%) of yellow crystals: mp 124–126 °C; ir (Nujol) 1760 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.41 (t, 2, J = 2.0 Hz), 2.91 (t, 2, J = 2.0 Hz), 1.28 (s, 3), 1.17 (s, 3).

Anal. Calcd for $C_9H_{10}O_2$: C, 72.03; H, 6.66. Found: C, 72.16; H, 6.67.

7-Spirocyclopentane-2,3-dichlorobicyclo[2.2.1]-hept-5-ene-2,3-diol Carbonate. Precursor to 8. A solution of spiro[4.4]nona-2,4-diene[12] (1.1 g) and dichlorovinylene carbonate (7.35 g) was heated in a sealed tube at 130 °C for 21 h. Removal of excess carbonate, chromatography of the residue on silica gel, and elution with benzene–ligroin (1:1) gave 0.6 g of a light yellow solid consisting of only one isomer. Recrystallization from hexane after decolorization with charcoal gave 0.45 g (18%) of colorless crystals: mp 110–111 °C; ir (Nujol) 1840 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.7 (t, 2, J = 2.0 Hz), 3.23 (t, 2, J = 2.0 Hz), 2.25–1.43 (m, 8).

Anal. Calcd for $C_{12}H_{12}Cl_2O_3$: C, 52.42; H, 4.36. Found: C, 52.60; H, 4.44.

7-Spirocyclopentanebicyclo[2.2.1]hept-5-ene-2,3-dione (8). A solution of the carbonate precursor (0.285 g) in 30 ml of 95% ethanol was titrated with 15.94 ml of 0.26 M NaOH in 95% ethanol. The reaction mixture was poured into a separatory funnel containing 200 ml of H_2O and 200 ml of $CHCl_3$. After shaking, the $CHCl_3$ layer was separated and dried over $MgSO_4$. Removal of $CHCl_3$ gave 0.165 g (90%) of a viscous yellow liquid that was purified by GLC (30% SE-30/Chromosorb P column, 180 °C) to give a yellow solid: mp 37 °C; ir (melt) 1755 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.42 (t, 2, J = 2.0 Hz), 3.03 (t, 2, J = 2.0 Hz), 1.37–1.50 (m, 8).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.95; H, 6.78.

1-Methylbicyclo[2.2.1]hept-5-ene-2,3-dione (9) and 5-Methylbicyclo[2.2.1]hept-5-ene-2,3-dione (10). A solution of methylcyclopentadiene dimer (4.0 g) and dichlorovinylene carbonate (2.5 g) was heated to reflux for 30 min. After removal of unreacted carbonate and excess dimer, the residue was chromatographed on silica gel and eluted with ethyl acetate–ligroin (1:49) giving partial separation of the four Diels–Alder adducts, the exo and endo carbonate precursors to **9** and **10**. The last fraction was rechromatographed giving a carbonate precursor to **9** essentially pure: mp 111–113 °C; ir (Nujol) 1830 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.43 (q, 1, J = 3.3 and 5.8 Hz), 6.16 (q, 1, J = 1.3 and 5.8 Hz), 3.54 (m, 1), 1.98 (d, 2, J = 1.7 Hz), 1.58 (s, 3). It was unnecessary, however, to separate the above adducts since titration with alcoholic NaOH (4 equiv) and workup (see preparation for **8**) gave a mixture of **9** and **10** which could be separated by GLC (30% SE-30/Chromosorb P column, 180 °C). Compound **10** was obtained as a viscous yellow liquid in 95% purity: ir (neat) 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.13 (m, 1), 3.35–2.80 (m, 3), 2.46 (broad d, 1, J = 10.5 Hz), 1.98 (d, 3, J = 1.5 Hz). Compound **9** was obtained analytically pure as a yellow solid: mp 46–47 °C; ir (melt) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.57 (q, 1, J = 3.5 and 5.0 Hz), 6.27 (broad d, 1, J = 5.0 Hz), 3.36 (m, 1), 2.92 (q, 1, J = 2.1 and 11.0 Hz), 2.32 (broad d, 1, J = 11.0 Hz), 1.33 (s, 3).

Anal. Calcd for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.69; H, 5.66.

Acknowledgment. We gratefully acknowledge financial support of this work by the Research Corporation.

Registry No.—**5**, 60526-38-7; **5** *endo*-carbonate precursor, 60526-39-8; **5** *exo*-carbonate precursor, 60562-31-4; **6**, 60526-40-1; **6** *exo*-carbonate precursor, 60526-41-2; 6 *endo*-carbonate precursor, 60562-32-5; **7**, 0526-42-3; 7 *endo*-carbonate precursor, 60526-43-4; **8**, 60526-44-5; 8 carbonate precursor, 60526-45-6; **9**, 60526-46-7; **9** *exo*-carbonate precursor, 60526-47-8; **9** *endo*-carbonate precursor, 60562-33-6; **10**, 60526-48-9; **10** *exo*-carbonate precursor, 60526-49-0; **10** *endo*-carbonate precursor, 60562-34-7; dichlorovinylene carbonate, 17994-23-9; dimethylfulvene, 2175-91-9; spiro[4.2]hepta-2,4-diene, 765-46-8; 5,5-dimethyl-1,3-cyclopentadiene, 4125-18-2; spiro[4.4]-nona-2,4-diene, 766-29-0; methylcyclopentadiene dimer, 26472-00-4.

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Determination of the Configuration and Conformation of α-, β-, and Isotripiperideine by Carbon-13 Nuclear Magnetic Resonance Spectroscopy[1]

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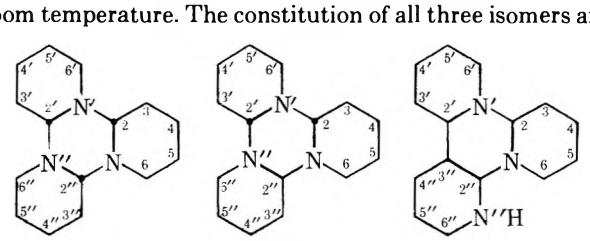
The constitution, configuration, and conformation of the three isomeric tripiperideines (α-, β-, and iso-) have been established by ^{13}C NMR spectroscopy. α-Tripiperideine (**1**) exhibits a five-line spectrum at room temperature which changes to a 15-line spectrum at low temperatures. This is due to a slowing down of the equilibration between three asymmetric topomers of conformation B, which, at room temperature, average to apparent C_3 symmetry. The conformation F of β-tripiperideine (**2**) is established by comparison of the observed ^{13}C chemical shifts with calculated ones using the approach of empirical increments. The same procedure enables one to prove the dominant configuration and conformation I of isotripiperideine (**3**). By comparison of the most stable conformations of **1**, **2**, and **3** it was possible to estimate the energetic limits of the syn-axial lone pair interaction (generalized anomeric effect) between two nitrogen atoms.

NMR spectroscopic investigations of the conformation and dynamic behavior of heterocyclic six-membered ring systems have attracted considerable interest.[3] During the last few years ^{13}C NMR investigations have provided new information about the constitution of natural products[4] and the ground state conformation[5] of a number of saturated heterocycles. In connection with our interest in dynamic ^{13}C NMR studies[6] we report here our investigation of tripiperideines. The temperature dependence of their ^{13}C NMR spectra gives information about constitution, configuration, and conformation as well as about the mechanism and the kinetics of intramolecular rate processes, in contrast to the ^1H NMR spectra of these compounds, which are complex and less informative. In this paper we present our results regarding the ground state conformation of the tripiperideines.

Constitution and Configuration. By dehydrohalogenation of *N*-chloropiperidine three isomeric trimers have been obtained.[7] The α (**1**) and β isomers (**2**) result from the normal trimerization reaction of the azomethine and differ only in the relative configuration of the three asymmetric methine carbons, whereas the iso compound is constitutionally isomeric to the α and β compounds.[8]

α- and β-tripiperideine each contain three asymmetric carbon atoms. The configurational isomers differ in their overall symmetry: one of the compounds is dissymetric (C_3 symmetry, racemic mixture of *RRR* and *SSS* chirality), the other is asymmetric (C_1 point group, also a racemic mixture in this case of *RRS* and *SSR* chirality). The assignment of the configuration of **1** and **2** is easy by ^{13}C NMR spectroscopy: at room temperature the α isomer shows five sharp signals (C_3 symmetry), the β isomer 15 (C_1 symmetry) (Figure 1).

Isotripiperideine (**3**) has only two tertiary carbon atoms (C-2 and C-2″) attached to two nitrogen atoms (signals at 80.9 and 81.8 ppm, Table I) but one tertiary carbon (C-2′) which is attached to only one nitrogen atom (64.2 ppm) and another one (C-3″) which has only carbon neighbor atoms (47.7 ppm).[9] Altogether 15 carbon signals are seen in the spectrum of **3** at room temperature. The constitution of all three isomers and



1 = α **2** = β **3** = iso

the configuration of **1** and **2** are thus directly evident from ^{13}C NMR spectroscopy.

Conformation[10] of 1. The C_3 symmetric conformation of α-tripiperideine requires axial orientation of all three lone pairs of the nitrogen atoms. In conformation A all rings are trans fused.[11] The resulting electron pair repulsion (generalized anomeric effect or "rabbit ear effect")[5a,12] destabilizes

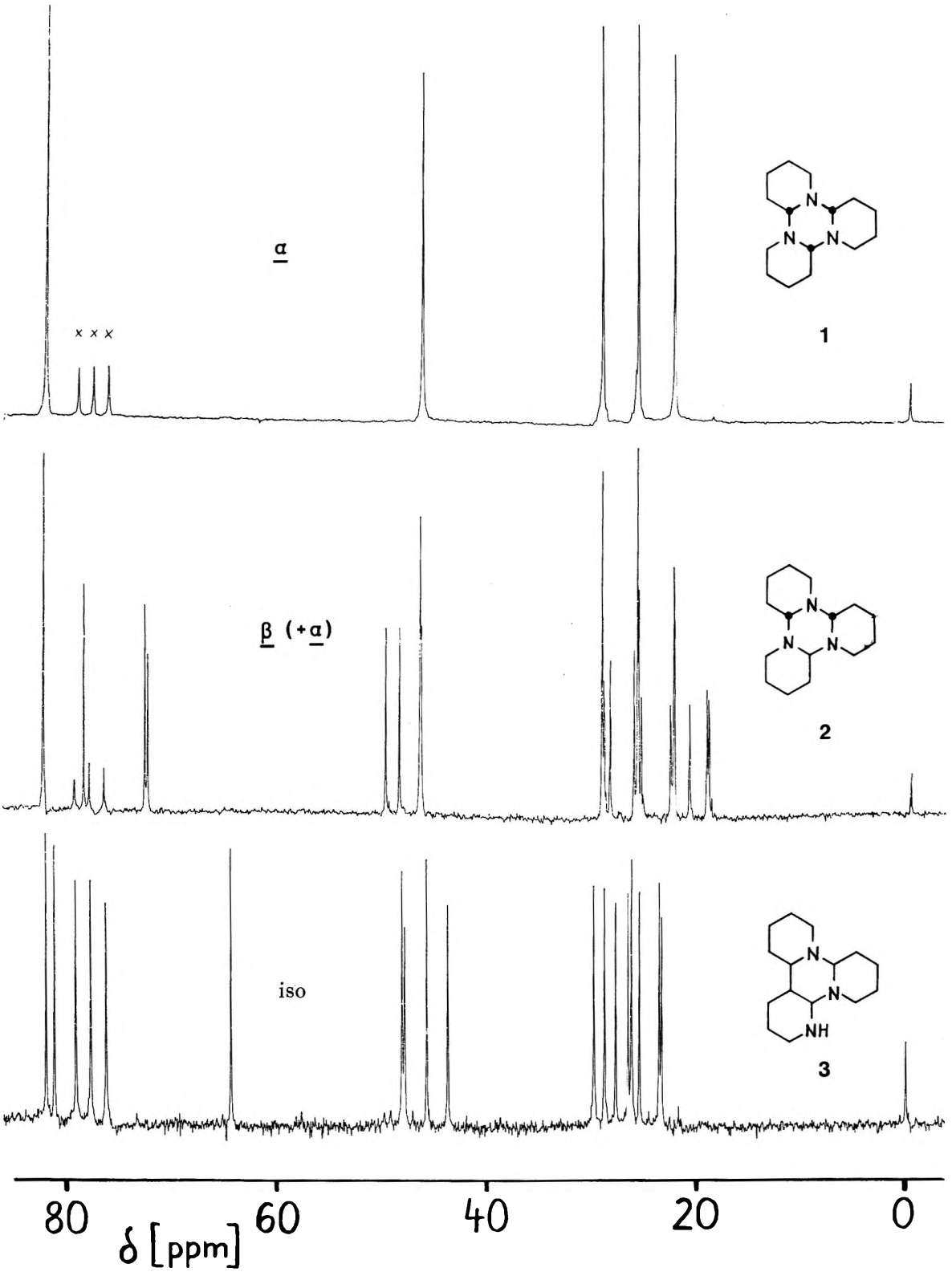


Figure 1. ^{13}C NMR spectra of tripiperideines at room temperature in $CDCl_3$ (X = solvent peaks; 2 contains about 40% of 1).

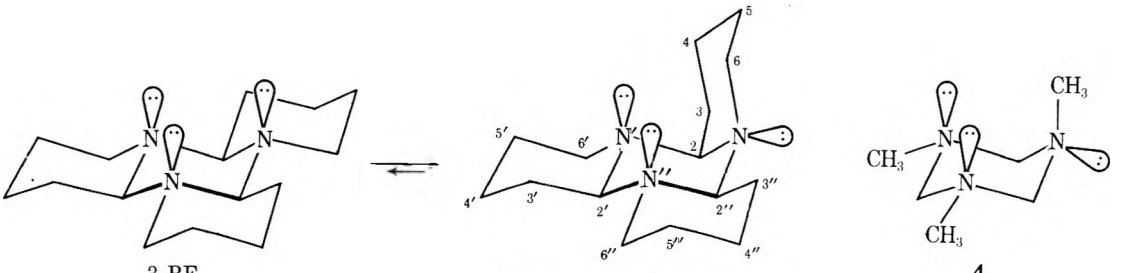
this conformation. The repulsion may be diminished through inversion of one, two, or three nitrogen atoms (conformations B, E, and D),[13] but the inversion of more than one nitrogen atom would lead to strong 1,3-diaxial interactions between the nitrogen-bound CH_2 groups. Thus the only reasonable possibility to reduce the "rabbit ear effect" RE[14] involves the conformation with one nitrogen atom having the lone pair in the equatorial position (conformation B). The number of gauche interactions[14] in B is larger than in A, but in going from A to B the 1,3 interaction of three axial lone pairs is replaced by the interaction of two lone pairs and one axially oriented piperidine ring. E has two syn-axial interactions and C and D have six; C also suffers from three rabbit ear effects. It is evident that the order of stability is A,B > E > D > C but the question remains if the energy of 2 RE is larger than 2 GI_N' + 1 GI_N[14] (i.e., B is more stable than A) or vice versa. The preference of conformation 4 for *N,N',N''*-trimethyl-1,3,5-triazane has recently been observed.[15] Considering this result one would expect B to be more stable than A.

Although conformation B is asymmetric, a rapid inter-

Table I. ^{13}C NMR Spectra of α-, β-, and Isotripiperideine

α-Tripiperideine (1)					β-Tripiperideine (2)			Isotripiperideine (3)			
		δ, ppm[a]			δ, ppm[a]			δ, ppm[a]			
δ, ppm[a,b]	m[c]	Exp[d]	Calcd[e,f]	Position	Exp[g]	Calcd[f,h]	Position	Exp[g]	m[c]	Calcd[f,i]	Position
		85.9	82.9	2′	78.1	81.0	2″	81.8	d	82.9	2 } j
82.2	d	81.8	80.2	2″	72.3	74.0	2′	80.9	d	82.9	2″ } j
		78.0	77.5	2	72.0	71.8	2	64.2	d	63.7	2′
		49.7	48.0	6′ } j	49.6	48.0	6′	48.0	t	49.6	6′
46.6	t	48.4	48.0	6″ } j	48.3	45.4	6″	47.7	d	46.6	3″
		40.6	39.3	6	46.2	44.9	6	45.6	t	48.0	6
		30.2	28.2	3′ } j	29.0	28.2	3′	43.6	t	47.1	6″
29.5	t	28.6	28.2	3″ } j	28.4	26.1	5 } j	29.6		28.6	3′
		28.2	25.6	3	26.1	26.1	5′ } j	28.6		28.2	3
		26.2	26.1	5 }	25.7	25.6	3	27.6		26.1	5 }
26.2	t	25.7	26.1	5′ } j	25.4	25.2	3″	26.4		26.1	5′ } j
		25.4	26.1	5″ }	22.7	23.3	4′ } j	26.1		26.1	5″ }
		24.5	23.3	4′ } j	20.8	23.3	4″ }	25.3		25.0	4′
22.7	t	23.8	23.3	4″ } j	19.2	20.8	5″	23.4		24.1	4″
		18.7	17.9	4	19.0	17.9	4	23.2		23.3	4

[a] From internal Me_4Si. [b] In CD_2Cl_2 at 32 °C. [c] Multiplicity in proton off-resonance decoupled spectra: d = doublet, t = triplet. [d] In CD_2Cl_2 at −90 °C. [e] Conformation B. [f] The procedure of calculation is described in the text. [g] In $CDCl_3$ at 32 °C. [h] Conformation F. [i] Conformation I. [j] Relative assignments uncertain.



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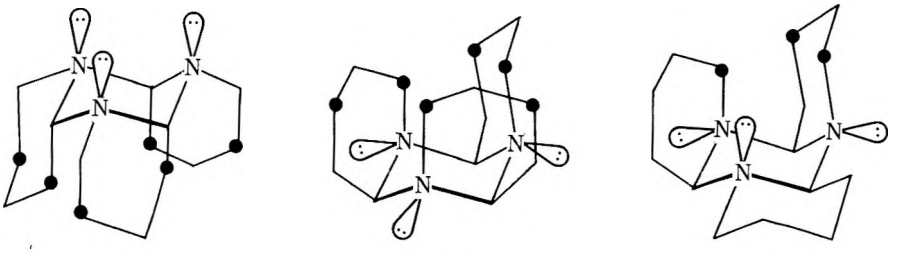


conversion between the three topomers,[16] each of them with another nitrogen atom inverted, will account for the averaged five-line spectrum of 1 at room temperature. The change of the spectrum on lowering the temperature proves that this is the case: each signal splits into three at temperatures below about −50 °C (Figure 2, details about the kinetics will be given elsewhere[31]). No signals of a molecule of C_3 symmetry remain at low temperature. Conformation A is therefore at least 1.1 kcal/mol higher in free energy than B.[17] However, because of the threefold degeneracy of conformation B we have to correct the value $\Delta G°$ for the entropy term ($T\Delta S° = RT \ln 3 = 0.49$ kcal/mol). Thus the enthalpy difference between A and B is larger than 1.1 − 0.5 = 0.6 kcal/mol. B is destabilized by three gauche interactions: two C–N–C–N segments (GI_N') and one C–C–C–N segment (GI_N). Thus it follows that

$$2\,RE > 2\,GI_N' + 1\,GI_N + 0.6\ \text{kcal/mol} \qquad (1)$$

The assignment of the signals in the high-temperature spectrum of 1 which is based on literature data makes possible the grouping of corresponding resonances at low temperature. The chemical shift values in the low-temperature spectrum (Table I) in turn provide convincing proof of the proposed conformation B. Assignment of signals in this spectrum rests on comparison of the experimental chemical shifts with the values of calculated data from replacement of three CH groups by nitrogen atoms in perhydrotriphenylene (PHT) of equal configuration.[18]

Since the ^{13}C chemical shift data of the appropriate configuration of perhydrotriphenylene were not available in the literature we calculated these values by eq 2 using the parameters of Dalling and Grant, which were derived from perhydroanthracenes and perhydrophenanthrenes.[19,20c]

$$\delta_{PHT} = \delta_{const} + \delta_{vic} + \delta_{HH} \qquad (2)$$

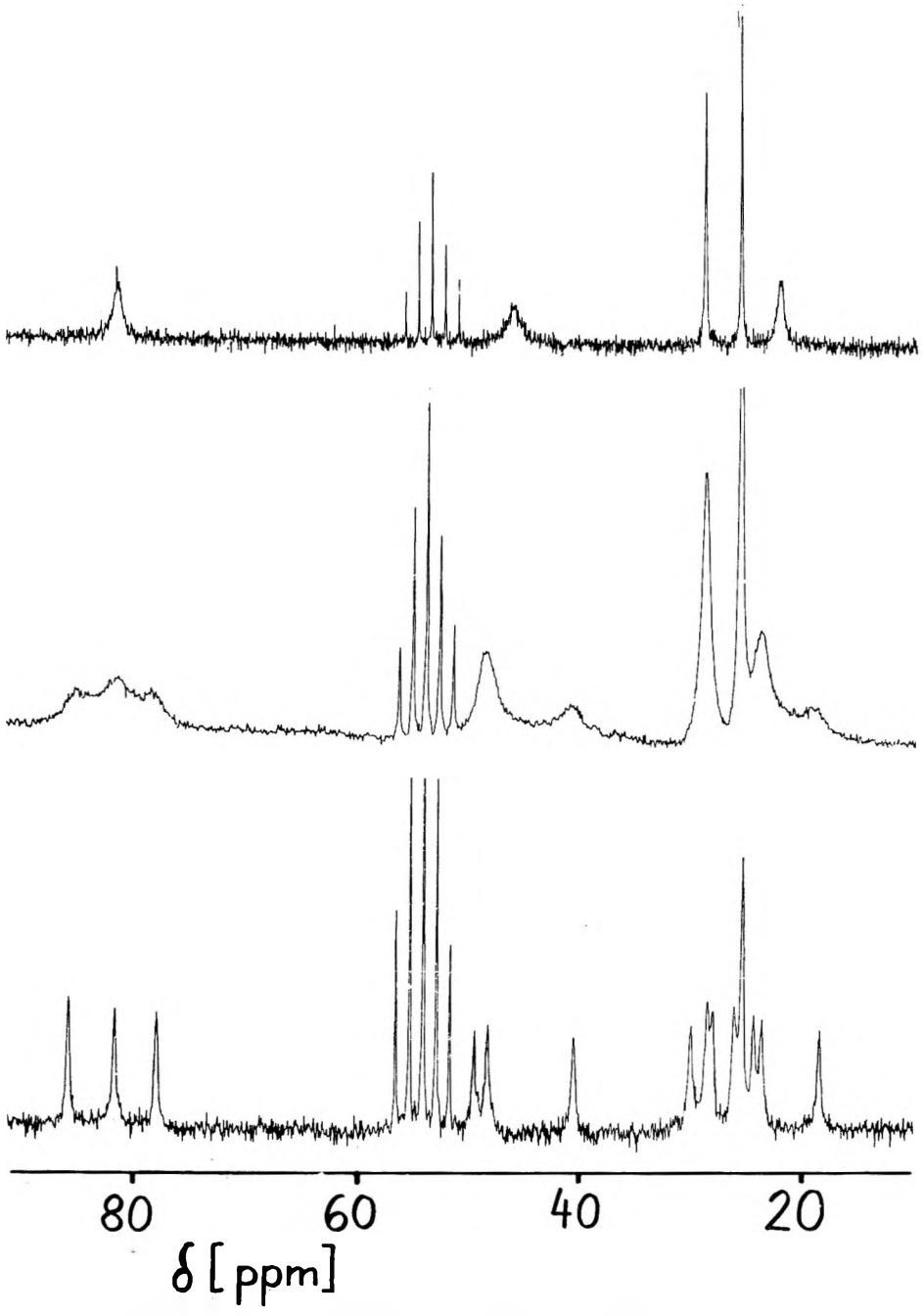


Figure 2. Temperature dependent ^{13}C NMR spectrum of **1** in CD_2Cl_2: top, −20.6 °C, middle, −49.0 °C; bottom, −67.5 °C.

where δ_{PHT} = resulting chemical shift of a carbon in perhydrotriphenylene, δ_{const} = the sum of the constitutional parameters, δ_{vic} = the sum of vicinal gauche and trans parameters, and δ_{HH} = the sum of 1,6 hydrogen–hydrogen interactions.

Replacement of the CH groups by N was then simulated by

$$\delta_{Tripip} = A\,\delta_{PHT} + B \qquad (3)$$

The parameters A and B originate from the comparison of the ^{13}C chemical shifts of *trans*-decalin and quinolizidine, a molecule which contains only one nitrogen atom.[22]

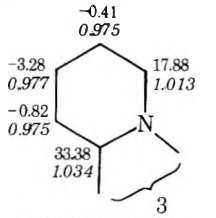
The following example illustrates the procedure for the signal of C-6″. In the analogous perhydrotriphenylene there are two carbons in α and three carbons in β position; C-6″ is involved in two V_g and one V_t interactions; one of its protons is interacting with one of the C-3′ protons. Hence the predicted chemical shift of the hydrocarbon is given by

$$\delta_{PHT}^{6''} = \underbrace{-2.49 + 2\alpha + 3\beta}_{\delta_{const}} + \underbrace{2V_g + V_t}_{\delta_{vic}} + \gamma_{HH} = 29.72 \text{ ppm}$$

The CH → N replacement for this nonbridged carbon involves one α-nitrogen effect and two γ-nitrogen effects:

$$\delta_{Tripip}^{6''} = 1.013 \cdot 29.72 + \alpha_N + 2\gamma_N = 47.99 \text{ ppm}$$

In this fashion the correction terms for CH → N substitution in our system are calculated to be as follows.[23]



A values italic
B values Roman

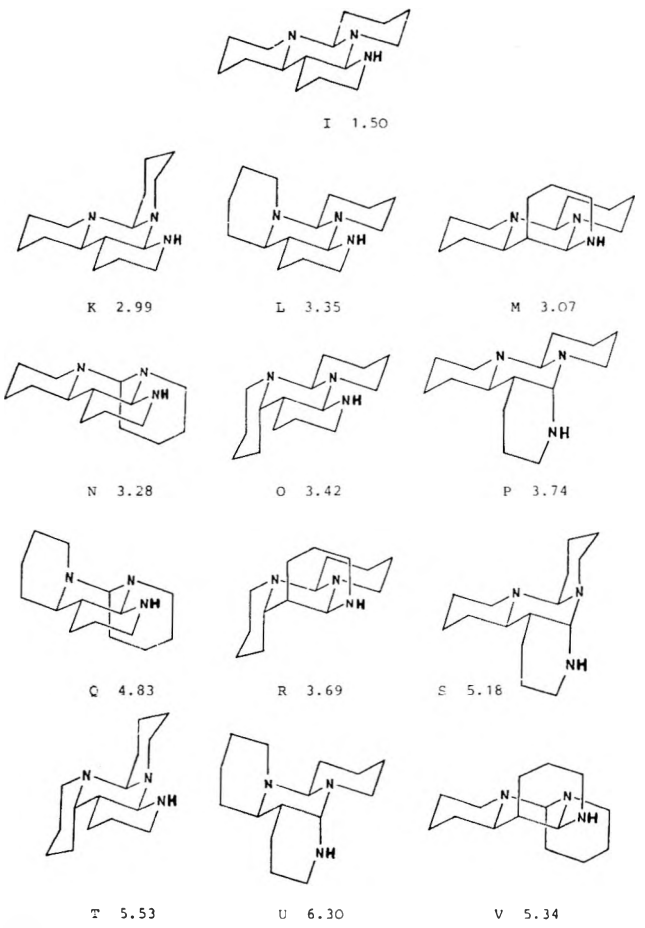


Figure 3. Standard deviations from calculated and observed ^{13}C NMR chemical shifts of some isotripiperideine structures.

The agreement of calculated and observed chemical shifts is satisfying (Table I; standard deviation 1.48 ppm).

Conformation of 2. Definite conclusions about the conformation of **2** may also be drawn from the carbon-13 chemical shifts. The three low-energy conformations (i.e., the conformations without skew pentane interactions), F, G, and H, will be considered in which the C-2″, C-3″ bond is axially oriented.

In these conformations the nitrogen atom N″ has to have an axial lone pair. From the differing steric interactions indicated below the formula[14] it can be seen that the energy difference between G and H is the same as between A and B in **1**, but because of the absence of an entropy term (0.5 kcal/mol in B) the difference in $\Delta G°$ (>1.1 kcal/mol between A and B) is smaller (>1.1 − 0.5 ≥ 0.6 kcal/mol between G and H). F is favored energetically by one gauche interaction, GI′ compared with H. The order of stability therefore should be F > H > G. The energy difference between F and H might lead to a measurable participation of H in the equilibrium. Unfortunately, because of the low stability of **2** we did not succeed in recording a low-temperature spectrum.

Table II. Observed and Calculated[a] Signals (ppm) of the Carbons in 2 Position of 2

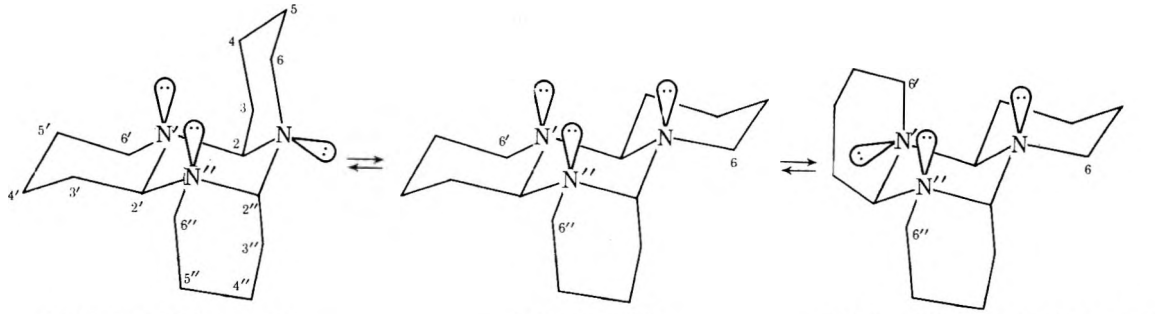
		Conformation		
Position	Obsd	F	G	H
C-2″	78.1	81.0	77.5	77.8
C-2′	72.3	74.0	74.1	68.7
C-2	72.0	71.8	77.2	74.5

[a] The procedure of calculation is described in the text.

The agreement between observed and calculated ^{13}C chemical shifts (Table I; for method of calculation see above) supports the assumption that F is the most stable conformation. A least-squares calculation yields a standard deviation of 1.70 ppm for F, 1.83 ppm for G, but 2.48 ppm for H. Hence H could be excluded. A further experimental criterion for distinguishing conformations F, G, and H is the shift of the carbon at position 6. Whereas C-6′ in H would suffer a strong upfield shift compared to C-6 and C-6″ (calculated for H: C-6 = 48.0, C-6′ = 39.3, C-6″ = 45.4 ppm; compare C-6 in B), the experimental values for all three signals are in the range of 46–50 ppm, in agreement with the calculated values for F (44.9 − 48.0 ppm). The absence of a high-field shift for C-6 (in contrast to B) results from the lack of a γ_{HH} interaction (−5.53 ppm[20c]), between the C-3″ and the C-6 hydrogen atoms in conformation F. The most clear-cut distinction between F and G is based on the carbon signals of position 2. Whereas in F the experimental data (two high-field signals, one low-field signal) are well simulated by empirical calculations, this would not be true for G (Table II). Thus F is the predominant isomer in the equilibrium.

The calculated values of Table I were obtained without consideration of any special lone pair effect.[24]

Conformation of 3. The four asymmetric carbon atoms of isotripiperideine a priori lead to 16 configurational isomers (eight enantiomeric pairs). Inversion of one or both hexahydropyrimidine nitrogen atoms increases the number of possible structures even more. Some conformations are excluded by steric restraint. In addition, we took into consideration only those structures which do not involve 1,3-diaxial interactions of CH_2 groups. The carbon chemical shift values of the remaining 13 conformations (seven configurational isomers) were estimated by calculation of the corresponding configurational isomers of perhydrotriphenylene (carbon analogues) and application of the CH → N replacement shifts in the manner described above.

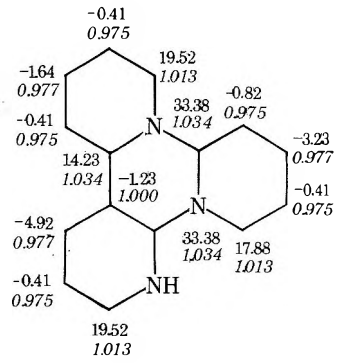


1 RE + 2 GI_N' + 1 GI_N F

3 RE + 1 GI′ G

1 RE + 1 GI′ + 2 GI_N' + 1 GI_N H

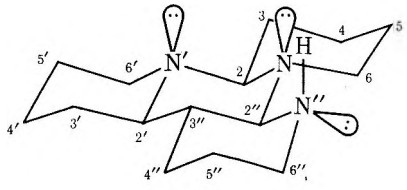
The following replacement parameters were used in eq 2:



A values italic

B values Roman

The resulting shift values were compared to the experimental data. The standard deviations for all 13 structures are exhibited in Figure 3. The least-squares method unequivocally favors conformation I, in which all rings are trans fused and no additional gauche interaction is present.



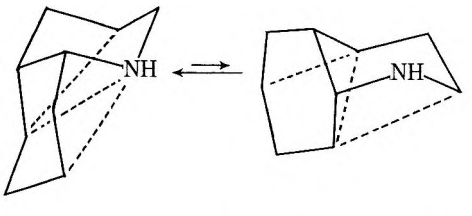
I

It is reasonable to assume that the hydrogen on N″ in the piperidine ring is axially oriented[26] both for steric grounds and to avoid additional rabbit ear effects. Thus, in I at least one generalized anomeric effect of two lone pairs (N and N′) is present. Inversion of the nitrogen atom N′ (leading to conformation L in Figure 3) involves an increase of energy by 1 GI_N' plus 1 GI plus 1 GI′,[14] while inversion of the atom N (K, Figure 3) increases the energy by 1 GI_N plus 1 GI_N' plus 1 GI′.[32] Thus (because $GI_N < GI$) it follows that

$$1\ RE < 1\ GI_N + 1\ GI_N' + 1\ GI' \qquad (4)$$

Conclusion

Carbon-13 NMR spectroscopy provides a simple method for assigning the configuration of α- and β-tripiperideine by symmetry arguments. Furthermore, the dynamic behavior of the α compound (1) indicates its conformation to be B whereas the conformation of β-tripiperideine (2) was deduced from the chemical shift data in conjunction with empirical increment calculations to be very largely F. The same procedure was applied to select the dominant structure I from the 13 possible stereoisomers of isotripiperideine (3). Determination of numeric values for the generalized anomeric effect of two nitrogen lone pairs requires knowledge of the energies of the different types[14] of gauche interactions. The gauche interaction of butane GI is known to be 0.85 kcal/mol;[27] the value of GI_N can be estimated from *N*-methylcyclohexylamine[28] to 0.5 kcal/mol. From the equilibrium of *cis*-decahydroquinolines[5c,k] eq 5 is derived.



$$1\ GI + 2\ GI_N = 2\ GI + GI' - 1.05\ kcal/mol \qquad (5)$$

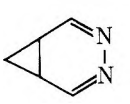
Thus a value of 1.2 kcal/mol results for the gauche interaction GI′ in an 2-azabutane moiety. The increment of GI_N' is not known; thus we assume the values of GI_N and GI_N' to be the same. (This assumption probably results in a too low value of GI_N'.)

The application of these values to eq 1 and 4 yields the limits of the rabbit ear effect in our system:

$$1.05\ kcal/mol < 1\ RE < 2.2\ kcal/mol^{32}$$

This energy given here for the generalized anomeric effect is higher than normally assumed,[5a,33] but it is only approximate since it is based on the gauche interaction of a C–N–C–N segment, GI_N' which is not precisely known.

It is interesting to compare our results with those of similar hexahydrotriazine structures. NMR results of *N,N′,N″*-trimethylhexahydrotriazine (**4**)[15] are in accord with the findings concerning the conformation of **1**. The piperideine structure is also inherent in 3,4-diazanorcaradiene (**5**).[29] This species



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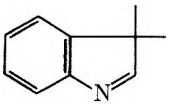

6

forms three different trimeric compounds one of which (compound C in ref 29) apparently shows C_3 symmetry in the ^1H NMR spectrum and should thus correspond to **1**.

On the other hand, the trimer of β,β-dimethylindolenine (**6**) has C_1 symmetry.[30] We think that this compound corresponds to **2**, since in our opinion there is no strong evidence for the postulated boat conformation of the hexahydrotriazine system.

Experimental Section

α-Tripiperideine (**1**) and β-tripiperideine (**2**) (*RRR/SSS*, respectively *RRS/SSR* racemic mixture of dodecahydro-1*H*,6*H*,11*H*-tripyrido[1,2-*a*:1′,2′-*c*:1″,2″-*e*]-*s*-triazine) and isotripiperideine (**3**) (tetradecahydro-2*H*,11*H*-tripyrido[1,2-*a*:1′,2′-*c*:3″,2″-*e*]pyrimidine) have been prepared as described previously.[7] The ^{13}C FT NMR spectra were recorded at 22.63 MHz using a Bruker HX 90 spectrometer equipped with a Nicolet 1083 computer and a Bruker temperature control unit; 8K data points were used resulting in a resolution of 0.03 ppm for the 2500-Hz spectra in Table I. Usually 3000–8000 FID's were accumulated; the low-temperature spectra in the exchange region required 30 000 FID's. The chemical shifts relative to internal Me_4Si were determined with an accuracy of ±0.2 ppm.

Acknowledgments. We wish to thank very much Professor E. L. Eliel and Dr. F. W. Vierhapper for helpful discussions. The financial support of the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

Registry No.—**1**, 2583-71-3; **2**, 60537-08-8; **3**, 60537-09-9.

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(9) Empirical estimates.
(10) In this work we consider structural isomers which result from nitrogen inversion as conformers.
(11) We only consider chair conformations because there is no evidence of very strong interactions which would force the molecule to have one or more rings in boat conformation; see, e.g., G. M. Kellie and F. G. Riddell, *Top. Stereochem.*, **8**, 225 (1974).
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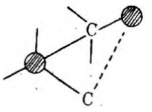
(13) Followed by ring inversion of the adjacent piperidine ring.
(14) RE = generalized anomeric effect, "rabbit ear effect". For gauche interactions the following notations are used:



Gl = butane segment (C–C–C–C)
Gl′ = 2-azabutane segment (C–N–C–C)
Gl_N = propylamine segment (C–C–C–N)
Gl_N' = 2-azapropylamine segment (C–N–C–N)

(15) C. H. Bushweller, M. Z. Lourandos, and J. A. Brunelle, *J. Am. Chem. Soc.*, **96**, 1591 (1974).
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(17) I.e., at −90 °C the contribution of A is less than 5%.[31]
(18) Whereas in smaller cyclic systems distinct ^{13}C chemical shift increments caused by alkyl substitution were successfully applied for calculation of nonbridgehead carbons in methylcyclohexanes,[20a] methyldecalines,[20b] methylpiperidines,[5b–d,21] alkyldecahydroquinolines,[5c,f] and methylquinolizidines,[22] this method may lead to wrong values of bridgehead or bridgehead neighbored carbon atoms in polycyclic systems such as methyldecalines[20b] and perhydrophenanthrenes and -anthracenes.[20c] For recent results see ref 5k.
(19) It is also possible to build up the data for PHT using the *experimental* values from corresponding segments of perhydroanthracenes and perhydrophenanthrenes. This results in a slightly better agreement with the observed data. As a consequence also assignments of some carbon signals in the less significant high-field region may have to be interchanged.
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(23) The *A* parameter only considers the nearest nitrogen position. The *B* parameter is the sum of the literature values for the three nitrogen positions. We neglected δ and ϵ effects, which are expected to be small.
(24) C-3″ and C-5″ in F, G, and H suffer the effect of an antiperiplanar lone pair of N-1″. One expects an upfield shift of about −3.5 ppm[25] compared to the calculated values. In our case such an effect could be present in an amount of maximally 2–4 ppm if we change the assignments in the high-field region, but when one does this the standard deviation between observed and calculated values increases.
(25) (a) The observed effect in the pairs **2, 2m,** and **19, 19m** in ref 5f amounts to about −9.5 ppm. It contains also the upfield shifting "γ_g" and "buttressing" effects[5f] (about −6 ppm). (b) E. L. Eliel, V. S. Rao, F. W. Vierhapper, and Z. Juaristi, *Tetrahedron Lett.*, 4339 (1975).
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(32) **Note Added in Proof.** A low temperature investigation of **3** gives evidence for conformational heterogenity of isotripiperidеine (65% I, 23% K, and 12% L at −110 °C). This ratio leads to

$$1\,RE = 1\,Gl_N + 1\,Gl_N' + 1\,Gl' - 0.35\ \text{kcal/mol} \qquad (5)$$

With the assumptions made above ($Gl_N' \approx Gl_N$) it follows that 1 RE = 1.85 kcal/mol.[33]
(33) The relative high value of RE could origin from the rigidity of the polycyclic ring system, whereas the literature values are derived from monocyclic compounds in which ring deformation is facilitated.

Syntheses and Chemistry of *N*-Acyl Substituted Dihydroimidazo[2,1-*b*]thiazolium Salts

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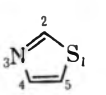
The syntheses of both *N*-acetyl- (**5**) and *N*-carbomethoxy-5,6-dihydroimidazo[2,1-*b*]thiazolium fluoroborate (**6**) from the corresponding *N*-acyl substituted thioimidazolines (**7** and **8**) are described. The reactivity of each of these salts with bases has been evaluated. Treatment of both **5** and **6** with methoxide yielded the known deacylated 3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (**14**). Addition, however, of triethylamine to nitromethane solutions containing **5** and **6** gave yellow, crystalline solids, **15** and **17**, respectively. Spectral analysis indicated that the products obtained were 1:1 adducts of the salts and the solvent. Substitution of nitroethane for nitromethane in each of these reactions yielded the expected homologous adducts (**16** ad **18**). The structure of one of these adducts, **15**, was determined by x-ray crystallography. Formation of **15–18** is believed to occur by the initial nucleophilic addition of the conjugate base of the solvent to the thiazolium ring of the salt to generate a tetrahedral intermediate. Fragmentation of this intermediate in the subsequent step leads to the observed adducts.

Although thiazoles (**1**) and thiazolium salts (**2**) are stable, isolable aromatic compounds, they readily undergo a variety of interesting reactions with nucleophiles.[1,2] The alkylated salts (**2**) are substantially more reactive toward nucleophilic agents than are their neutral precursors (**1**).[1,2]



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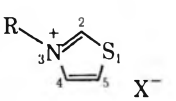
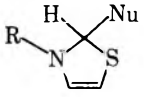


2

Three general pathways have been observed for the interaction of nucleophiles with thiazolium salts (**2**). Typically, the nucleophile adds directly to the aromatic nucleus **2**.[1-4] Addition occurs at C-2 unless this position is sterically hindered, to give the tetrahedral intermediate **3**. Fragmentation of the ring (**3**) usually occurs in a subsequent step. Alternatively, the nucleophilic species can abstract one of the thiazolium ring protons to generate a zwitterion.[5,6] In the parent salt (**2**), the C-2 hydrogen is the most acidic. Deprotonation in this case yields the zwitterion **4**. This last process has been proposed for the initial step in the numerous enzymatic reactions observed for thiamin (vitamin B_1) with α-keto acids.[5,6] In addition to these two types of reactions, the *N*-alkyl substituent in **2** can be attacked by the incoming nucleophile to displace the parent thiazole (**1**).[7]



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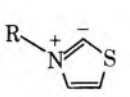

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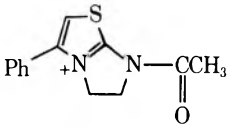
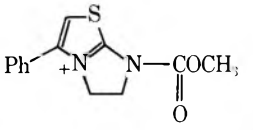
In light of this diverse group of reactions it was of interest to us to examine the reactivity of two recently prepared 5,6-dihydroimidazo[2,1-*b*]thiazolium salts **5** and **6**. Both of these



5 BF_4^-



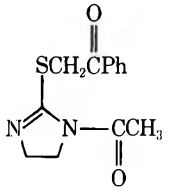
6 BF_4^-

substrates also contain an activated carbonyl system, thereby further increasing the potential number of sites for nucleophilic attack. These salts were initially synthesized as potential model substrates for a current study dealing with the mechanism of biotin catalysis.[8]

In this communication we would like to report both the syntheses and reactivity of these thiazolium compounds as well as their neutral precursors. Of particular interest here is the reactivity of these substrates with various nucleopiles. In a number of cases studied, these reactions led to the isolation of stable crystalline adducts possessing many of the structural features that have been proposed for the active intermediate in the decarboxylation and condensation reactions of α-keto acids by vitamin B_1.[5,6]

Results and Discussion

The thiazolium salts (**5** and **6**) were synthesized directly from the neutral percursors **7** and **8**. In turn, the substituted thioimidazolines (**7** and **8**) could be prepared in two steps from the commercially available imidazolidinethione.[8,9] Although most of the physical and chemical properties for **7** and **8** were consistent with their close similarity in structure, the rectivity of each of these substrates toward methoxide ion was markedly different.



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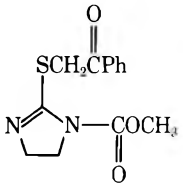
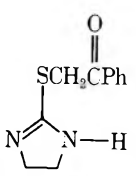


8

Reactivity of 7 and 8 toward Methoxide Ion. Treatment of **7** in CH_2Cl_2 with 1 equiv of 0.5 M sodium methoxide–methanol solution gave a 91% yield of the known deacylated 2-phenacylthioimidazoline (**9**).[10] However, when **8** was treated with 1 equiv of sodium methoxide under the identical conditions used for **7**, the deacylated thioimidazoline (**9**) was not



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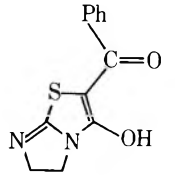
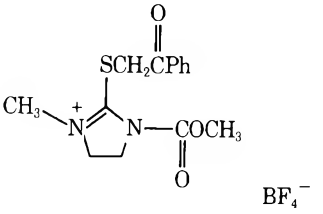


10

obtained. Instead the bicyclic 2-benzoyl-3-hydroxy-5,6-dihydroimidazo[2,1-*b*]thiazole (**10**) was isolated in 71% yield.[8]

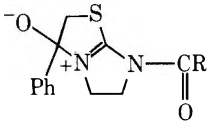
Formation of the bicyclic adduct (**10**) can be envisioned to occur by initial nucleophilic attack of the carbomethoxy carbonyl group by the enolate anion of **8**. Substitution in this case proceeds with the expulsion of methoxide ion to give the bicyclic adduct (**10**) rather than the release of a thioimidazoline anion.

Syntheses of 5 and 6. Methylation of **7** in nitromethane with 1.3 equiv of trimethyloxonium fluoroborate[11] gave the thiazolium salt (**5**) in 46% purified yield along with at least two other products (NMR analysis). *N*-Acetyl-3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazolium fluoroborate (**5**) was isolated by the selective extraction of the unidentified compounds from the product mixture with chloroform. Similarly, when **8** was treated with 1.5 equiv of trimethyloxonium fluoroborate[11] *N*-carbomethoxy-3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazolium fluoroborate (**6**) as well as the N-alkylated *N*-methyl-*N'*-carbomethoxy-2-phenacylthioimidazolinium fluoroborate (**11**) were isolated in 27 and 61% yields, respectively.[8] In this case again, **6** could be isolated by trituration of the product mixture with chloroform.



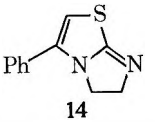
11

The formation of both **5** and **6** can be envisioned to occur by the initial tautomerism of **7** and **8**, respectively, to give the isomeric N-substituted 3-oxido-3-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazolium salts (**12** and **13**). Subsequent methylation at oxygen followed by rearomatization by loss of methanol would give the bicyclic thiazolium salts, **5** and **6**. Analogously, it has been reported that treatment of *N*-methyl-2-phenacylthioimidazoline with hydrobromic acid gave the corresponding *N*-methyl-3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazolium bromide.[12]



12; R = CH_3
13; R = OCH_3

Reactivity of 5 and 6 with Bases. The structural assignments of **5** and **6** are supported by the reaction of these salts with methoxide ion. In both cases, methanolysis gave the known 3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (**14**)[9,10] in 56 and 72%[8] yields, respectively.



14

Treatment of thiazolium salts **5** and **6** with triethylamine in nitromethane, however, did not lead to the deacylated

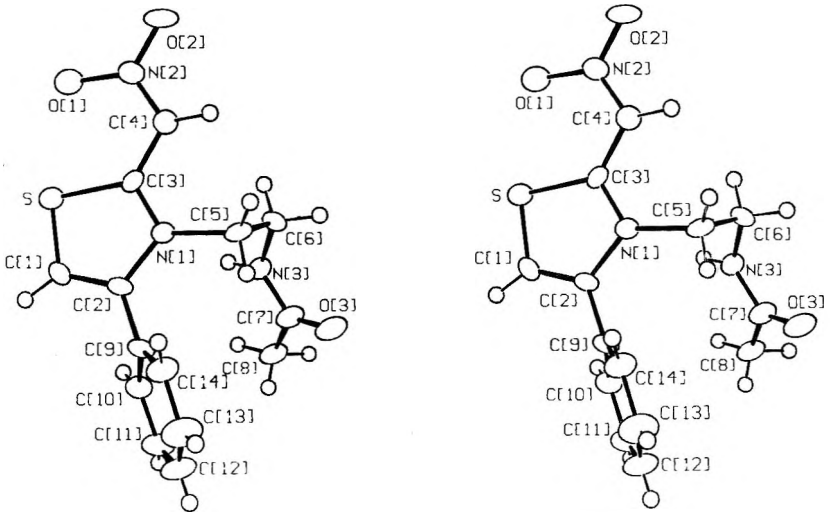


Figure 1. Stereoscopic representation of **15**, showing the atoms numbering scheme used in the presentation and discussion of crystallographic results.

product **14** observed in the sodium methoxide reactions. Instead, a brilliant yellow crystalline material (**15**) was isolated from the reaction of **5** with 1 equiv of the amine in nitromethane. Mass spectrometry showed a molecular ion at *m/e* 305. The infrared spectrum showed a strong band at 1675 cm^{-1} and the absorption was tentatively assigned to an acetamide carbonyl group.[13] This assignment, however, was jeopardized by the corresponding ^1H NMR spectrum. The Me_2SO-d_6 NMR sample did not show a peak in the δ 2.0 region typically observed for acetamide methyl protons.[14] Instead a sharp singlet was obtained at δ 1.62, a position which is considerably higher field than previously reported for acetamide methyl protons.[14] Examination of the proton decoupled ^{13}C NMR spectrum, on the other hand, revealed three carbon resonances (22.4, 36.2, 46.9 ppm) in the 20–50-ppm region. In a selective decoupling experiment (irradiation at δ 7.12), one of these peaks (22.4 ppm) gave rise to a residual quartet pattern. Unlike the ^1H NMR data, comparison of this chemical shift position to ^{13}C NMR correlation tables[15] suggested that the resonance at 22.4 ppm was due to an acetamide methyl group.

Elemental analysis (C, H, N, S) of **15** is consistent with an empirical formula of $C_{14}H_{15}N_3O_3S$, and in agreement with the earlier obtained mass spectral data. Although the precise structure of the adduct eluded us, the combined results of the elemental analysis and the mass spectral data strongly suggested that **15** was a 1:1 adduct of the salt (**5**) with the solvent, nitromethane. It was of interest, therefore, to rerun the reaction in nitroethane.

Treatment of **5** with 1 equiv of triethylamine in nitroethane again led to a brilliant yellow crystalline material **16** upon workup. Mass spectrometry showed a parent peak at *m/e* 319. The infrared spectrum showed a potential acetamide carbonyl absorption at 1660 cm^{-1}, while the ^1H NMR again exhibited the unusually high field singlet at δ 1.62. In addition, the low-field singlet (1 H) in **15** at δ 7.82 was replaced by a sharp singlet (3 H) in **16** at δ 2.53. The empirical formula of $C_{15}H_{17}N_3O_3S$ obtained from elemental analysis (C, H, N, S) was in agreement with the mass spectral data. Both **15** and **16** then appeared to arise from an interaction of **5** with the solvent.

Substitution of the *N*-carbomethoxy-3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazolium fluoroborate[8] (**6**) for **5** in each of the above two reactions (nitromethane and nitroethane) led to the isolation of two additional yellow crystalline compounds, **17** and **18**, respectively. Examination of the spectral data for these four compounds (**15–18**) (see Experimental Section) reinforces the conclusions that these compounds fall into two homologous series (**15, 16** and **17, 18**) and that these two series of compounds are structurally related.

The structural identity, however, of any one of these four compounds still remained obscure. In order to clarify this problem, a single crystal x-ray structure determination of **15** was carried out. A stereoview illustrating the molecular conformation for **15** is depicted in Figure 1, which also presents the (arbitrary) numbering system used in the presentation and discussion of the crystallographic results.

Bond distances are consistent with considerable delocalization through the sequence N(1)–C(3)–C(4)–nitro: C(3)–N(1), 1.352 (9); C(3)–C(4), 1.386 (11); C(4)–N(2), 1.348 (12); N(2)–O(1), 1.268 (8); and N(2)–O(2), 1.259 (8) Å. Thus, the C(3)–N(1) distance agrees well with the corresponding distance in one other structure in which such conjugation occurs: 1.353 (6) Å in 2-mercaptobenzothiazole.[16] This distance is noticeably longer than in structures in which the bond is largely double in character: 1.324 (4) Å in 2-(α-hydroxyethyl)-3,4-dimethylthiazolium bromide;[17] 1.32 Å (average, no esd reported) in 1-phenyl-3-(thiazolin-2-yl)-2-thiourea;[18] 1.280 (9) Å in 2-(*o*-hydroxyphenyl)benzothiazole;[19] 1.308 (5) Å in *N*-benzyl-4-methylthiazolium bromide;[20] 1.297 (3) Å in 2-methylaminobenzothiazole;[21] and 1.307 (2) Å in 2-amino-4,5-dihydro-7,8-dimethyoxy[1,2-*d*]thiazole.[22]

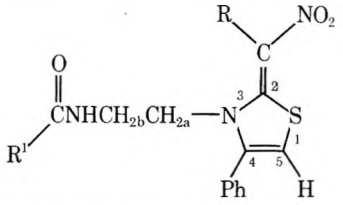
The atoms S, N(1), C(1), C(2), C(3) of the five-membered ring are coplanar to within 0.02 Å, with atom C(4) also in this plane to within experimental error. The nitro group is twisted out of this plane by only 5.6°.

Conclusions

After the structure for **15** was revealed by the x-ray study, the peak assignments in the ^1H NMR spectra for compounds **15–18** were made (Table I).

Of interest in the ^1H NMR spectra are the high field assignment to the substituted acetamide methyl protons in **15** and **16**, and the apparent quartet observed for the high field methylene protons (CH_{2b}) in **16, 17**, and **18**. Although at first surprising, this high field assignment is not unprecedented after the NMR solvent (Me_2SO-d_6) used in this study is taken into consideration. In a control experiment, the chemical shift position of the acetamide methyl resonance in acetamide itself was determined in $CDCl_3$ and Me_2SO-d_6. An upfield shift from δ 1.99 to δ 1.83 was noted in going from $CDCl_3$ to Me_2SO-d_6. On the other hand, the apparent quartet patterns

Table I. ^{1}H NMR Data for 15–18[a]



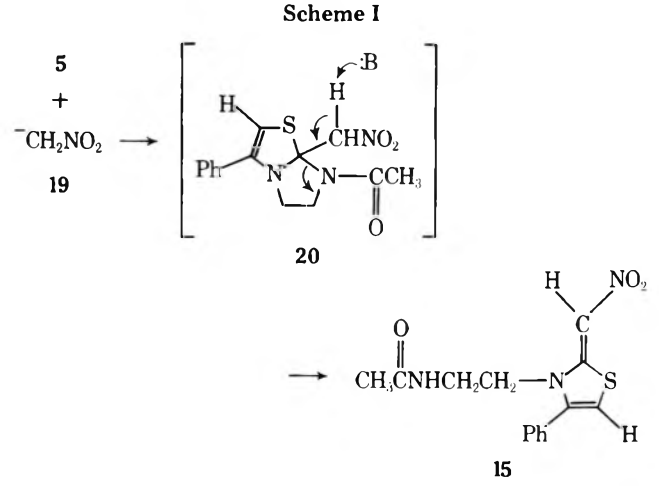
	15	16	17	18
R: H	7.82		7.78	
CH_3		2.53		2.54
R': CH_3	1.62	1.62		
OCH_3			3.30	3.37
Ph	7.50	7.42	7.45	7.57
C_5H	7.12	7.12	7.12	7.23
CH_{2a}	3.76–4.10 (t)[b]	4.13–4.40 (t)[b]	3.90–4.12 (t)[b]	4.27–4.47 (t)[b]
CH_{2b}	2.97–3.38 (m)	2.75–3.13 (q)[b]	2.97–3.24 (q)[b]	2.78–3.08 (q)[b]
NH	7.72–8.06[c]	7.60–7.75 (m)	6.98–7.10 (m)	7.03–7.14 (m)

[a] NMR spectra were run in Me_2SO-d_6 and chemical shifts are expressed in parts per million relative to Me_4Si. [b] $J \sim 6$ Hz. [c] Broad singlet.

(J = 6 Hz) observed for the high field methylene protons (CH_{2b}) are due to the extra coupling with a coincident J_{N-H} coupling of the neighboring N–H proton. This observation substantiates the assignment of these peaks in the ^{1}H NMR spectra to the CH_{2b} protons.

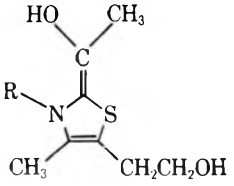
With the identity of the structure for **15** secure, a reasonable mechanism for the formation of this adduct can be formulated (Scheme I). Under the basic conditions of the reaction, proton abstraction from the solvent, nitromethane (pK_a = 10),[23] would give the corresponding conjugate base (**19**). Nucleophilic attack by this carbanion (**19**) at the central carbon of the thiazolium nucleus (C-2) gives the tetrahedral intermediate (**20**). In a subsequent step fragmentation of the ring (**20**) leads directly to **15**.

Scheme I



The eventual site of the nucleophilic attack in the thiazolium salts **5** and **6** is apparently a function of the structure of the nucleophilic species. With the carbanion (**19**), nucleophilic attack at the thiazolium nucleus leads initially to the tetrahedral intermediate (**20**), which subsequently fragments to **15**. Examples of the addition of nitromethide ion to quaternized heteroaromatic molecules have previously been observed.[24–27] On the other hand, with methoxide the product observed is the deacylated thioimidazoline (**14**). In this case formation of a comparable tetrahedral intermediate apparently does not lead to an isolable product.

The structure found for **15** is reminiscent of the proposed active intermediate for the decarboxylation and condensation reactions of α-keto acids by vitamin B_1.[5,6,28] Breslow has suggested that, for example, with pyruvic acid the thiazolium zwitterion reacts to give, after loss of carbon dioxide, the active intermediate **21**. Subsequent reaction of **21** with a proton source, a biological oxidant, or another carbonyl containing



21

compound leads to the observed enzymatic products.[6] Methylene adducts similar to those obtained in this study have previously been isolated.[1,2,29–31] In most cases, however, the compounds obtained were relatively unstable.

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (ir) were run on a Perkin-Elmer Model 700 and 237B spectrometer and calibrated against the 1601-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates Model T-60 and EM-390 instruments. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra, the corresponding ^{1}H spectra, as well as a series of selective decoupling experiments were determined at the JEOL Co. Laboratories, Cranford, N.J., on a JEOL FX60 spectrometer, through the courtesy of Mr. R. Omstead and Dr. K. Goto. Chemical shifts are expressed in parts per million relative to Me_4Si and coupling constants (J values) in hertz. Spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectral (MS) data were obtained at an ionizing voltage of 70 eV on a Hitachi Perkin-Elmer Model RMU-6H mass spectrometer. Elemental analyses were obtained at Spang Microanalytical Laboratories, Ann Arbor, Mich.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. When dry solvents were required, dichloromethane was distilled from phosphorus pentoxide, dimethoxyethane was distilled from lithium aluminum hydride, anhydrous ether was stored over sodium metal, and nitromethane and nitroethane were freshly distilled. All reactions were run under nitrogen, and all glassware was dried before use.

Reaction of *N*-Acetyl-2-phenacylthioimidazoline (7) with Sodium Methoxide. Preparation of 2-Phenacylthioimidazoline (9). To a stirred CH_2Cl_2 solution (25 ml) containing **7**[9] (0.79 g, 3 mmol), 6 ml of 0.5 M sodium methoxide in methanol (3 mmol) was added. The solution was stirred for 4 h at room temperature and then aqueous 5% $NaHCO_3$ (15 ml) added. The addition of the bicarbonate solution resulted in the immediate precipitation of a white solid. The

Table II. Experimental Summary

A. Crystal Data for 15 at −35 °C

$C_{14}H_{15}N_3O_3S$	Crystal system: monoclinic
Formula weight 305.36	Space group: $P2_1/c$ (no. 14)
a = 11.994 (3) Å	Z = 4; $F(000)$ = 640 e
b = 8.791 (3) Å	d_{calcd} = 1.46 g cm^{-3}
c = 13.230 (4) Å	d_{obsd} (room temperature, flotation in aqueous $ZnCl_2$) = 1.40 g cm^{-3}
β = 92.85 (3)°	
V = 1393.2 Å^3	

B. Data Collection at −35 °C

Radiation: Mo K$\bar{\alpha}$, = 0.71069 Å
Mode: ω scan
Scan range: symmetrically over 1.0° about K$\alpha_{1,2}$ maximum
Background: offset 1.0° in ω from K$\alpha_{1,2}$ maximum, each counted for time equal to $^1/_2$ the scan time
Scan rate: variable, 1.0 to 4.0° min^{-1}
Check reflections: four remeasured after every 96 reflections
2θ range: 4.0° to 50.0°
Reflections measured: 2458
Reflections accepted for structure analysis and refinement: 1467 with $I_o \geq 2.0\sigma(I_o)$
Absorption coefficient (Mo K$\bar{\alpha}$): 7.2 cm^{-1}; no absorption correction applied

precipitate was filtered from the H_2O-CH_2Cl_2 mixture, and then triturated with cold $CHCl_3$ and dried in vacuo, yield 0.24 g of **9**. The H_2O–CH_2Cl_2 mixture was then separated and the organic layer dried (Na_2SO_4), concentrated in vacuo, triturated with cold $CHCl_3$, and dried in vacuo to give an additional 0.36 g of **9**, total recovered yield 0.60 g (91%), mp 143–145 °C (lit.[10] mp 145–146 °C): ir (KBr) 1590 cm^{-1}; NMR (Me_2SO-d_6) δ 2.97–4.15 (m, 7 H), 6.70 (s, 1 H), 7.30–7.70 (m, 5 H).

Preparation of *N*-Acetyl-3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazolium Fluoroborate (5). Trimethyloxonium fluoroborate[11] (5.77 g, 39 mmol) in freshly distilled nitromethane (40 ml) was added dropwise to a stirred slurry containing **7**[9] (7.86 g, 30 mmol) in nitromethane (250 ml). The solution was allowed to stir at room temperature overnight and the products isolated by precipitation with Et_2O. The residue was dried in vacuo, and then triturated with $CHCl_3$. The remaining $CHCl_3$ insoluble, white solid was further purified by reprecipitation with Et_2O from a 1:1 nitromethane–dichloromethane solution: yield 4.60 g (46%); mp 204–205 °C; ir (KBr) 1675, 1515, 1415, 1315, 1125–1025 cm^{-1}; NMR (CD_3NO_2) δ 2.38 (s, 3 H), 4.97 (s, 4 H), 7.30 (s, 1 H), 7.58 (s, 5 H).

Anal. Calcd for $C_{13}H_{13}N_2OSBF_4$: C, 47.01; H, 3.95; N, 8.44. Found: C, 47.16; H, 3.92; N, 8.47.

Reaction of *N*-Acetyl-3-phenyl-5,6-dihydroimidazo[2,1-*b*]-thiazolium Fluoroborate (5) with Sodium Methoxide. Preparation of 3-Phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (14). **5** (1.33 g, 4 mmol) was added to 8 ml (4 mmol) of 0.5 M sodium methoxide in methanol and the solution allowed to stand overnight. The solution was then adjusted to pH 9 by the gradual addition of aqueous 5% HCl, and then concentrated in vacuo. The residue was added to aqueous 5% $NaHCO_3$ (20 ml) and then extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layer extracts were washed with H_2O (20 ml), dried (Na_2SO_4), and evaporated in vacuo to give 0.45 g (56% yield) of **14**: mp 109–112.5 °C (lit.[9] mp 112–113 °C); ir (KBr) 1600 cm^{-1}; NMR ($CDCl_3$) δ 3.52–4.40 (m, 4 H), 5.64 (s, 1 H), 7.37 (s, 5 H); MS *m/e* (rel intensity) 202 (100), 201 (69), 147 (12), 142 (22), 105 (95), 102 (47), 100 (44), 99 (50), 77 (18).

Preparation of (2*Z*)-3-(2′-Acetylaminoethyl)-2-nitromethylene-4-phenyl-2,3-dihyrothiazole (15). To a stirred nitromethane solution (30 ml) containing 0.76 g (2.3 mmol) of **5**, 0.23 g 2.3 mmol) of Et_3N was added. The solution was stirred for 48 h at room temperature during which time a yellow crystalline material separated. The solid was collected, dried (0.49 g), and then recrystallized from deionized H_2O: yield 0.30 g (43%); mp 237–238 °C; ir (KBr) 3320, 3110, 2930, 1675, 1520, 1490 cm^{-1}; NMR (Me_2SO-d_6) δ 1.62 (s, 3 H), 2.97–3.38 (m, 2 H), 3.28 (s, HOD), 3.76–4.10 (t, J = 6 Hz, 2 H), 7.12 (s, 1 H), 7.50 (s, 5 H), 7.72–8.06 (broad s, 1 H), 7.82 (s, 1 H). Upon addition of D_2O to the NMR sample the broad singlet at δ 7.72–8.06 disappears and the multiplet at δ 2.97–3.38 broadens. Addition of 1 N NaOD–D_2O (2 drops) to the sample results in the rapid exchange of the peaks at δ 7.12 and 7.82. Of the two, the higher field peak exchanges the most rapidly. The rest of the spectrum remains relatively unchanged upon the addition of base. ^{13}C NMR (Me_2SO-d_6) 22.4, 36.2, 46.9, 107.4, 110.2, 128.8, 129.3, 129.8, 143.7, 161.3, 169.6 ppm. Irradiation of the protons at δ 3.76–4.10, 7.12, and 7.82 in successive selective proton decoupling experiments identified the corresponding carbon resonances at 46.9, 110.2, and 107.4 ppm, respectively. MS *m/e* (rel intensity) 305 (23), 245 (5), 221 (53), 220 (23), 204 (17), 176 (22), 175 (73), 174 (71), 135 (17), 134 (100), 102 (44), 86 (96), 85 (35), 77 (21).

Anal. Calcd for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76; S, 10.50. Found: C, 55.05; H, 5.00; N, 13.72; S, 10.54.

X-Ray Structure Analysis. Crystals of **15** obtained by slow evaporation of a methanol solution were yellow plates. All x-ray work was carried out on a Syntex $P2_1$ autodiffractometer equipped with graphite monochromator and a Syntex LT-1 inert gas (N_2) low temperature (−35 °C) delivery system. Cell parameters were determined by least-squares analysis of 45 carefully centered reflections, 14° ≤ 2θ ≤ 23°. Details of crystal data and intensity data collection appear in Table II.

Data reduction and assignment of standard deviations (with p = 0.02) to the measured intensities were carried out as previously described.[12] Analysis of the 29 sets of check reflections revealed a mild fall-off of intensity with time. This fall-off was described[13] by the equation $X = 1 + At + Bt^2$, where t is exposure time in hours, and the least-squares values of A and B, respectively, were 0.000278 ± 0.000165 and −0.000006 ± 0.000002. A multiplicative correction, $1/X$, applied to the intensity data, ranged from 0.997 to 1.018. No correction for absorption was applied.

The structure was solved by application of direct methods, implemented by the program package MULTAN[14a] and refined by full-matrix least-squares methods.[14b] During the early stages of structure refinement, all nonhydrogen atoms (except sulfur) were assigned carbon atom scattering factors. Consideration of resulting B values and distances and angles soon verified the identity of the N and O atoms. After a few cycles of anisotropic refinement, a difference map revealed the positions of most hydrogen atoms. However, when these failed to refine satisfactorily, hydrogen atoms were included in the refinement in calculated ideal positions. Refinement then proceeded smoothly with all nonhydrogen atoms treated anisotropically and all hydrogen atoms isotropically.

Convergence was reached at $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.067$ and $R_W = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2} = 0.079$. In the final cycle of least-squares refinement, all shifts in nonhydrogen positional parameters were less than 20% of a corresponding estimated standard deviation (esd). No shift in an anisotropic thermal parameter exceeded 30% of its esd in this final cycle. All hydrogen position shifts were less than 30% of an esd and no hydrogen temperature factor shifted by more than 75% of an esd. The function minimized in refinement was $\Sigma w(|F_o| - |F_c|)^2$, where the weight w of each reflection was taken as the reciprocal square of the standard deviation of $|F_o|$. Neutral atom scattering factors for S, O, N, C,[35] and H[36] were used; the real and imaginary corrections due to anomalous dispersion were applied to the S atom scattering factor.[37] A final difference map showed only random features, not exceeding 0.4 eÅ^{-3}.

Final fractional coordinates for the nonhydrogen atoms appear in Table III. Supplementary data consisting of tables of final thermal parameters for nonhydrogen atoms, coordinates and thermal parameters for hydrogen atoms, bond lengths and angles, torsion angles, and selected least-squares planes will be found in the microfilm edition of this journal.[38]

Preparation of (2*Z*)-3-(2′-Acetylaminoethyl)-2-nitroethylidene-4-phenyl-2,3-dihydrothiazole (16). Et_3N (0.23 g, 2.3 mmol) was added to a stirred solution of **5** (0.76 g, 2.3 mmol) in 25 ml of nitroethane. The solution was heated at 40 °C for 24 h and the product isolated by precipitation with ether (450 ml). Purification of **16** was accomplished by dissolving the crude precipitate in CH_2Cl_2 (200 ml) and washing with H_2O (2 × 50 ml). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and reprecipitated from chloroform–ether: yield 0.18 g (25%); mp 208–211 °C; ir (KBr) 3280, 1660, 1540, 1350, 1325 cm^{-1}; NMR (Me_2SO-d_6) δ 1.62 (s, 3 H), 2.53 (s, 3 H), 2.75–3.12 (q, J = 6 Hz, 2 H), 3.27 (s, HOD), 4.13–4.40 (t, J = 6 Hz, 2 H), 7.12 (s, 1 H), 7.42 (s, 5 H), 7.60–7.75 (m, 1 H); MS *m/e* (rel intensity) 319 (10), 245 (9), 235 (25), 218 (7), 203 (8), 190 (10), 189 (33), 188 (100), 135 (7), 134 (17), 102 (12), 91 (8), 86 (24).

Anal. Calcd for $C_{15}H_{17}N_3O_3S$: C, 56.41; H, 5.37; N, 13.16; S, 10.04. Found: C, 56.30; H, 5.37; N, 13.07; S, 9.97.

Preparation of (2*Z*)-3-(2′-Carbomethoxyaminoethyl)-2-nitromethylene-4-phenyl-2,3-dihydrothiazole (17). To a stirred nitromethane solution (35 ml) containing 1.28 g (3.7 mmol) of **6**,[8] 0.37 g (3.7 mmol) of Et_3N was added. The solution was stirred for 48 h at room temperature during which time a yellow crystalline material

Table III. Fractional Coordinates for Nonhydrogen Atoms of 15[a]

Atom	*x*	*y*	*z*
S	−0.0690 (1)	0.7509 (2)	0.1169 (1)
O(1)	−0.1417 (4)	0.4750 (6)	0.1242 (4)
O(2)	−0.0517 (4)	0.2592 (6)	0.1408 (4)
O(3)	0.4747 (4)	0.8198 (6)	0.2220 (4)
N(1)	0.1405 (4)	0.7196 (6)	0.1054 (4)
N(2)	−0.0506 (5)	0.4018 (7)	0.1304 (5)
N(3)	0.3052 (5)	0.7698 (7)	0.2810 (5)
C(1)	0.0119 (6)	0.9100 (9)	0.1088 (6)
C(2)	0.1210 (6)	0.8771 (8)	0.1000 (5)
C(3)	0.0471 (5)	0.6361 (8)	0.1157 (5)
C(4)	0.0458 (6)	0.4792 (9)	0.1251 (6)
C(5)	0.2538 (6)	0.6524 (9)	0.1139 (6)
C(6)	0.2894 (7)	0.6291 (9)	0.2252 (6)
C(7)	0.3991 (6)	0.8533 (9)	0.2763 (6)
C(8)	0.4057 (7)	0.9873 (11)	0.3464 (7)
C(9)	0.2104 (6)	0.9866 (8)	0.0780 (5)
C(10)	0.2338 (6)	1.1082 (9)	0.1408 (6)
C(11)	0.3178 (8)	1.2108 (10)	0.1189 (7)
C(12)	0.3740 (8)	1.1946 (11)	0.0323 (7)
C(13)	0.3514 (8)	1.0758 (12)	−0.0315 (7)
C(14)	0.2696 (6)	0.9698 (9)	−0.0103 (6)

[a] See Figure 1 for identity of the atoms. Numbers in parentheses are the estimated standard deviations in the last significant digit.

separated out. The solid was collected, triturated with Et_2O, and reprecipitated from dichloromethane–hexanes: yield 1.03 g (87%); mp 233.5–235.5 °C; ir (KBr) 3290, 3100, 2960, 1710, 1510, 1420, 1350 cm^{-1}; NMR (Me_2SO-d_6) δ 2.97–3.24 (q, J = 6 Hz, 2 H), 3.30 (s, 3 H), 3.43 (s, HOD), 3.90–4.12 (t, J = 6 Hz, 2 H), 6.98–7.10 (m, 1 H), 7.12 (s, 1 H), 7.45 (s, 5 H), 7.78 (s, 1 H). Addition of D_2O to the NMR sample results in the disappearance of the multiplet at δ 6.98–7.10 and the broadening of the quartet at δ 2.97–3.24. Ms *m/e* (rel intensity) 321 (4), 221 (10), 204 (10), 186 (12), 175 (30), 174 (100), 134 (71), 102 (44), 101 (26), 89 (16), 77 (19).

Anal. Calcd for $C_{14}H_{15}N_3O_4S$: C, 52.32; H, 4.71; N, 13.08; S, 9.98. Found: C, 52.35; H, 4.67; N, 13.08; S, 10.09.

Preparation of (2*Z*)-3-(2′-Carbomethoxyaminoethyl)-2-nitroethylidene-4-phenyl-2,3-dihydrothiazole (18). Et_3N (0.10 g, 1 mmol) was added to a stirred solution of **6**[8] (0.35 g, 1 mmol) in 10 ml of nitroethane. The solution was allowed to stir at room temperature for 72 h, during which time a yellow solid separated. The precipitate was collected, washed with Et_2O, and reprecipitated from dichloromethane–hexanes: yield 0.27 g (81%); mp 199.5–201.5 °C; ir (KBr) 3290, 3080, 2945, 1695, 1525, 1400, 1325 cm^{-1}; NMR (Me_2SO-d_6) δ 2.54 (s, 3 H), 2.78–3.08 (q, J = 6 Hz, 2 H), 3.37 (s, 3 H), 3.43 (s, HOD), 4.27–4.47 (t, J = 6 Hz, 2 H), 7.03–7.14 (m, 1 H), 7.23 (s, 1 H), 7.57 (s, 5 H). Addition of D_2O to the NMR sample results in the disappearance of the multiplet at δ 7.03–7.14 and the broadening of the quartet at δ 2.73–3.08. MS *m/e* (rel intensity) 335 (9), 261 (5), 235 (18), 218 (6), 202 (10), 189 (32), 188 (100), 134 (19), 102 (22), 84 (13).

Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.72; H, 5.11; N, 12.53; S, 9.56. Found: C, 53.66; H, 5.03; N, 12.40; S, 9.56.

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Registry No.—**5,** 60498-93-3; **6,** 59864-00-5; **7,** 60498-94-4; **8,** 59863-93-3; **9,** 32188-99-1; **14,** 36065-41-5; **15,** 60498-95-5; **16,** 60498-96-6; **17,** 60498-97-7; **18,** 60498-98-8; trimethyloxonium fluoroborate, 420-37-1; nitromethane, 75-52-5; nitroethane, 79-24-3.

Supplementary Material Available. Tables of final thermal parameters for nonhydrogen atoms, coordinates and thermal parameters for hydrogen atoms, bond lengths and angles, torsion angles, and least-squares planes (8 pages). Ordering information is given on any current masthead page.

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Interaction of Alkali Metals with Unsaturated Heterocyclic Compounds. 3. Quinazoline and Its 2- and 4-Phenyl Derivatives

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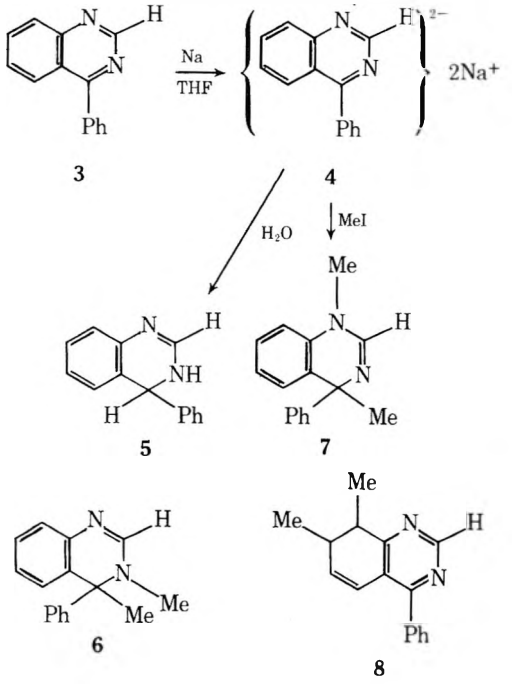
Prompted by an HMO calculation on the quinazoline radical anion which showed a high spin density in the 4 position, a study of the effect of a phenyl substituent at the 2 and 4 positions of the quinazoline nucleus upon reductive metalations of the compound was undertaken. Thus quinazoline, 2-phenyl- and 4-phenylquinazoline were reduced with sodium in tetrahydrofuran, the anionic derivatives characterized by chemical reactions, and the results compared with our earlier study of 2,4-diphenylquinazoline. 4-Phenylquinazoline formed a monomeric dianion which was characterized by protonation and alkylation (MeI). The latter reaction produced three dimethyldihydroquinazolines including one in which the alkylation had occurred in the benzo ring. Both quinazoline and 2-phenylquinazoline formed dimeric dianions which were characterized by protonation and oxidation. The dianion of 2-phenylquinazoline was examined further by alkylation (MeI) and acylation ($ClCO_2Et$). Regioselectivity was observed in these reactions and, in the case of the alkylation reactions, this was attributed to the steric effect of the 2-phenyl substituent.

Recently, the reductive metalation of 2,4-diphenylquinazoline by sodium to form a monomeric dianion has been described[1] as well as some aspects of the chemical behavior of this dianion. Since HMO calculations[2] applied to the quinazoline radical anion itself indicated that the charge density was high at the two heteroatoms while the spin density was especially high at the 4 position, the relative importance of the two phenyl substituents became of interest. It was expected that the 4-phenyl substituent would prove important in stabilizing the radical anion generated as an intermediate in the reduction while the 2-phenyl substituent would be relatively unimportant. The present report describes the results obtained in the reduction of quinazoline (**1**) and 2-phenyl- and 4-phenylquinazoline (**2** and **3**, respectively), which support these expectations.

Results

4-Phenylquinazoline (**3**) (Scheme I) in tetrahydrofuran (THF) was converted to a monomeric dianion **4** by reduction with sodium. This was established both by the amount of alkali metal which reacted and by the formation of 3,4-dihydro-4-phenylquinazoline (**5**) on protonation.

Scheme I. Reactions of the 4-Phenylquinazoline Dianion



In order to compare the chemical behavior of **4** with that of the related dianion[1] of 2,4-diphenylquinazoline, alkylation of **4** with methyl iodide was examined. As expected, both 3,4- and 1,4-dihydrodimethylquinazolines (**6** and **7**) were formed and identified by spectral correlations[3] with known analogues. However, unlike the earlier alkylation of the 2,4-diphenylquinazoline dianion, the 3,4-dihydro product **6** predominated.

A third methylation product, **8**, was isolated as well and its structure assigned on the basis of spectral data. The infrared spectrum showed absorption bands characteristic of the pyrimidine ring and the NMR spectrum showed resonances characteristic of vinyl protons while the methyl resonances appeared as doublets. Decoupling of the NMR spectrum suggested the substitution shown which is similar to that of a related product isolated elsewhere.[1]

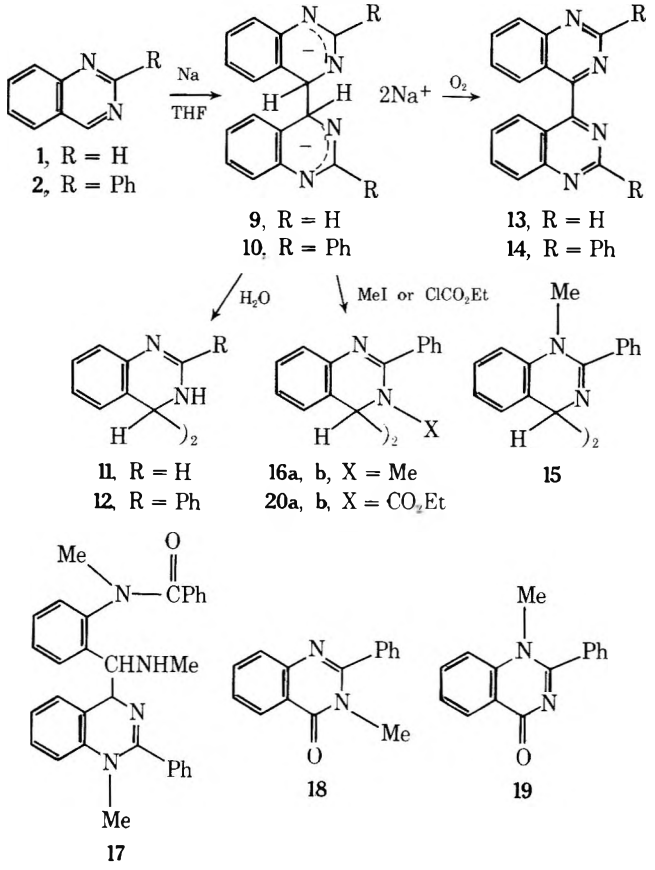
Quinazoline (**1**) and 2-phenylquinazoline (**2**) both formed dimeric dianions **9** and **10** (Scheme II) on similar reductions with sodium. Again this was indicated by the amount of alkali metal reacting and by the products formed on protonation. This last reaction produced the 4,4′-bis(3,4-dihydroquinazolinyl) derivates **11** and **12**, the former having been prepared[4] earlier by the electrochemical reduction of quinazoline.

The presence of some 3,4-dihydro-2-phenylquinazoline among the reaction products of the reductive metalation of **2** suggested that the formation of dianion **10** was not quantitative but either the radical anion or monomeric dianion of **2** was present. A similar situation has been reported for the reductive dimerization of Schiff bases[5] and, indeed, would account for the observation that predominantly one diastereomer[5,6] was formed in the dimerization of **1** and **2**.

Oxidation of the dimeric dianions **9** and **10** produced both the original quinazolines and the 4,4′-bisquinazolines **13** and **14**. Regeneration of the starting quinazoline again suggests that electron transfer from an equilibrium concentration of the monomer radical anion occurred rapidly resulting in a reversal of the dimerization. The rather favorable yield of **13** was unexpected in view of the reported failure[4] of the aromatization of **11** to **13** with alkaline ferricyanide which produced only **1**.

The chemical behavior of dianion **12** was examined further to see if any regioselective factors were operating to limit the potential formation of six isomeric–diasteromeric products. Indeed, alkylation of **12** with methyl iodide produced a complex mixture but this was, in part, due to the partial oxidation

Scheme II. Reactions of the Dimeric Dianions of Quinazoline and 2-Phenylquinazoline



of the products producing the oxoquinazoline **18** and, in one extreme case, **19**. In addition, a ring-opened alkylation product **17** was isolated. The assigned structure of **17** is compatible with the chemical shifts of the methyl groups in which the most upfield methyl was coupled to an amino hydrogen and the other two methyls have chemical shifts in agreement with model compounds.[3] The ultraviolet and infrared spectra support the assignment[3] of the 3,4-dihydroquinazoline structure.

Insofar as alkylation products were concerned, the major product was one of the diasteromeric bis(1,4-dihydroquinazolinyl) derivatives **15**; relatively small yields of the two diastereomeric bis(3,4-dihydroquinazolinyl) compounds **16a** and **16b** were isolated. Again the correlation[3] between structure and spectral properties was used in assigning structures **15** and **16**.

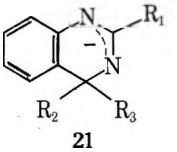
Acylation of **10** with ethyl chloroformate produced chiefly one diastereomer of the bis(3,4-dihydroquinazolyl) compound **20a**. A small yield of the second diastereomer **20b** was also obtained. Both these compounds are considered to be bis(3,4-dihydroquinazolinyl) derivatives because of the pattern of the absorption bands[3] in the 1550–1650-cm^{-1} region of the ir spectrum. In addition, a small yield of a third dimeric product, **21**, was isolated which, because of an AB quartet for the benzylic protons in the NMR spectrum, was considered to possess both a 1,4-dihydro- and 3,4-dihydroquinazolyl ring system. This assignment was supported by the ir spectrum, where bands characteristic of both ring systems were present.

Discussion

The experimental observations just described establish that a 4-phenyl substituent on a quinazoline nucleus has a profound effect on a reductive metalation while a 2-phenyl substituent does not. There are two possible explanations for this effect—either the 4-phenyl substituent prevents dimerization of the initially formed radical anion or the radical anion is sufficiently stabilized by the delocalizing effect on the 4-phenyl substituent that it can be reduced further to the monomeric dianion.

A consideration of the uv spectra of quinazoline and its phenylated derivatives is instructive. With the reservation that the compound with the greater number of phenyl substituents has the larger extinction coefficients, the spectra of 4-phenylquinazoline and quinazoline resemble one another, while that of 2-phenyl- and 2,4-diphenylquinazoline are also similar. This indicates that, while the 2-phenyl substituent is conjugated with the quinazoline ring, the 4-phenyl substituent is not, probaby owing to the interaction of the ortho protons with the proton at the 5 position. While this spectral data was obtained on the parent compounds, it is suggestive that in the case of the radical anions, it is steric rather than electronic effects which control the reductive metalation. This has been suggested earlier by Eisch[7] in cases involving the phenanthridine ring system.

Isomeric mixtures of 1,4-and 3,4-dihydroquinazolines arise by reaction of anionic species such as **21**[8] at either of the two



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heteroatoms N-1 or N-3. Kinetically, reaction should be favored at N-3 since this portion of the ambident anion resembles an aliphatic amine anion and would be expected to be more nucleophilic than the aromatic amine anionic site N-1. Thermodynamically, preference for reaction at N-3 can be anticipated as well, since in the product the double bond is conjugated with the benzo ring.

Approximately a 3:1 preference for reaction at N-3 is observed in the methylation of the 4-phenylquinazoline dianion, **4**. However, a 2-phenyl substituent reverses this regioselectivity so that a 2:1 preference for N-1 alkylation is seen both in the case of the dimeric dianion **10** and the monomeric dianion of 2,4-diphenylquinazoline.[1] This can be attributed to the steric effect of the 2-phenyl substituent which in combination with the R_2 and R_3 groups markedly slows reaction at N-3.

The regioselectivity observed in the acylation reactions cannot be considered until the possibility of rearrangement[9] of the ethoxycarbonyl group is excluded or established. Indeed, the completely opposite results obtained in the acylation of the dimeric dianion **10** and the monomeric dianion of 2,4-diphenylquinazoline[1] suggest strongly that factors additional to those mentioned in the alkylation reaction are operating.

The isolation of the benzo-alkylated product **8** is interesting in view of the earlier suggestion[1] that such products may arise by a single electron transfer (SET) mechanism with subsequent coupling of the radical anion-radical pair. Such a mechanism would be less likely for the primary halide used here than for the tertiary halide used in the earlier study. However, in the present case, two factors probably favored the SET mechanism. Firstly, the alkylation was effected at ambient temperatures which might permit electron transfer to compete with nucleophilic substitution. It is noteworthy that benzo-alkylation products were reduced markedly when the reaction temperature was reduced. Secondly an alkyl iodide was used in the present study, and these, as indicated by their half-wave reduction potentials, are particularly prone to reduction by single electron transfer.

Experimental Section

Melting points were measured with a Mel-Temp apparatus usually in open capillaries and are uncorrected. A few melting points were

determined in nitrogen-filled sealed capillaries and these are designated (St). Infrared spectra were recorded on a Beckman IR-10 spectrometer using chloroform solutions unless otherwise specified. NMR spectra were determined on a Varian T-60 spectrometer using deuteriochloroform solutions with chemical shifts reported in δ units downfield from internal tetramethylsilane. Uv spectra were recorded on a Unicam SP800 spectrophotometer and mass spectra were determined with an AEI MS-30 double beam double focusing mass spectrometer at 70 eV with perfluorokerosene in the reference beam. Analyses were performed by MHW Laboratories, Garden City, Mich.

Quinazoline[10] (mp 48–49 °C), 2-phenylquinazoline[11] (mp 99–101 °C), and 4-phenylquinazoline[12] (mp 99–100 °C) were prepared by literature procedures.

The reductive metalation of the quinazolines was effected in Schlenk tubes by procedures described earlier[13] with 100% excess of sodium and 200 ± 25 ml of tetrahydrofuran (THF) per gram of substrate and a reaction time of 24 h. The anionic derivative was drained from excess sodium into a nitrogen-filled flask for further treatment. Unless otherwise specified, reaction products were isolated by diluting the reaction mixture with water, extracting with ether, drying the extract with magnesium sulfate, and concentrating on a rotary evaporator. Column chromatography of the crude products was effected on 0.05–0.20 mm silica gel (E. Merck) or neutral alumina (E. Merck).

Preliminary experiments in which aliquot samples of the anionic reduction products were quenched in water and the inorganic base titrated showed that the reductive metalations were complete in 24 h, and that the product contained the equivalent of 2.2 g-atoms of sodium per mole of 4-phenylquinazoline (deep blue solution) and 1.2 g-atoms of sodium per mole of quinazoline (violet solution, mauve precipitate) or 2-phenylquinazoline (greenish precipitate, yellow solution).

Monomeric Dianion, 4, of 4-Phenylquinazoline (3). A. Protonation. The deep blue solution of dianion **4** prepared from 0.41 g (2 mmol) of **3** was treated at −78 °C with water. The crude product was chromatographed on alumina using chloroform to give 37 mg (9%) of **3.** Chloroform-5% methanol removed a second fraction, 0.35 g (85%) of 3,4-dihydro-4-phenylquinazoline (**5**), mp 159–164 °C. Recrystallization from acetone raised the melting point to 165–166 °C, undepressed on mixing with authentic material.[11]

B. Methylation. The dianion, **4,** prepared from 0.51 g (2.5 mmol) of 4-phenylquinazoline, was treated at 20 °C with 0.85 g (6 mmol) of methyl iodide. After 4 h, water was added and the crude product isolated and chromatographed on 15 g of silica gel.[20] Benzene–ether (1:1, 200 ml) eluted 0.24 g of a mixture whose further separation is described below. A further 100 ml of solvent removed 92 mg (16%) of 1,4-dihydro-1,4-dimethyl-4-phenylquinazoline (**7**) as an oil: NMR δ 1.87 (s, 3, CMe), 3.20 (s, 3, NMe), 6.6–7.6 (m, 10, aromatic H and H-2); ir 1650, 1480, 1445, 1050, 700 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 283 (3.81), 220 nm (4.21); mass spectrum *m/e* (rel intensity) 236 (3, M^+) 222 (27), 221 (100), 159 (69), 110 (14). The hydrochloride was prepared and purified by repeated precipitation from ethanol by ether, mp 252–253 °C.

Anal. Calcd for $C_{16}H_{16}N_2$·HCl: C, 70.45; H, 6.28; N, 10.27; Cl, 13.00. Found: C, 70.50; H, 6.38; N, 10.11; Cl, 13.01.

Continued elution of the column with ether–benzene (1:1, 100 ml) and finally with methanol–chloroform (1:4) gave 0.24 g (42%) of 3,4-dihydro-3,4-dimethyl-4-phenylquinazoline (**6**) as an oil: NMR δ 1.98 (s, 3, CMe), 2.72 (s, 3, NMe), 6.4–7.7 (m, 10, aromatic H and H-2); ir 1620, 1600, 1570, 1485, 1370, 695 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 228 (4.17), 233 (4.18), 297 (3.84), 312 (3.75), 328 nm (3.45); mass spectrum *m/e* (rel intensity) 236 (9, M^+), 222 (17), 221 (100), 159 (56). The hydrochloride was prepared and purified as in the case of **7,** mp 265–266 °C. The analytical data suggested that the salt contained solvent of crystallization.[14]

Anal. Calcd for $(C_{16}H_{16}N_2$·HCl)·$\frac{3}{4}C_2H_5OH$: C 68.39; H, 7.05; N, 9.12; Cl, 11.54. Found: C, 67.94; H, 6.91; N, 9.13; Cl, 11.88.

The first fraction isolated by column chromatography was separated by preparative thin layer chromatography on silica gel using two developments with petroleum ether–ether (2:1). The second and third bands from the origin contained the largest portion of material. The material from the second band (87 mg) was rechromatographed to give 51 mg (10%) of 4-phenylquinazoline. The material from the third band (50 mg) was purified by rechromatography on a silica gel plate to give the analytical sample of **8**: NMR[15] δ 1.15 (d, 3, J = 8 Hz, 7-Me), 1.33 (d, 3, J = 8 Hz, 8-Me), 2.0–3.3 (m, 2, H-7 and H-8), 6.0–6.23 (q, 1, H-6, $J_{5,6}$ = 11, $J_{6,7}$ = 5 Hz), 6.5–6.7 (d, 1, H-5, $J_{5,6}$ = 11 Hz), 7.3–8.0 (m, 5, aromatic H), 8.99 (s, 1, H-2); ir 2970, 1545, 1450, 1440, 1410, 940, 695 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 242 (4.28), 269 (4.24), 305 nm (sh, 3.90); mass spectrum *m/e* (rel intensity) 237 (17), 236 (69, M^+), 235 (57), 221 (74), 118 (100).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83; N, 11.85. Found: C, 81.34; H, 6.95; N, 11.70.

Performing this alkylation at −78 °C gave a product mixture containing much less of **8** as indicated by the weak aliphatic methyl resonances in the 1.1–1.3 ppm region of the NMR spectrum of the crude reaction product.

Dimeric Dianion, 9, of Quinazoline (1). A. Protonation. The dianion **9** prepared from 0.62 (4.8 mmol) of quinazoline was treated under nitrogen at −78 ° with 2 ml of water. Saturated ammonium chloride solution (10 ml) was added and the mixture was poured into 400 ml of water. The mixture was washed by decantation with four 50-ml portions of ether. Evaporation of the ether gave 54 mg of 4,4′-bisquinazoline (**13**) (9%) identified by comparison of the ir and NMR spectra with those of an authentic sample.[17]

The precipitated hydrochloride salt of **11** was isolated by filtration of the aqueous layer and dried, 0.505 g (63%), mp 295–296 °C after recrystallization from ethanol. The free base was regenerated from 223 mg of the salt by treatment with ethanolic sodium hydroxide to give 140 mg (representing 51% yield) of **11,** mp 276–277 °C (reported[4] 274 °C) having an ir spectrum identical with that of an authentic sample.[16]

B. Oxidation. The dimeric dianion **9** prepared from 0.57 g (4.4 mmol) of quinazoline was cooled to −78 °C and dry oxygen passed through the solution for 10 min. The decolorized solution was warmed to 20 °C and treated with water and the crude product (0.48 g) isolated. Recrystallization from benzene gave 0.25 g (44%) of 4,4′-bisquinazoline (**13**): mp 246–248 °C (reported[17] 246–247 °C); ir 1618, 1560, 1540, 1490, 1370, 1325 cm^{-1}; NMR agreed with that reported[17]; mass spectrum *m/e* (rel intensity) 258 (50, M^+), 257 (100), 129 (10), 102 (17). The filtrate from **13** was evaporated and the residue sublimed (80 °C, 0.25 Torr) to give 0.10 g (17%) of quinazoline, mp 45–47 °C, as sublimate.

Dimeric Dianion 10 of 2-Phenylquinazoline (2). A. Protonation. The dianion **10** was prepared from 0.76 g (3.7 mmol) of 2-phenylquinazoline and protonated with water. The crude product was triturated with 5 ml of ether and filtered to give 0.56 g of **12** (74%) mp 182–190 °C (St). The crude **12** was purified by preparing the hydrochloride salt (benzene, gaseous HCl) and recrystallizing this from 1:1 ethanol–ether giving 0.42 g, mp 290–295 °C. The free amine was regenerated with aqueous potassium hydroxide and recrystallized from benzene–hexane (1:3) giving 0.26 g of **12**: mp 197–198 °C (St); NMR δ 5.03 (s, 2, H-4 and H-4′), 6.3–7.0 (broad s, 2, NH), 7.1–7.4 (m, 20, H-2, H-2′, and aromatics); ir 3440 (NH), 1620 w, 1595 m, 1565 s (3,4-dihydroquinazoline pattern[3]), 1515, 1490, 1475, 1445, 690 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 325 (4.00), 305 (4.06), 235 nm (4.55).

Anal. Calcd for $C_{28}H_{22}N_4$: C, 81.14; H, 5.35; N, 1352. Found: C, 81.10; H, 5.36; N, 13.52.

The ether-soluble material from the initial treatment of the crude reaction product was separated by preparative TLC (silica gel) with benzene–pentane as developing solvent to give 42 mg of **12,** 36 mg (5%) of 3,4-dihydro-2-phenylquinazoline, and 21 mg of 2-phenylquinazoline, identified via their spectral properties.

B. Oxidation. The dianion **10** prepared from 0.51 g (2.5 mmol) of 2-phenylquinazoline was treated at −78 °C with oxygen for 25 min and then allowed to warm to 20 °C while agitated by a continuous stream of oxygen. Water was added and the crude product isolated and triturated with 20 ml of diethyl ether. The insoluble material, 78 mg (15%), mp 287–288 °C dec, was 4,4′-bis(2-phenylquinazoline) (**14**). An analytical sample was obtained by passing a benzene solution through a short column of alumina (35 g): mp 288–289 °C dec: ir (KBr) 1610, 1560, 1530, 1480, 1450, 1440, 1375, 1330, 755, 695, 675 cm^{-1}; uv (dioxane) λ_{max} (log ϵ) 267 (4.85), 336 nm (3.92); mass spectrum *m/e* (rel intensity) 410 (M^+, 100), 409 (100), 258 (25), 257 (47), 205 (60), 103 (32), 102 (60).

Anal. Calcd for $C_{28}H_{18}N_4$: C, 81.93; H, 4.42; N, 13.65. Found: C, 81.80; H, 4.56; N, 13.48.

The ether-soluble fraction was chromatographed on alumina (activity III) using benzene as eluent to give 0.34 g (66%) of 2-phenylquinazoline and 64 mg (12%) (eluted with chloroform–methanol) of **12,** both identified by comparison of their spectra with those of authentic samples.

C. Methylation. The dimeric dianion **10** prepared from 1.06 g (52 mmol) of 2-phenylquinazoline was treated at −78 °C with 0.74 g (52 mmol) of methyl iodide. After 1 h reaction, the solution was allowed to warm to 20 °C and stand for 24 h and the crude reaction product (1.22 g) isolated. Trituration with 10 ml of ether gave 0.59 g of insoluble material which was dissolved in 5 ml of hot benzene and precipitated with 20 ml of 80–100 °C petroleum ether. The precipitated

material (0.30 g) was chromatographed on 50 g of alumina (activity III) using benzene–chloroform (3:1) graded to chloroform to give, in order of elution, 36 mg (3%) of **16a** and 0.26 g of **15.**

The isolated **16a** was purified by precipitation from hot chloroform with petroleum ether to give an analytical sample: mp 262–265°C dec (St); NMR δ 2.8 (s, 6, NCH_3), 4.5 (s, 2, benzylic H), 6.9–7.8 (m, 18, aromatic H); ir 2940 (broad), 1590, 1550, 1530, 1480, 1400, 1170, 1060 cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 240 (4.38), 312 (4.05), 323 nm (4.045); mass spectrum *m/e* (rel intensity) 442 (0.2, M^+), 441 (0.3), 222 (28), 221 (100), 206 (28), 179 (13).

Anal. Calcd for $C_{30}H_{26}N_4$: C, 81.41; H, 5.93; N, 12.66. Found: C, 81.14; H, 6.01; N, 12.42.

The isolated **15** was recrystallized from benzene–petroleum ether (1:2) to give the analytical sample: mp 221–223 °C dec (St); NMR δ 2.45 (s, 6, NCH_3), 5.15 (s, 2, benzylic H), 6.5–7.8 (m, 18, aromatic H); ir 2940 (broad), 1630, 1480, 1380, 1350, 1060 cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 236 (4.39), 301 nm (3.80); mass spectrum *m/e* (rel intensity) 442 (0.3, M^+), 441 (0.5), 222 (22), 221 (76), 207 (21), 206 (100), 205 (30), 179 (55), 103 (21).

Anal. Calcd for $C_{30}H_{26}N_4$: C, 81.41; H, 5.93; N, 12.66. Found: C, 81.31; H, 5.96; N, 12.64.

The combined solvent-soluble portion of the reaction product (0.92 g) was chromatographed on 100 g of alumina (activity III) using benzene graded to benzene–chloroform (1:1) to give in order of elution 66 mg of **18** (5%), 153 mg (13%) of **17,** 148 mg (13%) of **16b,** 293 mg of an unresolved mixture, and finally 186 mg of additional **15** (total yield 39%).

The **18** was purified by recrystallization from 3:1 petroleum ether–benzene: mp 136–137 °C (reported[18,19] 136–138 and 133 °C); the NMR, ir, and uv spectra agreed with those reported[19] and the analytical data confirmed the structure; mass spectrum *m/e* (rel intensity) 236 (60, M^+), 235 (100), 118 (13).

The **17** was recrystallized from petroleum ether–25% benzene to give an analytical sample: mp 194–195 °C; NMR δ 2.70 (s in presence of D_2O, 3, $CHNHCH_3$), 3.04 (s, 3) and 3.24 (s, 3) (aryl NCH_3), 5.4 (broad s, 1, $NHCH_3$), 5.65 and 6.07 (AB q, 2, J = 10.5 Hz, benzylic H), 6.4–7.8 (m, 18, aromatic H); ir 3460 (NH), 1620 (C=O), 1480, 1370, 1060 cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 238 (4.30), 292 (3.82), 312 nm (sh, 3.68); mass spectrum *m/e* (rel intensity) 474 (0.2, M^+), 473 (0.3), 253 (3), 222 (18), 221 (100), 206 (7), 118 (9), 105 (16).

Anal. Calcd for $C_{31}H_{30}N_4O$: C, 78.44; H, 6.38; N, 11.81. Found: C, 78.46; H, 6.39; N, 11.80.

The **16b** was purified by precipitation from hot chloroform with petroleum ether: mp 268–271 °C dec (St); NMR δ 2.50 (s, 6, CH_3), 4.81 (s, 2, benzylic H), 7.0–7.8 (m, 18, aromatic H); ir 2940 (broad), 1550, 1480, 1400, 1340, 1160, 1060, cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 245 (4.35), 310 (4.06), 330 nm (4.01); mass spectrum *m/e* (rel intensity) 442 (0.1, M^+), 441 (0.2), 222 (25), 221 (100), 206 (21), 179 (9), 119 (9).

Anal. Calcd for $C_{30}H_{26}N_4$: C, 81.41; H, 5.93; N, 12.66. Found: C, 81.64; H, 5.97; N, 12.61.

During the course of one methylation reaction, the reaction product was isolated with diethyl ether containing an appreciable amount of peroxide and extensive oxidation occurred. The crude product was separated into an acid soluble and an acid-insoluble fraction by extraction of a chloroform solution with aqueous sodium bisulfate. The chloroform soluble material (0.51 g) had spectral properties (NMR, ir) identical with those of **18** isolated previously.

The material recovered from the aqueous bisulfate solution by adding base and extracting with ether (0.52 g) was boiled with 10 ml of 1:1 benzene–petroleum ether. The soluble material (0.20 g had a complex NMR spectrum and was not further investigated. The insoluble material (0.215 g) was chromatographed on alumina (activity III) with benzene graded to chloroform to give 151 mg of **19.** Three recrystallizations from benzene gave a sample of mp 166–168 °C (reported[19] 165–166 °C) with ir, NMR, and uv spectra agreeing with those reported[19] and with satisfactory elemental analysis.

D. With Ethyl Chloroformate. The crude reaction product (1.38 g) from the dimeric dianion generated from 1.04 g (5 mmol) of 2-phenylquinazoline and 0.85 g (7.8 mmol) of ethyl chloroformate was heated with 30 ml of diethyl ether. After cooling, the insoluble solid, **20a,** was filtered and dried, 0.76 g (54%), mp 243–244 °C. Recrystallization from ethanol gave an analytical sample: mp 244–245 °C; NMR δ 0.73 (t, 6, J = 7 Hz, CH_2CH_3), 3.4–4.2 (m, 4, CH_2CH_3), 5.34 (s, 2, benzylic H), 6.0–8.4 (m, 18, aromatic H); ir 1730 (C=O), 1600, 1570, 1380, 1340, 1250 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 225 (4.35), 231 (4.35), 240 (4.33), 266 (4.28), 310 nm (4.28); mass spectrum *m/e* (rel intensity) 558 (0.1 M^+), 280 (20), 279 (100, $M^+/2$), 235 (67), 207 (71), 206 (31).

Anal. Calcd for $C_{34}H_{30}N_4O_4$: C, 73.10; H, 5.41; N, 10.03. Found: C, 73.36; H, 5.48; N, 10.06.

The ether was evaporated from the ether-soluble products and the residue (0.58 g) treated with 3 ml of ether. The insoluble material, 0.12 g, mp 182–190 °C, consisted of 14% **20a** and 86% **20b** (by NMR) (7% yield of **20b**). Two recrystallizations from ethanol gave an analytical sample: mp 198–199 °C; NMR δ 0.73 (t, 6, J = 6 Hz, CH_2CH_3), 3.90 (q, 4, J = 6 Hz, CH_2CH_3), 5.46 (s, 2, benzylic H), 6.7–8.0 (m, 18, aromatic H); ir (CCl_4) 1730 (C=O), 1600, 1560, 1380, 1330, 1260, 690 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 231 (4.37), 242 (4.36), 266 (4.23), 317 nm (4.22); mass spectrum *m/e* (rel intensity) 558 (0.1, M^+), 280 (23, 279 (100, $M^+/2$), 208 (14), 207 (91), 206 (25).

Anal. Calcd for $C_{34}H_{30}N_4O_4$: C, 73.10, H, 5.41; N, 10.03. Found: C, 72.97; H, 5.16; N, 10.28.

The ether filtrate from the impure **20b** was evaporated and the residue (0.37 g) was chromatographed on 50 g of silica gel using 30–60 °C petroleum ether–20% diethyl ether as eluting solvent and collecting the eluent in 20-ml fractions. Fractions 34–41 (128 mg) were crystallized from 2 ml of hot ethanol to give 16 mg of **20b,** mp 195–198 °C, undepressed on mixing with an authentic sample. The filtrate was evaporated and the residue (93 mg) recrystallized from 30–60 °C petroleum ether to give 73 mg (5% yield) of "unsymmetrically acylated dimer", **21**: mp 117–121 °C; NMR δ 0.87 and 0.95 (two t, J = 7 Hz, 6, CH_2CH_3), 3.4–4.4 (m, 4, CH_2CH_3), 5.02 and 5.44 (AB q, J = 10 Hz, 2, CHCH), 6.1–8.4 (m, 18, aromatic H); ir 1730 (C=O), 1640, 1590, 1570 (1,4- and 3,4-dihydroquinazolinyl bands), 1370, 1250 cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 241 (4.45), 314 nm (4.05); mass spectrum *m/e* (rel intensity) 280 (31), 279 (63), 236 (21), 235 (69), 208 (21), 207 (100), 206 (25), 205 (15), 179 (18), 129 (20).

Anal. Calcd for $C_{34}H_{30}N_4O_4$: C, 73.10; H, 5.41; N, 10.03. Found: C, 73.27; H, 5.43; N, 10.06.

Fractions 42–50 from the chromatography (112 mg) contained additional **21** but its isolation could not be effected.

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Registry No.—**1,** 253-82-7; **2,** 25855-20-3; **3,** 17629-01-5; **4,** 60621-22-9; **5,** 1904-72-9; **6,** 60538-79-6; **6** HCl, 60538-80-9; **7,** 60538-81-0; **7** HCl, 60538-82-1; **8,** 60538-83-2; **9,** 60538-84-3; **10,** 60538-85-4; **11,** 60662-04-6; **11** HCl, 60538-86-5; **12,** 60662-05-7; **12** HCl, 60538-87-6; **13,** 963-80-4; **14,** 60538-88-7; **15,** 60538-89-8; **16a,** 60538-90-1; **16b,** 60538-91-2; **17,** 60538-92-3; **20a,** 60538-93-4; **20b,** 60538-94-5; **21,** 60538-95-6; methyl iodide, 74-88-4; ethyl chloroformate, 541-41-3.

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Selective Reductive Displacement of Alkyl Halides and Sulfonate Esters with Cyanoborohydride Reagents in Hexamethylphosphoramide

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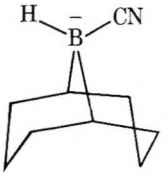
The combination of sodium or tetrabutylammonium cyanoborohydride, sodium or potassium 9-cyano-9-hydrido-9-borabicyclo[3.3.1]nonane (9-BBNCN), or polymeric cyanoborane in hexamethylphosphoramide furnishes a convenient, efficient, and mild system for the reduction of alkyl halides and sulfonate esters. The reagents are exceptionally selective in that most other functional groups including ester, carboxylic acid, amido, cyano, alkene, nitro, sulfone, ketone, aldehyde, and epoxide are essentially inert under the reaction conditions and thus the reductive procedure is attractive for synthetic schemes where minimum damage to other sensitive portions of the molecule is demanded. The displacement by hydride occurs predominantly with inversion of configuration and, in general, the leaving ability pattern follows the order I > Br ≈ SO_2R > Cl ≫ F, as expected for an S_N2 process. The method is less successful for vinylic, aromatic, and certain tertiary halides.

The reductive removal of organic halides and sulfonate esters is utilized extensively in organic synthesis as an effective tactic for the introduction of methyl and methylene groups. Consequently, considerable effort has been devoted to the development of techniques capable of such transformations.[1,2] Of the successful methods, the most useful generally employ a metal hydride to furnish a hydride anion as a displacement nucleophile. Often, however, such reductions are met with problems which arise because many hydride reagents, such as lithium aluminum hydride, which are powerful enough to displace leaving groups also molest other functionalities or act concomitantly as strong bases. This severely limits the usefulness of such reagents to those molecules devoid of other sensitive moieties and restricts the approaches to synthetic targets.

One relatively recent approach toward tempering the destructiveness of hydride reagents has involved the replacement of a hydrogen on borohydride with a cyanide substituent. This strongly electron-withdrawing group increases the Lewis acidity of the corresponding cyanoborane and thus the cyanoborohydride anion is more reluctant to deliver a hydride. The result is a greatly moderated reducing capability (and an increased stability) which allows a substantially more discriminate selection among functional groups.[3] Furthermore, cyanoborohydride is remarkably stable (among hydrides) toward water and acid (to pH ca. 2–3)[4] and the reducing capabilities of the reagent are exceptionally pH dependent. For instance, at pH >6 the reduction of aldehydes and ketones, normally very sensitive moieties, is essentially negligible.[5] In fact, the only groups which are reduced in neutral media appear to be imminium ions and alkyl halides and sulfonates, these latter only in polar aprotic solvents.[1] Evidently in such S_N2 enhancing media, cyanoborohydride serves very adequately as a source of nucleophilic hydride ion for displacement reactions, but not for attack on unactivated carbonyls and other functional groups. This suggested that exceptionally selective displacements of halides and other good leaving groups with hydrogen might be attainable using cyanoborohydride in hexamethylphosphoramide (HMPA), apparently the most potent polar aprotic solvent available for accelerating S_N2 reactions.[6]

Preliminary investigations revealed that, indeed, such conversions were facile with either sodium or tetrabutylammonium cyanoborohydride[1] and the selectivity, convenience, and gentleness displayed highly recommended the reagents for synthetic applications. This prompted a more thorough and systematic study of the scope and utility of the reagents and, in addition, with two other modified cyanoborohydride derivatives, 9-cyano-9-hydrido-9-borabicyclo[3.3.1]nonane (9-BBNCN$^-$) (1) and polymeric cyanoborane (2). This selection of reagents allowed a range of reduction possibilities to be explored. Thus, tetrabutylammonium cyanoborohydride functions as a phase-transfer reagent[1b,7] which permits reductions in nonpolar solvents. The use of 9-BBNCN$^-$ allows the effect of alkyl groups to be tested while polymeric cyanoborane 2 may conceivably be viewed as a cyanoborohydride ylide which can serve as a source of nucleophilic hydride. The presence of the positive nitrogen attached to boron should render the corresponding boron considerably more electron deficient and consequently further lower the hydride donating (and reducing) ability of the anion compared to cyanoborohydride.



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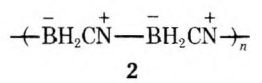

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This article incorporates systematic investigations of the various cyanoborohydride reagents for displacements with particular emphasis given to uncovering the functional group selectivity possible with each. The results are tabulated systematically in Table I. For convenience, these are grouped according to structural types and leaving group and considered separately below.

Results and Discussion

Reagents Sodium cyanoborohydride is available commercially and is satisfactory as obtained.[8] Tetrabutylammonium cyanoborohydride (TBAC) was prepared and purified as previously described.[1a,9] Sodium and potassium 9-borabicyclo[3.3.1]nonane cyanoborohydride (Na and K-9-BBNCN) were secured by the reaction of sodium or potassium cyanide with 9-BBN in THF.[1c] Polymeric cyanoborane was prepared as described by Spielvogel[11] from $NaBH_3CN$ and HCl or from Bu_4NBH_3CN and methyl iodide in methylene chloride.[12]

Reductions of Alkyl Monohalides and Sulfonate Esters. Our initial investigation stemmed from the observation that 1-iodododecane suffered considerable reduction to *n*-dodecane (60–80%) when subjected to $NaBH_3CN$ in a sulfolane–dimethylformamide mixture. Considerable experimentation established that hexamethylphosphoramide[6] (HMPA), an exceptional medium for enhancing displacement reactions, provided the most effective solvent[14] and that a 4:1 ratio of

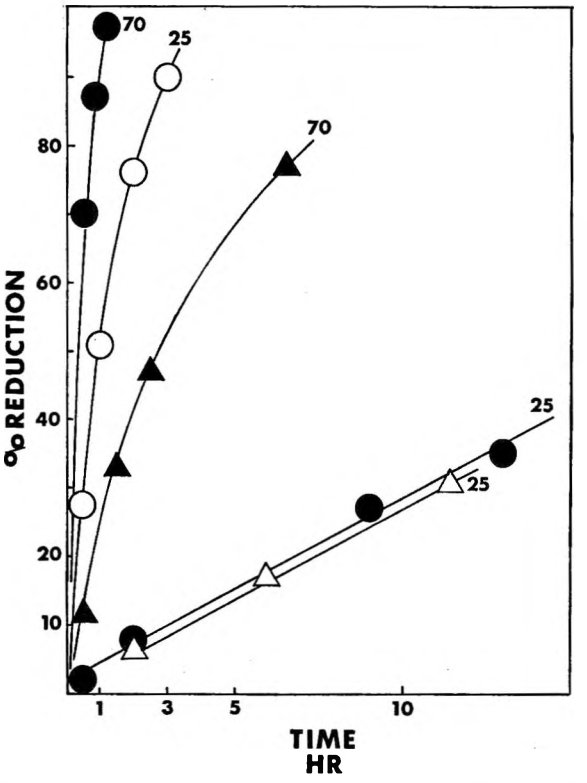


Figure 1. Reduction of alkyl halides and tosylates with sodium cyanoborohydride in hexamethylphosphoramide. All reactions were 0.2 M in the compound, 0.8 M in $NaBH_3CN$. The reaction temperature for each compound is indicated on each plot. The percent reductions were determined by GLC analysis using internal standards and detector response factors: ●, 1-bromododecane; ○, 1-iododododecane; ▲, 1-dodecyl tosylate; △, 2-iodooctane.

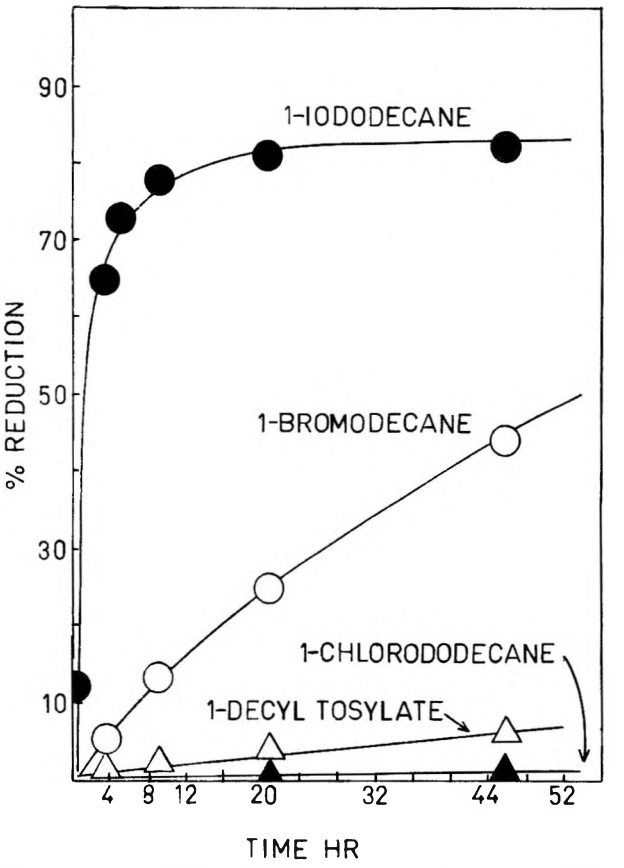


Figure 2. Reduction of primary halides and tosylate with TBAC in HMPA at 25 °C. All solutions were 0.2 M in the compound, 0.8 M in TBAC. The percent reductions were determined by GLC using internal standards.

cyanoborohydride:substrate furnished the most consistently high yields in reasonably short reaction times. In order to establish optimal conditions, the reduction rates for a collection of representative halides were followed with $NaBH_3CN$, Bu_4NBH_3CN, and polymeric cyanoborane; the results are presented in Figures 1–3. Although the rates varied considerably, all demonstrated the same relative patterns for the halides and tosylate leaving groups. Thus, with $NaBH_3CN$ (Figure 1) primary iodo groups are removed readily at 25 °C (90% in 3 h). In fact, at this temperature, the relatively slow reduction of primary bromo, tosyloxy, chloro (i.e., at 25 °C less than 2% reduction of 1-chlorododecane in 92 h), and secondary iodo (all <10% in 3 h) suggests that primary iodo can be selectively displaced in their presence. At higher temperatures (>70 °C) adequate yields of hydrocarbons are obtained from these latter derivatives, except chloro (Table I). Similar results were obtained for Bu_4NBH_3CN and polymeric cyanoborane except that the former (Figure 2) displayed slightly slower rates while the latter (Figure 3) required substantially more vigorous conditions (105 °C) to effect reduction and considerably longer reaction times. With these initial observations, a convenient and simple general experimental procedure was devised. The compound and the cyanoborohydride were dissolved in HMPA (or other solvents with Bu_4NBH_3CN or 9-BBNCN anions; see Table I) so that the concentrations were 0.2 M in the substrate and 0.8 M in cyanoborohydride for analytical reactions or two to three times these concentrations for preparative scale reactions. The solutions were then stirred at the appropriate temperatures for the durations listed in Table I. Upon completion, the mixtures were diluted with water or saturated brine and isolated, generally from cyclohexane or ether. This procedure was followed throughout the investigation except where otherwise noted; in fact, the only

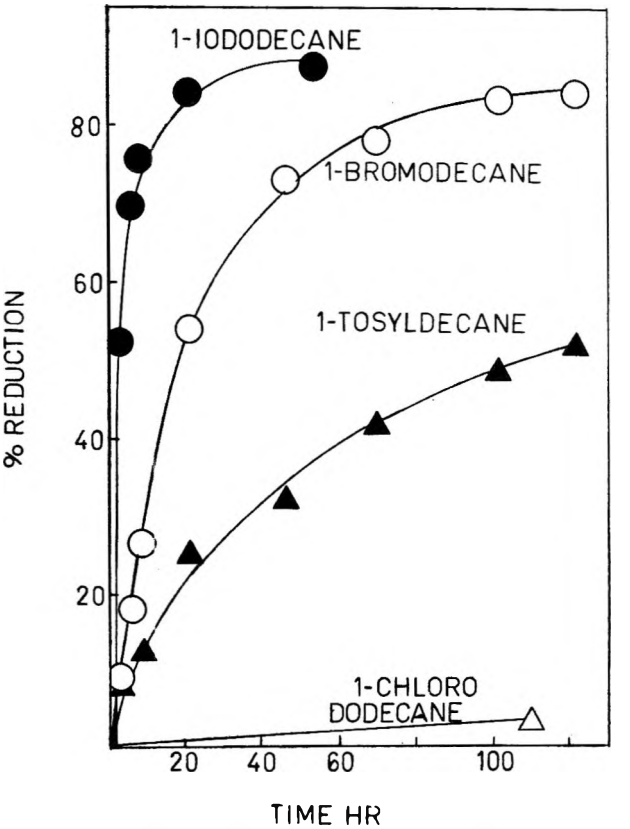


Figure 3. Reduction of alkyl halides and tosylate with cyanoborane polymer in HMPA at 105 °C. The solutions were 0.2 M in the compound and 0.8 M in cyanoborane polymer. The percent reductions were determined by GLC using internal standards and are corrected for detector response.

Table I. Reduction of Halides and Sulfonate Esters with Cyanoborohydrides

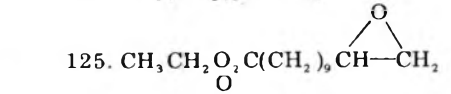
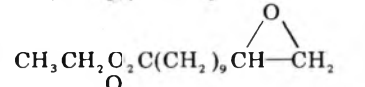
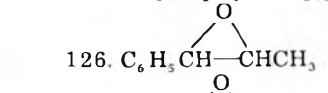
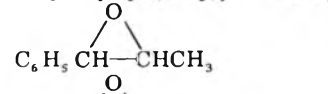
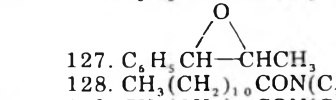
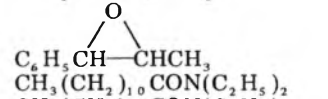
Registry no.	Entry, compd	Reducing agent (mol ratio) (mol redn agent)/ (mol compd)	Solvent[a]	Time, h	Temp, °C	Product	% yield[b] (isolated)
4292-19-7	1. $CH_3(CH_2)_{11}I$	$NaBH_3CN$ (4)	HMPA	0.35	100	$CH_3(CH_2)_{10}CH_3$	100
	2. $CH_3(CH_2)_{11}I$	$NaBH_3CN$ (4)	HMPA	1	50	$CH_3(CH_2)_{10}CH_3$	96
	3. $CH_3(CH_2)_{11}I$	$NaBH_3CN$ (4)	HMPA	3.5	25	$CH_3(CH_2)_{10}CH_3$	91
	4. $CH_3(CH_2)_{11}I$	$NaBH_3CN$ (4)	DMSO	2	100	$CH_3(CH_2)_{10}CH_3$	74
2050-77-3	5. $CH_3(CH_2)_9I$	$NaBH_3CN$ (1.5)	HMPA	2	70	$CH_3(CH_2)_8CH_3$	(88–90)
	6. $CH_3(CH_2)_9I$	TBAC (4)	HMPA	21	25	$CH_3(CH_2)_8CH_3$	81
	7. $CH_3(CH_2)_9I$	TBAC (4)	C_6H_6	7	80	$CH_3(CH_2)_8CH_3$	81
	8. $CH_3(CH_2)_9I$	Na 9-BBNCN (4)	HMPA	1	25	$CH_3(CH_2)_8CH_3$	92
60633-77-4	9. 3β-(3-Iodopropionoxy)pregn-5-en-20-one	$NaBH_3CN$ (4)	HMPA	1	70	3β-Propionoxypregn-5-en-20-one	(89)
60828-67-3	10. **9**	$NaBH_3CN$ (4.6)	HMPA	8	70	**10**	(77)[c]
	11. $CH_3(CH_2)_9I$	Na 9-BBNCN (4)	THF	2	25	$CH_3(CH_2)_8CH_3$	94
	12. $CH_3(CH_2)_9I$	Na 9-BBNCN (4)	HMPA	1	25	$CH_3(CH_2)_8CH_3$	89
	13. $CH_3(CH_2)_9I$	$(BH_2CN)_n$ (4)	HMPA	26	105	$CH_3(CH_2)_8CH_3$	83
143-15-7	14. $CH_3(CH_2)_{11}Br$	$NaBH_3CN$ (4)	HMPA	1.1	70	$CH_3(CH_2)_{10}CH_3$	97
112-29-8	15. $CH_3(CH_2)_9Br$	TBAC (4)	HMPA	137	25	$CH_3(CH_2)_8CH_3$	69
						$CH_3(CH_2)_9Br$	10
	16. $CH_3(CH_2)_9Br$	TBAC (4)	C_6H_6	24	80	$CH_3(CH_2)_8CH_3$	89
112-82-3	17. $CH_3(CH_2)_{15}Br$	Na 9-BBNCN (4)	HMPA	1.5	70	$CH_3(CH_2)_{14}CH_3$	95
	18. $CH_3(CH_2)_9Br$	$(BH_2CN)_n$ (4)	HMPA	70	105	$CH_3(CH_2)_8CH_3$	78
60633-78-5	19. *o*-(2-Bromoethoxy)-benzaldehyde	$NaBH_3CN$ (2)	HMPA	4	70	*o*-Ethoxybenzaldehyde	(56)
60633-79-6	20. **11**	$NaBH_3CN$ (4)	HMPA	12[d]	70	**12**	63
60633-80-9	21. $CH_3CO(CH_2)_3CO_2(CH_2)_3Br$	$NaBH_3CN$ (4)	HMPA	4	70	$CH_3CO(CH_2)_3CO_2(CH_2)_2CH_3$	63
2834-05-1	22. $HO_2C(CH_2)_{10}Br$	$NaBH_3CN$ (3)	HMPA	24	70	$CH_3(CH_2)_9COOH$	(96)[e]
20965-27-9	23. $NC(CH_2)_9Br$	$NaBH_3CN$ (4)	HMPA	3	100	$CH_3(CH_2)_9CN$	85
14660-52-7	24. $C_2H_5O_2C(CH_2)_4Br$	$NaBH_3CN$ (4)	HMPA	25	70	$CH_3(CH_2)_3CO_2C_2H_5$	88
	25. $C_2H_5O_2C(CH_2)_4Br$	TBAC (4)	HMPA	3	70	$CH_3(CH_2)_3CO_2C_2H_5$	78
	26. $C_2H_5O_2C(CH_2)_4Br$	Na 9-BBNCN (4)	HMPA	1	70	$CH_3(CH_2)_3CO_2C_2H_5$	92
112-52-7	27. $CH_3(CH_2)_{11}Cl$	$NaBH_3CN$ (4)	HMPA	92	25	$CH_3(CH_2)_{10}CH_3$	2
						$CH_3(CH_2)_{11}Cl$	98
	28. $CH_3(CH_2)_{11}Cl$	$NaBH_3CN$ (4)	HMPA	27	100	$CH_3(CH_2)_{10}CH_3$	72
						$CH_3(CH_2)_{11}Cl$	12
	29. $CH_3(CH_2)_{11}Cl$	TBAC (4)	HMPA	137	25	$CH_3(CH_2)_{10}Cl$	99
						$CH_3(CH_2)_{10}CH_3$	0
1002-69-3	30. $CH_3(CH_2)_9Cl$	Na 9-BBNCN (4)	HMPA	96	25	$CH_3(CH_2)_9Cl$	78
						$CH_3(CH_2)_8CH_3$	10
	31. $CH_3(CH_2)_9Cl$	$(BH_2CN)_n$ (4)	HMPA	39	105	$CH_3(CH_2)_9Cl$	91
						$CH_3(CH_2)_8CH_3$	0
7205-98-3	32. $C_6H_5SO_2CH_2Cl$	$NaBH_3CN$ (2)	HMPA	7	100	$C_6H_5SO_2CH_3$	0
						$C_6H_5SO_2CH_2Cl$	73
	33. $C_6H_5SO_2CH_2Cl$	$NaBH_3CN$ (4)	HMPA	24	150	$C_6H_5SO_2CH_3$	0
334-56-5	34. $CH_3(CH_2)_9F$	$NaBH_3CN$ (4)	HMPA	120	70	$CH_3(CH_2)_8CH_3$	0
39686-83-4	35. **13**	$NaBH_3CN$ (8)	HMPA	48	110	**14**	(44)
10157-76-3	36. $CH_3(CH_2)_{11}OTs$	$NaBH_3CN$ (4)	HMPA	6.5	70	$CH_3(CH_2)_{10}CH_3$	78
	37. $CH_3(CH_2)_{11}OTs$	$NaBH_3CN$ (4)	HMPA	12	80	$CH_3(CH_2)_{10}CH_3$	(73–78)
	38. $CH_3(CH_2)_{11}OTs$	$NaBH_3CN$ (1.5)	HMPA	8	70	$CH_3(CH_2)_{10}CH_3$	(52)

5509-08-0	39. $CH_3(CH_2)_9OTs$	TBAC (4)	C_6H_6	24	80	$CH_3(CH_2)_8CH_3$	74
	40. $CH_3(CH_2)_9OTs$	Na 9-BBNCN (4)	HMPA	9	25	$CH_3(CH_2)_8CH_3$	11
	41. $CH_3(CH_2)_9OTs$	Na 9-BBNCN (4)	THF	21	25	$CH_3(CH_2)_8CH_3$	39
	42. $CH_3(CH_2)_9OTs$	$-(BH_2CN)_n$ (4)	HMPA	102	105	$CH_3(CH_2)_8CH_3$	49
			Allylic Halides				
4392-24-9	43. $C_6H_5CH{=}CHCH_2Br$	$NaBH_3CN$ (4)	HMPA	0.5	70	$C_6H_5CH{=}CHCH_3$	76
	44. $C_6H_5CH{=}CHCH_2Br$	$NaBH_3CN$ (4)	HMPA	2.5	25	$C_6H_5CH{=}CHCH_3$	64
	45. $C_6H_5CH{=}CHCH_2Br$	TBAC (4)	HMPA	1.5	70	$C_6H_5CH{=}CHCH_3$	62
	46. $C_6H_5CH{=}CHCH_2Br$	TBAC (4)	HMPA	3	25	$C_6H_5CH{=}CHCH_3$	64
	47. $C_6H_5CH{=}CHCH_2Br$	Na 9-BBNCN (4)	HMPA	0.5	25	$C_6H_5CH{=}CHCH_3$	80
2687-12-9	48. $C_6H_5CH{=}CHCH_2Cl$	$NaBH_3CN$ (4)	HMPA	4	70	$C_6H_5CH{=}CHCH_3$	62
	49. $C_6H_5CH{=}CHCH_2Cl$	TBAC (4)	HMPA	9	70	$C_6H_5CH{=}CHCH_3$	46
	50. $C_6H_5CH{=}CHCH_2Cl$	Na 9-BBNCN (4)	HMPA	2	70	$C_6H_5CH{=}CHCH_3$	72
60633-81-0	51. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	$NaBH_3CN$ (4)	HMPA	17	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	57
	52. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	TBAC (4)	HMPA	17	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	62
	53. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	Na 9-BBNCN (4)	HMPA	1.8	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	92
	54. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	$NaBH_3CN$ (4)	HMPA	23	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	48
	55. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	TBAC (4)	HMPA	23	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	24
3360-52-9	56. 2-Phenyl-3-chloropropene	TBAC (8)	80% aq HMPA	17	70	2-Phenylpropene	55
	57. 2-Phenyl-3-chloropropene	Na 9-BBNCN (4)	HMPA	1	70	2-Phenylpropene	75
3355-31-5	58. $C_6H_5C{\equiv}C{-}CH_2Cl$	$NaBH_3CN$ (4)	HMPA	8	70	$C_6H_5C{\equiv}C{-}CH_3$	34
	59. $C_6H_5C{\equiv}C{-}CH_2Cl$	Na 9-BBNCN (4)	HMPA	1	70	$C_6H_5C{\equiv}C{-}CH_3$	60
			Benzyl Halides				
100-11-8	60. *p*-$NO_2C_6H_4CH_2Br$	$NaBH_3CN$ (4)	HMPA	15	70	*p*-$NO_2C_6H_4CH_3$	(85)
	61. *p*-$NO_2C_6H_4CH_2Br$	TBAC (4)	HMPA	4	70	*p*-$NO_2C_6H_4CH_3$	62
	62. *p*-$NO_2C_6H_4CH_2Br$	Na 9-BBNCN (4)	HMPA	5	25	*p*-$NO_2C_6H_4CH_3$	56
2014-83-7	63. 2,6-di$ClC_6H_3CH_2Cl$	$NaBH_3CN$ (4)	HMPA	17	70	2,6-di$ClC_6H_3CH_3$	94
	64. 2,6-di$ClC_6H_3CH_2Cl$	TBAC (4)	HMPA	17	70	2,6-di$ClC_6H_3CH_3$	91
	65. 2,6-di$ClC_6H_3CH_2Cl$	Na 9-BBNCN (4)	HMPA	1.25	70	2,6-di$ClC_6H_3CH_3$	84
			Secondary Halides				
557-36-8	66. $CH_3(CH_2)_5CHICH_3$	$NaBH_3CN$ (4)	HMPA	2	70	$CH_3(CH_2)_6CH_3$	91
	67. $CH_3(CH_2)_5CHICH_3$	TBAC (4)	HMPA	2.5	70	$CH_3(CH_2)_6CH_3$	85
	68. $CH_3(CH_2)_5CHICH_3$	K 9-BBNCN (4)	HMPA	1	70	$CH_3(CH_2)_6CH_3$	85
60686-40-0	69. 3-Cholesteryl iodide	$NaBH_3CN$ (4)	HMPA	5	70	2,5- and 3,5-cholestadiene	(95)
13187-99-0	70. $CH_3(CH_2)_9CHBrCH_3$	$NaBH_3CN$ (4)	HMPA	24	70	$CH_3(CH_2)_{10}CH_3$	97
	71. $CH_3(CH_2)_9CHBrCH_3$	TBAC (4)	HMPA	36	70	$CH_3(CH_2)_{10}CH_3$	83
	72. $CH_3(CH_2)_9CHBrCH_3$	Na 9-BBNCN (4)	HMPA	18	70	$CH_3(CH_2)_{10}CH_3$	68
615-96-3	73. $CH_3(CH_2)_3CHBrCO_2C_2H_5$	$NaBH_3CN$ (4)	HMPA	3	70	$CH_3(CH_2)_4CO_2C_2H_5$	90
	74. $CH_3(CH_2)_3CHBrCO_2C_2H_5$	TBAC (4)	HMPA	4	70	$CH_3(CH_2)_4CO_2C_2H_5$	86
	75. $CH_3(CH_2)_3CHBrCO_2C_2H_5$	Na 9-BBNCN (4)	HMPA	0.5	70	$CH_3(CH_2)_4CO_2C_2H_5$	86
60633-82-1	76. $CH_3(CH_2)_{10}CHBrCO_2C_2H_5$	$NaBH_3CN$ (4)	HMPA	3	70	$CH_3(CH_2)_{11}CO_2C_2H_5$	(50)
14980-93-9	77. $CH_3(CH_2)_{15}CHBrCOOH$	$NaBH_3CN$ (3)	HMPA	20	70	$CH_3(CH_2)_{16}COOH$	(97)
2534-77-2	78. *exo*-2-Norbornyl bromide	$NaBH_3CN$ (4)	HMPA	15	150	Norbornane	67

Continued

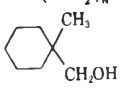
Table I (*Continued*)

Registry no.	Entry, compd	Reducing agent (mol ratio) (mol redn agent)/ (mol compd)	Solvent[a]	Time, h	Temp, °C	Product	% yield[b] (isolated)
		Secondary Benzyl Halides and Sulfonate Esters					
585-71-7	79. $C_6H_5CHBrCH_3$	$NaBH_3CN$ (4)	HMPA	6	70	$C_6H_5CH_2CH_3$	78
	80. $C_6H_5CHBrCH_3$	TBAC (4)	HMPA	5.25	70	$C_6H_5CH_2CH_3$	78
	81. $C_6H_5CHBrCH_3$	Na 9-BBNCN (4)	HMPA	1	70	$C_6H_5CH_2CH_3$	70
672-65-1	82. $C_6H_5CHClCH_3$	$NaBH_3CN$ (4)	HMPA	8	100	$C_6H_5CH_2CH_3$	26
	83. $C_6H_5CHClCH_3$	Na 9-BBNCN (4)	HMPA	57	70	$C_6H_5CH_2CH_3$	51
						$C_6H_5CHClCH_3$	35
776-74-9	84. $(C_6H_5)_2CHBr$	$NaBH_3CN$ (4)	HMPA	3	70	$(C_6H_5)_2CH_2$	91
	85. $(C_6H_5)_2CHBr$	TBAC (4)	HMPA	6	70	$(C_6H_5)_2CH_2$	70
	86. $(C_6H_5)_2CHBr$	Na 9-BBNCN (4)	HMPA	2	70	$(C_6H_5)_2CH_2$	61
90-99-3	87. $(C_6H_5)_2CHCl$	$NaBH_3CN$ (4)	HMPA	45	70	$(C_6H_5)_2CH_2$	30
	88. $(C_6H_5)_2CHCl$	TBAC (4)	HMPA	45	70	$(C_6H_5)_2CH_2$	12
						$(C_6H_5)_2CHCl$	65
60633-83-2	89. (+)-$C_6H_5CH(OMs)CO_2CH_3$	$NaBD_3CN$ (2.2)	HMPA	4	110	(−)-$C_6H_5CHDCO_2CH_3$	(64)[f]
60686-41-1	90. (±)-$C_6H_5CH(OMs)CO_2CH_3$	$NaBH_3CN$ (3)	HMPA	3.5	115	$C_6H_5CH_2CO_2CH_3$	(72)
		Tertiary Halides					
596-43-0	91. $(C_6H_5)_3CBr$	$NaBH_3CN$ (4)	HMPA	2	70	$(C_6H_5)_3CH$	88
	92. $(C_6H_5)_3CBr$	TBAC (4)	HMPA	2	70	$(C_6H_5)_3CH$	87
	93. $(C_6H_5)_3CBr$	Na 9-BBNCN (4)	HMPA	2	70	$(C_6H_5)_3CH$	87
76-83-5	94. $(C_6H_5)_3CCl$	$NaBH_3CN$ (4)	HMPA	4	70	$(C_6H_5)_3CH$	94
	95. $(C_6H_5)_3CCl$	TBAC (4)	HMPA	2	70	$(C_6H_5)_3CH$	88
	96. $(C_6H_5)_3CCl$	Na 9-BBNCN (4)	HMPA	2	70	$(C_6H_5)_3CH$	85
768-90-1	97. 1-Bromoadamantane	$NaBH_3CN$ (8)[g]	HMPA	77	150	Adamantane	36
		Vicinal and Geminal Dihalides					
93-52-7	98. $C_6H_5CHBrCH_2Br$	$NaBH_3CN$ (4)	HMPA	20	70	$C_6H_5CH_2CH_3$	77
						$C_6H_5CH{=}CH_2$	11
	99. $C_6H_5CHBrCH_2Br$	TBAC (4)	HMPA	47	70	$C_6H_5CH_2CH_3$	40
						$C_6H_5CH{=}CH_2$	25
						$C_6H_5CHBrCH_2Br$	20
	100. $C_6H_5CHBrCH_2Br$	Na 9-BBNCN (4)	HMPA	12	70	$C_6H_5CH_2CH_3$	16
						$C_6H_5CH{=}CH_2$	30
						$C_6H_5C{=}CH_2$ (Br)	31
6269-92-7	101. $CH_3(CH_2)_5CHBrCH_2Br$	$NaBH_3CN$ (4)	HMPA	37	70	$CH_3(CH_2)_6CH_3$	72
						$CH_3(CH_2)_5CHBrCH_3$	7
						$CH_3(CH_2)_5CHBrCH_2Br$	13
	102. $CH_3(CH_2)_5CHBrCH_2Br$	TBAC (4)	HMPA	24	70	$CH_3(CH_2)_6CH_3$	26
						$CH_3(CH_2)_5CHBrCH_3$	18
						$CH_3(CH_2)_5CHBrCH_2Br$	50
	103. $CH_3(CH_2)_5CHBrCH_2Br$	Na 9-BBNCN (4)	HMPA	12	70	$CH_3(CH_2)_6CH_3$	58
						$CH_3(CH_2)_5CH{=}CH_2$	24
2415-79-4	104. **3**	$NaBH_3CN$ (4)	HMPA	18	100	**5**	21
						4	77

31236-94-9	105. 2-Bromocyclododecanone	$NaBH_3CN$ (1.5)	HMPA	1.5	70	Cyclododecanone	(56)
	106. 2-Bromocyclododecanone	$NaBH_3CN$ (1.0)	HMPA	1.5	70	Cyclododecanone	(64)
103-64-0	107. $C_6H_5CH{=}CHBr$	$NaBH_3CN$ (4)	HMPA	40	70	$C_6H_5CH{=}CH_2$	0
						$C_6H_5CH{=}CHBr$	94
	108. $C_6H_5CH{=}CHBr$	TBAC (4)	HMPA	40	70	$C_6H_5CH{=}CH_2$	0
						$C_6H_5CH{=}CHBr$	79
	109. $C_6H_5CH{=}CHBr$	Na 9-BBNCN (4)	HMPA	22	70	$C_6H_5CH{=}CH_2$	0
						$C_6H_5CH{=}CHBr$	65
						$C_6H_5C{\equiv}CH$	7
						$C_6H_5CH_2CH_3$	2
			Aryl Halides				
90-14-2	110. 1-Iodonaphthalene	$NaBH_3CN$ (4)	HMPA	38	100	Naphthalene	88
	111. 1-Iodonaphthalene	TBAC (4)	HMPA	38	100	Naphthalene	85
	112. 1-Iodonaphthalene	Na 9-BBNCN (4)	HMPA	14	100	Naphthalene	15
90-11-9	113. 1-Bromonaphthalene	$NaBH_3CN$ (4)	HMPA	66	100	Naphthalene	93
	114. 1-Bromonaphthalene	TBAC (4)	HMPA	66	100	Naphthalene	99
90-13-1	115. 1-Chloronaphthalene	$NaBH_3CN$ (4)	HMPA	72	100	1-Chloronaphthalene	92
						Naphthalene	3
	116. 1-Chloronaphthalene	TBAC (4)	HMPA	132	100	Naphthalene	46
						1-Chloronaphthalene	55
			Other Functional Groups				
112-44-7	117. $CH_3(CH_2)_9CHO$	$NaBH_3CN$ (4)	HMPA	1	70	$CH_3(CH_2)_9CHO$	91
				2	70	$CH_3(CH_2)_9CHO$	81
	118. $CH_3(CH_2)_9CHO$	TBAC (4)	HMPA	45	25	$CH_3(CH_2)_9CHO$	97
124-19-6	119. $CH_3(CH_2)_7CHO$	TBAC (4)	CH_2Cl_2	10	40	$CH_3(CH_2)_7CHO$	84
	120. $CH_3(CH_2)_7CHO$	TBAC (4)	C_6H_6	24	80	$CH_3(CH_2)_7CHO$	39
	121. $CH_3(CH_2)_9CHO$	Na 9-BBNCN (4)	HMPA	1	25	$CH_3(CH_2)_9CHO$	8
927-49-1	122. $[CH_3(CH_2)_4]_2CO$	$NaBH_3CN$ (4)	HMPA	5	70	$[CH_3(CH_2)_4]_2CO$	99
112-12-9	123. $CH_3(CH_2)_8COCH_3$	TBAC (4)	HMPA	97	25	$CH_3(CH_2)_8COCH_3$	98
	124. $CH_3(CH_2)_8COCH_3$	Na 9-BBNCN (4)	HMPA	1	25	$CH_3(CH_2)_8COCH_3$	65
60633-84-3	125. 	$NaBH_3CN$ (4)	HMPA	4	70		73
4436-22-0	126. 	TBAC (4)	HMPA	12	70		86
	127. 	Na 9-BBNCN (4)	HMPA	12	70		92
3352-87-2	128. $CH_3(CH_2)_{10}CON(C_2H_5)_2$	$NaBH_3CN$ (4)	HMPA	24	70	$CH_3(CH_2)_{10}CON(C_2H_5)_2$	95
	129. $CH_3(CH_2)_{10}CON(C_2H_5)_2$	TBAC (4)	HMPA	69	25	$CH_3(CH_2)_{10}CON(C_2H_5)_2$	100
	130. $CH_3(CH_2)_{10}CON(C_2H_5)_2$	Na 9-BBNCN (4)	HMPA	23	25	$CH_3(CH_2)_{10}CON(C_2H_5)_2$	100
872-05-9	131. $CH_3(CH_2)_7CH{=}CH_2$	Na 9-BBNCN (4)	HMPA	6.5	25	$CH_3(CH_2)_7CH{=}CH_2$	85

[a] Usually the solutions were 0.2 M in the compound and 0.8 M in the reducing agent for analytical runs. Preparative runs were commonly carried out at twice the above concentrations. [b] The yields were determined by GLC using internal standards and detector response factors unless specified otherwise. [c] Reference 13, H. Kuzuhara, K. Sato, and S. Emoto, *Carbohydr. Res.*, 43, 293 (1975); several carbohydrate derivatives were successfully reduced by these workers. [d] Reduction was slowed by inductive and steric effects; product was 2% reduced in 4 h when subjected to the reaction conditions. [e] Initial product contained B—H and CN, apparently from reaction between the carboxylic acid and cyanoborohydride. Treatment with concentrated HCl; overnight at 70 °C released the carboxylic acid. [f] α_{obsd} +2.9°. [g] Added in two portions, the second one after 53 h.

Table II. Direct Conversion of Alcohols into Hydrocarbons with Methyltriphenoxyphosphonium Iodide and Cyanoborohydride

Registry no.	Entry	Alcohol	Time[a] meth- iodide, h	Time[b] redn, h	% yield[c]
112-30-1	1.	$CH_3(CH_2)_9OH$	0.5[d]	1.0[e]	100
	2.	$CH_3(CH_2)_9OH$		1.5[e]	99
104-54-1	3.	$C_6H_5CH{=}CHCH_2OH$	0.5[d]	2.0[e]	68
17976-80-6	4.	$HO(CH_2)_6CN$	0.5[d]	1.0[e]	66
14064-13-2	5.		3.0[e]	8.0[g]	58

[a] Solutions 0.2 M in alcohol, 0.4 M in methiodide. [b] Final solutions 0.8 M in $NaBH_3CN$. [c] Yields determined by GLC using internal standards and corrected for detector response. [d] At 25 °C. [e] At 70 °C. [f] Solution 0.2 M in alcohol, 0.4 M in the iodide, and 0.8 M in $NaBH_3CN$ at 70 °C. [g] At 100 °C, sealed tube, 1.2 M in $NaBH_3CN$.

major deviation was noted with molecules containing a carboxylic acid (i.e., entries 22, 77, Table I) which gave uncharacterized B–CN containing products which had to be hydrolyzed with HCl prior to isolation in order to retrieve the acid products.

Reduction of Monoalkyl Halides. The reduction of primary halogen compounds (except chlorides and fluorides) was realized with all cyanoborohydrides in HMPA. The ease of reduction of the primary iodides by three of these reagents at 25 °C (i.e., $NaBH_3CN$, 3.5 h, 91%; TBAC, 21 h, 81%; Na 9-BBNCN, 1 h, 91.5%) recommends such removals for synthetic transformations and, as mentioned, should be successful in the presence of most other functional groups including chlorides, bromides, and sulfonate esters. In addition the reduction of primary iodides could also be accomplished in benzene and THF with TBAC (entry 7) and Na 9-BBNCN (entry 11), respectively. Thus, the reduction of iododecane with TBAC in refluxing benzene gave an 81% yield of decane in 7 h, while a 94% yield of decane was realized with Na 9-BBNCN at 25 °C in 26 h. However, reductions in these solvents were slow compared to the reduction in HMPA. The reduction of tosylates, though much slower at 25 °C, gave fairly good yields at higher temperature (entries 36–42) while chlorides and fluorides are sluggish even at 100 °C. Unlike the situation with $LiAlH_4$,[15] no alkene or alcohol side products were observed. While secondary iodo compounds were reduced with relative ease, the reduction of secondary bromides requires longer reduction times. Thus the reduction of 2-iodooctane occurred readily in 1–2.5 h at 70 °C (entries 66–68) while 2-bromododecane requires at least 24 h under the same conditions (entries 70–72) with all cyanoborohydride reagents. Sulfonate esters also require more vigorous reaction conditions (entries 89, 90) while secondary chlorides are quite unreactive (entries 82–83, 87, 88). Tertiary alkyl halides such as 1-adamantyl bromide are reduced, but very slowly (entry 97). As expected, an S_N2 process is consistent with the observation that only one of the three hydrides of cyanoborohydride is available for replacement of halide. Thus, while a fourfold molar excess of $NaBH_3CN$ gave 96% of dodecane in 1 h at 50 °C (entry 2), the reduction of 1-iododecane with 0.5 M $NaBH_3CN$ gave only 42% of decane after 2 h at 50 °C and no further reaction occurred with longer reaction times.

For synthetic applications, the superior selectivity possible with cyanoborohydride is demonstrated by the inertness toward almost all other functional groups in neutral or basic media. Thus, esters (entries 10, 21, 24–26, 73–76, 89, 90), carboxylic acid (entries 22, 77), amido (entries 128–130), nitro (entries 60–62), cyano (entry 23), alkene (entries 9, 43–59, 107–109, 131), sulfone (entries 32, 33), and even such normally sensitive groups as epoxides (entries 20, 125–127), ketones (entries 9, 21, 105, 106, 122–124), azide (entry 10), and, to a lesser extent, aldehydes (entries 19, 117–121). The exceptional discrimination possible is well illustrated by the selective stripping of the iodo group from the polyfunctional steroid in entry 9 which contains an ester, alkene, and ketone group in addition to the target iodine; the excellent isolated yield (89%) strongly recommends the reagent for such selective removals. The selective displacement of the bromine from 3-bromo-1,2-epoxy-1-phenylpropane is also noteworthy (entry 20). An additional example of the discrimination possible is provided by the selective removal of the primary methanesulfonate group from 3,4,5-trimesyl-1,2-diisopropylidene-D-glucopyranose[16] (entry 35). These latter three examples are illustrated below. The superior selectivity coupled with the ready availability of deuterated (or tritiated) cyanoborodeuteride[3,5] allows the preparation of chiral $RCHDR^1$ compounds as demonstrated by the conversion of methyl-*O*-mesyl mandelate to optically active methyl-*2-d*-phenyl acetate (entry 89).[17]

Direct Conversion of Primary Alcohols to Hydrocarbons. The facile reduction of primary iodides coupled with the inertness of $NaBH_3CN$ toward most reagents suggested a convenient two-step-in-one process in which primary alcohols may be converted to hydrocarbons. The procedure involves conversion of the alcohol (1 mmol) into the iodide with methyltriphenoxyphosphonium iodide[18] (2 mmol) in HMPA (5 ml) at ambient temperature followed by addition of $NaBH_3CN$ (4 mmol) and stirring at 70 °C for the durations listed in Table II. Alternately, both steps may be combined with no loss in yield (entry 2, Table II). Noteworthy is the conversion of a neopentyl alcohol into the hydrocarbon in respectable yield (entry 5, Table II) considering that the reaction involves two steps.[19]

Attempts to extend the procedure to secondary and tertiary alcohols were unsuccessful. In the former case, the products were invariably either an alkene or a mixture consisting of the corresponding alkane and alkene. In fact, by leaving out the $NaBH_3CN$, excellent yields of alkenes were obtained from most secondary alcohols thus providing an excellent method for the overall selective dehydration of such compounds.[20] This unexpected diversion of secondary systems also prevents the successful reduction of secondary iodides which are especially positioned for facile elimination. Thus, for example, cholesteryl iodide afforded only elimination products upon treatment with $NaBH_3CN$ (entry 69, Table I); apparently axial iodides favor elimination over substitution. Tertiary alcohols, on the other hand, are unreactive with the iodonation reagent in HMPA and may be recovered unchanged.

Reduction of Benzylic and Allylic Halides. Primary benzylic halides are smoothly reduced by all three cyanoborohydrides selectively with no complications (entries 60–65). Likewise, secondary benzylic bromides afford good to excellent yields of the corresponding alkanes with no evidence for double bond production (entries 79–81, 84–86). In all cases, the chloro derivatives were reduced at a much slower rate compared to the bromides (i.e., entries 82, 83, 87, 88) as expected for a displacement mechanism rather than one involving initial ionization and subsequent hydride capture as observed for $NaBH_4$ in aqueous diglyme.[21] We were therefore surprised to observe that the tertiary halides triphenylmethyl bromide and chloride (entries 91–96) afforded excellent yields to triphenylmethane. Apparently, $NaBH_3CN$, as previously observed for $NaBH_4$ (in Me_2SO)[2d,22] and $LiAlH_4$,[2a] attacks halide generating a cation (or radical) which traps a hydrogen. Other tertiary halides which cannot form stable ionic (or radical) intermediates are not reduced as readily. Thus 1-adamantyl bromide was only slowly and incompletely reduced

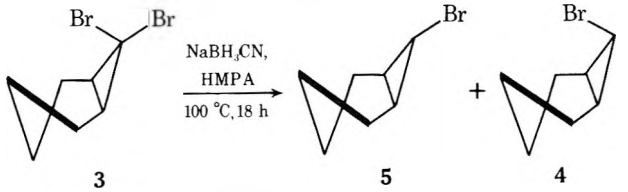
at 100 °C even with a large excess of reducing reagent (entry 97).

The reduction of allylic halides with boron hydride reagents is often complicated by the production of boron intermediates which may subsequently hydroborate alkenes. Thus, $NaBH_4$ in Me_2SO or sulfolane[2g] (or HMPA)[23] successfully removes allylic halides, but the yield of alkene products is lowered by subsequent hydroboration.

A variety of allylic halides were subjected to reduction with $NaBH_3CN$, TBAC, and Na 9-BBNCN. As evident from Table I, all three reagents convert allylic halides to the alkenes (entries 43–59), but the yields varied considerably and depended upon the reagent. With $NaBH_3CN$ and TBAC only fair to moderate yields were obtained (entries 43–46, 48, 49, 51, 52, 54–56, 58). Since no other organic products or starting materials were found, these reagents apparently furnish cyanoborane which cyanohydroborates the alkene products and/or starting materials; in fact, as mentioned previously, cyanoborane is conveniently synthesized by the reaction of $NaBH_3CN$ with organic halides. The most effective reagent was Na 9-BBNCN, which consistantly afforded 60–91% yields of alkenes (entries 47, 50, 53, 57, 59); the advantage is evidently a reflection of the inability of the reagent to furnish a hydroborating species.[24]

Reduction of Vicinal and Geminal Dihalides. The reduction of 1,2-dihalides to the corresponding hydrocarbons is generally complicated by competing elimination to the alkene,[25] although the combination of $NaBH_4$ in Me_2SO is successful.[2d] The cyanoborohydrides appear less applicable for such reductions. Thus, while $NaBH_3CN$ afforded predominantly ethylbenzene (77%) from styrene dibromide along with a minor amount of styrene (11%; entry 98), TBAC reacted only reluctantly and gave primarily styrene and starting material (entry 99) and Na 9-BBNCN produced α-bromostyrene as the principal product (entry 100); apparently the latter, sterically hindered reagent functions well as a base. Likewise, 1,2-dibromooctane reductions were only partly successful and gave mixtures of octane, 2-bromooctane, and unreduced starting material (entries 101–103). Here again, Na 9-BBNCN gave substantial elimination (entry 103).

Geminal dihalides appear to be smoothly reduced by cyanoborohydride initially to the monohalide. Thus, 7,7-dibromobicyclo[4.1.0]heptane (3) gave 77% of the cis isomer 4



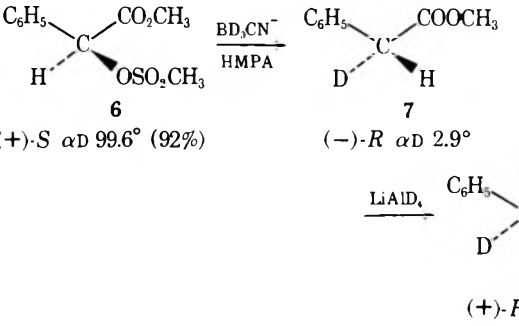
3 5 4

and 21% trans 5 (entry 104) similar to the results with $LiAlH_4$.[2a]

Reduction of Vinylic and Aromatic Halides. Vinylic halides seem quite resistant toward all three cyanoborohydrides (entries 107–109); only Na 9BBNCN gave detectable reaction with β-bromostyrene and then only to the extent of less than 10% in 22 h at 70 °C. The reduction of aryl halides also was of limited utility. The only successful applications found were the removal of iodo and bromo from naphthalene (entries 110–114); benzene derivatives were resistant. The remaining entries further illustrate the inertness of the cyanoborohydrides, especially toward normally sensitive functional groups such as aldehydes, ketones, and epoxides.

Mechanism of Hydride Displacements. Reduction of Optically Active Systems. Hydride substitutions of primary and secondary halides and sulfonate esters with BH_3CN^- in polar aprotic solvents ostensibly are best accommodated by an S_N2 process as has been implicated in analogous hydride displacements. As previously mentioned, this is evidenced by the expected relative rate order: iodides > bromides ≈ sulfonate esters > chlorides with fluorides unreactive. Since these reductions provide a potentially valuable synthetic procedure for the introduction of deuterium or tritium and for the preparation of optically active RCHDR[1] molecules,[26] the stereoselectivity possible in the reduction was of considerable interest and was probed using the sequence outlined in Scheme I. From the known configuration of (+)-(*S*)-methyl-*o*-mesyl mandalate (6) and (+)-(*R*)-2-phenyl-1,1,2-ethanol-d_3 (8), the displacement of mesyl by D was determined to occur with a minimum of ca. 67% inversion to give optically active 7 which was further reduced with $LiAlD_4$ to 8.[27] Thus, the high stereoselectivity recommends the procedure for the introduction of deuterium or tritium particularly when both stereo- and functional group selectivity are desired (i.e., 7).

Scheme I



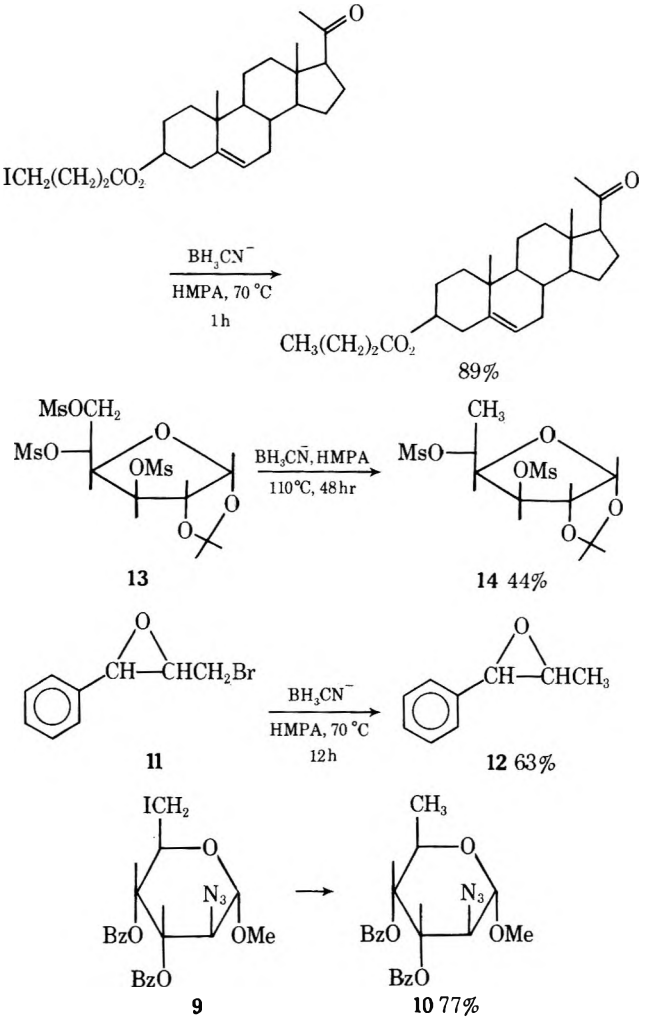
6 (+)-S α_D 99.6° (92%)

7 (−)-R α_D 2.9°

8 (+)-R α_D 0.90°

Conclusions and Summary

The results presented amply suggest that the combination of cyanoborohydride in HMPA provides a mild, effective, and



selective reagent system for the reductive displacement of primary and secondary alkyl halides and sulfonate ester in a wide variety of structural types. Particularly noteworthy synthetic applications include (a) the selective reduction of iodides and bromides in the presence of nearly all other functional groups (in neutral or basic media) including such normally sensitive moieties as aldehydes, ketones, and epoxides; (b) the facile removal of allylic and benzylic halides, particularly with 9-BBNCN$^-$, with a minimum of damage to alkenes; (c) the reduction of tertiary halides which are capable of forming stable carbonium ions (i.e., triphenylmethyl halides); (d) the stereoselective and chemoselective introduction of D (and presumably T) into molecules. The cyanoborohydride reagents described herein all appear effective in these applications and thus the commercially available $NaBH_3CN$ seems sufficient for most applications except when the use of other solvents such as benzene, CH_2Cl_2, etc., is desired. In these cases, TBAC or 9-BBNCN$^-$ are useful; the latter is also apparently the reagent of choice for allylic systems since a hydroborating species is not generated. Polymeric cyanoborane, although capable of halide reductions, is sluggish in its reactions and offers no apparent synthetic advantage.

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrometer either as films or in potassium bromide disks. Proton nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer typically as 10–20% solutions using tetramethylsilane as an internal reference. Microanalyses were performed by Chemanalytics Inc., Tempe, Ariz. Gas chromatographic (GLC) analyses were performed on a Hewlett-Packard Model 5250B instrument coupled to an L & N Model W recorder equipped with a disk integrator. Yields of products were determined by GLC using internal standards and corrected for detector response factors. Preparative GLC was also performed on this instrument. All analyses were carried out on either a 6 ft × 0.125 in. or 10 ft × 0.125 in. stainless steel column packed with 10% OV-1 or 20% Carbowax 20M on 80/100 mesh Chromosorb W (DMCS).

Materials. Sodium cyanoborohydride obtained from Alfa Inorganics was purified by decolorizing with alkaline Norit-A in hot tetrahydrofuran (THF) followed by solvent removal at reduced pressure. Samples obtained from Aldrich Chemical Co. were used as received. All the other chemicals used were either commercially available or prepared by standard procedures. Hexamethylphosphoramide (HMPA), obtained from Fisher Scientific Co., was distilled over CaH_2 and stored over 13 A molecular sieves. Tetrahydrofuran was distilled over $LiAlH_4$ and stored over 4 A molecular sieves. Drying of organic solvents was accomplished with anhydrous $MgSO_4$. Tetrabutylammonium cyanoborohydride was prepared as previously described.[1b,9]

Sodium 9-Cyano-9-hydrido-9-borabicyclo[3.3.1]nonane (1). Fisher certified sodium cyanide (13.4 g, 0.27 mol) was dried under vacuum and then added to 250 ml of THF. To this stirred slurry was added 500 ml of 0.5 M 9-BBN solution in THF under nitrogen and the reaction mixture was stirred at 25 °C for 12 h, during which time most of the NaCN dissolved. The solution was then filtered to remove undissolved NaCN and the solvent was removed on a rotary evaporator. The remaining solvent was removed under vacuum to obtain a hygroscopic, white semisolid. This was then redissolved either in THF or HMPA to obtain a ca. 1 M solution of the reducing agent in the corresponding solvent. Attempts to purify the solid were only partly successful; the material was dissolved in anhydrous ether and centrifuged to remove suspended particles. Evaporation of the ether gave a white solid material.

Anal. Calcd for $C_9H_{15}BNNa$: C, 63.2; H, 8.84. Found: C, 61.80; H, 9.09. IR (neat) 2270, 2240 s (BH); 2160 cm^{-1} s (CN). No 1560-cm^{-1} absorption characteristic of B–H–B bridge was observed.

Polymeric Cyanoborane. The general procedure of Spielvogel[11] or a modified method described for diborane[12] was employed to generate the reagent.

Method A.[11] Into a stirred slurry of 6.3 g (0.1 mol) of $NaBH_3CN$ in 100 ml of anhydrous ether was passed HCl gas for 1.5 h. The reaction mixture was filtered and the solvent removed on a rotary evaporator to obtain 2.77 g (71%) of polymeric cyanoborane as a white semisolid: IR (neat) 2469, 2441, and 2429 (B–H); 2295 cm^{-1} (–CN). The product was dissolved in a suitable solvent (HMPA or CH_2Cl_2) and used fresh.[28]

Method B. The preparation of cyanoborane was accomplished analogous to that used for diborane.[12] The cyanoborane was prepared in situ by dissolving the required amount of either $NaBH_3CN$ or TBAC in a suitable solvent (diglyme or CH_2Cl_2) containing 2 mmol of the compound, followed by the dropwise addition of excess (1:2) methyl iodide at 0 °C.

General Reduction Procedure for Halides and Sulfonate Esters. For analytical scale reductions, the compound (2 mmol), reducing agent (8 mmol), and a suitable hydrocarbon internal standard (2 mmol) were dissolved in 10 ml of HMPA. The mixture was stirred at the appropriate temperature (usually 25 or 70 °C) as indicated in Table I. The reactions were conveniently monitored by periodically removing samples, quenching in water, extracting with a small amount of cyclohexane, and analyzing the extracts by GLC. After the appropriate time period (Table I), the products were often isolated in the same manner. For preparative scale reactions the quantity of solvent was usually reduced two- or threefold. Isolation was usually accomplished by dilution with water or brine followed by extraction with cyclohexane or ether, or by filtration in the case of solids. Exceptions included carboxylic acids which required heating the initially formed boron containing product overnight with concentrated HCl to release the free acid. The procedure is illustrated for representative cases below; another detailed description has appeared previously.[1c]

Reduction of 3β-(3-Iodopropionoxy)pregn-5-en-20-one with $NaBH_3CN$. A solution of the iodo steroid[29] (415 mg, 0.85 mmol) and $NaBH_3CN$ (214 mg, 3.4 mmol) in 5 ml of HMPA was heated for 1.0 h at 70 °C and then diluted with 25 ml of water. The resulting white precipitate was filtered and recrystallized from acetone–water to give 280 mg (89%) of shiny, ivory crystals, mp 112–113 °C, identical in all respects with an authentic sample of 3β-propionoxypregn-5-en-20-one.[30]

Reduction of 1-Bromohexadecane with Na 9-BBNCN. A solution of 1-bromohexadecane (3.05 g, 10 mmol) and 40 ml of a 1 M solution of Na 9-BBNCN in HMPA was stirred and heated at 70 °C for 1.5 h. Water was then added and the reaction mixture was extracted with ether (3 × 30 ml). The ether solution was washed with water, dried, and concentrated on a rotary evaporator. Distillation afforded 2.05 g (91%) of hexadecane, bp 114–115 °C (1 mm), identical with an authentic sample.

Reduction of 7-Hydroxyheptanenitrile to Heptanenitrile. A solution of 7-hydroxyheptanenitrile (127 mg, 1.0 mmol) and methyltriphenoxyphosphonium iodide (905 mg, 2.0 mmol) in 5 ml of HMPA was stirred at 25 °C for 30 min. $NaBH_3CN$ (252 mg, 4 mmol) was then added and the solution was heated at 70 °C for 1.0 h, then diluted with water. Cyclohexane (5 ml) and undecane (internal standard) were added and the organic solution analyzed by GLC (10 ft OV-1 column), indicating a 66% yield of heptanenitrile.

Reduction of (+)-(*S*)-Methyl o-Mesylmandalate with $NaBD_3CN$ (Table I, Entry 89). A solution of (+)-(*S*)-methyl *o*-mesylmandalate [1.5 g, 6.[illegible] mmol, $[\alpha]^{25}D$ +99.6° (c 18, $CHCl_3$), 89.8% optical purity][31] and $NaBD_3CN$ (0.90 g, 13.7 mmol, 90% deuterium) in 7 ml of dry HMPA was prepared in a flask equipped with a condenser and protected by a drying tube. The solution was heated at 110 °C for 4 h, then cooled and diluted with 10 ml of water. The resulting slurry was extracted with ether, and the ether solution was washed with brine, dried, and concentrated on a rotary evaporator. The residue was distilled in vacuo to obtain 0.60 g (64%) of (–)-(*R*)-methyl-2-*d*-2-phenyl acetate, $\alpha^{25}D$ 2.9° (neat, *l* = 1).

(+)-(*R*)-2-Phenylethanol-*1,1,2-d*$_3$. A solution of (–)-(*R*)-methyl phenylacetate-α-*d* (7, 440 mg, 3 mmol, $\alpha^{25}D$ –2.9°, neat) in 5 ml of dry THF was added slowly to a stirred slurry of $LiAlD_4$ (0.20 g, 5 mmol) and 10 ml of dry THF. The mixture was heated at reflux for 3 h and the excess hydride cautiously destroyed by successive addition of 0.2 ml of H_2O, 1 ml of 15% aqueous NaOH, and 0.2 ml of H_2O. The solution was decanted from the precipitated salts, dried, and concentrated. Distillation in a short-path apparatus afforded 0.28 g (76%) of (+)-(*R*)-2-phenylethanol-*1,1,2-d*$_3$ (8), bp 47–53 °C (0.03 mm), $\alpha^{25}D$ +0.90° (lit.[27] $\alpha^{26}D$ +1.49°).

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Registry No.—**1**, 60645-80-9; **2**, 60633-76-3; **7**, 53546-38-6; **8**, 60633-85-4; sodium cyanide, 143-33-9; 9-borabicyclo[3.3.1]nonane,

280-64-8; $NaBH_3CN$, 25895-60-7; 3β-hydroxypregn-5-en-20-one, 145-13-1; 3-iodopropionyl chloride, 41518-22-3; 3β-propionoxypregn-5-en-20-one, 54552-01-1; propionyl chloride, 79-03-8.

References and Notes

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(7) For an excellent and recent review of phase-transfer reagents in organic synthesis see E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, **13**, 170 (1974).

(8) We noted previously[1a] that $NaBH_3CN$ obtained from past sources gave best results if purified before use for the reduction of halides containing other sensitive groups, presumably because of some residual $NaBH_4$. Recent samples appear satisfactory without purification.

(9) (a) R. O. Hutchins and D. Kandasamy, *J. Org. Chem.*, **40**, 2530 (1975). (b) Several tetraalkylammonium cyanoborohydrides have been prepared in a similar fashion as described in ref 9a; see J. E. Repasky, C. Weidig, and H. C. Kelly, *Synth. React. Inorg. Metal-Org. Chem.*, **5**, 337 (1975).

(10) We have experienced difficulty in purifying 9-BBNCN as either the Na or K salt; both are obtained as tacky solids which defy attempts at crystallization. However, spectral data are in accord with the proposed structure (see Experimental Section).

(11) (a) B. F. Spielvogel, R. F. Bratton, and C. G. Moreland, *J. Am. Chem. Soc.*, **94**, 8597 (1972). (b) Several amine–cyanoborane complexes have been described by Kelly and co-workers: S. S. Uppal and H. C. Kelly, *Chem. Commun.*, 1619 (1970); C. Weidig, S. S. Uppal, and H. C. Kelly, *Inorg. Chem.*, **13**, 1763 (1974).

(12) The preparative method employed is analogous to that reported for borane using Bu_4NBH_4; see A. Brandstrom, U. Juneggren, and B. Lamm, *Tetrahedron Lett.*, 3173 (1972).

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(23) Unpublished observations. This problem may be alleviated by the use of $NaBH(OCH_3)_3$ which is incapable of forming a hydroborating reagent.

(24) The combination of $NaBH_3CN$ in acidic methanol is also successful in avoiding hydroboration of alkenes in certain cases; see H. O. House and L. F. Lee, *J. Org. Chem.*, **41**, 863 (1976).

(25) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949).

(26) R. O. Hutchins, D. Masilamani, and C. A. Maryanoff, presented at the 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1974, Abstracts, No. ORGN-21.

(27) The α_{max} for **8** has been determined by Morrison and Mosher to be 1.49°. We thank Professor Morrison for communicating their results prior to publication. At least part of the loss of optical activity may be due to racemization incuced by the strong base $LiAlD_4$. We hope to alleviate this possible problem via a nonbasic reducing reagent such as AlH_3 or 9-BBN.

(28) A word of caution is in order at this point. Although no problems have been encountered with fresh preparations of the viscous polymeric reagent, on one occasion an old sample which had solidified caught fire when an attempt was made to scrap the sample from flask (in air). Professor Spielvogel has informed us (private communication) of a similar experience with a sample which had been stored for some time in a hydrocarbon solvent in the presence of air. Therefore, to avoid possible hazards, reductions were carried out with freshly prepared material. The polymer was kept in solution in the absence of air whenever possible and otherwise treated with care and respect which *all* borane derivatives deserve. Also, HMPA has been shown to be a carcinogen and thus should be handled with due caution.

(29) Prepared by reaction of 3β-hydroxypregn-5-en-20-one with 3-iodopropionyl chloride in pyridine, mp 129–131 °C (acetone–water). Anal. Calcd for $C_{24}H_{35}O_3I$: C, 57.83; H, 7.09. Found: C, 57.96; H, 7.16.

(30) Prepared from the 3β-alcohol and propionyl chloride in pyridine, mp 112–113 °C (acetone–water). Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.59; H, 9.50. Found: C, 77.70; H, 9.43.

(31) Prepared acccrding to a procedure of J. D. Morrison (private communication); reported $[\alpha]^{20}D$ +111.0° (c 6.6, $CHCl_3$).

Thermal and Photochemical Interconversion of Several 1,8-Naphtho(C_4H_4) Hydrocarbons. Tests of the Woodward–Hoffmann Rules

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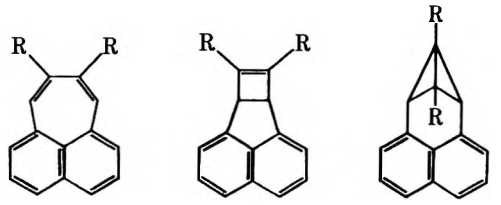
The photochemical and thermal interconversions of both deuterated and nondeuterated pleiadiene (**1**), 1,8-naphthobicyclo[3.2.0]hepta-2,6-diene (**2**), and 1,8-naphthotricyclo[4.1.0.$0^{2,7}$]heptene (**3**) are reported. All of these isomerizations may be preliminarily explained in terms of allowed and forbidden pathways. For several of the reported examples, however, a more complex interpretation is required by the experimental data.

Even though there has been much work done on the higher members of the pleiadiene family,[2] there are only a few reports on the preparation and isomerizations of the parent molecule (**1a**) and the isomeric molecules **2a** and **3a**.[3] Literature records the formation of pleiadiene (**1a**) from 1,8-

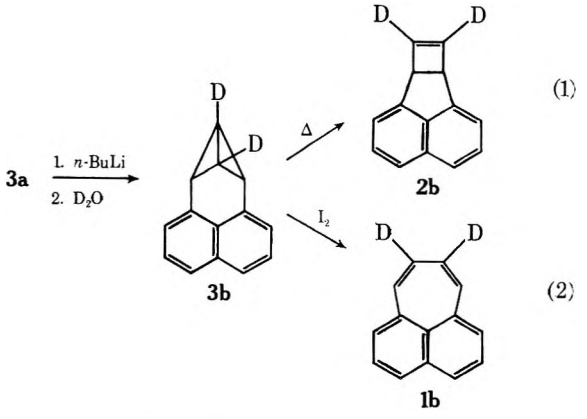


1 **2** **3**

a, R = H; **b**, R = D

naphthobicyclo[3.2.0]hepta-2,6-diene (**2a**) by an unusual two-photon process,[3a] and also by thermal isomerization at high temperatures (250 °C), a process which is forbidden in the Woodward–Hoffmann sense.[3a,b] On the other hand, **1a** could be obtained by the photolysis of 1,8-naphthotricyclo[4.1.0.$0^{2,7}$]heptene (**3a**), whereas heating **3a** resulted in the exclusive formation of **2a**.[3b] Our work described here was an attempt to trace the origin and paths for these isomerizations.

Preparation of Hydrocarbons. The preparation and purification of the nondeuterated hydrocarbons **1a**, **2a**, and **3a** has been described previously.[4] Compound **3b** was prepared by treating an ether solution of **3a** with excess *n*-bu-



(1)

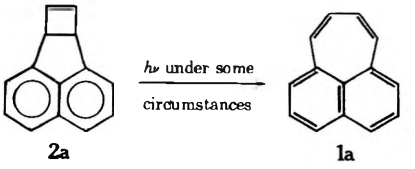
(2)

3b **2b** **1b**

tyllithium followed by quenching with D_2O. Thermal isomerization of **3b** then afforded **2b**, while treatment of **3b** with a catalytic amount of I_2 afforded pleiadiene-d_2 (**1b**).[5]

Absorption and Emission Studies. The absorption and emission parameters of both **2a** and **3a** closely resemble those of naphthalene, whereas those of **1a** are markedly different. The absorption of **1a** extends up to 570 nm, which makes the compound red.[2a] The fluorescence of **2a** and **3a** resembled the fluorescence of naphthalene, was structured, and extended from 325 to 390 nm at room temperature in ether, cyclohexane, acetonitrile, and EPA. Both **2a** and **3a** had a long-lived phosphorescence ($\tau \sim 3$ s) in the region 480–600 nm at 77 K in EPA glass; however, no phosphorescence from **2a** or **3a** was observed in solution at room temperature. Unfortunately, pleiadiene (**1a**) did not show any emission either at low or room temperature. The spectroscopic data are summarized in Table I.

Photoisomerization of 2a into 1a. As has been reported by Meinwald and co-workers,[3a] **2a** was found to be totally inert upon direct irradiation ($\Phi < 10^{-4}$) at room temperature in a variety of solvents. This is particularly intriguing because the photoisomerization of **2a** into **1a** did occur upon direct irradiation at 77 K (450-W medium-pressure lamp) in 3-methylpentane (3-MP). Furthermore, the photoreaction will occur at low temperature if **2a** is irradiated simultaneously with two



(3)

2a **1a**

light sources of different wavelengths (see ref 3a and below). Triplet sensitization of **2a** (E_{T_1} = 59.5 kcal/mol, Table I), on the other hand, with either benzophenone (E_{T_1} = 69.5 kcal/mol) or 2-acetonaphthone (E_{T_1} = 59.3 kcal/mol) did not afford any pleiadiene (**1a**).

The above data suggest that the lowest singlet (S_1) and triplet states of **2a** are not responsible for the isomerization. By what mechanism is **2a** converted into pleiadiene (**1a**)? The following observations strongly suggest that the photoisomerization occurs from an upper triplet state of **2a**.

First, keep in mnd that 1,8-naphthobicyclo[3.2.0]hepta-2,6-diene (**2a**) has no electronic absorption above 330 nm. Irradiation of **2a** at 77 K in 3-MP or EPA with monochromatic light at 260 ± 10 nm (**2a** has $\epsilon \sim 2 \times 10^3$ in this region) did not give **1a**. This establishes that the lowest singlet state (S_1) of **2a** is insufficient to bring about the reaction. But the product was obtained at 77 K in less than 1 h when the irradiation was conducted with two lamps, one exciting **2a** at S_1 (λ 260 ± 10 nm) and the other above 350 nm (450-W xenon–mercury lamp with Corning glass filter 3-75), at right angles. Irradiation of **2a** with the above two light sources at room temperature, however, did not yield any **1a**. These results suggest that a second photon absorption must occur before the reaction can take place and that the species absorbing the second photon is long lived at 77 K but not at room temperature. Because T_1 of **2a** has a lifetime of 3.3 s at 77 K, while S_1 has a lifetime of only 48×10^{-9} s at 77 K ($\tau = 33 \times 10^{-9}$ s at 295 K), T_1 seems a likely candidate for the species absorbing the second photon.

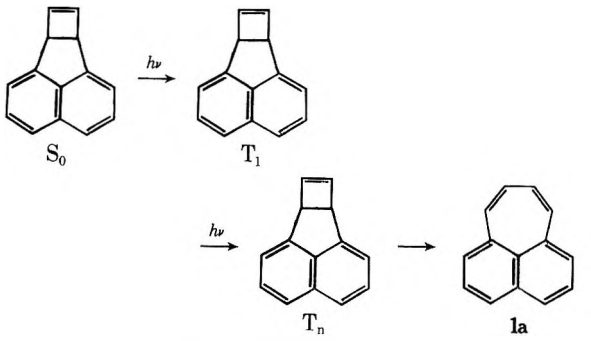
An interesting result was obtained when the wavelength of

Table I. Spectroscopic Properties of 1a, 2a, and 3a

	E_{S_1},[a] kcal/mol	E_{T_1},[b] kcal/mol	τ_{S_1}, s (77 K)[c]	τ_{S_1}, s (275 K)[d]	τ_{T_1},[e] s (77 K)	Φ_{fl}
Naphthalene	91	61		96×10^{-9}	2.4	0.10
1a	51	?	No emission from S^1 or T^1 at room temperature or 77 K			
2a	88	59.5	48×10^{-9}	33×10^{-9}	3.3	0.40[f]
3a	88	59.5	43×10^{-9}	36×10^{-9}	2.8	0.47[f]

[a] Values are based on the fluorescence spectrum; in the case of 1a it was based on the absorption spectrum. [b] Values are based on phosphorescence emission. [c] The lifetimes were measured by the single photon counting technique in EPA glass. [d] The lifetimes were measured in CH_3CN (1×10^{-3} M) under N_2. [e] The triplet lifetime was measured by flash photolysis in EPA glass. [f] The quantum yields are based on the value of 0.60 for acenaphthene and maintaining the OD at 296 nm as 0.2.

the secondary light source was changed. No product was formed when the secondary source had λ <350 nm or >440 nm; irradiation in the region of 350–440 nm, however, did produce pleiadiene (**1a**). Since naphthalene triplets undergo T–T transitions in the 350–440-nm region[6] and the absorption and emission properties of **2a** are so similar to those of naphthalene, **2a** would be expected to also have T–T transitions in the same region. The rough correspondence of product formation and T–T absorption leads us to believe that the reaction originates from a higher triplet (eq 4) as suggest earlier for related compounds.[2]



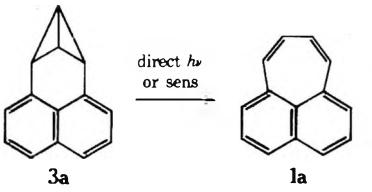
(4)

The results above have clearly demonstrated the existence of an energy barrier in going from **2a** to **1a** from both S_1 and T_1. The absence of formation of **1a** upon irradiation, either direct or triplet sensitization, up to 90 °C is consistent with the postulate that vibrationally excited T_1 is not the reactive species.

One other point should be mentioned about the photoisomerization, **2a** → **1a**. The reaction occuring from T_n of **2a** could in fact generate **1a** in the excited state by an adiabatic photoprocess. Both singlet (S_1) and triplet (T_1) energies of **2a** are well above those of **1a**.[7] Unfortunately, the detection of an excited state of **1a** was not possible for several reasons. Firstly, pleiadiene does not emit light from its S_1 and T_1 states. Secondly, the triplet state (T_1) of pleiadiene (**1a**), the likely excited state product of the reaction, is so low in energy[7] that efficient energy transfer to another molecule which does emit is precluded. Finally, photolysis of pleiadiene does notgive a "unique" product (see below) whose appearance in the photolysis of **2a** would indicate that pleiadiene is formed in the excited state.

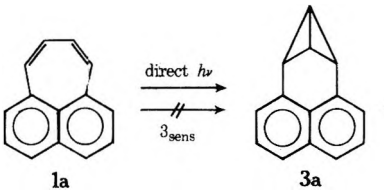
The disrotatory opening of cyclobutenes to butadienes is normally an allowed process in the excited state. Both the S_1 and T_1 state of cyclobutenes have been shown to correlate with the corresponding excited states of butadienes by theoretical calculations.[8] Intuitively, one would expect the S_1 and T_1 states of the cyclobutene (**2a**) also to correlate with the corresponding states of the butadiene (**1a**). The actual diagram, as originally constructed by Michl,[9] would indicate otherwise. The lowest excited state of **2a**, for example, correlates with an unusual doubly excited state of **1a**. Likewise, there is no correlation between the lowest excited state of **1a** and its counterpart in **2a**. Michl has concluded that for systems having this unusual type of correlation diagram there should be large barriers to reaction in the excited state.[2,9] The photoisomerization of **2a** → **1a** represents another example where this predicted phenomenon has actually been observed.

Photointerconversion of 3a and 1a. Unlike the unusual behavior of **2a** upon excitation, **3a** was smoothly converted into **1a** from either the S_1 or T_1 state. Direct irradiation of **3a** (<300 nm) in various solvents gave pleiadiene (**1a**) as determined by NMR, uv, and VPC retention time. Sensitization of **3a** with either benzophenone or 2-acetonaphthone also affords **1a**.



(5)

Irradiation of pleiadiene (**1a**) either at S_1 (<460 nm) or S_2 (>280 nm) gave a product mixture which was mainly a polymeric material plus less than 15% of **3a** which was identified by uv, VPC retention time, and mass spectrometry. Triplet sensitization of **1a** with benzophenone and 2-acetonaphthone, both of which should have triplet excitation energies greatly in excess of that anticipated for pleiadiene (**1a**),[7] failed to produce either **2a** or **3a**.



+ polymer (6)

Although **1a** and **3a** interconvert photochemically, it is clear that the interconversion pathways differ in some fundamental way. It would seem reasonable that **3a** isomerizes to **1a** in its S_1 and T_1 states by a symmetry-allowed ring opening. That the frontier orbital of **3a**, the lowest antibonding orbital of **3a**, may have a dominant role in determining the course of the reaction is borne out by the fact that the radical anion of the bicyclobutane (**3a**), whose highest occupied molecular orbital (MO) is identical with the highest occupied MO of S_1 and T_1 states of **3a**, ring opens to the radical anion of **1a**.[10]

$$\mathbf{3a}^{\cdot -} \rightarrow \mathbf{1a}^{\cdot -} \quad (7)$$

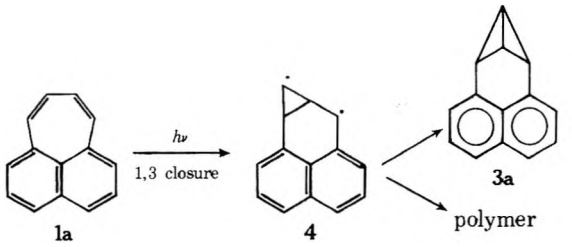
The reverse photoreaction must proceed differently because of the preponderant formation of polymer. Perusal of Table I shows that the lowest singlet and triplet excited states of **1a** arebelow any excited state of **3a**. This means that adiabatic photoconversion of **1a** into any excited state of **3a** is very unlikely. Furthermore, simple energy considerations suggest that the S_1 state of **1a** is above the ground state of **3a**, while the T_1

Table II. Activation Parameters for Thermal Rearrangements

Reaction	E_a, kcal/mol	Log A	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
3a → 2a[a]	32.9 ± 3.5	13.2 ± 3.2	32.1 ± 3.5	−1.0 ± 3.5
2a → 1a[b]	39.3 ± 0.8	14.6 ± 0.2	38.4 ± 0.8	5.5 ± 0.9

[a] The kinetics were run by NMR on the disappearance of 3a. [b] The kinetics were run by visible–uv on the appearance of 1a.

state is not. If this energetic array is correct, it would mean that S_1 state of pleiadiene (**1a**) could still isomerize to **3a**, perhaps in a stepwise fashion, but the T_1 state could not. This interpretation is in line with the experimental observations. A plausible mechanism for this isomerization is shown below.

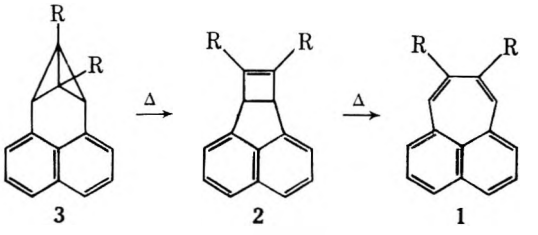


(8)

(9)

One other point concerning the photochemistry of **1a** is worth noting and that is the fact that **1a** does not isomerize to **2a**. This is perfectly understandable in light of Michl's correlation diagram discussed previously.[2]

Thermal Interconversion of Hydrocarbons. The thermal isomerizations of **1**, **2**, and **3**, both for the deuterated and nondeuterated hydrocarbons, are shown below.[3a,b,4] It would



(10)

R = H and R = D

appear that at least in part the driving force for each of the reactions is relief of strain.

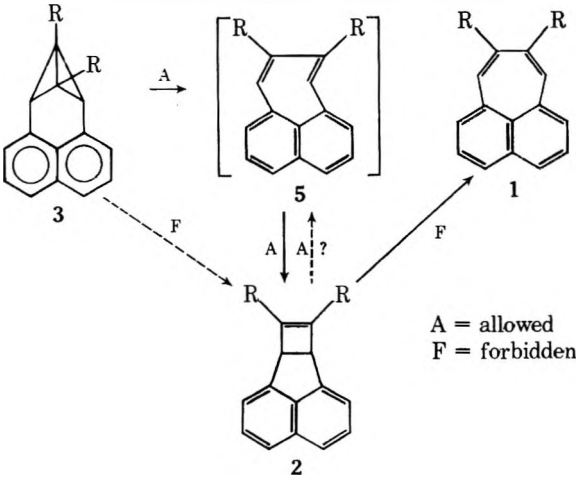
The activation parameters for each of the isomerizations were determined for the nondeuterated materials and are reported in Table II.

Both isomerizations could proceed either by symmetry-controlled pathways[3b] or by stepwise mechanisms involving the formation of biradical-like intermediates. The nature of the product in each reaction and the labeling experiments are perfectly consistent with the symmetry-controlled processes. However, as will be shown below, analysis of the activation parameters suggest that these reactions may proceed through biradical intermediates.

The conversion of the bicyclobutane (**3**) into the cyclobutene (**2**) can be explained by a two-step process involving an initial symmetry-allowed ring opening to give *cis,trans*-pleiadiene (**5**) followed by a symmetry-allowed conrotatory closure to give **2**. The cis,trans isomer (**5**), if formed, is not observed in the reaction for it would be a very strained molecule and it would be expected to isomerize very rapidly to **2** (Scheme I).

The conversion of **2** into pleiadiene (**1**) must of necessity involve a disrotatory ring opening of **2** which is a thermally forbidden reaction. This can be seen vividly in the previously

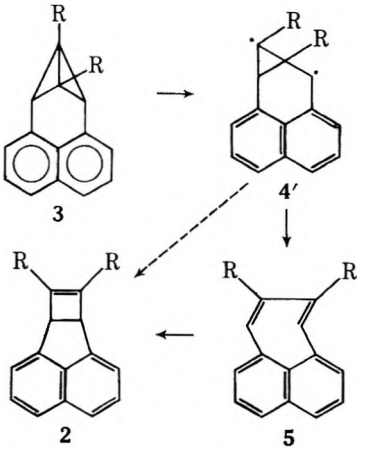
Scheme I. Symmetry-Controlled Pathways for the Interconversion of 3 into 2 and 2 → 1



described correlation diagram connecting **2** and **1**.[2,9] Conrotatory ring opening of **2**, which is thermally allowed, would form the very highly strained *cis,trans*-pleiadiene (**5**). It would appear in this case that if the conversion of **2** into **1** were a concerted reaction the allowed pathway would have a higher energy of activation than the forbidden one because of the anticipated strain energy associated with the allowed product (**5**). Even if the allowed process were to occur, the reaction would be hidden, for **5** should rapidly reclose to **2**.

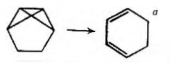
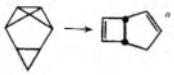
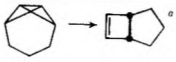
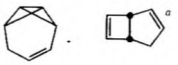
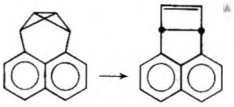
Are biradicals formed in the conversion of **3** into **2** or is this strictly a symmetry-controlled process? A comparison of the activation parameters for this process with systems that undergo similar reactions (Table III) suggests that the initial reaction of **3** involves a single cleavage of a bicyclobutane bond. It can be seen that the energies of activation for the first three reactions in the table are much higher than the one reported in this work or the fourth entry. As a matter of fact, all the activation parameters are similar for the last two reactions described in Table III. Christl and co-workers have argued convincingly[11] that this fourth reaction proceeds via a biradical intermediate. The lower E_a for this process compared to the first three can be attributed to the stabilizing influence of the double bond in going from reactant to the biradical intermediate. In the naphthobicyclobutane (**3a**), stabilization by the naphthalene ring (benzylic stabilization) would have a comparable influence in lowering the E_a. This suggests that the thermal isomerization of **3** proceeds through initial formation of a biradical (Scheme II). Of course, without knowing

Scheme II. Biradical Mechanism for the Thermal Isomerization of 3 into 2



how substituent effects alter the activation parameters one cannot be totally certain that this is the case.

Table III. Comparison of Kinetics of Thermal Rearrangements of Endo,Endo' Bridged Bicyclobutanes

	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	E_a	Log A
	40.7 ± 1.0	0.6 ± 1.5	41.7 ± 1.0	13.6 ± 0.5
	37.6 ± 1.0	1.5 ± 1.0	38.5 ± 1.0	13.7 ± 0.5
	37.9 ± 1.5	−1.1 ± 3.0	38.8 ± 1.5	13.2 ± 0.7
	31.5 ± 0.6	1.1 ± 1.1	32.4 ± 0.6	13.6 ± 0.4
	32.1 ± 3.5	−1.0 ± 3.5	32.9 ± 3.5	13.2 ± 3.2

[a] Reference 11. [b] This work.

Table IV. Energies of Activation for Cyclobutene Ring Openings

Compd	E_a, kcal/mol	Ref
	32.70	*a*
	31.55	*b*
	37.30	15c
	26.00	*c*
	24.50	*d*
	45.86	15b
	43.20	15c
	39.30	This work

[a] W. Cooper and W. D. Walters, *J. Am. Chem. Soc.*, 80, 4220 (1958). [b] H. M. Frey, B. M. Pope, and R. F. Skinner, *Trans. Faraday Soc.*, 63, 1166 (1967). [c] M. Pomerantz and P. H. Hartman, *Tetrahedron Lett.*, 991 (1968). [d] J. I. Brauman and W. C. Archie, Jr., *Tetrahedron*, 27, 1275 (1971).

If the biradical 4' [12] were formed, would it be expected to yield **2**? The answer is yes. Dewar has suggested convincingly[14] that the stereoselective ring opening of bicyclobutanes begin with a single bond cleavage. The resulting biradical "remembers" its origin and its subsequent selectivity is assumed. Similar reasoning can be applied to the present case.

Can we infer the existence of biradicals in the "forbidden" conversion of the cyclobutene (**2**) to pleiadiene (**1**) or is the process a truly concerted forbidden reaction? In other constrained cyclobutenes, where the energy of activation of the allowed conrotation is high, the isomerizations have been proposed to go through biradical intermediates to give nonstereospecific products.[15] A comparison of the activation energies for the ring opening of **2** with other cyclobutenes is shown in Table IV.

It can be seen that the activation energy for the ring opening of **2** is indeed higher than for those cases where an allowed conrotation is not prevented because of ring strain of the product. It would appear then that the "forbidden" character of the ring opening of **2** does influence the E_a for the reaction. On the other hand, the E_a's for the forbidden ring opening of bicyclo[3.2.0]heptene and bicyclo[4.2.0]octene are substantually higher than the value for **2**. The naphthalene π electrons must have a stabilizing influence on the ring opening as do phenyl groups of the simple cyclobutenes shown in the table. Whether one can attribute this lowering of the E_a to the formation of a stabilized benzylic biradical or some other effect cannot be known for certain at this time.

Another interesting aspect of the forbidden ring opening of **2** to pleiadiene (**1**) is that the reaction may be another example of a thermally induced chemiluminescent reaction. The activation energy (39.3 kcal/mol) coupled with the strain energy of the cyclobutene (29.8 kcal/mol) and the low values for E_{S_1} and E_{T_1} of the product (**1**) could produce **1** in either the S_1 or T_1 state. However, as mentioned previously, there are at present no practical methods for detecting the excited states of pleiadiene.

Concluding Remarks. The above data demonstrate that one must analyze very carefully those reactions for which the Woodward–Hoffmann rules can be applied, as with the thermal and photochemical isomerization of **2** into **1**. Other reactions which are fully in accord with the rules such as the thermal isomerization of **3** into **2** may actually proceed via biradicals. Much more experimental work will have to be done, however, to validate this interpretation.

Experimental Section

Emission spectra were recorded on a Perkin-Elmer Model MPF-3L spectrofluorimeter and electronic absorption spectra on Cary-17 instruments. NMR spectra were recorded on a Varian A-60 spectrometer. VPC analysis was made using a Varian Aerograph series 1200 equipped with flame ionization detector. The condition for the analysis of **1a**, **2a**, and **3a** was 5% 1,1-bis(2-cyanoethoxy)propane, 3 ft × 0.5 in. column at 110 °C. Under our VPC analysis condition partial conversion of **3a** to **1a** was observed. The singlet lifetime was measured using a home-built nanosecond singlet photon counter and triplet lifetime using a microsecond flash photolysis apparatus equipped with xenon lamp. Irradiations were conducted using a 450-W medium-pressure mercury lamp or 450- or 1000-W high-pressure xenon–mercury lamp using appropriate Corning glass filters or Aminco-Bowman monochromator.

Solvents used in the study (cyclohexane, ethyl ether, and acetonitrile) were once distilled before use. EPA (MCB phosphosimetry grade) and 3-MP (Aldrich 99+%) used for low-temperature study were passed once through an alumina column. Syntheses of compounds **1a**, **2a**, and **3a** are already in the literature.[4]

Kinetics of 3a to 2a. A solution of **3a** in cyclohexane was degassed and sealed in vacuo in an NMR tube. The tube was heated in a ther-

mostated oil bath, and NMR measurements were made periodically after quenching the tube in water. The kinetics were followed by the disappearance of the bicyclobutane signals relative to an assumed constant aromatic region.

Kinetics of 2a to 1a. A solution of **2a** (6.7×10^{-3} M) in cyclohexane was placed in a visible–uv cell equipped with a graded seal and ground glass joint. The tube was sealed in vacuo. The cell was heated in a thermostated oil bath and measurements were made periodically after quenching the cell in the water. The kinetics were followed by the appearance of **1a** in the visible; an infinity reading was taken after heating the cell at >190 °C for 10 h.

Preparation of 3b. To a solution of 300 mg (1.69 mmol) of **3a** in 50 ml of ether under nitrogen was added 3.0 ml of 2.0 N *n*-butyllithium (6.0 mmol) in hexane. The resulting dark orange solution was stirred at room temperature for 1 h after which it was quenched with D_2O. Workup afforded an almost quantitative yield of **3b**. Mass spectral and NMR analysis revealed an 83% incorporation of deuterium into the bridgehead positions with less than 2% incorporation into the benzylic positions.

Preparation of 1b and 2b. These were prepared by the literature method used to prepare **1a** and **2a** only beginning with the **3b** described above.

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Registry No.—**1a**, 208-20-8; **2a**, 30736-79-9; **3a**, 40480-63-5.

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(1) (a) Columbia University; (b) University of Tennessee.
(2) (a) J. Kolc and J. Michl, *J. Am. Chem. Soc.*, **95**, 7391 (1973), and references cited therein; (b) J. M. Labsum, J. Kolc, and J. Michl, *ibid.*, **96**, 2636 (1974).
(3) (a) J. Meinwald, G. E. Samuelson, and M. Ikada, *J. Am. Chem. Soc.*, **92**, 7604 (1970); (b) R. M. Pagni and C. R. Watson, *Tetrahedron Lett.*, 59 (1973); (c) I. Murata and K. Nakasuji, *ibid.*, 47 (1973).
(4) C. R. Watson, Jr., R. M. Pagni, J. R. Dodd, and J. E. Bloor, *J. Am. Chem. Soc.*, **98**, 2551 (1976).
(5) These reactions were first described by R. M. Pagni, C. R. Watson, Jr., P. A. Bouis, J. E. Bloor, J. R. Dodd, and R. F. Winton, Southeastern Regional Meeting of the American Chemical Society, Norfolk, Va., Oct 1974.
(6) R. L. DeGroot and G. J. Hoytink, *J. Chem. Phys.*, **46**, 4523 (1967); W. H. Melhuish, *ibid.*, **50**, 2779 (1969).
(7) E_T, of **2a** is not known but has been calculated to be approximately 30 kcal/mol.[2a]
(8) W.T.A.M. Van der Lugt and L. J. Oosterhoff, *J. Am. Chem. Soc.*, **91**, 6042 (1969); D. Grimbert, G. Segal, and A. Devaquet, *ibid.*, **97**, 6629 (1975).
(9) J. Michl, *Mol. Photochem.*, **4**, 287 (1972).
(10) J. R. Dodd, R. F. Winton, R. M. Pagni, C. R. Watson, Jr., and J. Bloor, *J. Am. Chem. Soc.*, **96**, 7846 (1974).
(11) M. Christl, V. Heinemann, and W. Kristof, *J. Am. Chem. Soc.*, **97**, 2299 (1975).
(12) Note that **4'** and **4** appear to be identical in structure and yet do not have the same chemical behavior. It could be that these diradicals are lumomers[13,14] which should not interconvert and should have unique chemical behavior. Note also that one of the species is formed in a thermal reaction while the other is formed in a photochemical reaction.
(13) (a) M. J. S. Dewar, S. Kirschner, and H. W. Kollmar, *J. Am. Chem. Soc.*, **96**, 5240 (1974); (b) M. J. S. Dewar, S. Kirschner, H. W. Kollmar, and L. E. Wade, *ibid.*, **96**, 5242 (1974).
(14) M. J. S. Dewar and S. Kirschner, *J. Am. Chem. Soc.*, **97**, 2931 (1975).
(15) (a) D. M. Golden and J. I. Braumann, *Trans. Faraday Soc.*, **65**, 464 (1969); (b) G. R. Branton, H. M. Frey, D. C. Montagne, and D. D. R. Stevens, *Ibid.*, **62**, 659 (1966); (c) G. R. Branton, H. M. Frey, and R. F. Skinner, *ibid.*, **62**, 1546 (1966).

Stepwise Elaboration of Diamondoid Hydrocarbons. Synthesis of Diamantane from Adamantane

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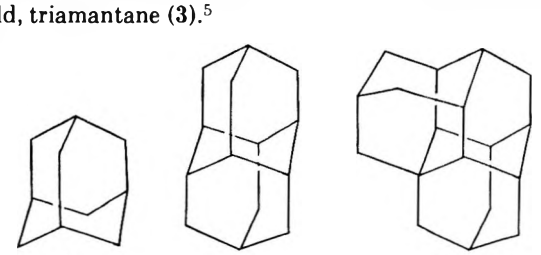
Diamantane (**2**) has been synthesized in a stepwise manner starting with adamantane (**1**). The key steps involve functionalization, ring closures by diazo ketone-derived carbene insertions (**7** → **8** and **23** → **24** + **25**), and rearrangement to give the diamantane skeleton (**13**, **14** → **2**). This method is general, and could in principle be used to elaborate any lower diamondoid hydrocarbon to a higher one.

Polycycloalkanes with diamond lattice structure generally possess ultimate thermodynamic stabilities.[2] Consequently, Lewis acid catalyzed carbocationic isomerizations provide remarkably successful syntheses of many molecules of this type,[2] e.g., adamantane (**1**),[3] diamantane (**2**),[4] and, in lower yield, triamantane (**3**).[5]



1 2 3

However, an attempt to prepare a tetramantane by this route failed; instead, isomerization of a $C_{22}H_{28}$ precursor led to "bastardane", a compound with an irregular rather than a diamondoid structure.[6] This result demonstrates that thermodynamic control cannot always be realized, owing evidently to high barriers for certain of the rearrangement steps when the dihedral angles are unfavorable[7] or to the required involvement of high-energy intermediates.

A viable synthetic alternative might be to elaborate a more readily available lower diamondoid hydrocarbon (e.g., adamantane, **1**) to a higher one (e.g., diamantane, **2**) by adding four new carbons and two new rings. We have developed such a general procedure which should permit the synthesis of unknown higher polyamantanes.[8]

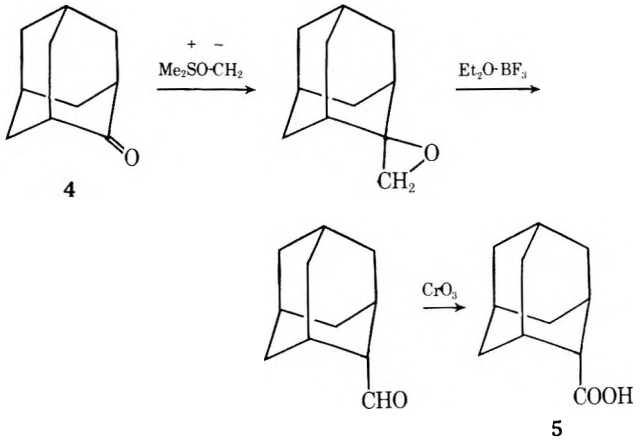
Synthetic Design and Results

Our objective was to convert adamantane (**1**) to diamantane (**2**) in a stepwise manner. The first part of the synthesis [ac-

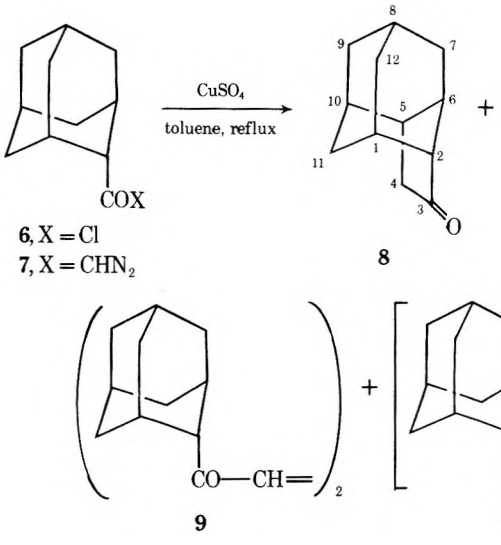
tually starting from adamantanone[9] (**4**)] was reported in preliminary form in connection with the study of the corresponding hydrocarbon, ethanoadamantane (tetracyclo-[6.3.1.$0^{2,6}$.$0^{5,10}$]dodecane).[10] We give here the pertinent details.

After development of a simple method which produced 2-adamantanecarboxylic acid (**5**) (Chart I),[11] the corresponding acid chloride (**6**) and diazo ketone (**7**) could be prepared easily on a reasonably large scale. However, the ketocarbene insertion[12] performed as described[12b] gave less than 10% yield of tetracyclo[6.3.1.$0^{2,6}$.$0^{5,10}$]dodecan-3-one (**8**). The main product (42%) was the enedione (**9**) formed by the dimerization of the ketocarbene (or more probably of its complex with the metal ions[13]). The yield of **8** was increased to over 55% (based on the acid chloride, **6**) by using a high-dilution apparatus designed for thermally unstable reactants.[14] At the same time the yield of **9** dropped to 1–2% (the balance appeared to consist of oligomers of ketene **10**).[15]

Chart I

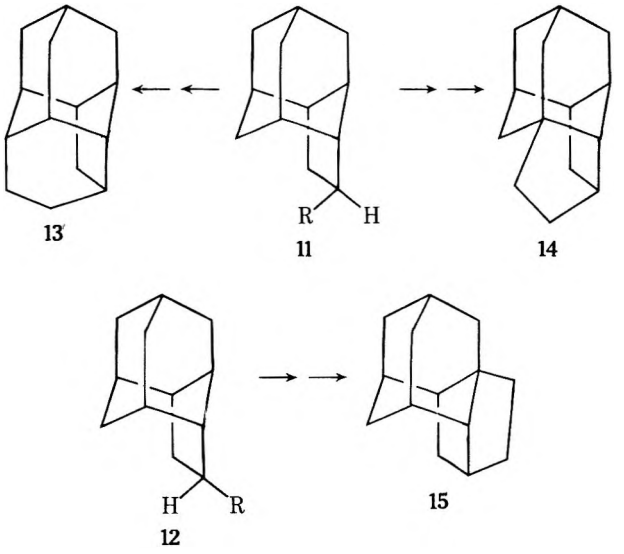


4 5



8 9 10

Continuing from the tetracyclic ketone **8**, the synthetic sequence needs to be repeated, the second bridge being anchored in the place of the carbonyl group. The product of such a synthesis must have a nondiamondoid structure, but we expected that an acid-catalyzed rearrangement would correct this defect easily and cleanly. The new carbon chain should be introduced in the endo (**11**) rather than in the exo configuration (**12**) (exo and endo isomers are defined as indicated in ref 28b). If the last two-carbon bridge was built from **11**, **13** or **14** should result, while the same operation starting with **12** would lead to **15**. Both **13** and **14** should be convertible to diamantane (**2**) by simpler rearrangement processes (fewer steps and less strained intermediates) than **15**. Structure **13** is especially appealing, since it represents a "protodiamantane",[16] just one Wagner–Meerwein shift away from **2**.



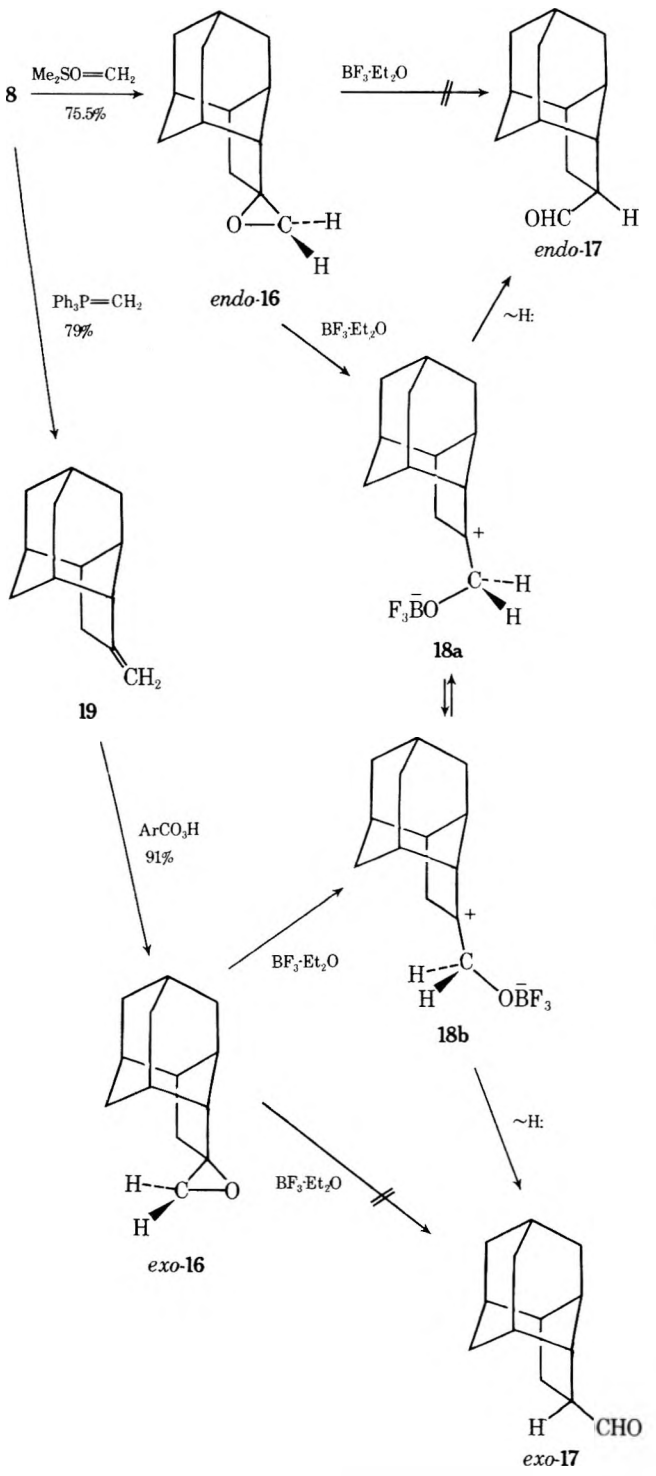
13 11 14 12 15

Examination of molecular models indicated the endo side of the two-carbon bridge in **8** to be shielded by a hydrogen atom at C-11. A reactant can be expected to attack this ketone from the exo side. Therefore, the synthesis had to achieve the introduction of an endo substituent by exo attack. We hoped at first to achieve this goal by a duplication of the sequence shown in Chart I. The reaction of **8** with dimethylsulfoxonium methylide[11,17] was expected to give predominantly the *endo*-3-(epoxymethylene)ethanoadamantane (*endo*-**16**) (Chart II). There are literature examples of the formation of carbonyl compounds from epoxides in which a 1,2 shift is concerted (or nearly so) with the ring opening.[18] If this were the case, isomerization of *endo*-**16** should lead to the aldehyde *endo*-**17**. The same result would be achieved via the carbocation **18** if the carbon–carbon bond rotation in the latter (**18a** ⇄ **18b**) is much slower than the hydride shift.

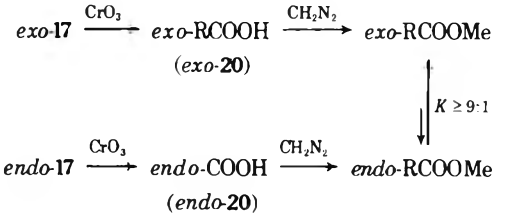
The first assumption (stereoselectivity of attack at C-3 of **8**) was tested by preparing the two stereoisomeric epoxides **16**. The epoxide obtained by the reaction of **8** with dimethylsulfoxonium methylide exhibited an AB pattern in the NMR spectrum ($\Delta\delta$ 0.07 ppm, J = 5 Hz) centered at 2.62 ppm, for the CH_2O group, and was assigned the endo configuration (*endo*-**16**, Chart II). On the other hand, 3-methyleneethanoadamantane (**19**), prepared[19] from **8** by a Wittig reaction, gave on Prilezhayev (peracid) oxidation[20] an epoxide which showed a sharp singlet at δ 2.68 ppm for the $-CH_2O-$ group in the NMR spectrum, and was assigned the exo configuration (*exo*-**16**, Chart II). No mutual contamination was detected in either case.

However, on treatment with boron trifluoride etherate[11,21] both epoxides gave aldehyde mixtures, exhibiting two aldehyde proton signals at δ 9.56 and 9.58. These were assigned to *exo*- and *endo*-**17**, rather than to a splitting due to H–H coupling (no coupling was seen, for instance, in the spectrum of 2-adamantanecarboxaldehyde[11]). The peaks had similar intensity, but the chemical shifts were too close to allow accurate integration. Therefore, the mixture was oxidized[11] and the resulting acids were esterified with diazomethane. The signals for the carbomethoxy groups (δ 3.60 and 3.63 ppm) were sharp, and integrated for 1.2 and 1.8 protons, respectively (2:3 molar ratio of isomers). The same ratio was found for the esters originating from *exo*-**16**, as for the esters originating from *endo*-**16**. (Since the aldehyde mixtures from *exo*- and *endo*-**16** also exhibited identical NMR spectra, it was concluded that

Chart II



no epimerization took place during chromic acid oxidation of the aldehydes.) The 2:3 ratio did not represent an equilibrium mixture, since boiling the esters with 0.08 M methanolic sodium methoxide for 90 h changed the peak intensity ratio to ca. 9:1 (it was not established if final equilibrium was reached). Therefore, the downfield methoxy peak was assigned to the endo (least stable) isomer.



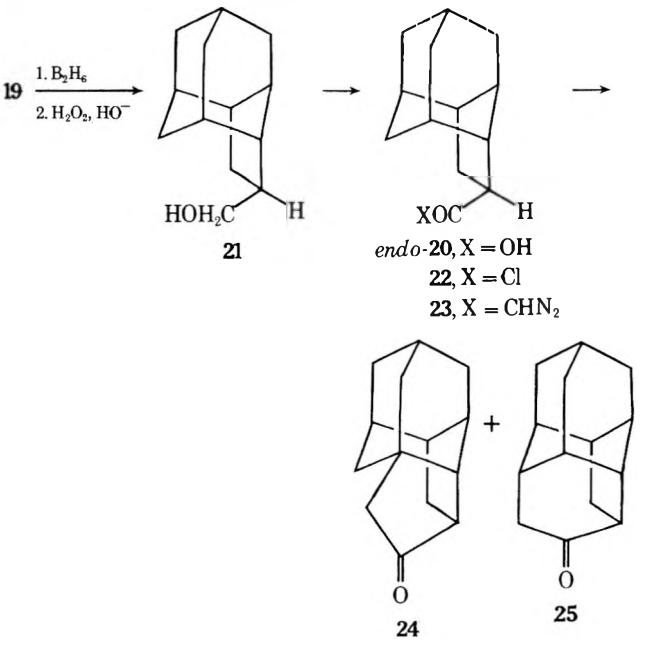
The epimerization by BF_3 of the aldehydes *after* their formation is unlikely, because identical mixtures (by NMR) were obtained from *endo*-**16** with an epoxide to BF_3 ratio of 1.35 or 1.75. Thus the 2:3 ratio, favoring the less stable isomer, should be kinetically controlled and reflect the ratio of hydride shift taking place in conformation **18a** and **18b**, respectively (Chart II).

The shielding of the endo side in the ethanoadamantane system was also indicated by the large difference in the rates of air oxidation of *exo*- and *endo*-**17**. On standing (neat or in carbon tetrachloride solution) only exo acid was formed and could be isolated in pure (NMR) form from the mixture. While this reaction could in principle be used to separate the two isomers, it was of no use to us, since for our synthetic plan the exo acid was merely lost material.

The above observation of stereoselective attack on the double bond of **19** was used in the synthesis of the endo alcohol **21** by hydroboration–oxidation.[22] Subsequent treatment of **21** with chromic acid gave virtually pure *endo*-**20**, in 60% yield based on olefin **19**. (The NMR spectrum of the methyl ester indicated that about 0.5% exo isomer might be present.)

Duplication of the reaction sequence used for the synthesis of **8**, starting from *endo*-**20**, led to a mixture of ketones **24** and **25** (separated from other products and from each other by column chromatography) in ca. 3:1 ratio. As in other cases,[12c,23] the five-membered ring ketone **24** ($\nu_{C=O}$ 1750 cm^{-1}), albeit more strained, was favored over the six-membered ring isomer **25** ($\nu_{C=O}$ 1715 cm^{-1}) (Chart III). The yield of the last

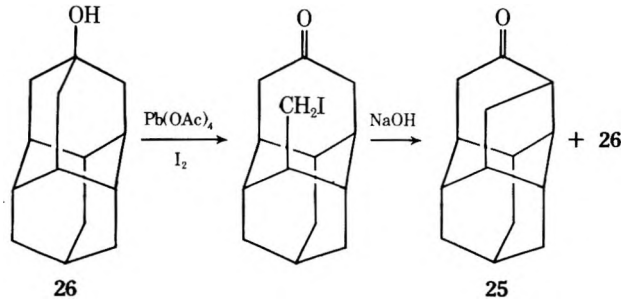
Chart III



step was unexpectedly low (20–25%, based on the acid chloride **22**), although competitive dimerization of the ketocarbene was minimized by use of the high-dilution technique.[14] (The ir spectrum of the crude reaction mixture exhibited a very weak peak at 1670 cm^{-1} which can be attributed to the enedione dimer, based on analogy with **9**.) Possibly, the larger part of the product consisted of oligomers of the ketene formed by Wolff rearrangement. Also, some four-membered ring insertion product[24] could not be ruled out, since a peak at a 1780 cm^{-1} was also seen in the ir spectrum of the reaction mixture. Variations of the catalyst[25] and the reaction conditions[25b] might possibly increase the yield of **24** and **25** significantly.

In order to secure these structural assignments, protodiamantanone **25** was synthesized independently. Treatment of 4-diamantanol (**26**)[26] with lead tetracetate and iodine, then

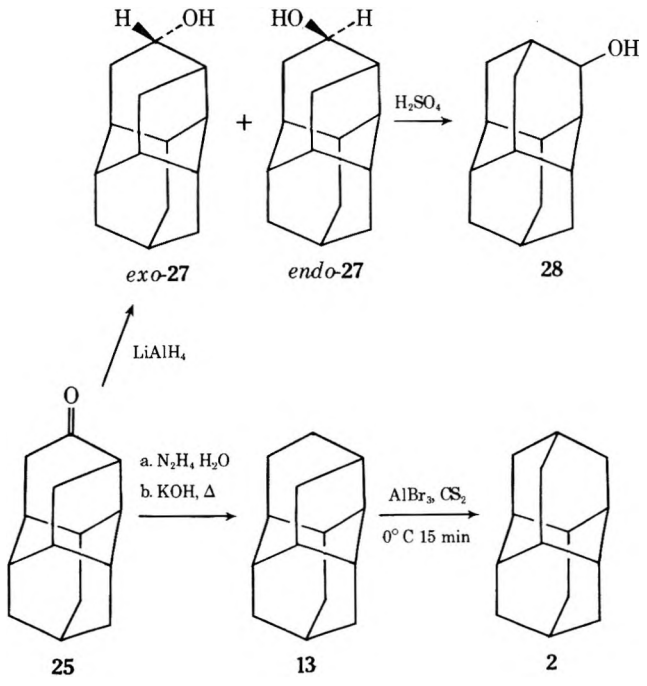
with base,[27] gave a ketone identical with the second product of ketocarbene insertion:



26 25

As expected, rearrangement of the protodiamantane to the diamantane skeleton was very easy.[28] Thus, lithium aluminum hydride reduction of **25** produced a mixture of two alcohols (*exo*- and *endo*-**27**), which were converted to 3-diamantanol (**28**)[26] by dilute sulfuric acid at room temperature with unequal speed, but in very high yield. On the other hand, Wolff–Kishner reduction of **25** led to protodiamantane (**13**), quantitatively converted to diamantane (**2**) by aluminum bromide at 0 °C (Chart IV).

Chart IV

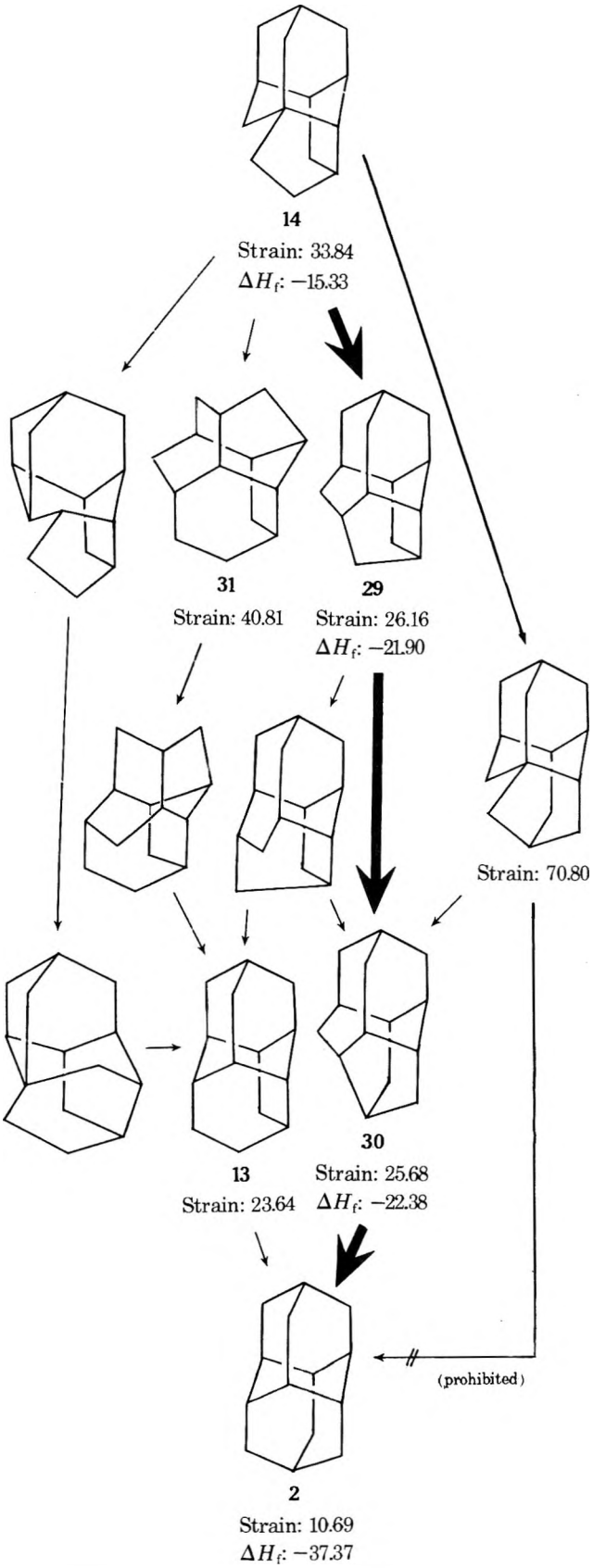


The conversion to diamantane of the hydrocarbon **14**, corresponding to the ketone **24**, might be expected to be less smooth. **14** contains a tetrasubstituted carbon[4b] and therefore is relatively strained. This might result in an increased tendency toward fragmentation and disproportionation[10] on treatment with isomerization catalysts. However, an examination of the portion of the $C_{14}H_{20}$ rearrangement graph[4b] which contains **14** and **2** has shown that there is at least one path (**14** → **29** → **30** → **2**) for which each step is exothermic and no shift is difficult on stereoelectronic grounds (Chart V).[29]

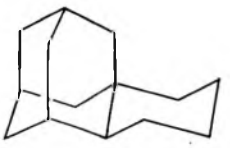
Indeed, treatment of **14** with aluminum bromide in boiling cyclohexane led to over 95% diamantane (**2**) (by GLC) with a mere trace of the disproportionation product, **32**.[19] The isolated yield was only 60%, but the small quantities used probably resulted in manipulation losses. The same reaction in carbon disulfide at reflux was slow and gave a less pure product, with a ratio **2**:**32** of about 19:1.

In conclusion, the successful completion of the synthesis of diamantane (**2**) from adamantane (**1**) has demonstrated the feasibility of the stepwise building of a diamondoid skeleton. The synthetic scheme used for **2** should be applicable to higher members of the series (e.g., **3**, or tetramantane). The regioselectivity in construction of a bridge (as shown by **13** + **14**

Chart V. Partial Representation of the $C_{14}H_{20}$ Rearrangement Graph[a]



[a] Strain energies and heats of formation[29] are given in kcal/mol.



32

vs. **15**) based on the stereoselectivity in introducing a substituent (*endo*-**20** vs. *exo*-**20**) has been used subsequently for the synthesis of the three isomeric ethanonoradamantanes.[30]

Experimental Section

General. Melting points (Mettler FPI apparatus) are uncorrected. Elemental analyses were performed by Hoffmann-La Roche, Inc. The NMR spectra were taken at 60 MHz (Varian A-60A instrument). Mass spectra were determined at 70 eV (AEI-MS9 instrument).

2-Adamantanecarboxylic Acid Chloride (6).[31] The acid[11] (24 g, 0.133 mol) was treated with thionyl chloride (50 ml) for 3 h at room temperature and for 7 h at 95–100 °C. Evaporation of the excess reactant and distillation of the residue gave **6** (25.6 g, 96% yield) as a colorless liquid, bp 99–100 °C (0.9 mm).

2-Adamantyl Diazomethyl Ketone (7). An alcohol-free solution of diazomethane in ether, prepared[32] from 119 g of Diazald (Aldrich), was dried on two portions of potassium hydroxide pellets (1 h each), then over sodium (2 h) at 0 °C. To this solution, vigorously stirred at −5 °C and protected from moisture, a solution of 9.18 g (46 mmol) of **6** in 100 ml of anhydrous ether (containing 5 drops of thionyl chloride) was added during 1 h. The solution was stirred for another 2 h at 0–3 °C, then left at room temperature overnight. Filtration through glass wool and evaporation of solvent left a shiny yellow solid which was used directly in the next step.

3-Ethanoadamantanone (8). Anhydrous copper sulfate (38 g, 238 mmol) was suspended in dry toluene (750 ml) in a 3-l. three-necked flask and refluxed for 12 h using a Dean-Stark trap to remove the last traces of water. The high dilution installation[14] was then mounted on the flask and a solution of **7** (from 9.18 g, 46 mmol, of acid chloride) in 1100 ml of toluene was added from a cooled (below 0 °C) dropping funnel into the mixing chamber[14] maintained at 0 °C. Drying tubes were placed at the top of the reflux condenser and dropping funnel. The rate of dropping was adjusted to maintain a dilution ratio of 10–15; addition took 16 h. The copper tubing[14] was cooled by an air stream; vigorous stirring was maintained at all times. The mixture was refluxed for another 8 h, then cooled and filtered. The filtrate was extracted once with water, twice with 10% sodium hydroxide solution (50 ml each), then twice with water. (On acidification of the basic washings very little acid precipitated, and this was not investigated further.) The dried (Na_2SO_4) organic solution was concentrated under vacuum and the part of the residue which was soluble both in methanol and in pentane was chromatographed on silica gel (600 g). Elution sequentially with hexane (700 ml), hexane–benzene mixtures (750 ml), and then with benzene produced a number of fractions with $\nu_{C=O}$ 1700–1810 cm^{-1}, then virtually pure **15** (mp 178–182 °C) (4.56 g, 56% yield). For analysis **8** was sublimed at 110 °C (12–14 mm) (mp 184–185 °C); NMR and ir spectra have been published.[10]

Anal. Calcd for $C_{12}H_{16}O$: C, 81.76; H, 9.15. Found: C, 81.70; H, 9.20.

1,2-Bis(2-adamantylcarbonyl)ethylene (9). The diazo ketone (**7**) prepared from 7.5 g (37.7 mmol) of acid chloride, dissolved in 250 ml of cyclohexane, was added to the stirred suspension of 4 g (26 mmol) of anhydrous copper sulfate in 500 ml of boiling cyclohexane during 5 h. After cooling, filtering, and washing as above, the material *in*soluble both in methanol and pentane was collected (2.83 g, 42% yield), mp 220.3–222.6 °C dec (from benzene). For analysis **9** was sublimed at 175–180 °C (0.15 mm): ir (KBr disk) 3024, 1670, 1640 cm^{-1} (vw); NMR ($CDCl_3$) δ 1.79 and 1.94 (two broad, overlapping signals, 24 H), 2.42 (broad, 4 H), 2.80 (broad, 2 H), and 7.22 ppm (s, 2 H); M *m/e* 352 (mass spectrometry).

Anal. Calcd for $C_{24}H_{32}O_2$: C, 81.76; H, 9.15. Found: C, 81.82; H, 9.36.

***endo*-3-(Epoxymethylene)ethanoadamantane (*endo*-16).** Treatment of **8** (1.34 g, 7.5 mmol) with dimethylsulfoxonium methylide[17] (from 9.55 mmol of trimethylsulfoxonium iodide and 9.25 mmol of 41% sodium hydride) as described[11] gave a mixture of *endo*-**16** and starting material (by ir). Repetition of the treatment for 1 h at room temperature and 4 h at 50–55 °C gave an almost complete conversion into epoxide (liquid, 1.075 g, 75% yield): ir 3030 cm^{-1} (neat); NMR (CCl_4) δ 0.71–2.38 (complex, 16 H) and 2.62 ppm (2 H, AB system, Δδ 0.07 ppm, J = 5 Hz).

***exo*-3-(Epoxymethylene)ethanoadamantane (*exo*-16).** To the alkene (**19**)[19] (0.8 g, 4.6 mmol) dissolved in methylene chloride (5 ml), *m*-chloroperbenzoic acid (1.15 g, 85% peracid, 5.65 mmol) in methylene chloride (12 ml) was added over a period of 30 min at 15 °C, with stirring. The mixture was stirred for 5 more h at 25 °C and extracted twice with aqueous sodium sulfite, then once with sodium carbonate solution. After drying ($MgSO_4$), evaporation of the solvent left 0.8 g (91%) of *exo*-**16**, as a solid: ir (CS_2) 3022 cm^{-1}, NMR (CCl_4) 1.05–2.35 (complex, 16 H) and 2.68 ppm (2 H, s).

***exo*- and *endo*-Ethanoadamantane-3-carboxaldehyde (17).** Treatment of either *exo*- or *endo*-**16** with 0.56, 0.74 (for *endo*-**16**), or 1.01 equiv (for *exo*-**16**) of boron trifluoride etherate as described[11] led to the same mixture of aldehydes (liquid): ir (neat) 1722 cm^{-1}; NMR (CCl_4) 9.56 and 9.58 ppm (CHO), and an envelope between 1.1 and 3.0 ppm, with a strong band centered at 1.80 ppm. The ir spectrum indicated the presence of some carboxylic acid, by the bands at 3600–2500 and 1696 cm^{-1} (weak, growing in time), which disappeared after washing with base, then reappeared on longer standing.

***exo*-Ethanoadamantane-3-carboxylic Acid (*exo*-20).** The aldehyde mixture (*exo*- + *endo*-**17**) prepared from 1.07 g of *endo*-**16** was left for 24 h at room temperature, then diluted with ether and extracted with aqueous sodium carbonate. Acidification of the aqueous layer, extraction with chloroform, drying (Na_2SO_4), and evaporation of solvent gave 0.199 g (17%) of *exo*-**20**: mp 119.3–121.0 °C (from aqueous methanol); NMR (CCl_4) complex absorption between 1.25 and 2.87 ppm (17 H) with a strong peak at 1.76 ppm; also 11.9 ppm (1 H, COOH).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.72; H, 8.90.

***exo*- and *endo*-Ethanoadamantane-3-carboxylic Acids (*exo*- and *endo*-20), and Methyl Esters.** Oxidation of the mixture of *exo*- and *endo*-**17**, obtained from *exo*- or *endo*-**16**, with chromic acid as described[11] gave a mixture of acids (melting over a range of temperature) in 65–75% yield based on the epoxide. The NMR spectrum of the product can be accounted for as a mixture of *exo*- and *endo*-**20**. Treatment with an excess of diazomethane in ether solution gave the methyl esters in quantitative yield. (In the NMR spectrum the carboxyl proton was replaced by two carbomethoxy signals at δ 3.60 and 3.63, integrating for ca. 1.2 H and 1.8 H, respectively.)

Methyl Ester of *exo*-Ethanoadamantane-3-carboxylic Acid (*exo*-20 Methyl Ester) by Epimerization. The mixture of esters prepared above (0.12 g) was boiled under reflux with a solution of sodium methoxide (from 0.03 g of sodium and 15 ml of anhydrous methanol) for 90 h. Neutralization with acetic acid followed by evaporation of solvent under vacuum with addition of benzene to ensure the complete removal of methanol gave a slightly yellow liquid: NMR δ 3.60 (ca. 2.85 H), 3.63 ppm (ca. 0.15 H). The remainder of the spectrum was almost identical with that of *exo*-**20** obtained from the air oxidation of the aldehyde.

An attempt to epimerize the acids directly by heating with 7.5 N aqueous potassium hydroxide[33] (5 ml for 0.103 g of acid) on an oil bath of 130 °C for 69 h was unsuccessful (no significant change of the NMR spectrum of the acid was noticed).

***endo*-3-(Hydroxymethyl)ethanoadamantane (21).** To a solution of 6.1 g (35 mmol) of **19** (obtained from **8** in 79% yield[19]) in dry tetrahydrofuran (55 ml), water cooled and magnetically stirred under nitrogen, 39 ml of a 1 M diborane solution in THF was injected through a rubber septum during 25 min. The mixture was stirred for another 3.5 h at room temperature and for 0.5 h at 35 °C. Aqueous sodium hydroxide (3 N, 9 ml) was added slowly with water cooling, followed by 30% hydrogen peroxide (18 ml). The mixture was warmed to 50 °C and stirred for 3 h at this temperature, then at room temperature overnight. The THF was distilled off, solid sodium chloride was added, and the water solution was extracted five times with ether. Drying (Na_2SO_4) and evaporation of solvent gave an oil which solidified several days later: NMR ($CDCl_3$) δ 3.86 (2 H, d, J = 7 Hz, CH_2O), 2.60 (1 H, OH), 1.0–2.3 ppm (complex, 16 H). The material was used directly in the next step.

***endo*-Ethanoadamantanone-3-carboxylic Acid (*endo*-20).** To the crude alcohol (**21**) (prepared from 35 mmol of **19**) dissolved in acetone (65 ml), Jones reagent[11] (55 ml) was added during 1 h with stirring. Intermittent ice cooling maintained the temperature between 18 and 21 °C. The mixture was stirred for another 4.5 h at room temperature, rinsing the walls of the reaction flask with acetone (55 ml) occasionally; the mixture was then poured onto 300 ml of ice–water, and thoroughly extracted with chloroform. The residue from the chloroform solution was treated with 500 ml of 5% aqueous sodium hydroxide (in two portions) and the solid washed twice with water (100 ml each). The combined water solution was acidified (H_2SO_4), satu-

rated with KSO_4H, and extracted with chloroform (eight times). Evaporation of the dried (Na_2SO_4) chloroform solution gave 4.4 g of *endo*-**20** (60% yield based on **19**): mp 148.8–151.0 °C (from aqueous methanol); NMR (CCl_4) complex absorption between δ 1.1 and 3.3 ppm (17 H) with sharp peaks at 1.85 (very strong) and 2.07, and a much weaker one at 1.77 ppm; also 11.43 ppm (1 H, COOH).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H. 8.80. Found: C, 75.70; H, 8.76.

The methyl ester, obtained with diazomethane, exhibited a carbomethoxy peak at δ 3.63 ppm with a mere trace (perhaps 0.5%) of the δ 3.60 ppm isomer (*exo*-**20**).

***endo*-3-Ethanoadamantanecarboxylic acid chloride (22)** was prepared as described for **6**, from 4.3 g (20.86 mmol) of *endo*-**20**, yield 90% (4.21 g), bp 139–140 °C (0.9 mm).

Pentacyclo[5.5.1.1^{1,5}.0^{3,8}.0^{10,13}]tetradecan-11-one (24) and Pentacyclo[8.3.1.0^{2,8}.0^{4,13}.0^{7,12}]tetradecan-5-one (25). The acid chloride **22** (4.18 g, 18.7 mmol) was treated with diazomethane, as shown for **7**. The crude diazo ketone (**23**, yellow solid) was dissolved in 500 ml of toluene and added to a predried suspension of 21 g (131 mmol) of $CuSO_4$ in 350 ml of toluene, during 13 h, using the high-dilution apparatus.[14] After refluxing another 10 h, the reaction mixture was worked up as described for **8**; very little carboxylic acid and 0.4 g (ca. 10%) of material insoluble both in pentane and methanol were obtained as by-products. Column chromatography (250 g of silica gel, with benzene as eluent) of the fraction soluble in both pentane and methanol gave a sizable amount of (mostly oily) material, $\nu_{C=O}$ 1700–1810 cm^{-1}. Then, 0.585 g (15.5%) of **24** and 0.169 g (4.5%) of **25** were eluted in this order. (In another run, starting with a mixture of *exo*- and *endo*-**20** in a ratio of 2:3, a combined yield of 15% **24** and **25** was obtained, i.e., 25% based on the endo isomer.)

Pentacyclo[5.5.1.1^{1,5}.0^{3,8}.0^{10,13}]tetradecan-11-one (24): mp 118–121 °C (softening around 105 °C); ir (CCl_4) 2890, 1750 (vs), 1490, 1463, 1452, 1405, 1220, 1190, 1160, 1103, 1078, 1048 cm^{-1}; NMR (CCl_4) complex absorption between 1.10 and 2.55 ppm, with a strong peak at 1.84 ppm.

Anal. Calcd for $C_{14}H_{18}O$: M, 202.1358. Found: M, 202.1357 (by high-resolution mass spectrometry).

Pentacyclo[8.3.1.0^{2,8}.0^{4,13}.0^{7,12}]tetradecan-5-one (Protodiamantanone, 25): mp 113–116 °C (softening around 110 °C); ir (CCl_4) 2890, 1720 (vs), 1460, 1436, 1412, 1228 cm^{-1} (all weak); NMR (CCl_4) 1.50–2.08 (broad, 15 H) with a peak at 1.87 ppm, and 2.12–2.62 (broad, 3 H), with peaks at 2.22 and 2.53 ppm.

Anal. Calcd for $C_{14}H_{18}O$: M, 202.1358. Found: M, 202.1353.

Synthesis of Protodiamantanone (25) from 4-Diamantanol (26).[27] A mixture of 2.7 g (13.2 mmol) of **26** and 5.75 g (13.2 mmol) of lead tetraacetate in 100 ml of dry benzene, containing 3.5 g (13.2 mmol) of iodine, was heated to reflux for 2 h. The cooled mixture was filtered and the filter paper washed with 50 ml of ether. The combined ether solution was washed with two portions, 50 ml each, of 5% sodium bisulfite, then twice with 5% $NaCO_3H$, and finally with water. (GLC of the reaction mixture on a 3 m, 10% Carbowax 20M column at 190 °C indicated a 22% conversion of **26**.)

The entire mixture was refluxed with ethanol (50 ml) containing NaOH (1 g) for 3 h. The mixture was diluted with water and extracted twice with ether (100 ml each), then dried ($MgSO_4$) and concentrated. The residue, dissolved in cyclohexane (10 ml), was chromatographed on a neutral alumina (activity I) column, eluting with a 1:1 cyclohexane–ethyl acetate mixture. **25** was eluted first (0.51 g, 21% yield) and recrystallized from hexane to yield 0.48 g (19%, crude mp ca. 91 °C). A further purification by preparative GLC gave a material exhibiting identical spectral properties (ir, NMR) and GLC retention time with the product obtained from the diazo ketone **23**.

Reduction of 25 with Lithium Aluminum Hydride. To 400 mg (2 mmol) of **25** in 10 ml of ether, lithium aluminum hydride (0.2 g) was added and the mixture was refluxed for 2 h. The mixture was then hydrolyzed by the addition of water (10 ml) and 2 drops of HCl. The ether layer was extracted with 3 × 20 ml of water, dried ($MgSO_4$), and concentrated, yielding 380 mg (95%) of a mixture of endo and exo protodiamantanols (*endo*- and *exo*-**27**) in the ratio of 41:59 (mp 121–125 °C). A sample of this mixture isolated by GLC had the following spectral properties: ir (CCl_4) 3600, 3400, 2880, 1465, 1445, 1250 cm^{-1}; NMR (CCl_4) δ 4.0 (b, 0.4 H), 3.15 (b, 0.6 H), 2.1 (b, 1 H), 1.8 (m, 17 H), 1.3 (s, 1 H), 0.9 ppm (m, 1 H); mass spectrum *m/e* 204, 187, 186.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.36; H, 9.87. Found: C, 82.12; H, 10.21.

Rearrangement of the Mixture of Protodiamantanols (27) with Sulfuric Acid. A mixture of 200 mg (0.00096 mol) of the protodiamantanols and 5% H_2SO_4 in 50% water–acetone solution was stirred for 2 h at room temperature. Analysis by GLC of the reaction products at 0.5-h intervals indicated that the initial products were disappearing and that diamantan-3-ol[26] was being formed. At the end of the reaction the mixture was diluted with water (10 ml) and the product extracted with ether (30 ml). The ether layer was washed with water (30 ml) and 5% Na_2CO_3 (20 ml), dried, and concentrated, yielding 190 mg of a crude product, which, when purified by GLC, had the same melting point and ir spectrum as diamantan-3-ol. (A second component of this mixture corresponded in retention time to the 59% component in the original protodiamantanol mixture and presumably[28] was the endo isomer.)

Preparation of Protodiamantane (13).[34] A solution of 180 mg (0.00089 mol) of **25** in 0.25 ml of 85% hydrazine hydrate, 2 drops of acetic acid, and 4 ml of glycerine was heated to between 80 and 90 °C for 24 h under an atmosphere of dry nitrogen. At the end of this period, 2 g of dry potassium hydroxide was added to the mixture and the solution was heated to 190 °C for 5 h under nitrogen. During this period, the protodiamantane sublimed on the Claisen head. The collected product was resublimed to give 140 mg (87%), mp 136–136.5 °C.

Anal. Calcd for $C_{18}H_{20}$: C, 89.29; H, 10.17. Found: C, 89.60; H, 10.36.

Rearrangement of Protodiamantane (13) with Aluminum Bromide. A solution containing 100 mg (0.53 mmol) of protodiamantane in 15 ml of carbon disulfide was stirred at 0 °C with 10 mg of freshly sublimed aluminum bromide. The rearrangement to diamantane was monitored by GLC (Carbowax 20M, 1.2 m, 130 °C). The formation of diamantane was complete within 15 min. No intermediates were revealed by GLC nor were any other final products observed.

Pentacyclo[5.5.1.1^{1,5}.0^{3,8}.0^{10,13}]tetradecane (14). Ketone **24** (0.4625 g, 2.29 mmol) dissolved in 30 ml of triethylene glycol containing 25 drops of acetic acid was treated with 3 ml of 97% hydrazine hydrate at 84–86 °C for 48 h under nitrogen. Solid potassium hydroxide (3.5 g) was added, the solution was heated to 195 °C in 1 h, then to 200 °C in another 0.5 h, and stirred at 200–205 °C for 6 h.

After cooling, the product was extracted with pentane; the pentane solution when dried (Na_2SO_4) and concentrated gave 0.43 g of solid, which was chromatographed on 26 g of silica gel (eluent pentane). **14** was obtained as a transparent solid (0.3355 g, 78%): mp 101–104 °C (from ethanol) after becoming a glassy mass at ca. 70 °C; NMR (CS_2) broad absorption from 1.00 to 2.22 ppm, with peaks at 1.17, 1.24, 1.71, and 1.90 ppm.

Anal. Calcd for $C_{14}H_{20}$: M, 188.1565. Found: M, 188.1576.

The chromatographed product was 95% pure; ethanoadamantane (ca. 5%) was a possible impurity.

Rearrangement of 14 with Aluminum Bromide. A solution of 0.048 g (0.25 mmol) of **14** in cyclohexane (0.5 ml) was stirred with 0.1995 g of aluminum bromide at 65 °C for 4 h and at 85 °C for 8 h, then left overnight at room temperature. The reaction mixture was extracted several times with boiling cyclohexane and the extract was neutralized (KOH). GLC of the solution showed complete conversion of **14** into **2**, with six other peaks, amounting to a fraction of a percent each. (Less than 1% of **32** was present.)

Evaporation of solvent gave 0.029 g of material: mp 234–237 °C (after pressing on a filter paper); NMR 1.75 ppm (s); MS *m/e* 189 (M + 1, 15.2), 188 (M, 100), 187 (16.0), 159 (6.4), 131 (7.5), 91 (10.2), 79 (7.4). The NMR and mass spectra verified the structure of the product **2**.[4a]

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Registry No.—**2**, 2292-79-7; **6**, 40079-92-3; **7**, 53803-41-1; **8**, 41171-93-1; **9**, 60526-50-3; **13**, 60526-51-4; **14**, 60526-52-5; *endo*-**16**, 60526-53-6; *exo*-**16**, 60562-35-8; *exo*-**17**, 60526-54-7; *endo*-**17**, 60562-36-9; **19**, 41171-89-5; *exo*-**20**, 60526-55-8; *exo*-**20** Me ester, 60526-56-9; *endo*-**20**, 60562-37-0; *endo*-**20** Me ester, 60562-38-1; *endo*-**21**, 60526-57-0; *endo*-**22**, 60526-58-1; *endo*-**23**, 60526-59-2; **24**, 60526-60-5; **25**, 60526-61-6; **26**, 30651-03-7; *exo*-**27**, 60526-62-7; *endo*-**27**, 60562-39-2; diazomethane, 334-88-3; dimethylsulfoxonium methylide, 5367-24-8; lithium aluminum hydride, 16853-85-3.

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Photochemistry of 17β-Hydroxyestra-5(10),9(11)-dien-3-one. Synthesis of AB Spiro Steroids[1,2]

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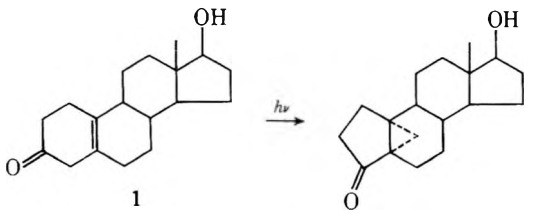
17β-Hydroxyestra-5(10),9(11)-dien-3-one (**3**) was photoisomerized via a 1,3 acyl shift to (10*S*)-17β-hydroxy-3,10-cyclo-3,4-seco-10α-estra-4,9(11)-dien-1-one (**4a**) whose structure was proven by x-ray analysis. Irradiation of **4a** caused photodecarbonylation to 2,10-cyclo-2,3-seco-*A*-norestra-3(5),9(11)-dien-17β-ol (**5a**) plus photoisomerization back to **3**. Acetone photosensitization of **3** did not yield any isolable photoproducts.

Several years ago the unusual spectroscopic properties of β,γ-unsaturated cyclic ketones caused us to investigate their photochemistry.[3-7] It was found that upon direct irradiation 17β-hydroxyestra-5(10)-en-3-one (**1**) afforded 17β-hydroxy-5α,19-cyclo-*A*-nor-10β-androstan-3-one (**2**) via a 1,2 acyl

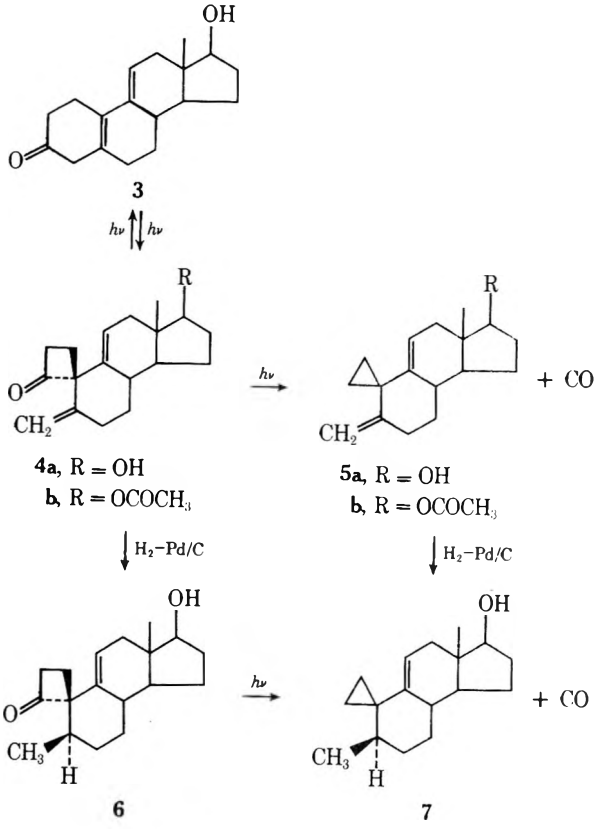


1 2

shift.[5,6] Since direct irradiation of cyclic β,γ-unsaturated ketones usually afforded products resulting from 1,3 acyl shifts, rather than 1,2,[8] it was thought that the "semiplanar" A ring conformation[9] led to this unusual reaction pathway. To test this hypothesis 17β-hydroxyestra-5(10),9(11)-dien-3-one (**3**) was irradiated since **3** contains a similar "semiplanar" A-ring conformation[9] which is now part of a β,γ,δ,ε dienone chromophore.

Results and Discussion

Direct irradiation of **3** in benzene with a medium pressure mercury arc (Hanovia 450W) through a Pyrex filter gave two products plus recovered **3** (53%) which were separated by chromatography on alumina. The first photoproduct (**4a** 36%) was acetylated to aid in crystallization and yielded 17β-acetoxy-3,10-cyclo-3,4-seco-10α-estra-4,9(11)-dien-1-one (**4b**) on the basis of the following data. Elemental analysis of the acetate **4b** indicated that the alcohol **4a**, from which it was derived, was isomeric with **3**. The infrared spectrum of **4a** showed a hydroxyl band at 3610 cm^{-1}, and **4a** showed an ester carbonyl at 1725 cm^{-1}. Both spectra contained absorption



bands at 1770 cm^{-1} characteristic of a cyclobutanone. The NMR spectra of **4a** and **4b** both showed a multiplet centered at δ 5.40 and 5.47, respectively, due to the olefinic C-11 hydrogens, and two singlets at δ 4.78 and 4.64 each integrating for one proton, due to the exocyclic methylene hydrogens on C-4. It is interesting to note that the exocyclic methylene hydrogens in **4b** have different chemical shifts and are moved upfield from their absorption in photoproduct **5b.** This may be explained by the stereochemistry of the spiro system in **4b.** The exocyclic hydrogens in **4b** are positioned in the shielding cone of the cyclobutanone carbonyl as one was much closer than the other. This effect was also noticed in the NMR spectrum of 6-methylenespiro[4,5]decan-1-one.[7]

The second product, formed in 7% yield, was also acetylated and afforded 2,10-cyclo-2,3-seco-*A*-norestra-3(5),9(11)-dien-17β-acetate (**5b**). Elemental analysis of **5b** showed that carbon monoxide had been lost from **4b.** Furthermore, the cyclobutanone carbonyl had disappeared from the infrared spectrum of **4b** leaving only that of the acetate at 1720 cm^{-1}. The absence of an ultraviolet absorption maximum above 220 nm further supported the loss of the carbonyl group. The NMR spectrum of **5b** showed a multiplet at δ 5.44 due to the olefinic C-11 hydrogen, a multiplet centered at δ 4.98 due to the C-17 hydrogen, and a two-hydrogen singlet at δ 4.85 due to the exocyclic methylene hydrogens on C-4. A broad multiplet from δ 0.72 to 0.22 integrating for four hydrogens was assigned to the cyclopropyl group that would result when carbon monoxide was lost from the cyclobutanone. The infrared spectrum of **5b** showed absorption at 3060, 1645, and 890 cm^{-1} characteristic of olefinic and cyclopropyl hydrogens. Irradiation of the photoproduct **4a** also gave a mixture of **3, 4a,** and **5a** in which **3** was again the major product. This indicates that **3** and **4a** are in a photochemical equilibrium. The photoreversibility of this reaction and the spectral data of the photoproduct establish its structure as the spirocyclobutanone **4a.** The structure of the second photoproduct is the cyclopropyl compound **5a** due to its spectral properties and mode formation from **4a.** Furthermore, the photoisomerization of **3** to **4a** followed by photodecarbonylation to **5a** has recently

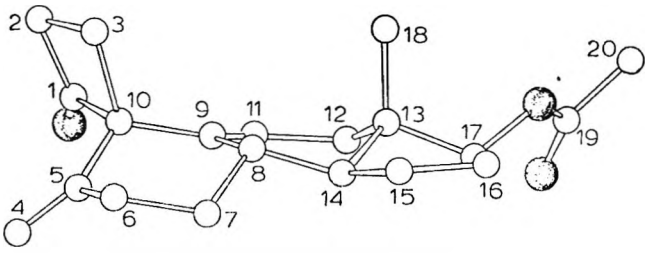


Figure 1. X-ray analysis structure of photoproduct **4b.**

been reported by other workers.[10] In a closely related study Nakanishi et al. has observed a photochemically induced 1,3 acyl shift to yield a cyclobutanone followed by photodecarbonylation to a cyclopropyl compound.[11]

To determine whether the carbonyl group in **4** was α or β, an x-ray analysis was done on **4b.** The results of this analysis[12] (see Figure 1) prove that the steroid **4** has the 10*S* configuration.

Inspection of a Dreiding model of **4** showed the spatial arrangements of the carbonyl and olefinic groups to be such that the optical rotatory dispersion rule for β,γ-unsaturated ketones cannot be applied in this case.[3c,13] Furthermore, the ORD curve of **6** $[\Phi]_{330}$ −11, $[\Phi]$ +68, shows an extremely weak negative Cotton effect similar to those previous observed for this configuration.[3c] Catalytic reduction of **4a** should proceed from the less hindered side. In the above case this is the α side (see Figure 1) and yields the reduction product **6.** Photodecarbonylation of **6** yielded **7** prepared by catalytic reduction of **5a.**

The photoisomerization of **3** to **4** proceeds via a singlet or short-lived triplet state, since the reaction could not be quenched with 2,5-dimethylhexa-2,4-diene or 1,3-cyclohexadiene. Photosensitization experiments with acetone or acetophenone led to the disappearance of starting material, but no triplet product could be isolated. Similar results have been observed for other β,γ-unsaturated ketones.[14]

The conformation of the chromophore in **3** is planar, the same as that for 17β-hydroxy-5(10)-estren-3-one (**1**), based on the results of hydride reduction products,[15] strain-energy minimization calculations,[16] and x-ray analyses.[9] Therefore, if conformation was the controlling factor in their photoreactivity, they should both exhibit the same photochemistry.[8] However, they do not and other factors must be involved.[8] Photolysis of **3** proceeds from either an excited singlet state or a short-lived triplet state via a 1,3 acyl shift to afford **4a.** On the other hand, photolysis of **1** proceeds from the excited triplet state via a 1,2 acyl shift (oxadi-π-methane rearrangement) to afford the cyclopropyl ketone **2.**[7] These results support the previously reported generalizations concerning the photochemistry of β,γ-unsaturated ketones,[8] which have been rationalized by spin density distribution arguments[17] and molecular orbital calculations.[18]

Photolysis of **3** affords a convenient entry into AB spiro steroids which have recently attracted attention for their androgenic activity.[19] The presence or absence of alkyl groups on C-10 has greatly affected their physiological properties,[20] and this synthesis of a spiro structure at C-10 while still retaining functionality at C-5 and C-11 should offer a ready access to a number of very interesting spiro steroids.

Experimental Section

Ir spectra were recorded on Perkin-Elmer 137 and 225 spectrometers. Uv absorption spectra were measured in methanol solution with a Cary 14 spectrophotometer. NMR spectra were recorded at 100 MHz on a Varian XL-100 spectrometer. Chemical shifts are reported in δ (ppm) from the internal standard Me_4Si. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. VPC analyses were performed on an F and M Model 700

gas chromatograph using a 3-ft, 3% OV-17 on 100–120 mesh Gas-Chrom Q column at 150 °C. Elemental analyses were performed by Micro-Analysis Inc., Wilmington, Del.

17β-Hydroxyestra-5(10),9(11)-dien-3-one (3). 17β-Hydroxy-5(10)-estren-3-one[21] (880 mg) was brominated and dehydrobrominated according to the method of Levine and Eudy[14] previously used for the 17β-acetate. The intermediate 17β-hydroxyestra-4,9-dien-3-one was crystallized from petroleum ether–acetone (1:1) as chunky crystals: mp 176 °C; NMR ($CDCl_3$) δ 5.80 (s, 1, H-4) and 0.72 (s, 3, H-18). 3,3-Dimethoxyestra-5(10),9(11)-dien-17β-ol was isolated as a gum: uv max (EtOH) 238.5 nm (ε 21 800); ir ($CHCl_3$) 3620 cm^{-1} and no carbonyl absorption; NMR ($CDCl_3$) δ 5.51 (m, 1, H-11), 3.18 (s, 6, OCH_3), and 1.74 (s, 3, H-18).

To a solution of the entire ketal (800 mg) in 24 ml of acetone was added with stirring at room temperature 440 mg of malonic acid in 3.5 ml of H_2O and 26 ml of acetone and the solution was let stir for 3 h. The reaction mixture was diluted with 60 ml of benzene and 20 ml of 10% $NaHCO_3$, and the organic layer was separated and washed twice with 50 ml of $NaHCO_3$, dried (Na_2CO_3), and freed of solvent under reduced pressure leaving 500 mg of amorphous products.[22a,b] Crystallization from acetone–hexane gave 17β-hydroxyestra-5(10),9(11)-dien-3-one (**3**) as chunky crystals: mp 119–120 °C; uv max (EtOH) 240 nm (ε 21 000), 297 (160); ir ($CHCl_3$) 3620 (OH), 1720 cm^{-1} (3-one); NMR ($CDCl_3$) δ 5.51 (m, 1, H-11) as expected for 17β-hydroxyestra-5(10),9(11)-dien-3-one (**3**).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.89. Found: C, 78.98; H, 8.80.

Photolysis of 17β-Hydroxyestra-5(10),9(11)-dien-3-one (3). A solution of **3** (250 mg) in benzene (250 ml) stirred with a stream of N_2 was irradiated with a 450-W Hanovia lamp through a Pyrex filter. The reaction, which reached an equilibrium in about 4 h, was monitored by VPC. Evaporation of the solvent in vacuo yielded a gum (280 mg). A total of 1.0 g of this crude gum from combined runs was chromatographed over alumina (activity III, 85 g). Initial elution with 200 ml of petroleum ether–acetone (92:8) afforded 70 mg of 2,10-cyclo-2,3-seco-*A*-norestra-3(5),9(11)-dien-17β-ol (**5a**) in 7% yield, which resisted crystallization: ir ($CHCl_3$) 3610 (OH), 3060 cm^{-1} and no carbonyl absorption; NMR (C_6D_6) δ 5.54 (m, 1, H-11), 4.69 (s, 1, H-3), 4.62 (s, 1, H-3), and 0.65–0.41 (m, 4, cyclopropyl). Acetylation of the alcohol **5a** gave 2,10-cyclo-2,3-seco-*A*-norestra-3(5),9(11)-diene 17-acetate (**5b**) as needles: mp 129 °C; ir (KBr) 3060, 1645, 1720 (acetate), 890 cm^{-1} (exo methylene); NMR (C_6D_6) δ 5.44 (m, 1, H-11), 4.98 (m, 1, H-17), 4.85 (s, 2, H-3), 0.95 (s, 3, H-18), and 0.72–0.22 (m, 4, cyclopropyl).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.41; H, 9.49. Found: C, 78.98; H, 9.53.

Further elution with 350 ml of petroleum ether–acetone (88:12) yielded 360 mg (36%) of **4a** as an amorphous product, which resisted crystallization uv (MeOH) 305 nm (ε 65); ir ($CHCl_3$) 3610 (OH), 1770 (cyclobutanone), and 900 cm^{-1}; NMR ($CDCl_3$) δ 5.52 (m, 1, H-11), 4.68 (s, 1, H-4), 4.61 (s, 1, H-4) exocyclic methylene. Acetylation of the alcohol **4a** afforded (10*S*)-17β-acetoxy-3,10-cyclo-3,4-seco-10α-estra-4,9(11)-dien-1-one (**4b**) as long needles: mp 124–125 °C; uv 305 nm (ε 65); ir (KBr) 1770 (cyclobutanone), 1725 cm^{-1} (acetate); NMR ($CDCl_3$) δ 5.47 (m, 1, H-11), 4.78 (s, 1, H-4), 4.64 (s, 1, H-4), 2.95 (s, 2, H-2, J = 8 Hz), and 0.78 (s, 3, H-18).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.37; H, 8.23. Found: C, 76.66; H, 7.93.

Further elution with the same solvent yielded starting material, **3a** (530 mg, 53%), which was very unstable due to autoxidation.

Irradiation[23] for 4 h of the photoproduct **4a** also gave a mixture of **3**, **4a**, and **5a** in which **4a** was again the major product.

Sensitization and Quenching Experiments. Samples of **3** (10 mg) in benzene (10 ml) with sufficient benzophenone to capture >95% of the incident light were irradiated in sealed, degassed test tubes. VPC analysis indicated that **3** disappeared but no photoproducts were observed. Similar results were obtained using acetone as the solvent. When 2,5-dimethylhexa-2,4-diene and 1,4-cyclohexadiene were used in 0.01, 0.1, and 2.0 M concentrations as quenchers, no quenching of the formation of **4a** and **5a** was observed, according to VPC analyses of the solutions.

(10*S*)-17β-Hydroxy-3,10-cyclo-3,4-seco-10α-estra-9(11)-en-1-one (6). To a solution of cyclobutanone **4a** (50 mg) in benzene (10 ml), 5% platinum on Darco G-60 catalyst (50 mg) was added, and the mixture hydrogenated at room temperature in a Parr series 3910 low-pressure hydrogeation apparatus at a starting pressure of 60 lb. One equivalent of hydrogen was consumed after 2 h. After removal of catalyst by filtration, the filtrate was evaporated under reduced pressure and afforded 46 mg (92% yield) of **6**: mp 145–146 °C; uv (CH_3OH) 290 nm (ε 98); ir 1770 cm^{-1} (cyclobutanone); NMR (C_6H_6) δ 5.80 (m, 1, H-11), 4.91 (m, 1, H-17), 2.78 (t, 2, H-2, J = 8 Hz), 1.27 (d, 3, H-4, J = 7 Hz), 0.93 (s, 3, H-18).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.55. Found: C, 78.74; H, 9.59.

2,10-Cyclo-2,3-seco-*A*-norestra-9(11)-en-17β-ol (7). A solution of **5a** (20 mg) in benzene was hydrogenated and worked up as described above. The solvent was evaporated at a reduced pressure, and afforded 18 mg (90% yield) of **7** as colorless needles: mp 135–136 °C; ir (KBr) 3260, 3060 cm^{-1} and no carbonyl absorption; NMR (C_6D_6) δ 5.45 (m, 1, H-11), 3.69 (m, 1, H-17), 1.25 (d, 3, H-3, J = 7 Hz), 0.89 (s, 3, H-18), 0.75–0.40 (m, 4, cyclopropyl).

Anal. Calcd for $C_{17}H_{26}O$: C, 82.61; H, 10.63. Found: C, 82.79; H, 10.61.

Photolysis of (10*S*)-17β-Hydroxy-3,10-cyclo-3,4-seco-10-estra-9(11)-en-1-one (6). A solution of **6** (25 mg) in benzene (25 ml), stirred with a stream of N_2, was irradiated[23] for 7 h; the reaction was monitored by VPC. Evaporation of solvent at a reduced pressure yielded a gum (23 mg), which was chromatographed on an alumina plate (1000 μ) developed with 50 ml of petroleum ether–acetone (9:1). Elution with methanol afforded 15 mg (79% yield) of crystalline product. After several recrystallizations colorless needles were obtained, the ir and NMR spectra of which were identical with those of **7**, melting point and mixture melting point 135–136 °C. Also two very minor products were observed.

Acknowledgment. The authors wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This investigation was also supported by Public Health Research Contract HD-3-2749 from the National Institute of Child Health and Human Development.

Registry No.—**3**, 5218-51-9; **4a**, 56296-11-8; **4b**, 58576-63-9; **5a**, 56250-04-5; **5b**, 60538-75-2; **6**, 60538-76-3; **7**, 60538-77-4; 17β-hydroxy-5(10)-estren-3-one, 1089-78-7; 17β-hydroxy-4,9-dien-3-one, 6218-29-7; 3,3-dimethoxyestra-5(10),9(11)-dien-17β-ol, 53303-90-5; 2,5-dimethylhexa-2,3-diene, 36721-80-9; 1,4-cyclohexadiene, 628-41-1.

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Approaches to the Mitomycins. A Meta Photo-Fries Reaction

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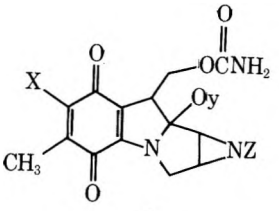
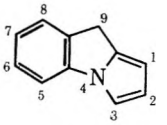
The synthesis of pyrrolo[1,2-*a*]indole **25** is accomplished using a unique meta photo-Fries reaction. The novelty of the rearrangement required a structure proof of the product by x-ray crystallography.

The tricyclic pyrrolo[1,2-*a*]indole framework of the mitomycin antibiotics **1** has been the target compound in several synthesis programs. In our laboratory and one other[1] the aromatic heterocycle **2**, incompletely substituted, has been the starting material for studies of the introduction of C_{10} and the aziridine. We felt it necessary to develop a scheme for the synthesis of 5,6,7,8-substituted heterocycle as a possible starting material so that our model studies could be extended to a system that would be in the natural series.



1



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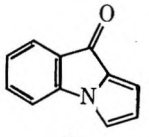

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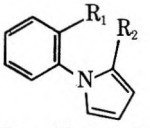
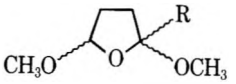


4, R_1 = H; R_2 = CO_2H
5, R_1 = CO_2H; R_2 = H

An attractive route to this hetero analogue of fluorene involves reduction of the ketone **3** which in turn has been prepared by Friedel–Crafts cyclizations of two different acids **4** and **5**.[2] Pyrroles of type **4** are readily prepared from anilines and the tetrahydrofuran **6a** while type **5** pyrroles arise from anthranilic acids and tetrahydrofuran **6b**.[1] Since convenient

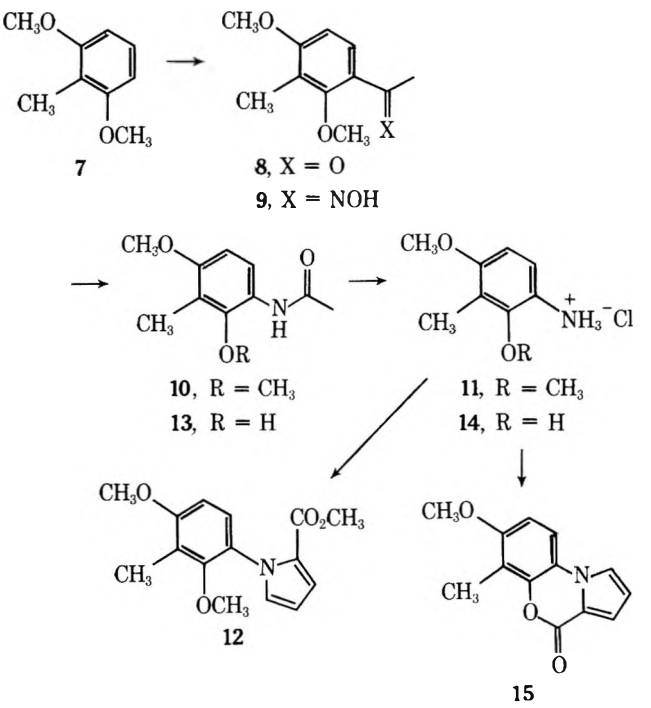


6a, R = CO_2H
b, R = H

syntheses and inexpensive commercial starting materials for the alkoxy toluic acid precursors to the anthranilic acids required for the type **5** approach were not available, we focused on producing a type **4** compound. The preparation of starting materials is outlined in Scheme I.

Our manipulation of aromatic functionality began with dimethoxytoluene **7**. Nitrogen was introduced indirectly via acylation followed by Beckmann rearrangement of the oxime of acetophenone **8**. Acetanilide **10** could be converted to pyrrole **12** first by generation of the free aniline **11** followed by heterocyclization using tetrahydrofuran **6a**. Interestingly, the deactivated pyrrole of **12** was competitive in reactivity toward electrophiles with the carbocyclic ring. Thus attempts to introduce the final substituent in **12** failed; and the intramolecular Friedel–Crafts reaction of the pyrrole carboxyl to the meta position which would have formed a nearly complete tricyclic also failed. Acetanilide **10** could be cleanly demethylated using $AlCl_3/CH_2Cl_2$ to afford the free phenol **13**. Hydrolysis of **13** afforded the air-sensitive amine hydrochloride

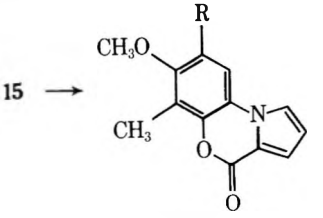
Scheme I



7
8, X = O
9, X = NOH
10, R = CH_3
13, R = H
11, R = CH_3
14, R = H
12
15

14 which was condensed with tetrahydrofuran **6a** in an atmosphere of oxygen-free nitrogen to yield the highly crystalline lactone **15**.

In contrast to pyrrole ester **12**, the lactone **15** was remarkably stable to electrophilic attack. For example, nitration with nitric acid–sulfuric acid, conditions which usually result in oxidative degradation as well as nitration, in this case gave a

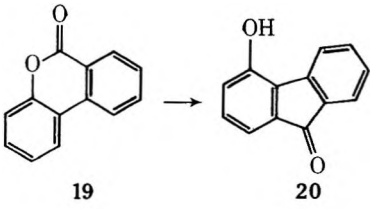


16, R = NO_2
17, R = NH_2
18, R = NHAc

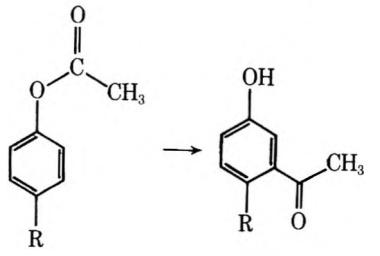
clean mononitro derivative **16**. The nitro compound could be reduced cleanly to the amine **17** provided that the Pd catalyst was prereduced and that a nonprotic solvent such as ether was used. The acetanilide **18** was prepared as well.

With these compounds, every atom required for the target heterocycle **2** is present and an intramolecular acylation of the free aromatic position is all that is required to complete the scheme. When **18** was subjected to the acid-catalyzed Fries-rearrangement conditions (polyphosphoric acid, 90 °C, $TiCl_4$, $PhNO_2$, 60 °C) no reaction was observed. Thus we undertook a photo-Fries reaction. Although the ortho–para photo-Fries

is well known,[3] only three examples of meta orientation have been detected. The single example of product isolation is the work of Finnegan,[4] where a very low yield of fluorenone **20** was obtained upon photolysis of lactone **19**. In the case of simple

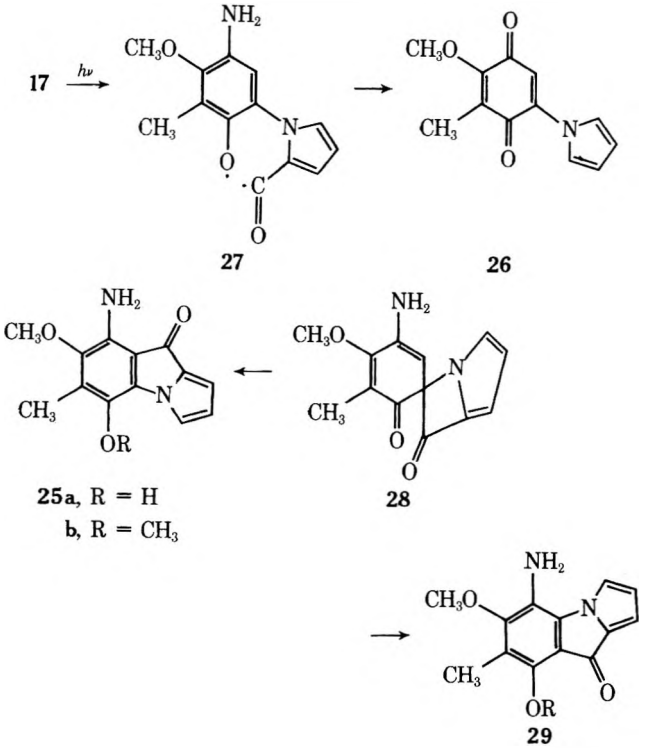


19 **20**



21, R = H **22**, R = H
23, R = CH_3 **24**, R = CH_3

esters, Andersen and Reese[5] using GLC detected 0.3% of meta product **22** upon photolysis of **21**, while Adam detected a CIDNP signal for **24** while irradiating **23**.[6] Furthermore, Adam has used CIDNP evidence and sensitization and quenching experiments to demonstrate that the photo-Fries reaction proceeds via a singlet excited state and forms free radicals that then are partitioned through several product-forming pathways.[7] In the event of irradiation of **17** with a sun lamp through a plate-glass filter (wavelengths greater than 310 nm transmitted) in THF solvent with a purge of oxygen-free nitrogen, a clean and essentially quantitative conversion to an isomer **25** occurred. These conditions were developed when,



25a, R = H
b, R = CH_3

27 **26** **28** **29**

in photolyses without rigorous oxygen exclusion or with less effective hydrogen-donating solvents, there was isolated a compound presumed to be quinone **26**. This air sensitivity was taken as evidence that an intermediate diradical such as **27**

Table I

hkl			*E*	Phase angle	
2	19	0	3.91	0	Origin
0	10	5	2.91	0	
3	0	9	2.66	$3\pi/2$	
4	9	9	3.09	$\pi/2$	Enantiomorph
6	8	0	2.65	0	From Σ_1
8	14	0	2.37	0	
8	0	2	2.06	π	
0	0	6	1.83	π	
2	7	3	3.03	$\pi/4, 3\pi/4, 5\pi/4, 7\pi/4$	

was present and that oxidation could consume it in competition with a cyclization pathway. Although the proposed structure **25** is consistent with this mechanistic speculation, there exists an alternate structural assignment.[8] Diradical **27** could form the spiro intermediate **28** which could rearrange to either **25** or **29**. This spiro intermediate has been invoked by Gutsche to explain the alcoholysis of dihydrocoumarins upon photolysis.[9] No evidence for Fries products was detected in his experiments. Shift reagent studies on methyl ether **25b**, readily prepared from **25a** using methyl sulfate, gave gradients as follows: NH_2, 9.82; pyrrole C_1 H, 4.18; C_2 H, 1.52; C_3 H, 2.51; OCH_3, 1.87, 1.67; CCH_3, 1.97. The crucial assignment of the pyrrole proton resonances is based on the coupling constants of 2.6 and 0.8 Hz for the signal at 7.06 (C_3 H), 3.8 and 0.8 Hz at 6.53 (C_1 H), and 3.8 and 2.6 Hz at 6.11 (C_2 H). These values are consistent with those obtained in our earlier work.[10] Thus, by locating the europium at a position where chelation can occur,[11] we can rationalize the observation that C_1 H in **25** could have the largest shift gradient. For C_1 H to have the greatest gradient in **29b**, one would have to assume a chelation of the Eu between the carbonyl and methoxy groups (and a concomitant methoxy gradient) rather than complexation at the free NH_2. If the latter, expected locus of Eu were to obtain, then C_3 H should have had a higher gradient. For a reaction of this uniqueness, it was decided to reinforce our structure proof with an x-ray crystallographic study.

The crystals of the molecule believed to be **25b** were studied. The system was orthorhombic with the unit cell parameters a = 8.955 (2), b = 16.250 (3), c = 8.794 (2) Å. The space group was determined by systematic absences to be $P2_12_12_1$. Three-dimensional x-ray diffraction data were collected using an Enraf-Nonius CAD-4 diffractometer with Cu Kα radiation. The intensities of 1448 reflections were measured significantly above background. The structure was solved by direct methods with a program[12] based on the tangent formula. The set of starting phases used is given in Table I. The phases of the 281 strongest normalized structure factors were calculated. When the phase of the general reflection was set at $5\pi/4$, the resulting phase set led to an R_K value of 0.157. The E map from this set revealed the 19 nonhydrogen atoms corresponding to the expected isomer. Using a block-diagonal least-squares program,[12] an R value of 0.061 was obtained after anisotropic refinement. The hydrogen atoms were then found from a difference-electron density map. Refining on these isotropically and the nonhydrogen atoms anisotropically resulted in a final R value of 0.034. The bond distances and angles are given in Figure 1. Not shown are the estimated standard deviations of the bond angles, all 0.2°.[13]

In a brief study carried out to test the generality of the reaction, lactones **15**, **16**, and **18** were also photolyzed. While **15** was photostable, both **16** and **18** were consumed upon irradiation using conditions similar to those that were successful for the cyclization of **17**. Nitro derivative **16** yielded an extremely complex mixture of products and we were not successful in characterizing satisfactorily any cyclized product.

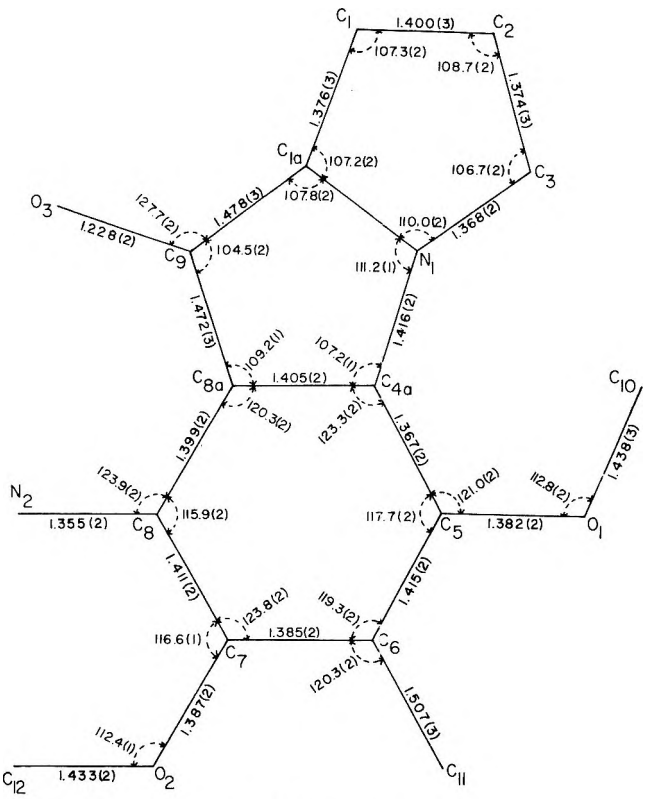
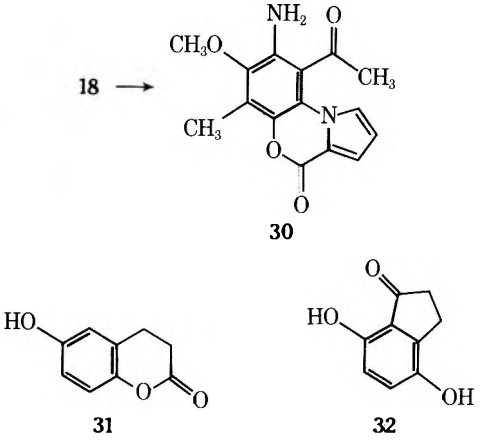


Figure 1. Bond lengths and bond angles for **25b.**

Acetanilide **18** appeared to undergo cleavage of the amide function (disappearance of the ir peak at 1690 cm^{-1}). An ortho Fries product **30** could then undergo a photoreduction to a product simply characterized by its intact lactone carbonyl. We also studied a simple dihydrocoumarin **31** with a strongly activating group[14] which should be a better substrate for cyclization than any studied by Gutsche. We independently synthesized[15] the desired indanone cyclization product **32.** Photolysis of **31** led to its disappearance and the formation of many new compounds. However, no trace of **32** could be detected. Presumably, the carbonyl radical in this example does not have the lifetime required for cyclization.[16]



Experimental Section

^1H NMR spectra were recorded on Varian Models A-60, A-60A, and XL-100 instruments. Infrared spectra were recorded on a Perkin-Elmer Model 137. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

2,4-Dimethoxy-3-methylacetophenone (8). In a three-neck flask fitted with a reflux condenser, mechanical stirrer, and addition funnel was placed a solution of 50 g (0.262 mol) of titanium tetrachloride and 20.4 g (0.262 mol) of acetyl chloride. After being cooled to 0 °C, a solution of 20 g (0.131 mol) of 2,6-dimethoxytoluene (Aldrich, 99%) in 60 ml of dry benzene was added dropwise under an atmosphere of argon. The mixture was stirred for an additional 20 min at 0 °C and then quenched by the cautious addition of 5% HCl.

The organic layer was separated and the aqueous layer was extracted with 60 ml of ether. The combined organic portions were then washed successively with 5% HCl, saturated sodium bicarbonate, and finally with water. After drying with sodium sulfate the solvent was removed and the remaining dark oily residue was then distilled in vacuo with product distilling over at 107 °C (1.5 mm). The product crystallized upon standing and was recrystallized from hexane: mp 31–32 °C; yield 25.1 g (99%); NMR ($CDCl_3$, Me_4Si) δ 1.76 (s, 3 H), 2.18 (s, 3 H, $PhCH_3$), 3.34 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3); ir ($CHCl_3$) 1670 (s, ArC=O), 2850 cm^{-1} (m, OCH_3).

2,4-Dimethoxy-3-methylacetophenone Oxime (9). In a 250-ml round-bottom flask fitted with a reflux condenser, drying tube, and magnetic stirrer were placed 19.13 g (0.099 mol) of the previously prepared 2,4-dimethoxy-3-methylacetophenone (**8**), 20.3 g (0.292 mol) of hydroxylamine hydrochloride, 30 ml of reagent grade pyridine, and 30 ml of absolute ethanol. After heating under reflux for 3 h, the ethanol and pyridine were removed on a rotary evaporator. Distilled water was then added to the residue and the milky mixture was extracted with chloroform. After drying the organic layer over anhydrous sodium sulfate and removing the solvent, there was left a solid residue, which was recrystallized from hexane: mp 86–88 °C; yield 19.3 g (72%); NMR ($CDCl_3$, Me_4Si) δ 2.18 (s, 3 H, $ArCH_3$), 2.27 (s, 3 H, N=CCH_3), 3.70 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3); ir ($CHCl_3$) 3400 (-OH), 1570 (s, N=O), 945 (m, N-O), 2850 cm^{-1} (s, OCH_3).

Anal. Calcd for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.07; H, 7.21; N, 6.68.

2,4-Dimethoxy-3-methylacetanilide (10). In a 250-ml round-bottom flask filled with a reflux condenser and cooled to 0 °C in an ice bath were placed 14.0 g (0.0699 mol) of the previously prepared oxime and 15 ml of trifluoroacetic acid. After allowing the mixture to come to room temperature with stirring, it was gently refluxed for 20 min. Excess TFA was then destroyed by the addition of saturated sodium bicarbonate solution. The anilide was extracted out of solution with chloroform and this chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue recrystallized several times from distilled water: mp 119–120 °C; yield 13.76 g (98%); NMR ($CDCl_3$, Me_4Si) δ 2.21 (s, 6 H, O=CCH_3 and $ArCH_3$), 3.72 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3); ir ($CHCl_3$) 1760 (s, C=O), 3650 cm^{-1} (m, NH).

Anal. Calcd for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.09; H, 7.28; N, 6.73.

2-Hydroxy-4-methoxy-3-methylacetanilide (13). In a dry 250-ml three-neck flask fitted with an addition funnel, reflux condenser, and magnetic stirrer was placed 13.2 g (0.1 mol) of anhydrous aluminum chloride. To this was added, under an atmosphere of N_2, 9.0 g (0.043 mol) of the previously prepared 2,4-dimethoxy-3-methylacetanilide (**10**) in 110 ml of dry methylene chloride. The mixture was stirred at room temperature overnight under an atmosphere of N_2. The mixture was then cooled to 0 °C in an ice bath and any excess aluminum chloride destroyed by the cautious addition of 5% hydrochloric acid. The organic layer was separated and the aqueous layer was extracted three times with methylene chloride. The combined organic portions were dried over anhydrous sodium sulfate. The solvent was removed and the resulting residue recrystallized from carbon tetrachloride: mp 117–119 °C; yield 6.24 g (74%); NMR ($CDCl_3$, Me_4Si) δ 2.21 (s, 6 H, O=CCH_3 and $PhCH_3$), 3.81 (s, 3 H, OCH_3), 8.0–10.4 (m 2 H, PhH), 7.63–7.85 (m 1 H, NH); ir ($CHCl_3$) 1639 (s, C=O), 2941 cm^{-1} (m, NH).

2-Hydroxy-4-methoxy-3-methylaniline Hydrochloride (14). In a 500-ml three-neck round-bottom flask was placed 8.44 g of the phenol **13** dissolved in 154 ml of absolute ethanol. After thoroughly degassing the system, 79 ml of a solution of 50% HCl in water was added dropwise. This mixture was refluxed for 24 h under nitrogen which was passed through Fieser's solution.[17]

After refluxing the solvent was removed leaving a brown residue which was diluted with water and extracted with chloroform. The remaining aqueous layer was reduced to dryness in vacuo. The resulting residue can be partially purified by boiling in chloroform, yield 6.12 g (75%).

6-Methyl-7-methoxy-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (15). In a 100-ml round-bottom flask were placed 3.0 g (0.0158 mol) of the anilinium salt **14,** 3.04 g (0.0158 mol) of tetrahydrofuran **6a,** 1.3 g of sodium acetate, and 37 ml of glacial acetic acid.[18] The mixture was refluxed for 24 h under nitrogen passed through Fieser's solution. After refluxing the mixture was diluted with water and extracted five times with chloroform. The combined chloroform layers

were dried over anhydrous sodium sulfate and the solvent removed. The dark residue which resulted was then heated in methanol and the brown crystals of lactone **16** were collected by suction and dried: mp >300 °C; yield 1.96 g (54%); NMR (TFA) δ 2.24 (s, 3 H, $PhCH_3$), 3.93 (s, 3 H, OCH_3), 6.62–6.92 (m, 2 H, vinylic), 7.35–7.72 (m, 2 H, ArH).

6-Methyl-7-methoxy-8-nitro-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]-benzoxazine (16). A solution of 2.6 g of concentrated nitric acid and 3.3 g of concentrated sulfuric acid was stirred for 5 min and then 100 ml of glacial acetic acid was added. A 2-g (8.8 mmol) portion of 6-methyl-7-methoxy-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (**15**) was then slowly added with stirring and within 2–3 min after addition a solid crystallized from the reaction mixture. Stirring was continued for an additional 30 min. The reaction mixture was poured onto ice and the crude solid was filtered with suction and washed several times with water yielding 2.5 g (99%) of nitrolactone **16**, mp 237–238 °C. The crude product was dissolved in chloroform and passed through a sintered glass funnel filled with dry column silica gel. A yellow band which moved rapidly through the silica gel was collected. Evaporation of the solvent yielded 2.8 g (91%) of **16** as a pale yellow solid. An analytical sample was prepared by two recrystallizations from acetone yielding the desired nitrolactone **16** as white needles: mp 251–252 °C; ir (chloroform) 2994, 1749, 1605, 1522, 1410, 1372, 1349, 1294, 1154, 1104, 1063, 1043, 996, 924 cm^{-1}; uv (ethanol) 205 nm (ε 24 400), 227 sh (13 800), 268 (14 000); NMR (chloroform-d_1–dimethyl sulfoxide-d_6) δ 2.38 (s, 3, CH_3), 3.89 (s, 3, OCH_3), 6.76 (dd, 1, J_{12} = 2.8, J_{23} = 3.8 Hz, C-2), 7.33 (dd, 1, J_{23} = 3.8, J_{13} = 1.3 Hz, C-3), 8.37 (dd, 1, J_{12} = 2.8, J_{13} = 1.3 Hz, C-1), 8.66 ppm (s, 1, C-9).

Anal. Calcd for $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.22. Found: C, 56.85; H, 3.81; N, 10.20.

6-Methyl-7-methoxy-8-amino-4-oxo-4*H*-pyrrolo[2,1-*c*]-[1,4]benzoxazine (17). A solution of 286 mg (1.1 mmol) of 6-methyl-7-methoxy-8-nitro-4-oxo-4*H*-pyrrolo[2,1-c][1,4]benzoxazine (**16**), 60 mg of 10% Pd/C, and 125 ml of ethyl acetate was hydrogenated at atmospheric pressure for 1.5 h. The catalyst was removed by filtration with suction through Celite 545. Evaporation of the solvent yielded 269 mg (100%) of a crude brown solid. Thin layer chromatography on silica gel eluting with chloroform indicated three major components with R_f values of 0.55, 0.17, and 0.08 corresponding to nitrolactone **16**, product amine **17**, and a by-product of the reaction, respectively. All attempts at purification of the crude material were unsuccessful. Elution chromatography on a silica gel column 0.13 cm in diameter and eluting with chloroform yielded 36 mg of recovered nitrolactone **16** as a light yellow solid. Successive elution with increasing percentages of ethyl acetate in chloroform and finally pure ethyl acetate failed to isolate the desired product. Chromatography on a silica gel preparative thin layer plate eluting with chloroform was also unsuccessful. For this reason the amine was always used as a crude material.

Ir (chloroform) 3461, 3372, 2939, 1728, 1628, 1505, 1467, 1417, 1367, 1305, 1169, 1071, 995 cm^{-1}; uv (ethanol) 237 nm (ε 11 200), 267 (5500), 332 (5100); NMR (chloroform-d_1) δ 2.38 (s, 3, CH_3), 3.82 (s, 3, OCH_3), 6.64 (dd, 1, J_{12} = 2.9, J_{23} = 3.9 Hz, C-2), 6.81 (s, 1, C-9), 7.34 (dd, 1, J_{23} = 3.9, J_{13} = 1.5 Hz, C-3), 7.48 ppm (dd, 1, J_{12} = 2.9, J_{13} = 1.5 Hz, C-1).

Irradiation of 6-Methyl-7-methoxy-8-amino-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (17) in Anhydrous Tetrahydrofuran. A solution of 200 mg of crude 6-methyl-7-methoxy-8-amino-4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (**17**) and 200 ml of anhydrous tetrahydrofuran, freshly distilled from lithium aluminum hydride, was placed in a photochemical reaction vessel equipped with a water-cooled immersion well. Nitrogen gas, passing through Fieser's solution to remove traces of oxygen in the tank of nitrogen, was continually bubbled through the solution. The solution was irradiated with a Sears-Roebuck sun lamp no. 7081 mounted 2.5 cm from the reaction vessel. Two thicknesses of plate glass served as a filter. The progress of the reaction was followed by thin layer chromatography on silica gel eluting with chloroform and following the disappearance of the starting aminolactone **17** with an R_f of 0.18. After 22 h the solution had turned from a pale yellow to a deep orange, and no more **17** could be detected. Thin layer chromatography indicated the presence of an orange component with an R_f of 0.13. Evaporation of the solvent yielded a crude red oil which was chromatographed on a silica gel dry column 40 cm long and 2.5 cm in diameter eluting with chloroform. A light yellow band moved with the solvent front and after elution from the column yielded 42 mg (21%) of recovered nitrolactone **17**. An orange band, approximately 10 cm from the origin, was removed and the material eluted from the silica gel with tetrahydrofuran. Evaporation of the solvent yielded 67 mg (34% yield, 48% conversion) of crude product. An analytical sample was prepared by preparative thin layer chromatography on silica gel eluting with chloroform. A bright orange band, 2.5 cm from the origin, was removed and the material was eluted from the silica gel with tetrahydrofuran. Evaporation of the solvent yielded 27 mg (14% yield, 19% conversion) of a red solid. Two recrystallizations from ethyl acetate afforded bright red crystals, mp 222–232 °C dec, of **25a**: ir (chloroform) 2924, 2899, 1724, 1667, 1613, 1456, 1357, 1290, 1093, 1031 cm^{-1}; uv (ethanol) 208 nm (ε 23 900), 222 (25 300), 244 (16 400), 298 (7400), 310 sh (5800), 419 (6700); NMR (dimethyl sulfoxide-d_6) δ 5.83 (bs, exchangeable protons, NH_2, OH), 6.25 (m, 1, C-2), 6.62 (m, 1, C-1), 7.35 (m, 1, C-3); *m/e* 244.0848 (calcd for $C_{13}H_{12}N_2O_3$, 244.0846).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.65; H, 4.69; N, 11.05.

8-Amino-5-hydroxy-7-methoxy-6-methyl-9-keto-9*H*-pyrrolo-[1,2-*a*]indole (25a). A hydrogenation catalyst was prepared by reducing a mixture of 120 mg of 10% Pd/C and 250 ml of K_2CO_3 stirred with 250 ml of EtOAc under an atmosphere of H_2. To this was added 600 mg of powdered nitrolactone **16** through a side arm connection of Gooch tubing. When hydrogen uptake was complete, detected both by volume measurements and the complete disappearance of the suspension of the highly insoluble nitro compound, the catalyst was removed and the solvent was evaporated yielding **17**. The resultant aminolactone **17** was then photolyzed as described above in 500 ml of THF for 11.5 h. Upon solvent removal, there was obtained 534 mg (99%) of crystalline **25a**, comparable in purity to that of the analytical sample.

8-Amino-5,7-dimethoxy-6-methyl-9-keto-9*H*-pyrrolo[1,2-*a*]indole (25b). A mixture of 20 mg (0.082 mmol) of aminophenol **25a**, 7.6 μl (0.082 mmol) of $(CH_3)_2SO_4$, 2 ml of acetone, and anhydrous K_2CO_3 was stirred at 25 °C for 4 h. The mixture was diluted with water and extracted with $CHCl_3$. The organic extract yielded material which was purified by preparative TLC on silica gel by threefold elution with chloroform. The desired methyl ether **25b** was obtained as 20 mg of an orange solid (95% yield) which could be recrystallized from $CHCl_3$–hexane to afford crystals, mp 135–137 °C, which were submitted for x-ray analysis: NMR ($CDCl_3$) δ 2.12 (3 H, s, CCH_3), 3.60, 3.66 (each 3 H, s, $ArOCH_3$), 5.23 (2 H, bs, NH_2), 6.09 (1 H, dd, H_2), 6.51 (1 H, dd, H_1), 7.04 (1 H, dd, H_3).

Registry No.—**6a**, 60512-79-0; **8**, 60512-80-3; **9**, 60512-81-4; **10**, 60512-82-5; **13**, 60512-83-6; **14**, 60512-84-7; **15**, 55609-73-9; **16**, 55609-74-0; **17**, 55609-75-1; **25a**, 55609-76-2; **25b**, 55609-77-3; acetyl chloride, 75-36-5; 2,6-dimethoxytoluene, 5673-07-4.

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Synthesis of Oxazinomycin (Minimycin)[1]

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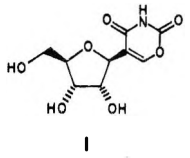
The C-nucleoside antibiotic oxazinomycin (1) has been synthesized, starting with the 2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribofuranosylacetonitriles **3** and **4**. Formylation of **3** and **4** with bis(dimethylamino)-*tert*-butoxymethane afforded the 3-dimethylamino-2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribosyl)acrylonitriles **5** and **6**, which by reaction with hydroxylamine were converted to the 5-amino-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribosyl)isoxazoles **8** and **9**. Hydrogenation of **8** and **9** gave the 3-amino-2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribosyl)acrylamides **10** and **11**. These were subjected to hydrolysis and subsequent reaction with *N,N′*-carbonyldiimidazole to furnish the 5-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribosyl)-1,3-oxazinediones **13** and **14**, which after removal of the protecting groups gave oxazinomycin (1) and its α anomer **15**, respectively.

Much of the interest in C-nucleoside antibiotics[2,3] is due to their varied biological activities, which result from the close structural relationship of these substances to the "normal" nucleoside metabolites. Oxazinomycin (minimycin), **1**,[4,5] an illustrative example of this class of compounds, is elaborated by several *Streptomyces* species.[4-8] This antibiotic inhibits the growth of both gram-positive and gram-negative bacteria[6] and has shown significant activity against transplantable tumors.[4,6] Its structural similarity to uridine and pseudouridine is quite obvious. We now wish to describe a synthesis of oxazinomycin (**1**).



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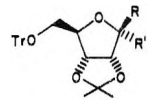


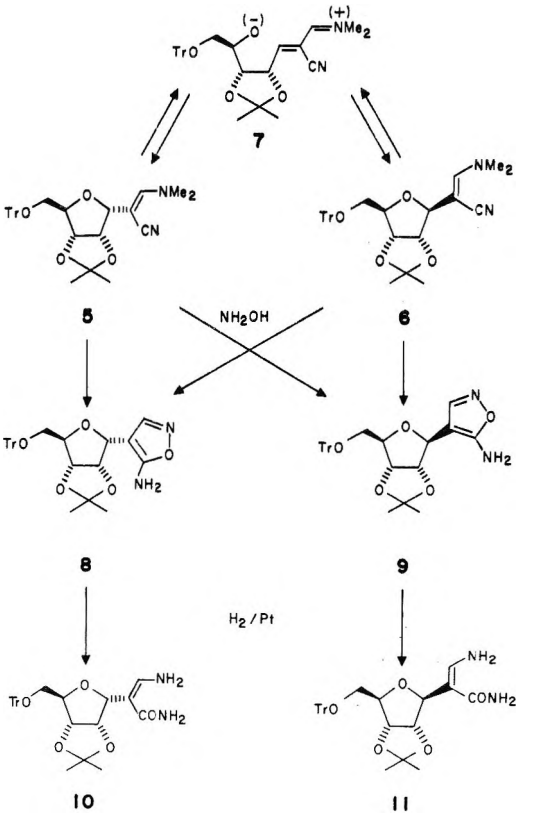
2 R,R′ : OH, H
3 R : H; R′ : CH_2CN
4 R : CH_2CN; R′ : H
Tr = $C(Ph)_3$

A short time after this work had been initiated, the preparation of the epimeric ribosylacetonitriles **3** and **4** by Wittig reaction of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribose (**2**)[9] with cyanomethyltriphenylphosphorane was reported.[10] We prefer to obtain these compounds by the Horner modification, using sodium diethyl cyanomethylphosphonate in dimethoxyethane. Under these conditions, the reaction proceeds to completion at room temperature, affording a 1:2 mixture of **3** and **4**. Formylation with bis(dimethylamino)-*tert*-butyloxymethane,[11] whether performed on pure **3** or **4** or on the mixture of both, results in formation of the two 2-(1′-ribosyl)-3-dimethylaminoacrylonitriles **5** and **6** (2:1). Evidently, epimerization occurs readily between **3** and **4**,[9,10] as well as between **5** and **6**, presumably via opening and reclosure of the furanose ring, requiring base catalysis in the first case, and involving a dipolar intermediate **7** in the latter.

The assignment of the configuration at C-1′ in **5** and **6** (as well as in subsequent intermediates) is based on ^1H NMR spectral data, in accord with literature precedence. Thus, Moffatt et al.[10] have convincingly demonstrated that in a series of *C*-glycosides derived from 2,3-isopropylidene-5-trityl-D-ribofuranose (**2**), including **3** and **4**, those with α configuration at the "anomeric" carbon consistently have values for the coupling constant $J_{3',4'}$ of 0–1 Hz, while in those with β configuration the magnitude of $J_{3',4'}$ is 4–5 Hz. This finding is the observable consequence of the preferred conformation of the heavily substituted tetrahydrofuran ring, which imposes a dihedral angle between H-3′ and H-4′ of ca. 90° in the α epimer and of ca. 160° in the β epimer.[10]

In agreement with this rule, the NMR signal (in $CDCl_3$), observed for H-4′ of **5**, appears as a simple triplet at 4.22 ppm ($J_{3',4'} = 0$ Hz), while H-4′ of **6** gives rise to a quartet at 4.05 ppm ($J_{3',4'} = J_{4',5'} = 4$ Hz). The ultraviolet spectra[12] of **5** and **6** are distinguished by an absorption maximum at ca. 275 nm (ε 17 000 and 18 000, respectively). It should be noted that the geometry around the acrylonitrile double bond, as drawn in **5** and **6**, is arbitrary, although according to published analogies,[13] the *Z* isomer would be expected to be much more preponderant.

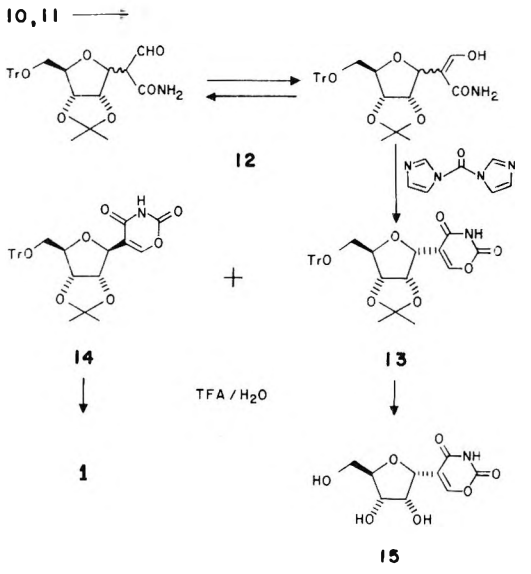
When the enamines **5** and **6** (individually or together) are allowed to react with hydroxylamine in DMF,[14] the aminoisoxazoles **8** and **9** are obtained. Both of these are characterized



by a uv absorption maximum at 247 nm (ε 8000). In agreement with the assigned stereochemistry, the NMR spectrum of **8** contains a triplet for H-4′ (δ 4.06 ppm) and that of **9** has a doublet of triplets (quartet, δ 3.96 ppm, $J_{3',4'} = J_{4',5'} = 4$ Hz). Catalytic hydrogenation of **8**, when carried out over Pt in dimethoxyethane, proceeds with consumption of 1 equiv of hydrogen to give the aminoacrylamide **10**. Analogously, reduction of **9** furnishes **11**. The ir spectra of both compounds (**10** and **11**) exhibit a strong amide band at 1660 cm^{-1}. Hydrolysis of the primary enamine function of **10**, or equally well

of **11**, is effected under mild conditions in a two-phase system consisting of 0.05 N aqueous hydrochloric acid and chloroform. From the NMR spectra, it is evident that the resulting 2-(1′-ribofuranosyl)-2-formylacetamide **12** is a mixture of aldehyde/enol tautomers, as well as of C-1′ epimers.

At this point, this seemingly circuitous sequence makes available the proper functionalities for the final steps of the oxazinomycin synthesis, without having required prohibitively harsh (basic) solvolysis conditions. Reaction of **12** with *N,N′*-carbonyldiimidazole (CDI) in dimethoxyethane, in the presence of a catalytic amount of base, completes the 1,3-oxazine heterocycle and furnishes the two epimeric products **13** and **14** (2:3). Upon aqueous workup of the reaction mixture,



some starting material is regenerated, presumably arising from the carbonylation product of that portion of enolized **12** which has *E* geometry. Separation of **13** and **14** is accomplished by preparative high-pressure liquid chromatography. The assignment of their respective stereochemistry is again possible with the help of the H-4′ NMR signal, which in **13** is observed as a triplet at δ 4.19 ppm, and in **14** as a quartet at δ 4.03 ppm ($J_{3',4'} = J_{4',5'} = 4$ Hz). The infrared spectra of both compounds contain a strong absorption band at 1790 cm^{-1}, which is characteristic for the oxazinedione system.[4] Removal of the protecting groups from **13** proceeds readily in 90% trifluoroacetic acid to afford the 1′-α epimer of oxazinomycin **15.** Analogous treatment of **14** gives oxazinomycin **1.** The physical properties of **15,** including ir, uv, and mass spectra, are very similar to those of **1.** Characteristic differences, however, exist in the NMR spectra of the two compounds, as expected. The properties of our synthetic **1** are in full agreement with those reported for oxazinomycin. In direct comparison by melting point, mixture melting point, and thin layer chromatography, our synthetic oxazinomycin is identical with material from a microbial source.[7]

Experimental Section

General. Melting points were taken on a Kofler hot stage melting point apparatus (Reichert) and are uncorrected. Infrared (ir) and ultraviolet (uv) spectra were recorded on Digilab FTS 14 and Cary Model 16 spectrophotometers, respectively. ^1H NMR spectra were obtained on Varian XL-100 and HA-100 instruments, and are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained ona CEC-110 mass spectrometer. Rotations were measured on a Perkin-Elmer 141 polarimeter. A Waters Associates Model ALC-202/R410 instrument was used for preparative high-pressure liquid chromatography.

Silica gel 60 (0.063–0.200 mm) and plates precoated with silica gel 60 F-254 (both from E. Merck) were used for column and thin layer chromatography, respectively.

Pyridine was distilled from BaO, and 1,2-dimethoxyethane (DME) from CaH_2. All the other solvents were dried with Davison 4A Molecular Sieves.

Some of the described experiments utilize extensive chromatography, most of which can be (and has been) omitted in routine runs, i.e. in the preparation of material to be used in the next step.

2′,3′-*O*-Isopropylidene-5′-*O*-trityl-D-ribofuranosylacetonitrile (3 and 4). To a suspension of 2.00 g (83.3 mmol) of NaH in 300 ml of dry DME (stirred under argon) was added dropwise (over 30 min) 17 ml (107.7 mmol) of diethyl cyanomethylphosphonate while cooling in an ice–water bath. After evolution of H_2 had ceased, the cooling was discontinued and 30 g (69.36 mmol) of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribose[9] in 200 ml of dry DME was added to the clear solution within 30 min. The reaction mixture was maintained for 2 h at room temperature under argon. It was then distributed between 2 l. of Et_2O and 1 l. of H_2O. The aqueous layer was extracted with 1 l. of Et_2O. The combined extracts were washed to neutrality with half-saturated brine (2 × 500 ml), diluted with benzene (500 ml), dried (Na_2SO_4), and evaporated to dryness in vacuo. The residual oil was dissolved in 40 ml of AcOEt–cyclohexane (1:4) and the solution chromatographed on a column (105 × 6 cm) containing 1.15 kg of silica gel. The column was developed with 5 l. of AcOEt–cyclohexane (1:4).

Early fractions afforded 9.92 g of crystalline **2,3-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranosylacetonitrile (3)**, mp 130 °C, from MeOH (reported[10] 130 °C); $[\alpha]^{25}D$ 10.1° (c 0.9982, $CHCl_3$) (reported[10] 9.8°). Further elution gave 14.32 g of **2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosylacetonitrile (4)**, contaminated with a minor amount of **3** (<10%), and finally 6.38 g of pure **4** as a colorless syrup, $[\alpha]^{25}D$ −5.5° (c 0.999, $CHCl_3$). The combined yield was 97%.

3-Dimethylamino-2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribosyl)acrylonitrile (5 and 6). A mixture (2:3) of **3** and **4** (30.5 g, 67 mmol) was dissolved in 250 ml of dry DMF and the solution was placed in a 500-ml flask fitted with a reflux condenser. An excess of bis(dimethylamino)-*tert*-butoxymethane[11] (45 ml) was added in one portion and the reaction mixture was stirred under argon for 3 h at 55 °C. The excess aminal ester and most of the solvent were evaporated in vacuo at 50 °C. The remaining dark syrup was taken up in $CHCl_3$ (ca. 30 ml) and the solution applied to a column containing 400 g of silica gel. The column was developed with $CHCl_3$ (200 ml) and $CHCl_3$–MeOH, 99.5:0.5 (2500 ml), the eluate being monitored by TLC ($CHCl_3$–MeOH, 98:2).

Fractions containing the epimeric mixtures of **5** and **6** were pooled. After evaporation of the solvents, the residue was dissolved in $CHCl_3$ (ca. 40 ml); dilution with Et_2O (300 ml) in portions yielded, after cooling, 17.38 g of crystalline **3-dimethylamino-2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α-D-ribosyl)acrylonitrile (5)**. Mother liquors and washings (Et_2O) were evaporated in vacuo. The light brown residue, dried at 50 °C (0.01 mmHg), was purified by chromatography on 540 g of silica gel. The column, packed in $CHCl_3$, was eluted with $CHCl_3$–MeOH, 99:1 (1500 ml) and 98:2 (3000 ml). The oil obtained from the early fractions was taken up in Et_2O. Upon concentration of the solution to ca. 25 ml, dilution with cyclohexane (60 ml) in portions, and cooling, 6.36 g of pure **3-dimethylamino-2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribosyl)acrylonitrile (6)** was obtained (as a solvate with 1 mol of cyclohexane).

Later fractions contained an epimeric mixture of **5** and **6.** Fractional crystallization of the residue gave another 1.43 g of the α epimer **5** (total 18.82 g) from $CHCl_3$–Et_2O, then an additional 1.60 g of solvated β epimer **6** from Et_2O–cyclohexane. A further amount of crystalline **6** (1.66 g, 9.62 g in total) could be isolated by chromatography of the mother liquors on 400 g of silica gel in AcOEt–cyclohexane, 3:7. The epimer **5** had mp 180–181.5 °C; $[\alpha]^{25}D$ −51.8° (c 0.9856, $CHCl_3$); uv (EtOH) infl 230 nm (ε 11 500), max 276 (16 900); ir ($CHCl_3$) 2810, 2180, 1634, 1107, 1074, 708 cm^{-1}; NMR ($CDCl_3$) δ 1.33 and 1.56 [2 s, $C(CH_3)_2$], 3.11 [s, $N(CH_3)_2$], 3.20 (ddd, CH_2OTr), 4.22 (t, H-4′), 4.56 (t, H-2′), 4.64 (2 d H-1′ and H-3′), 6.61 (s, vinylic), 7.20–7.55 (m, 15, aromatic).

Anal. Calcd for $C_{32}H_{34}N_2O_4$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.11; H, 6.46; N, 5.50.

The epimer **6** had mp 78–83 °C; $[\alpha]^{25}D$ −28.7° (c 0.9917, $CHCl_3$); uv (EtOH) infl 230 nm (ε 11 500), max 274–275 (18 200); ir ($CHCl_3$) 2815, 2190, 1637, 1075, 708 cm^{-1}; NMR ($CDCl_3$) δ 1.32 and 1.53 [2 s, $C(CH_3)_2$], 3.06 [s, $N(CH_3)_2$], 3.28 (d, OCH_2Tr), 4.05 (q, H-4′, J = 4 Hz), 4.15 (d, H-1′, J = 5 Hz), 4.51 (dd, H-3′), 4.66 (dd, H-2′), 6.55 (s, vinylic), 7.20–7.60 (m, 15, aromatic).

Anal. Calcd for $C_{32}H_{34}N_2O_4 \cdot C_6H_{12}$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.81; H, 8.14; N, 4.79.

The combined yield was 79.2%.

5-Amino-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribosyl)-isoxazole (8 and 9). A mixture (2:1) of **5** and **6** (30.69 g, 57.34 mmol) was dissolved in 300 ml of dry DMF. To this solution was added 50 ml of dry pyridine and 5.10 g (73.3 mmol) of NH_2OH·HCl. Upon stirring at 68–70 °C under argon, a clear solution was obtained within 15 min. The reaction was kept at 70 °C for 6.5 h while monitoring by TLC (Et_2O–cyclohexane, 10:3). The solvents were then evaporated in vacuo at 45 °C and the residual syrup was distributed between $CHCl_3$ (1200 ml) and H_2O (600 ml). The aqueous layer was extracted with a second portion of $CHCl_3$ (600 ml). The organic extracts were combined, washed with half-saturated brine (3 × 400 ml), dried (Na_2SO_4), and evaporated in vacuo. The residual syrup was chromatographed on 400 g of silica gel, successively with $CHCl_3$–MeOH, 98.5:1.5 (900 ml) and 98:2 (1500 ml). Early fractions were rechromatographed on 600 g of silica gel ($CHCl_3$–MeOH, 98:2, 3500 ml) to give 0.610 g of unreacted **5** and **6**, 2.726 g of crystalline **5-amino-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribosyl)isoxazole (9)** (from Et_2O–petroleum ether, 30–60 °C) as a solvate with 1 mol of Et_2O, and 4.432 g of **5-amino-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α-D-ribosyl)isoxazole (8)** as an amorphous foam.

Later fractions, upon rechromatography on 1.1 kg of silica gel (Et_2O–cyclohexane, 10:3, 4500 ml), yielded an additional 0.985 g of crystalline **9** and 11.211 g of **8**.

The still unresolved fractions were further chromatographed on silica gel (Et_2O–cyclohexane, 10:3) to give in total 19.608 g of **8** as a white foam and 5.638 g of **9** (solvated with 1 mol of Et_2O). The combined yield was 85.8%.

Pure **8** had $[\alpha]^{25}D$ −11.5° (*c* 0.9960, $CHCl_3$); uv (EtOH) max 247 nm (ε 8000); ir ($CHCl_3$) 3490, 3390, 1646, 1505, 1495, 1105, 1074, 706 cm^{-1}; NMR (Me_2SO-d_6) δ 1.24, 1.44 [2 s, $C(CH_3)_2$], 3.10 (m, CH_2OTr), 4.06 (t, H-4′), 4.54 (q, H-2′), 4.62 (d, H-3′), 4.72 (d, H-1′), 6.54 (broad s, exchangeable, NH_2), 7.20–7.50 (m, 15 aromatic), 8.01 (s, =CH–).

Anal. Calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.07; N, 5.61. Found: C, 71.49; H, 6.07; N, 5.67.

Pure **9**, a solvate with 1 mol of Et_2O, had mp 90–96 °C; $[\alpha]^{25}D$ −13.4° (*c* 0.9890, $CHCl_3$); uv (EtOH) max 248 nm (ε 8400); ir 3485, 3370, 1653, 1514, 1505 (w), 1080, 707 cm^{-1}; NMR (Me_2SO-d_6) δ 1.09 (t, CH_3 of Et_2O), 1.27, 1.49 [2 s, $C(CH_3)_2$], 3.13 (d, CH_2OTr), 3.37 (q, CH_2 of Et_2O), 3.96 (q, H-4′), 4.50–4.78 (m, H-3′, H-2′, H-1′), 6.78 (broad s, $-NH_2$), 7.16–7.52 (m, 15, aromatic), 8.10 (s, =CH–).

Anal. Calcd for $C_{30}H_{30}N_2O_5$·$C_4H_{10}O$: C, 71.31; H, 7.04; N, 4.89. Found: C, 71.29; H, 7.15; N, 4.84.

3-Amino-2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α-D-ribosyl)acrylamide (10). A solution of 5.01 g (10.05 mmol) of **8** in 75 ml of dry DME was hydrogenated at room temperature in the presence of 250 mg of PtO_2. The consumption of H_2 was 285 ml within 25 min (theoretical 274 ml). The mixture was stirred under nitrogen with a small amount of decolorizing carbon and filtered through a pad of Celite. After evaporation of the solvents in vacuo at <30 °C, the residue was taken up in 250 ml of $CHCl_3$. The solution was washed with 2 × 200 ml of H_2O, dried (Na_2SO_4), and evaporated under reduced pressure. Upon drying at 0.005 mmHg at room temperature for 2 days and at 50 °C for 2 h, 5.20 g (90%) of **10** was obtained as a white foam: $[\alpha]^{25}D$ −27.2 (*c* 0.8655, $CHCl_3$); uv (EtOH) max 271 nm (ε 10 000); ir ($CHCl_3$) 3510, 3375, 1660, 1576, 1100, 1070, 705 cm^{-1}; NMR (Me_2SO-d_6) δ 1.18, 1.34 [2 s, $C(CH_3)_2$], 2.80–3.25 (m, CH_2OTr), 4.03 (t, H-4′), 4.32–4.64 (m, H-1′, H-2′, H-3′), 6.20 (broad s, NH_2), 6.72 (t, =CH–; s, upon D_2O exchange), 7.00–7.64 (m, 15, aromatic and NH_2, exchange), 8.24 ($CHCl_3$).

Anal. Calcd for $C_{30}H_{32}N_2O_5$·0.65$CHCl_3$: C, 63.67; H, 5.69; N, 4.85. Found: C, 63.83; H, 5.80; N, 4.53.

3-Amino-2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribosyl)acrylamide (11), prepared analogously by hydrogenation of **9**, was a white foam from $CHCl_3$: $[\alpha]^{25}D$ −12.7° (*c* 0.8694, $CHCl_3$); uv (EtOH) max 273 nm (ε 12 100); ir ($CHCl_3$) 3510, 3485, 3355, 1665, 1580, 1100, 706 cm^{-1}; NMR (Me_2SO-d_6) δ 1.26, 1.46 [2 s, $C(CH_3)_2$], 3.21 (m, CH_2OTr), 3.87 (q, H-4′), 4.14 (q, H-2′ or H-3′), 4.60 (m, H-1′ and H-2′ or H-3′), 6.26 (broad s, NH_2, exchange), 6.81 (t, =CH–, collapses slowly to a s upon D_2O exchange), 7.10–7.55 (m, 15, aromatic and NH_2), 8.29 ($CHCl_3$).

Anal. Calcd for $C_{30}H_{32}N_2O_5$·0.65$CHCl_3$: C, 63.67; H, 5.69; N, 4.85. Found: C, 63.99; H, 5.93; N, 4.67.

2-Formyl-2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribosyl)-acetamide (12). A solution of **10** (4.218 g) in 250 ml of $CHCl_3$ was vigorously stirred for 7 h at room temperature together with 500 ml of 0.05 N HCl. Then 250 ml of $CHCl_3$ was added and the layers were separated. The aqueous phase was extracted with 250 ml of $CHCl_3$. The combined extracts were washed with 3 × 300 ml of H_2O, dried (Na_2SO_4), and evaporated in vacuo at <35 °C. The residue was dissolved in 10 ml of AcOEt–Et_2O, 1:1, and the solution was chromatographed on 400 g of silica gel with AcOEt–Et_2O, 35:65 (2500 ml). The residue obtained from the first fractions (0.540 g) was enriched in the α epimers (α/β ca. 2:1, as determined by integration of the CHO protons in NMR), while the subsequent eluate gave a white foam (2.415 g) in which the β epimers were largely predominant (α/β ca. 2:9). This material (2.955 g, 70%) was used in the next step without any further purification.

Both fractions had very similar spectral properties: uv (EtOH) max 266 nm (ε 2600); (0.1 N KOH) sh 230 nm (9600), max 270 (12 300); ir ($CHCl_3$) 3480, 3345, 1710 (w), 1655 cm^{-1}; (pyridine) 1728, 1690, 1658 cm^{-1}; NMR (partial, Me_2SO-d_6) δ 4.07 (q, H-4′ of β epimers), 4.33 (t, H-4′ of α epimers), 9.58–9.72 (m, CHO, integration for less than one proton, indicating presence of tautomeric forms).

5-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-D-ribosyl)-1,3-oxazine-2,4-dione (13 and 14). To a stirred suspension of 353 mg of KH (22.5% in oil, 2 mmol) in 20 ml of dry DME was added dropwise at 10 °C a solution of 2.48 g (4.94 mmol) of **12** in 25 ml of DME. After evolution of H_2 had ceased, 1.62 g (10 mmol) of 1,1′-carbonyldiimidazole dissolved in 35 ml of DME was added dropwise at 10 °C to the clear solution. The reaction mixture was stirred under argon at room temperature for 6 h. It was then diluted with 500 ml of Et_2O and 175 ml of cold 0.15 N HCl. The aqueous layer was extracted with a second portion of Et_2O. The organic extracts were washed with H_2O (4 × 100 ml), diluted with 150 ml of benzene, dried (Na_2SO_4), and evaporated at 35 °C under reduced pressure. The residue was dissolved in 8 ml of AcOEt–Et_2O, 35:65, and the solution chromatographed on 400 g of silica gel with 2000 ml of the same solvent mixture. Epimeric 5-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribosyl)-1,3-oxazine-2,4-dione (**13** and **14**, 1.245 g, 47.7%) was eluted first. Starting material (0.535 g) was recovered from later fractions, giving an actual yield of 64%.

Partial separation of the epimers was achieved by column chromatography. Thus, 3.20 g of a mixture of **13** and **14** was dissolved in 10 ml of AcOEt–Et_2O–cyclohexane, 30:10:60, and the solution applied to a column (80 × 4.6 cm) packed with 600 g of silica gel. Elution with AcOEt–Et_2O–cyclohexane, 30:10:60 (4000 ml, 1.5 ml/min), afforded 0.897 g of the less polar **5-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α-D-ribosyl)-1,3-oxazine-2,4-dione (13)** as an amorphous, white powder, which after evaporation from AcOEt–*n*-heptane and drying at 70 °C (0.005 mmHg) for 24 h had $[\alpha]^{25}D$ −48.4° (*c* 1.0015, $CHCl_3$); uv (EtOH) infl 230 nm (ε 12 700), 259 (980), 270 (480); ir ($CHCl_3$) 3390, 1790, 1757, 1725, 1705, 1080, 708 cm^{-1}; NMR (Me_2SO-d_6) δ 1.23, 1.33 [2 s, $C(CH_3)_2$], 3.16 (d, CH_2OTr), 4.19 (t, H-4′), 4.66 (d, H-3′), 4.87 (t, H-2′), 4.93 (d, H-1′), 7.20–7.50 (m, 15, aromatic), 7.64 (s, =CH–), 12.02 (s, exchanges, NH).

Anal. Calcd for $C_{31}H_{29}NO_7$: C, 70.58; H, 5.54; N, 2.65. Found: C, 70.59; H, 5.49; N, 2.71.

The residue obtained from the remaining fractions could be resolved into its components by preparative high-pressure liquid chromatography. Thus, batches of ca. 500 mg of the mixture were chromatographed on an 8 ft × 0.375 in. column packed with Porasil A, using AcOEt–*n*-heptane, 1:4, as the eluent. Two recycles provided complete separation of the epimers. After evaporation of the fractions in vacuo, the residues were dried at 70 °C (0.005 mmHg) for 24 h to give an additional 0.350 g of **13** and 1.771 g of **5-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribosyl)-1,3-oxazine-2,4-dione (14)** as a white, amorphous powder: $[\alpha]^{25}D$ 8.4° (*c* 0.9912, $CHCl_3$); uv (EtOH) infl 230 nm (ε 13 400), 260 (950), 270 (450); ir ($CHCl_3$) 3390, 1790, 1760, 1725, 1085, 710 cm^{-1}; NMR (Me_2SO-d_6) δ 1.25, 1.47 [2 s, $C(CH_3)_2$], 3.13 (d, CH_2OTr), 4.03 (q, H-4′), 4.55 (t, H-3′), 4.64–4.83 (m, H-1′, H-2′), 7.20–7.50 (m, 15 aromatic), 7.79 (s, =CH–), 12.01 (s, exchanges, NH).

Anal. Calcd for $C_{31}H_{29}NO_7$: C, 70.58; H, 5.54; N, 2.66. Found: C, 70.63; H, 5.72; N, 2.66.

5-α-D-Ribofuranosyl-1,3-oxazine-2,4-dione (15). A solution of 791 mg (1.50 mmol) of **13** in 25 ml of 90% CF_3COOH was stirred at room temperature for 2.5 h. The solvents were removed at ca. 30 °C (0.2 mmHg) and the residue was dried azeotropically by evaporation from absolute EtOH. The resulting solution was triturated with 25 ml of benzene and the suspension stirred at room temperature for 1 h. The insoluble matter was collected by filtration and washed with several small portions of Et_2O to give 368 mg (100%) of **15** as a white, crystalline powder, mp 163–167 °C dec (with previous softening), pure by TLC.

Recrystallization from a small volume of MeOH–H_2O (5:1) afforded 250 mg of needles: mp 168–170 °C; $[\alpha]^{25}D$ −82.6 (*c* 0.9918, H_2O); uv max (H_2O) 230 nm (ε 4420); ir (KBr) 3400, 3320, 1795, 1770, 1690, 1675, 1653 cm^{-1}; NMR (D_2O) δ 3.74, 3.97 (CH_2, 2 dd, J_{vic} = 2.5, 5, J_{gem} = 12.5 Hz), 4.04 (H-4′, ddd, J = 2.5, 5, 7.5 Hz), 4.33 (H-3′, dd, J = 4, 7.5 Hz), 4.46 (H-2′, dd, J = 4, 3 Hz), 5.12 (H-1′, dd, J = 3, 1.5 Hz), 7.77 (vinylic, d, J = 1.5 Hz); MS *m/e* 245 (M^+), 227 ($M - H_2O$), 201 (M −

CO_2), 184 (M − HNCO), 140, 112.

Anal. Calcd for $C_9H_{11}NO_7$: C, 44.09; H, 4.52; N, 5.71. Found: C, 43.98; H, 4.40; N, 5.58.

5-β-D-Ribofuranosyl-1,3-oxazine-2,4-dione (Oxazinomycin, 1). A solution of 1.298 g (2.46 mmol) of **14** in 35 ml of 90% CF_3COOH was stirred at room temperature for 3 h. The solvents were removed at ca. 30 °C (0.2 mmHg). The residue was dried azeotropically by evaporation from absolute EtOH and purified by chromatography on 200 g of silica gel. The column was developed with AcOEt–AcMe–MeOH–H_2O, 70:10:5:5, and appropriate fractions were evaporated in vacuo at 30 °C. Crystallization of the residue from MeOH containing a small amount of H_2O afforded 387 mg of oxazinomycin (**1**), mp 153–155 °C. The mother liquors, after evaporation, gave an additional 98 mg of **1** from AcMe, mp 152–154 °C, total yield 80%, mmp with an authentic sample[7] 153–155 °C. Occasionally, upon slow recrystallization from water–methanol, a second polymorph was obtained, which had mp 161–162 °C dec (reported[4-6] 161 °C). Synthetic **1** and natural oxazinomycin had identical R_f values in several TLC systems; e.g., in EtOAc–AcMe–H_2O, 70:10:5:5, the R_f was 0.34: $[\alpha]^{25}D$ +15.29° (c 0.9942, H_2O); uv max (H_2O) 230 nm (ε 4700); ir (KBr) 3470, 3420, 1797, 1773, 1678 cm^{-1}; NMR (D_2O) δ 3.77, 3.90 (CH_2, 2 dd, J_{vic} = 5, 3, J_{gem} = 12.5 Hz), 4.06 (H-4′, ddd, J = 5,3,5 Hz), 4.19 (H-3′, t, J = 5, 5 Hz), 4.34 (H-2′, t, J = 5, 5 Hz), 4.72 (H-1′, d, J = 5 Hz), 7.88 (vinylic, s); MS *m/e* 227 (M − H_2O), 209, 202, 196.

Anal. Calcd for $C_9H_{11}NO_7$: C, 44.09; H, 4.52; N, 5.71. Found: C, 44.22; H, 4.52; N, 5.70.

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Registry No.—**1**, 32388-21-9; **3**, 56779-60-3; **4**, 56703-40-3; **5**, 60526-02-5; **6**, 60526-03-6; **8**, 60526-04-7; **9**, 60526-05-8; **10**, 60526-06-9; **11**, 60526-07-0; α-**12**, 60526-08-1; β-**12**, 60526-09-2; α-**12** keto anomer, 60526-10-5; β-**12** keto anomer, 60526-28-9; **13**, 60526-11-6; **14**, 60526-12-7; **15**, 60526-13-8; diethyl cyanomethylphosphonate, 2537-48-6; 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribose, 55726-19-7; bis(dimethylamino)-*tert*-butoxymethane, 5815-08-7.

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Carbon-13 Nuclear Magnetic Resonance Studies of Fungal Metabolites, Aflatoxins, and Sterigmatocystins

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^{13}C NMR spectra are reported for 12 of the fungal metabolites which contain the fused bisdihydrofuran ring system and are produced by certain strains of *A. flavus*, *A. parasiticus*, and *A. versicolor*. Included are the aflatoxins B_1, B_2, B_{2a}, B_3 (parasiticol), D_1, G_1, G_2, and G_{2a} and sterigmatocystin, dihydrosterigmatocystin, o-methylsterigmatocystin, and o-methyldihydrosterigmatocystin. Chemical shifts have been assigned on the basis of known substituent effects, off-resonance decoupling experiments, and comparison among the related compounds.

The aflatoxins and related sterigmatocystins, fungal metabolites produced by certain strains of *Aspergillus flavus*, *Aspergillus parasiticus*, and *Aspergillus versicolor*, are of considerable interest because of their widespread occurrence in human and animal foodstuffs and their carcinogenic effects in all laboratory animals with which they have been tested.[1,2] The common structural feature of these compounds is the bisfuran ring system, which in the aflatoxins is fused to a substituted coumarin structure. Previous studies have shown that the above compounds are derived biosynthetically from a polyketide (acetate) precursor[3-7] and that sterigmatocystin is a precursor of aflatoxin B_1.[8] Although the structures of these compounds have been elucidated previously,[1] the recent advances in ^{13}C NMR toward smaller sample sizes and the wealth of information available from ^{13}C NMR[9] makes ^{13}C NMR a valuable tool for the identification of these metabolites and the structure determination of future metabolites.

Two reports[4,5] have appeared recently on the ^{13}C NMR spectrum of aflatoxin B_1 in connection with ^{13}C labeling studies into the biosynthetic origin of aflatoxin B_1. However, the two reports differ in their assignment of the carbon chemical shifts of aflatoxin B_1. In view of the importance of the aflatoxins and related compounds, we wish to report here our studies of the ^{13}C NMR spectra of eight related aflatoxins. A consistent assignment of the ^{13}C chemical shifts of the aflatoxins is made which is in agreement with one of the previous assignments.[4] In addition, ^{13}C NMR data are also reported for sterigmatocystin and three derivatives. The results are consistent with a previous assignment of the ^{13}C NMR spectrum of sterigmatocystin.[7]

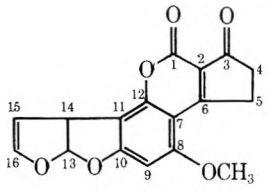
Experimental Section

Natural abundance, proton-decoupled ^{13}C NMR spectra were obtained on a JEOL PFT-100 spectrometer equipped with the JEOL EC-100 data system. Fourier transform spectra were obtained using spectral widths of 5000 and 6250 Hz, with 8K data points. A pulse angle of ~40° was used with a repetition rate of 3 s. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane and are considered accurate to 0.1 ppm. Single frequency, off-resonance proton decoupled (sford) spectra were obtained on each sample.

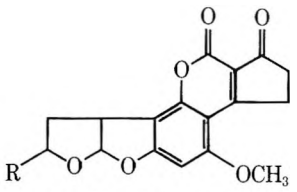
The compounds reported in this investigation were available in one of our laboratories, with the exception of aflatoxin D_1. The sample of aflatoxin D_1 was obtained from the Southern Regional Research Center, New Orleans, La. No impurity peaks were observed in any of the spectra. Samples were prepared in either $CDCl_3$ or Me_2SO-d_6, depending on the solubility. Variations in ^{13}C chemical shifts for $CDCl_3$ vs. Me_2SO-d_6 may be as large as ≥0.5 ppm for all carbons. The concentrations of the NMR samples were from 0.1 to 0.5 M, depending on the quantity of sample available.

Results and Discussion

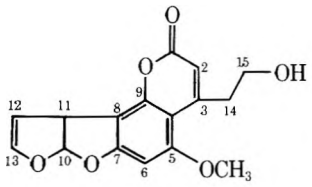
The structures of the compound reported in this investigation are given below. ^{13}C chemical shifts obtained for the



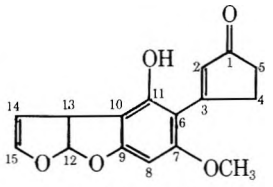
1, aflatoxin B_1



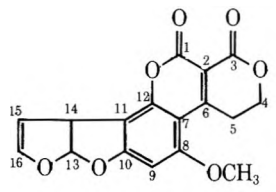
2, R = H, aflatoxin B_2
3, R = OH, aflatoxin B_{2a}



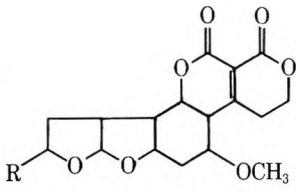
4, aflatoxin B_3



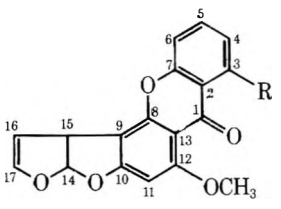
5, aflatoxin D_1



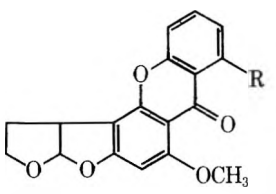
6, aflatoxin G_1



7, R = H, aflatoxin G_2
8, R = OH, aflatoxin G_{2a}



9, R = OH, sterigmatocystin
11, R = OCH_3, *O*-methylsterigmatocystin



10, R = OH, dihydrosterigmatocystin
12, R = OCH_3, *O*-methyldihydrosterigmatocystin

aflatoxins (**1**–**8**) are given in Table I and those for the sterigmatocystins (**9**–**12**) in Table II.

The chemical shifts obtained for aflatoxin B_1 (**1**) agree to within ±1 ppm with those reported previously.[4,5] Differences in concentration could account for the minor variations. Comparisons of the spectra of **1**, **2**, and **3**, off-resonance decoupling experiments, and the substituent effect of the hydroxy group confirm the previous assignments[4,5] of C-13–16. The previous assignments of the ^{13}C spectrum of **1**, however, differ in their assignments of C-1, C-2, and C-7. The data obtained for **4** and **5** allow a clarification of these assignments.

Comparisons of the spectra of **1** and **4** shows, among other differences, the disappearance of a peak at 117.0 ppm in **1** (sford singlet) and the appearance of a new peak at 110.8 ppm (sford doublet) in **4**. Since the carbon in **1** which should give a doublet in the sford spectrum also shows doublets within experimental error in the spectrum of **4**, the peak at 117.0 ppm in **1** and at 110.8 ppm in **4** can only be due to C-2. This assignment is in agreement with the previous assignment of **1** which was based on carbon–carbon coupling constant data.[4] The disappearance of the peak at 200.6 in **4** compared to **1** and its presence in the spectrum of **5** at 208.6 is consistent with the assignment of this peak to C-3 in **1**. Another major difference in the spectra of **1** and **4** is that the peak at 176.5 ppm (sford singlet) in **1**, which was assigned to C-6,[4] is absent in the spectrum of **4**. It is well established that conjugation of a carbonyl group with a double bond results in a downfield shift of the β carbon of the double bond.[9] Comparison of the spectra of cyclohexene[10] with 2-cyclohexenone[11] shows this downfield shift to be 22.6 ppm. Therefore, the resonance due to C-3 in **4** should be upfield by approximately 22 ppm compared to its position in **1**. Comparison of the spectra of **1** and **4** indeed shows a peak at 154.7 ppm (sford singlet) in **4** which is not present in **1**. Therefore, this peak is assigned to C-3 of **4**.

The remaining discrepancy in the previous assignments of the spectrum of **1** is C-1. The lack of carbon–carbon coupling for the peak at 154.7 ppm in the spectrum of **1** which was grown with $^{13}CH_3{}^{13}CO_2Na$, was used to assign C-13 in one report[4] while the chemical shift of the related carbon in coumarin at 160.4 ppm[12] was used as the basis of the assignment in the other report.[5] The major difference between coumarin and **1** (as far as C-1 in **1** is concerned) is that the α- and β-unsaturated carbons of coumarin are substituted and the carbonyl is not part of a 1,3-dicarbonyl system. Comparison of data for 2-cyclopentenone and 2-cyclohexenone with 2,3-dimethyl-2-cyclopentenone and 2,3-dimethyl-2-cyclohexenone,[11] respectively, indicates that substitution in the α- and β-unsaturated carbons of coumarin should have little effect on the chemical shifts of the carbonyl carbon. However, comparison of data for 2-pentanone with 2,4-pentadione shows that the introduction of a carbonyl group β to an existing carbonyl group results in an upfield shift of ~5 ppm for the carbonyl carbon. Similar results were obtained for ethyl acetoacetate compared to methyl butanoate.[9] Therefore, it seems clear that the resonance of C-1 in **1** should be upfield from the corresponding shift in coumarin (160.4 ppm) and that the assignment (154.7 ppm) based on coupling constant data is the correct assignment.[4] If this analogy is correct, one should observe a downfield shift for C-1 on going from **1** to **4**. Therefore the sford singlet at 158.6 ppm is assigned to C-1 in **4**. The remainder of the carbons in **1**, **2**, **3**, and **4** were assigned from sford spectra, substituent effects, and from comparison of the spectra.

The carbons in the cyclopentenone ring of **5** (C-1–C-5) were assigned by comparison with the spectrum of 3-methyl-2,3-cyclopentenone.[11] Carbons 9–15 of **5** were assigned by comparison of the spectra of **1**–**4**. The remaining carbons of **5** were assigned using substituent effects, sford spectra, and comparison with the spectra of **1**–**4**.

The assignments of the ^{13}C spectra of aflatoxins G_1 (**6**), G_2 (**7**), and G_{2a} (**8**) were based on the assignments of **1**, **2**,and **3**. Compared to the spectrum of **1**, the spectrum of **6** should differ principally in the position of the resonances of C-2–C-6 because of the differences between the cyclopentenone and cyclohexenolide rings. The upfield shifts for C-2 and C-6 in **6** compared to **1** are consistent with the difference between an α,β-unsaturated ketone (**1**) and an α,β-unsatrated ester (**6**).[9] Similarly, the differences observed for C-4 and C-5 in

Table I. Carbon-13 Chemical Shifts for Some Aflatoxins[a]

Carbon	1[b]	2[c]	3[c]	4[c]	5[c]	6[b]	7[b]	8[c]
1	154.7	155.8	153.9	[158.6][d]	208.6	154.8	154.9	153.9
2	117.0	115.6	117.4	110.8	131.5	113.2	113.7	111.0
3	200.6	200.0	200.0	154.7	170.9	159.9	160.0	159.6
4	35.0	34.6	34.6	103.5	31.9	64.3	64.3	64.1
5	29.0	28.5	28.5	[158.8][d]	34.2	28.8	28.9	28.4
6	176.5	176.6	176.7	91.0	[106.1][d]	161.1	161.3	161.9
7	103.7	105.5	106.9	160.6	159.5	106.9	102.1	105.3
8	161.0	160.8	160.8	106.8	86.6	161.0	161.0	161.6
9	90.6	90.0	90.5	150.7	158.6	91.0	90.3	91.1
10	165.3	165.8	165.3	112.6	[106.7][d]	164.6	166.1	164.9
11	107.5	105.9	108.6	47.2	151.3	107.5	106.6	108.6
12	152.5	152.0	152.0	102.0	111.5	151.7	152.2	151.6
13	113.2	113.3	113.6	145.1	47.6	113.2	113.7	113.7
14	47.8	42.8	41.3	41.1	103.1	47.7	43.9	41.9
15	102.3	30.6	37.2	59.9	144.1	102.3	31.4	41.9
16	144.8	66.9	99.7			144.8	67.7	91.1
OCH_3	56.4	56.6	56.6	56.4	55.8	56.4	56.4	56.7

[a] In parts per million downfield from Me_4Si. [b] In $CDCl_3$. [c] In Me_2SO-d_6. [d] Assignments may be reversed.

Table II. Carbon-13 Chemical Shifts for Some Sterigmatocystins[a,b]

Carbon	9	10	11	12
1	180.9	180.8	174.6	174.7
2	108.8	108.7	106.2	106.0
3	154.7	154.6	156.5	156.3
4	106.4	105.5	106.2	106.0
5	135.4	135.2	133.4	133.1
6	111.0	110.7	108.9	108.7
7	162.1	161.9	160.4	160.3
8	153.7	154.6	152.9	153.2
9	106.4	106.7	106.2	106.0
10	164.3	165.7	162.7	164.1
11	90.4	89.6	90.3	89.5
12	163.0	163.1	162.7	162.7
13	105.7	105.1	105.6	104.2
14	113.1	113.1	112.9	112.8
15	47.9	44.2	48.1	44.3
16	105.7	31.4	102.6	31.5
17	145.1	67.6	145.0	67.5
CH_3O^-	56.6	56.6	56.3	56.3
CH_3O^-			56.3	56.3

[a] In parts per million downfield from Me_4Si. [b] In $CDCl_3$ solution.

comparing 1 with 6 are consistent with the differences in the data for an ethyl ester (6).[9] The upfield shift for C-3 in 6 compared to 1 is in the expected direction. The assignment of the remainder of the carbons in 6, 7, and 8 follows from the assignment of similar carbons in 1, 2, and 3.

The assignment of the ^{13}C NMR spectra of sterigmatocystin (9, Table II) has been reported previously.[7] Our data for 9 agree with those reported previously, considering that the spectra were obtained on solutions of different concentrations. The assignment of the spectrum of 10 was based on the assignment of 9 and on the differences in the spectra of 1 and 2. Major differences between the spectra of 9 and 10 were in the chemical shifts of C-15, C-16, and C-17 as expected. The assignment of the spectrum of 11 was based on that of 9 by taking into account the substituent effect difference between the hydroxy and methoxy groups.[9] The upfield shift observed for C-1 in 11 compared to 9 is probably due to a steric difference between the methoxy and hydroxy groups and to the absence of hydrogen bonding to the carbonyl group in 11.[9] Assignment of the spectrum of 12 follows from that of 11 and the above discussion.

Comparison of the spectra of 1–8 and 9–12, in conjunction with other data, allows a consistent assignment for the carbons of all compounds to be made. Even though the compounds reported here are similar, there are significant differences in their ^{13}C NMR (Tables I and II) which allow one to distinguish the compounds. These data should prove useful in identifying these fungal metabolites in future investigations.

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Registry No.—1, 1162-65-8; 2, 7220-81-7; 3, 17878-54-5; 4, 23315-33-5; 5, 52373-83-8; 6, 1165-39-5; 7, 7241-98-7; 8, 20421-10-7; 9, 10048-13-2; 10, 6795-16-0; 11, 17878-69-2; 12, 24945-81-1.

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Maytoline, Maytine, and Maytolidine, Novel Nicotinoyl Sesquiterpene Alkaloids from *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek[1]

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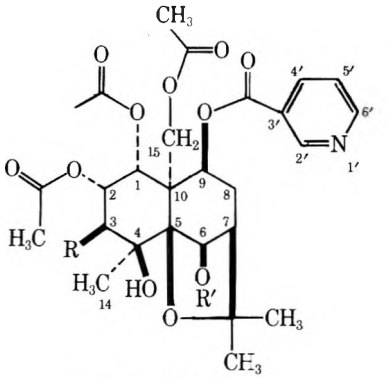
Three novel nicotinoyl sesquiterpene alkaloids, maytoline (**1**, $C_{29}H_{37}NO_{13}$), maytine (**2**, $C_{29}H_{37}NO_{12}$), and maytolidine (**4**, $C_{36}H_{41}NO_{14}$), have been isolated from the fruit of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek. The structure of **1** was determined by x-ray crystallography of its methiodide and is the prototype of a new class of alkaloids found in the Celastraceae. The structures of **2** and **4** were shown to be 3-deoxymaytoline and 3-acetyl-6-deacetyl-6-benzoylmaytoline, respectively, by a study of the physical properties, in particular mass and NMR spectroscopy.

Maytoline (**1**) and maytine (**2**), the major alkaloids from the fruit of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek, have been reported to be the prototypes of a new alkaloid family present in the Celastraceae.[2] We report herein our detailed studies on the isolation and physical and chemical properties of maytoline (**1**) and maytine (**2**) and of the related compound, maytolidine (**4**).



1, R = OH; R′ = Ac
2, R = H; R′ = Ac
3, R = OAc; R′ = Ac
4, R = OAc; R′ = Bz

The aqueous ethanol extract of the dried fruit of *M. serrata*[3] was chromatographed on SilicAR CC-7. The 5% methanol-chloroform eluate was separated by chromatography on alumina into a chloroform eluate and a methanol eluate. Rechromatography of the methanol eluate, followed by acid extraction and TLC of the bases, yielded the major component, maytoline (**1**), $C_{29}H_{37}NO_{13}$. Rechromatography of the chloroform eluate followed by TLC yielded the related alkaloid maytine (**2**), $C_{29}H_{37}NO_{12}$. The remainder of the chloroform eluate on acid extraction gave a mixture, which was separated by chromatography to yield maytolidine (**4**), $C_{36}H_{41}NO_{14}$. Although separable by TLC on alumina, **1** and **2** were inseparable by TLC on silica gel. The three alkaloids were weakly basic and gave faint positive reactions with Dragendorff's reagent. The molecular formulas were determined by comparison of the elemental analysis and high-resolution mass spectroscopic measurements.[4]

The mass spectral fragmentations of **1** and **2** were similar and both showed ions for the loss of CH_3 (presumably from the C-11 *gem*-dimethyl group), H_2O, and CH_3CO_2H, but little additional information could be derived from the high mass region.

The infrared spectra of **1** and **2** were very similar, and both contained bands assignable to hydroxyl (2.8 μ), ester carbonyl (5.75 μ, broad), and a pyridine ring (6.29 μ). The ultraviolet spectra [λ_{max} 221, 258 (infl), 265, and 271 nm (infl) (ϵ 9600, 2500, 2700, 2300) for **1**] were almost identical, and on addition of acid showed very similar changes [λ_{max} 220, 257 (infl), 263, 268 nm (infl) (ϵ 8300, 4300, 4800, 4200)], characteristic of a nicotinoyl chromophore [e.g. nicotinic acid, λ_{max} (MeOH) 212, 262.5 nm (ϵ 6600, 3600); λ_{max} (MeOH + H^+) 217, 263 nm (ϵ 4900, 4900)[5]]. Confirmation of this assignment came from the NMR spectra of **1** and **2**, which both contained signals at τ 2.62 (dd, $J_{5',6'} = 5$, $J_{4',5'} = 8$ Hz, 5′-H), 1.73 (dt, $J_{4',5'} = 8$, $J_{4',6'} = J_{2',4'} = 2$ Hz, 4′-H), 1.21 (dd, $J_{5',6'} = 5$, $J_{4',6'} = 2$ Hz, 6′-H), and 0.77 (d, $J_{2',4'} = 2$ Hz, 2′-H), which were shown by double resonance studies to be intercoupled. These signals could be assigned to the protons on a 3-carboxypyridine ring [e.g., ethyl nicotinate,[6] τ 2.65 (dd, J = 4.7, 7.9 Hz, 5-H), 1.73 (dt, J = 7.9, 1.9 Hz, 4-H), 1.27 (dd, J = 1.9, 4.7 Hz, 6-H), and 0.81 (d, J = 1.9 Hz, 2-H)]. Intense peaks present in the MS of both **1** and **2** at *m/e* 124.0397 (100%, $C_6H_6NO_2$ requires 124.0398) and 106 were assigned to the protonated nicotinic acid ion formed with double hydrogen migration[7] and to the nicotinoyl ion, respectively.

As well as the nicotinoyl proton signals, the NMR spectrum of **1** (see Table I) contained signals assignable to a D_2O-exchangeable proton (τ 6.32) and to protons on carbon atoms carrying a primary ester group, four secondary ester groups, and a secondary alcohol. From the coupling constants the partial structure ·CHOAc·CHOAc·CHOH· could be deduced and this was assigned to C-1, C-2, and C-3. The spectrum of **2** (Table I) was very similar, except that it lacked the signal for the proton on the carbon carrying the secondary hydroxyl, and the signal assigned to the adjacent proton appeared as a multiplet, superimposed upon the signal assigned to the C-9 proton. Attempts to resolve this system by changing the solvent were unsuccessful. The partial structure, ·CHOAc·CHOAc·CH_2·, was consequently proposed for maytine.

The spectra both contained seven singlets for methyl groups at τ 7.70–7.91 (3 Me) and at 8.35–8.50 (4 Me). Of the second group three signals were assigned to quaternary methyl groups and one to a C-1 acetyl methyl group, which must be shielded by the diamagnetic effects of the nicotinoate ring substituted at C-9.

These assignments were confirmed by protonation or hydrogenation of the heteroaromatic ring. When trifluoroacetic acid was added to the solution of **2** the methyl signals appeared at τ 7.61, 7.73, 7.76, *8.20*, 8.31, 8.36, 8.46, and the signals for the protons on the protonated pyridine ring appeared at τ 0.50, 0.72, 0.89, 1.72. Attempts to hydrogenate **2** in ethyl acetate over Pd/C failed, but with a PtO_2 catalyst hydrogenation yielded tetrahydromaytine (**5**). The ultraviolet spectrum, λ_{max} 290 nm (ϵ 13 600), was very similar to that of 3-ethoxycarbonyl-2-piperidine, λ_{max} 290 nm (ϵ 20 000),[8] and in agreement the NMR spectrum contained a signal for only one olefinic proton at τ 2.61 (d, J = 6.5 Hz). The positions of the methyl group signals τ 7.78, 7.90 (6 H), *8.18*, 8.46 (6 H), and 8.52 were

Table I. NMR Spectra of Nicotinoate Alkaloids and Derivatives from *Maytenus serrata*[a]

Compd	C-1	C-2	C-3	C-6	C-9	C-15[b]	CH_3C	CH_3CO	OH
1[c]	4.09 d (3.5)	4.40 t (3.5)	6.40 d (3.5)	3.84 s	4.51 bd (7.5)	5.04, 5.60 (13)	8.39 (3 H), 8.46 (6 H)	7.70, 7.82, 8.35[d] 7.85	6.32
2[c]	4.41 d (3.5)	4.53 m		3.87 s	4.53 m	5.07, 5.61 (13)	8.44 (3 H), 8.49 (6 H)	7.74, 7.90, 8.40[d] 7.91	6.90
3[c]	4.20 d (3.5)	4.60 t (3.5)	5.13 d (3.5)	3.92 s	4.54 bd (8)	5.10, 5.62 (13)	8.41 (3 H), 8.45 (3 H), 8.48 (3 H)	7.72, 7.87, 8.39[d] 7.74, 7.88	6.60
4[e]	4.16 d (3.5)	4.58 t (3.5)	5.10 d (3.5)	3.77 s	4.48 bd (7.5)	5.10, 5.57 (13)	8.41 (3 H), 8.39 (3 H), 8.45 (3 H)	7.66, 7.86, 8.36[d] 7.70	6.41

[a] Spectra measured as $CDCl_3$ solutions at 100 MHz. Coupling constants in parentheses in hertz. Multiplicity: d, doublet; t, triplet; bd, broadened doublet; m, multiplet; s, singlet. [b] AB quartet. [c] Spectrum also contained signals for four nicotinoate protons. [d] Acetyl peak at high field distinguished by its sharpness compared to CH_3C. [e] Spectrum also contained signals for benzoate and nicotinoate protons.

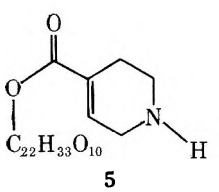
significantly changed compared to the spectrum of **2**, but the rest of the spectrum was quite similar. It was observed that the signal (in italics), which had changed downfield in protonated **2** and in **5**, was sharper than the other high field signals, which were thus assigned to quaternary methyl groups. (See Table I.)

On treatment with acetic anhydride in pyridine, **2** was unchanged and **1** formed the acetate (**3**). The NMR spectrum of **3** contained an additional methyl signal at τ 7.74 and the signal assigned to the C-3 proton now appeared at τ 5.13 (d, J = 3.5 Hz). Thus **3** contained the partial structure $-(CHOAc)_3-$. As the infrared spectra of **3** and **2** both contained a band at 2.8 μ, **1**, **2**, and **3** could be assumed to contain a tertiary hydroxyl group.

Hydrolysis of **1** and **2** led respectively to maytol (**6**, $C_{15}H_{26}O_8$) and 3-deoxymaytol (**7**, $C_{15}H_{26}O_7$). The formulas were determined by high-resolution mass spectral measurement of the strong $M^+ - 15$ peaks. The spectra also contained peaks for multiple losses of 18 mass units from both the molecular ion and the $M^+ - 15$ ion. The NMR spectra of **6** and **7** contained no signals below τ 5 (confirming an absence of olefinic protons), a multiplet at τ 5.0–6.5 (for protons on carbon carrying hydroxyl), and three quaternary methyl group signals at τ 8.2–8.5. The infrared spectra lacked carbonyl bands; thus the four acetyl groups and the nicotinoyl group had been hydrolyzed in each case. As **6** and **7** apparently contained no double bonds or carbonyl groups they must be tricyclic and a sesquiterpenoid origin was proposed.

In order to determine the structure of the nucleus and the location of the acyl substituents, the methiodide of maytoline was prepared and the relative stereochemical structure for **1** was determined by x-ray crystallographic analysis.[2,9] Unfortunately the results did not permit an assignment of absolute stereochemistry.

From the similarities of the NMR spectra of **1** and **2**, and of **6** and **7**, it was assumed that the structure of **2** was closely related to that of **1**. Although the differences in the NMR spectra suggested a change from C-3 CHOH to C-3 CH_2, the presence of a C-1 CH_2 group and a C-3 CHOAc group in **2** might be expected to result in a very similar spectrum. Examination of models of **1** and comparison with the x-ray crystallographic structure of the methiodide showed that only the C-1 acetyl group methyl should come under the diamagnetic influence of the pyridine ring. As the spectra of both **1** and **2** contained a high field acetyl group signal, sensitive to changes in the pyridine ring, maytine was proposed to contain a C-1 acetyl group and was therefore assigned structure **2**.



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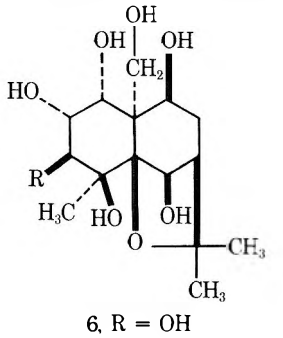

6, R = OH
7, R = H

The mass spectrum of the third alkaloid, maytolidine (**4**, $C_{36}H_{41}NO_{14}$), contained peaks corresponding to the loss of CH_3, H_2O, and CH_3CO_2H from the molecular ion. At lower masses peaks were present at *m/e* 124, 106, assignable to a nicotinoyl group, and also at *m/e* 105, assignable to a benzoyl ion. The molecular formula of **4** was derived from the elemental analysis and high-resolution mass spectral measurement and corresponded to benzoylmaytoline. The ultraviolet spectrum contained considerably increased absorption at 227 nm compared to **1** in addition to bands corresponding to a nicotinoyl group. The NMR spectrum was very similar to that of **3** but contained additional signals overlapping the nicotinoyl proton signals at τ 1.6–1.9 and 2.4–2.7, which were assigned to a benzoate group [e.g., methyl benzoate τ 1.99 (2 H), 2.66 (2 H), and 2.53 (1 H)[10]].

Hydrolysis of **4** yielded maytol (**6**) and acetic and benzoic acids. A possible direct relationship between **1** and **4** was investigated by the benzoylation of **1** with benzoic acid anhydride in pyridine. 3-Benzoylmaytoline was obtained in very poor yield and its NMR spectrum contained acetyl methyl signals at τ 7.73, 7.85, 7.91 similar to the positions in the spectrum of **1** but different from the spectrum of **4** (Table I). In order to determine the position of the benzoate substituent the NMR spectra of **3** and **4** were compared (Table I). The only significant difference was in the position of the C-6 proton signal at τ 3.77 compared to τ 3.92 in **3**. This shift is of the magnitude and direction found in model compounds[11] and therefore structure **4** was proposed for maytolidine.

Small quantities of additional pyridine alkaloids were detected in the remaining chromatographic fractions and mother liquors but they could not be isolated. Further studies on the alkaloids of the fruit of *M. serrata* have yielded the ansamacrolide tumor inhibitor maytansine.[12]

Following the preliminary communication reporting the novel structure of maytoline, the structures of over 20 related alkaloids from the family Celastraceae have been elucidated.[13] All are polyesters of hydroxylated agarofurans and contain either a nicotinic or substituted nicotinic acid. Some of the alkaloids had been isolated previously but, although they had been recognized as nicotinate esters, the structure of the polyhydroxy agarofuran group had not been determined. These included evonine[14] from *Euonymus europeaus*, wilfordine[15] from *Tripterygium wilfordii*, and cathidine D[16] from *Catha edulis*, the last of these being based on 6-deoxymaytol. A number of related nonbasic polyesters have been also reported from the Celastraceae,[13] including euolalin, based on

7,[17] and alatolin, based on an isomer of **7**,[18] both from *E. alatus*.

Experimental Section

Uv spectra were measured on a Coleman Hitachi EPS-3T spectrometer. Ir spectra were measured on a Perkin-Elmer 257 spectrometer. NMR spectra were measured on $CDCl_3$ solutions with a Varian HA-100 spectrometer. Mass spectra were determined on Perkin-Elmer RMU-6E or AEI-MS9 spectrometers. Analyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Isolation of Alkaloids from *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek. The dried ground fruit (5 kg) of *M. serrata* was extracted for 3 days with cold aqueous EtOH. The extract (780 g) was partitioned between EtOAc and H_2O. The EtOAc-soluble fraction (115 g) was chromatographed on a SilicAR CC-7 column (1.4 kg), which was eluted with $CHCl_3$ (6 l.). Elution with 5% MeOH/$CHCl_3$ (7 l.) then yielded an oil (44 g). The oil was chromatographed on neutral alumina (440 g), which was eluted with $CHCl_3$ to give fraction A (20 g) and with MeOH to yield fraction B (6 g).

Fraction A was chromatographed on silica gel (600 g). Elution with ether yielded fraction C (16 g), and then with EtOAc yielded fraction D (800 mg). Fraction D (292 mg) was separated by TLC on alumina (EtOAc) to yield the major component maytine (**2**, 57 mg): uv (MeOH) λ_{max} 221, 258 (infl), 265, and 271 nm (infl) (ϵ 10 700, 3200, 3300, 2700); uv (MeOH + H^+) λ_{max} 220 (infl), 255 (infl), 262, 268 nm (infl) (ϵ 7150, 4200, 5200, 4200); ir ($CHCl_3$) 2.83, 5.73 b, 6.29, 7.29, 11.5 μ; MS *m/e* 591.2316 (M^+, calcd for $C_{29}H_{37}NO_{12}$, 591.2315).

The other components from fraction D and fraction C were combined with corresponding fractions from other extractions to give an oil (20 g). The oil was dissolved in EtOAc (250 ml) and extracted with 2 N HCl (three 50-ml portions). The acidic solution was neutralized and extracted with EtOAc to give an oil (873 mg), which on examination by TLC on silica gel or alumina contained a number of basic components.

The non-acid-soluble EtOAc solution was evaporated and the residue dissolved in ether (500 ml). The ethereal solution was extracted with 2 N HCl (100 ml, two 50-ml portions). The combined acid solutions were washed with Et_2O, neutralized, and extracted with Et_2O. This Et_2O extract was dried and evaporated to give a solid (1.6 g), which by TLC on alumina (EtOAc) contain two major basic components.

The solid was chromatographed on neutral alumina to give two fractions on elution with EtOAc. The first fraction (497 mg) was recrystallized twice from EtOAc/Et_2O to yield maytolidine (**4**, 152 mg): mp 128–132°C; uv (MeOH) λ_{max} 227, 259 (infl), 265, 271 (infl), 282 nm (infl) (ϵ 19 400, 4600, 5000, 4800, 3000); uv (MeOH + H^+) λ_{max} 227, 257 (infl), 263, 269, 283 nm (infl) (ϵ 17 500, 6200, 7350, 6900, 3000); ir ($CHCl_3$) 2.8, 5.71, 5.83, 6.29, 7.30, and 9.09 μ.

Anal. Calcd for $C_{36}H_{41}NO_{14}$: C, 60.75; H, 5.80; N, 1.97; M^+, 711.2526. Found: C, 60.29; H, 6.06; N, 1.88; M^+, 711.2597.

The second fraction (1.02 g) was rechromatographed on alumina to yield more **4** (500 mg). The remaining fractions showed the presence of other pyridine alkaloids but these could not be isolated in sufficient yield for identification, using a number of different solvent systems.

Fraction B (MeOH eluate from alumina) was chromatographed on silica gel and elution with EtOAc yielded a fraction (1.4 g) with the same R_f on silica gel as **2**. This fraction was dissolved in EtOAc (50 g) and extracted with 2 N HCl (three 25-ml portions). The acid was neutralized and extracted with EtOAc to give a mixture (650 mg). The mixture was separated by TLC on alumina (10% MeOH/EtOAc) to give the major component, maytoline (**1**, 123 mg): $[\alpha]^{25}D$ 0.3° (*c* 0.75, $CHCl_3$); uv (MeOH) λ_{max} 221, 258 (infl), 265, 271 nm (infl) (ϵ 9600, 2500, 2700, 2300); uv (MeOH + H^+) λ_{max} 220, 257 (infl), 263, 268 nm (infl) (ϵ 8300, 4300, 4800, 4200); ir ($CHCl_3$) 2.85, 5.75 b, 6.29 μ; MS *m/e* 607.2251 (calcd for $C_{29}H_{37}NO_{13}$, 607.2264), 592.2045 (calcd for $C_{28}H_{34}NO_{13}$, 592.2029), 547.2062 (calcd for $C_{27}H_{33}NO_{11}$, 547.2053).

Tetrahydromaytine (5). A solution of maytine (20 mg) in EtOAc (3 ml) was hydrogenated over PtO_2. The product was filtered through alumina to yield a mixture which was separated by TLC on silica gel to yield, as a gum, tetrahydromaytine (**5**, 4.9 mg): uv (MeOH) λ_{max} 290 nm (ϵ 13 600); ir ($CHCl_3$) 2.89, 5.75, 5.99, 6.17 μ; MS *m/e* 595.2628 (M^+, calcd for $C_{29}H_{41}NO_{12}$, 595.2628) and 537.

Acetylmaytoline (3). A solution of maytoline (30 mg) in pyridine (1 ml) and acetic anhydride (0.5 ml) was left overnight. After workup the product was separated by TLC to give, as a gum, acetylmaytoline (**3**, 13 mg): uv (MeOH) λ_{max} 221.5, 258 (infl), 264, 271 nm (infl) (ϵ 8700, 2800, 2900, 2300); uv (MeOH + H^+) λ_{max} 207, 256 (infl), 262, 268 nm (infl) (ϵ 6900, 3600, 4600, 3800); ir ($CHCl_3$) 2.8, 5.71, 6.29, 7.29, 9.09 μ; MS *m/e* 649.2345 (M^+, calcd for $C_{31}H_{39}NO_{14}$, 649.2370).

3-Benzoylmaytoline. A solution of maytoline (25 mg) and benzoic anhydride (60 mg) in pyridine (1 ml) was left for 3 days at room temperature. Workup gave a product, which was separated by TLC on alumina to give 3-benzoylmaytoline (2.2 mg) with the same R_f as maytolidine on TLC on either silica gel (EtOAc) or alumina (EtOAc): MS *m/e* 711 (M^+) 686, 124, 105.

Maytol A. From Maytolidine. A solution of maytolidine (**4**, 38 mg) in 2 N NaOH (1 ml) and MeOH (0.5 ml) was kept at room temperature for 1.5 h. The solution was acidified and extracted with ether (two 10-ml portions), which was dried and evaporated to give a solid (4.2 mg) smelling of acetic acid. The solid was sublimed at 80 °C (10 mm) to yield benzoic acid, mp 120–121.5 °C.

The aqueous solution was evaporated to yield a solid, which was extracted with MeOH. The methanolic solution was evaporated and the residue extracted with $CHCl_3$ to yield a gum (5.6 mg). The gum was filtered through silica gel to yield maytol (**6**, 3.6 mg): mp 229–237 °C; no uv absorption; ir (KBr) 2.9 μ b; NMR (acetone-d_6) τ 8.48 (s, 3 H), 8.32 (s, 3 H), 8.27 (s, 3 H), 5.0–6.8 m; MS *m/e* 319.1401 (M^+ − 15, calcd for $C_{14}H_{23}O_8$, 319.1392), 316 (M^+ − 18), and repeated 18 mu losses from both ions.

B. From Maytoline. A solution of maytoline (24 mg) in MeOH (1 ml) and 2 N NaOH was kept at room temperature for 1.5 h. The solution was then acidified and washed with Et_2O (two 5-ml portions). The acid solution was evaporated and the residual solid repeatedly extracted with hot $CHCl_3$, which was evaporated to give a gum (8 mg). The gum was separated by TLC on silica gel (10% MeOH/EtOAc) to give maytol (2.6 mg), identical with material from maytolidine by NMR and MS.

Deoxymaytol (7). A solution of maytine (49 mg) in MeOH (1 ml) and 2 N NaOH (1 ml) was kept at room temperature for 1.5 h. The solution was acidified and washed with Et_2O (two 5-ml portions). The aqueous solution was evaporated and the residue was extracted with hot $CHCl_3$ to yield an oil (25 mg). The oil was separated by TLC on silica gel (25% MeOH/$CHCl_3$) to give the major component, deoxymaytol (**7**, 11.6 mg): NMR (acetone-d_6) τ 8.50 (s, 3 H), 8.32 (s, 3 H), 8.25 (s, 3 H), 5.3–6.5 m; MS *m/e* 303.1438 (M^+ − 15, calcd for $C_{14}H_{23}O_7$, 303.1445), 300 (M^+ − 18), and repeated losses of 18 Mu from both fragments.

Maytoline Methiodide. A solution of maytoline (30 mg) in benzene (0.4 ml) and methyl iodide (0.1 ml) was left in the dark at room temperature for 3 days. An oil separated and the mother liquor was decanted. The oil on precipitation from MeOH with Et_2O gave a solid, which was crystallized twice from MeOH/Et_2O to give crystals of maytoline methiodide (the crystals were unstable in air and rapidly lost solvent of crystallization to give a powder): mp 190–193 °C dec; uv (MeOH) λ_{max} 219, 260 (infl), 266, 272 nm (ϵ 20 000, 4000, 4950, 4100); ir ($CHCl_3$) 5.72 μ.

Registry No.—**1**, 31146-55-1; **2**, 31146-56-2; **3**, 60512-70-1; **4**, 60512-69-8; **5**, 31146-57-3; **6**, 31230-10-1; **7**, 31146-58-4; 3-benzoylmaytoline, 60512-71-2; maytoline methiodide 31146-59-5.

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Synthesis of DL-Methyl Meromycolate

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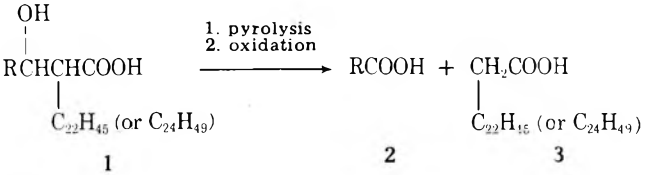
A flexible total synthesis is reported of a biscyclopropane methyl meromycolate, a product derived from the tuberculosis bacterium. The approach was to synthesize two major sections separately, namely, the bistrimethylenedithiol derivative of 10-oxo-*cis*-13,14-methylenedotriacontanal and the ethylene glycol acetal of 22-bromo-*cis*-19,20-methylenedocosanal, and then to combine them just before the final stages.

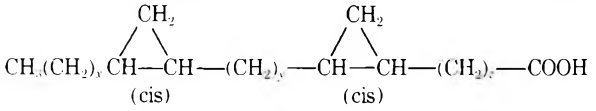
Degradation of the cell wall of tuberculosis organisms has given a number of products, among which is a family of lipids collectively called "mycolic acids".[1] These are all high molecular weight carboxylic acids **1** with a long straight chain at the carboxylic α position and a hydroxy group at the β position. Pyrolysis of mycolic acid (**1**) produces an aldehyde plus



1 **2** **3**

either tetracosanoic or hexacosanoic acid (**3**). Oxidation of the aldehyde ("meromycolaldehyde"), generally with silver oxide, yields the corresponding meromycolic acid (**2**).[2-9] We wish to contribute to this area by developing flexible total syntheses leading to meromycolates of assured structure. Not only would these be available for reference and comparison but they would also be used for the synthesis of mycolic acids as well as larger liposaccharide cell wall components.

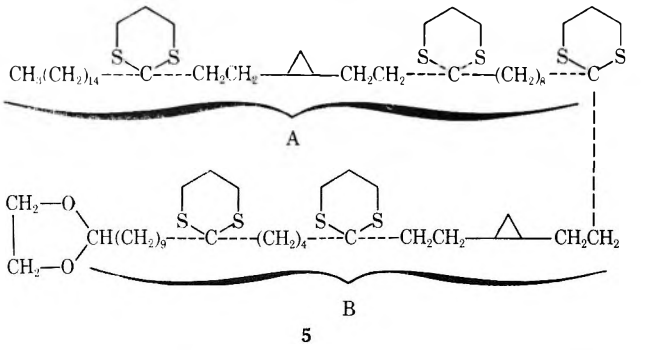
The meromycolic acids (**2**) include a subgroup having cyclopropane rings at two points along an extended carbon chain, as in **4**.[6,10] Since the literature data on this subgroup



4

provide a defensible basis for the structural assignment, we took this kind of meromycolic acid as our first synthesis target. Different sets of x, y, z values in **4** have been reported for the most abundant component in the samples investigated.[11] We chose the set $x = 17$, $y = 14$, $z = 17$,[12] because the corresponding meromycolic acid is representative, and because it has in fact been obtained as a degradation product. The present paper reports our work, which has for the first time furnished a large molecular weight synthetic meromycolate of unequivocal structure.

To assemble the pieces that would give meromycolic acids **4** we first tried the mixed Kolbe anodic coupling process,[13] which proved not to be satisfactory. Alkylation of metalated 1,3-dithianes[14] gave much better results, and we relied on the dithiane method throughout the synthesis. Formulation **5** shows the fragments contributing carbon atoms to the meromycolic ester selected as the synthesis target (**4**: $x = 17$, $y = 14$, $z = 17$). Moieties A and B were constructed separately—the dotted lines indicate the several bonding points—and then were combined to give the complete carbon skeleton. The cyclopropane rings in the two parts were both introduced in the form of the same 3,4-methylenehexane unit, specifically as compound **16**, whose synthesis is described below.



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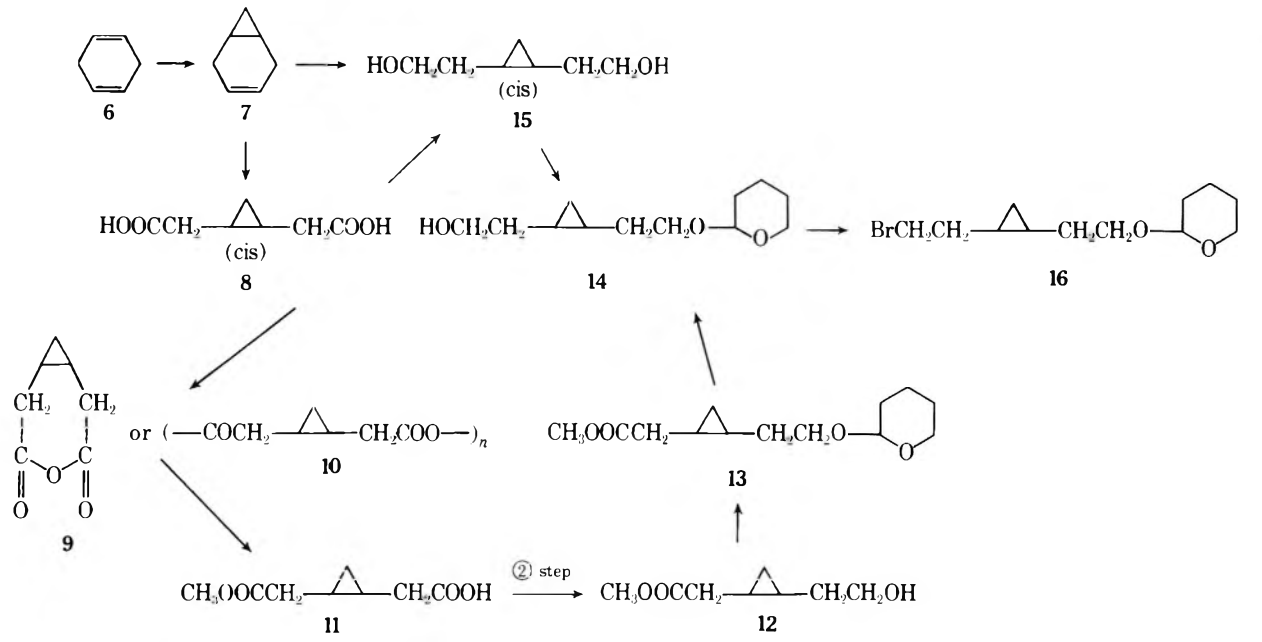
Synthesis of the Cyclopropane Portion (16). Norcarene (**7**), from 1,4-cyclohexadiene (**6**), can be converted by ozonolysis to *cis*-1,2-cyclopropanediacetic acid (**8**).[15] It was expected that anhydride formation from diacid **8** would give cyclic anhydride **9**, which would acylate methanol without complication to give half-ester **11** as the sole product. The half-ester was, in fact, obtained but only as a 2:1:1 mixture with the corresponding diester and diacid. This result is consistent with the formulation of the acid anhydride as a linear polymer **10** instead of the cyclic monomer **9**. The separated half-ester **11** was converted to the ester–acid chloride and then reduced with borohydride to ester alcohol **12**. Reaction with dihydropyran furnished intermediate **13**, which with lithium aluminum hydride gave alcohol **14**. Further conversions provided the properly functionalized tetrahydopyranyl–alkyl bromide synthon **16**. An alternate pathway called for direct sodium borohydride reduction of the ozonide from norcarene (**7**) to diol **15**, which could also be obtained from diacid **8**. The diol treated with dihydropyran under controlled conditions gave the desired monotetrahydropyranyl derivative **14** in modest single-pass conversions (35%) though in high yield when corrected for the recovered, reusable materials.[16] The shorter path via diol **15** was preferred.

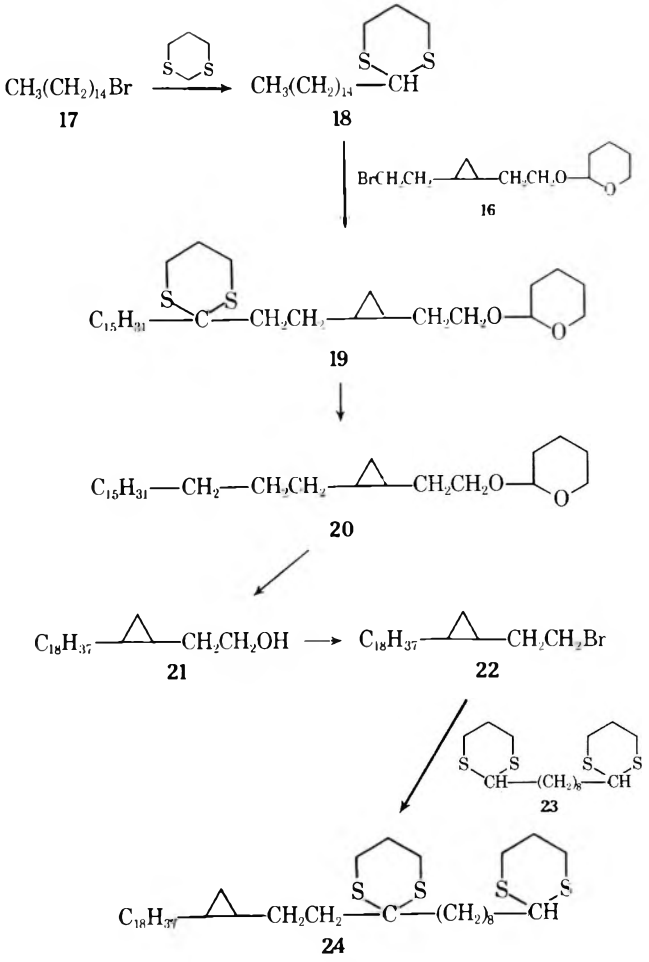
Fragment **16** provides all the asymmetric centers of the finished meromycolic acid. In the present work we used racemic **16** and so obtained an optically inactive final product. In work to be continued we plan to insert the resolved forms

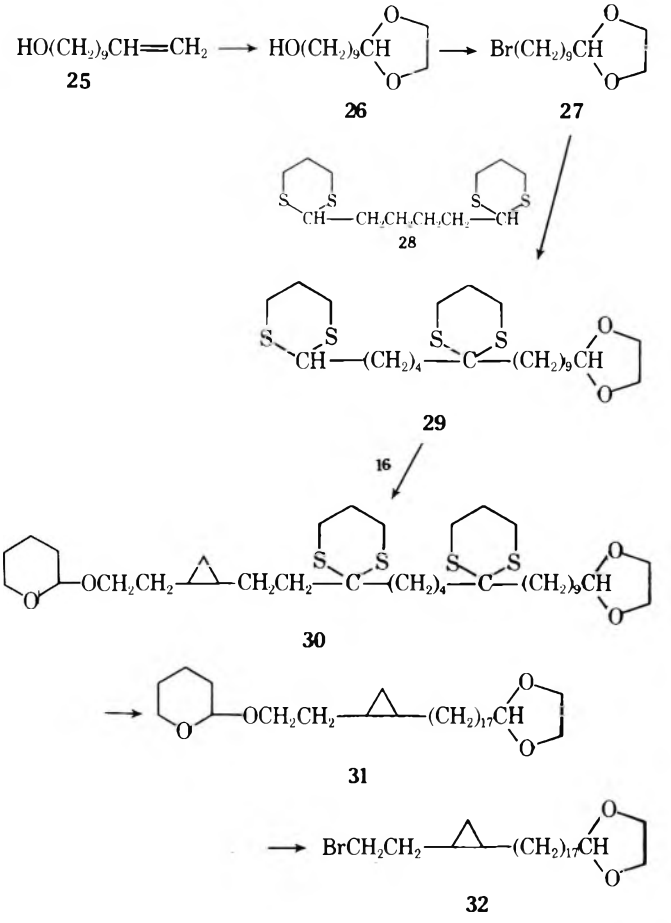


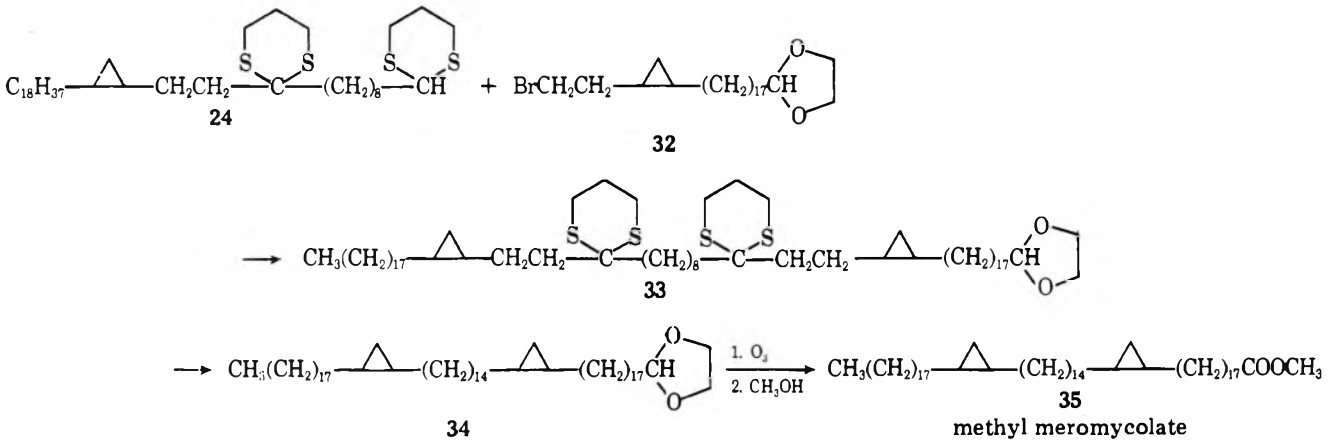
of **16**, and thus, by ringing the changes with the two enantiomers, to arrive at the optically active forms of meromycolic acid **4**.

Synthesis of the Methyl End (5-A or 24) of Meromycolic Acid. 2-Pentadecyl-1,3-dithiane (**18**) was obtained by alkylating the lithio derivative of 1,3-dithiane with pentadecyl bromide (**17**). A second alkylation, this time with the cyclopropane-containing bromide **16**, afforded the 2,2-disubstituted dithiane **19** which, after desulfurization with Raney nickel[17] to **20**, was hydrolyzed to *cis*-3,4-methylenedocosanol (**21**) and then converted to the corresponding bromide **22**. Finally, bisdithiane derivative **23** was monoalkylated with this bromide to **24**, which was one of the two major sections (**5-A**) making up the meromycolic acid product. A variation by which the chain was extended by alkylating bisdithiane **23** not with **22** but instead with the bromide corresponding to **19** was explored. However, removing six atoms of sulfur at once from the trisdithiane in the last stages of the synthesis was disadvantageous, and this approach was not pursued.

Synthesis of the Carboxyl End (5-B or 32) of Meromycolic Acid. At first we planned to synthesize this part of the molecule with the terminal vinyl group carried through in place of carboxyl. Oxidation at the last stage would cleave the double bond and develop the acid group. This approach was dropped when model experiments indicated that the vinyl







group would be saturated during the intermediate Raney nickel desulfurizations.[18]

The synthesis that was realized started with the ozonolysis of 10-undecenol (**25**) to 10-hydroxydecanal, which was converted directly to acetal **26**. The chain was extended by six carbon atoms by coupling the corresponding bromide **27** with bisdithianyl derivative **28**. A second alkylation, this time with the cyclopropane synthon **16**, led to intermediate **30**. To complete the sequence, the bisdithiane molecule **30** was desulfurized to **31** and the tetrahydropyranyl end of the chain was transformed to bromide, as in **32**. In the acid-catalyzed removal of the tetrahydropyranyl group, the problem of avoiding loss of the aldehyde blocking group at the far end of the chain was solved simply by including high concentrations of ethylene glycol in the reaction mixture.

Synthesis of Methyl Meromycolate (35). Coupling of the lithio derivative of bisdithiane intermediate **24** with alkyl bromide **32** gave the expected product **33**. A minor heterogeneity was more conveniently removed in the next step, after desulfurization, than at this stage. An unexpected complication was encountered in the desulfurization step. The product, biscyclopropane **34**, requires a ratio of 0.5 for the nuclear magnetic resonance signals at δ 0.85 (*C*-methyl) and 0.55 ppm (cyclopropane H's cis to each other). The fact that the observed ratio was greater than 0.5 indicated extra methyl groups and (or) fewer cyclopropane rings. Hydrogenolysis of the cyclopropane rings would account for this result. The presence of extra hydrogen atoms in the desulfurization product, which turned out to be a mixture, was confirmed when mass spectra showed molecular peaks not only at *m/e* 840 as calculated for **34** but also at *m/e* 842. Recrystallizations from dilute methylene chloride solutions separated the mixture cleanly into a higher melting material (mp 69–72 °C), taken as the desired product **34**, and a lower melting material (mp 45–49 °C), taken as the overreduced product. Mass spectra on the separated fractions confirmed the assignments, since the higher melting materials (**34**) had a molecular peak at *m/e* 840 and no significant peak at *m/e* 842, while the lower melting material showed a molecular peak at *m/e* 842 but practically nothing at *m/e* 840.

Why the cyclopropane ring breaks during the Raney nickel desulfurization of bisdithiane **33** is not clear. In preliminary model experiments, exposing *cis*-1,2-dipropylcyclopropane[19] to Raney nickel under the conditions used in the desulfurization of **33** did not effect the ring and allowed recovery of more than 90% of unchanged material. Nor was there any sign of cyclopropane ring cleavage in the Raney nickel desulfurization of intermediates **19**, nor of **30**. The only obvious difference is the higher molecular weight of compound **34**.

The last stages in the synthesis were to be accomplished by hydrolyzing acetal **34** to meromycolaldehyde and then oxidizing the aldehyde to meromycolic acid. Preliminary work showed that the ethylene glycol acetal of decanal could be smoothly hydrolyzed under mildly acidic conditions that had no effect on either *cis*-1,2-dipropylcyclopropane or on methyl *cis*-9,10-methyleneoctadecanoate. Despite these favorable results, no conditions could be found that allowed an uncomplicated hydrolytic unmasking of acetal **34**. Either no reaction occurred or unmanageable mixtures developed.[20] This behavior jibes with the cyclopropane hydrogenolysis in the preceding step in indicating unusual sensitivity to ring cleavage. Possibly in a molecule as large as **34** intramolecular forces can fold the molecule in a way that strains the ring(s). Also, the acetal may be buried in a hydrocarbon region of low dielectric, which could hinder access to the hydrolysis catalyst as well as to the polar water molecule.

Rather than switching to more readily hydrolyzable acetals, we tried an ozonolysis procedure which has been used to oxidize acetals to esters.[21] When applied to acetal **33**, this process smoothly formed the expected hydroxyethyl meromycolate ester. Direct base-catalyzed ester interchange then converted the hydroxyethyl ester to the end product, methyl meromycolate (**35**). The properties determined for the product are fully consistent with formulation **35**, and we regard this structure as secure.

In work to be continued we plan to carry the synthesis through with optically active cyclopropane synthons **16** so as to reach individual, chirally homogeneous, methyl meromycolates.[22] These will be compared with the appropriate degradation methyl meromycolate. They will also be elaborated to mycolic acid[23] and then further to more complex molecules.[24]

Experimental Section

General. Melting points and boiling points are uncorrected. Most of the nuclear magnetic resonance curves were determined with a 60-MHz instrument, with chloroform replacing tetramethylsilane as a reference compound whenever it was necessary to avoid interference with the high-field signal for cyclopropane hydrogen. When ether or tetrahydrofuran was used as reaction solvent, they were distilled over lithium aluminum hydride and collected directly in the reaction flask. Solvents were removed from solutions of temperature-sensitive material by using a rotary evaporator under reduced pressure with the heating bath maintained at or below the temperature specified. Thin layer chromatography made use of commercial silica gel plates impregnated with a fluorescent material enabling visualization with ultraviolet light. Iodine vapor and, for molecules containing divalent sulfur, a spray of 1% palladous chloride in 6 N hydrochloric acid were also useful. Analyses for elements were reported by Galbraith Laboratories, Inc., Knoxville, Tenn.

Norcarene (7).[25] A mixture of 52 g (0.53 mol) of anhydrous powdered cuprous chloride, 35 g (0.53 mol) of 20-mesh granulated zinc, and 150 ml of anhydrous ether was stirred and refluxed for 75 min in a moisture-protected apparatus. 1,4-Cyclohexadiene (25 g, 0.31 mol) mixed with 71 g (0.27 mol) of diiodomethane was added, and the suspension was stirred and refluxed for 21 h. Appropriate processing gave 5.2 g (50% when corrected for recovered 1,4-cyclohexadiene) of norcarene (**7**), bp 112–116 °C. Use of norcarene containing small amounts of 1,4-cyclohexadiene in the next step offered no great disadvantage.

1,2-*cis*-Cyclopropanediacetic Acid (8) from Norcarene (7). The ozonolysis procedure of Weinstein and Sonnenberg[15] was modified in a number of ways. Ozone in oxygen was passed through a 10% solution of norcarene (7) in methanol at 0 °C until the effluent gases oxidized hydriodic acid to iodine. After all volatiles were stripped away (temperature below 15 °C), the viscous residue was allowed to react with 30% hydrogen peroxide in formic acid first at room temperature and then for a short time at 50 °C. The crude product from the reaction mixture, when triturated with two parts of ethyl acetate, gave white prisms of *cis*-1,2-cyclopropanediacetic acid (8), mp 130–132 °C (lit.[15] mp 131–133 °C). The yields ranged from 50 to 65%.

Half Methyl Ester 11 of *cis*-1,2-Cyclopropanediacetic Acid. A mixture of the diacid 8 (3.0 g, 0.019 mol) and *N,N'*-dicyclohexylcarbodiimide (3.9 g, 0.019 mol) in 30 ml of absolute tetrahydrofuran was stirred at 0 °C for 1 h and then at room temperature for 3 h. The precipitate was separated and rinsed with tetrahydrofuran (15 ml). Distillation of solvent at temperatures no higher than 30 °C left the acid anhydride **9** or **10** of *cis*-1,2-cyclopropanediacetic acid as a viscous orange oil: ir (film) 1820 and 1750 cm^{-1} but no carboxyl hydroxyl absorption and no C=N stretch vibration at 2125 cm^{-1}.

The crude anhydride was stirred at 25 °C with 35 ml of absolute methanol for 20 h in a moisture-free system. After distilling away excess methanol (temperature no higher than 30 °C), the oily residue was diluted with 10 ml of anhydrous ether and the mixture was filtered to remove some insoluble dicyclohexylurea. All volatiles were stripped, and the residue was distilled to yield about 2 g (50–60%) of colorless half-ester **11**: bp 98–100 °C (0.10 mm) [lit.[26] bp 150–155 °C (6 mm); 141–142 °C (3 mm)]; mp below 25 °C; ir (film) 3675–2400, 1740, 1710 cm^{-1}; NMR (CCl_4) δ 3.6 (s, 3, $COOCH_3$), 2.4–2.2 (m, 4, 2 CH_2COO), 1.5–0.5 ppm (m, 4, cyclopropane H's). In a 25% solution the one-proton signal for carboxyl H appeared at δ 9.0 ppm; in a 15% solution it appeared at δ 12 ppm.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.59; H, 7.31.

Diacid 8 remained in the pot as residue, whereas dimethyl *cis*-1,2-cyclopropanediacetate distilled from the reaction mixture at bp 89 °C (0.1 mm) in about 25% yield: ir (film) 1735 cm^{-1}; NMR (CCl_4) δ 3.7 (s, 6, 2 $COOCH_3$), 2.36 (d, J = 6 Hz, 4, 2 CH_2COO), 1.5–0.6 ppm (m, 4, cyclopropane H's).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.89; H, 7.53.

Similar results were obtained when acetic anhydride was substituted for dicyclohexylcarbodiimide, or when the diacid was taken in very low concentration. With acetyl chloride as reagent, the methanolysis product was practically all diester, presumably the result of traces of hydrogen chloride. When sodium methoxide (1.5 mol) in hot or cold tetrahydrofuran was used in place of methanol with the anhydride formed with dicyclohexylcarbodiimide, the 2:1:1 mixture was again obtained. All attempts at purifying the anhydride failed. Distillation at temperatures up to 160 °C (0.1 mm) gave no volatile product and left an intractable brown gum in the flask.

Methyl 6-Hydroxy-*cis*-3,4-methylenehexanoate (12). Oxalyl chloride (2.2 g, 0.017 mol) was added in one portion to a moisture-protected solution of half-ester **11** (2.0 g, 0.011 mol) in 20 ml of dry benzene. After stirring the solution at 25 °C for 3 h, all volatiles were stripped away at temperatures below 45 °C. The pale-yellow residual ester–acid chloride dissolved in 10 ml of dry dioxane was added over 5 min to a stirred mixture of sodium borohydride (0.88 g, 0.023 mol) in 30 ml of dioxane. Stirring was continued for 20 h. The mixture was treated dropwise with 10 ml of water and then brought to pH 4 with sulfuric acid. The dioxane together with some water was distilled off at reduced pressures, and the product was then extracted thoroughly with ether. Removing ether from the dried extracts left a pale yellow oil (ca. 1.9 g). Repetition of this procedure starting with 2.1 g of the half-ester gave about the same results. Distillation of the combined products through a short column furnished 3.0 g (79%) of colorless hydroxy ester **12**: bp 73–75 °C (0.15 mm); ir 3400, 3055, 1735 cm^{-1}; NMR ($CDCl_3$) δ 3.68 (t, J = 7 Hz, CH_2O–), 3.6 (s, $COOCH_3$), 3.35 (s, 1, OH), 2.33 (d, J = 6.8 Hz, 2, CH_2COO), 1.78–0.53 ppm (m, 6, cyclopropane H's plus CH_2CH_2OH). The combined integration for the first two signals corresponded to five protons.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.70; H 8.94. Found: C, 60.88; H, 8.99.

***cis*-3,4-Methylene-1,6-hexanediol (15) from Norcarene (7).** Ozonized oxygen was bubbled into a solution of 3-norcarene (3.1 g, 0.033 mol) in 40 ml of absolute chloroform at −78 °C until the effluent gases began to release iodine from aqueous potassium iodide. After the excess ozone was swept out in a stream of oxygen, the stirred mixture at 0 °C was treated with sodium borohydride (9.9 g, 0.26 mol) in 70 ml of 1:1 ethanol–water over a period of 1 h. Stirring was continued for 18 h at room temperature. Acidification to pH 2 with dilute sulfuric acid was followed by thorough extraction with chloroform. The dried extracts were fractionated through a short-path column to give *cis*-3,4-methylene-1,6-hexanediol (**15**, 2.6 g, 70%) as a colorless, viscous liquid: bp 88–89 °C (0.005 mm) [Vogel et al.[15] report bp 136–137 °C (0.01 mm)]; ir (neat) 3500–3300 cm^{-1}; NMR ($CDCl_3$) δ 4.45 (s, 2, 2 OH), 3.67 (t, J = 6 Hz, 4, 2 CH_2O), 1.7–1.3 (broad m, 4, 2 CH_2CH_2O), 0.7 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (broad m, 1, cyclopropane H cis to substituents). The 4.45-ppm signal disappeared when D_2O was introduced.

The same diol product **15** was obtained by reducing *cis*-1,2-cyclopropanediacetic acid (8) or its dimethyl ester with lithium aluminum hydride in tetrahydrofuran.

Monotetrahydropyranyl Derivative 14 of *cis*-3,4-Methylene-1,6-hexanediol. A. From Diol 15. To a solution of diol **15** (3.0 g, 0.023 mol) in dry dichloromethane (120 ml) at 3 °C was added a cold solution of dihydropyran (1.9 g, 0.023 mol) in tetrahydrofuran (30 ml) and then 20 mg of *p*-toluenesulfonic acid in 5 ml of tetrahydrofuran. The mixture was stirred for 1 h at 3 °C and then for 5 h at 10 °C. Triethylamine (0.5 g) was added before removing almost all of the volatiles (temperature below 45 °C). Extraction with pentane removed the tetrahydropyranyl derivatives and left practically pure unchanged diol **15** as a second phase. Distillation of the material in the pentane gave 2.8 g (36% conversion) of the desired monotetrahydropyranyl derivative **14**, bp 100–109 °C (0.003 mm). This product gave a single spot on a TLC plate (ether): ir 3500 cm^{-1}; NMR ($CDCl_3$) δ 4.40 (broad s, 1, tetrahydropyranyl OCHO), 1.4 (broad s, 10, CH_2's next to cyclopropane plus tetrahydropyran 3, 4, and 5 positions), 0.5 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (broad m, 1, cyclopropane H cis to alkyls). Also evident was a multiplet at δ 3.45 (CH_2OTHP plus the tetrahydropyran 6-methylene) topped by a triplet (J = 6 Hz, CH_2OH) and accompanied by a singlet at 3.35 ppm (OH), which together integrated for 7 protons. The 3.35 ppm signal vanished when D_2O was added.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.10; H, 10.36.

B. From Methyl 6-Hydroxy-*cis*-3,4-methylenehexanoate (12). A mixture of ester alcohol **12** (1.0 g, 6.3 mmol), 0.78 g (9.5 mmol) of dihydropyran, and 30 mg of *p*-toluenesulfonic acid in 30 ml of benzene was stirred at 25 °C for 1 day. The mixture was washed with dilute aqueous sodium hydroxide, dried, and then stripped of all volatile material to give 1.5 g of the tetrahydropyranyl derivative **13** of ester alcohol **12**.

A solution of product **13** in ether (10 ml) was added under nitrogen to lithium aluminum hydride (0.5 g, 12 mmol) suspended in 30 ml of ether, and the mixture was stirred at room temperature for 1 day. Excess reagent was decomposed by adding 10 ml of water dropwise to the reaction mixture cooled to below 0 °C followed by 30 ml of 5% aqueous sodium hydroxide. The aqueous layer was extracted thoroughly with ether, and the combined, dried, ether solutions were stripped of all solvent at temperatures no higher than 40 °C to leave the monotetrahydropyranyl derivative **14** as a faintly yellow oil (1.4 g).

Tetrahydropyranyl Bromo Derivative 16. The general procedure as detailed in the preparation of bromo intermediate **27** was followed. Monotetrahydropyranyl derivative **14** (2.6 g, 0.012 mol) in pyridine (25 ml) plus 2.6 g (0.014 mol) of *p*-toluenesulfonyl chloride gave rise to 5.0 g of the corresponding tosylate as a pink oil: ir free of absorption at 3600–3300 cm^{-1}; NMR, consistent with the presence of the tosylate group.

Anhydrous lithium bromide (3.4, 0.039 mol) with 3.2 g of the monotosylate of derivative **14** in 240 ml of dry acetone gave crude product **16**, which on distillation yielded 1.84 g (85% from **14**) of homogeneous (thin layer chromatography with benzene) tetrahydropyranyl derivative **16** of 6-bromo-*cis*-3,4-methylenehexanol: bp 82–92 °C (0.01 mm); NMR ($CDCl_3$) δ 4.45 (broad s, 1, tetrahydropyranyl OCHO), 3.5 (m, 3 CH_2O), 3.30 (t, J = 6 Hz, CH_2Br), 1.5 (broad s, 10, CH_2's next to cyclopropane ring plus CH_2's at tetrahydropyran 3,4,5 positions), 0.6 (m, 3, cyclopropane H's cis to each other), −0.2 ppm (m, 1, cyclopropane H cis to alkyls). The combined integration for the 3.5 and 3.3 ppm signals corresponded to six protons.

Anal. Calcd for $C_{12}H_{21}BrO_2$: C, 51.99; H, 7.63; Br, 28.82. Found: C, 51.69; H, 7.80; Br, 28.64.

The bromo compound deteriorated at room temperature and was routinely stored at 5 °C. The triphenylphosphine–*N*-bromosuccinimide conversion[27] of alcohol **14** to bromide **16** was not satisfactory; the tetrahydropyran ring was attacked to some extent, and the mixture was difficult to purify. When lithium chloride was substituted for lithium bromide, the chloride corresponding to bromide **16** was formed. To check this last process the tetrahydropyranyl protecting

group was removed by exposure to 95% alcohol containing a trace of *p*-toluenesulfonic acid, whereupon 6-chloro-*cis*-3,4-methylenehexanol was obtained.

2-Pentadecyl-1,3-dithiane (18) by Alkylating Dithiane with Pentadecyl Bromide (17).[28] After preparing 2-lithio-1,3-dithiane by metalating 1,3-dithiane (1.24 g, 10.3 mmol) at −30 to −20 °C with butyllithium (10.5 mmol in 2.33 M hexane solution) in 50 ml of absolute tetrahydrofuran, pentadecyl bromide (3.00 g, 10.3 mmol) was injected, and the alkylation was allowed to proceed for 1.5 h and then for 20 h at −7 °C. Water (10 ml) was added and volatiles were removed at reduced temperature (<50 °C). The alkylation product was extracted with ether, and the ether solution was washed thoroughly with water and with dilute aqueous alkali before drying. On crystallization of the crude product from chloroform–methanol, white plates of 2-pentadecyl-1,3-dithiane (**18**, 2.73 g, 80%), mp 44–45.5 °C, homogeneous according to thin layer chromatography (10:1 pentane–ether), was obtained: ir ($CHCl_3$) 2900, 905 cm^{-1}; NMR ($CDCl_3$) δ 4.02 (t, J = 6.0 Hz, 1, dithiane SCHS), 2.97–2.72 (m, 4, 2 CH_2S), 2.25–1.90 (m, dithiane 4-CH_2), 1.27 (broad band, linear CH_2's), 0.92 ppm (t, J = 6.8 Hz, CH_3C). Integration from 2.25–0.92 indicated 33 protons as required.

Anal. Calcd for $C_{19}H_{38}S_2$: C, 68.99; H, 11.61; S, 19.40. Found: C, 69.19; H, 11.76; S, 19.54.

Formation of Intermediate 19 by Coupling 2-Pentadecyl-1,3-dithiane (18) with Bromide 16. The alkylation process was carried out in a scrupulously dry three-necked flask under a small positive pressure of argon or nitrogen dried by passage through a tower of calcium sulfate. Tetrahydrofuran (50 ml) was distilled directly from lithium aluminum hydride into the flask, which already contained 2-pentadecyl-1,3-dithiane (**18**, 455 mg, 1.5 mmol) and triphenylmethane (3 mg). With stirring and with the reaction flask at −30 °C (solid CO_2 in ethanol) 0.8 ml of 2.25 M butyllithium in hexane (1.8 mmol) was injected by syringe through a stopple. The argon inlet needle was withdrawn, and the sealed reaction mixture was stirred for 3.5 h at −30 to −20 °C. The pink triphenylmethide color, detected after about 10 min, reached a maximum intensity after approximately 0.5 h.

Again under argon, 300 mg (1.08 mmol) of the tetrahydropyranyl derivative of 6-bromo-*cis*-3,4-methylenehexanol (**16**) was injected, and the mixture, which became colorless after a few minutes, was stirred at −30 to −20 °C for 1 h.

Water (2 ml) was added, after which the mixture was concentrated at 40 °C. The pale yellow oily residue was shaken with water (50 ml) and several portions of ethyl acetate. The ethyl acetate extract was rinsed with water, dried, and evaporated to furnish the alkylation product **19** (736 mg). Preparative layer chromatography, using benzene as the developing solvent and ultraviolet light for visualization, separated this product into a faster moving fraction (R_f 0.7), which proved to be unchanged pentadecyldithiane (**18**, 175 mg, 0.53 mmol), and a slower moving fraction (R_f 0.4), which was the desired product **19** (474 mg, 83% based on bromo compound **16**). Analytical thin layer chromatography showed a single spot with trace impurities: NMR ($CDCl_3$) δ 4.40 (broad s, 1, tetrahydropyranyl OCHO), 3.5 (m, 4, 2 CH_2O), 2.60 (m, 4, 2 CH_2S), 2.0–1.1 (m, 41, as against 40 calculated, cyclic and linear CH_2's), 0.70 (t, J = 5 Hz, CH_3C), 0.5 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (m, cyclopropane H cis to alkyls). The integration of the last three signals corresponded to seven protons as required by formulation **19**.

***cis*-3,4-Methylenedocasanol (21) by Desulfurization and Hydrolysis of Intermediate 19.** Activated Raney nickel (ROC/RIC Inc.) stored under water was washed in succession with ten portions of water, six of 95% alcohol, six of absolute alcohol, and eight of cyclohexane. A vigorously stirred 70 °C solution of dithiane **19** (960 mg, 1.83 mmol) in cyclohexane (80 ml) was treated at 15-min intervals with 10-, 5-, and 2.5-g portions of this Raney nickel in hexane. Fifteen minutes after the last portion was added, the solids (still pyrophoric) were separated by filtration through diatomaceous earth (Celite), and were rinsed several times with warm cyclohexane. Removing solvent from the combined filtrates left 620 mg of colorless oil. To remove the remaining sulfur, this oil, redissolved in 60 ml of cyclohexane, was treated as before with a fresh portion of Raney nickel (3 g). The resulting colorless, sulfur-free dihydropyran derivative **20** of *cis*-3,4-methylenedocosanol (600 mg) had the following properties: ir, no absorption at 3600–3300 cm^{-1}; NMR ($CDCl_3$) δ 4.50 (broad s, 1, OCHO), 3.50 (m, 4, 2 CH_2O), 1.70–1.10 (m, ca. 42, CH_2's), 0.80 (t, J = 6 Hz, CH_3C), 0.5 (broad s, cyclopropane H's cis to each other), −0.3 ppm (m, 1, cyclopropane H cis to alkyls). The integration value of the 0.8–0.5 ppm signals corresponded to six protons.

To remove the tetrahydropyranyl protecting, the oily product **20** was allowed to stand for 18 h at room temperature in a solution of ethanol (50 ml), water (2 ml), and 11 N hydrochloric acid (1 ml). After 1 ml of triethylamine was added, the mixture was stripped of volatiles at temperatures no higher than 50 °C. Some water was added, and the product **21** was extracted into ethyl acetate. The extract, rinsed twice with water, dried, and stripped of all solvent, left *cis*-3,4-methylenedocosanol (**21**) as a colorless residue weighing 520 mg (85%): mp 50–51 °C; homogeneous according to thin layer chromatography using 1:5 ether–benzene as developing solvent; NMR ($CDCl_3$) δ 3.65 (t, J = 6 Hz, 2, CH_2O), 2.05 (s, 1, OH), 1.5–1.1 (s with shoulder, 36, linear CH_2's), 0.80 (t, J = 6 Hz, CH_3C), 0.55 (broad s, cyclopropane H's cis to each other), −0.3 ppm (m, 1, cyclopropane H cis to alkyls). Integration of the 0.8 and 0.55 ppm signals indicated six protons; the 2.05 ppm signal for hydroxyl disappeared when D_2O was added.

Anal. Calcd for $C_{23}H_{46}O$: C, 81.58; H, 13.69. Found: C, 81.31; H, 13.93.

***cis*-3,4-Methylenedocosanyl Bromide (22).** The general procedure by which the alcohol was tosylated and then transformed to bromide was similar to that described for the conversion of alcohol **26** to bromide **27**. *cis*-3,4-Methylenedocosanol (**21**, 520 mg, 1.54 mmol) in 8 ml of pyridine freshly distilled from solid potassium hydroxide was treated with 382 mg (2.0 mmol) of tosyl chloride. The resulting white solid *cis*-3,4-methylenedocosanyl tosylate (650 mg, 86% yield) showed no infrared absorption in the 3600–3300-cm^{-1} region but did show nuclear magnetic resonance signals at δ 7.33 and 7.77 ppm. A solution of this tosylate (630 mg, 1.28 mmol) in dry acetone (50 ml) containing 600 mg of lithium bromide (6.9 mmol) was refluxed for 3 h. Isolation of the bromide product **22** made use of chloroform for extraction instead of ethyl acetate. The *cis*-3,4-methylenedocosanyl bromide (**22**, 520 mg of 87% from the alcohol) was obtained as a straw-colored oil liquid at room temperature but solid at 0 °C. Thin layer chromatography (benzene solvent) showed one major spot as well as some very faint extra spots: NMR ($CDCl_3$) δ 3.42 (t, J = 5 Hz, 2, CH_2Br), 1.1 (s with shoulder at 1.5, 36, linear CH_2's), 0.85 (t, J = 6 Hz, CH_3C), 0.55 (s, cyclopropane H's cis to each other), −0.25 ppm (m, 1, cyclopropane H cis to alkyls). Integration from 0.85 to 0.55 ppm indicated 6.5 protons as against the required 6 protons. The mass spectral equal-intensity peaks at m/e 400 and 402 corresponded to the molecular formula, $C_{23}H_{45}Br$. No peaks were noted at higher m/e values.

1,4-Bisdithianylbutane (28) and 1,8-Bisdithianyloctane (23).[28] 1,3-Dithiane (3.34 g, 0.0278 mol) in 80 ml of tetrahydrofuran containing 12.4 ml of 2.33 M butyllithium in hexane (0.029 mol) was allowed to stand at −40 to −20 °C for 1.25 h. After 1,4-dibromobutane was added, the mixture was stirred at the same temperature for 2 h and then allowed to stand at −7 °C for 20 h. The crude product, on recrystallization from chloroform–methanol, furnished 3.32 g (81%) of 1,4-bisdithianylbutane (**28**) in two crops, both with mp 103–103.5 °C. The product showed only a single spot on thin layer chromatography (either with 5:1 pentane–ether or with chloroform): ir ($CHCl_3$) 2900, 905 cm^{-1}; NMR ($CDCl_3$) δ 4.04 (t, J = 6 Hz, 2, 2 SCHS), 3.03–2.73 (m, 8, 4 CH_2S), 2.35–1.30 ppm (m, 12, all other H's).

Anal. Calcd for $C_{12}H_{22}S_4$: C, 48.86; H, 7.54; S, 43.60. Found: C, 48.89; H, 7.74; S, 43.43.

The corresponding octane derivative **23** was prepared in an analogous way by using 22.6 mmol of butyllithium in hexane, 50 ml of tetrahydrofuran, 2.65 g (22.1 mmol) of 1,3-dithiane, and 3.00 g (11.0 mmol) of 1,8-dibromooctane. One crystallization of the product from chloroform gave 3.38 g (88%) of 1,8-bisdithianyloctane (**23**) as shiny white plates, mp 80–81.5 °C, showing a single spot on thin layer chromatography (5:1 pentane–ether): ir ($CHCl_3$) 2850, 905 cm^{-1}; NMR ($CDCl_3$) δ 4.09 (t, J = 6.8 Hz, 2, 2 SCHS), 3.10–2.75 (m, 8, 4 CH_2S), 2.25–1.15 ppm (m, 20, all other H's).

Anal. Calcd for $C_{16}H_{30}S_4$: C, 54.77; H, 8.64; S, 36.58. Found: C, 54.86; H, 8.59; S, 36.73.

Intermediate 24 by Alkylation of Bisdithianyloctane (23) with *cis*-3,4-Methylenedocosanyl Bromide (22).[28] Metalation was accomplished by exposing bisdithianyloctane (**23**, 700 mg, 2.00 mmol) in 70 ml of tetrahydrofuran containing 5 mg of triphenylmethane to the action of butyllithium (2.1 mmol, 1.0 ml, of 2.1 M reagent in hexane) for 4 h at −20 °C. The pink solution was then treated with 510 mg (1.27 mmol) of *cis*-3,4-methylenedocosanyl bromide (**22**) in 10 ml of dry tetrahydrofuran, and the alkylation was allowed to proceed for 1.5 h. The crude reaction product was separated by preparative-plate chromatography (2:3 ligroin–benzene) into three bands, with R_f 0.7, 0.5, and 0.25. The slowest moving material proved to be unchanged 1,3-dithiane (356 mg, 1.02 mmol). The least polar fraction (R_f 0.7), recovered from the plate as a pale yellow oil (150 mg), was considered to be the dialkylation product; the integration ratio of the nuclear magnetic resonance signal at −0.3 ppm to that at 2.75 ppm (CH_2S's) came to 2:8, as required.

The fraction of intermediate polarity (R_f 0.5), isolated as a faintly yellow oil, was taken as the desired monoalkylation product **24**. This oily material (540 mg, 0.80 mmol), which did not solidify at ice-bath temperatures, showed a single spot on a thin layer chromatographic plate (1:1 ligroin–benzene) accompanied by some very faint trace spots: NMR ($CDCl_3$) δ 3.95 (t, J = 6 Hz, 1, SCHS), 2.75 (m, 8, 4 CH_2S), 2.1–1.3 (m), and 1.13 (s, 58, linear CH_2's plus 2 dithiane CCH_2C), 0.80 (t, J = 4 Hz, 3, CH_3C), 0.50 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (m, 1, cyclopropane H cis to alkyls).

Ethylene Glycol Acetal 27 of 10-Bromodecanal. Ozone in oxygen was passed into a solution of 10-undecenol (5.0 g, 0.029 mol) in 50 ml of methanol at 0 °C for about 1 h, or until ozone was no longer absorbed. The excess ozone was blown out in a stream of nitrogen gas. Dimethyl sulfide (4.0 g, 0.065 mol) was added, and the solution was held at 0 °C for 0.5 h and then at 25 °C for 1 h. Crude 10-hydroxydecanal was obtained as a colorless oil after stripping away all volatiles at temperatures below 30 °C.

To prepare the corresponding acetal **26**, the crude product was stirred with 20 ml of ethylene glycol containing 20 mg of *p*-toluenesulfonic acid at room temperature for 18 h. The mixture was diluted with 200 ml of water and was extracted thoroughly with benzene. Fractionation of the dried extract gave 3.5 g (55%) of the ethylene glycol acetal **26** of 10-hydroxydecanal: bp 106–115 °C (0.004 mm); NMR ($CDCl_3$) δ 4.85 (t, J = 4 Hz, 1, OCHO), 3.91 (m, 4, ring CH_2's), 3.61 (t, J = 6 Hz, 2, $HOCH_2$), 2.68 (s, 1, OH), 1.3 ppm (broad s, 16, linear CH_2's). Thin layer chromatography (benzene) produced only one spot.

The alcoholic function was tosylated by dissolving the hydroxy acetal **26** (3.0 g, 0.014 mol) in 20 ml of carefully dried pyridine, cooling the solution to 3 °C, and then with stirring adding *p*-toluenesulfonyl chloride (3.5 g, 0.018 mol) that had been crystallized from petroleum ether. After 20 h at 0 °C, the tosylate of **26** could be isolated as a straw-colored oil (4.9 g, 94% from the hydroxy acetal): NMR ($CDCl_3$) δ 7.77 and 7.33 (two d's, J = 9 and 4 Hz, aromatic H's), 7.55 (impurity), 4.81 (t, J = 4 Hz, 1, OCHO), 4.00 (t, J = 6 Hz, CH_2OTs), 3.89 (m, ring CH_2's), 2.44 (s, 3, CH_3Ar), 1.90–1.10 ppm (m, 16, 8 linear CH_2's). Integration of the 4.00 and 3.89 ppm signals agreed with a total of six protons.

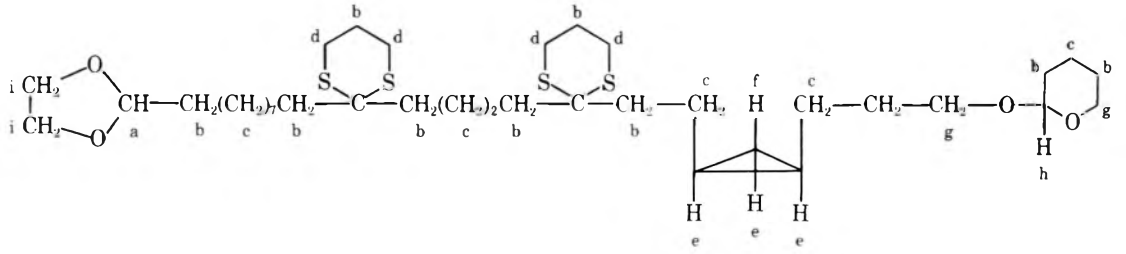
Without purification, the tosylate (4.5 g, 0.012 mol) was dissolved in 300 ml of acetone freshly distilled from anhydrous potassium carbonate, lithium bromide (4.7 g, 0.054 mol) dried at 100 °C for 1 day was added, and the solution was refluxed for 1.5 h. After suitable treatment, the reaction mixture furnished 2.2 g of 10-bromodecanal ethylene glycol acetal (**27**), bp 109–113 °C (0.017 mm). The yield from crude tosylate was 66%; the overall yield in the four-step process from 10-undecenol (**25**) was 34%. Thin layer chromatography of the distilled bromide **27** using benzene as solvent developed only a single spot. Interestingly, instead of the expected twin mass spectral molecular peaks at M − 1 and M + 1 (278 and 280), the peaks appeared at M − 2 and M (277 and 279), a result, presumably, of the molecule ion losing hydrogen readily from the OCHO grouping: NMR ($CDCl_3$) δ 4.84 (t, J = 4 Hz, 1, OCHO), 3.90 (m, 4, ring CH_2's), 3.40 (t, J = 6 Hz, 2, CH_2Br), 1.30 ppm (broad s, 16, 8 linear CH_2's).

Anal. Calcd for $C_{12}H_{23}BrO_2$: C, 51.62; H, 8.30; Br, 28.62. Found: C, 51.32; H, 8.22; Br, 28.86.

Bisdithiane Acetal 29 by Alkylation of 1,4-Bisdithianylbutane (28) with Bromo Acetal 27. A solution of 1,4-bisdithianylbutane (**28**, 1.00 g, 3.40 mmol) and triphenylmethane (3 mg) in 100 ml of tetrahydrofuran was treated at −25 °C with 1.70 ml of 2.2 M butyllithium in hexane (3.74 mmol) and, after 3.5 h, with bromo acetal **27** (0.600 g, 2.15 mmol). The reaction mixture was allowed to stand at −25 °C for 1.5 h. Processing essentially as before[28] afforded a pale yellow oil, which was chromatographed on a column of 60–200 mesh silica gel using benzene (1 l.) followed by 1:9 ether–benzene (0.5 l.) as developing solvents. The material eluted in the benzene fractions was unchanged 1,4-bisdithianylbutane (490 mg, 1.67 mmol). The material eluted with ether–benzene proved to be the desired alkylation product **29** (820 mg, 77% from the bromide **27**), showing a single spot on a thin layer chromatography plate (benzene): NMR ($CDCl_3$) δ 4.82 (t, J = 4 Hz, 1, OCHO), 4.10 (t, J = 4 Hz, SCHS), 3.90 (m, OCH_2CH_2O), 2.80 (m, 8, 4 CH_2-S), 2.1–1.3 ppm (complex, 33 vs. 30 calculated, all other CH_2's). Integration of the 4.10 and 3.90 ppm signals indicated five protons as required.

Anal. Calcd for $C_{24}H_{44}O_2S_4$: C, 58.49; H, 9.00. Found: C, 58.41; H, 8.82.

Bisdithiane Intermediate 30 by Alkylation of Bisdithiane 29 with the Tetrahydropyranyl Derivative of 6-Bromo-*cis*-3,4-methylenehexanol (16).[28] The alkylation used 620 mg (1.2 mmol) of bisdithiane **29**, 5 mg of triphenylmethane, 75 ml of tetrahydrofuran, and 1.68 mmol of butyllithium (2.25 M hexane solution), followed after metalation was complete by 320 mg (1.15 mmol) of bromo compound **16**. The yellow, oily, crude product was purified by preparative layer chromatography with benzene as solvent. Appreciable unchanged bisdithiane starting material (**29**) was recovered (100 mg, 0.22 mmol) together with 605 mg (77% based on **16**) of the desired product **30**. Thin layer chromatography of this material showed a single spot accompanied by some very faint additional spots indicating the presence of trace impurities; NMR ($CDCl_3$) δ 4.8 (t, J = 4 Hz, 1, a), 4.6 (broad s, 1, h) 3.9 and 3.8 (two multiplets, 8, i and g), 2.8 (m, 8, d), 2.1–1.3 (m, 41.4 as compared to the required 42, c and b), 0.75 (broad s, 3, e), −0.2 ppm (m, 1, f).



Anal. Calcd for $C_{36}H_{64}O_4S_4$: C, 62.74; H, 9.36; S, 18.61. Found: C, 62.55; H, 9.22; S, 18.69.

Intermediate 31 by Desulfurization of Bisdithianyl Derivative 30. A solution of bisdithiane **30** (955 mg, 1.39 mmol) in 100 ml of cyclohexane was stirred at 70 °C with 9 g of Raney nickel prepared as described above. After 15 min, an additional 9 g of Raney nickel was added, and the mixture was stirred further for 15 min. The supernatant liquid was decanted from the solids and filtered directly through Celite. The still pyrophoric solids were rinsed several times with portions of hot cyclohexane. Evaporating the combined cyclohexane solutions at temperatures no higher than 45 °C left a colorless oil, which was redissolved in cyclohexane and stirred at 70 °C with fresh Raney nickel (4 g) and then, 15 min later, with a second 4-g portion of Raney nickel for an additional 15 min.

The sulfur-free product **31** was isolated as before as a solvent-free, colorless oil (390 mg) that solidified below 10 °C: ir, no peaks at 3600–3300 or at 1730 cm^{-1}; NMR ($CDCl_3$) δ 4.67 (t, J = 4 Hz, 1, dioxolane OCHO), 4.46 (broad s, 1, tetrahydropyran OCHO), 3.75 and 3.50 (complex, 8, 4 O-CH_2), 1.60–1.10 (complex, 45, undesignated H's), 0.50 (broad s, 3, cyclopropane H's cis to each other), −0.3 ppm (m, 1, cyclopropane H cis to alkyls). No olefinic signals appeared downfield from δ 4.67 ppm.

Ethylene Glycol Acetal 32 of 22-Bromo-*cis*-19,20-methylenedocosanal. The oily tetrahydropyranyl derivative **31** from two runs (750 mg, 1.56 mmol) was allowed to stand for 20 h at room temperature in a solution of 70 ml of tetrahydrofuran containing 2 ml of water, 4 ml of ethylene glycol, and 1 ml of 11 M hydrochloric acid. After addition of triethylamine (1 ml), the reaction mixture was stripped of volatile material at temperatures no higher than 50 °C. Water (60 ml) was added, and the product was extracted into ethyl acetate. The extract, washed with water, dried, and evaporated (<45 °C), left a colorless oil that crystallized to a white, waxy solid (726 mg), which was taken as the acetal of 22-hydroxy-*cis*-19,20-methylenedocosanal, ir 3500 cm^{-1} (no absorption at 1740–1720 cm^{-1}).

The alcohol in 15 ml of dry pyridine was tosylated by reaction with *p*-toluenesulfonyl chloride (480 mg, 2.51 mmol) over an 18-h period. The pale yellow tosylation product was purified by preparative layer chromatography (3% ether in benzene) followed by recrystallization of the solid fraction (540 mg) from ether. The silky white needles of the acetal tosylate (270 mg, 18% calculated from bisdithiane **30**) showed mp 69–70 °C; TLC (benzene) developed only a single spot. The mother liquor contained more of this tosylate (ca. 210 mg) plus about 50 mg of a second unidentified component.

Anal. Calcd for $C_{32}H_{54}O_5S$: C, 69.78; H, 9.88; S, 5.81. Found: C, 69.99; H, 9.75; S, 5.74.

A solution of crystalline tosylate (240 mg, 0.44 mmol) and anhydrous lithium bromide (250 mg, 2.87 mmol) in 25 ml of dry acetone

was stirred and refluxed for 3 h. The desired bromide **32** was isolated as a colorless oil (196 mg, 97%), mp ca. 20 °C; analysis by TLC (benzene) showed some very faint spots indicating traces of extraneous material; ir, no absorption maxima at either 3600–3300 or 1730 cm^{-1}; mass spectroscopy gave twin molecular peaks at *m/e* 458 and 460 corresponding to $C_{25}H_{47}BrO_2$; NMR ($CDCl_3$), all features satisfactory except that some of the high-field integrations deviated slightly from the expected value.

Completing the Carbon Skeleton (as in 33) by Alkylating Bisdithiane 24 with Bromide 32.[28] Bisdithiane **24** (670 mg, 1.0 mmol) was lithiated by exposure to butyllithium (0.55 ml of a 2.1 M solution in hexane, 1.1 mmol) in 70 ml of tetrahydrofuran containing 3 mg of triphenylmethane for 4 h at −25 to −15 °C. After bromide **32** (200 mg, 0.44 mmol) as a solution in 8 ml of tetrahydrofuran was added, the reaction was allowed to proceed for 1.5 h at −25 °C and for 16 h at −10 °C. The triphenylmethide pink color gradually faded and disappeared altogether in about 0.5 h. Isolation of product[28] gave a pale yellow oil, which was fractionated conveniently by preparative layer chromatography (benzene) into two bands. The faster moving material was unchanged bisdithiane **24** (388 mg, 0.58 mmol). The slower moving material, taken as the desired alkylation product **33**, was obtained as a viscous oil (360 mg, 82%) solidifying below 5 °C and showing only a single spot on thin layer chromatography. Although the nuclear magnetic resonance spectrum showed only the expected features, some discrepancy in the integration ratios pointed to the presence of impurity. Whatever the nature of this impurity, it did not disturb the calculated ratios corresponding to an intact dioxolane ring, two intact dithiane rings, and two cyclopropane rings. Thus the signal ratios at δ 4.75 (t, J = 4 Hz, OCHO), 3.80 (m, OCH_2CH_2O), 2.75 (m, 4 CH_2S's), and 0.55 ppm (broad s, cyclopropane H's cis to each other) came to 0.82:4.4:7.7:6.0, values that compared well with the required ratios of 1:4:8:6.

Attempted purification by gel filtration (Bio-beads 5 × 4 available from Bio-rad Laboratories and designed for molecular weights up to 1400) showed no sign of successful separation.

Formation of Intermediate 34 by Desulfurization of 33. The procedure was similar in general to that used in the desulfurization that led to *cis*-3,4-methylenedocosanol (**21**). Intermediate **33** (150 mg, 0.14 mmol) containing unidentified heterogeneity was stirred with Raney nickel (prepared as before) in cyclohexane solvent (25 ml) at 70 °C. The initial 3-g portion of Raney nickel was followed after 15 min with a second 3-g portion. Then, after 15 min, the reaction mixture was processed to recover the substrate, which was redissolved in cyclohexane (25 ml) and stirred again with Raney nickel (2 g) for 15 min. Product **34** was isolated as a white solid whose low solubility in most solvents presented problems. On analytical thin layer chromatography (benzene), this material developed two spots, R_f 0.45 and 0.55, both free of sulfur. The slower running component had the same R_f (0.45) as the starting material **33**, an observation suggesting that the R_f 0.45 fraction could be identified tentatively with the above-mentioned heterogeneity in the starting material, and further that the heterogeneity could not have contained sulfur.

Crystallizations of the white solid from 10 ml of acetone gave white, needlelike crystals of acetal **34** (70 mg, 60%), mp 66–70 °C, or from a different run, mp 60–75 °C. Preparative plate chromatography (benzene) was also effective in separating the contaminant from the desired product. Product **34** was soluble to only a very limited extent in chloroform, ether, dichloromethane, cyclohexane, or benzene. Thin layer chromatography on silica gel plates (carbon tetrachloride or benzene) produced a single spot. On an alumina plate (2:3 petroleum ether–benzene), the product showed two barely resolved spots; an alumina preparative plate did not give a clean separation. The infrared absorption spectrum was free of carbonyl absorption at 1730 cm^{-1}; and only the expected signals were seen on the nuclear magnetic resonance spectra ($CDCl_3$), including δ 3.90 (m, acetal OCH_2CH_2C) and 0.5 and −0.3 ppm (cyclopropane H's) peaks. Because of limited solubility and the resulting low intensity signals, integration was difficult. However, estimates of the ratio of methyl hydrogens (δ 0.85) to cis-cyclopropane H's gave values clearly greater than the 3:6 required for biscyclopropane **34**. High-resolution mass spectrometry (base peak at *m/e* 73 for the 2-dioxolane ion radical), with *m/e* peaks at 840 ($C_{58}H_{112}O_2$ as required for **34**) and 842 ($C_{58}H_{114}O_2$) clearly indicated the presence of material with two extra H's.

Eventually, successful separation was effected by recrystallizations from dilute (about 1%) dichloromethane solution. The less soluble white solid (25 mg), mp 69–72 °C, which precipitated at ice-bath temperatures, was taken as the desired product **34**, while the material from the mother liquor (ca. 23 mg), with mp 45–49 °C, was taken as the overreduced molecule. Thin layer chromatography of the separated fractions on either silica or alumina gave single spots, with the same respective R_f values; ir for the two materials was essentially identical.

Estimates based on the 100-MHz nuclear magnetic resonance curves of the two materials showed that the δ 0.56 ppm signal (cyclopropane H's cis to each other) for the higher melting material was considerably more intense than the same signal in the low-melting form; that in the higher melting product, the intensity ratio of the δ 0.56 ppm signal to the −0.3 to −0.4 ppm signal came close to 6:2, as required for compound **34**; that the ratio of the 0.8 (methyl H's) to 0.5 ppm signals was considerably lower in the high-melting product **34** than in the low-melting product; and that, in the curve for the higher melting form, repeated integrations for the OCH_2CH_2O signals at 3.90 ppm and the cyclopropane hydrogen signal at −0.35 ppm gave an average ratio of 4:2 (±20%), corresponding again to **34**.

Mass spectral analysis: calcd for the molecular mass of **34** ($C_{58}H_{112}O_2$), *m/e* 840.8662. Found: 840.8675, with no peak at 842 other than M + 2. Calcd for the molecular mass of $C_{58}H_{114}O_2$: *m/e* 842.8819. Found: 842.8820, with no significant peak at 840.

Methyl Meromycolate (35) from Acetal 34. At −65 °C, a saturated standardized solution of ozone in dichloromethane (0.7 ml containing 0.017 mmol) was added to a −40 °C solution of 5.0 mg (0.0059 mmol) of acetal **34** (mp 69–72 °C) in 10 ml of chloroform. After 5 min, another 0.6 ml of the cold ozone solution (total 0.033 mmol) was introduced, and the mixture was allowed to stand in the Dewar flask for 15 min. Removing all solvent at temperatures no higher than 0 °C left a white solid, which gave a single spot on thin layer chromatography running slower than the starting acetal, and which was taken as the desired hydroxyethyl meromycolate.

A solution of this solid in chloroform (4 ml) plus methanol (8 ml) containing potassium cyanide[29] (30 mg) was refluxed for 1.25 h, and then stripped of solvents at temperatures below 25 °C. The residue, to which a small volume of water was added, was extracted thoroughly with chloroform, and the chloroform extract was shaken with saturated salt solution before drying and removing solvent. The residual white solid was separated by preparative layer chromatography (0.25 mm layer, with benzene solvent) into methyl meromycolate (**35**, 1.9 mg, 0.0023 mmol, 40%) and unchanged starting acetal **34** (ca. 0.5 mg). Methyl meromycolate (**35**), mp 63–69 °C, showed only single spots on thin layer chromatography (alumina with benzene, or silica gel with either benzene or dichloromethane): ir ($CHCl_3$) 2930, 2850, 1735, 1440 cm^{-1}; NMR (at 100 MHz in dilute $CDCl_3$ solution with benzene as internal standard) δ 3.57 (s, CH_3O, 3.0–3.1), 2.22 (t, J = 7.5 Hz, $CH_2C{=}O$, 1.9–2.0), 1.2 (s, broad, CH_2's), 0.82 (t, J = 5 Hz, CH_3C), 0.54 (broad m, cyclopropane H's cis to each other), −0.36 ppm (m, cyclopropyl H's cis to alkyls, 1.9). From repeated instrument integrations, the ratio of the 3.57 to the −0.36 ppm signals was determined to be 3.1/1.9 (±6% av dev). The tailing from the intense δ 1.2 peak that reached under the 0.82 and 0.54 signals blocked attempts at integrating the latter two peaks. Mass spectral molecular peak: calcd for $C_{57}H_{110}O_2$ (**35**), *m/e* 826.8505; found, *m/e* 826.8503. A very low intensity peak (3% of height of the molecular peak) appeared at *m/e* 840 as the only unexpected feature in the fragmentation pattern.

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Registry No.—**6**, 592-57-4; **7**, 16554-83-9; **8**, 59014-42-5; 8 dimethyl ester, 54281-40-2; 8 polymer, 59014-43-6; **9**, 59014-44-7; **10**, 59043-33-3; **11**, 59014-45-8; **12**, 59014-46-9; **13**, 59014-47-0; **14**, 59014-48-1; **15**, 59014-49-2; **16**, 59014-50-5; **17**, 629-72-1; **18**, 59014-51-6; **19**, 59014-52-7; **20**, 59014-53-8; **21**, 59014-54-9; **21** tosylate, 59014-55-0; **22**, 59014-56-1; **23**, 59014-57-2; **24**, 59014-58-3; **25**, 112-43-6; **26**, 59014-59-4; **26** tosylate, 59043-32-2; **27**, 59014-60-7; **28**, 4883-04-9; **29**, 59014-61-8; **30**, 59014-62-9; **31**, 59014-63-0; **32**, 59014-64-1; **33**, 59014-65-2; **34**, 59014-66-3; **35**, 59014-67-4; diiodomethane, 75-11-6; dihydropyran, 110-87-2; 2-litho-1,3-dithiane, 36049-90-8; 1,3-dithiane, 505-23-7; 1,4-dibromobutane, 110-52-1; 1,8-dibromooctane, 4549-32-0; 10-hydroxydecanal, 22136-92-1; 22-hydroxy-*cis*-19,20-methylenedocosanal ethylene acetal, 59014-68-5; 22-hydroxy-*cis*-19,20-methylenedocosanal ethylene acetal tosylate, 59014-69-6.

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(28) The general procedure described for the alkylation of 2-pentadecyl-1,3-dithiane (**18**) with bromide **16** to form intermediate **19** was followed. In agreement with published results [E. L. Eliel, A. A. Hartmann, and A. G. Abatjoglou, *J. Am. Chem. Soc.*, **96**, 1807 (1974); A. Streitwieser, Jr., and S. P. Ewing, *Ibid.*, **97**, 190 (1975)] we found that metalation of 1,3-dithiane itself was appreciably faster than metalation of monosubstituted 1,3-dithianes. We routinely and conveniently followed the course of the metalations by determining the nuclear magnetic resonance integration value for the proton(s) remaining at the dithiane 2 position after quenching aliquots with deuterium oxide. This assay also served to check the minimum concentration of our stock butyllithium in hexane, since when pure 1,3-dithiane was allowed to react (0.5 h, −30 °C) with 1 equiv of butyllithium as calculated from the concentration on the label and then quenched, the recovered dithiane showed a decrease in the δ 3.7 ppm signal (SCH_2S) from 2 to 1 (±5%). No sign of dideuteration was detected with an excess of butyllithium. Interestingly, the 2-monodeuterio-1,3-dithiane showed a one-proton triplet (J = 2 Hz) instead of a singlet at δ 3.7 ppm, a result attributable to proton–deuterium coupling (see Eliel et al.).

The progress of the alkylations generally was followed by thin layer chromatography, with drops taken directly from the reaction mixture and spotted on the plate. Benzene proved to be a useful developing solvent. For the most part, alkylations either of 2-unsubstituted or 2-monosubstituted dithianes gave good yields.
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Structure Determination of Cyclopropane-Substituted Acids by Mass Spectrometry

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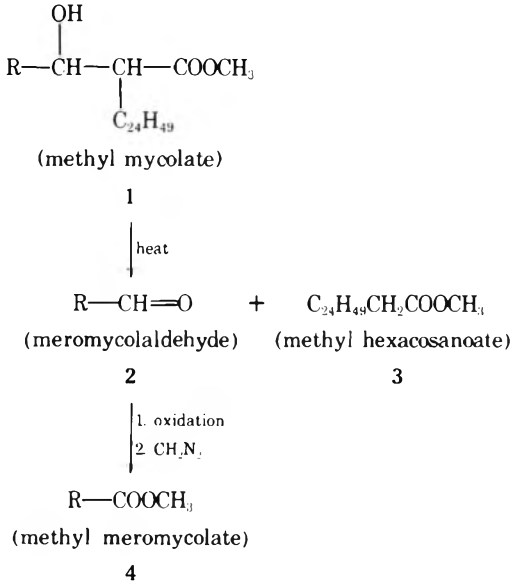
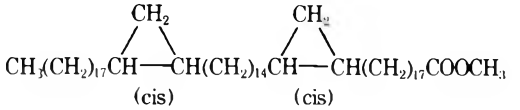
Calibration information has been obtained that will be useful in mass spectral studies of bis cyclopropane meromycolic compounds derived from mycobacterial mycolic acids. The compounds examined include a synthetic meromycolic ester, its monoketo derivatives, and its pyrrolidide. Methyl *cis*-9,10-methyleneoctadecanoate and its derivatives were also examined. The study shows that the monoketo compounds are to be preferred.

The mycolic acids, isolated from tuberculosis bacteria, are high molecular weight β-hydroxycarboxylic acids carrying a tetracosanyl (or docosanyl) group on the α position.[1,2] In the many inquiries into the nature of these compounds, pyrolysis of the methyl esters **1** to the corresponding meromycolaldehydes (**2**) plus methyl hexacosanoate (**3**) has been a standard procedure. Nuclear magnetic resonance and infrared absorption data for the corresponding meromycolate esters **4** as well as for the parent mycolates **1**, and, even more important, their mass fragmentation patterns, have provided much of the detailed structural information. The mass spectral studies, however, have invariably been complicated by the fact that the materials examined, instead of single pure compounds, have been groups of functionally and structurally related molecules.[2b] Another serious handicap has been the absence of appropriate model compounds. As a result there has been a certain degree of uncertainty—sometimes disagreement—in the structural assignments.[3]



We have recently completed a total synthesis of a representative methyl meromycolate (**5**) of the type containing cis-disubstituted cyclopropane rings.[4] The availability of this compound made it possible for the first time to provide a reliable reference standard. With this purpose in mind we determined the fragmentation pattern of the synthetic ester **5**



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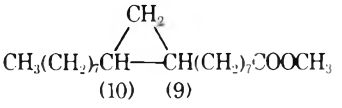
as well as of two promising derivatives, the monoketo esters and the meromycolic pyrrolidide. To obtain further pertinent data, we also examined a related cyclopropane compound, methyl *cis*-9,10-methyleneoctadecanoate. The present paper reports our results.

Methyl *cis*-9,10-Methyleneoctadecanoate (6). Methyl *cis*-9,10-methyleneoctadecanoate, taken as a reasonable starting point for modeling the more complex bis cyclopropane ester **5**, gave a mass spectrum that was not particularly useful for locating the cyclopropane ring.[5-13] We then turned to two methods for modifying cyclopropane compounds, which we hoped would make the mass spectra more informative.[8,11,12,14-16]

Monoketo Derivatives 7 and 8 of Methyl *cis*-9,10-Methyleneoctadecanoate. Promé reported that the chromium(VI) oxidation of cyclopropanes fused on a straight chain converts the alkyl methylene group next to the three-membered ring to an oxo group.[15,17] He also showed[8] that the tendency for mass spectral cleavage on either side of the carbonyl group[18] carries over to the cyclopropyl ketones. With methyl *cis*-9,10-methyleneoctadecanoate (**6**) as the starting point, the 8-keto and the 11-keto derivatives **7** and **8** were obtained as products. In analyzing the mass spectra we sought to use the



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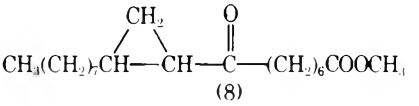

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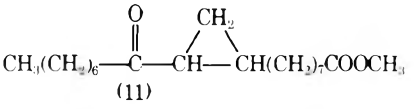

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data in as unbiased and straightforward a way as possible. We simply ordered the peaks according to relative abundance and then, relying only on the prominent peaks, proceeded to relate *m/e* values to structural features.

The fragmentation pattern of the 8-keto derivative **7** shows an intense and obvious molecular peak at M 324 (rel intensity 28). The base peak at *m/e* 171 (100), which can be associated with preferred cleavage α to the keto group, is alone enough to locate the three-membered ring on the chain at the 9,10 position. The prominent companion peak at *m/e* 181 (29% and ninth in abundance order) corresponding to cleavage on the other side of the keto group, supports the assignment. Other high-intensity peaks, although all confirmatory according to Promé's interpertations,[8] are less straightforward and, so far as locating the ring is concerned, are redundant.

In the mass spectrum of the 11-keto derivative **8**, the most intense peak at *m/e* 127 (100), corresponding to one of the

α-keto cleavages, again immediately and correctly positions the three-membered ring at 9,10. The other α-keto cleavage (*m/e* 225, rel intensity 4) does not stand out and therefore is not used for the assignment. The peak at *m/e* 324 (17), appearing seventh in the order of relative intensity, is unmistakably the molecular peak.

Clearly the mass spectral data from the two monoketone derivatives of cyclopropane ester **6** convincingly bracket the ring at the 9,10 position.

Pyrrolidide 9 of *cis*-9,10-Methyleneoctadecanoic Acid. In their search for a derivative of unsaturated straight-chain acids whose mass spectra would help to locate the double bonds, Vetter et al.[19] found that the acyl pyrrolidides showed considerable promise. Holmann and his colleagues[16,20,21] extended and consolidated this observation, and also suggested that mass spectral data from the pyrrolidides of cyclopropane fatty acid could help to determine the position of the three-membered ring along the chain. To check this possibility, we investigated the fragmentation pattern of *cis*-9,10-methyleneoctadecanoic pyrrolidide (**9**). As before, the approach was to seek information only from the abundant peaks.

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Table I, which lists the first dozen peaks according to their intensity, identifies the McLafferty cleavage fragment (*m/e* 113) as the most abundant by far. The molecular mass peak at *m/e* 349 and the isotope (M + 1) peak at 350 are also prominent. Beginning with *m/e* 98, a series of peaks appear that correspond to $(CH_2)_nCONC_4H_8$ as well as to this fragment plus or minus protons. The prominent peak at 182 (n = 6) requires a minimum of six methylene groups extending from the amide carbonyl toward the cyclopropane ring. The next higher homologue (n = 7, *m/e* 196) is about half as intense and is not included in Table I. These data, although not fixing the ring, suggest correctly that it is located at or beyond the 8,9 position of **9**.

The higher mass region of the fragmentation pattern includes peaks for the series $(CH_2)_n(C_3H_4)CONC_4H_8$, the first two members of which (*m/e* 236 and 250 for n = 0 and 1) are sufficiently intense to be listed in Table I. The *m/e* 250 peak, corresponding to a cyclopropylmethyl system, emerges as the most prominent peak of this homologous series. If further work with other model pyrrolidides supports the tentative conclusion that such cyclopropylmethyl cleavage is preferred, this peak alone would suffice to locate the ring.

Test was made of an adaptation of the rule developed originally[20] for locating olefinic double bonds. The rule depends on noting where the maxima between *m/e* signal clusters are separated by 12 instead of the more usual 14 mass units. Inspection of the mass spectrum of pyrrolidide **9** shows that the significant interval comes between *m/e* 196 and 208. If the *m/e* 196 peak is identified with the fragment terminating at position 8 ($C_{12}H_{12}NO$) and the *m/e* 208 peak is identified with the fragment terminating at position 9 ($C_{13}H_{24}NO$ minus 2 H), the extended rule[20] would place the cyclopropane ring at the 9,10 position, where in fact it is. This adaptation treats the cyclopropane ring as if it were simply a double bond at the point of ring fusion. How reliable this approach will prove to be must await further work with other model pyrrolidides.

In summary, the mass spectrum of the parent methyl *cis*-9,10-methyleneoctadecanoate (**6**) gives no simple and uncomplicated structural information. On the other hand, the easily derived cyclopropyl keto esters produce data that locate the ring in a straightforward manner. While the pyrrolidide appears promising, further investigation is called for.

Table I. Prominent Peaks in the Mass Spectrum of *cis*-9,10-Methyleneoctadecanoic Pyrrolidide (9)[a]

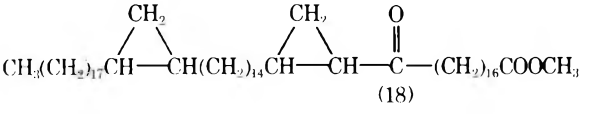
m/e	Rel intensity	Assignment	
		Formula	Parent structural feature
113	648	$C_6H_{11}NO$	$CH_2CONC_4H_8$ plus H
126	460	$C_7H_{12}NO$	$(CH_2)_2CONC_4H_8$
M 349	230	$C_{23}H_{43}NO$	**9**
98	145	C_5H_8NO	$CONC_4H_8$
250	100	$C_{16}H_{28}NO$	$CH_2(C_3H_4)(CH_2)_7CONC_4H_8$
114	93	$C_{16}H_{12}NO$	$CH_2CONC_4H_8$ plus 2H
127	89	$C_7H_{13}NO$	$(CH_2)_2CONC_4H_8$ plus H
168	70	$C_{10}H_{18}NO$	$(CH_2)_5CONC_4H_8$
236	63	$C_{15}H_{26}NO$	$(C_3H_8)(CH_2)_7CONC_4H_8$
350	62	$C_{23}H_{43}NO$[b]	(M + 1) isotope peak[b]
140	52	$C_8H_{14}NO$	$(CH_2)_3CONC_4H_8$
182	47	$C_{11}H_{20}NO$	$(CH_2)_6CONC_4H_8$
279	34	$C_{19}H_{35}O$	$CH_3(CH_2)_7(C_3H_4)(CH_2)_7CO$

[a] Includes peaks from *m/e* 90 to 360. [b] Calcd (M + 1)/M for $C_{23}H_{43}NO$: 0.26. Found: 0.27.

Synthetic Methyl Meromycolate (5). The next stage was to evaluate mass spectral approaches in locating the cyclopropane rings in the methyl meromycolate (**5**) of known structure.

The mass spectrum of this ester shows that the most abundant peak in the *m/e* 220 to 850 region is the molecular peak at *m/e* 826 (100). The (M + 1) and even the (M + 2) peaks are also high as can be expected from a C_{51} compound. The intense peak at *m/e* 74 (rel intensity 326) for the McLafferty cleavage fragment demands an unsubstituted methylene group next to the ester carbonyl. But aside from these features, the fragmentation pattern appears not to serve in any straightforward way in determining structure, or, more to the point, in locating the two cyclopropane rings.

Monoketones from Synthetic Methyl Meromycolate. Chromium(VI) trioxide oxidation of meromycolate **5** furnished the expected cyclopropyl ketones **10–13**, which were



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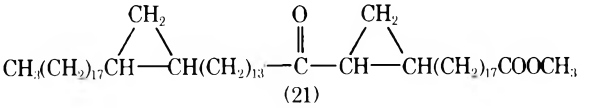

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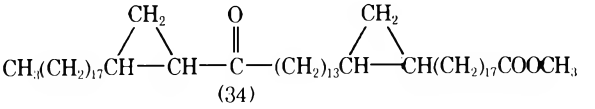

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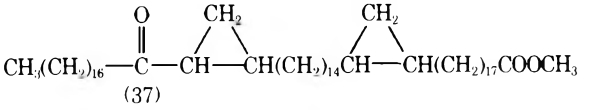

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isolated and examined as a mixture of the four compounds. If their fragmentation pattern could serve in an uncomplicated manner to locate the keto groups, the structure of the carbon skeleton would follow automatically. As with the simpler monoketo derivatives of methyl *cis*-9,10-methyleneoctade-

Table II. Prominent Peaks in the Mass Spectrum of Monoketo Esters 10–13[a]

m/e	Rel intensity	Assignment: Formula	Assignment: Parent structural feature
M 840	185	$C_{57}H_{108}O_3$	**10, 11, 12, 13**
841	110	$C_{57}H_{108}O_3$	(M + 1) isotope peak[b]
557	100	$C_{39}H_{73}O$	$CH_3(CH_2)_{17}(C_3H_4)$-$(CH_2)_{14}(C_3H_4)CO$
842	80		
326	65	$C_{20}H_{38}O_3$	$CHCO(CH_2)_{16}COOCH_3$ plus 2 H
558	55	*c*	*c*
601	55	$C_{40}H_{73}O_3$	$CO(C_3H_4)(CH_2)_{14}(C_3H_4)$-$(CH_2)_{17}COOCH_3$
808	47	$C_{56}H_{104}O_2$	M minus CH_4O
809	45	$C_{56}H_{105}O_2$	M minus CH_3O
311	42	$C_{19}H_{35}O_3$	$CO(CH_2)_{16}COOCH_3$
602	36	*d*	*d*
267	34	$C_{18}H_{35}O$	$CH_3(CH_2)_{16}CO$

[a] Includes peaks from *m/e* 150 to 850. [b] Calcd (M + 1)/M for $C_{57}H_{108}O_3$: 0.63. Found: 0.59. [c] This is a composite peak due in part to the isotopic $C_{39}H_{73}O$ fragments from *m/e* 557. Calcd (M + 1)/M for $C_{39}H_{73}O$: 0.43. Found: 0.55. [d] A composite peak due in part to isotopic $C_{40}H_{73}O_3$ fragments (nominal *m/e* 601). Calcd (M + 1)/M for $C_{40}H_{73}O_3$: 0.45. Found: 0.65.

canoate, we sought for relationships between the mass numbers of prominent peaks and recognized modes of cleavage.

Table II shows that the most abundant fragment in the *m/e* 150 to 850 sweep comes at *m/e* 840 and corresponds to the molecular mass of the keto esters **10–13**. The high peaks at *m/e* 557 and 311 (respectively third and tenth in intensity) neatly match the fragments arising from cleavage on either side of the 18-keto group in keto ester **10**. The related peaks at *m/e* 503 (rel intensity 29) and 365 (16) for the 21-keto group in **11** appear in the mass spectrum, but they fail to stand out and thus do not meet our criterion of usefulness. However, these peaks are not needed, since either of the abundant fragments from the 18-keto compound is alone enough to establish the presence of a fused cyclopropane ring at the 19,20 position.

So far as the other ring is concerned, the intense peaks at *m/e* 601 and 267 (seventh and twelfth in intensity) correlate with α-cleavage in the 37-keto derivative **13**; either one fixes the distal cyclopropane ring at the 35,36 position. The fragments from the 34-keto compound **12** (*m/e* 547 with intensity 20, and *m/e* 321 with intensity 31) are not prominent and are not used.

Accordingly, readily identified peaks furnish more than enough information to place the two rings of the bis cyclopropane meromycolate **5** correctly at position 19,20 and 35,36. The analysis and conclusions with this more complicated compound are as direct as with the simpler 9,10-methyleneoctadecanoic ester **6**. None of the remaining peaks of Table II contradicts the structural assignment, and in fact at least one (*m/e* 326) provides further confirmation. The chromium oxidation method may be accepted as reliable and of proved value when applied to related bis cyclopropanes of unknown structures.

Pyrrolidide 14 of Methyl Meromycolate. To round out our calibration data we next examined the fragmentation pattern of pyrrolidide **14**. The most abundant peak by far (cf. Table III) is the molecular peak at *m/e* 865; the isotope peak

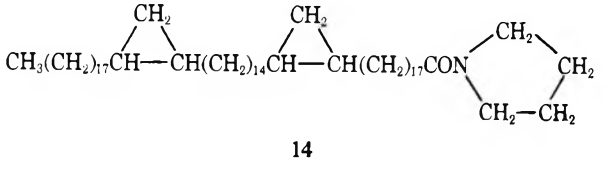

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Table III. Prominent Peaks in the Mass Spectrum of Meromycolic Pyrrolidide 14[a]

m/e	Rel intensity	Assignment: Formula	Assignment: Parent structural feature
M 865	955	$C_{60}H_{115}NO$	**14**
795	760	$C_{56}H_{107}O$	$CH_3(CH_2)_{17}(C_3H_4)(CH_2)_{14}$-$(C_3H_4)(CH_2)_{17}CO$
866	667	$C_{60}H_{115}NO$[b]	(M + 1) isotope peak[b]
796	485	$C_{56}H_{107}O$[c]	*m/e* (795 + 1) isotope peak[c]
867	485		
797	348		
868	227		
864	197	$C_{60}H_{114}NO$	14 minus H
798	150		
168	100	$C_{10}H_8NO$	$(CH_2)_5CONC_4H_8$
577	100	$C_{39}H_{73}O$	$CH_2(C_3H_4)(CH_2)_{14}(C_3H_4)$-$(CH_2)_{17}CO$ plus H
390	94	$C_{26}H_{48}NO$	$CH_2(C_3H_4)(CH_2)_{17}CONC_4H_8$
262	79		Composite
869	78		
853	76		
308	76	$C_{20}H_{38}NO$	$(CH_2)_{15}CONC_4H_8$
350	76		

[a] Includes peaks from *m/e* 150 to 890. [b] Calcd (M + 1)/M for $C_{60}H_{115}NO$: 0.67. Found: 0.69. [c] Calcd (M + 1)/M for $C_{56}H_{107}O$: 0.62. Found: 0.64.

at *m/e* 866 is also correspondingly high. Identification of the fragments contributing to the intense *m/e* 867, 868, and 869 peaks will have to await high-resolution mass spectral studies. The intense peak at *m/e* 795 (also its isotopic peak at *m/e* 796) corresponds to the acylium fraction formed by loss of the entire pyrrolidine section. The fragmentation pattern for the smaller pyrrolidide **9** includes a corresponding acylium fragment, but in much lower relative abundance. In the intermediate mass region, the three most intense peaks come at *m/e* 168, 577, and 390. The *m/e* 390 peak can be matched with a cyclopropylcarbinyl rupture (cf. Table III). Although the cyclopropylcarbinyl fragment containing two rings ($C_{43}H_{80}NO$, *m/e* 626, rel intensity 33) does not stand out,[22] the *m/e* 577 peak (Table III) might serve in its place.

The mass spectrim of pyrrolidide **14** presents a series of peaks at mass values below 200, which can be associated with the fragments $(CH_2)_nCONC_4H_8$, or with this grouping plus or minus a proton, and which gives limiting information about the location of one of the cyclopropane rings. The abundances for those with n = 0, 1, 2, and 3 (*m/e* 97 and 98, 112, 126, and 127, and 140) are all high. After this there is a downward trend, with the peaks for n = 4–10 appearing with intensities 40–100% on the scale of Table III. This series could be interpreted as demonstrating at least ten methylene groups extending back from the amide carbonyl. The exceptionally intense peak at *m/e* 308 (76) could be used to justify extending the chain to n = 15; the correct value of n = 17 is not indicated in any obvious way. A similar argument could be made concerning the chain of CH_2 groups between the two cyclopropane rings, that is, about the fragments $(CH_2)_n(C_3H_4)(CH_2)_{17}CONC_4H_8$. Here, however, a limiting value for n cannot be arrived at in a clear-cut way, so that this kind of data treatment—and for that matter a similar analysis of the peaks on the terminal methyl side of the second ring—appears not particularly rewarding.

In applying the possible extension of the Andersson–Holman rule (see above), an *m/e* 12 increment between adjacent cluster maxima can be found at *m/e* 364 and 376. By the same

analysis as with the lower molecular weight pyrrolidide **9**, this would place the first cyclopropane ring at the 21,22 position, whereas in fact it is at the 19,20 position. In the higher *m/e* region of the mass spectrum, where information about the second cyclopropane ring would be sought, the sequence of cluster maxima is not regular enough to warrant applying the increment approach.

Summary. Mass spectral results with methyl *cis*-9,10-methyleneoctadecanoate (**6**) and with synthetic methyl meromycolate (**5**) as well as with their pyrrolidides and their monoketo derivatives show that while all the compounds are useful for determining molecular weight, only the monoketones serve in a straightforward way in locating the cyclopropane rings. The monoketones may be recommended for structural work with bis cyclopropane acids obtained by degrading the natural products.

In our hands, trial of an adaptation of a device developed originally for fixing the position of olefinic double bonds in pyrrolidides of unsaturated straight-chain acids for the purpose of locating the rings in cyclopropane acids did not give wholly convincing results. In the pyrrolidides tested, whether cleavage to produce cyclopropylcarbinyl fragments will prove to be a generally preferred mode and therefore reliable in providing structural information must await further work with other cyclopropane pyrrolidides.

Experimental Section

General Information. Most of the mass spectra were determined by direct injection into an AEI MS-9 instrument at 70 eV. Some of the determinations, especially of the lower molecular weight compounds, were run with a Hitachi Perkin-Elmer RMU-6L mass spectrometer. Generally, preparative layer chromatography made use of 0.25 mm silica plates (E. Merck) measuring 5 × 20 or 20 × 20 cm. Where isotopic abundance ratios are calculated, the formulas given by Beynon[23] were used.

Methyl *cis*-9,10-Methyleneoctadecanoate (6). Methyl oleate was converted to the desired cyclopropane **6** by taking 3.0 g (10 mmol) of the oleate with 60 g of diiodomethane and 20 g of zinc–copper couple in 150 ml of ether.[9,10,24] To remove the persistent residue of about 15% of unsaturated material (δ 5.3 ppm), the straw-colored oily product (3.0 g) in 100 ml of chloroform was stirred with *m*-chloroperbenzoic acid (0.40 g of 85% reagent or 1.8 mmol) at 25 °C for 3 h. The methyl *cis*-9,10-methyleneoctadecanoate obtained after this treatment showed ir 1745 cm^{-1}; NMR ($CDCl_3$) δ 5.3 (no signal), 3.67 (s, 3 protons, OCH_3), 2.20 (t, J = 8 Hz, 2 H, CH_2CO), 1.20 [broad s, 26 H, $(CH_2)_7$ plus $(CH_2)_6$], 0.90 (t, J = 5 Hz, 3 H, CH_3C), 0.55 (broad s, 3 H, *cis*-cyclopropane H's), −0.35 ppm (m, 1 H, cyclopropane H cis to alkyl groups). Later work showed that the cyclopropane product **6** was quite stable in contact with ozone at low temperature, so that treatment with ozone offers an alternate way of getting rid of unused oleic ester. Calcd for $C_{20}H_{38}O_2$: mol wt, 310. Found: *m/e* 310 (injection port 180 °C).

Cyclopropyl Ketones 7 and 8 from Methyl *cis*-9,10-Methyleneoctadecanoate (6). An oxidation mixture was made up by dissolving 0.41 g of chromium trioxide in 3.3 ml of 1:1 acetic anhydride–acetic acid and diluting with 23.5 ml of carbon tetrachloride. Methyl *cis*-9,10-methyleneoctadecanoate (10 mg) in 0.2 ml of carbon tetrachloride on treatment with 0.84 ml of the oxidation mixture at 0 °C for 2 h furnished the keto products which were separated by preparative layer chromatography. Analytical thin layer chromatography showed single spots with R_f 0.25 for the 8-keto compound **7** and 0.30 for the 11-keto compound **8**.[8]

Calcd for $C_{20}H_{36}O_3$: mol wt, 324. Found for both compounds: *m/e* 324.

Pyrrolidide 9 of *cis*-9,10-Methyleneoctadecanoic Acid. Essentially by following earlier directions,[19,20] 10 mg of methyl *cis*-9,10-methyleneoctadecanate with pyrrolidine and acetic acid furnished pyrrolidide **9** (10 mg) as a faintly yellow oil.

Calcd for $C_{23}H_{43}NO$: mol wt, 349. Found: *m/e* 349.

Monoketo Derivatives (10–13) of Synthetic Methyl Meromycolate (5). The bis cyclopropane methyl meromycolate (2.0 mg) in 0.18 ml of carbon tetrachloride was allowed to stand for 1 h with 0.08 ml of the oxidation mixture. Another 0.05-ml portion was then added, followed after 1.5 h by a third portion. After a total reaction period of 4.5 h, the oxidation mixture was processed as before. Preparative-plate chromatography (silica, benzene solvent) afforded the desired mixture of monoketo esters (**10–13**) as a white solid showing a single spot on analytical thin layer chromatography (R_f 0.55 with benzene on silica).

Pyrrolidide 14 of Synthetic Meromycolic Acid (5). By employing directions essentially the same as these used for methyleneoctadecanoic compound **9**, 1.2 mg of the bis cyclopropane methyl meromycolate (**5**) was warmed with 0.5 ml of pyrrolidine plus 0.05 ml of glacial acetic acid. The crude product was purified on a preparative-layer plate (ether–benzene, 2:3), to give the white solid pyrrolidide **14**.

Calcd for $C_{60}H_{115}NO$: mol wt, 865. Found: *m/e* 865, with only traces of peaks at *m/e* greater than 865.

Acknowledgment. This investigation has been supported by U.S. Public Health Service Grant 09308 from the National Institute of Allergy and Infectious Diseases.

Registry No.—**5**, 59014-67-4; **6**, 3971-54-8; **9**, 60103-87-9; **10**, 60103-88-0; **11**, 60103-89-1; **12**, 60103-90-4; **13**, 60103-91-5; **14**, 60103-92-6; methyl oleate, 112-62-9.

Supplementary Material Available. The full mass spectral line diagrams for all compounds discussed in this paper (8 pages). Ordering information is given on any current masthead page.

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Trehalose Covalently Conjugated to Bovine Serum Albumin

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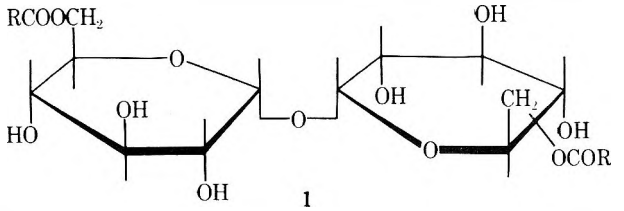
Trehalose has been covalently bonded to bovine serum albumin through both primary hydroxyl groups at the disaccharide 6 and 6′ positions, and also singly bonded through one of these positions.

The family of bacterial liposaccharides collectively called "cord factors" or 6,6′-dimycolyltrehalose (1)[1] exhibits a variety



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of significant physiological, biochemical, and immunological properties.[2,3] For several of these activities, the presence of the trehalose portion substituted at the 6,6′ positions has been found to be either necessary or optimal.[3-5] From these observations and from the fact that cord factor simply mixed with a protein before administration is more active than cord factor alone,[5,6] we were led to consider the effect of *covalently* linking trehalose through its 6- and 6′-hydroxyl groups to a protein carrier. The present paper describes the first example of such a conjugated protein (**11**) in which bovine serum albumin is taken as the protein and *p*-aminobenzoic acid units serve conveniently as connecting links. Further, to allow determination of the effect of only one link between disaccharide and protein, we synthesized the same kind of conjugated protein attached to trehalose through *p*-aminobenzoic acid but only at the disaccharide 6 position (cf. **17**).

The synthesis plan relied either on a useful difference in reactivity between the primary and secondary hydroxyl groups of trehalose or on suitably blocked molecules. Although the literature describes several selective reactions favoring the primary positions,[7] our own attempts at direct esterifications at the trehalose 6,6′ positions gave only unsatisfactory mixtures.[8] An attractive sequence starting with the well-characterized 6,6′-ditrityltrehalose[9] proved disappointing when it was found that the open 2,3,4,2′,3′,4′-hydroxyl groups resisted complete alkylation with methoxymethyl halide.[10] We then turned to octa(trimethylsilyl)trehalose (**3**), which could be prepared in good yield by treating trehalose with trimethylsilyl chloride in dry pyridine. This octasilylated derivative could be selectively desilylated to hexasilylated trehalose **4** having both primary hydroxyl groups exposed, or to the heptasilylated trehalose **12** with only one primary hydroxyl exposed.[11] The presence of two hydroxyl groups in **4** was confirmed by forming diacetyl derivative **5.**

Evidence that the exposed hydroxyl groups correspond to the two primary hydroxyl groups at the 6,6′ positions was provided by the NMR data. Thus, in hexasilylated trehalose **4,** the signal at δ 2.1 ppm for the hydroxyl groups (lost on addition of deuterated water) appears as a two-proton triplet, a feature consistent only with two equivalent OH's both adjacent to vicinal methylene groups, as in assigned structure **4.** Furthermore, in the derived diacetate **5,** the δ 3.6 ppm signal for the 6,6′-methylene groups integrates to four protons, which value would not be obtained if one or both of the acetyl groups were attached anywhere other than to the two primary hydroxyls.

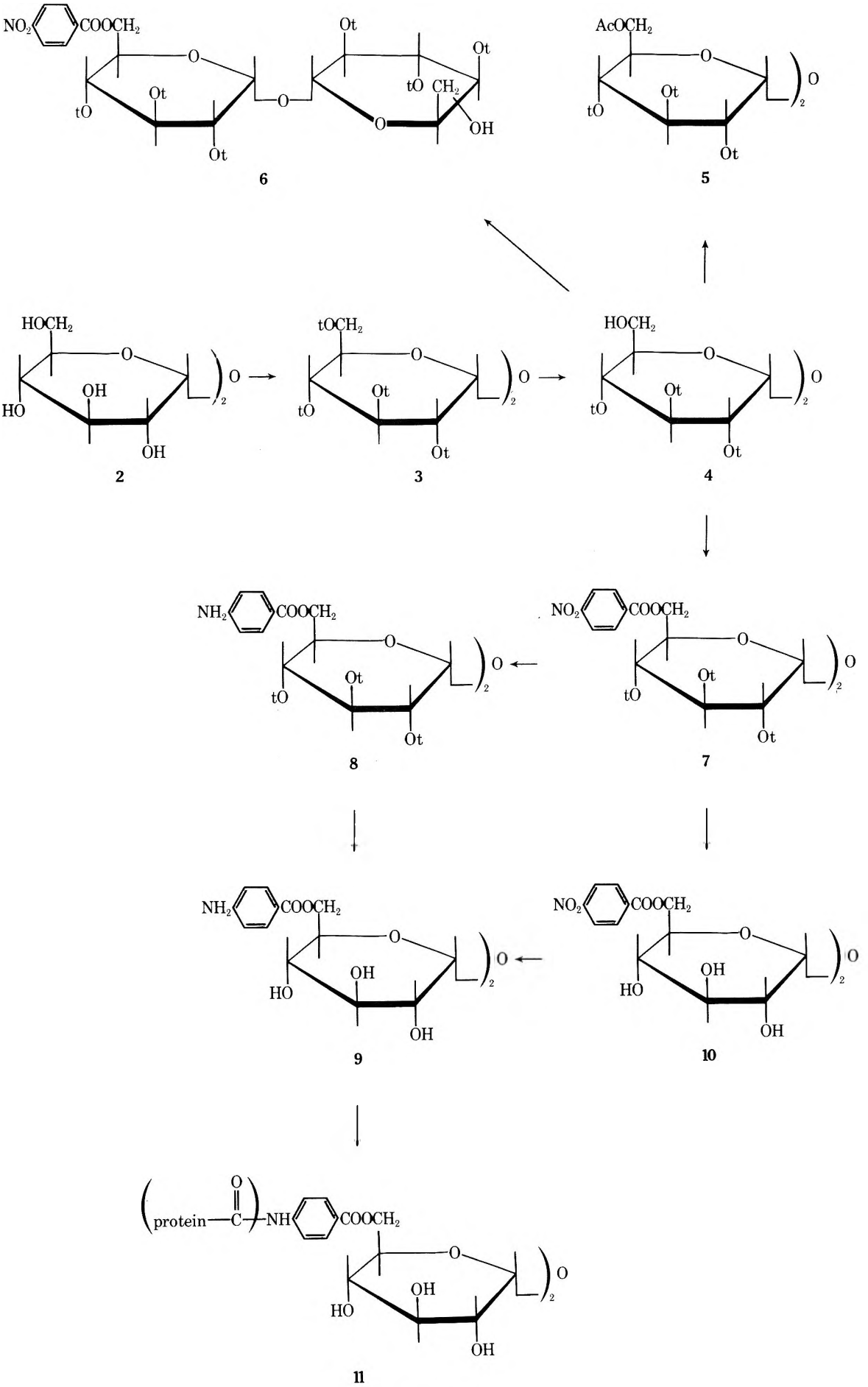
In order to provide the bridging *p*-aminobenzoate sections, the primary hydroxyl groups at the 6,6′ positions were first esterified with *p*-nitrobenzoyl groups. Taking *p*-nitrobenzoyl chloride as reagent, the only pure product isolated in low yield was monoester **6.** The possibility that chloride ion, by displacing one or more trimethylsilyl blocking groups, led to undesirable products was supported by the observation that persilylated trehalose **3** dissolved in pyridine containing pyridinium hydrochloride was completely converted to a mixture after standing at room temperature for 1 day.[12] Esterification with the mixed anhydride of *p*-nitrobenzoic and benzenesulfonic acids[13] furnished the desired di(*p*-nitrobenzoyl) ester **7** plus small amounts of monoester **6.** Catalytic hydrogenation reduced the nitro groups of **7** and gave hexasilylated 6,6′-di(*p*-aminobenzoyl)trehalose (**8**), which was easily transformed to 6,6′-di(*p*-aminobenzoyl)trehalose (**9**). The alternate course of first removing the protecting groups from the di(*p*-nitrobenzoate) **7** and then reducing the resulting 6,6′-di(*p*-nitrobenzoyl)trehalose (**10**) offered little advantage.

To arrive at the conjugated protein, a water-soluble carbodiimide was used to form amide links between side-chain carboxyl groups of bovine serum albumin and the amino groups of diamine **9.**[14] After the coupling, dialysis and lyophilization yielded the finished product **11,** which by assay was shown to carry an average of seven prosthetic groups per molecule of protein.

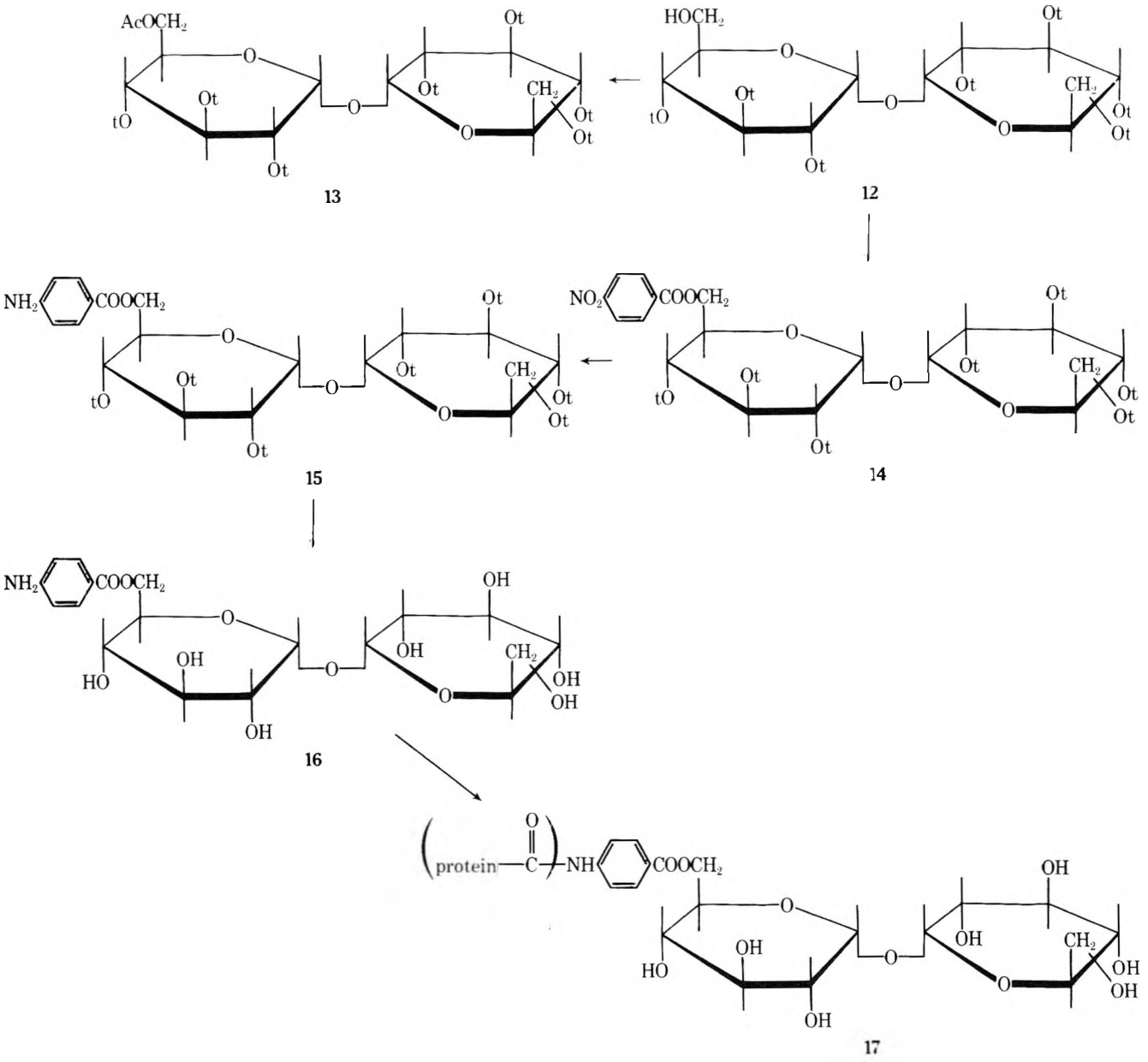
Under properly controlled conditions, the persilylated trehalose **3** could be converted to 2,3,4,2′,3′,4′,6′-hepta(trimethylsilyl)trehalose (**12**). Although the conversion was modest (40%), the yield corrected for recovered starting material **3** and hexasilylated derivative **4** was over 90%. The presence of an open hydroxyl group in **12** was confirmed by acetylation to monoacetyl derivative **13.** The lone exposed hydroxyl group in heptasilylated compound **12** was shown to be the primary group at the 6 (or 6′) position, since the derived nitrobenzoyl derivative **14** obtained by acylating the heptasilylated derivative **12** proved to be identical with the compound obtained by silylating the mononitrobenzoyl from the 6,6′-dihydroxy hexasilylated trehalose **6.** The assignment for **12** was further supported by controlled hydrolysis of the heptasilylated derivative **12,** which led to the 6,6′-dihydroxy compound **4.**

The procedures for attaching the *p*-nitrobenzoyl group to form **14,** hydrogenation to 6-(*p*-aminobenzoyl)hepta(trimethylsilyl)trehalose (**15**), and then removing the masking groups to give 6-(*p*-aminobenzoyl)trehalose (**16**) were similar to those employed in the bis series, as was the final coupling process that produced the conjugated protein **17.** This material assayed for four to five prosthetic groups per molecule of protein.

Samples of the two conjugated proteins **11** and **17** have been distributed to several laboratories for biological assays. Our further plans call for synthesis of analogous conjugated proteins, varying the protein as well as the nature and length of the connections between protein and trehalose.



6 5 2 3 4 8 7 9 10 11



Experimental Section

General. Temperatures are uncorrected. The nuclear magnetic resonance curves were determined at 60 MHz, with the chloroform peak (δ 7.42 ppm) used as an internal reference in place of tetramethylsilane when it was necessary to avoid interference with the signals from the trimethylsilyl groups. Sodium 3-(trimethylsilyl)-2,2,3,3-tetradeuteriopropionate served as an internal reference in the aqueous systems. The reactions were run under nitrogen gas that had been passed through a column of anhydrous calcium sulfate (Drierite). When anhydrous pyridine was used as solvent, it was distilled from calcium hydride and then stored over a molecular sieve (3 Å) under nitrogen. Almost all starting reagents were distilled just before use. The petroleum ether used here boiled at 38–40 °C. We relied on commercial 5 × 20 cm silica plates (0.25 mm thickness) for thin layer chromatography, with spots brought out by spraying the plate with 5% concentrated sulfuric acid in ethanol and then heating. Analysis for elements were reported by Galbraith Laboratories, Inc., Knoxville, Tenn. Molecular weight determinations were performed by mass spectrometry on an AEI MS-9 instrument.

Octa(trimethylsilyl)trehalose (3). Anhydrous trehalose 2[15] (6.8 g, 0.020 mol) was dissolved in dry pyridine (200 ml), and to this solution at room temperature was added trimethylsilyl chloride (21.8 g, 0.20 mol) over a 0.5-h period. After stirring at room temperature for 1 day, the mixture was refluxed for 2 h. Solvent was removed by distillation at reduced pressures at temperatures below 50 °C. The residue, treated with 200 ml of dry petroleum ether, was filtered. Distillation of the concentrated filtrate in a wide-bore short-path still afforded 12 g (66%) of persilylated trehalose **3**, bp 195–200 °C (0.1 mm), which showed one spot on TLC, R_f 0.86 (ether–petroleum ether, 1:15), and melted at 75–78 °C. GLC through 3% SE-30 supported on Chromosorb at a column temperature of ca. 295 °C gave one peak with retention time 21 min; ir, no absorption around 3500 cm^{-1}; NMR ($CDCl_3$) δ 4.9 (d, J = 3 Hz, 2, H-1,1′), 4.1–3.2 (m, 12, all other HCO's), 0.2 ppm [s, 72, $(CH_3)_3Si$'s].

Anal. Calcd for $C_{36}H_{86}O_{11}Si_8$: C, 47.06; H, 9.37; Si, 24.40. Found: C, 47.22; H, 9.28; Si, 24.19.

Hexa(trimethylsilyl)trehalose (4) with Unsubstituted 6- and 6′-Hydroxy Groups. Water (0.9 g, 50 mmol) was added to an 8–10 °C solution of persilylated trehalose **3** (4.6 g, 5.0 mmol) in 100 ml of pyridine. Glacial acetic acid (0.6 g, 10 mmol) was then introduced, and the cold solution was stirred under nitrogen for 5 h. At this time no TLC spot corresponding to starting material could be detected. The reaction mixture was poured over crushed ice and water (400 ml), and the two-phase system was extracted with several portions of petroleum ether. After the combined extract was washed several times with cold water, the organic layer was dried and concentrated at room remperature under water-pump vacuum. The resulting solid was placed on a Florisil column and chromatographed, using as eluents 400 ml of ether–petroleum ether (1:5) (the first 150 ml was discarded) and then ether–petroleum ether (1:3). Complete removal of all volatiles under reduced pressure at room temperature left 3.0 g (76%) of the desired product **4**: mp 116–118 °C; TLC showed one spot, R_f 0.4, using ether–petroleum ether (1:1); ir ($CHCl_3$) 3600 cm^{-1}; NMR ($CDCl_3$) δ 4.8 (d, J = 3 Hz, 2, H-1,1′),4.1–3.2 (m, 12, all other HCO's), 2.1 (broad t, J = 3 Hz, 2, 2 OH's), 0.15–0.13 ppm (m, 54, all CH_3Si). When a drop of deuterated water was added, the 2.1-ppm signal disappeared in favor of one at 4.7 ppm.

Anal. Calcd for $C_{30}H_{70}O_{11}Si_6$: C, 46.51; H, 9.04; Si, 21.71; mol wt, 774. Found: C, 46.62; H, 9.03; Si, 21.64, mol wt, 774 (30 eV, with injection port at ca. 210 °C).[16]

Hepta(trimethylsilyl)trehalose (12) with Unsubstituted 6-Hydroxy Group. Pyridine (150 ml) was injected onto 4.6 g (5.0 mmol) of persilyltrehalose **3** in a three-necked flask stoppered with rubber septums. After the mixture was cooled to 5 °C, water (0.45 g, 25 mmol) followed by acetic acid (0.3 g, 5 mmol) was introduced, and the solution was stirred for 2 h. When TLC results (ether–petroleum ether, 1:15) showed that the intensity of the developing spot at R_f 0.65 had peaked, the mixture was quenched on ice–water (500 ml) and extracted with petroleum ether. The extract was washed with several portions of cold water, dried without delay (Na_2SO_4), and concentrated under reduced pressures at temperatures no higher than ambient. The viscous residue, which contained three components by TLC, was chromatographed through a 30 × 1.3 cm Florisil column using the sequence of solvents, petroleum ether (300 ml), 1:15 ether–petroleum ether (150–200 ml), and ether (50 ml). Unchanged persilylated trehalose (mp 75–78 °C, R_f 0.86) emerged first with the petroleum ether (1.7 g, 37% recovery); the desired monohydroxy product **12** came next with the mixed solvent, followed finally by 0.5 g (19%) of the dihydroxy compound **4** (mp 116–113 °C, R_f 0.28). Monohydroxy derivative **12** was obtained as a colorless, very viscous liquid (1.05 g, 39%), which slowly hardened when allowed to stand at room temperature under vacuum. It showed only one TLC spot with R_f 0.65 using 1:15 ether–petroleum ether or 0.75 with 1:1 ether–petroleum ether: ir ($CHCl_3$) 3600 cm^{-1}; NMR ($CDCl_3$) δ 4.95 (complex t, J = 3 Hz, 2, H-1, 1′), 4.2–3.3 (m, 12, all HCO), 1.85 ppm (broad triplet, 1, OH). With ordinary chloroform as internal standard, the trimethylsilyl group signals were seen at δ 0.3 ppm (m, 62 H as compared to the required 63). The OH peak disappeared when D_2O was added.

Anal. Calcd for $C_{33}H_{78}O_{11}Si_7$: C, 46.81; H, 9.22; Si, 23.17; mol wt, 846. Found: C, 46.94; H, 9.06; Si, 23.30; mol wt, 846 (mass spectrometric value obtained at 30 eV with injection temperature at ca. 205 °C).

When heptasilylated trehalose **12** (0.42 g) in 15 ml of pyridine was stirred for 4 h at 5–10 °C with 0.09 g of water and 0.10 g of glacial acetic acid, and the reaction mixture was processed essentially as before, the product was the hexasilylated derivative **4** (62%), mp 116–118 °C, one spot on TLC with R_f 0.4 (1:1 ether–petroleum ether).

6,6′-Diacetylhexa(trimethylsilyl)trehalose (5). With moisture rigorously excluded, 1 ml of acetic anhydride was injected into a stirred mixture of dihydroxy compound **4** (0.19 g, 0.24 mmol) and dry pyridine (10 ml) at 10–15 °C. After 40 h of stirring at room temperature, the mixture, which according to TLC no longer contained starting material, was poured into ice–water (150 ml). Filtering the precipitate and then drying gave crude diacetylated product **5**. Chromatography through a 12 × 0.5 cm column of Florisil with 30 ml of ether–petroleum ether (1:5) as solvent afforded 0.13 g (59%) of 6,6′-diacetylhexa(trimethylsilyl)trehalose (**5**): mp 158–160 °C; one spot on TLC with ether–petroleum ether (1:7) solvent, R_f 0.71; NMR ($CDCl_3$) δ 5.05 (d, J = 3 Hz, 2, H-1,1′), 4.4–3.85 (m, 8), 3.6 (m, 4, 2 CH_2O), 2.15 (s, 6, 2 CH_3COO), 0.15 ppm [m, 51 as compared to 54 required, $(CH_3)_3Si$'s].

Anal. Calcd for $C_{34}H_{74}O_{13}Si_6$: C, 47.55, H, 8.62; Si, 19.58; mol wt, 858. Found: C, 47.64; H, 8.65; Si, 19.81; mass spectral mol wt (70 eV with injection port at ca. 215 °C), 858, as a low-intensity peak. A very minor peak was also seen at m/e 934.

6,6′-Di(*p*-nitrobenzoyl)hexa(trimethylsilyl)trehalose (7). Benzenesulfonyl chloride (1.4 g, 8.0 mmol) in one portion was injected into a 0–5 °C stirred solution of sublimed *p*-nitrobenzoic acid (0.67 g, 4.0 mmol) dissolved in 100 ml of dry pyridine. After the mixture had been stirred for about 5 min, a solution of dihydroxy derivative **4** (1.6 g, 2.0 mmol) in pyridine (10 ml) was added over a 1-min period. The stirred mixture was held at 0–5 °C for 24 h before it was poured into 300 ml of ice–water. Filtration gave the crude product, which was dried for a short time and then chromatographed through a 30 × 0.5 cm column of Florisil with ether–petroleum ether (1:15) as solvent.

Mono-*p*-nitrobenzoate **6** (0.13 g, 7%), coming out in the first 200 ml of eluate, showed mp 63–65 °C and R_f 0.5 (ether–petroleum ether, 1:5).

The next 300 ml removed the desired di(*p*-nitrobenzoyl)hexa(trimethylsilyl)trehalose (0.84 g, 39%), homogeneous by TLC (R_f 0.21), but crystallized only with difficulty from petroleum ether: mp 87–91 °C; ir ($CHCl_3$) 1750 cm^{-1} with no OH absorption at 3500 cm^{-1}; NMR ($CDCl_3$) δ 8.25 (s, 8, ArH's), 4.98 (d, J = 3 Hz, 2, H-1,1′), 4.5–3.3 (m, 13 as against 12 required for HCO's), 0.15 ppm [m, 54, $(CH_3)_3Si$'s].

Anal. Calcd for $C_{44}H_{76}N_2O_{17}Si_6$: C, 49.25; H, 7.09; N, 2.61; Si, 15.67; mol wt, 1072. Found: C, 49.40; H, 6.93; N, 2.62; Si, 15.77; mass spectral mol wt (30 eV at injection temperature ca. 215 °C), 1072.

As proved by TLC monitoring, esterification attempts using separately prepared *p*-nitrobenzoic anhydride[13] in hot pyridine failed, the starting material persisting unchanged.

6-(*p*-Nitrobenzoyl)-2,3,4,2′,3′,4′-hexa(trimethylsilyl)trehalose (6). *p*-Nitrobenzoyl chloride (0.48 g, 2.6 mmol) in 10 ml of pyridine was injected through a septum into pyridine (100 ml) under a nitrogen atmosphere. This was followed by hexasilylated trehalose **4** (1.0 g, 1.3 mmol) in 10 ml of pyridine, and the stirred mixture was refluxed for 1 h. Complete removal of volatiles under reduced pressures and at temperatures no higher than 50 °C left a dry residue, a solution of which in dry petroleum ether was filtered to remove insoluble pyridinium hydrochloride. After solvent was removed, the mixture remaining was chromatographed through Florisil with 1:10 ether–petroleum ether as solvent (ca. 100 ml). Those fractions showing only a single TLC spot at R_f 0.5 (ether–petroleum ether, 1:5) were combined and stripped of volatiles. (*p*-Nitrobenzoyl) hexasilylated trehalose **6** (0.13 g, 12%) was obtained in this way with mp 63–65 °C. Crystallization from petroleum ether, although possible, was not satisfactory: ir ($CHCl_3$) 3500, 1750 cm^{-1}; NMR ($CDCl_3$) δ 8.25 (s, 4, ArH's), 5.0 (t, J = 2 Hz, 2, 2 H-1's), 4.9–3.3 (m, 12, remaining OCH's), 0.15 ppm [m, 54, $(CH_3)_3Si$]. A signal at δ 1.25 ppm was attributed to the hydroxyl group, although the integration was too small for one proton.

Anal. Calcd for $C_{37}H_{73}NO_{14}Si_6$: C, 48.10; H, 7.90; N, 1.51; Si, 18.20; mol wt, 923. Found: C, 47.99; H, 7.94; N, 1.48; Si, 18.13; mass spectral mol wt (30 eV with T = 215 °C), 923.

When a sample of this material **6** was exposed to the action of trimethylsilyl chloride in pyridine and the course of the reaction monitored by TLC, a progressively darker spot developed corresponding exactly in its R_f value with that of 6-(*p*-nitrobenzoyl)hepta(trimethylsilyl)trehalose (**14**).

Carrying out the *p*-nitrobenzoyl chloride esterification at room temperature instead of at the boiling point of pyridine gave no reaction at all.

6,6′-Di(*p*-aminobenzoyl)hexa(trimethylsilyl)trehalose (8). After 25 mg of 5% palladium on carbon had been stirred for a few minutes with 50 ml of ethyl acetate under a small positive pressure of hydrogen, a 0.10-g (0.090 mmol) sample of dinitro compound **7** already in the hydrogenation vessel was tipped into the catalyst mixture. Stirring for 4 h resulted in the uptake of the calculated amount of hydrogen, after which time no more hydrogen was absorbed. Filtration followed by evaporation of the filtrate under reduced pressure at temperatures no higher than 40 °C left a solid, mp 226–227 °C, which was chromatographed on a 20 × 1 cm column of Florisil using ether–petroleum ether (7:3) as solvent. The eluted, essentially pure product (71 mg, 82%) was crystallized with difficulty from ether–petroleum ether (1:1) to give needlelike crystals of 6,6′-di(aminobenzoyl)hexa(trimethylsilyl)trehalose (**8**): mp 226–227 °C; homogeneous according to TLC with R_f 0.5 (ether solvent); ir (KBr) 3500, 3400, 1720 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (d, 4, 4 H ortho to carbonyls), 6.6 (d, 4, 4 H ortho to NH_2 groups), 4.95 (d, J = 3 Hz, 2, H-1,1′), 4.7–3.3 (m, 16, remaining HC and HN's), 0.15 ppm [m, 53 as compared with the calculated 54, $(CH_3)_3Si$'s].

Anal. Calcd for $C_{44}H_{80}N_2O_{13}Si_6$: C, 52.17; H, 7.90; N, 2.76; Si, 16.60, mol wt, 1012. Found: C, 51.95; H, 8.14; N, 2.69; Si, 16.71, mass spectral mol wt (30 eV at 275 °C), 1012.

6,6′-Di(*p*-nitrobenzoyl)trehalose (10). The masking trimethylsilyl groups were removed from 0.27 g (0.25 mmol) of 6,6′-di(*p*-nitrobenzoyl)hexa(trimethylsilyl)trehalose (**7**) by refluxing the material for 2.5 h with 25 ml of methanol and 5 ml of water plus 1 drop of acetic acid. The solvent-free product, 6,6′-di(*p*-nitrobenzoyl)trehalose (**10**), was isolated in near quantitative yield. TLC using chloroform–methanol (2:1) as solvent developed only a single spot, R_f 0.21. Crystallization from methanol gave 0.12 g of product with mp 149–151 °C (previous softening); ir (KBr) 3400, 1725 cm^{-1}; NMR (in deuterated dimethyl sulfoxide–water–acetone mixed solvent) δ 8.4 (d of d, 8, ArH's), 5.1 (broad d, J = 2.5 Hz, 2, H-1,1′), 4.25 (s, HOD), 4.8–3.2 ppm (m, 12, remaining H's).

Anal. Calcd for $C_{26}H_{28}N_2O_{17}\cdot 2H_2O$: C, 46.15; H, 4.73; N, 4.14. Found, C, 45.91; H, 4.82; N, 4.00.

6,6′-Di(aminobenzoyl)trehalose (9). A. A slightly turbid solution of 0.63 g (0.59 mmol) of 6,6′-di(*p*-aminobenzoyl) hexasilylated trehalose **8** and 1 drop of acetic acid in methanol (100 ml) plus water (15 ml) was refluxed for 1.5 h, at which point starting material could no longer be detected by TLC. The residue remaining after solvent was removed (vacuum at 50 °C) was dissolved in water, and the mixture was filtered. Complete evaporation of the water at 50 °C under reduced pressure left 0.29 g (77%) of slightly hygroscopic di(aminobenzoyl)trehalose (**9**): mp 115–119 °C with previous softening; one spot (R_f 0.5) on TLC with methanol–chloroform (1:1); NMR (D_2O)

δ 7.8 (d of d, 4 + 4, 8 ArH's), 5.2 (broad m, 2, H-1,1'), 4.85 (s, HOD), 4.65–3.4 ppm (m, 14 as compared to 12 required, all remaining HC's).

Anal. Calcd for $C_{26}H_{32}N_2O_{13}\cdot H_2O$: C, 52.17; H, 5.68; N, 4.68. Found: C, 51.98; H, 5.54; N, 4.55.

B. 6,6'-Di(*p*-nitrobenzoyl)trehalose (**10**, 64 mg, 0.10 mmol) in 100 ml of 1:1 methanol–ethyl acetate in the presence of 5 mg of 5% palladium on carbon was stirred under an atmosphere of hydrogen for 7 h. Removal of catalyst and solvent left 37 mg (64%) of 6,6'-di(aminobenzoyl)trehalose (**9**), mp 115–119 °C (softening). Repeated recrystallizations from methanol did not change the melting point. Although some minor spots appeared on a TLC plate (methanol–chloroform, 1:1), the single predominant spot showed an R_f value mtching that of the material described in part A; a mixture of the two diamines **9** showed mp 116–121 °C (preliminary softening).

6-Acetylhepta(trimethylsilyl)trehalose (13). Acetic anhydride (1 ml) was injected into a stirred, 0–5 °C solution of 0.85 g (1.0 mmol) of hepta(trimethylsilyl)trehalose **12** in 25 ml of pyridine, and the mixture was stirred at room temperature for 48 h. Pouring the mixture into 200 ml of ice–water precipitated a solid, which was collected on the funnel, dried, and chromatographed through Florisil using ether–petroleum ether (1:30) as eluting solvent. Homogeneous 6-acetylhepta(trimethylsilyl)trehalose (**13**) (R_f 0.68 with 1:15 ether–petroleum ether) was obtained in this way as a solid (0.72 g, 80%): mp 82–85 °C; NMR ($CDCl_3$) δ 4.98 (t, J = 3 Hz, 2, H-1,1'), 4.4–3.3 (m, 12, remaining OCH's), 2.1 (s, 3, CH_3CO), 0.15 ppm [m, 59 with 63 required for **13**, $(CH_3)_3Si$'s].

Anal. Calcd for $C_{35}H_{80}O_{12}Si_7$: C, 47.29; H, 9.00; Si, 22.07; mol wt, 888. Found: C, 47.44; H, 9.07; Si, 22.09; mass spectral mol wt, 888.

6-(*p*-Nitrobenzoyl)hepta(trimethylsilyl)trehalose (14). The procedure developed for the di(*p*-nitrobenzoyl) derivative **7** was applied in its essentials to the reactants hepta(trimethylsilyl)trehalose **12** (3.4 g, 4.0 mmol), *p*-nitrobenzoic acid (1.0 g, 6.0 mmol), and benzenesulfonyl chloride (2.1 g, 12 mmol) in pyridine (150 ml). The crude oily product was taken up in petroleum ether (300 ml), and the solution was washed with water, dried, and stripped of solvent without heating. The residue was chromatographed as before. After the first 150 ml of eluate was rejected (1:15 ether–petroleum ether), the next 300 ml was collected and stripped of volatiles to leave 1.3 g (32%) of homogeneous 6-(*p*-nitrobenzoyl)hepta(trimethylsilyl)trehalose (**14**): mp 60–63 °C; R_f 0.54 on TLC with ether–petroleum ether (1:15) as developing solvent; ir (KBr) 1750 cm^{-1}; NMR ($CDCl_3$) δ 8.4 (s, 4, ArH's), 5.2 (broad t, J = 2.5 Hz, 2, H-1,1'), 4.9–3.3 (m, 12, remaining OCH's), 0.15 ppm [m, 62 vs. 63 required, $(CH_3)_3Si$'s].

Anal. Calcd for $C_{40}H_{81}NO_{14}Si_7$: C, 48.24; H, 8.14; N, 1.40; Si, 19.65; mol wt, 995. Found: C, 48.44; H, 8.29; N, 1.46; Si, 19.81; mass spectral mol wt, 995.

6-(*p*-Aminobenzoyl)hepta(trimethylsilyl)trehalose (15). Hydrogenation of 0.50 g (0.5 mmol) of the mono(*p*-nitrobenzoyl) compound **14** in 40 ml of ethyl acetate was conducted essentially the same way as described for the di(*p*-nitrobenzoyl) derivative **7**. After 100 min of stirring and the absorption of 120% of the calculated volume of hydrogen, no further hydrogen uptake was noted. Evaporation of the ethyl acetate afforded 0.47 (98%) of solid with mp 211–213 °C that was taken as aminobenzoylhepta(trimethylsilyl)trehalose **15**. Recrystallization of this material (one spot on TLC with R_f 0.57 using ether–petroleum ether, 8:2) from 1:1 ether–petroleum ether failed to give well-formed crystals, and did not change the melting point: ir (KBr) 3400, 3325, and 1725 cm^{-1}; NMR ($CDCl_3$ with $CHCl_3$ as internal reference with δ 7.42 ppm) δ 7.89 (d, 2, H's ortho to amino), 6.65 (d, 2, H's ortho to ester carbonyl), 4.95 (distorted t, 2, H-1,1'), 4.87–3.15 (m, 14, remaining OCH's), 0.13 [m, 63, $(CH_3)_3Si$].

Anal. Calcd for $C_{40}H_{83}NO_{12}Si_7$: C, 49.74; H, 8.60; N, 1.45; Si, 20.31; mol wt, 965. Found: C, 49.76; H, 8.74; N, 1.42; Si, 20.31; mass spectral mol wt, 965.

6-(*p*-Aminobenzoyl)trehalose (16). The trimethylsilyl protecting groups were removed from 0.29 g (0.30 mmol) of *p*-aminobenzoyl heptasilylated trehalose **15** dissolved in 25 ml of methanol by following the directions for the di(*p*-aminobenzoyl) analogue **8**. The reaction was complete in 2 h. The dry product **16**, homogeneous by TLC (R_f 0.38 with 4:1 methanol–chloroform) and obtained in 95% yield, was crystallized from methanol to give 6-(*p*-aminobenzoyl)trehalose (**16**): mp 148–151 °C; ir (KBr) 1725 cm^{-1}; NMR (D_2O) δ 7.95 (d, 2, 2 H ortho to ester), 6.79 (d, 2, 2 H ortho to amino), 5.28 (t or overlapping d, J = 2 Hz, 2, H-1,1'), 4.85 (s, HOD), 4.7–3.4 ppm (m, 12, all other CH's).

Anal. Calcd for $C_{19}H_{27}NO_{12}\cdot 1.5H_2O$: C, 46.72; H, 6.14; N, 2.86. Found: C, 46.81; H, 6.53; N, 2.67.

Attaching the Prosthetic Groups 9 and 16 to Protein. A solution of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (0.5 g, 1.2 mmol) in 1.5 ml of water was added to a solution of 100 mg of either the diamino compound **9** (0.17 mmol) or the monoamino compound **16** (0.20 mmol) plus 50 mg of fatty acid-free bovine serum albumin (Sigma) in 2.5 ml of water. The mixtures (unadjusted pH's 6.8 and 6.1, respectively) were gently stirred at room temperature for 6 h.

The clear solution (A) from the diamino reaction mixture was decanted from the oil (B) adhering to the side of the flask into a 30 × 1.2 cm tube of 0.002-in. cellulose membrane and was dialyzed against distilled water for 48 h. The water was changed every 12 h. Controlled trials showed that no diamino (or monoamino) material remained in the dialysis tube after 6–8 h. The above-mentioned viscous, water-insoluble oil (B) was dissolved in 1% aqueous sodium dodecylsulfonate (2 ml) and was dialyzed separately. After 48 h, this dialysis mixture contained some solid. The two dialyzed solutions were lyophilized separately to give 21 mg of dry coupled protein **11** from the soluble fraction A and 34 mg from the oily fraction B. The former fraction decreased markedly in solubility after lyophilization, since it now proved to be insoluble in water or in 1% aqueous sodium dodecylsulfonate, as well as in buffers from pH 2 to 8.1.

In the monoamino coupling, the originally clear reaction mixture eventually deposited a viscous material sticking to the glass. The aqueous portion was dialyzed as described above, and the oily portion as a solution in 1:1 dioxane–water was dialyzed separately. After dialysis, the contents of the two tubes, both of which now contained small amounts of precipitate, were lyophilized separately. The water-soluble fraction yielded 28 mg, the dioxane–water-soluble fraction 22 mg, of powdery coupled products. The solubility of the first fraction decreased sharply after lyophilization, since it now was practically insoluble in water, dilute detergent, or buffers at pH 4–8.1. The material was reasonably soluble, however, at pH 2.

Ultraviolet absorption measurements served to determine the number of prosthetic groups coupled to the protein. Ethyl *p*-acetamidobenzoate, mp 105–107 °C (lit.[17] mp 103–104 °C), was taken as an appropriate comparison standard. A useful absorption difference between bovine serum albumin and the *p*-acetamidobenzoate, both in 1:10 dioxane–water, was found at 260 nm, where the protein (mol wt 66 000) had ε 26 × 10^3 and the benzoate had ε 7 × 10^3. With this information, the apparent molecular extinction coefficients at 260 nm of the coupled proteins **11** and **17**, also in 1:10 dioxane–water, showed that the protein coupled to both ends of trehalose carried an average of 7 (fraction A) and 2.5 (fraction B) trehalose units per protein molecule, and that the protein coupled only to the 6 position carried an average of 4–5 trehalose units per protein molecule.

Acknowledgment. This investigation has been supported by U.S. Public Health Service Grant 09308 from the National Institute of Allergy and Infectious Diseases.

Registry No.—**2**, 99-20-7; **3**, 42390-78-3; **4**, 59578-12-0; **5**, 60065-00-1; **6**, 60065-01-2; **7**, 60065-02-3; **8**, 60084-56-2; **9**, 60065-03-4; **10**, 60065-04-5; **12**, 60065-05-6; **13**, 60065-06-7; **14**, 60065-07-8; **15**, 60065-08-9; **16**, 60065-09-0; trimethylsilyl chloride, 75-77-4; *p*-nitrobenzoic acid, 62-23-7; *p*-nitrobenzoyl chloride, 122-04-3.

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(16) **Note Added in Proof.** After this paper was submitted for publication, we became aware of work by R. Toubiana, B. C. Das, J. Defaye, and B. Mompon, *Carbohydr. Res.*, **44**, 308 (1975), in which the same hexasilylated compound **4** was prepared by selective desilylation of octasilylated trehalose **3** with potassium carbonate in methanol. The reported melting was 115–118 °C in agreement with our value.
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A Stereospcific Synthesis of Biotin via Thiophene Intermediates[1a]

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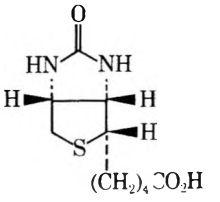
A total synthesis of the vitamin biotin (1) is described. Catalytic hydrogenation of the easily prepared thiophene **22** was found to occur stereospecifically and proceed in excellent yield. This approach features a selective ring closure of the amino diacid **6** to the eight-membered lactam **7**. A number of interesting rearrangements were discovered during the course of a modified Curtius reaction involving the mixed anhydride **16**, which led to the key aromatic substrate for reduction. A novel and efficient ring closure of the mixed diurethane **24** to the imidazolidone moiety of biotin was used to complete the synthesis.

Initially, the biological activity of biotin (1), a member of the B vitamin complex, was confined to its prevention of dermatitis and other degenerative effects in experimental animals.[1b] In recent years, however, researchers have discovered many new applications of this natural product in the areas of nutrition and growth promotion.[2] These findings have generated a renewed interest in the total synthesis of biotin, and this has led to the development of several new syntheses.[3,4]



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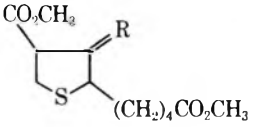
An examination of the structure of biotin (1) reveals the presence of three contiguous asymmetric centers, which requires a high degree of stereocontrol over synthetic intermediates. In addition, the three substituents on the tetrahydrothiophene ring are present in the thermodynamically least stable all-cis configuration.

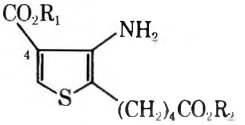
Recently, we have disclosed a solution to this problem which involved a novel oxidative rearrangement of an olefinic thiazolidine.[4] Earlier workers[5] have employed catalytic hydrogenation of a dihydrothiophene in this regard with varying degrees of success. Their efforts were often complicated by a lack of stereospecificity in the reduction step as well as other complications related to the chemistry of dihydrothiophenes. Therefore, it seemed reasonable that a synthesis of biotin based on readily available aromatic intermediates would offer several advantages. For example, the thiophene ring can be considered to be a protecting group for sulfur during the elaboration of the ring substituents. Furthermore, this protection may be dismantled by catalytic hydrogenation, conditions which in principle can simultaneously introduce the all-cis ring hydrogens of biotin in one operation. To date, no synthetically useful approach to biotin based on this concept has been reported,[6] reflecting the marked resistance of thiophenes to reduction.[7]

In this report we describe a highly stereospecific synthesis of biotin which incorporates an efficient reduction of the aromatic precursor **22** to the requisite oxidation level with concomitant introduction of the three cis hydrogens.

An easy entry into the appropriately substituted thiophenes begins with the readily available ketone **2**, prepared in large quantities from pimelic acid and methyl mercaptopropionate.[8] Treatment of **2** with hydroxylamine in pyridine at room



2, R = O
3, R = NOH



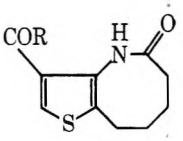
4, $R_1 = R_2 = CH_3$
5, $R_1 = CH_3$; $R_2 = H$
6, $R_1 = R_2 = H$; · HCl

temperature yielded the corresponding oxime **3** in quantitative yield. The two units of unsaturation present in the oxime functionality were induced to migrate into the thiophane ring system by simply dissolving the oxime **3** in ether saturated with hydrogen chloride for 24 h.[9] This rearrangement, which seems to require an electron-withdrawing group in position α to the oxime, afforded in 96% combined yield a mixture of the amino diester **4** and the corresponding amino acid **5**, in a ratio of 6:1. The water derived from the oxime dehydration presumably is the source of the by-product **5**, which is easily isolated by simple extraction.

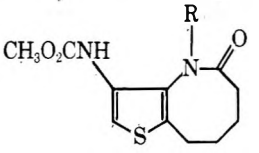
Our synthetic plan at this point required that a Curtius reaction be carried out on the aromatic carbomethoxy group attached to C(4). Treatment of the amine diester **4** with hydrazine failed to distinguish between the two esters. Although the amino acid **5** carried the requisite differentiated groups,

its preparation from the diester **4** could not be achieved in a practical manner. The problem of selecting between the redundant functionality present in **4** was efficiently solved by first hydrolyzing the crude mixture of **4** and **5** to the amino diacid **6**, which was isolated as its hydrochloride salt in 95% overall yield based on the ketone **2**. When a suspension of the amino diacid **6** in xylene was heated under reflux (Dean-Stark trap), a smooth cyclization to the eight-membered ring lactam **7** occurred. The product crystallized on cooling and was isolated in 87% yield. Similarly, the amino acid **5** underwent cyclization to the ester lactam **8**; however, the diester **4** failed to react under these conditions.

Reaction of the ester **8** with hydrazine for 2 min at 25 °C yielded the carbohydrazide **9**. Diazotization of **9** afforded the expected acyl azide **10**, which underwent to Curtius rearrangement[10] upon heating in methanol under reflux. The product urethano lactam **11** was isolated in an overall yield of 95% based on the ester **8**.

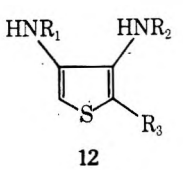


7, R = OH
8, R = OCH_3
9, R = $NHNH_2$
10, R = N_3



11, R = H
23, R = CO_2Et

We had secured in the urethane **11** a thiophene of general structure **12** which contained the required five-carbon side chain attached to C(2) and the necessary carbon–nitrogen bonds at both C(3) and C(4). The oxidation state of every atom in the substituents was now correct for conversion to biotin with the contrived exception of the thiophene nucleus. Reduction of the urethane **11** by catalytic hydrogenation led to the desired all-cis tetrahydrothiophene **13**. The yield in this step was disappointingly low, and the intermediate **13** was not isolated from the product mixture but directly hydrolyzed with barium hydroxide to the diamino acid **14**. Conversion to the target molecule was accomplished by exposure of **14** to phosgene, thereby yielding a sample of *dl*-biotin (**1**), isolated as its methyl ester **15**, and shown to be identical in all respects with an authentic sample. This result served to establish the validity of our approach and encouraged further studies on the prime intermediate carboxy lactam **7**.



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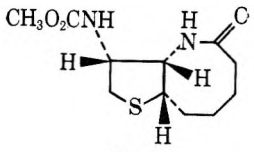

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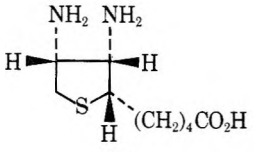

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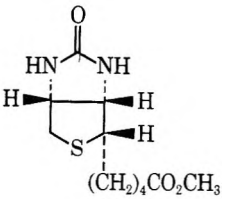

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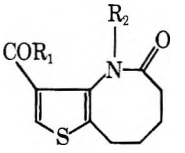
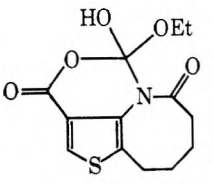
Treatment of **7** with ethyl chloroformate, the first step in the modified Curtius reaction,[11] did not yield the expected mixed anhydride **16**. Instead, the carboxy imide **17**, a product of acyl transfer to the relatively unreactive C(3) nitrogen, was generated. This result implicates the intramolecular acylation shown in structure **18**. Addition of a second equivalent of ethyl chloroformate then presumably afforded the desired imido mixed anhydride **19** which was treated without isolation with sodium azide. Of the four potentially reactive carbonyls present in **19** only the one derived from the initial C(4) carboxyl group is affected. The resulting imido acyl azide **20** is thus available in virtually quantitative yield from the carboxy lactam **7**. Heating **20** in methanol under reflux led primarily to the diurethane **21**, a result of the expected Curtius rearrangement of the acyl azide [leading to the methyl urethane at C(4)] and a selective methanolysis of the imide function at the original lactam carbonyl [affording the ethyl urethane at C(3) and a methyl ester at the side chain terminus]. A small amount of by-product **11**, arising from the alternate mode of imide methanolysis, was also obtained. Treatment of the mixture with aqueous sodium hydroxide yielded the desired acid **22** (easily separable from the unreactive **11** by simple extraction), which was isolated in 80% yield based on the acyl azide **20**.



16, $R_1 = OCO_2Et$; $R_2 = H$
17, $R_1 = OH$; $R_2 = CO_2Et$
19, $R_1 = OCO_2Et$; $R_2 = CO_2Et$
20, $R_1 = N_3$; $R_2 = CO_2Et$



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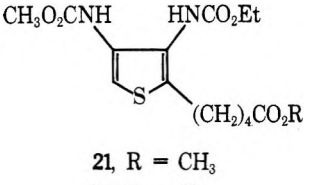
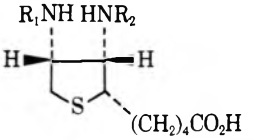


21, R = CH_3
22, R = H

A useful conversion of the by-product **11** to the main-line intermediate **21** was also achieved. Treatment of the urethane **11** in neat ethyl chloroformate under reflux quantitatively acylated the C(3) nitrogen and yielded the imido urethane **23**. Methanolysis of **23** led directly to the desired diurethane **21**. Fortunately, in spite of the presence of both a methyl and ethyl urethane in our intermediates, no traces of urethane exchange reactions in methanol were ever detected.

Catalytic hydrogenation of the now readily available thiophene acid **22** gave an excellent yield (>95%) of the corresponding all-cis tetrahydrothiophene acid **24**.[12] The product was obtained as an oil, homogeneous in several TLC systems.



24, $R_1 = CO_2CH_3$; $R_2 = CO_2Et$
25, $R_1 = CO_2CH_3$; $R_2 = H$
26, $R_1 = H$; $R_2 = CO_2Et$

The all-cis structural assignment was easily confirmed by its conversion to *dl*-biotin (**1**) exclusively, without any detectable trace of the other biotin stereoisomers. This last transformation was achieved by simply treating the mixed diurethane **24** with aqueous barium hydroxide at reflux, conditions which served to cyclize the urethanes and generated the imidazolidone moiety. This led directly to *dl*-biotin (**1**), which separated in high yield upon acidification. The material so obtained was shown to be identical in all respects with an authentic sample.

This direct conversion to the cyclic urea portion of the biotin molecule implicates the intermediacy of the amino ure-

thanes **25** and/or **26**. We expected a difference in the rate of hydrolysis of a methyl vs. an ethyl urethane, especially with the latter group flanked by the side chain at C(2). Once generated, compounds such as **25** and **26** seem to undergo cyclization to biotin rather than suffer any further hydrolysis to the diamino acid **14**. This result obviates the need for a subsequent phosgene treatment of the hydrolysate, an undesirable feature of most published biotin syntheses.[13]

Thus, *dl*-biotin is available from the ketone **2** in an overall yield of 37% by a synthesis which features a number of novel steps: (1) the smooth closure of an eight-membered lactam ring (**6** → **7**); (2) the rearrangements of the various intermediates in the modified Curtius reaction (**7** → **21**); (3) a high-yield stereospecific hydrogenation of a trisubstituted thiophene (**22** → **24**); and (4) the ring closure of a diurethane to an imidazolidone derivative (**24** → **1**).

Finally, since the resolution of *dl*-biotin to the naturally occurring *d* enantiomer has been described,[14] these results constitute a total synthesis of *d*-biotin.

Experimental Section

Melting points were determined on a Rinco Model M-50 melting point apparatus and are uncorrected. Ir spectra were obtained using a Beckman IR-9 spectrophotometer. A Cary 14 recording spectrophotometer was used for uv absorption spectra. NMR spectra were determined with Varian T-60 and HA-100 spectrometers using tetramethylsilane as the internal reference. Mass spectra were recorded on a CEC 21-110B mass spectrometer at 70 eV using a direct insertion probe. Thin layer chromatography was carried out using Merck F-254 silica gel plates.

4-Carbomethoxy-2-[4,5-dihydrothiophen-3(2*H*)-one]valeric Acid Methyl Ester Oxime (3). A solution of 151.4 g (0.553 mol) of 4-carbomethoxy-2-[4,5-dihydrothiophen-3(2*H*)-one]valeric acid methyl ester (**2**) in 470 ml of pyridine was treated with 42.2 g (0.608 mol) of hydroxylamine hydrochloride, and the reaction mixture was stirred at 25 °C for 24 h. Excess pyridine was removed on the rotary evaporator. The residue was taken up in 500 ml of dichloromethane and washed with 200 ml of 1 N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness to yield 158.0 g (0.546 mol, 99%) of the oxime **3** as a pale yellow oil, suitable for use in the next step: ir (CH_2Cl_2) 3400, 3200 (oxime), 1740 cm^{-1} (esters).

3-Amino-4-carbomethoxy-2-thiophenevaleric Acid Methyl Ester (4) and 3-Amino-4-carbomethoxy-2-thiophenevaleric Acid (5). Gaseous hydrogen chloride was bubbled into a round-bottom flask containing a solution of 110 g (0.381 mol) of the oxime **3** in 1500 ml of anhydrous ether previously cooled to 0 °C. After 1.0 h, the reaction flask was stoppered and stored at 25 °C for 24 h. The mixture was concentrated on a rotary evaporator, and the residue was taken up in 500 ml of water and made basic by the addition of 1000 ml of 10% sodium bicarboate solution. The mixture was then extracted three times with 500-ml portions of dichloromethane. The organic phases were dried over anhydrous sodium sulfate and evaporated to afford 90.0 g (0.316 mol, 83%) of the amino diester **4** as a pale yellow, crystalline solid, mp 50–52 °C. For analysis, a sample was recrystallized from ether and melted at 51–52 °C: ir (KBr) 3460, 3370 (NH_2), 1735, 1700 (esters), 1610 cm^{-1}; uv max (CH_3OH) 218 nm (sh) (ε 16 500), 248 (sh) (8500), 325 (2200); NMR ($CDCl_3$) δ 7.76 (s, 1 H, aromatic H), 4.32 (bs, 2 H, NH_2), 3.84 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 2.60 (t, 2 H, $ArCH_2$), 2.36 (t, 2 H, CH_2), 1.69 (m, 4 H, CH_2CH_2); mass spectrum *m/e* 271 (M^+), 170 (base), 138.

Anal. Calcd for $C_{12}H_{17}NO_4S$ (271.34): C, 53.12; H, 6.32; N, 5.16; S, 11.82. Found: C, 53.17; H, 6.35; N, 5.28; S, 11.80.

The aqueous phase was acidified with 6 N hydrochloric acid to pH 4 and extracted three times with 300-ml portions of dichloromethane. The organic extracts were dried over anhydrous sodium sulfate and evaporated to afford 13.0 g (0.048 mol 13%) of the amino acid **5** as a white solid, mp 130–132 °C. An analytical sample was obtained by recrystallization from ethyl acetate and afforded colorless crystals: mp 131–132 °C; ir (KBr) 3450, 3360 (NH_2), 2700–2500 (CO_2H), 1720 (ester), 1705 cm^{-1} (acid); uv max (CH_3OH) 203 nm (ε 1500), 220 (13 580), 249 (7900), 325 (2210); NMR (Me_2SO) δ 7.87 (s, 1 H, aromatic H), 3.77 (s, 3 H, CO_2CH_3), 2.60 (t, 2 H, $ArCH_2$), 2.25 (t, 2 H, CH_2), 1.54 (m, 4 H, CH_2CH_2); mass spectrum *m/e* 257 (M^+), 170 (base), 138.

Anal. Calcd for $C_{11}H_{15}NO_4S$ (257.31): C, 51.35, H, 5.88; N, 5.44; S, 12.46. Found: C, 51.47; H, 5.94; H, 5.60; S, 12.31.

3-Amino-4-carboxy-2-thiophenevaleric Acid Hydrochloride (6). A mixture of 18.64 g of the amino diester **4** and the amino acid **5** was prepared by the method outlined in the previous reaction. This material was dissolved in 400 ml of methanol and was treated with 185 ml (0.185 mol) of 1 N sodium hydroxide. The reaction mixture was refluxed for 1 hr, cooled, and concentrated. The residue was acidified to pH 1 with 50 ml of 6 N hydrochloric acid and evaporated to dryness leaving 23.0 g of the amino diacid **6** as its hydrochloride, admixed with the sodium chloride by-product. This mixture can be used directly in the next step. Further purification can be achieved by extraction of the residue with hot ethanol. The residue obtained by evaporation of the ethanol extract was recrystallized from methanol–ether to give **6** as a white solid: mp 186–187 °C dec; ir (KBr) 3000–2500 (NH_3^+), 1700–1660 cm^{-1} (acids); uv max (CH_3OH) 240 nm (ε 6000), 320 (940); NMR ($CDCl_3$) δ 8.18 (s, 1 H, aromatic H), 8.00 (b, 4 H, NH_2 + 2 CO_2H), 2.89 (t 2 H, $ArCH_2$), 2.23 (t, 2 H, CH_2), 1.10 (m, 4 H, CH_2CH_2); mass spectrum *m/e* 243 (M^+), 224, 208, 197, 156 (base).

3-Amino-4-carboxy-2-thiophenevaleric Acid ζ-Lactam (7). A suspension of 29.0 g (0.104 mol) of the amino diacid hydrochloride **6** in 3.8 l. of xylene was heated under reflux for 2.0 days, using a Dean-Stark trap to remove water. The solution was filtered to remove polymeric material and the filtrate was allowed to cool. The product carboxy lactam **7** separated, and was filtered and washed with ether. The yield of pure material was 19.8 g (0.088 mol, 85%). A sample was recrystallized from xylene–ethanol (trace)–petroleum ether to afford white crystals: mp 216–217 °C; ir (KBr) 3280 (N–H), 2700–2500 (CO_2H), 1680 (aromatic acid), 1630 (amide), 1260 cm^{-1}; uv max (CH_3OH) 213 nm (ε 22 100), 275 (infl) (1810); NMR (Me_2SO) δ 12.50 (b, 1 H, CO_2H), 8.82 (bs, 1 H, NH), 8.06 (s, 1 H, aromatic H), 2.69 (t, 2 H, $ArCH_2$), 2.05 (t, 2 H, CH_2), 1.67 (m, 4 H, CH_2CH_2); mass spectrum *m/e* 225 (M^+), 169 (base), 138.

Anal. Calcd for $C_{10}H_{11}NO_3S$ (225.27): C, 53.32; H, 4.92; N, 6.22; S, 14.23. Found: C, 53.64; H, 5.00; N, 6.41; S, 14.07.

3-Amino-4-carbomethoxy-2-thiophenevaleric Acid Lactam (8). A suspension of 15.0 g (0.0554 mol) of the amino acid **5** in 1500 ml of xylene was heated to reflux and maintained at that temperature for 1 week employing a Dean-Stark trap to remove water. The solvent was removed on the rotary evaporator using a high vacuum pump. The residue was taken up in 100 ml of dichloromethane and washed with 30 ml of 10% sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and evaporated to afford 13.5 g (0.0534 mol, 96%) of crude ester lactam **8**. Recrystallization from ethyl acetate yielded 11.8 g (0.0467 mol, 84%) of the product as a white solid: mp 167–168 °C; ir (KBr) 3230 (NH), 1703 (ester), 1675 (lactam), 1250, 745 cm^{-1}; uv max (CH_3OH) 213 nm (ε 2300), 245 (infl) (7000), 275 (sh) (1880); NMR ($CDCl_3$) δ 8.02 (bs, 1 H, NH), 7.84 (s, 1 H, aromatic H), 3.82 (s, 3 H, OCH_3), 2.78 (t, 2 H, $ArCH_2$), 2.25 (t, 2 H, CH_2), 1.83 (m, 4 H, CH_2CH_2); mass spectrum *m/e* 239 (M^+), 211, 208, 196, 183 (base).

Anal. Calcd for $C_{11}H_{13}NO_3S$ (239.29): C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.25; H, 5.49; N, 5.89; S, 13.39.

3-Amino-4-carbazoyl-2-thiophenevaleric Acid Lactam (9). A sample of 15.0 g (0.0628 mol) of the ester lactam **8** was dissolved at 25 °C in 25 ml of 95% hydrazine. After 2 min, the product began to crystallize. The reaction was allowed to proceed for 0.5 h and then the mixture was evaporated to dryness. The residue was filtered and washed with cold ethanol to afford 15.0 g (0.0628 mol, 100%) of the carbohydrazide **9**, mp 191–192 °C. An analytical sample was prepared by recrystallization from ethanol: ir (KBr) 3390–3050 ($NHNH_2$), 1640 (amide, lactam), 1250, 990 cm^{-1}; uv max (CH_3OH) 213 nm (ε 25 100), 260 (infl) (4300); NMR (Me_2SO) δ 9.37 (bs, 1 H, NH), 8.85 (bs, 1 H, NH), 7.77 (s, 1 H, aromatic H), 4.44 (b, 2 H, NH_2). 2.70 (t, 2 H, aromatic CH_2), 2.00 (t, 2 H, CH_2), 1.75 (m, 4 H, CH_2CH_2); mass spectrum *m/e* 239 (M^+), 208 (base).

Anal. Calcd for $C_{10}H_{13}N_3O_2S$ (239.30): C, 50.19; H, 5.48; N, 17.56; S, 13.40. Found: C, 50.25; H, 5.39; N, 17.71; S, 13.47.

3-Amino-4-azidocarbonyl-2-thiophenevaleric Acid Lactam (10). To a solution of 12.24 g (0.052 mol) of the carbohydrazide **9** in 100 ml of 1 N hydrochloric acid was added dropwise at 0 °C 4.4 g (0.062 mol) of sodium nitrite in 30 ml of water (previously cooled to 0 °C) over a 15-min period. The heterogeneous mixture was stirred for 0.5 h, and then extracted four times with 50-ml portions of chloroform. The extracts were dried over anhydrous sodium sulfate and evaporated to afford 13.0 g (0.052 mol, 100%) of the acyl azide **9** as a colorless oil, suitable for use directly in the next step: ir (CH_2Cl_2) 2100 cm^{-1} (CON_3).

3-Amino-4-carbomethoxyamino-2-thiophenevaleric Acid Lactam (11). A solution of 13.0 g (.052 mol) of the acyl azide **10** in 500 ml of dry methanol was heated to 50 °C. After 15 min at that tem-

perature, the solution was brought up to reflux; the rate of heating was determined by the amount of vigorous gas evolution. The solution was then refluxed for 6.0 h. The solution was cooled and evaporated to afford 12.5 g (0.0491 mol, 95%) of the urethane **11** as a white, crystalline solid, mp 208–210 °C. For analysis, a sample was recrystallized from methanol to yield colorless crystals: mp 209–210 °C; ir (KBr) 3210 (NH), 1705, 1695 (urethane), 1647 (lactam), 1570, 1070 cm^{-1}; uv max (CH_3OH) 220 nm (ϵ 22 300), 250 (infl) (5980); NMR (Me_2SO) δ 8.82 (bs, 1 H, NH), 8.60 (bs, 1 H, NH), 7.03 (s, 1 H, aromatic), 3.63 (s, 3 H, OCH_3), 2.60 (t, 2 H, aromatic CH_2), 1.9 (t, 2 H, CH_2), 1.7 (m, 4 H, CH_2CH_2); mass spectrum *m/e* 254 (M^+), 226, 225, 211 (base), 198.

Anal. Calcd for $C_{11}H_{14}N_2O_3S$ (254.31): C, 51.95; H, 5.55; N, 11.02; S, 12.61. Found: C, 51.74; H, 5.52; N, 10.92; S, 12.88.

Reduction of the Urethane 11. A solution of 1.0 g (0.004 mol) of the urethane **11** in 200 ml of glacial acetic acid was placed in a steel autoclave. After addition of 1.0 g of 10% Pd/C catalyst the reaction mixture was hydrogenated at 100 °C and 1800 psi for 10.0 h. The autoclave was cooled and vented, and the catalyst was filtered and washed with 100 ml of acetic acid. The solvent was removed, and the residue containing the tetrahydrothiophene **13** was taken up in 50 ml of water to which 10.0 g of $Ba(OH)_2 \cdot 8H_2O$ has been added.

The reaction mixture was refluxed for 20.0 h and cooled. Carbon dioxide was bubbled in until the pH dropped to 4. The precipitated barium carbonate was filtered and washed with 20 ml of water. The filtrate was acidified with 1 N sulfuric acid and the precipitated barium sulfate was filtered. The filtrate was then evaporated to dryness, and the residue was taken up in 120 ml of 10% by weight sodium carbonate and cooled to 0 °C. Gaseous phosgene was bubbled in for 5 min until the medium was acidic to Congo red. After 2.0 h an impurity was filtered off and the filtrate was evaporated to dryness. The residue, containing *dl*-biotin, was suspended in 70 ml of dry methanol and treated with 1 drop of sulfuric acid. The mixture was refluxed for 1 h, cooled, and filtered. The filtrate was evaporated, and the residue was partitioned between 50 ml of chloroform and 20 ml of water. The aqueous phase was extracted three times with 20-ml portions of chloroform. The organic phases were combined, dried over anhydrous sodium sulfate, and evaporated to give 0.300 g (0.00116 mol, 29%) of crude *dl*-biotin methyl ester. The mixture was taken up in 3 ml of dichloromethane and plated on three thick layer silica plates. Elution was with 10% by volume methanol–chloroform solution. After two elutions, a sample of pure *dl*-biotin methyl ester, mp 131–132 °C, mmp 131–132 °C, was obtained by removal of the band at R_f 0.26 and recrystallization from ethyl acetate.

4-Azidocarbonyl-3-carbethoxyamino-2-thiophenevaleric Acid Lactam (20). A solution of 2.25 g (0.010 mol) of the carboxy lactam **7** in 40 ml of acetone to which 2 ml of water had been added was cooled in an ice bath for 15 min. At this point, 4.6 ml (0.033 mol) of triethylamine in 40 ml of acetone was added, followed immediately by the dropwise addition of 3.3 ml (0.033 mol) of ethyl chloroformate in 4.5 ml of acetone over a 10-min period. The reaction mixture was stirred at 0 °C for 1 h and then treated dropwise with a solution of 2.13 g (0.33 mol) of sodium azide in 10 ml of water over a 5-min period. The reaction mixture was further stirred at 0 °C for 2 h and then partitioned between 100 ml of dichloromethane and 75 ml of ice water. The aqueous phase was extracted three times with 30-ml portions of dichloromethane. The organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to leave 3.20 g (0.009 mol, 100%) of the acyl azide **20** as a crystalline solid, which was used directly in the next step, ir (CH_2Cl_2) cm^{-1} (CON_3).

3-Carbethoxyamino-4-carbomethoxyamino-2-thiophenevaleric Acid Methyl Ester (21). A solution of 3.20 g (0.099 mol) of the acyl azide **20** in 75 ml of methanol was heated slowly to reflux. The reaction was allowed to proceed for 6 h at this temperature. The methanol was then removed, leaving 3.12 g (0.087 mol, 87%) of the diurethane **21**. Recrystallization from diethyl ether afforded 2.88 g (80%) of pure **21** as a white solid: mp 60–61 °C; ir (KBr) 3330 (NH), 1740 (ester), 1720 (urethanes), 1560, 1260 cm^{-1}; ir (KBr) 3330 (NH), 1740 (ester), 1720 (urethanes), 1560, 1260 cm^{-1}; uv max (CH_3OH) 206 nm (ϵ 24 980), 258 (infl) (5200); NMR ($CDCl_3$) δ 7.22 (bs, 1 H, NH), 7.14 (s, 1 H, aromatic), 6.41 (bs, 1 H, NH), 4.20 (q, 2 H, CH_2O), 3.73 (s, 3 H, urethane), 3.63 (s, 3 H, OCH_3), 2.67 (t, 2 H, aromatic CH_2), 2.32 (t, 2 H, CH_2), 1.65 (m, 4 H, CH_2CH_2), 1.26 (t, 3 H, CH_3); mass spectrum *m/e* 358 (M^+), 326, 312, 298, 280.

Anal. Calcd for $C_{15}H_{22}N_2O_6S$ (358.41): C, 50.27; H, 6.19; N, 7.82; S, 8.95. Found: C, 50.34; H, 6.33; N, 7.95; S, 8.95.

The mother liquors from the recrystallization were chromatographed over silica (eluent chloroform–methanol, 98:2) to yield 0.210 g (8%) of the by-product **11**, identical in all respects with the sample prepared from the carbohydrazide **9**.

Conversion of the Urethane 11 to the Diurethane 21. A suspension of 1.0 g (0.00393 mol) of the urethane **11** in 15 ml of ethyl chloroformate was heated under reflux for 2.0 h. The reaction mixture was cooled and evaporated to dryness. The residue, consisting primarily of the imide **23**, was taken up in 25 ml of anhydrous methanol and heated under reflux for 3–5 h. The reaction mixture was cooled and evaporated to dryness to give 1.4 g (0.00390 mol, 100%) of the diurethane **21**, identical in all respects with the sample prepared from the carboxy lactam **7**.

3-Carbethoxyamino-4-carbomethoxy-2-thiophenevaleric Acid (22). A solution of 0.136 g (0.00380 mol) of the diurethane **21** in 5 ml of methanol was treated with 0.55 ml of 1 N sodium hydroxide. The reaction mixture was heated under reflux for 3.0 h, cooled, and evaporated. The residue was partitioned between 30 ml of dichloromethane and 30 ml of water. The aqueous phase was acidified with 2 ml of 1 N hydrochloric acid and extracted three times with 30-ml portions of dichloromethane. The organic phases were pooled, dried over anhydrous sodium sulfate, and evaporated to yield 0.129 g (000376 mol, 99%) of the acid **22** as a white solid. An analytical sample, mp 159–160 °C, was prepared by recrystallization from methanol: ir (KBr) 3340 (NH), 3150–2850 (acid), 1720 (urethanes), 1700 (acid), 1550, 1241 cm^{-1}; uv max (CH_3OH) 206 nm (ϵ 21 500), 250 (infl) (5300); NMR (Me_2SO) δ 9.05 (b, 1 H, OH), 8.9 (b, 2 H, NH), 7.05 (s, 1 H, aromatic H), 4.04 (q, 2 H, OCH_2), 3.14 (s, 3 H, OCH_3), 2.58 (t, 2 H, $ArCH_2$), 2.18 (t, 2 H, CH_2), 1.54 (m, 4 H, CH_2CH_2), 1.30 3 H, CH_3); mass spectrum *m/e* 344 (M^+), 330, 312, 298 (base), 280.

Anal. Calcd for $C_{14}H_{20}N_2O_6S$ (344.39): C, 48.83; H, 5.85; N, 8.13; S, 9.31. Found: C, 48.61; H, 5.94; N, 8.26; S, 9.00.

***all-cis*-3-Carbethoxyamino-4-carbomethoxyamino-2-tetrahydrothiophenevaleric Acid (24).** A solution of 0.344 g (0.001 mol) of the acid **22** in 200 ml of glacial acetic acid was hydrogenated at 1800 psi in a steel autoclave at 50 °C for 10 h using 0.344 g of 10% Pd/C catalyst. The autoclave was cooled and vented, and the catalyst was filtered and washed with 100 ml of glacial acetic acid. The solvent was removed under vacuum to afford 0.328 g (0.00095 mol, 95%) of the tetrahydrothiophene acid **24** as a colorless oil, homogeneous in several TLC systems: ir (CH_2Cl_2) 3280 (NH), 2850–2500 (acid), 1740 (urethanes), 1720 (acid), 1520, 915 cm^{-1}; NMR ($CDCl_3$) δ 5.5 (bs, 2 H, NH), 5.5 (b, 1 H, OH), 4.30 (q, 2 H, CH_2O), 4.30 (m, 2 H, CHN), 3.7 (s, 3 H, OCH_3), 3.21 (m, 2 H, CH_2), 2.40 (t, 2 H, CH_2S), 2.21 (t, 2 H, CH_2), 1.51 (m, 6 H, $CH_2CH_2CH_2$), 1.2 (t, 3 H, CH_3); mass spectrum *m/e* 331, 273, 259, 247 (base), 184.

***dl*-Biotin (1).** A suspension of 150 mg (0.43 mmol) of the all-cis tetrahydrothiophene acid **24** in 7 ml of water was treated with 1.0 g (5.2 mmol) of barium hydroxide monohydrate. The mixture was heated under reflux for 1 h, cooled, and filtered to remove inorganics. The solids were washed with water, and the filtrate was acidified with 1 N hydrochloric acid and concentrated. Pure *dl*-biotin crystallized from the solution upon cooling and was obtained as 50.0 mg (48%) of a white solid, mp 232–233 °C, mmp 232–233 °C. From the mother liquors, a second crop of 28.1 mg (27%) was isolated to give a total yield of 75% of pure material identical in all respects with an authentic sample of *dl*-biotin (1): ir (KBr) 3250, 3125 (NH), 2700–2500 (acid), 1705 (urea), 1695 cm^{-1} (acid); NMR (Me_2SO) δ 6.56 (bs, 1 H, NH), 6.44 (bs, 1 H, NH), 4.28 (m, 2 H, NCHCHN), 3.15 (b, 1 H, CHS), 2.72 (m, 2 H, CH_2S), 2.22 (t, 2 H, CH_2), 1.45 (bm, 6 H, $CH_2CH_2CH_2$); mass spectrum *m/e* 244 (M^+), 184, 112, 97 (base), 85.

Anal. Calcd for $C_{10}H_{16}N_2O_3S$ (244.29): C, 49.16; H, 6.60; N, 11.47; S, 13.12. Found: C, 49.22; H, 6.62; N, 11.34; S, 13.20.

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Registry No.—**1**, 22377-59-9; **1** Me ester, 60562-11-0; **2**, 59851-05-7; **3**, 59851-06-8; **4**, 59851-07-9; **5**, 59851-08-0; **6** HCl, 59851-10-4; **7**, 59851-11-5; **8**, 59851-12-6; **9**, 59851-13-7; **10**, 59851-14-8; **11**, 59851-15-9; **20**, 59851-19-3; **21**, 59851-20-6; **22**, 59851-21-7; **24**, 60512-75-6; hydroxylamine hydrochloride, 5470-11-1; ethyl chloroformate, 541-41-3.

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Reaction of *O*-Methyl-*N,N′*-diisopropylisourea with Amino Acids and Amines

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The reaction of *O*-methyl-*N,N′*-diisopropylisourea with amino acids and amines, as their hydrochlorides, has been examined, and exhaustive methylation has been found to be the reaction pattern. Thus conversion of L-proline, L-*N*-methylproline, L-4-hydroxyproline, and DL-2-aminobutyric acid to the corresponding betaines was effected in good yield. Also, the hydrochlorides of benzylamine and codeine gave the quaternary derivatives, benzyltrimethylammonium chloride and codeine methochloride. Clean conversion of morphine to codeine could be realized without N-methylation; however, reaction of this aminophenol was solvent sensitive and in methanol and acetonitrile α-codeimethine was formed as a minor side product. In each case, the more nucleophilic site in the molecule was selectively alkylated.

The utility of *O,N,N′*-trialkylisoureas in the conversion of carboxylic acids to esters,[1,2] phenols to arylalkyl ethers,[3,4] thiophenols to arylalkyl sulfides,[5,6] and thiols to dialkyl sulfides,[7] and in the alkylation of β-diketones[6] and thymidine and uridine,[8] has been demonstrated. Much less is known about the reactivity of these reagents toward compounds containing more than a single nucleophilic site, and such reactions have received only cursory attention.[5-7]

We now report our findings on the reaction of *O*-methyl-*N,N′*-diisopropylisourea (**1**) with amino acids, amine hydrochlorides, and an aminophenol. These reactions and results appear to be applicable to a variety of other amines and *O,N,N′*-trialkylisoureas.

Conversion of Amino Acids to Betaines. When the amino acids, L-proline (**2**), L-*N*-methylproline (**4**), L-4-hydroxyproline (**5**), and DL-2-aminobutyric acid (**7**), were allowed to react with excess isourea **1** in methanol at room temperature for several days, the corresponding betaines **3, 6,** and **8** were isolated in moderate to high yield (Table I). In no case was esterification observed, and no etherification of the hydroxyl group of **5** was detected.

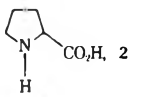
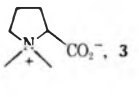
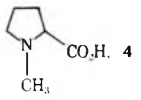
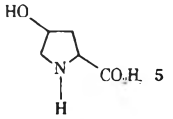
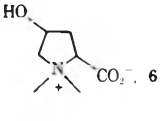
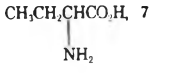
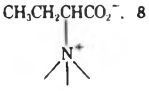
The rationalization for betaine formation lies in the relative nucleophilicities of the amino and carboxyl functionalities present in the reaction. Following protonation of **1**, the amino acid species is present as the carboxylate anion. N-Methylation leading to betaine formation is attributed to the amino group being a more powerful nucleophile than the carboxylate anion in the ensuing SN2 reaction.

An interesting solvent dependence was observed in the reaction of L-proline (**2**) with isourea **1**. Whereas betaine formation was the sole process occurring at room temperature in methanol or water, both formation of betaine **3** and L-proline methyl ester were detected in *tert*-butyl alcohol or methoxyacetonitrile under reflux. O-Alkylation leading to methyl ester formation can be attributed to the decreased solvation, and, hence, greater availability as a nucleophile, of the more electronegative carboxylate oxygen in *tert*-butyl alcohol and methoxyacetonitrile relative to the more polar and protic methanol and water.

Use of isourea **1** to prepare betaines directly from amino acids affords a mild and effective alternative to the more classical procedures of treating an amino acid with silver oxide and methyl iodide,[9-11] an alkali metal hydroxide and a methylating agent,[9,12,13] or diazomethane[9,14,15] that have been employed to prepare some of these, as well as other betaines. Further, optical activity measurements show the recrystallized product obtained by the isourea method to be optically pure.

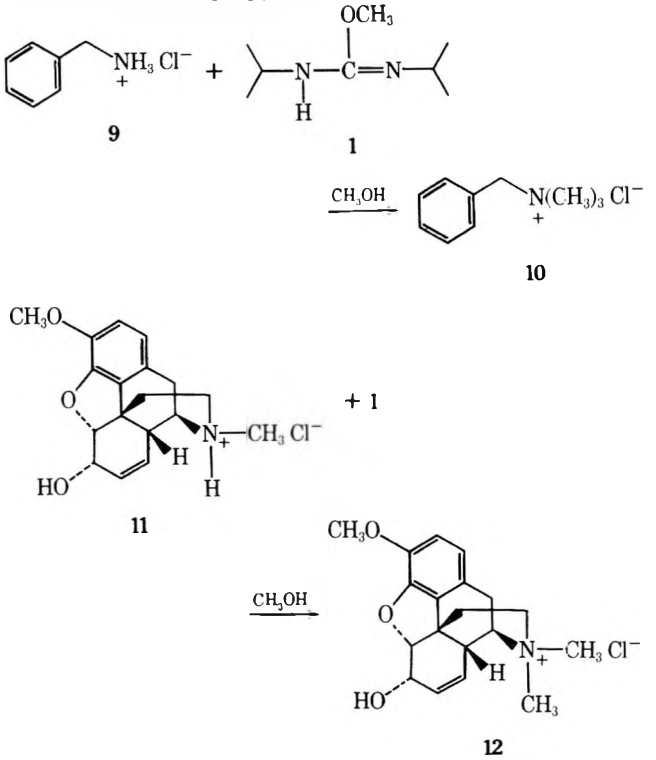
Exhaustive Methylation of Amine Hydrochlorides. The mechanism for alkylation with *O,N,N′*-trialkylisoureas requires a proton source and a sufficiently powerful nucleophile.[1,2,16] In view of the ease of betaine formation from amino acids, it was postulated that an amine hydrohalide could serve as both proton source and nucleophile and react with excess *O*-methyl-*N,N′*-diisopropylisourea (**1**) to yield the corresponding quaternary ammonium halide. In agreement with the prediction, treatment of benzylamine hydrochloride (**9**) and codeine hydrochloride (**11**) with excess isourea **1** in methanol at room temperature for several days resulted in the formation of benzyltrimethylammonium chloride (**10**) and codeine methochloride (**12**), respectively. The low isolated yields of **10** and **12**, 17 and 25%, were attributed to incomplete

Table I. Reaction of *O*-Methyl-*N,N'*-diisopropylisourea (1) with Amino Acids to Form Betaines

Amino acid	Betaine	Yield, %[a]
 2	 3	86 (68)
 4	3	87 (60)
 5	 6	100 (74)
 7	 8	63 (44)

[a] Chromatographed yield (recrystallized yield).

reaction under the conditions used. No attempt was made to determine the extent to which 1 decomposes to methyl chloride and *N,N'*-diisopropylurea.



Conversion of Morphine (13) to Codeine (14). It is known that phenols can be etherified with isoureas in good yield.[3,4] Furthermore, it has been shown that thiophenols are alkylated by these reagents and that the resultant thioether formation is not affected by the presence of phenolic, amino, or carboxyl groups.[5,6] It was of interest to treat morphine (13), an aminophenol, with *O*-methyl-*N,N'*-diisopropylisourea (1) to determine if selective O-alkylation to codeine could be realized.

Treatment of morphine (13) with excess isourea 1 in methanol under reflux resulted in moderate yields of codeine (14) and formation of α-codeimethine (15) as a minor product (see Table II). Comparison of GC peak areas indicated the extent of conversion of 13 to methine 15 to be about 5–10% that of 13 to codeine. The formation of 15 to about the same extent was also observed when the reaction was performed in methanol at room temperature.

Table II. Reaction of *O*-Methyl-*N,N'*-diisopropylisourea (1) with Morphine (13) to Form Codeine (14)

Mol %			% isolated yield		
13	1	Conditions[a]	14	13	15
100	112	CH_3OH, Δx, 24 h	47	34	Not detd
100	307	CH_3OH, Δx, 100 h	71	Not detd	5
100	501	THF, Δx, 48 h	56	46	None
100	200	THF, Δx, 24 h	10	87	None
100	200[b]	THF, Δx, 24 h	21	40	None
100	502	CH_3CN, Δx, 48 h	73	12	<4
100	499	Neat, 100 °C, 7 h	89	5	<1
100	501	Neat, 100 °C, 20 h	83	5	<1

[a] All reactions in which solvent was employed were done at morphine (13) concentration of 0.25 M; Δx = reflux. [b] Reaction performed in the presence of added *N,N'*-diisopropylurea (16) (200 mol %).

When morphine was allowed to react with excess isourea 1 in acetonitrile under reflux, moderate yields of codeine were again realized. Since the extent of α-codeimethine formation was decreased (relative GC peak areas of 14:15 ~ 18.5:1), a clean conversion to codeine appeared possible in a less polar solvent. Accordingly, treatment of 13 with excess 1 in THF under reflux resulted in good yields of 14 without concomitant formation of 15; isolated codeine and recovered morphine accounted for greater than 90% of starting morphine.

In neither acetonitrile nor THF could total reaction of 13 be achieved. While the heterogeneity of the reaction mixture and the relatively nonpolar nature of the solvent can be blamed for retardation of the reaction rate, these factors cannot explain the failure to achieve complete reaction. Interference in the desired reaction by an increasing concentration of *N,N'*-diisopropylurea (16) as the reaction progresses was considered a possible explanation. However, in a reaction in THF in which a twofold excess of 16 was added, neither the rate of reaction nor the yield of codeine was adversely affected.

The preparation of codeine (14) from morphine (13) without solvent was effected in high yield by stirring a suspension of 13 in excess isourea 1 for several hours at 100 °C. With this procedure, yields of 14 of 90% were attained and contamination by 15 was less than 1%.

The formation of α-codeimethine (15) arises from N-methylation of codeine and subsequent Hofmann elimination of the resulting ammonium salt. In proceeding from protic, polar methanol to acetonitrile and THF, it appears that the lessened solvation, and, hence, increased nucleophilicity, of the more electronegative phenoxide oxygen would increase the extent of O-alkylation at the expense of N-alkylation. While a decrease in the extent of N-alkylation, ultimately leading to 15, was observed in acetonitrile, it was in THF that this effect was fully realized.

Although reaction conditions were not optimized, our results show that the use of THF as solvent affords a clean conversion of morphine (13) to codeine (14) with a high recovery of unreacted 13, and that performing the reaction in the absence of solvent affords a high-yield conversion of 13 to 14. Since the strongly alkaline conditions and high temperatures required by more traditional procedures[17,18] are avoided, this method offers a mild, effective alternative for the preparation of codeine. Unlike the Rodionov procedure,[17,18] in which methine 15 is also a side product, there is no contamination by codeine methyl ether.[19] Also, it appears that this method will be applicable to the synthesis of a variety of *O*-3-ethers of morphine.

This investigation of the reactions of isourea 1 with compounds containing more than a single nucleophilic site indicates that selective alkylation of the more nucleophilic func-

tion can be achieved. It is also reasonable to expect the reactions discussed to be general for a variety of isoureas.

Experimental Section

General. O-Methyl-N,N'-diisopropylisourea (1) was prepared as described.[20] All melting points are uncorrected. Microanalyses were performed by the Analytical Laboratory, University of California, Berkeley. NMR spectra were recorded on a Varian T-60 spectrophotometer. Mass spectra were obtained on an MS12 instrument. Optical rotations were recorded on a Bendix Ericsson ETL-NPL automatic polarimeter, Type 143A. Thin layer chromatography was done on Camag silica gel and column chromatography was done with Merck silica gel (0.063–0.2 mm), unless otherwise specified. Conversion of morphine (13) to codeine (14) was followed analytically by GC using an Aerograph HY-FI Model 600-D with a 6 ft × 0.125 in. glass column packed with 3% OV-17 on Aeropak 30; column temperature, 235 °C; He flow rate, 67 ml/min. Retention times relative to morphine (1.00) follow: codeine (14), 0.78; α-codeimethine (15), 0.70.

L-Proline Betaine (Stachydrine) (3). A solution of 346 mg (3.0 mmol) of L-proline (2) and 1.59 g (10.0 mmol) of 1 in 6 ml of absolute methanol was stirred at room temperature for 48 h, the mixture was diluted with 5 ml of H_2O and filtered to remove precipitated urea 16, and the filtrate was evaporated to give 583 mg of an oily white solid. Chromatography on 50 g of silica gel with CH_3OH/concentrated NH_3/$CHCl_3$ (10:1.5:13.5) as eluent gave 370 mg (86%) of betaine 3 as a white solid, R_f 0.32. Recrystallization from absolute C_2H_5OH/Et_2O gave 290 mg (67.5%) of 3, mp 220–230 °C dec (lit.[21] mp 235 °C dec). The product was identical by TLC and NMR with an authentic sample.[10]

L-Proline Betaine (3) from L-N-Methylproline (4). A solution of 107 mg (0.83 mmol) of L-N-methylproline[22] (4) and 269 mg (1.64 mmol) of 1 in 2 ml of absolute CH_3OH was stirred at room temperature for 48 h. Isolation as described above gave 104 mg (87%) of 3 after chromatography and 71 mg (60%) after recrystallization, mp 227–235 °C dec (lit.[21] mp 235 °C dec).

L-4-Hydroxyproline Betaine (Betonicine) (6). A solution of 302 mg (2.30 mmol) of L-4-hydroxyproline (5) and 1.455 g (9.19 mmol) of 1 in 6 ml of absolute CH_3OH was stirred at room temperature for 72 h. Isolation as described above gave 368 mg (100%) of 6 after chromatography as a white solid, R_f 0.10. Recrystallization from absolute C_2H_5OH/acetone gave 270 mg (74%) of 6: mp 244–245 °C dec (lit. mp 252–253,[11] 243–244 °C[23]); $[\alpha]^{24}D$ −36.1° (c 0.956, H_2O) [lit. $[\alpha]^{20}D$ −34.2° (c 1.0, H_2O),[11] $[\alpha]^{15}D$ −36.6° (c 4.88, H_2O)[23]]. The product was identical by TLC and NMR with an authentic sample.[11]

DL-2-Aminobutyric Acid Betaine (8). A solution of 310 mg (3.01 mmol) of DL-2-aminobutyric acid (7) and 1.91 g (12.1 mmol) of 1 in 10 ml of absolute CH_3OH was stirred at room temperature for 5 days. Isolation as described above gave 274 mg (62.7%) of 8 as a solid, R_f 0.25. Recrystallization from absolute C_2H_5OH/Et_2O gave 193 mg (44.1%): mp 218–220 °C dec; NMR [D_2O, internal $(CH_3)_3Si(CH_2)_3SO_3Na$] δ 0.97 (t, 3 H, J = 8 Hz), 1.90–2.23 (m, 2 H), 3.20 (s, 9 H), 3.40–3.70 (AB q, 1 H); mass spectrum m/e 144 ($M^+ - 1$, 1.0%), 86 ($M^+ - CO_2CH_3$, $M^+ - C_3H_9N$, 81.5%), 59 (C_3H_9N, 73.6%), 58 (C_3H_8N, 100%).

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.9; H, 10.4; N, 9.6. Found: C, 57.5; H, 10.5; N, 9.6.

Benzyltrimethylammonium Chloride (10). A solution of 144 mg (1.00 mmol) of benzylamine hydrochloride (9) and 640 mg (4.05 mmol) of 1 in 4 ml of absolute CH_3OH was stirred at room temperature for 5 days and evaporation of the solvent gave 632 mg of a residue which was filtered through 30 g of silica gel using ethyl acetate/methanol/acetic acid (16:4:1) as eluent, to remove 16 and unreacted 1 and 9. A CH_3OH wash of the column gave 57 mg (31%) of 10 which was recrystallized from acetone to give 31 mg (17%), mp 220–235 °C (lit.[24] mp 243 °C).

Codeine Methochloride (12). A solution of 334 mg (1.00 mmol) of codeine hydrochloride (11) and 319 mg (2.01 mmol) of 1 in 2 ml of absolute CH_3OH was stirred at room temperature for 11 days, solvent was evaporated, and the residue of 591 mg was filtered through 10 g of silica gel with $CHCl_3$/15% CH_3OH as eluent, removing 16 and unreacted 11. A CH_3OH wash of the column gave 122 mg of methochloride 12 which was recrystallized from absolute C_2H_5OH to give 87 mg (25%) of 12, mp 258–265 °C dec (lit.[25] mp 260–265 °C dec).

Reaction of Morphine (13) with O-Methyl-N,N'-diisopropylisourea (1) to Yield Codeine (14). In CH_3OH. A solution of 285 mg (1.00 mmol) of morphine (13) and 485 mg (3.07 mmol) of 1 in 4 ml of absolute CH_3OH was heated under reflux in a nitrogen atmosphere for 100 h. Evaporation of the solvent and chromatography of the residue on 30 g of silica gel with $CHCl_3$/15% CH_3OH as the eluent gave 211 mg (71%) of codeine (14), and 61 mg of a yellow oil containing 14, R_f 0.40, α-codeimethine (15), R_f 0.27, and 13, R_f 0.14. Sublimation of the codeine (14) fraction at 130 °C (0.05 mm) gave 14, mp 151–154 °C, identical by GC, TLC, NMR, and MS with an authentic sample.

The mixture of 13, 14, and 15 was partitioned between 10 ml of $CHCl_3$ and 5 ml of 2 N NaOH, the $CHCl_3$ was removed, and the aqueous portion was extracted with an additional 10 ml of $CHCl_3$. The combined $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated to give 29 mg of an oil containing 14 and 15. Chromatography on silica gel with $CHCl_3$/15% CH_3OH as the eluent gave 14.0 mg (4.5%) of 15, mp 113–117 °C (lit.[26] mp 118.5 °C) after recrystallization from ether, identical with an authentic sample[26] by GC, TLC, NMR, and MS.

In THF. A suspension of 286 mg (1.00 mmol) of 13 in a solution of 793 mg (5.01 mmol) of 1 in 4 ml of THF was heated under reflux in a nitrogen atmosphere for 48 h. The solvent was removed, the residue of 684 mg was partitioned between 15 ml of $CHCl_3$ and 5 ml of 2 N NaOH, the $CHCl_3$ was removed, and the aqueous portion was extracted with an additional 15-ml portion of $CHCl_3$. The combined $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated to give 362 mg of an oil which was chromatographed on 40 g of silica gel with $CHCl_3$/15% CH_3OH as the eluent to give 166 mg (56%) of 14 as a yellow solid. Sublimation at 130 °C (0.03 mm) gave 136 mg (45%) of pure codeine.

The alkaline aqueous portion was brought to pH 8.5 with 2 N HCl and extracted with 3 × 15 ml of $CHCl_3$/25% 2-propanol; the combined organic extracts were evaporated to give 131 mg (46%) of recovered morphine.

In Acetonitrile. A suspension of 283 mg (0.99 mmol) of 13 in a solution of 795 mg (5.02 mmol) of 1 with 4 ml of CH_3CN was heated under reflux in a nitrogen atmosphere for 48 h. Isolation as described above gave 216 mg (73%) of codeine (14). From the alkaline aqueous portion was recovered 33 mg (12%) of morphine (13).

Neat. A suspension of 285 mg (1.00 mmol) of 13 in 790 mg (4.99 mmol) of 1 was stirred in a 100 °C bath in a nitrogen atmosphere for 7 h. Isolation as described above gave 267 mg (89%) of codeine (14). From the alkaline aqueous portion was recovered 14.3 mg (5%) of morphine (14).

Registry No.—1, 54648-79-2; 2, 147-85-3; 4, 475-11-6; 5, 51-35-4; 7, 2835-81-6; 8, 60526-21-8; 9, 3287-99-8; 11, 1422-07-7; 13, 57-27-2.

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A New and Simple Method of Resolution. Preparation of 3-Fluoro-D-alanine-*2-d*

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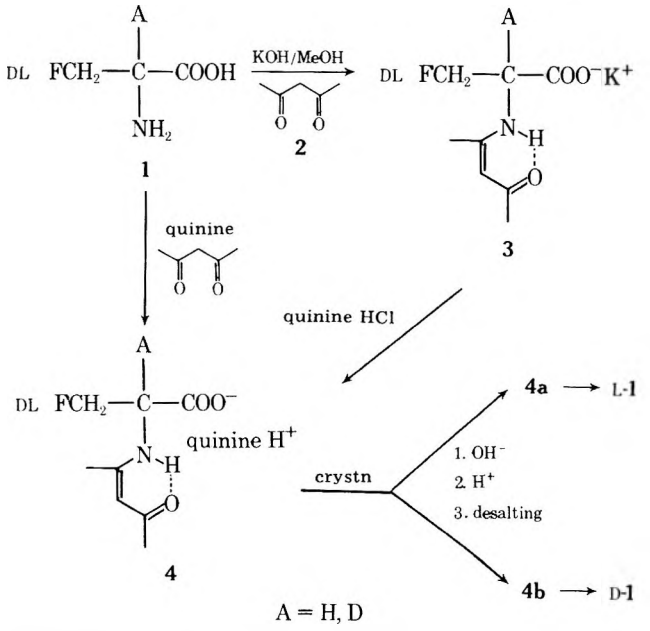
A simple method for resolving 3-fluoro-DL-alanine-2-*d* and its protio analogue is described. The highly acid labile *N*-(1-methyl-2-acetylvinyl)amino acids were prepared as the quinine salts and the diastereomers were separated by crystallization.

It was recently reported[1] that the combination of 3-fluoro-D-alanine-2-*d* (1) and a derivative of the antibiotic cycloserine is a potent gram-positive and gram-negative antibacterial agent. We report here a new method of resolution for DL-**1**, which is also applicable to its protio analogue,[5] alanine itself, and presumably many other amino acids.

β-Diketones have been previously used for protecting α-amino acids as their enamines during peptide synthesis.[2,3] Prior to our report these derivatives were synthesized as their potassium salt[2,4] or the more crystalline dicycohexylamine salt.[3] We explored the possibility of using an optically active base to form their crystalline diastereomers, and found that the quinine salt crystallized easily in good yield and excellent purity. Further advantages of this resolution method include the one-step derivatization–salt formation and the ease of removing the protecting group.

Conversion of 3-fluoro-DL-alanine (**1**)[5,6] to the quinine *N*-(1-methyl-2-acetylvinyl)-3-fluoro-DL-alaninate (**4**) is accomplished by warming **1** with quinine and 2,4-pentanedione

Scheme I



in methanol. The L isomer **4a** crystallizes from the reaction mixture in high (≈99%) optical purity.

The quinine salt **4** can also be made by treatment of the potassium salt **3** with 1 equiv of quinine HCl. From the resolved **4a** or **4b** the quinine is separated by extraction with chloroform of the basified solution. The masking group is readily cleaved from the resolved substrate by mild acid hydrolysis and separated by extraction. In the final step ion exchange is employed for the removal of inorganics. The L-**1** or D-**1** is eluted with 0.5 N ammonium hydroxide and isolated by crystallization after reducing the volume of eluate in vacuo.

The scope of the method has not been explored. We have also resolved alanine by this procedure, and Southard's work[3b] describing the preparation of numerous amino acid enamine derivatives suggests that this method should be generally applicable.

In the Experimental Section are detailed procedures for direct quinine salt formation with 3-fluoroalanine-2-*d* and alanine itself, and the K-salt method with 3-fluoroalanine.

Experimental Section

All optical rotations were determined on a Carl Zeiss photoelectric precision polarimeter Model LEP A1 as a 6% solution in 1 N hydrochloric acid at 25 °C unless otherwise specified. NMR spectra were obtained with a Varian T-60 spectrometer and sodium 3-(trimethylsilyl)propanesulfonate as the internal standard and interpreted by Dr. Alan W. Douglas. Microanalyses were done through the courtesy of Mr. J. P. Gilbert and associates. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected.

Resolution of 3-Fluoro-DL-alanine-*2-d* (1). Racemic 3-fluoroalanine-2-*d*[6] (100 g, 0.935 mol), 2,4-pentanedione (103 g, 1.03 mol), and quinine (320 g, 0.99 mol) in 1870 ml of anhydrous methanol were treated under reflux in a nitrogen atmosphere for 1 h. After cooling and stirring for 1 h at 20 °C the quinine salt of *N*-(1-methyl-2-acetylvinyl)-3-fluoro-L-alanine-2-*d* (**4a**) CH_3OH solvate was collected, washed with cold CH_3OH, and dried in vacuo at room temperature to give 176 g, $[\alpha]^{25}D$ −89.6° (c 2.0, 95% EtOH), mp 143–144 °C dec.

Anal. Calcd for $C_{28}H_{36}FN_3O_5 \cdot CH_3OH$: C, 63.83; H, 7.39; F, 3.48; N, 7.70. Found: C, 63.78; H, 7.30; F, 3.69; N, 7.90.

Removal of the solvent from the filtrate and washes, followed by crystallization of the residue from 500 ml of EtOAc, gave after 16 h at 0 °C a second crop of 55.2 g. The yield of analytically pure first and second crops was 96.6%. The anhydrous form was obtained by drying a sample at 50 °C for 2 h.

Anal. Calcd for $C_{28}H_{36}FN_3O_5$: C, 65.48; H, 7.07; F, 3.70; N, 8.18. Found: C, 65.66; H, 7.46; F, 3.77; N, 8.23.

The residue (**4b**) from the second crop was dissolved in 360 ml of water and basified by adding 450 ml of 1.2 N (0.54 mol) sodium hydroxide with stirring at 10–15 °C. The liberated quinine was removed by chloroform extraction and the aqueous phase was acidified and stirred with 500 ml of 2 N hydrochloric acid at 15–20 °C. After 15 min, the protecting group was removed as evidenced by the dissolution of the precipitated *N*-(1-methyl-2-acetylvinyl)-3-fluoro-D-alanine-2-*d*. After extraction with chloroform to remove 2,4-pentanedione, the aqueous phase was clarified with charcoal and the filtrate was percolated through 1.1 l. of Dowex 50W × 4 (H^+ form). The column was washed free of Cl^- with water, then the product was eluted with 0.5 N ammonium hydroxide, collecting and concentrating in vacuo the ninhydrin-positive fractions until the product crystallized (≈150 ml). The mixture was cooled to 5 °C and aged for several hours, and the crystalline 3-fluoro-D-alanine-2-*d* was collected, washed with cold water, and vacuum dried at 40 °C to give 28.5 g (57%), mp 174–175 °C, $[\alpha]^{25}D$ −10.4°.

Anal. Calcd for $C_3H_6NO_2F$: C, 33.65; H, 5.65; N, 13.08; F, 17.74. Found: C, 33.41; H, 5.74; N, 12.96; F, 17.53.

3-Fluoro-L-alanine-2-*d* was separated from the crystalline quinine *N*-(1-methyl-2-acetylvinyl)-3-fluoro-L-alaninate-2-*d* (231.5 g) as described above for its enantiomer. In this manner 35.5 g (68%) of 3-fluoro-L-alanine-2-*d* was obtained, mp 174–175 °C, $[\alpha]^{25}D$ +10.3°.

Anal. Calcd for $C_3H_6NO_2F$: C, 33.65; H, 5.65; N, 13.08; F, 17.74. Found: C, 33.45; H, 5.78; N, 13.01; F, 17.77.

Potassium *N*-(1-Methyl-2-acetylvinyl)-3-fluoro-DL-alaninate

(3). To a suspension of 10.71 g (100 mmol) of 3-fluoro-DL-alanine in 40 ml of 90% methanol was added a solution of 5.61 g (100 mmol) of potassium hydroxide in 20 ml of 90% MeOH followed by the addition of a solution of 10.1 g (100 mmol) of 2,4-pentanedione in 60 ml of methanol. The mixture was refluxed for 20 min and concentrated in vacuo. Recrystallization from 2-propanol (300 ml) yielded 17.6 g (78%) of product.

Anal. Calcd for $C_8H_{11}NO_3FK$: C, 42.27; H, 4.87; N, 6.16; F, 8.35. Found: C, 42.30; H, 4.88; N, 6.23; F, 8.11.

^1H NMR (D_2O): δ 1.97 (s, 3, CH_3), 2.02 (s, 3, CH_3), 4.4 (m, 1, CH, $J_{H-F} \approx 31$ Hz), 4.8 (m, 2, CH_2F, $J_{H-F} \approx 46$ Hz).

Resolution of 3-fluoro-DL-alanine was performed starting from potassium *N*-(1-methyl-2-acetylvinyl)-3-fluoro-DL-alaninate.

To a solution of 22.72 g (100 mmol) of potassium *N*-(1-methyl-2-acetylvinyl)-3-fluoro-DL-alaninate (3) in 200 ml of methanol was added 40.5 g (102.5 mmol) of quinine hydrochloride dihydrate. The mixture was heated under reflux for a period of 1 h. Application of the same method as described above for the separation and isolation gave 3-fluoro-D-alanine, $[\alpha]^{25}D$ −10.4°, and 3-fluoro-L-alanine, $[\alpha]^{25}D$ +10.4°, in 54.2 and 64% yield, respectively.

Resolution of DL-Alanine. Application of the same method gave quinine *N*-(1-methyl-2-acetylvinyl)-L-alaninate in 93% yield, mp 142–143 °C, $[\alpha]^{25}D$ −73.8°.

Anal. Calcd for $C_{28}H_{37}N_3O_5 \cdot \frac{1}{2}H_2O$: C, 66.64; H, 7.59; N, 8.33. Found: C, 66.45; H, 7.80; N, 8.10.

L-Alanine was obtained from the crystalline enamine–quinine salt as described above for the fluoroalanine in 76% yield, $[\alpha]^{25}D$ +12.8° (c 5%, 5 N HCl) (lit.[7] +13°).

Registry No.—DL-**1**, 16652-37-2; D-**1**, 35455-20-0; L-**1**, 35455-21-1; **2**, 123-54-6; **3**, 60526-14-9; **4a**, 60526-16-1; **4b**, 60526-18-3; quinine, 130-95-0; potassium hydroxide, 1310-58-3; DL-alanine, 302-72-7; quinine *N*-(1-methyl-2-acetylvinyl)-L-alaninate, 60526-20-7; L-alanine, 56-41-7.

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Some Novel, Acid-Labile Amine Protecting Groups[1]

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Under certain circumstances the lability of the *t*-Boc protecting group to 50% aqueous acetic acid is a shortcoming during the synthesis of large polypeptides in solution. The somewhat more stable 1-methylcyclobutyloxycarbonyl protecting group has been found to overcome this problem, but still is sufficiently acid labile to be useful as a temporary protecting group. Selected small ring carbamates exhibiting varying degrees of acid lability have also been prepared and evaluated. During cleavage in trifluoroacetic acid partial isomerization of the protecting group was observed in the case of *N*-cyclopropylcarbinyloxycarbonyl phenylalanine. The significance of this observation for the design of protecting groups is discussed. The effect of added nucleophile on the rate of protecting group removal for three selected N-protected phenylalanine derivatives has also been studied, and the implications of this effect in peptide synthesis are noted.

In the synthesis[2] of some large peptide fragments of ribonuclease S-protein using *tert*-butyloxycarbonyl (*t*-Boc) for temporary protection of α-amino nitrogen, substantial undesired loss of this protecting group was occasionally encountered during purification by gel filtration in 50% aqueous acetic acid. For example, after the purification of the synthetic N-terminal *t*-Boc eicosapeptide ribonuclease fragment 21–40 the loss of about 3–7% of the protecting group was demonstrated.[3] This result is consistent with the reported[4] half-life of *t*-Boc glycine ethyl ester of 10 days in 60% aqueous acetic acid at 22–25 °C, even if one considers that N-terminal *t*-Boc peptides are more stable to acid, presumably due to the fact that the terminal urethane group in N-carbamoylated peptides is less basic than that of the N-protected amino acid.[5]

To avoid undesired loss of the *t*-Boc group we undertook the search for an acid-labile protecting moiety more stable than *t*-Boc in 50% acetic acid, yet readily and completely removable by relatively mild acid treatment. At the same time we sought to avoid both introduction of a new asymmetric center and significant reduction of the solubility of the protected peptides by a new protecting group.

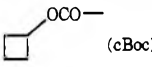
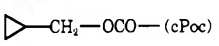
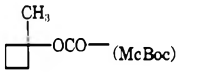
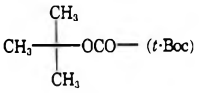
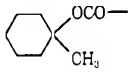
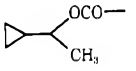
Some years ago Blaha and Rudinger[6] demonstrated a direct correlation of alkylcarbamate stability with the rates of ethanolysis of the corresponding *p*-toluenesulfonates. We were forced to adopt a more empirical approach, owing mainly to the lack of solvolytic rate data on derivatives of *tert*-butyl alcohol required to establish a relationship to the *t*-Boc group. Using published solvolytic data[7-11] as a rough guide to the selection of synthetic targets, we prepared and studied several derivatives of L-phenylalanine (see Chart I) in the hope that they would comprise a series of graded stability.

The alkoxycarbonyl amino acids were prepared by conversion of the corresponding alcohols into chloroformates by reaction with phosgene. The chloroformates were allowed to react with either phenylalanine in a dilute solution of sodium bicarbonate or with phenylalanine methyl ester in chloroform solution in the presence of triethylamine.

Rates of removal of the various protecting groups were compared by measuring the liberation of amino acid or dipeptide ester in either trifluoroacetic acid or formic acid. Trifluoroacetic acid was appropriate for study of the more stable protecting groups, formic acid for study of the more labile groups (see Table I).

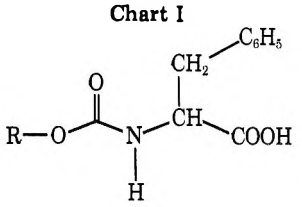
The data suggested that the 1-methylcyclobutyloxycar-

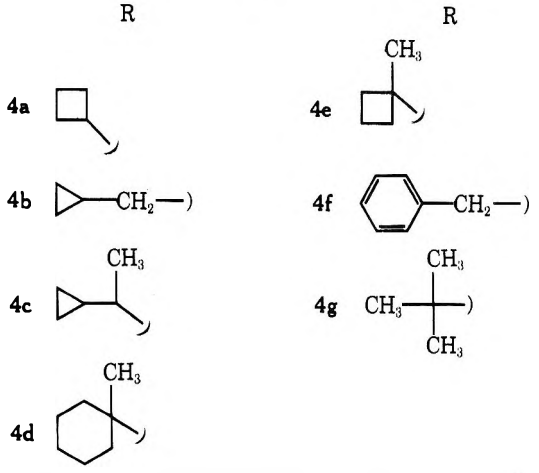
Table I. Acid-Mediated Cleavage of Various N-Protecting Groups of Phenylalanine and Phenylalanyl–Alanine Methyl Ester

X	Compd	$t_{1/2}$ (X-Phe), min (25 °) TFA	$t_{1/2}$ (X-Phe), min (25 °) HCOOH	$t_{1/2}$ (X-Phe-Ala-OCH_3), min (25 °C) TFA	$t_{1/2}$ (X-Phe-Ala-OCH_3), min (25 °C) HCOOH
$C_6H_5CH_2$—OCO— (Cbz)	4f	300			
 (cBoc)	4a	>300[c]			
 (cPoc)	4b	40		~50[c] (57282-36-7)[d]	
 (McBoc)	4e	2		3 (59602-95-8)[d]	180
 (t-Boc)	4g	1[a,b]	4	<2[a] (15186-29-5)[d]	10
	4d	1[a]	2		
	4c		1.5		

[a] Complete cleavage observed. [b] Direct NMR probe of the reaction of **4g** in deuteriotrifluoroacetic acid demonstrated the generation of nearly 1 equiv of *tert*-butyl trifluoroacetate, as evidenced by a characteristic methyl group signal at δ 1.63 ppm.[12a] In this medium, therefore, a continuous source of the *tert*-butyl cation is present, lending support to the rationale for the use of nucleophilic scavengers during protecting group removal in TFA.[12b] [c] Determined by TLC after solvent removal. [d] Registry no.

Chart I





bonyl (McBoc) protecting group would be sufficiently stable in 50% acetic acid to be useful in gel filtration, yet labile enough to be removable under mild acidic conditions. In accord with this prediction, after 48 h in 50% acetic acid more than 99% of McBoc phenylalanine (**4e**) remained unchanged; whereas under the same conditions amino acid was liberated from *t*-Boc phenylalanine (**4g**) to the extent of about 10–15%.[13] Complete removal of McBoc was achieved by treatment of **4e** with trifluoroacetic acid at 25 °C for 30 min.

We are not recommending that the McBoc protecting group should generally replace the widely used *t*-Boc group in peptide synthesis. We do regard McBoc as appropriate for protection of the amino termini of large peptides of limited solubility, where the favorable solvent properties of 50% aqueous acetic acid have proved useful for purification procedures.

In the course of these studies we noted that removal of the cPoc protecting group of **4b** proceeded to the extent of only about 65% in the time indicated as sufficient for completion based on kinetic data obtained during initial stages of the cleavage. The dilemma was resolved when we found that the relatively acid-stable cyclobutyloxycarbonyl derivative **4a** comprised about 40% of the remaining "unreacted" starting material (which extrapolates to approximately 20% of cBoc phenylalanine at zero remaining cPoc isomer).[14] This observation points out that certain urethane-protected derivatives are potentially susceptible to rearrangement to more stable isomers. The known isobornyloxycarbonyl group[15] is a possible case in point. Is such instances the initial rate of generation of free amine could give misleading information about the utility of such a temporary protecting group. Furthermore, in synthetic operations more vigorous conditions or extended reaction times required for complete removal of a rearranged (more stable) protecting group would risk unwanted concomitant exposure of other protected functionality.

In view of the expected rapid rate of decarboxylation of carbamates after solvent separation,[16] we believe that the observed urethane isomerization is likely to have occurred via internal return. That is, rearrangement is thought to have taken place in advance of solvent separation along the reaction pathway.[17,18]

We have also noted that the relative rates of removal of two protecting groups will be affected by the presence or absence of inert diluents, and by nucleophiles. Nucleophilic scavengers are often employed in peptide synthesis to trap unwanted cations generated during the removal of various protecting groups.[12b,19] The effect of any compound introduced into the reaction medium on the rate of an S_N1 process should reflect its contribution to the overall polarity of the solvent system; whereas the effect on the rate of an S_N2 process should be related to the nucleophilicity of the added component. Thus, addition of either methylene chloride or dimethyl sulfide *decreases* the rate of solvolytic removal of the *t*-Boc protecting group [presumably a reflection of the destabilizing effect of diminished solvent polarity on carbonium ion (*tert*-butyl) intermediates]. On the other hand, the nucleophilic dimethyl

Table II. Relative Half-Times ($t_{1/2}$) for Removal of N-Protection

Substrate	$t_{1/2}$, min		
	Formic acid	4:1 formic acid/DMS[a]	4:1 formic acid/CH_2Cl_2[c]
t-Boc-Phe (4g)	4	26	21
	TFA[b]	4:1 TFA/DMS	4:1 TFA/benzene
Cbz-Phe (4f)	300	60	600
cPoc-Phe (4b)	40	110	110

[a]DMS = dimethyl sulfide. [b]TFA = trifluoroacetic acid. [c]Benzene is not miscible with HCOOH.

Table III

Compd	Yield,[a] %	Mp, °C	^{1}H NMR, δ_{Me_4Si} ($CDCl_3$), ppm	TLC R_f (system)	Anal., %	Calcd	Found
4a	75	121–123	7.21 (s, 5 H, phenyl) 1.7–2.3 (broad d, 6 H, cyclobutyl) 4.7 (m, 1 H, cyclobutyl) methine)	0.75 (D) 0.38 (E)	C H N ($C_{14}H_{17}NO_4 \cdot {}^1/_2H_2O$)	61.76 6.66 5.14	61.66 6.46 5.10
4b	57	105–107	7.20 (s, 5 H phenyl) 0.1–1.1 (m, 5 H, cyclopropyl) 3.78 (d, J = 6 Hz, 2 H, —OCH_2—)	0.72 (D) 0.36 (E)	C H N ($C_{14}H_{17}NO_4 \cdot {}^1/_2H_2O$)	61.76 6.66 5.14	61.87 6.41 5.18
4c		91–93.5	7.23 (s, 5 H, phenyl) 1.25 (d, J = 7 Hz, 3 H, CH_3) 4.22 (m, 1 H, —CHO—)	0.80 (B)	C H N ($C_{15}H_{19}NO_4$)	64.96 6.91 5.05	65.09 6.74 5.20
4d		Oil	7.16 (s, 5 H, phenyl) 1.40 (s, 3 H, CH_3)	0.60 (D)			
4e		60–62	7.18 (s, 5 H, phenyl) 1.6–2.0 (envelope, 6 H, cyclobutyl) 1.47 (s, 3 H, CH_3)	0.71 (B)	C H N ($C_{15}H_{19}NO_4$)	64.96 6.91 5.05	64.65 7.05 5.13

[a]Based on phenylalanine.

sulfide enhances the rate of cleavage of the Cbz protecting group, whereas an inert, nonpolar solvent reduces the rate of Cbz cleavage (see Table II). Thus, the presence of dimethyl sulfide as scavenger clearly reduces the selectivity of protecting group removal in peptides containing both *t*-Boc and Cbz.[3] The distinctly different behavior of these two protecting groups must be related to a difference in their respective mechanisms for acidolysis (i.e., S_N1 vs. S_N2, respectively). The data in Table II suggest that with respect to mechanism of solvolysis cPoc is more closely related to *t*-Boc than to Cbz.

Development of the relatively stable McBoc protecting group should allow one to take advantage of the favorable solvent properties of aqueous acetic acid in working with large peptides. The other urethane protecting groups reported may be of value in organic syntheses where gradations of greater or lesser lability are sought. Finally, mechanistic relationships must be considered whenever two acid-labile protecting groups are chosen for use in a synthesis, where at some point one group is to be selectively removed in the presence of the other.

Experimental Section[20]

Capillary melting points were determined on a Thomas-Hoover apparatus and are reported uncorrected. Thin layer chromatograms were developed on silica gel (Quantum Industries, Q-1 plates), and components were visualized by either *tert*-butylhypochlorite–KI reagents[21] or by ninhydrin reagent. Systems used in TLC were as follows: EtOAc–pyridine–HOAc–H_2O, 5:5:1:3 (A); $CHCl_3$–CH_3OH–H_2O–HOAc, 80:20:2:1 (B); $CHCl_3$–CH_3OH, 9:1 (C); $CHCl_3$–OH–H_2O–HOAc, 85:15:1.5:1 (D); EtOAc–HOAc–isooctane–H_2O, 7:2:7:10 upper layer (E). Amino acids were all of the L configuration.

Alkoxycarbonyl Phenylalanine Derivatives (4a–e). Two methods of preparation were used, depending upon the stability of the precursor alkoxycarbonyl chloride in question.

Method A (More Stable Derivatives: 4a, 4b). A solution of 20 mmol of either cyclobutanol (Columbia Organic Chemicals, 97%) or cyclopropylcarbinol (Aldrich) in 10 ml of dry ether was treated at 0 °C with 40–60 mmol of phosgene gas. The excess phosgene was allowed to evaporate by slow nitrogen purge at 20–25 °C overnight; and finally, any residual phosgene was removed by evacuation at 0 °C under water aspirator pressure to give in 80–90% crude yield a nearly colorless liquid, ir λ_{max} (film) 1770 cm^{-1} (COCl), which was used without further purification.

Thus, a solution of 8.0 mmol of phenylalanine in 40 ml of 1.0 M $NaHCO_3$ was treated portionwise under vigorous stirring with either cBoc or cPoc chloride, using TLC (system A) to confirm disappearance of phenylalanine. After an additional 0.5 h, 2.5 N HCl was added dropwise to bring the reaction mixture to pH 3, and the resulting solid was isolated by filtration, washed with water, dried in vacuo, and crystallized from hot ethyl acetate/hexane (see Table III).

Method B (Less Stable Derivatives: 4c, 4d, 4e). A solution of about 40 mmol of phosgene in 20 ml of dry benzene was prepared at 0 °C. Then a mixture of 20 mmol of either 1-methylcyclohexyl alcohol (Aldrich), 1-cyclopropylethanol (K & K), or 1-methylcyclobutyl alcohol[22] and 20 mmol of pyridine in 20 ml of benzene was added over a period of about 20 min. After 2 h the reaction vessel was fitted with a reflux condenser connected to a water aspirator via a tube filled with Drierite and then carefully evacuated at 0 °C to remove excess phosgene, and the filtrate was concentrated in vacuo to a volume of ca. 5–10 ml, maintaining the temperature at 0 °C. Thus prepared, the sample, owing to its instability,[23] was used immediately without purification in the next step.

A sample of 0.60 g of phenylalanine methyl ester hydrochloride[24] suspended in chloroform was treated with 1 equiv of triethylamine ("pH 8" as measured on moistened narrow range indicator papers). The solution of alkoxycarbonyl chloride was added portionwise at 0 °C with stirring, alternating with addition of triethylamine to maintain "pH 8". After 2 h the reaction was quenched by addition of 5% $NaHCO_3$. Additional chloroform was added, and the organic phase was washed with 50% saturated NaCl, 0.2 N H_2SO_4, and 50% saturated NaCl (two portions), and dried over anhydrous Na_2SO_4. Solvent removal gave a colorless oil, R_f >0.90 (systems B, C), which was subjected to saponification without further purification.

The sample of N-protected phenylalanine methyl ester in 50% aqueous methanol was maintained at pH 12 using 1 N NaOH. The progress of the reaction was monitored by TLC, and complete saponification required about 46 h. The reaction mixture was then adjusted to pH 6 using 0.2 N H_2SO_4, the solvent was almost completely

removed under reduced pressure, and dilute $NaHCO_3$ was added. The aqueous layer was washed with two portions of ether. After acidification (concentrated H_2SO_4 to pH 3), the product was extracted into ethyl acetate. The organic extract was washed with two portions of saturated NaCl and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to give product, which was purified by crystallization or column chromatography, as appropriate (Table III).

cPoc Phenylalanine (4b) *N*-Hydroxysuccinimide Ester. A solution of 531 mg (2.02 mmol) of cPoc phenylalanine and 233 mg (2.01 mmol) of *N*-hydroxysuccinimide in 3.0 ml of dry, peroxide-free THF, cooled to 0–5 °C, was treated with 0.48 g (15% excess) of DCC. The reaction mixture was stored overnight at 0–5 °C, then filtered to remove precipitated dicyclohexylurea. The solvent was removed under reduced pressure to give an oily residue, which slowly crystallized upon the addition of isopropyl alcohol. This crude product was isolated by filtration and recrystallized once from isopropyl alcohol to give 305 mg (42% yield) of colorless needles, mp 135–135.5 °C.

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.71; H, 5.75; N, 7.80.

cPoc Phenylalanyl–Alanine Methyl Ester. A solution of 241 mg (0.67 mmol) of cPoc phenylalanine *N*-hydroxysuccinimide ester and 120 mg of L-alanine methyl ester hydrochloride[24] in 10 ml of methylene chloride was treated with triethylamine ("pH 7.6–8.0" as measured on moistened narrow range indicator papers). After 6 h the mixture was transferred to a separatory funnel, and the solution was washed successively with portions of 5% $NaHCO_3$, 50% saturated NaCl, 0.2 N H_2SO_4, and 50% saturated NaCl (twice), and dried over anhydrous Na_2SO_4. The solvent was removed to give a solid residue, which was recrystallized from hot ethyl acetate–hexane to give 207 mg (85% yield) of fluffy, white needles, mp 147–147.5 °C. Amino acid analysis after acid hydrolysis: Ala, 1.00, Phe 1.00.

Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 61.86; H, 7.15; N, 8.17.

***t*-Boc Phenylalanyl–Alanine Methyl Ester.** A solution of 732 mg (2.02 mmol) of *tert*-butyloxycarbonyl phenylalanine *N*-hydroxysuccinimide (Cyclo Chemicals) and 342 mg of L-alanine methyl ester hydrochloride[24] in 30 ml of methylene chloride was treated with triethylamine ("pH 7.5–8.0" as measured on moistened narrow range indicator papers). After 6 h the reaction mixture was processed as described in the preceding experiment to afford a solid which was recrystallized from ethyl acetate–hexane, giving 353 mg (48% yield) of fluffy needles, mp 108–109 °C. Amino acid analysis after acid hydrolysis: Ala, 1.00; Phe 1.00.

Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 61.70; H, 7.48; N, 8.00. Found: C, 61.57; H, 7.68; N, 8.07.

1-Methylcyclobutyloxycarbonyl (McBoc) Phenylalanyl–Alanine Methyl Ester. To a solution of 140 mg of McBoc phenylalanine (**4e**) and 83 mg of alanine methyl ester hydrochloride[24] in 4 ml of acetonitrile was added 80 μl of triethylamine (ca. 1 equiv), followed by a solution of 119 mg of DCC in 2 ml of acetonitrile. After 20 h at 25 °C, the excess DCC was destroyed by the addition of 5 drops of 50% acetic acid, and workup proceeded in a standard fashion, with crystallization from hot ethyl acetate–hexane giving 130 mg of dipeptide, mp 113.5–115 °C. Amino acid analysis after acid hydrolysis: Phe, 1.00; Ala, 1.03.

Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.96; H, 7.23; N, 7.73. Found: C, 62.83; H, 7.14; N, 7.66.

Studies of the Cleavage Rates of Amine Protecting Groups. A sample of the protected amino acid or peptide was dissolved in the solvent mixtures indicated in Tables I and II. Except where noted in the tables, the quantity of amino group released was measured by the colorimetric assay developed by Burton,[25a] based on the 2,4,6-trinitrobenzenesulfonic acid–sulfite procedure reported by Fields.[25b] Thus, aliquots were removed at various time intervals and quenched by direct transfer to the reagent solution in a cuvette for uv analysis. Infinity values were determined after at least 10 half-lives.

Relative Stability of McBoc Phenylalanine vs. t-Boc Phenylalanine in 50% Acetic Acid. Samples of 5.6 mg of solid McBoc phenylalanine (**1**) and 5.5 mg of *t*-Boc phenylalanine (**2**) were each dissolved in 0.10 ml of 50% acetic acid, determining amino group released after 48 h: A (**1**), 0.01; A (**2**), 0.15 (ca. 10–15% loss of *t*-Boc).

Isolation of cBoc Phenylalanine from Trifluoroacetolysis of cPoc Phenylalanine (4b). A sample of 147 mg of cPoc phenylalanine was dissolved in 3.0 ml of anhydrous TFA at 23–24 °C and allowed to stand for 17 h (calculated as ca. 25 half-lives based on study of kinetics). The reaction mixture was then transferred to 12 ml of ethyl acetate, and the resulting solution was washed three times with water and once with saturated NaCl, and dried over anhydrous $MgSO_4$. It was then evaporated and flushed three times with benzene, then twice with $CHCl_3$, to remove residual TFA, affording after dry column chromatography (system E, 5:2:9:10, silica gel) an oil which deposited fluffy crystals, mp 121–122.5 °C (mixture with authentic **4a**, mp 121.5–123.5 °C) from ethyl acetate/hexane, upon seeding with cBoc phenylalanine (**4a**). Additional crystalline solid recovered upon concentration of the mother liquor was shown to contain no cPoc phenylalanine (**4b**) by NMR, δ Me_4Si ($CDCl_3$) 3.12 (doublet, J = 7 Hz, 2 H, benzylic), 1.6–2.4 (broad envelope, 6 H, cyclobutyl), 4.88 ppm (triplet, J = 9 Hz, 1 H, cyclobutyl methine), indicative of almost exclusively cBoc isomer.[14]

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Registry No.—**4a**, 60538-78-5; **4b**, 57282-35-6; **4c**, 57282-38-9; **4d**, 47187-53-1; **4e**, 59602-94-7; **4f**, 1161-13-3; **4g**, 13734-34-4; cyclobutanol, 2919-23-5; cyclopropylcarbinol, 2516-33-8; phenylalanine, 673-06-3; 1-methylcyclohexyl alcohol, 590-67-0; 1-cyclopropylethanol, 765-42-4; 1-methylcyclobutyl alcohol, 20117-47-9; cPOC phenylalanine *N*-hydroxysuccinimide ester, 57282-37-8; *N*-hydroxysuccinimide, 6066-82-6; L-alanine methyl ester HCl, 2491-20-5; *tert*-butyloxycarbonyl phenylalanine *N*-hydroxysuccinimide, 3674-06-4.

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Cholecystokinin-Pancreozymin. 2.[1] Synthesis of a Protected Heptapeptide Hydrazide Corresponding to Sequence 17–23

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The partially protected heptapeptide hydrazide *tert*-butyloxycarbonyl-β-benzyl-L-aspartyl-L-prolyl-L-seryl-L-histidyl-L-arginyl-L-isoleucyl-L-serine hydrazide, corresponding to sequence 17–23 of cholecystokinin, was prepared in solution by stepwise chain lengthening with active esters.

The amino acid sequence of the porcine gastrointestinal hormone cholecystokinin-pancreozymin (CCK) was determined by Mutt and Jorpes.[2] The C-terminal dodecapeptide, a biologically active tryptic fragment of the 33-membered chain, was synthesized by Ondetti and his associates;[3] the N-terminal octapeptide by Bodanszky and his coworkers.[1] In position 27 of the sequence a tyrosine *O*-sulfate residue is present. Esterifiction of the phenolic hydroxyl group of tyrosine can be carried out on C-terminal sequences which do not contain a serine residue. Beyond that point, the presence of serine, unless an enzyme-catalyzed process is found, should interfere with selective esterification. It seems to be difficult to carry out an entirely stepwise synthesis[4] of CCK, because the tyrosine sulfate moiety is partially decomposed under the conditions of acidolysis generally applied for the removal of acid labile protecting groups, such as the *tert*-butyloxycarbonyl group. The alternative deblocking of α-amino groups by hydrogenolysis is impeded by the presence of methionine residues in the sequence. Thus, a fragment condensation approach was designed. The partial sequences 1–8,[1] 9–16, 17–23, 24–26, and 27–33 were selected as intermediates that can be combined in an order to be determined in exploratory experiments. Synthesis of a partially protected heptapeptide hydrazide corresponding to sequence 17–23 is reported in this paper. The scheme of the synthesis is shown in Chart I.

Stepwise chain lengthening from serine, the C-terminal residue of the heptapeptide, was uneventful until the last residue, aspartic acid, was incorporated. This was first attempted by acylation with *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid *N*-hydroxysuccinimide ester.[5] In this case, however, in addition to the desired protected heptapeptide methyl ester XI, a second product formed in which the side chain of the C-terminal serine was also acylated with *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid. Model experiments[6] revealed that the imidazole in the side chain of the histidine residue (in position 20) is responsible for extensive O-acylation. Subsequently, more favorable conditions were found and applied: the protected aspartyl residue was introduced in the form of the *p*-nitrophenyl ester[7] in the presence of 1-hydroxybenzotriazole.[8] This approach produced the expected protected heptapeptide ester XI in satisfactory yield and purity. Compound XI was then partially deblocked by hydrogenation and converted to the hydrazide XIII. In exploratory experiments,[9] XIII was treated with nitrous acid and the azide thus formed was used for the acylation of L-aspartyl-L-arginyl-L-aspartic acid methyl ester (CCK_{24-26}). The partially protected decapeptide ester could be secured, albeit in moderate yield, in homogeneous form after chromatography. Thus, the partially protected heptapeptide hydrazide XIII seems to be a suitable intermediate for the total synthesis of CCK.

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Experimental Section

Capillary melting points are reported uncorrected. Thin layer chromatograms (silica gel, Merck) were developed with the following solvent systems: A, 1-butanol–acetic acid–water (4:1:1); B, chloroform–methanol (8:2); C, EtOAc–pyridine–AcOH–H_2O (30:20:6:11). Spots were revealed by uv, iodine vapor, charring,[10] and by the Sakaguchi or Pauly reagents. For amino acid analysis, samples were hydrolyzed with constant boiling hydrochloric acid in evacuated, sealed ampules at 110 °C for 16 h, and analyzed by the method of Spackman, Stein, and Moore[11] on a Beckman-Spinco 120C instrument.

The following abbreviations were used: DCC, dicyclohexylcarbodiimide; DCU, dicyclohexylurea; DMF, dimethylformamide; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

Benzyloxycarbonyl-L-isoleucyl-L-serine Methyl Ester (I). To a solution of serine methyl ester hydrochloride[12] (3.2 g, 20 mmol) in DMF (25 ml), triethylamine was added, followed by benzyloxycarbonyl-L-isoleucine *p*-nitrophenyl ester[13] (8.49 g, 22 mmol). The solution was kept slightly basic by the addition of the same base. After 2 days, *unsym*-dimethylaminopropylamine (0.51 g, 5 mmol) was added.[14] One hour later, the reaction mixture was diluted with ethyl acetate (300 ml), and the organic phase was washed with 0.5 N ammonia solution (20-ml portions), twice with 1 N HCl (20 ml), water (2 × 20 ml) and saturated NaCl solution (2 × 20 ml). The solution was dried over Na_2SO_4, filtered, and concentrated in vacuo to a small volume. The precipitate that formed was filtered with the aid of several portions of ethyl acetate. The air-dried product weighed 6.0 g (82%), mp 177–178 °C. Recrystallization from ethanol raised the melting point to 178–179 °C; $[\alpha]^{25}D$ +3.7° (c 1, DMF); TLC R_f (B) 0.7.

Anal. Calcd for $C_{18}H_{26}N_2O_6$: C, 59.0; H, 7.1; N, 7.6. Found: C, 59.0; H, 7.1; N, 7.9.

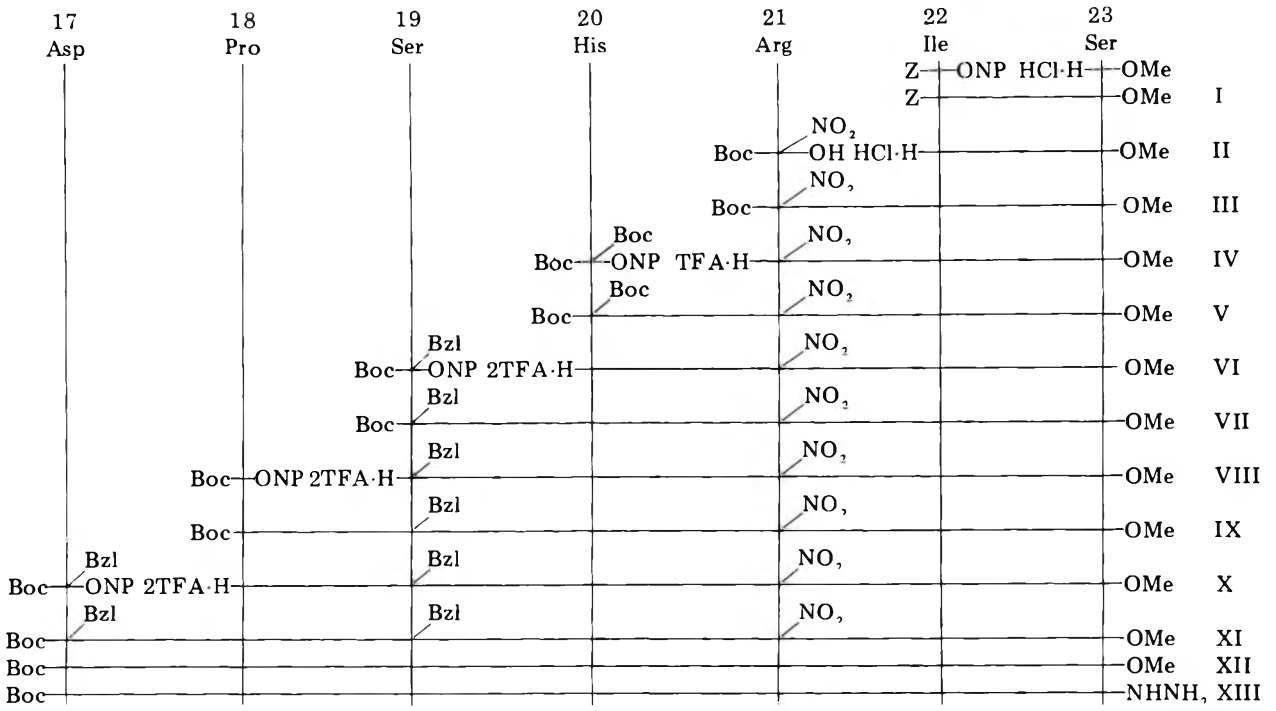
Compound I was prepared also by coupling of Z-L-Ile with Ser-OCH_3 with DCC as condensing agent. The physical properties of this preparation were the same as those of the one described above, but the yield was poor.

***tert*-Butyloxycarbonylnitro-L-arginyl-L-isoleucyl-L-serine Methyl Ester (III). A.** The protected dipeptide I (3.66 g, 10 mmol) was hydrogenated for 3 h in a mixture of methanol (120 ml) and 1 N aqueous HCl (10 ml) in the presence of a 10% Pd on charcoal catalyst (750 mg). The reaction mixture was filtered from the catalyst and evaporated in vacuo to a small volume, and the dipeptide hydrochloride (II) was precipitated with dry ether (50 ml). The product was collected on a filter and dried in vacuo over P_2O_5 and KOH. Compound II [2.5 g, 93%, mp 197–198 °C, TLC R_f (A) 0.48] was dissolved in DMF (20 ml), and *tert*-butyloxycarbonylnitro-L-arginine (2.97 g, 9.3 mmol) and 1-hydroxybenzotriazole[15] (1.62 g, 12 mmol) were added with stirring. After complete dissolution, the mixture was cooled in ice, and triethylamine (1.3 ml, 9.3 mmol) was added, followed by DCC (1.92 g, 9.3 mmol). Stirring in the cold was continued for 30 min, then overnight at room temperature. The DCU was filtered off, the solvent removed in vacuo, and the residue dissolved in ethyl acetate (250 ml). The solution was successively washed with 3% citric acid (2 × 15 ml), saturated bicarbonate solution (3 × 1 ml), and water (4 × 15 ml). The solvent was evaporated without prior drying. The crystals were collected and washed on a filter with ethyl acetate. The air-dried product weighed 3.53 g (66%): mp 174–175 °C dec; $[\alpha]D$ −9° (c 1, DMF); TLC R_f (A) 0.72, R_f (B) 0.6. Amino acid analysis: Arg + Orn 0.9, Ile 1.0, Ser 0.9. Recrystallization from methanol–ether did not raise the melting point.

Anal. Calcd for $C_{21}H_{39}N_7O_9$: C, 47.3; H, 7.3; N, 18.4. Found: C, 47.1; H, 7.1; N, 18.3.

B.[16] Compound II (6.65 g, 24.8 mmol) was dissolved in DMF (50

Chart I. Scheme of the Synthesis of Boc-Asp-Pro-Ser-His-Arg-Ile-Ser-NHNH$_2$ (XIII)



ml), and triethylamine (3.5 ml, 25 mmol) and *tert*-butyloxycarbonylnitro-L-arginine *N*-hydroxysuccinimide ester[3] (14.85 g, 34.5 mmol) were added. After 5 h at room temperature, the mixture was diluted with EtOAc to 1 l.; the solution was washed with a 2% solution of citric acid (4 × 200 ml), water (200 ml), 1 M $NaHCO_3$ (4 × 200 ml), and water (3 × 200 ml), dried over Na_2SO_4, and concentrated to about 200 ml. Next day, the crystals were filtered and washed with hot EtOAc, hot tetrahydrofuran, and once more with hot EtOAc. They weighed 9.1 g (69%), mp 180–182 °C dec. A less pure second crop (2.0 g) melted (after sintering at 174 °C) at 178–179 °C dec. Recrystallization of a sample of the first crop from DMF–EtOAc raised the melting point to 183–185 °C dec, $[\alpha]^{23}D$ −9° (*c* 2, DMF).

Anal. Found: C, 47.3; H, 7.6; N, 18.4.

N^{α}-N^{im}-Bis(*tert*-butyloxycarbonyl)-L-histidylnitro-L-arginyl-L-isoleucyl-L-serine Methyl Ester (V). The protected tripeptide III (3.21 g, 6 mmol) was dissolved in TFA (15 ml). After 15 min, the acid was evaporated in vacuo, and dry ether (70 ml) was added. The tripeptide trifluoroacetate IV was collected on a filter, washed with ether, and dried in vacuo over P_2O_5 and KOH [mp 104–105 °C, TLC R_f (A) 0.45]. It was dissolved in DMF (15 ml), and diisopropylethylamine[17] (1.95 ml, 12 mmol) was added, followed by N^{α}-N^{im}-bis(*tert*-butyloxycarbonyl)-L-histidine *p*-nitrophenyl ester[18] (3.43 g, 7.2 mmol). After 2 days, petroleum ether (50 ml) was added. The mixture was vigorously stirred, and the petroleum ether was decanted. This procedure was repeated once more, then ether (100 ml) was added. The product solidified within a few minutes. It was collected and thoroughly washed with ether and ethyl acetate. The material was treated with a few milliliters of THF and precipitated with ethyl acetate. The air-dried product weighed 4.16 g (88%), mp 133–134 °C. Reprecipitation of a sample from THF–ethyl acetate did not raise the melting point: $[\alpha]^{24}D$ −10° (c 1, DMF); TLC R_f (A) 0.78, R_f (B) 0.62. Amino acid analysis: His 1.0, Arg + Orn 0.9, Ile 1.0, Ser 0.9.

Anal. Calcd for $C_{42}H_{54}O_{12}N_{10}\cdot H_2O$: C, 48.7; H, 7.2; N, 17.8. Found: C, 49.0; H, 7.1; N, 17.6.

***tert*-Butyloxycarbonyl-*O*-benzyl-L-seryl-L-histidylnitro-L-arginyl-L-isoleucyl-L-serine Methyl Ester (VII).** The protected tetrapeptide V (4.74 g, 6 mmol) was dissolved in TFA (15 ml). After 15 min, the acid was removed in vacuo and the product was precipitated with dry ether (60 ml). It was filtered, washed with ether, and dried in vacuo: 5.2 g (97%); mp 88–89 °C; TLC R_f (A) 0.17. The tetrapeptide ditrifluoroacetate VI was added to a solution of *tert*-butyloxycarbonyl-*O*-benzyl-L-serine *p*-nitrophenyl ester[18] (7.5 mmol) in DMF (15 ml) containing diisopropylethylamine (1.95 ml, 12 mmol). The solution was kept slightly basic, and 2 days later the DMF was removed in vacuo. Dry ether (60 ml) was added and, after a few hours in the cold, the supernatant solution was decanted. This treatment was repeated twice. The residue was dissolved in a few milliliters of DMF and poured into ethyl acetate (400 ml) in a separatory funnel. The organic phase was washed with 0.5 N ammonia solution and then with several portions of water until neutral. The ethyl acetate was removed in vacuo, and the crystalline residue was filtered and washed with ethyl acetate. The air-dried product weighed 3.35 g (66%): mp 128–129 °C; $[\alpha]D$ −15° (c 1, DMF); TLC R_f (A) 0.54, R_f (B) 0.37. Amino acid analysis: Ser 2.0, Arg + Orn 0.9, His 1.0, Ile 1.1. For analysis, a sample was recrystallized from ethyl acetate, without change in the melting point.

Anal. Calcd for $C_{37}H_{57}N_{11}O_{12}$ (847.9): C, 52.4; H, 6.8; N, 18.2. Found: C, 52.2; H, 7.0; N, 18.0.

***tert*-Butyloxycarbonyl-L-prolyl-*O*-benzyl-L-seryl-L-histidylnitro-L-arginyl-L-isoleucyl-L-serine Methyl Ester Dihydrate (IX).** The protected pentapeptide VII (2.97 g, 3.5 mmol) was dissolved in TFA (10 ml). After 15 min, the TFA was removed in vacuo, and the product (VIII) was precipitated with dry ether (60 ml) and dried in vacuo: 3.43 g (quantitative); mp 109–110 °C; TLC R_f (A) 0.30. The entire amount was added to a solution of *tert*-butyloxycarbonyl-L-proline *p*-nitrophenyl ester[19] (4 mmol) in DMF (10 ml) containing triethylamine (1 ml, 7 mmol). After 2 days, the DMF was removed in vacuo, and ether (50 ml) was added. The mixture was cooled and the ether was decanted. This procedure was repeated twice. The residue was dissolved in methanol, and the solution was poured into ethyl acetate (350 ml). The organic phase was washed with 0.5 N ammonia and then with water. Evaporation of the ethyl acetate (without prior drying) and precipitation with ether yielded 2.54 g (75%), mp 202–203 °C dec, with softening at 200 °C. Recrystallization from methanol gave mp 204–205 °C dec; $[\alpha]^{24}D$ −29° (c 1, DMF); TLC R_f (A) 0.48, R_f (B) 0.31. Amino acid analysis: Pro 1.0, Ser 1.8, His 1.1, Arg + Orn 1.0, Ile 1.0.

Anal. Calcd for $C_{42}H_{64}N_{12}O_{13}\cdot 2H_2O$ (981.1): C, 51.4; H, 7.0; N, 17.1. Found: C, 51.3; H, 6.8; N, 17.0.

***tert*-Butyloxycarbonyl-β-benzyl-L-aspartyl-L-prolyl-*O*-benzyl-L-seryl-L-histidylnitro-L-arginyl-L-isoleucyl-L-serine Methyl Ester (XI). A.** The protected hexapeptide IX (8.5 g, 8.7 mmol) was dissolved in TFA (30 ml). After 15 min, the acid was removed in vacuo, and the product was precipitated with dry ether (100 ml). The yield after drying in vacuo was 9.3 g, mp 97–98 °C, TLC R_f (A) 0.19.

The hexapeptide ditrifluoroacetate (X) was dissolved in DMF (10 ml). Triethylamine (2.2 ml, 16 mmol) was added, followed by *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid *N*-hydroxysuccinimide ester[5] (4.63 g, 11 mmol) and 1-hydroxybenzotriazole (1.08 g, 8 mmol). The reaction mixture was kept slightly basic. Next day, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate (600 ml). The solution was washed five times with saturated $NaHCO_3$

solution and with water until neutral and concentrated in vacuo. The product was precipitated by the addition of ether (100 ml), collected on a filter, and washed with ether. The air-dried material weighed 8.15 g. The crude product showed two major spots on TLC, R_f (A) 0.65 and 0.74, R_f (B) 0.45 and 0.71. For the separation of the components and isolation of XI in pure form, cf. the following paper.

B. The hexapeptide ditrifluoroacetate X (100 mg, 0.1 mmol) was dissolved in DMF (0.6 ml) and treated with diisopropylethylamine (0.017 ml, 0.11 mmol), *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid *p*-nitrophenyl ester (Bachem, 42 mg, 0.1 mmol), and 1-hydroxybenzotriazole (13 mg, 0.1 mmol). Next day, ether (40 ml) was added and the mixture was kept overnight in the refrigerator. The resulting solid was disintegrated, filtered, washed with ether (25 ml), and dried over P_2O_5 in vacuo. The product weighed 115 mg (98%), mp 109–110 °C, $[\alpha]^{24}D$ −35° (*c* 1, DMF). On TLC, in addition to the main product [R_f (A) 0.65, R_f (B) 0.45], only a trace of the *O*-acyl derivative [R_f (A) 0.74, R_f (B) 0.71] could be detected. Amino acid analysis: Asp 1.0, Ser 1.7, Pro 1.0, Ile 1.0, His 1.1, Arg + Orn 1.0.

Anal. Calcd for $C_{53}H_{75}N_{13}O_{16}\cdot H_2O$: C, 54.4; H, 6.6; N, 15.6. Found: C, 54.5; H, 6.7; N, 15.6.

***tert*-Butyloxycarbonyl-L-aspartyl-L-prolyl-L-seryl-L-histidyl-L-arginyl-L-isoleucyl-L-serine Hydrazide (XIII).** A sample (1.12 g) of the protected heptapeptide ester XI was dissolved in a mixture of 95% ethanol (125 ml), H_2O (20 ml), and AcOH (2.5 ml) and hydrogenated in the presence of a 10% Pd on charcoal catalyst (0.3 g) for 3 days. The catalyst was removed by filtration and the solvent by evaporation in vacuo, and the residue was treated with dry ether (50 ml). The solid product was collected on a filter, washed with dry ether, and dried in vacuo over P_2O_5 and KOH for 24 h. The product (XII) weighed 0.80 g: mp 77–78 °C; $[\alpha]^{24}D$ −57° (*c* 1, MeOH); TLC R_f (A) 0.33. No significant uv absorption was found at 270 nm. Elemental analysis suggests the retention of both acetic acid and water.

Anal. Calcd for $C_{39}H_{64}N_{12}O_{14}\cdot 2.5CH_3COOH\cdot 2H_2O$: C, 47.7; H, 7.2; N, 15.5. Found: C 47.5; H, 7.1; N, 15.6.

A sample (0.88 g) of the partially protected heptapeptide methyl ester XII was dissolved in CH_3OH (18 ml) and treated with hydrazine hydrate (2 ml). After 12 h, the solvent was removed in vacuo, and the residue dried in vacuo over P_2O_5 and concentrated H_2SO_4 for 24 h. The product was dissolved in H_2O and freeze-dried. This was repeated four times. The hydrazide XIII (0.88 g) melted at 99–100 °C; $[\alpha]^{24}D$ −53° (c 1, CH_3OH); TLC R_f (A) 0.18, R_f (C) 0.33. Amino acid analysis: Asp 1.0, Ser 1.8, Pro 0.95, Ile 1.0, His 1.0, Arg 1.0.

Anal. Calcd for $C_{38}H_{64}N_{14}O_{13}\cdot 6H_2O$: C 44.2; H, 7.6; N, 19.5. Found: C, 43.9; H, 7.5; N, 19.3.

Loss of weight on drying at room temperature for 24 h and then at 60 °C for 16 h was 8.3%. Calcd (for $6H_2O$): 10.7. After this drying, the melting point changed to 124–133 °C dec, with sintering at 118 °C.

Acknowledgment. This study was supported by a grant from the U.S. Public Health Service (NIH AM-12473).

Registry No.—I, 60526-22-9; II, 60562-29-0; III, 60526-23-0; IV, 60562-30-3; V, 60526-24-1; VI, 60526-26-3; VII, 60526-27-4; VIII, 60526-29-6; IX, 60526-30-9; X, 60526-32-1; XI, 60512-76-7; XII, 60526-33-2; XIII, 60526-34-3; serine methyl ester hydrochloride, 5680-80-8; benzyloxycarbonyl-L-isoleucine nitrophenyl ester, 2130-99-6; z-L-Ile, 3160-59-6; Ser-OCH_3, 2788-84-3; *tert*-butyloxycarbonylnitro-L-arginine, 2188-18-3; *tert*-butyloxycarbonylnitro-L-argine *N*-hydroxysuccinimide ester, 60526-35-4; N^{α}-N^{im}-bis-(*tert*-butyloxycarbonyl)-L-histidine *p*-nitrophenyl ester, 20866-47-1; *tert*-butyloxycarbonyl-*O*-benzyl-L-serine *p*-nitrophenyl ester, 16948-39-3; *tert*-butyloxycarbonyl-L-proline *p*-nitrophenyl ester, 28310-65-8; *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid *N*-hydroxysuccinimide ester, 13798-75-9; *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid *p*-nitrophenyl ester, 26048-69-1.

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Side Reactions in Peptide Synthesis. 4. Extensive O-Acylation by Active Esters in Histidine Containing Peptides[1]

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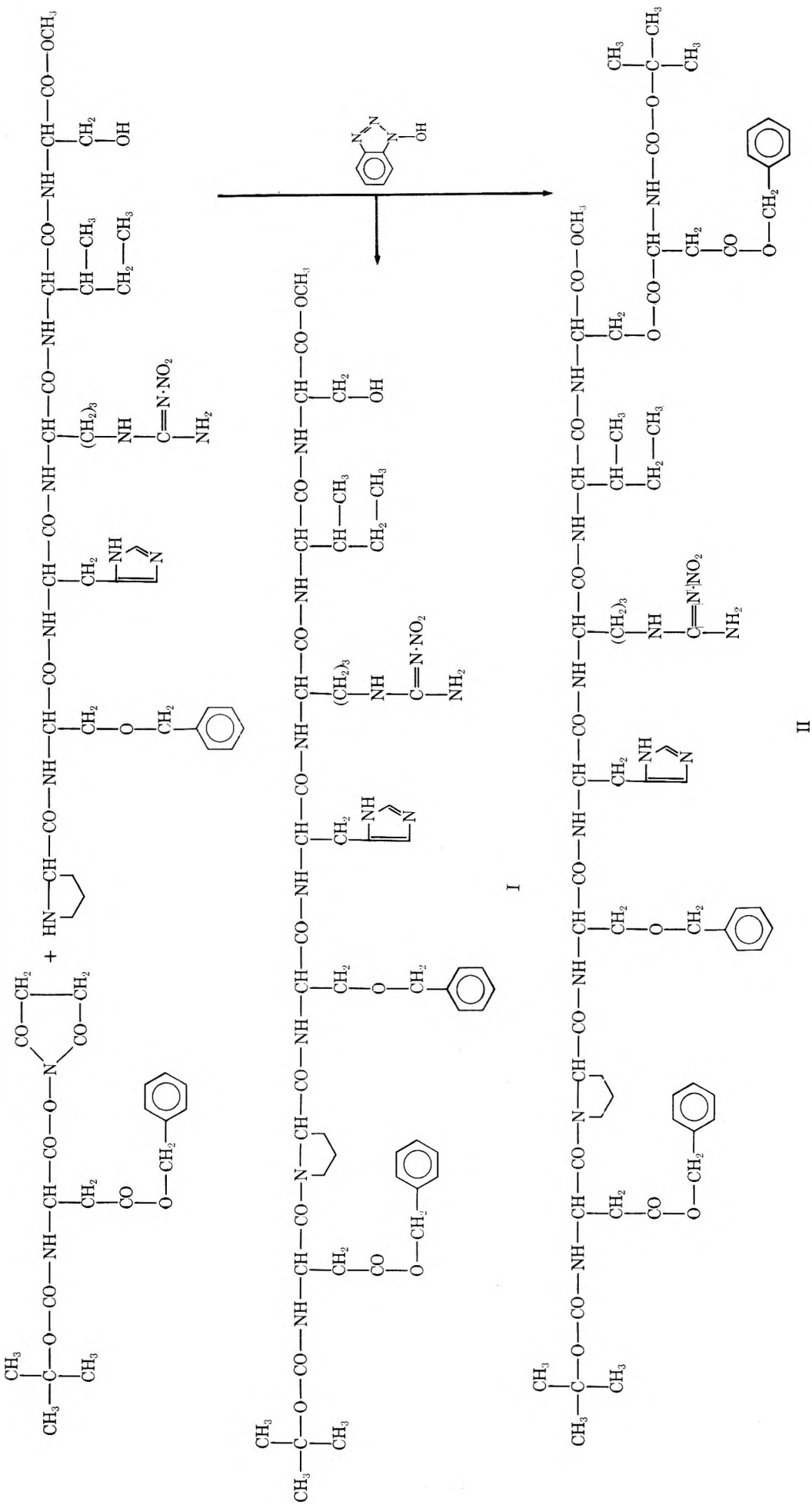
Acylation of the partially protected hexapeptide Pro-Ser(Bzl)-His-Arg(NO_2)-Ile-Ser-OCH_3 with the *N*-hydroxysuccinimide ester of *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid in the presence of 1-hydroxybenzotriazole produced, in addition to the desired heptapeptide derivative, a by-product, often in significant amounts. Examination of this material revealed that acylation of the free amino group of the partially protected hexapeptide was accompanied by acylation of the unprotected hydroxyl group of the C-terminal serine residue. Model experiments demonstrated that the extensive O-acylation was due to the presence f a histidine residue in the amino component. The imidazole in the side chain of this amino acid acts as catalyst in the alcoholysis of the active esters used for chain lengthening. Conditions that can reduce the extent of O-acylation were explored. The implications of this side reaction on the problems of minimal vs. global protection and of the application of excess acylating agents ("the principle of excess") are also discussed.

In the course of our continued effort[2] toward the synthesis of the gastrointestinal hormone cholecystokinin,[3] a protected heptapeptide corresponding to the partial sequence 17–23 of the 33-membered chain was prepared. Building of the protected derivative *tert*-butyloxycarbonyl-β-benzyl-L-aspartyl-L-prolyl-*O*-benzyl-L-seryl-L-histidylnitro-L-ar-

‡ The Hebrew University of Jerusalem.

Scheme I. Formation of an *O*-acyl Derivative (II) in the Preparation of Compound I



ginyl-L-isoleucyl-L-serine methyl ester (I)[4] by stepwise chain lengthening[5] with active esters[6] was carried out without major difficulties until the hexapeptide stage was reached. For the incorporation of the N-terminal residue, aspartic acid, *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid *N*-hydroxysuccinimide ester[7] was applied, and the reaction was catalyzed by the addition of 1-hydroxybenzotriazole[8] (Scheme I). Care was taken to use the acylating agent in only moderate excess, and to keep the reaction mixture only slightly alkaline by the controlled addition of tertiary base. Nevertheless, an examination of the crude product by thin layer chromatography (TLC) revealed the presence of impurities. One of these, a material that moved faster on the silica gel plates than the desired product, was present in varying but always significant amounts, in some cases exceeding that of the desired heptapeptide derivative (I). The by-product (II) was isolated by chromatography on a silica gel column, and was secured in crystalline form. Both elemental analysis and amino acid analysis indicated the incorporation of *two* protected aspartyl residues. Firm evidence for the assignment of structure II (Scheme I) was found in the chromic acid oxidation of II, followed by hydrolysis and amino acid analysis. Two moles of serine was present in the hydrolysate, while in a parallel experiment, in which compound I was similarly oxidized and hydrolyzed, the serine content was reduced almost to 1 mol. Thus, the second aspartyl residue was attached, via an ester bond, to the hydroxyl group of the C-terminal serine.[9]

Reaction of active esters with alcohols is not obvious: most of these compounds can be recrystallized from boiling ethanol[10] if care is taken that basic materials, that could catalyze their alcoholysis, are absent. Still, unexpected O-acylation of a tyrosine residue was reported by Ramachandran[11] and that of a serine side chain by Zahn and his associates.[12] In our laboratories, however, by avoiding an excess of the tertiary base used for the liberation of a free amine from a salt of the amino component, we were able to build peptides in excellent yield and high purity by stepwise cain lengthening with nitrophenyl esters without protection of the hydroxyl group of tyrosine residue. E.g., a hendecapeptide corresponding to the C-terminal sequence of the vasoactive intestinal peptide (VIP) from chicken[13] Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Val-Leu-Thr-NH_2[14] was prepared in this manner. Similarly, no O-acylation was observed when this sequence was assembled again, with both the serine and tyrosine side chains unprotected. Therefore, the extensive O-acylation which produced *significant* amounts of II was unexpected, and prompted an examination of the conditions that are conducive to this side reaction.

Since the participation of the imidazole[15] in the side chain of the histidine residue in the alcoholysis of the active ester was suspected, Boc-Arg(NO_2)-Ile-Ser-OCH_3 (III), the C-terminal (protected) tripeptide intermediate of the synthesis of the heptapeptide, was chosen as a model in which no histidine is present. Samples of III were treated with trifluoroacetic acid, and the partially deprotected tripeptide ester trifluoroacetate salt was acylated, in the presence of tertiary base, with active esters of *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid. The reactions were carried out in the presence and in the absence of catalyst (1-hydroxybenzotriazole, HOBt), and also with and without the addition of imidazole that was used to play the role of the histidine side chain. The crude products were examined by TLC; the results are summarized in Table I.

With hydroxysuccinimide esters, the presence of HOBt was relatively harmless: the expected protected tetrapeptide Boc-Asp(Bzl)-Arg(NO_2)-Ile-Ser-OCH_3 (IV) was the main product, while only a small amount of *N,O*-diacyl derivative (V) could be detected. The addition of imidazole, however, led to a substantial increase in the formation of V, as did the presence of both imidazole and HOBt. With the *p*-nitrophenyl ester as acylating agent, the effects of HOBt and imidazole were similar in causing the formation of V in substantial quantity, but *very little diacyl derivative was found in the crude product of the experiment in which both HOBt and imidazole were added* to the mixture of the reactants. Since in histidine-containing peptides with unprotected imidazole the choice is reduced to the addition or omission of HOBt, the *p*-nitrophenyl rather than the *N*-hydroxysuccinimide ester of (protected) aspartic acid was applied for the preparation of the desired heptapeptide derivative, and HOBt was used to counteract the influence of the imidazole of histidine. The results were encouraging: only a very small amount of V could be detected by TLC in the crude protected heptapeptide.[4]

Table I.[a] Products Formed in the Acylation of Arg(NO_2)-Ile-Ser-OCH_3[b] with Active Esters of Boc-Asp(Bzl)

Active ester	Additives	Relative amounts[c] of *N*-Acyl deriv IV, R_f 0.28	*N,O*-Diacyl deriv V, R_f 0.55
OSu		90	10
OSu	HOBt	90	5–10
OSu	Im	50	50
OSu	HOBt + Im	70	30
OTC		95	5
ONP		95	5
ONP	HOBt	70	30
ONP	Im	40	60
ONP[d]	Im	Trace	>90
ONP	AcOH + Im	40	60
ONP	HOBt + Im	90	5–10

[a] HOBt, 1-hydroxybenzotriazole; Im, imidazole; OSu, *N*-hydroxysuccinimide ester; ONP, *p*-nitrophenyl ester; OTC, 2,4,5-trichlorophenyl ester. [b] Applied as trifluoroacetate salt in the presence of triethylamine. [c] Estimated by inspection of TLC plates under uv and after charring. [d] In this experiment, 2.5 mmol of active ester was used for 1 mmol of tripeptide derivative, while in all other experiments, 1.25 mmol of active ester was applied.

Discussion

The model experiments revealed the role of the imidazole moiety in the histidine in the observed O-acylation of serine side chains. No clear rationale can be offered at this time for the different effects with the two kinds of active esters. The role of HOBt also requires further clarification. Its weak acidic character does not provide a satisfactory explanation: the addition of acetic acid instead of HOBt produced no beneficial effect. The need for a study in depth is indicated, including comparisons of various active esters, imidazole protecting groups, and additives. There are, however, several reasons for reporting these findings prior to such extensive investigations. A similar case of O-acylation, in the HOBt-catalyzed[8] reaction of a 2,4,5-trichlorophenyl ester[16] with a *histidine-containing* peptide, was reported—without discussion—by Geiger and his associates.[17] It seems to be necessary, therefore, to call attention to this side reaction before it is encountered by other investigators as well, and to point out not only the risk of the formation of O-acylated products, but also possible means for decreasing the extent of this side reaction. This report was motivated also by the desire to express certain reservations about approaches in peptide synthesis originating from this laboratory. The inertness of *p*-nitrophenyl esters toward alcoholysis[10] suggested that these mild acylating agents can be applied to amino components carrying minimal protection, possibly only on lysine and cysteine side chains. The observations here presented, and others reported by us recently,[1,18] show certain limitations in the application of minimal pro-

tection, even with mild acylating agents. It should also be pointed out that the "principle of excess",[19] that is, the use of the acylating agents in high enough concentration to secure practical reaction rates with amino components that cannot be present in high molar concentration, might be incompatible—at least in certain cases—with minimal protection.[20]

Conclusions

The presence of histidine in peptides is conducive to O-acylation of (unprotected) side chain hydroxyl groups by active esters. It was possible to keep this side reaction at a minimum when the acylation was carried out with a *p*-nitrophenyl ester in the presence of 1-hydroxybenzotriazole. The "principle of excess" in the use of acylating agent and minimal protection are probably mutually exclusive.

Experimental Section

Capillary melting points are reported uncorrected. Thin layer chromatograms were run on silica gel plates (Merck) with the solvent system $CHCl_3$–CH_3OH (9:1). Spots were revealed by charring. For amino acid analysis, samples were hydrolyzed in evacuated, sealed ampules with constant boiling hydrochloric acid at 110 °C for 16 h, and analyzed on a Beckman Spinco 120C instrument.

Boc-Asp(Bzl)-Pro-Ser(Bzl)-His-Arg(NO_2)-Ile-Ser-OCH_3 (I) and Compound II. A sample (1.0 g) of the crude mixture of I and II[4] was dissolved in $CHCl_3$ (3.5 ml) and applied to a column of silica gel (Baker, 2 × 58 cm). Fractions of 25 ml were collected. $CHCl_3$ was first used for elution; this was changed to $CHCl_3$ containing 5% (v/v) CH_3OH after four fractions were eluted. From fraction 15 on, the methanol ontent was raised to 8%, and from fraction 24 on, to 10%. The individual fractions were examined by TLC and evaporated to dryness with a stream of N_2. The weight of the residues were plotted. Two major peaks emerged: the one containing II (fractions 15–21), the second containing the originally expected heptapeptide derivative I (fractions 30–38). By pooling fractions 16–20, compound II was obtained: 0.35 g; mp 104 °C, sintering at 96 °C; $[\alpha]^{25}D$ −37° (*c* 1, CH_3OH); TLC R_f 0.43. Amino acid analysis: Asp 2.2, Ser 1.95, Pro 0.95, Ile 1.0, His 1.0, Arg (+ Orn) 0.85.

Anal. Calcd for $C_{69}H_{94}N_{14}O_{21}$: C, 56.9; H, 6.5; N, 13.5. Found: C, 57.0; H, 6.8; N, 13.4.

The protected heptapeptide ester I was secured from fractions 31–37: 0.34 g; mp 132 °C, sintering from 120 °C; TLC R_f 0.18. Amino acid analysis: Asp 1.0, Ser 1.8, Pro 0.85, Ile 1.0, His 1.0, Arg (+ Orn) 0.85.

Anal. Calcd for $C_{53}H_{75}N_{13}O_{16}\cdot H_2O$: C, 54.5; H, 6.5; N, 15.6. Found: C, 54.7; H, 6.7; N, 15.7.

Oxidation with Chromic Acid. A sample of compound II (1.2 mg) was dissolved in acetic acid (0.25 ml) containing CrO_3 (8.3 mg) and pyridine (8.3 μl). The mixture was left to stand for 18 h at room temperature, 95% EtOH (5 ml) was added, the solvents were removed with a stream of N_2, and the residue was hydrolyzed for amino acid analysis. The following ratios were determined: Asp 2.2, Ser 1.9, Pro 0.8, Ile 1.0, His 1.0, Arg 0.6. A similarly treated sample of the protected heptapeptide derivative I gave Asp 1.2, Ser 1.1, Pro 0.9, Ile 1.0, His 1.0, Arg 0.6.

Model Experiments. The protected tripeptide ester Boc-Arg(NO_2)-Ile-Ser-OCH_3[4] (0.23 g, 0.44 mmol) was treated with 98% trifluoroacetic acid at room temperature for 15 min. The acid was removed by evaporation, and the residue was washed with ether and dried in vacuo. The trifluoroacetate salt was dissolved in DMF (0.5 ml); triethylamine (0.10 ml, 0.7 mmol) and *tert*-butyloxycarbonyl-β-benzyl-L-aspartic acid *p*-nitrophenyl ester, 2,4,5-trichlorophenyl ester, or *N*-hydroxysuccinimide ester (0.55 mmol) were added. In certain experiments, as indicated in Table I, imidazole (30 mg, 0.44 mmol) and/or 1-hydroxybenzotriazole (54 mg, 0.35 mmol) was also added. The reaction mixtures were stirred overnight. The solvent was removed in vacuo; the residues were taken up in EtOAc (30 ml) and extracted, several times, with saturated $NaHCO_3$ solution and water. The solvent was removed in vacuo, and the product precipitated with ether (10 ml), collected on a filter, washed with ether, and dried. Amino acid analysis of the two main products, separated by preparative TLC, showed that the faster moving material corresponds to the *N,O*-diacyl derivative V, while the slower moving band is that of the expected protected tetrapeptide ester IV. For the relative amounts of these materials in the crude products, cf Table I.

Acknowledgments. Amino acid analyses were carried out by Mrs. Delores J. Gaut, elemental analyses by the Baron Consulting Co., Orange, Conn. This study was supported by grants from the U.S. Public Health Service (NIH AM-12473 and HL-14187).

Registry No.—I, 60512-76-7; II, 60512-77-8; Boc-Asp(Bzl)-OSu, 13798-75-9; Boc-Asp(Bzl)-OTC, 43189-58-8; Boc-Asp(Bzl)-ONP, 26048-69-1; Arg(NO_2)-Ile-Ser-OCH_3, 60512-78-9.

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Biomimetic Polyene Cyclizations.[1] Synthesis and Cyclization of 1,3-Dimethyl-2-(3-methyl-*trans*-3,7-octadienyl)cyclohex-2-en-1-ol

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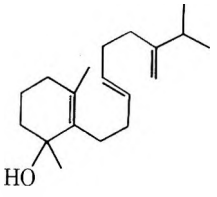
The aim of this study was to determine if the trienol **5**, having a trisubstituted internal olefinic bond, would undergo biomimetic polyene cyclization to give products of "natural" configuration derived from the hypothetical cation **6**, having two angular methyl groups in a 1,3-diaxial relationship. Alkylation of Hagemann's ester **7** with the bromodiene **8** gave the keto ester **9**. Saponification followed by decarboxylation (to give **10**) and treatment with methyllithium afforded the trienol **5**. On shaking with anhydrous formic acid in pentane, the trienol **5** underwent cyclization to give the tricyclic products **17**, **19**, and **20** isolated in yields of 9, 3.6, and 56%, respectively. These substances were shown to belong to the same stereochemical series by interconversion experiments and by reductive degradation to the hydrocarbon **22**, which was independently synthesized from substance **23** via a stereorational route.

As part of a study in our laboratory of allylic cation promoted biomimetic polyene cyclizations,[3] it was previously shown that the trienol **1**, on treatment with anhydrous formic acid at room temperature, was converted in 94% yield into a mixture of the hydrocarbons **2** and the carbinol **3**. The cyclization proved to be stereospecific since these products were separated and shown to belong to the same stereochemical series having the "natural" anti,trans configuration, by interconversion experiments and by their reductive transformation into the natural product, fichtelite **4**.[4]



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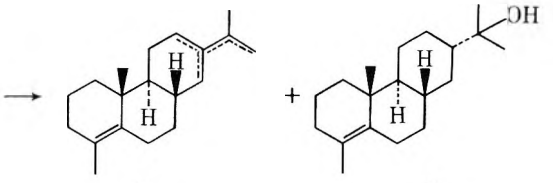
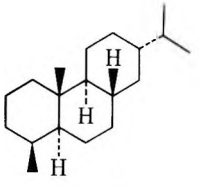
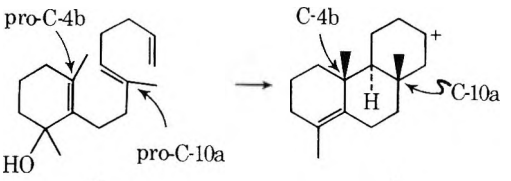


2 **3**



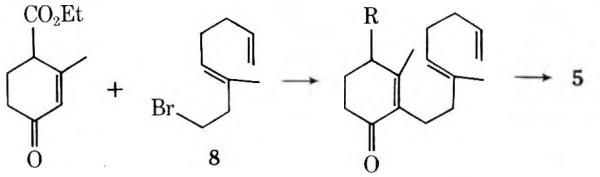
4

The present study was undertaken in order to ascertain if the trienol **5**, which differs from **1** by having a tri- instead of a disubstituted internal olefinic bond, would undergo cyclization in an analogous manner. In this event, the expected products would be those derived from the hypothetical cation **6**, having two β-oriented angular methyl groups (at C-4b and C-10a, phenanthrene numbering) in a 1,3-diaxial relationship—a structural feature found in most of the polycyclic triterpenoids formed by the biocyclization of squalene. It was considered important to determine if the aforementioned 1,3-diaxial interaction of the angular methyl groups might be "felt" in the transition state of the cyclization to such an extent that the normal reaction would be inhibited. The study described in the present paper shows that this is not the case, and that the cyclization of the trienol **5** does indeed proceed stereospecifically to give products derived from cation **6**, thereby providing a model for the production of an important structural feature in many polycyclic isoprenoids.



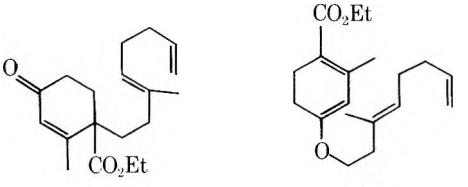
5 **6**

Synthesis of the Trienol 5. The synthetic scheme was analogous to that employed in the preparation of trienol **1**,[4] involving alkylation of Hagemann's ester **7** with the appropriate bromodiene **8**, followed by hydrolysis and decarboxylation of the resulting keto ester **9**, and finally by reaction with methyllithium.



7 **8** **9**, R = CO_2Et; **10**, R = H

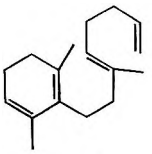
Alkylation of the enolate anion of **7** with the known bromodiene **8**[5] under a variety of conditions always afforded the desired α-alkylated product **9** contaminated with the isomeric products **11** and **12** resulting from γ- and O-alkylation. When the reaction was conducted in *N*,*N*-dimethylformamide at 52 °C, a 41% yield of C-alkylated products was obtained along with 23% of the enol ether **12**. The structure of this product **12** was determined by ir and NMR spectroscopy (see Experimental Section), and by its facile degradation by acid-catalyzed hydrolysis which afforded a convenient means of eliminating it from the reaction mixtures. The extent of O-alkylation could be markedly reduced by conducting the reaction at room temperature in either dimethyl sulfoxide or *tert*-butyl alcohol.[6] Thus alkylation of **7** in *tert*-butyl alcohol at 23 °C



11 **12**

in the presence of potassium iodide followed by treatment with dilute hydrochloric acid afforded a 67% yield of C-alkylated product consisting of 93% of the desired keto ester **9** contaminated with 7% of the γ-alkylated material **11**, as determined by vapor phase chromatographic (VPC) analysis. The desired enone **10** was obtained in 84% yield and in >99% purity by submitting the above C-alkylated mixture to selective saponification under conditions (see Experimental Section) which were too mild to attack the more hindered ester group of substance **11**.[4,7]

Two consecutive treatments of the trienone **10** with methyllithium gave in 83% yield the trienol **5**, the structure and configuration of which were confirmed by ir and NMR spectroscopy. As in the case of the related trienol **1**, the cyclization substrate **5** was exceedingly prone to dehydration. Heating with a trace of acid or dissolution in acetic acid converted **5** into a 56:44 mixture of tetraenes **13** and **14**.



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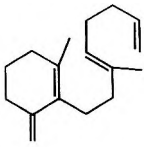
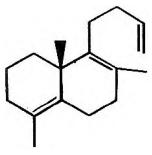


14

Cyclization Studies. A mixture of trienol **5**, anhydrous formic acid, and pentane was shaken for 5 min at room temperature. The crude product was treated with lithium aluminum hydride to cleave formate esters, and then was separated by column chromatography into a hydrocarbon ($C_{17}H_{26}$) and alcoholic ($C_{17}H_{28}O$) fraction, isolated in yields of 29 and 65%, respectively.

The hydrocarbon fraction consisted of four major components, A, B, C, and D, in a ratio of 5:48:17:30, as estimated by their relative VPC peak areas. The components were separated by preparative VPC, evaporatively distilled, and characterized by their spectral properties. Hydrocarbon A evidently decomposed during its purification and was not further examined. The ir and NMR spectra of hydrocarbons B and C were very similar, both exhibiting ir absorptions at 6.05, 10.05, and 10.95 μ characteristic of a terminal vinyl group. The NMR spectra showed the presence of two vinyl methyl groups and one angular methyl group. Absorptions for three vinyl protons at δ 4.78–6.10 ppm appeared in the spectrum of B, whereas the spectrum of C showed four vinyl protons as overlapping multiplets at δ 4.75–6.20 ppm. These data are consistent with the bicyclic structures **15** and **16** for B and C,



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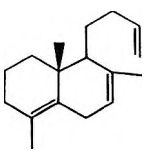
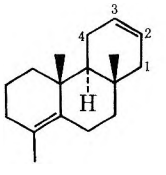


16

respectively. The NMR spectrum of hydrocarbon D showed absorptions for one vinyl methyl group, two angular methyl groups, and two vinyl protons. The signals for the vinyl protons were broad and complex, indicating extensive allylic coupling characteristic of a Δ^2 (see formula **17**) rather than a Δ^1 system.[8] Hydrogenation of D over platinum catalyst in ethanol gave a single crystalline product, dihydro-D ($C_{17}H_{28}$), mp 54–56 °C, the NMR spectrum of which was similar to that of D, except that there were no absorptions for vinyl protons. Presuming that hydrocarbon D arises by deprotonation of cation **6**, the above data for D and dihydro-D are consistent with the tricyclic structures represented by formulas **17** and **18**.



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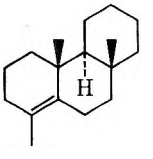
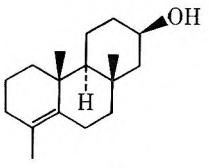


18

The alcohol fraction from the cyclization experiment appeared to consist of two components on thin layer chromatography (TLC). Separation by preparative TLC afforded two crystalline alcohols, A and B (in order of decreasing mobility), in yields of 3.6 and 56%, respectively. The NMR spectra of A and B were similar, exhibiting three-proton singlets for two angular methyl groups and one vinyl methyl group. The spectrum of alcohol A, mp 97–99 °C, displayed a one-proton multiplet of 13 Hz width centered at 4.03 ppm, characteristic of an equatorial proton on a carbon bearing an axial hydroxyl group. The corresponding absorption for alcohol B, mp 115–116 °C, was centered at 3.70 ppm with a width of 50 Hz, indicating an axial proton on a carbon bearing an equatorial hydroxyl group.[9] Oxidation of both alcohols with Jones reagent[10] gave the same crystalline ketone, mp 94.5–95.5 °C, thus providing firm evidence that A and B were epimeric at the carbon bearing the hydroxyl group. This conclusion was confirmed by reduction of the ketone with lithium aluminum hydride to give a mixture of alcohols A and B. Wolff–Kishner reduction of the ketone gave a crystalline hydrocarbon, mp 54–56 °C, in 82% yield, which was identical with hydrocarbon dihydro-D (see above), as shown by VPC behavior and ir and NMR spectroscopy, proving that alcohols A and B belonged to the same stereochemical series as tricyclic diene **17**. The evidence cited above, along with the presumption that alcohols A and B originate via formolysis of cation **6**, led to assignment of the structures **19**, **20**, and **21** to alcohols A and B and their



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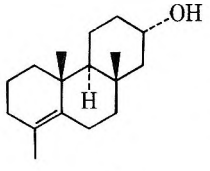

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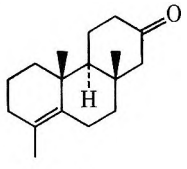
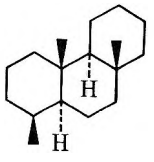


21

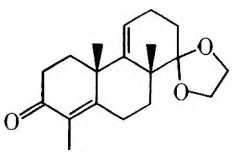
oxidation product, respectively. These assignments were further strengthened by the result of the reduction of ketone **21** with lithium tri-*tert*-butoxyaluminohydride, which gave alcohol **19** exclusively, in accord with the expected delivery of hydride to the less hindered α side of the carbonyl group.

Attempts to synthesize an authentic specimen of hydrocarbon **18** by an independent route from substance **23** of known stereochemistry were unsuccessful; however, the related perhydrophenanthrene **22** was produced in a stereorational manner as discussed below. This substance could be obtained from either the cyclization product **17** or the dihydro hydrocarbon **18**, by hydrogenation over platinum dioxide in acetic acid. The major component in both cases, isolated by preparative VPC, was a crystalline hydrocarbon, mp 45.0–46.5 °C, which was found to be identical with the synthetic perhydrophenanthrene **22**, described below.

Preparation of the Comparison Compound 22. The keto ketal **23** of known configuration[11] was reduced with lithium

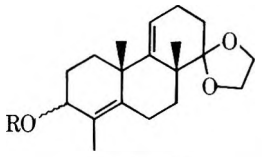


22

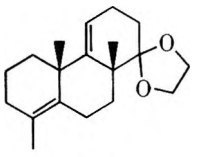


23

aluminum hydride to give a mixture of the epimeric α- and β-oriented allylic alcohols **24** in a ratio of 14:86 as evidenced by the C-4b angular methyl signals in the NMR spectrum of the crude product. Treatment of the corresponding acetates **25** with lithium in ethylamine[12] effected hydrogenolysis of the allylic acetoxy group to give the dienic ketal **26.** Hydrolysis



24, R = H
25, R = Ac



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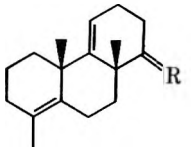
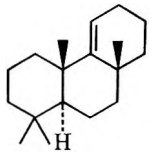
of ketal **26** gave the ketone **27** which was converted, by the Huang-Minlon modification[13] of the Wolff–Kishner reduction, into the diene **28** contaminated with 7% of other double



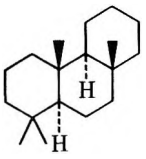
27, R = O
28, R = H_2

bond isomers. Purification by preparative VPC afforded the crystalline hydrocarbon **28,** mp 38–39 °C. All attempts to selectively reduce the trisubstituted double bond of diene **28** so as to give the compound **18** failed. Hydrogenation of diene **28** over platinum dioxide in acetic acid gave a mixture of four components in a ratio of 6:2:26:66 (in order of increasing retention time) as determined by VPC. The major component, isolated by preparative VPC, was identical (as shown by mixture melting point, VPC behavior, and NMR and ir spectroscopy) with hydrocarbon **22,** the predominant saturated hydrocarbon obtained by catalytic reduction of both **17** and **18.** Thus the tricyclic nature and gross structural features of the major cyclization products **17, 19,** and **20** have been firmly established.

Although the configuration of the 46 °C hydrocarbon has not been unequivocally established, it is most surely the trans,anti,trans substance **22.** Hydrogenation of the trisubstituted double bond of diene **28** would be expected to occur from the less hindered α side, thereby generating the trans B/C ring fusion. Reduction of the related compound **29** has been shown to result in exclusive formation of **30**;[11,14] more-



29



30

over, the literature abounds in examples of the catalytic hydrogenation of the double bond of 9,11-dehydro steroids to give the trans B/C ring fusion.[15] The stereochemical course of the hydrogenation of the olefinic bond in ring A of **18** and **28** to give the trans A/B ring fusion is analogous to the established course of the hydrogenation of hydrocarbon **2** to give *dl*-fichtilite (**4**).[4] The configurational similarities of hydrocarbon **22** and fichtilite (**4**) are reflected by the nearly identical positions of the C-4b and C-8 methyl signals in the NMR spectra. Finally the shifts in the position of the angular C-10a methyl absorption resulting from alterations of ring C substituents correlates well with observed shifts for trans-fused ring systems. Thus the signal, which occurs at 61.5 Hz with no substituent in ring C (hydrocarbon **18**), shows a shift of +14.5 Hz (predicted +15.0[16]) for the 2β-OH substituent (compound **19**). The shift is −1.5 Hz (predicted −1.5[16]) for the 2-keto substituent (compound **21**), and −1.5 Hz (predicted 0,[16] −3.0[17]) for the 2,3-dehydro substance (**17**).

Thus it has been demonstrated that the substrate **5** does indeed undergo cyclization to give tricyclic products having "natural configuration". This process involves the development of a transition state or an intermediate having two angular methyl groups with 1,3-diaxial interactions, which may account for the lower yield (66%) as compared with that (93%) obtained for cyclization of the trienol **1** with a di- instead of a trisubstituted internal olefinic bond. It is noteworthy that when the bicyclic products **15** and **16** were subjected to the cyclization conditions, they were recovered unchanged, and therefore they cannot be intermediates in the formation of the tricyclic products.

Experimental Section[18]

General Considerations. The prefix "*dl*" has been omitted from the names of the racemic compounds described in this section. Microanalyses were performed by E. H. Meier and J. Consul, Department of Chemistry, Stanford University. Melting points were determined on a Kofler hot-stage microscope.

Vapor phase chromatographic (VPC) analyses were performed on Aerograph Hi-Fi Models A-600B and A-600C instruments equipped with 7.5 ft × 0.125 in. columns packed with either 15% Carbowax or 5% SE-30 on Chromosorb W, 60/80 mesh. Preparative VPC separations were carried out on an Aerograph Model A-710 instrument equipped with 20 ft × 0.37 in. columns packed with either 20% Carbowax 20M or 20% SE-30 on Chromosorb W, 45/60 mesh.

Nuclear magnetic resonance (NMR) spectra were determined under the supervision of Dr. L. J. Durham on a Varian Associates A-60 or HA-100 NMR spectrometer. Unless otherwise stated, carbon tetrachloride was used as solvent for the samples; chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ_{TMS} 0.0 ppm). Infrared (ir) spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer, and ultraviolet (uv) spectra were obtained on a Cary Model 14M recording spectrophotometer. Refractive indices were determined on Bausch-Lomb Models 8885 and Abbe-3L refractometers.

Silica gel G (E. Merck AG) was used as the absorbent for thin layer chromatography (TLC) experiments. The spots were detected either by use of iodine or by spraying the plate with a 2% solution of ceric sulfate in 2 N sulfuric acid followed by heating the plate at 150 °C for 10 min.

Alkylation of Hagemann's Ester with the Bromodiene 8. A. In Dimethyl Sulfoxide. Isolation of the *O*-Alkylate 12. The dimethylsulfinyl carbanion was generated by a reported procedure.[19] A mixture of 182 mg (4.14 mmol) of a 54.7% dispersion of sodium hydride in mineral oil and 10 ml of dry dimethyl sulfoxide was heated under nitrogen for 0.5 h at 82 °C. The resulting solution was cooled to room temperature and 780 mg (4.3 mmol) of Hagemann's ester[20] was added. The solution was stirred for 15 min, 382 mg (1.88 mmol) of bromodiene 8[5] (n^{20}D 1.490) was added, and stirring was continued for 16 h at 23 °C. The mixture was diluted with 20 ml of water and extracted with pentane and ether.[18] The crude product was chromatographed on 30 g of neutral alumina (4% water added) with 92:8 petroleum ether–methylene chloride to give, after evaporative distillation at 125–135 °C (7 μ), 255 mg (44% yield) of C-alkylated material as a colorless oil and 61 mg (11% yield) of O-alkylated material as a colorless liquid. The *O*-alkylate (**12**) exhibited the following spectral properties: ir λ_{max} (film) 5.92 (ester C=O), 6.40 (enol ether), and 6.09, 10.05, and 10.95 μ (C=C); NMR 1.26 (t, J = 7 Hz, 3 H, ester CH_3), 1.67 (s, 3 H, octadienyl vinyl CH_3), 2.14 (s, 3 H, C-3 vinyl CH_3), 3.82 (t, J = 7 Hz, 2 H, C=$COCH_2$–), 4.10 (q, J = 7 Hz, 2 H, ester CH_2), 4.87 (s, 1 H, C-2 vinyl proton), and 4.75–6.10 ppm (m, 4 H, vinyl protons).

Anal. ($C_{19}H_{28}O_3$) C, H.

An ethereal solution of the enol ether **12** was shaken for a few minutes at 23 °C with 10% aqueous hydrochloric acid. Extraction with ether using a base wash[18] afforded a residue which exhibited new carbonyl absorptions at 5.75 and 5.95 μ in the ir spectrum. The enol ether absorption at 6.40 μ was appreciably diminished.

B. In *tert*-Butyl Alcohol. Isolation of 4-Carbethoxy-3-methyl-2-(3-methyl-*trans*-3,7-octadienyl)cyclohex-2-en-1-one (9). A solution of 39.0 g (0.214 mol) of Hagemann's ester 7[20] in 50 ml

of anhydrous *tert*-butyl alcohol was added over a period of 15 min to a stirred suspension prepared from 8.78 g (0.20 mol) of a 54.7% dispersion of sodium hydride in mineral oil and 300 ml of anhydrous *tert*-butyl alcohol under nitrogen. The resulting red-orange solution was stirred for 15 min; then a solution of 23.5 g (0.116 mol) of crude bromodiene 8[5] (prepared by W. R. Bartlett) in 20 ml of *tert*-butyl alcohol was added over a period of 10 min followed by the addition of a 16.0-g portion (0.096 mol) of potassium iodide (dried at 120 °C and 14 mm for 8 h). The mixture was stirred for 24 h at 23 °C and then heated at reflux for 2 h. The mixture was cooled and poured into 150 ml of water overlaid with 200 ml of ether. The aqueous layer was acidified to pH 3 with 10% aqueous hydrochloric acid and extracted with ether.[18] The crude product was chromatographed on 1 kg of neutral alumina (2.5% water added) with petroleum ether, bp 68–70 °C, and divided into three fractions as follows: fraction a amounted to 6.4 g of a mixture of mineral oil and unreacted bromide **8**; fraction b amounted to 21.7 g (62% yield) of the desired ester **9** contaminated with 4% of the γ-alkylated product **11** as shown by VPC (SE-30, 182 °C); fraction c amounted to 2.9 g (5% yield) of a mixture of **9** and **11** in a ratio of 69:31, as shown also by VPC.

Fraction b was used directly in the decarboxylation step described below. A sample of comparable material was evaporatively distilled at 125–135 °C (3 μ) to afford ester **9** as a colorless liquid: n^{25}D 1.496; ir λ_{max} (film) 5.75 (ester C=O), 5.95 (α,β-unsaturated C=O), 6.10, 10.03, and 10.95 μ (C=C); uv λ_{max} (95% EtOH) 248 nm (ε 9750); NMR 1.27 (t, J = 7 Hz, 3 H, ester CH_3), 1.65 (s, 3 H, octadienyl vinyl CH_3), 1.94 (s, 3 H, C-3 vinyl CH_3), 3.18 (t, J = 4 Hz, 1 H, C-4 proton), 4.16 (q, J = 7 Hz, 2 H, ester CH_2), and 4.75–6.1 ppm (m, 4 H, vinyl protons).

Anal. ($C_{19}H_{28}O_3$) C, H.

3-Methyl-2-(3-methyl-*trans*-3,7-octadienyl)cyclohex-2-en-1-one (10). A modification of a published procedure[21] was employed. An ice-cold 28-ml portion of a 15% solution of potassium hydroxide in 95% ethanol was added to 13.8 g (45.4 mmol) of the above chromatographed ester **9**. The resulting solution was stirred for 8 h at 5–10 °C under nitrogen, diluted with 40 ml of water, and extracted with ether[18] to give 0.94 g (7% recovery) of ester **11**. The aqueous layer was acidified to pH 3 with 10% aqueous hydrochloric acid and extracted with ether and dichloromethane[18] to afford a pale yellow, oily acid: ir λ_{max} (film) 2.9–3.4 (CO_2H), 5.75 (acid C=O), 6.0 (α,β-unsaturated C=O), 10.03 and 10.95 μ (C=C). The crude acid was evaporatively distilled at 140–145 °C (3 μ) from a flask filled with glass wool to give 9.09 g (86% yield) of a mixture of α,β-unsaturated ketone **10** and its β,γ isomer in a ratio of 12:88 as shown by VPC (SE-30, 189 °C): ir λ_{max} (film) 5.83 and 6.0 μ (β,γ- and α,β-unsaturated C=O).

The above mixture of ketones was isomerized by stirring under nitrogen for 3 h with 39 ml of a 10% solution of potassium hydroxide in ethylene glycol.[22] The mixture was diluted with water and extracted with ether and dichloromethane.[18] The crude product was evaporatively distilled at 140–145 °C (3 μ) to afford 8.83 g (84% overall yield) of ketone **10** as a pale yellow liquid which appeared to be >99% pure by VPC (SE-30, 173 °C). A sample of comparable material was evaporatively distilled at 100 °C (3 μ) to give an analytical specimen of **10** as a pale yellow liquid: n^{24}D 1.505; ir λ_{max} (film) 6.0 (α,β-unsaturated C=O), 10.05, and 10.95 μ (C=C); uv λ_{max} (95% EtOH) 245 nm (ε 11 100); NMR 1.63 (s, 3 H, vinyl CH_3), 1.91 (s, 3 H, vinyl CH_3 on ring), and 4.8–6.1 ppm (m, 4 H, vinyl protons).

Anal. ($C_{16}H_{24}O$) C, H.

The **2,4-dinitrophenylhydrazone** was obtained as red-orange crystals, mp 89–90 °C, after two recrystallizations from 95% ethanol.

Anal. ($C_{22}H_{28}N_4O_4$) C, H, N.

1,3-Dimethyl-2-(3-methyl-*trans*-3,7-octadienyl)cyclohex-2-en-1-ol (5). A solution of 3.10 g (13.4 mmol) of the distilled ketone **10** in 80 ml of anhydrous ether was stirred under nitrogen while 72 ml of a 1.2 M solution of methyllithium in ether was added. Stirring was continued for 0.5 h; then the mixture was poured onto 300 g of ice–brine and extracted with ether.[18] The ir spectrum of the crude product exhibited a weak carbonyl absorption at 6.0 μ indicative of the presence of unreacted enone **10**. The above procedure was repeated using 72 ml of a 2.1 M solution of methyllithium to afford 2.76 g (83% yield) of the trienol **5** after evaporative distillation at 100 °C (3 μ): n^{23}D 1.500; ir λ_{max} (film) 2.95 (OH), 6.09, 10.02, and 10.95 μ (C=C); NMR 1.22 (s, 3 H, C-1 CH_3), 1.64 (s, 3 H, vinyl CH_3), 1.65 (s, 3 H, vinyl CH_3), and 4.80–6.10 ppm (m, 4 H, vinyl protons).

Anal. ($C_{17}H_{28}O$) C, H.

Examination of trienol **5** by VPC (Carbowax, 170 °C) showed two overlapping peaks with retention times of 15.5 (41%) and 17.5 min (59%), which were identified as the tetraenes **13** and **14** (see below) by coinjection.

Dehydration of Trienol 5. A mixture of 156 mg (0.63 mmol) of trienol **5** (n^{23}D 1.500), 30 ml of acetic acid (distilled from chromium trioxide, bp 116–117 °C), and 6 drops of acetic anhydride was stirred under nitrogen for 20 min at room temperature, then poured into an ice-cold solution of 22 g of sodium hydroxide in 50 ml of water overlaid with 50 ml of ether. An additional 100 ml of water was added to dissolve the precipitated sodium acetate and the mixture was extracted with ether.[18] Chromatography of the crude product on 10 g of Woelm neutral alumina (4% added water; pentane) followed by evaporative distillation at 95–105 °C (3 μ) gave 112 mg (77% yield) of colorless oil which appeared to consist of tetraenes **13** and **14** in a ratio of 60:40 by VPC (Carbowax, 190 °C): ir λ_{max} (film) 6.10, 10.05, and 10.95 (C=C), and 6.14 μ (diene); λ_{max} (95% EtOH) 242 nm (ε 14 700) (trans diene of **14**) and 273 (345) (cis diene of **13**).

Anal. ($C_{17}H_{26}$) C, H.

The ratio of dienes **13** and **14** was estimated by integration of the NMR spectrum. Comparison of the total vinyl proton integral (5.5 protons) with that of the 5.30–6.15-ppm region (m, 1.6 H, vinyl proton on ring of **13** and chain C=CH) indicated a 59:41 ratio of dienes **13:14**. The ring methyl groups at 1.74 and 1.76 ppm integrated for 4.7 protons, which indicated a 56:44 ratio of **13:14**. The geminal protons for the exo methylene of diene **14** appeared as two signals at 4.62 and 4.80 ppm. The signal for the C-3 chain methyl group was at 1.63 ppm.

Cyclization of Trienol 5 with Formic Acid. A test tube containing 1.00 g (4.02 mmol) of the distilled trienol **5** was placed in a round-bottomed flask containing 17 ml of anhydrous pentane and 39 ml of formic acid [distilled from boric anhydride,[23] bp 19–21 °C (21 mm)]. After evacuation and flushing with nitrogen, the flask was inverted and shaken vigorously for 5 min. The contents of the flask were poured into 50 ml of water overlaid with 100 ml of pentane, and the flask and test tube were rinsed with water and pentane. The aqueous phase was saturated with sodium chloride and extracted with pentane using a base wash[18] to give 1.13 g of cloudy, pale yellow oil: ir λ_{max} (film) 5.80 (ester C=O), 6.10, 10.05, and 10.95 μ (C=C).

A solution of the above crude cyclization product in 5 ml of anhydrous ether was added to a suspension of 0.304 g (8.0 mmol) of lithium aluminum hydride in 10 ml of anhydrous ether. The mixture was stirred under nitrogen for 1 h at 23 °C; then it was cooled to 0 °C and 0.3 ml of water, 0.3 ml of 15% aqueous sodium hydroxide solution, and 0.9 ml of water were added in succession. The mixture was stirred until a white, granular suspension formed; then anhydrous magnesium sulfate was added and stirring was continued for 8 h. The mixture was filtered and the filtrate evaporated at reduced pressure to afford 0.94 g of cloudy, viscous oil which exhibited three spots by TLC (7:3 pentane–ether), R_f 0.17, 0.28, and 0.92.

The above 0.94-g sample of material was chromatographed on 30 g of Merck acid-washed alumina and separated into five fractions as follows: fraction a, eluted with petroleum ether, 68–70 °C, amounted to 270 mg (29% yield) of colorless oil which appeared to consist of a mixture of four hydrocarbons, A, B, C, and D, with VPC (Carbowax, 181 °C) retention times of 3.8 (5%), 5.5 (46%), 6.8 (16%), and 9.5 min (28%), respectively; fraction b, eluted with 9:1 petroleum ether–ether, amounted to 22 mg of material which appeared to be a complex mixture by TLC; fraction c, eluted with 4:1 petroleum ether–ether, amounted to 26 mg (2.6% yield) of alcohol A (R_f 0.28); fraction d, eluted with 4:1 petroleum ether–ether, amounted to 147 mg (14.7% yield) of a mixture of alcohol A and alcohol B (R_f 0.17); fraction e, eluted with 7:3 petroleum ether–ether, amounted to 477 mg (47.7% yield) of alcohol B.

A portion of fraction a was evaporatively distilled at 70–80 °C (3 μ) to afford a 98% recovery of colorless oil: ir λ_{max} (film) 6.10, 10.05, and 10.95 μ (C=C).

Anal. ($C_{17}H_{26}$) C, H.

The hydrocarbons A, B, C, and D were separated by preparative VPC (Carbowax, 205 °C) from the undistilled portion of fraction a and the collected fractions were evaporatively distilled at 70–80 °C (3 μ).

Examination of hydrocarbon A by VPC (Carbowax, 190 °C) revealed the presence of two new components in addition to hydrocarbon A. Apparently hydrocarbon A decomposed during the isolation procedure and was not further characterized.

Hydrocarbon B was assigned the bicyclic structure (**15**) on the basis of its spectral properties: ir λ_{max} (film) 6.09, 10.05, and 10.95 μ (C=C); NMR 1.11 (s, 3 H, angular CH_3), 1.60 (s, 6 H, vinyl methyls), and 4.78–6.30 ppm (m, 3 H, vinyl protons).

Anal. ($C_{17}H_{26}$) C, H.

Hydrocarbon C was assigned the bicyclic structure (**16**) on the basis of its spectral properties: ir λ_{max} (film) 6.09, 10.05, and 10.95 μ (C=C); NMR 0.88 (s, 3 H, angular CH_3), 1.53 (s, 3 H, vinyl CH_3), 1.70 (s, 3 H, vinyl CH_3), and 4.78–6.30 ppm (m, 4 H, vinyl protons).

Hydrocarbon D was identified as **4bβ,8,10aβ-trimethyl-Δ²,Δ⁸-4aα-decahydrophenanthrene (17):** NMR 1.00 (s, 3 H, angular CH_3), 1.58 (s, 3 H, vinyl CH_3), and 5.48 ppm (broad m, 2 H, vinyl protons).

Anal. ($C_{17}H_{26}$) C, H.

The components of fraction d were separated by preparative TLC (7:3 pentane–ether) to give 10 mg of alcohol A and 102 mg of alcohol B. These separated components were combined with fractions c and e, respectively.

Alcohol A (fraction c) was evaporatively distilled at 100–110 °C (7 μ) to afford 36 mg (3.6% yield) of **4bβ,8,10aβ-trimethyl-2β-hydroxy-Δ⁸-4aα-dodecahydrophenanthrene (19)** as colorless crystals, mp 97–99 °C: ir λ_{max} ($CHCl_3$) 2.70 and 2.85 μ (OH); NMR 0.95 (s, 3 H, angular CH_3), 1.23 (s, 3 H, angular CH_3), 1.60 (s, 3 H, vinyl CH_3), and 4.03 ppm (m, W = 13 Hz, 1 H, C-2 equatorial proton).

Anal. ($C_{17}H_{28}O$) C, H.

Alcohol B (fraction e) was evaporatively distilled at 100–110 °C (7 μ) to afford 560 mg (56% yield) of crystalline **4bβ,8,10aβ-trimethyl-2α-hydroxy-Δ⁸-4aα-dodecahydrophenanthrene (20),** mp 113–114 °C. Recrystallization from pentane gave an analytical sample as colorless prisms: mp 115–116 °C; ir λ_{max} ($CHCl_3$) 2.72 and 2.90 μ (OH); NMR 0.90 (s, 3 H, angular CH_3), 1.05 (s, 3 H, angular CH_3), 1.61 (s, 3 H, vinyl CH_3), and 3.70 ppm (m, W = 50 Hz, 1 H, C-2 axial proton).

Anal. ($C_{17}H_{28}O$) C, H.

Hydrogenation of Hydrocarbon D in Ethanol. A mixture of 15 mg (0.065 mmol) of hydrocarbon D, 18 mg of platinum dioxide, and 5.5 ml of 95% ethanol was stirred under hydrogen for 14 h at room temperature. The resulting mixture was filtered and the solvent was removed at reduced pressure to give, after evaporative distillation at 80 °C (3 μ), 10 mg (66% yield) of dihydro-D (**18**) as a colorless oil which appeared to be 97% of one component by VPC (Carbowax, 192 °C). The NMR spectrum and VPC behavior of this material were identical with those of hydrocarbon **18,** obtained via Wolff–Kishner reduction of ketone **21.** The ir spectra of the two hydrocarbons were also nearly identical.

4bβ,8,10aβ-Trimethyl-2-keto-Δ⁸-4aα-dodecahydrophenanthrene (21). A. By Oxidation of Alcohol A. A 0.2-ml portion of Jones reagent[10] was added to a cold (0 °C) solution of 16 mg (0.06 mmol) of alcohol A (**19**), mp 97–98 °C, in 5 ml of acetone. The mixture was stirred at 0 °C for 10 min and then poured into 50 ml of water. Ether extraction[18] followed by chromatography on 1 g of Merck acid-washed alumina (9:1 pentane–ether) afforded 10 mg (63% yield) of crystalline ketone **21,** mp 85–87 °C. Three recrystallizations from pentane gave **21** as colorless prisms, mp 94.5–95.5 °C.

B. By Oxidation of Alcohol B. Similar oxidation of 198 mg of alcohol B (**20**), mp 113–114 °C, afforded after chromatography on 10 g of Merck acid-washed alumina followed by evaporative distillation at 100–110 °C (9 μ), 169 mg (86% yield) of ketone **21,** mp 78–79 °C. An analytical sample was obtained after three recrystallizations from pentane as colorless prisms, mp 93.0–94.5 °C: ir λ_{max} (CCl_4) 5.85 μ (C=O); NMR 0.99 (s, 3 H, angular CH_3), 1.00 (s, 3 H, angular CH_3), and 1.63 ppm (s, 3 H, vinyl CH_3).

Anal. ($C_{17}H_{26}O$) C, H.

The **2,4-dinitrophenylhydrazone** was obtained as yellow-orange plates, mp 218–219 °C, after two recrystallizations from 95% ethanol.

Anal. ($C_{23}H_{30}N_4O_4$) C, H, N.

The mixture melting point of the recrystallized ketones obtained from alcohols A (**19**) and B (**20**) was 92–95 °C. The ir spectra of the two ketones were identical.

Wolff–Kishner Reduction of Ketone 21. The Huang-Minlon modification[13] of the Wolff–Kishner reduction was employed. A mixture of 97.3 mg (0.40 mmol) of ketone **21,** mp 78–79 °C, 224 mg of powdered potassium hydroxide, 2.9 ml of triethylene glycol, and 0.42 ml of anhydrous hydrazine was heated under nitrogen for 2.5 h at 90–104 °C in a flask fitted with a short-path condenser. The bath temperature was raised to 190–230 °C and heating was continued for an additional 3 h. After cooling to room temperature, the contents of the pot and the receiver were poured into 10 ml of water and the condenser was rinsed with ether. Ether extraction[18] followed by chromatography on 4 g of Merck acid-washed alumina (pentane) afforded 76 mg (82% yield) of **4bβ,8,10aβ-trimethyl-Δ⁸-4aα-dodecahydrophenanthrene (18)** as colorless crystals, mp 54–55 °C. An analytical sample was obtained by evaporative distillation at 80 °C (3 μ) as colorless prisms, mp 54–56 °C: NMR 0.89 (s, 3 H, angular CH_3), 1.03 (s, 3 H, angular CH_3), and 1.59 ppm (s, 3 H, vinyl CH_3).

Anal. ($C_{17}H_{28}$) C, H.

Reduction of Ketone 21 with Lithium Tri-*tert*-butoxyaluminohydride. A mixture of 17.8 mg (0.072 mmol) of ketone **21,** mp 78–79 °C, and 182 mg (0.72 mmol) of lithium tri-*tert*-butoxyaluminohydride[24] in 4 ml of dry THF was stirred at room temperature under nitrogen for 24 h; then 0.1 ml of water and 0.1 ml of 10% sodium hydroxide solution were added. The resulting mixture was stirred for 3 h, poured into 10 ml of water, and extracted with ether.[18] Chromatography of the crude product on 2 g of Merck acid-washed alumina (7:3 pentane–ether) followed by evaporative distillation at 100–110 °C (3 μ) afforded 10.9 mg (61% yield) of alcohol **19,** mp 96–98 °C, which appeared as one spot (R_f 0.28) on TLC (7:3 pentane–ether): ir λ_{max} ($CHCl_3$) 2.70 and 2.85 μ (OH).

Anal. ($C_{17}H_{28}O$) C, H.

Recrystallization from pentane did not raise the melting point of the alcohol which existed in dimorphic forms. Some crystals melted at 96–98 °C; then needles formed at 107–111 °C, which remelted at 127–129 °C. The ir spectra of this alcohol and alcohol A (**19**) obtained via cyclization were identical.

Hydrogenation of Hydrocarbon D (17) in Ethanol and Acetic Acid. A mixture of 23 mg (0.1 mmol) of hydrocarbon D (**17**), 25 mg of platinum dioxide, 10 ml of ethanol, and a few drops of acetic acid was stirred under hydrogen for 18 h at room temperature. The mixture was filtered and the solvent was evaporated at reduced pressure. The crude product was filtered through 1 g of Merck acid-washed alumina (pentane) to afford a colorless oil consisting of three major components with VPC retention times (Carbowax, 184 °C) of 10.5 (6%), 13 (11%), and 15 min (77%). The major component was isolated by preparative VPC (Carbowax, 200 °C), then evaporatively distilled at 70–80 °C (2 μ) to yield 9 mg (39% yield) of colorless needles, mp 45.0–47.5 °C. The VPC behavior, ir, and NMR spectra of this material were identical with those of hydrocarbon **22.** The mixture melting point of the two hydrocarbons was 44–47 °C.

Hydrogenation of Hydrocarbon 18 in Acetic Acid. A mixture of 22 mg (0.095 mmol) of hydrocarbon **18,** mp 54–55 °C, 20 mg of platinum dioxide, and 6.0 ml of acetic acid (distilled from chromium trioxide) was stirred under hydrogen for 24 h at room temperature. The mixture was filtered and the acetic acid was removed at reduced pressure (14 mm). The cloudy residue was washed through 1 g of Merck acid-washed alumina with pentane to yield 20.5 mg of material consisting of a mixture of five hydrocarbons with VPC retention times (Carbowax, 203 °C) of 7.0 (7%), 7.5 (5%), 8.3 (11%), 9.3 (74.5%), and 10.0 min (3%). The major component was isolated by preparative VPC (SE-30, 201 °C), then evaporatively distilled at 70–80 °C (3–5 μ) to afford 13 mg (59% yield) of hydrocarbon **22** as colorless needles, mp 45.0–46.5 °C.

Anal. ($C_{17}H_{30}$) C, H.

4bβ,8,10aβ-Trimethyl-1-ethylenedioxy-7-hydroxy-Δ⁴,⁸-decahydrophenanthrene (24). A suspension of 0.546 g (14.4 mmol) of lithium aluminum hydride in 12 ml of anhydrous ether was stirred under nitrogen while 3.00 g (9.94 mmol) of the keto ketal **23,**[11] mp 73.0–74.5 °C (prepared by K. Schmiegel), in 24 ml of anhydrous ether was added over a period of 10 min. The addition funnel was rinsed with 3 ml of ether and the mixture was stirred at room temperature for 4 h. The mixture was cooled to 0 °C and the excess hydride was decomposed with 2 ml of 10% sodium hydroxide solution, then an additional 35 ml of the base was added to dissolve the aluminum salts. The crude product was isolated by extraction with 1:1 benzene–ether (3 × 50 ml) and benzene (100 ml),[18] and then recrystallized from pentane to give 2.81 g (93% yield) of alcohol **24** as colorless prisms, mp 130–140 °C: ir λ_{max} (CCl_4) 2.9 μ (OH); NMR 14:86 peak ratio of two singlets at 1.24 and 1.32 (3 H, angular CH_3), 1.44 (s, 3 H, angular CH_3), two singlets at 1.73 and 1.78 (3 H, vinyl CH_3), 3.99 (s 4 H, ketal methylenes), and 5.49 ppm (m, 1 H, vinyl proton). A comparable sample, mp 130–139 °C, from another run was recrystallized several times from pentane to give colorless prisms, mp 138–139 °C.

Anal. ($C_{19}H_{28}O_3$) C, H.

4bβ,8,10aβ-Trimethyl-1-ethylenedioxy-7-acetoxy-Δ⁴,⁸-decahydrophenanthrene (25). A mixture of 2.77 g (9.10 mmol) of the hydroxy ketal **24,** mp 130–140 °C, 36 ml of anhydrous pyridine, and 27 ml of acetic anhydride was stirred at room temperature under nitrogen for 24 h. The solvent was removed at reduced pressure (0.05 mm) to give a yellow-orange oil which, upon crystallization from pentane–ether, afforded 1.82 g (58% yield) of ketal acetate **25** as colorless prisms, mp 109–110 °C: ir λ_{max} (CCl_4) 5.75 μ (ester C=O); NMR ($CDCl_3$) 1.33 (s, 3 H, angular CH_3), 1.42 (s, 3 H, angular CH_3), 1.57 (s, 3 H, vinyl CH_3), 2.06 (s, 3 H, acetate CH_3), 3.96 (s, 4 H, ketal methylenes), 5.25 (m, 1 H, C-7 proton), and 5.48 ppm (m, 1 H, vinyl proton).

Anal. ($C_{21}H_{30}O_4$) C, H.

The mother liquors from the above crystallization afforded a further 0.57 g (76% total yield) of crystalline acetate **25,** mp 108–110 °C.

4bβ,8,10aβ-Trimethyl-1-ethylenedioxy-Δ^{4,8}-decahydrophenanthrene (26). A modification of a published procedure[12] was employed. A solution of 1.705 g (4.92 mmol) of the allylic acetate **25**, mp 109–110 °C, in 125 ml of anhydrous ethylamine was cooled in a dry ice–isopropyl alcohol bath while 0.377 g (54.7 mmol) of lithium wire was added with vigorous stirring. The cooling bath was removed and stirring was continued until a dark blue color persisted. The mixture was recooled and poured into 200 ml of 1:1 benzene–ether; then the excess lithium was destroyed by the addition of ammonium chloride. The resultant mixture was diluted with 20 ml of water and extracted with benzene[18] to afford a white semisolid which appeared to be a mixture of the desired ketal **26** (R_f 0.60) and the allylic alcohol **24** (R_f 0.09) by TLC (7:3 pentane–ether). Chromatography on 40 g of neutral alumina (9:1 petroleum ether–ether) followed by recrystallization from pentane yielded 0.898 g (63% yield) of ketal **26** as colorless crystals, mp 86.5–89.0 °C. A second crop of 0.271 g (82% total yield) of **26**, mp 70–85 °C, was obtained from the mother liquors. An analytical sample was prepared from 8 mg of comparable material, mp 86.5–89.0 °C, by recrystallization from pentane to give 6 mg of colorless crystals, mp 89–90 °C: NMR 1.22 (s, 3 H, angular CH_3), 1.35 (s, 3 H, angular CH_3), 1.60 (s, 3 H, vinyl CH_3), 3.86 (s, 4 H, ketal methylenes), and 5.37 ppm (m, 1 H, vinyl proton).

Anal. ($C_{19}H_{28}O_2$) C, H.

4bβ,8,10aβ-Trimethyl-1-keto-Δ^{4,8}-decahydrophenanthrene (27). A mixture of 0.890 g (3.1 mmol) of the ketal **26**, mp 86.5–89.0 °C, 47 ml of acetone, and 10 ml of 10% hydrochloric acid solution was heated at reflux under nitrogen for 2 h. The mixture was diluted with 35 ml of water and extracted with ether.[18] The crude product was chromatographed on 30 g of Merck acid-washed alumina (9:1 petroleum ether–ether) to yield 0.679 g (90% yield) of ketone **27** as colorless crystals, mp 37–39 °C. A portion of comparable material from another experiment was evaporatively distilled at 100 °C (3 μ) to afford a >99% recovery of crystalline material, mp 37–39 °C, which appeared to be a mixture of the desired ketone and two impurities with retention times of 7.5 (94%), 6.5 (4%), and 8.5 min (2%) by VPC (SE-30, 200 °C). Recrystallization from methanol afforded an analytical sample of ketone **27** as colorless plates, mp 43–44 °C, which appeared uncontaminated on VPC: ir λ_{max} (CCl_4) 5.85 μ (C=O); NMR 1.30 (s, 3 H, angular CH_3), 1.35 (s, 3 H, angular CH_3), 1.57 (s, 3 H, vinyl CH_3), and 5.86 ppm (m, 1 H, vinyl proton).

Anal. ($C_{17}H_{24}O$) C, H.

The **2,4-dinitrophenylhydrazone** was obtained as yellow-orange plates, mp 141.5–142.5 °C, after one recrystallization from 95% ethanol–ethyl acetate.

Anal ($C_{23}H_{28}N_4O_4$) C, H, N.

4bβ,8,10aβ-Trimethyl-Δ^{4,8}-decahydrophenanthrene (28). A modification of a reported procedure[13] was employed. A mixture of 621 mg (2.54 mmol) of ketone **27**, mp 37–39 °C, 738 mg of powdered potassium hydroxide (85% minimal purity), 9.5 ml of triethylene glycol, and 1.4 ml of anhydrous hydrazine was heated at 105–115 °C under nitrogen for 2 h in a flask fitted with a short-path condenser. The pot temperature was raised to 190–210 °C and maintained at this temperature for 4 h. The mixture was cooled to room temperature and the combined contents of the pot and receiver were diluted with 30 ml of water. Extraction with ether[18] followed by chromatography on 25 g of Merck acid-washed alumina (pentane) afforded 563 mg of colorless oil which exhibited three peaks with retention times of 7.3 (3%), 8.5 (93%), and 9.5 min (4%) on VPC (SE-30, 175 °C). Isolation of the major component by preparative VPC (SE-30, 225 °C) followed by evaporative distillation at 100 °C (5 μ) gave 352 mg (60% yield) of diene **28** as fine colorless needles, mp 38–39 °C. A sample of comparable material, mp 38–39 °C, from another run was submitted for combustion analysis: NMR 1.20 (s, 3 H, angular CH_3), 1.36 (s, 3 H, angular CH_3), 1.60 (s, 3 H, vinyl CH_3), and 5.45 ppm (t, J = 4.5 Hz, 1 H, vinyl proton).

Anal. ($C_{17}H_{26}$) C, H.

The low retention time component of the crude product was also isolated and evaporatively distilled. The NMR spectrum exhibited absorptions for two vinyl protons as two overlapping multiplets from 5.23 to 5.50 ppm, indicating it to be the Δ^7-double bond isomer of **28**. The vinyl methyl absorption appeared at 1.63 ppm, and the two angular methyl signals appeared at 1.12 and 1.20 ppm.

4bβ,8β,10aβ-Trimethyl-4aα,8aα-perhydrophenanthrene (22). A mixture of 260 mg (1.13 mmol) of the diene **28**, mp 38–39 °C, 100 mg of platinum dioxide, and 20 ml of acetic acid (distilled from chromium trioxide) was stirred under hydrogen at room temperature for 17 h. The mixture was filtered and the acetic acid was removed at reduced pressure (14 mm) to afford 246 mg of colorless oil which appeared to be a mixture of four components with retention times of 7.0 (5.5%), 7.6 (2.4%), 9.0 (25.6%), and 10.0 min (66.5%) on VPC (SE-30, 180 °C). The major component was isolated by preparative VPC (SE-30, 220 °C), then evaporatively distilled at 100 °C (7 μ) to give 158 mg (60% yield) of the hydrocarbon **22** as colorless needles, mp 44–47 °C, which appeared to be 94% pure on VPC (Carbowax, 203 °C): NMR 0.77 (s, 3 H, angular CH_3), 0.88 (d, J = 7.5 Hz, 3 H, C-8 CH_3), and 0.92 ppm (s, 3 H, angular CH_3).

Anal. ($C_{17}H_{30}$) C, H.

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Registry No.—**5**, 60562-27-8; **7**, 59323-55-6; **8**, 19788-88-6; **9**, 60525-77-1; **10**, 60525-78-2; **10** β,γ isomer, 60525-79-3; **10** 2,4-DNPH, 60525-80-6; **11**, 60525-81-7; **11** free acid, 60525-82-8; **12**, 60525-83-9; **13**, 60525-84-0; **14**, 60525-85-1; **15**, 60525-86-2; **16**, 60746-45-4; **17**, 60525-88-4; **18**, 60525-89-5; **19**, 60525-90-8; **20**, 60525-91-9; **21**, 60525-92-0; **21** 2,4-DNPH, 60525-93-1; **22**, 60525-94-2; **23**, 60525-95-3; **24**, 60525-96-4; **25**, 60525-97-5; **26**, 60525-98-6; **27**, 60525-99-7; **27** 2,4-DNPH, 60526-00-3; **28**, 60526-01-4; acetic acid, 64-19-7; formic acid, 64-18-6.

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Reaction of Alkylhydrazines. 3. Reaction of Methylhydrazine and 1,1-Dimethylhydrazine with *cis*- and *trans*-Cyclohexane-1,2-dicarboxylic Anhydrides. Products and Reaction Sequence[1,2]

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The reaction of methylhydrazine (1) and 1,1-dimethylhydrazine (2) with the *cis*- and *trans*-cyclohexanedicarboxylic anhydrides (3 and 4, respectively) under controlled conditions has provided a series of hydrazine-containing compounds with potential significance for medicinal chemistry.[3] The single crystal x-ray and spectral analyses of the products enabled us to elucidate the pathways involved in these reactions. A possible applicability of the chemistry of the reactions to analogous systems is envisaged.

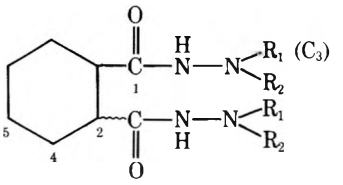
Results and Discussion

At room temperature the reaction of equimolar quantities of 1 and 3 afforded a 70:30 mixture of *cis*-*N*-methylaminocyclohexane-1,2-dicarboximide (**6**) and *cis*-2-methylcyclohexa[*d*]pyridazine-1,4-dione (**8**) (Scheme I). These products were separated by differential solubility and their structures were determined by ir, NMR, and MS spectrometries and microanalyses (data in Table II). The configuration of **6** was determined by a single crystal x-ray analysis[4] and **8** by a spectral comparison with its isomer, **9**, established by x-ray analysis to be trans.[4]

Heating **3** with excess 1 gave as an end product cyclohexane-1,2-bis(2-methylcarbohydrazide) (**10**) which proved to be trans by comparison of its ^{13}C NMR spectrum (Table I) with that of the tetramethyl analogue, **20**, a trans configuration according to the x-ray analysis.[5] The sequence of the reaction of **3** with 1 was determined by carefully monitoring the formation of the reaction intermediates at 5-min intervals by using thin layer chromatography, followed by a workup on the samples of interest. The structure elucidation was carried out by comparison of the spectra of each compound with those prepared under predetermined conditions and structurally established.

The first compound in the reaction sequence was assumed to be the methylhydrazinium salt or half acid-hydrazide (**5**), similar to its structurally identified analogues **17b** (vide infra). A rapid rate of cyclization of **5** to **6** did not permit its isolation. Treatment of **6** with 1 gave **7**, detected by TLC as a very unstable species in the hot reaction medium, but stable enough for isolation from the reaction at room temperature. The structure and configuration of **7** were proven by elemental analysis and comparison of its spectral data with those of **10**.

Table I. ^{13}C Chemical Shifts,[a] ppm



$R_1 = CH_3$; $R_2 = H$ (**10**)

$R_1 = R_2 = CH_3$ (**14**, **20**)

Compd	C_1	C_2	C_3	C_4	C_5
10	175.812	45.356	38.202	29.357	25.065
14	174.382	46.786	42.429	26.691	23.179
20	174.899	46.979	45.548	29.550	25.258

[a] Chemical shift reference, Me_4Si; solvent, D_2O.

Scheme I

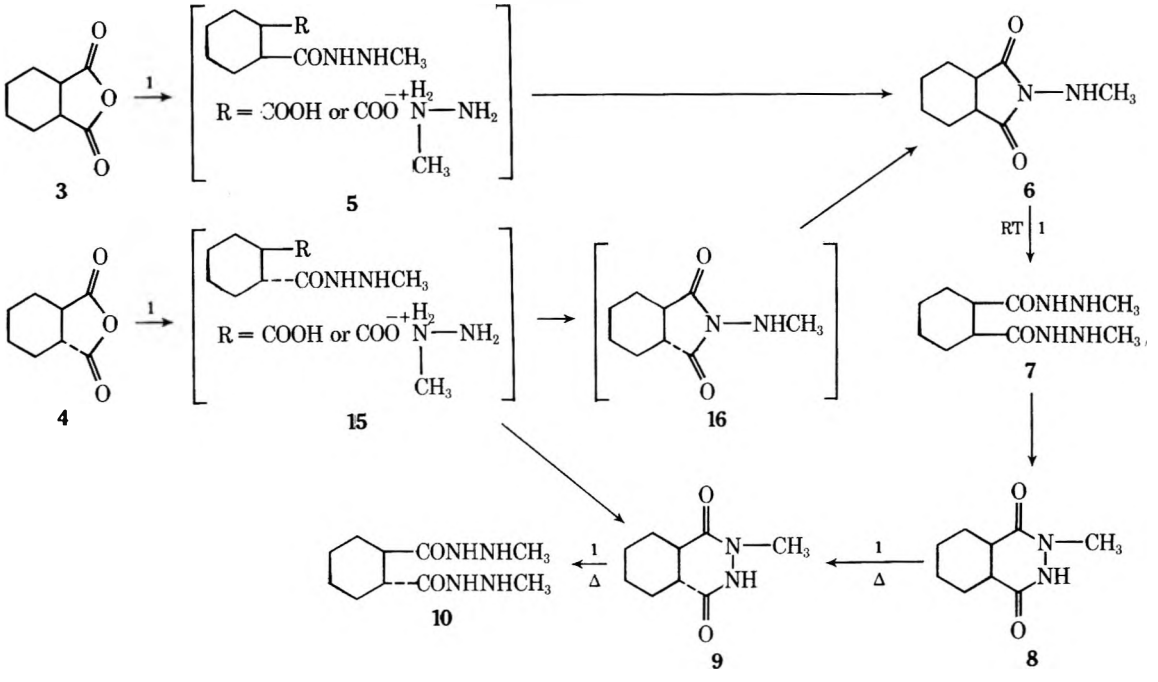


Table II.[a] Physical Properties of the Products

Compd	Yield,[b] %	Crystn solvent	Mp, °C	Ir (KBr), cm^{-1} C=O	Ir (KBr), cm^{-1} NH	NMR, δ, ppm (TFA–TPP) CH_3	NMR, δ, ppm (TFA–TPP) C_6H_{10}
6	60[c] 20[d]	C_7H_{16}–CH_3OH	94–95	1690 1770	3270	3.30 (s)	1.35–3.45 (m)
7[e]	50		116–120	1635	3250	3.18 (s)	1.33–3.23 (m)
8	20[c] 10[d]	C_6H_6–CH_3OH	171–172	1650	3200	3.40 (s)	1.30–3.25 (m)
9	64	C_6H_6–CH_3OH	226–227	1660	3200	3.35 (s)	1.00–2.70 (m)
10	81[c] 87[d]	C_6H_6–CH_3OH	239–240	1640	3280	3.25 (s)	1.15–3.05 (m)
12[g]	77		185–187	1545 1650		3.40 (s) 2.93[f] (t)	1.30–2.67 (m)
13	95[c] 30[d]	C_7H_{16}	69–70	1720 1770		3.63 (s)	1.30–3.35 (m)
14	80	C_6H_6–CH_3OH	194–195	1655	3210	3.40 (s)	1.40–3.15 (m)
17a	75	C_6H_6–CH_3OH	118–120	1710 1650	3250	3.40 (s)	1.20–3.0 (m)
17b[g]	97		121–124	1540 1640	3200	3.40 (s) 3.23 (s)	1.10–3.10 (m)
19	8	C_7H_{16}–$CH_3COOC_2H_5$	137–138	1660		3.65 (s)	1.20–3.50 (m)
20	40	C_6H_6–CH_3OH	258–260	1670	3220	3.28 (s)	1.10–2.95 (m)

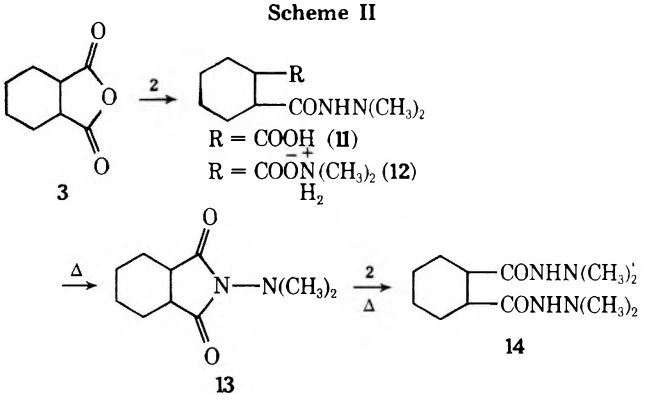
[a] Satisfactory analytical data (± 0.4% for C, H, N) were reported for all the compounds in this table. Compounds **12** and **17b** were not analyzed. [b] Partially purified product with melting point lower than that of the analytical samples. [c] Percent yield from the cis anhydride, **3**. [d] Percent yield from the trans anhydride, **4**. [e] Due to the lack of stability, **7** could not be crystallized. The sample for analysis was washed with dry ether. [f] The triplet in the NMR spectrum of **12** results from $H_2N^+(CH_3)_2$. The dimethylhydrazinium salt $H_2NN^+H(CH_3)_2$ moiety of **17b** gives only a singlet at δ 3.23. [g] The organic salts **12** and **17b** were not amenable to crystallization. The lack of broad melting range after washing with ether was indicative of the reasonable purity of the compounds.

In solution at room temperature **7** was slowly transformed to **8**. This rate was increased significantly at the elevated temperature.

The rapid rate of formation of **6** in the course of the reaction of **3** with **1** (TLC detected), as well as transformation of a pure sample of **6** to **8** (via **7**) in the presence of **1**, seemed to indicate the lack of direct formation of **8** from **5**. In contrast, the equimolar reaction of the trans anhydride, **4**, with **1** (Scheme I) provided a 25:10:60 mixture of **6**, **8**, and **9** with **9** resulting directly from **15**. Apparently the reaction intermediate, **15**, may cyclize both by the reaction of N_2 and N_1 of the hydrazide moiety with carboxylic C=O to give respectively a relatively stable *trans*-cyclohexapyridazine (**9**) and a relatively unstable trans imide, **16**, which isomerized to **6**, the precursor of **8**. Upon heating with **1**, **8** was isomerized to **9** which was then converted to **10**. The failure of **8** to isomerize to **9** in the presence of triethylamine, pyridine, or piperidine indicated that a base with the strength of **1** is apparently necessary for pulling off the methine proton from **8** to effect isomerization.

The course of the reaction of **3** with **2** (Scheme II) differed

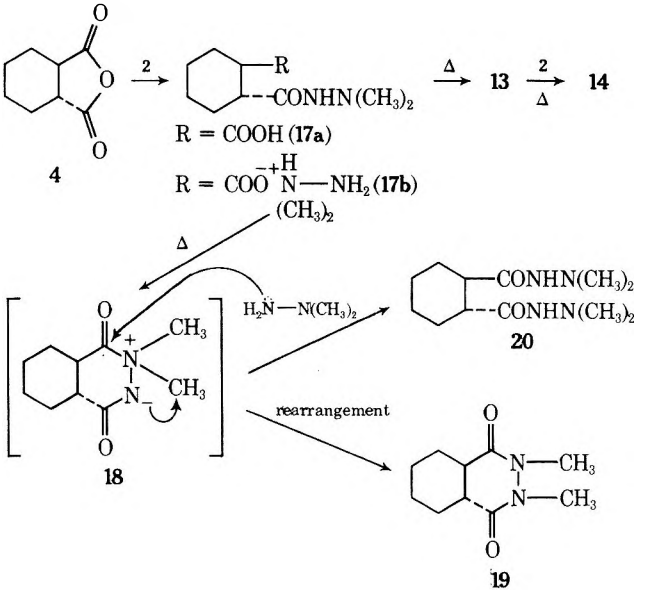
Scheme II



in two ways from that of **3** with **1**. First, the dimethylammonium salt[6] (**12**) of the half acid-hydrazide (**11**), unlike that of **5**, was amenable to purification and upon heating gave **13**. Second, heating **13** with **2** gave only a cis dihydrazide, **14**. This was probably due to the resistance of **14** to undergo cyclization like **7** to **8**, the precursors of **10**. The configuration of the imide, **13**, was assumed to be cis analogous to that of **6**, the only imide obtained from the reaction of both cis and trans anhydrides with **1**.

When the anhydride **4** was treated with **2** (Scheme III), both

Scheme III



the half acid-hydrazide (**17a**) and its dimethylhydrazinium salt[5] (**17b**) were isolated and characterized (Table II). Heating **17a** or **17b** with **2** gave a mixture of **13**, **19**, and **20** in the ratio of 30:10:50.

Similar to the reaction of **4** with **1**, **17a** in part cyclizes to the unstable trans imide whose isomerization affords **13**, the precursor of **14**. Cyclization of **17a** by the attack of N_2 of the hydrazide on C=O gives the inner salt, **18**. Rearrangement of **18** gives **19** or its reaction with **2** gives **20**.

Elucidation of the pathways in the reactions of the cyclohexane-1,2-dicarboxylic anhydrides with methylhydrazine and 1,1-dimethylhydrazine seems to possess general applicability. The scope and limitation of the hydrazine–anhydride reactions are being investigated in our laboratory.

Experimental Section

Melting points, uncorrected, were determined on a Thomas-Hoover apparatus using open capillaries. Infrared spectra were recorded on a Beckman IR-8, using KBr disks for the solid compounds and smears on sodium chloride for the semisolid and liquid compounds. Only the bands for C=O and NH stretching frequencies in wavenumber ν_{max} (cm^{-1}) were reported. ^1H NMR spectra were determined on a JEOL C-60 HL and R-12 using trifluoroacetic acid (TFA) as a solvent and sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate (TTP) as a reference. ^{13}C NMR spectra were determined on a Bruker WH-90 using D_2O as a solvent and Me_4Si as reference. The mass spectra were measured on a Du Pont 21-491 instrument. The thin layer chromatography was done on microscope slides coated with silica gel HF 254 + 366 (Brinkmann Instruments, Inc.). All evaporations were carried out in vacuo in a rotatory evaporator. The elemental analyses were done by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y. The single crystal x-ray analysis was done on a Syntex P_{21} diffractometer.

The following two experimental procedures exemplify the general method of synthesis of the compounds derived from *cis*- and *trans*-cyclohexane-1,2-dicarboxylic anhydrides.

Reaction of Methylhydrazine (1) with *cis*-Cyclohexane-1,2-dicarboxylic Anhydride (3). A mixture of 5.0 g (0.038 mol) of **3** and 1.75 g (0.038 mol) of **1** was left at room temperature for 24 h at which time the reaction was complete, determined by using TLC. The semisolid residue was washedseveral times with cold CCl_4 and dried to give 5.50 g (80%) of a mixture of **6** and **8** with a ratio of 70:30 (estimated from the NMR spectrum of the mixture). The imide **6** dissolved out of the mixture by using hot CCl_4. The sample of **6** for analysis was crystallized from a mixture of heptane and MeOH. The CCl_4-insoluble residue, **8**, was crystallized from a mixture of benzene and MeOH.

Reaction of 1,1-Dimethylhydrazine (2) with *trans*-Cyclohexane-1,2-dicarboxylic Anhydride (4). A mixture of 5.0 g (0.038 mol) of **4** and 5.40 g (0.09 mol) of **2** was heated under reflux for 12 h at which time the reaction was complete, determined by using TLC. The excess **2** was evaporated. The product was dried to give 7.50 g of a mixture of **13**, **19**, and **20** in the approximate ratio of 30:10:50, determined from the NMR spectrum. This mixture was heated in three successive 75-ml portions of CCl_4. The residue was filtered and dried to give 3.25 g (40%) of **20**. The combined filtrates were evaporated to dryness. This solid was heated in three successive 75-ml portions of heptane. The heptane-insoluble residue was dried to give 0.6 g (8%) of **19**. Evaporation of the combined filtrates, followed by washing and drying of the residue, afforded 2.25 g (30%) of **13**.

Acknowledgments. The authors wish to thank Dr. Dale Maness and Dr. Stephen Martin of the University of Texas for valuable suggestions in preparing this manuscript.

Registry No.—**1**, 60-34-4; **2**, 57-14-7; **3**, 13149-00-3; **4**, 14166-21-3; **6**, 18886-75-4; **7**, 60498-47-7; **8**, 60498-48-8; **9**, 60498-49-9; **10**, 60498-50-2; **12**, 60498-52-4; **13**, 18836-73-2; **14**, 60498-53-5; **17a**, 60498-54-6; **17b**, 60498-55-7; **19**, 60387-17-9; **20**, 60498-56-8.

References and Notes

(1) For the previous paper in this series, see J. Nematollahi, S. Kasina, and D. Maness, *J. Heterocycl. Chem.*, **11**, 351 (1974).
(2) Support of this investigation by the University of Texas Research Institute is gratefully acknowledged.
(3) There are a number of currently employed chemotherapeutic compounds with hydrazine moieties and imide structures. Tuberculostatic isonicotinic acid hydrazide, anticonvulsant substituted succinimides, and antihypertensive 1-hydrazinophthalazine may be cited as examples. Additionally, we are planning to employ some of our bicyclic compounds for azasteroids synthesis.
(4) S. Simonsen, R. Loghry, J. Nematollahi, and S. Kasina, *J. Heterocycl. Chem.*, **13**, 936 (1976).
(5) S. Simonsen and J. Nematollahi, unpublished results.
(6) We have observed that a homogeneous mixture of 1,1-dimethylhydrazinium salt of a carboxylic acid and 1,1-dimethylhydrazine gives dimethylammonium salt (see also ref 1). The absence of such species in the reaction of **4** with **2** is due to the precipitation of the hydrazinium salt, **17b**, from the reaction mixture.

A Unique Rearrangement of 3,4-Dihydro-5*H*-1,3,4-benzotriazepin-5-ones to 3-Methylamino-4(3*H*)-quinazolinones[1]

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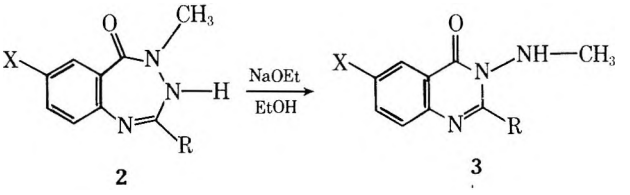
Received July 1, 1976

Ring contractions of benzo-fused seven-membered heterocyclics are well known in the literature and the field has recently been reviewed.[2] The majority of these rearrangements involve 1,4-benzodiazepines being converted to quinazolinones and quinoxalines but there are additional examples involving 1,5-benzodiazepines, various benzoxazepines, and benzothiazepines. However, with the exception of a photocatalyzed contraction of 3,1,4-benzoxadiazepines and an acid-induced rearrangement of 1,2,5-benzotriazepines, there have been very few studies on three heteroatom seven-membered systems.[3,4]

Recently we reported the synthesis of 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**2a–g**) by the reaction of anthranilhydrazides[5] (**1**) and ortho esters.[6] We have found these benzotriazepines to be extremely labile to alkoxide-induced ring contraction to 3-methylamino-4(3*H*)-quinazolinones (**3a–g**) (Scheme I).

Scheme I



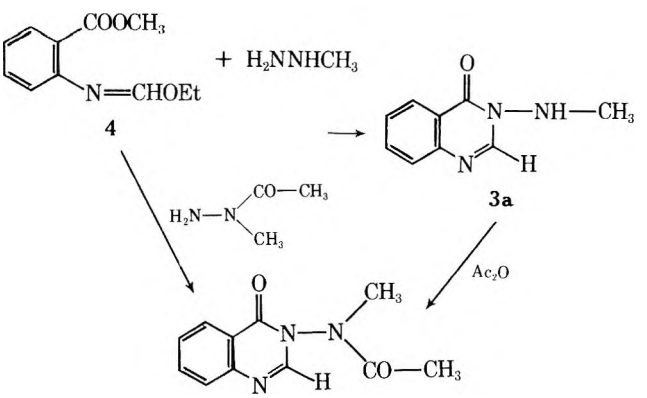
2 **3**

The latter products were identified by unique features of their ^1H NMR spectra, for example, an *N*-methyl doublet at δ 2.47–2.85 and a mutually coupled NH quartet at δ 6.17–6.38. Both of these resonances were considerably more shielded than the corresponding groups in the initial benzotriazepine, e.g., in **2a** the *N*-methyl appeared as a singlet at δ 3.22 and the NH as a doublet (coupled to C_2 H) at δ 8.65.

Upfield shifts for both the *N*-methyl and the NH resonances would be in accord with their rearrangement into loci no longer α to the deshielding influences of the nodal planes of the C=O and the N_1–C_2 double bond in **2a–g**. Furthermore, the presence of a newly formed $-NHCH_3$ moiety in the product is evidenced by the observed splittings.

Additional support for the assignment of the rearrangement products as 3-methylamino-4(3*H*)-quinazolinones was provided by alternative syntheses (Scheme II). Methyl 2-eth-

Scheme II



5

Table I. 3-Methylamino-4(3*H*)-quinazolinones[a]

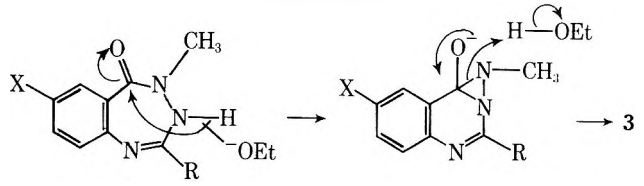
Registry no.	Compd	X	R	Yield, %	Mp, °C	Formula
60512-86-9	**3a**	H	H	50	108–109	$C_9H_9N_3O$
59169-44-7	**3b**	H	CH_3	95	111.5–112.0	$C_{10}H_{11}N_3O$
60512-87-0	**3c**	Cl	H	72	151–152	$C_9H_8ClN_3O$
60512-88-1	**3d**	NO_2	H	59	193–195	$C_9H_8N_4O_3$
60512-89-2	**3e**	Cl	CH_3	93	132–133	$C_{10}H_{10}ClN_3O$
60512-90-5	**3f**	Cl	C_6H_5	86	100.5–101.0	$C_{15}H_{12}ClN_3O$
60512-91-6	**3g**	Cl	C_2H_5	94	154–155	$C_{11}H_{12}ClN_3O$

[a] Analytical data were within ±0.3% for C, H, N. Ed.

oxymethyleneiminobenzoate[6] (**4**) upon condensation with methylhydrazine yielded **3a**, identical in all respects with the material obtained from the rearrangement of **2a**. In addition, treatment of **4** with 1-acetyl-1-methylhydrazine gave **5**, which was also obtained by acetylation of **3a**.

One plausible mechanism for this ring contraction is depicted in Scheme III. Base extraction of the N_2H proton would

Scheme III



lead to a resonance stabilized anion whose transannular attack on the carbonyl could give a diaziridine intermediate. Ring opening of the latter would produce the 3-methylaminoquinazolinones.

Experimental Section

Infrared spectra of solids were obtained in KBr disks and of liquids as thin films between NaCl plates on a Beckman IR-33 spectrophotometer. The ^1H NMR spectra were obtained on a Hitachi Perkin-Elmer R20A nuclear magnetic resonance spectrometer. Combustion analyses were provided by Dr. George I. Robertson, Florham Park, N.J.

A General Procedure for Rearrangement of 3,4-Dihydro-5*H*-1,3,4-benzotriazepin-5-ones (2a–g) to 3-Methylamino-4(3*H*)-quinazolinones (3a–g). A solution of 50 mmol of the requisite benzotriazepine (**2a–g**) in 50 ml of anhydrous ethanol was treated with a freshly prepared solution of 5.0 mmol of NaOEt in 25 ml of absolute ethanol (obtained by dissolution of 0.12 g of sodium in the 25 ml of alcohol). The deep red solution which resulted was heated with stirring at reflux for 20 h, chilled, and filtered in vacuo. The resulting 3-methylamino-4(3*H*)-quinazolinones were recrystallized from ethanol to analytical purity. The nitro isomer (**3d**) was recrystallized from 3:1 acetic acid–ethanol. Yields and properties are reported in Table I.

3-Methylamino-4(3*H*)-quinazolinone (3a) from Methyl 2-Ethoxymethyleneiminobenzoate (4). Methyl 2-ethoxymethyleneiminobenzoate[6] (**4**, 10.36 g, 50.0 mmol) was treated with 3.00 g (6.0 mmol) of methylhydrazine. Two minutes after the addition, evolution of considerable heat was noted and the product **3a** began to precipitate. The reaction mixture was chilled in an ice bath and the solid collected on a filter and washed with ether. Analytically pure, white crystals of the quinazolinone (8.00 g, 92%) were collected: mp 109–110.5 °C; ir (KBr) 3230 (N–H), 1675 (C=O), and 1650 cm^{-1} (C=N); NMR ($CDCl_3$) δ 2.89 (s, 3, CH_3), 5.97 (s, 1, NH), 7.20–8.30 (m, 5, ArH and C_2 H). The compound was spectrally identical (^1H NMR and ir), of identical melting point, and of undepressed mixture melting point with the material obtained by rearrangement of **2a**.

3-(*N*-Acetyl-*N*-methylamino)-4(3*H*)-quinazolinone (5) from Methyl 2-Ethoxymethyleneiminobenzoate (4). A solution was prepared from 50.0 mmol of **4** and 1-acetyl-1-methylhydrazine.[7] Immediately it developed a deep red color and precipitated the product quinazolinone (**5**). The mixture was chilled in ice, and the solid was filtered, washed with ether, and recrystallized twice from ethanol to yield 6.40 g (59%) of **5**: mp 119–120 °C; ir (KBr) 1690 (C=O), 1675 (C=O), and 1650 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.97 and 2.36 (s, 3, $COCH_3$), 3.40 and 3.59 (s, 3, NCH_3),[8] and 7.30–8.50 (m, 5, ArH and C_2 H).

Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 61.01; H, 5.08; N, 19.17.

Acetylation of 3-Methylamino-4(3*H*)-quinazoline. Preparation of 5. A mixture of 0.10 mol of acetic anhydride and 0.048 mol of **3a** was stirred and heated at reflux for 2 h and cooled to room temperature, and the excess acetic anhydride was removed on a rotary evaporator. The viscous, amber oil which resulted was induced to crystallize by trituration with a small quantity of ether. The crude product was recrystallized from ethanol to give 8.05 g (78%) of analytically pure **5**, mp 120–121 °C, identical in all respects with the material obtained by condensation of **4** and 1-acetyl-1-methylhydrazine.

Acknowledgments. This work was supported by a contract from Stuart Pharmaceuticals, Division of ICI United States Inc., to N.D.H., and was abstracted in part from the Ph.D. Thesis of R.W.L. (Lehigh University, 1975).

Registry No.—**2a**, 59169-76-5; **2b**, 59169-80-1; **2c**, 59169-77-6; **2d**, 59169-79-8; **2e**, 59169-81-2; **2f**, 59169-88-9; **2g**, 59169-84-5; **4**, 59204-51-2; **5**, 60512-92-7; methylhydrazine, 60-34-4; 1-acetyl-1-methylhydrazine, 3530-13-0.

References and Notes

(1) Presented at the 172d National Meeting of the American Chemical Society, Organic Chemistry Division, San Francisco, Calif., Aug. 30, 1976.
(2) H. C. Van Der Plas, "Ring Transformations of Heterocycles", Vol. 2, Academic Press, New York, N.Y., 1973, pp 282–321.
(3) W. Metlesics, G. Silverman, and L. H. Sternbach, *Monatsh. Chem.*, **98**, 633 (1967).
(4) S. Rissi, O. Pirola, and F. Selva, *Tetrahedron*, **24**, 6395 (1968).
(5) R. W. Leiby and N. D. Heindel, *Synth. Commun.*, **6**, 295 (1976).
(6) R. W. Leiby and N. D. Heindel, *J. Org. Chem.*, **41**, 2736 (1976).
(7) R. L. Hinman and D. Fulton, *J. Am. Chem. Soc.*, **80**, 1895 (1958).
(8) As another example of the slow rotation of bulky groups around the N_3 quinazolinone nitrogen [see J. B. Taylor, D. R. Harrison, and F. Fried, *J. Heterocycl. Chem.*, **9**, 1227 (1972)], the *N*-methyl and the acetyl methyl resonances were evidenced as two temperature-dependent double peaks in the ratio of 2:1 at room temperature.

Acidity Functions of Hydrochloric Acid, Perchloric Acid, and Sulfuric Acid and pK_a Values of Some Primary Aromatic Amines in 50% Volume/Volume Aqueous Ethanol[1]

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The general applicability of the Hammett acidity function has been strongly questioned.[2] In spite of this, this parameter still remains the principal measure of the ability of a medium to transfer a proton to a base. In fact many treatments of deviations from Hammett acidity function behavior are expressed in terms of the acidity function.[3] The original deter-

Table I. Physical Properties of Indicators

Aniline	Recrystn solvent[a]	Mp, °C Obsd	Mp, °C Lit.	Absorption max nm[b]	ϵ_B[c]	ϵ_{BH}[d]	$\Delta\lambda$[e]	pK_a[f]	Registry no.
3-NO_2, 4-CH_3	1:5	77.0–78.0	78[g]	361	1460	187		1.91	119-32-4
3-NO_2	1:3	112.0–112.8	112.6[h]	366	1300	62		1.35	99-09-2
3-NO_2, 4-Cl	1:3	102.5–103.5	102.7[i]	363	1180	152	+2	0.63	635-22-3
4-NO_2	1:2	146.0–147.0	147.2[j]	383	15 100	58	+3	−0.19	100-01-6
2-Cl, 5-NO_2	1:3	118.5–119.5	118.5[i]	368	2070	91	+2	−0.88	6283-25-6
2-NO_2	1:9	71.8–72.5	71.6–72.4[k]	415	4900	10	+2	−1.63	88-74-4
2-NO_2, 4-Cl	1:1	115.0–115.5	116.1–116.4[k]	423	4810	19	+3	−2.46	89-63-4
2,5-Cl_2, 4-NO_2	EtOH	153.5–154.0	153–154[l]	367	10 400	159	+4	−3.21	6627-34-5

[a] Ratio designates volume proportions of benzene and cyclohexane in solvent, EtOH = ethanol. [b] Absorption maximum in 50% v/v aqueous ethanol and at lowest percent protonation in acid solution. [c] Extinction coefficient of free base in 50% v/v aqueous ethanol. [d] Extinction coefficient of substituted anilinium ion at absorption maximum of free base measured in solution of $H_0 < pK_a - 2$. [e] Change in absorption maximum of free base over protonation range of 10% to 90%. [f] Average of pK_a values in HCl, $HClO_4$, and H_2SO_4 obtained by stepwise comparison and extrapolation (see Table II). [g] R. A. Morton and A. McGookin, *J. Chem. Soc.*, 901 (1934). [h] P. Putzeys and J. Brosteaux, *Ann. Soc. Sci. Bruxelles*, **53B**, 118 (1933). [i] M. A. F. Lobry de Bruyn, *Recl. Trav. Chim. Pays-Bas*, **36**, 126 (1917). [j] F. P. Zschiele and J. W. White, *Ind. Eng. Chem., Anal. Ed.*, **12**, 436 (1940). [k] L. C. Smith and L. P. Hammett, *J. Am. Chem. Soc.*, **67**, 23 (1945). [l] N. S. F. Berckmans and A. F. Holleman, *Recl. Trav. Chim. Pays-Bas*, **44**, 851 (1925).

minations of H_0 applied to aqueous acid solutions. This limited the usefulness of H_0 to some degree because of the problem of solubility of organic compounds in water. However, during the past 15 years an increasing number of acidity functions have been defined for nonaqueous or mixed organic–aqueous systems. Unfortunately, many of these have utilized solvents of low polarity in which ion association may become important or solvents with compounds of very different dielectric constant so that solvent segregation might occur. In addition, these H_0 values have been referred to an ideal solution in water as standard state, rather than to an ideal solution in the solvent used.

In the course of an investigation of an acid-catalyzed reaction, solubility problems were encountered. An equal-volume mixture of ethanol and water was chosen as the solvent because (1) it had the needed solvent properties, (2) the two components have about the same volatilities, (3) ethanol and water are "similar" protic solvents with respectable dielectric constants, (4) the two substances are readily available in pure form and are relatively inexpensive, and (5) the mixture is simply and easily prepared. Since acidity function scales for 50% v/v aqueous ethanol referred to the ideal solution in the same medium and employing primary amines[4] throughout as indicators to ensure similar activity coefficient behavior had not been previously determined, it was necessary to do this.

Experimental Section

Purification of Indicators. The various primary amines used in this study were available from the Aldrich Chemical Co. They were purified by initial crystallization from the solvent indicated in Table I followed by chromatography on alumina using ether as eluent and then two further recrystallizations. Physical properties are summarized in Table I.

Preparation of Acid Solutions. Concentrated sulfuric acid, concentrated hydrochloric acid, and 70% perchloric acid were titrated to determine their acid content. Their densities (at 30 °C) were estimated by pycnometer. From these measurements, the amount of water present in each acid was calculated. Then, enough 100% alcohol and water were added to make stock solutions containing 50% v/v water–ethanol. Aliquots of these stock solutions were diluted with 50% v/v water–ethanol to provide series of acid solutions differing in H_0 by 0.2 units or less. The concentrations of these diluted solutions were determined by titration and differed from the concentrations expected from the dilution procedure by less than 0.5%.

Measurement of Ionization Ratios. Stock solutions of each indicator were prepared by dissolving a carefully weighed sample of the substituted aniline in 50% v/v water–ethanol in a volumetric flask (the weight of sample was chosen so that a 31-fold dilution of the stock solution with 50% v/v water–ethanol resulted in a solution with an absorbance of about 0.8 at the absorption maximum of the free base). Mixtures of 0.100 ml of indicator stock solution and 3.00 ml of the various diluted acid solutions in spectrophotometer cells were thermostated at 30 °C and the absorbances of these mixtures at their maxima were determined.

The ionization ratios, $(BH^+)/(B)$, were obtained from the expression $(A_B - A)/(A - A_{BH})$ where A, A_B, and A_{BH} are the absorbances of the solution being measured, the absorbance of the unprotonated base, and the absorbance of the fully protonated base, all determined at the wavelength of maximum absorption for the solution being measured. A_B was obtained from a solution of 0.100 ml of indicator solution in 3.00 ml of 50% v/v water–ethanol and A_{BH} from a solution of 0.100 ml of indicator solution in 3.00 ml of acid solution with an H_0 value at least two units greater than the pK_a of the indicator. Each solution whose absorbance was determined was prepared in duplicate or triplicate with the measured optical densities varying by less than 1%.

In calculations involving the indicator ratios and acid concentrations, the latter were corrected for the amount consumed by reaction with the indicator base.

Results and Discussion

pK_a Values of Indicators. The pK_a values of the indicators employed in this investigation were determined by both the stepwise and extrapolation to infinite dilution procedures with the results shown in Table II. The first of these methods depends upon knowledge of the pK_a of at least one indicator (obtained by the second method), parallelism of plots of log $(BH^+)/(B)$ vs. acid concentration for the various indicators, and the relation

$$pK_{CH^+} - pK_{BH^+} = \log \frac{(CH^+)}{(C)} - \log \frac{(BH^+)}{(B)}$$

The maximum deviation from parallelism experimentally is ±0.06 log units (for 2,5-dichloro-4-nitroaniline in the sulfuric acid solutions) and the average deviation is ±0.02 log units for all of the indicators in the various acid solutions. Thus, the stepwise procedure for pK_a estimation has considerable validity in the systems used in this study. The pK_a of 3-nitro-4-methylaniline obtained by the extrapolation method was used as the basis of the stepwise comparison for the hydrochloric and perchloric acid solutions. Since the extrapolation is somewhat ambiguous for the sulfuric acid solutions (vide infra), the average of the pK_a values of 3-nitro-4-methylaniline in hydrochloric and perchloric acid served as the reference point for the sulfuric acid solutions.

pK_a values can also be obtained by extrapolating log $(BH^+)/(B)(H^+)$ vs. (H^+) to infinite dilution [i.e., $(H^+) = 0$]. Usually such plots are linear at low acid concentrations and

Table II. pK_a Values of Indicators in 50% v/v Aqueous Ethanol at 30.0 °C

	HCl solutions[a]		$HClO_4$ solutions[a]		H_2SO_4 solutions[a]			Lit. values	
Aniline	Step[b]	Extn[c]	Step[b]	Extn[c]	Step[b]	Extn[c]	Av[d]	Aq et[e]	H_2O[f]
3-NO_2, 4-CH_3	1.89[g]	1.89	1.92[g]	1.92	1.90[i]	(2.06)[j]	1.91 ± 0.02		2.90[l]
3-NO_2	1.38 ± 0.02	1.37	1.33 ± 0.03	1.34	1.35 ± 0.04	(1.44)[j]	1.35 ± 0.02	1.81[k]	2.50[m]
3-NO_2, 4-Cl	0.69 ± 0.03	0.71	0.59 ± 0.01	0.62	0.56 ± 0.03	(0.66)[j]	0.63 ± 0.05		
4-NO_2	−0.15 ± 0.01	−0.15	−0.22 ± 0.01	−0.19	−0.26 ± 0.01	(−0.09)[j]	−0.19 ± 0.04		0.99[m]
2-Cl, 5-NO_2	−0.81 ± 0.01	(−0.80)[h]			−0.95 ± 0.02	(−0.82)[h]	−0.88 ± 0.07		
2-NO_2	−1.57 ± 0.03	(−1.73)[h]			−1.68 ± 0.03	(−1.67)[h]	−1.63 ± 0.06		−0.29[m]
12-NO_2, 4-Cl	−2.42 ± 0.01	(−2.75)[h]			−2.50 ± 0.02	(−2.86)[h]	−2.46 ± 0.04		−1.03[m]
2,5-Cl_2, 4-NO_2	−3.12 ± 0.04	(−3.36)[h]			−3.29 ± 0.06	(−3.75)[h]	−3.21 ± 0.08		−1.82[m]

[a] Solutions of HCl, $HClO_4$, or H_2SO_4 in 50% v/v aqueous ethanol. [b] pK_a values obtained by stepwise comparison (see text). [c] pK_a values obtained by extrapolation to infinite dilution (see text). [d] Average of pK_a values not in parentheses. [e] 50% v/v aqueous ethanol. [f] Water. [g] Extrapolated value used as basis of stepwise comparison. [h] High acid concentrations cause these extrapolated values to be of questionable validity. [i] Average of pK_a values obtained by extrapolation in HCl and $HClO_4$ solutions. [j] Unknown extent of HSO_4^- dissociation in 50% aqueous ethanol at low (H_2SO_4) makes (H^+) uncertain so the resultant pK_a values are possibly in error. [k] At 20 °C, P. Vetesnik, K. Rothschein, J. Socha, and M. Vecera, *Collect. Czech. Chem. Commun.*, **24**, 1087 (1969). [l] At 25 °C, D. P. N. Satchell and J. L. Wardell, *J. Chem. Soc.*, 4134 (1964). [m] At 25 °C, C. H. Rochester, "Acidity Functions", Academic Press, New York, N.Y., 1970, p 67.

the extension of the experimental line to zero concentration is a simple matter. In this investigation, the extrapolation was performed by linear regression analysis (average correlation coefficient 0.932). The pK_a values of 2-chloro-5-nitroaniline, 2-nitroaniline, 2-nitro-4-chloroaniline, and 2,6-dichloro-4-nitroaniline derived in this way are of questionable validity since the concentrations of acid are large and the extrapolation to zero is over a wide range. In addition, the treatment of the experimental data in sulfuric acid solutions by the extrapolation procedure is uncertain. (H^+) was set equal to the molar concentration of sulfuric acid, but this is an underestimate, especially in dilute solution, because of the dissociation of HSO_4^-.

The pK_a values obtained by the stepwise comparison technique agree quite closely with those from the extrapolation to infinite dilution procedure. Surprisingly, this is true at all but the highest concentrations of acid (above 1.0 M HCl and H_2SO_4). Furthermore, the pK_a values obtained in different acids are also fairly similar, the maximum average deviation being only ±0.08 pK_a units.

These pK_a values for 50% v/v aqueous ethanol at 30 °C are compared with those for pure water at 25 °C in Table II. The difference between these pK_a values (ΔpK_a) varies from 1.0 to 1.4 units and seems to increase almost linearly with decrease in pK_a. Interpolation of the data of Gutbezahl and Grunwald[5] provides a ΔpK_a of about 0.7 for simple primary aromatic amines in water and 50% v/v aqueous ethanol, both at 25 °C (although other classes of amines have larger ΔpK_a's for this same medium change[6]). The temperature effect on pK_a for a change from 25 to 30 °C (about 0.08 pK_a units[7] for aniline) would increase the expected ΔpK_a when comparing a primary aromatic amine at 25 °C in water with the same compound in 50% v/v aqueous ethanol at 30 °C to about 0.8 units. The larger ΔpK_a's for the nitroanilines that served as indicators may be due to the peculiar activity coefficient behavior of nitro substituted compounds.[8] Substitution in the ortho position also seems to increase ΔpK_a[6] and this may be the cause of the larger ΔpK_a's for the less basic amines, all of which are ortho substituted.

The pK_a of 3-nitroaniline in 50% v/v aqueous ethanol at 20 °C was found to be 1.81 by a "method using buffers".[9] Since the procedure is not described in any more detail, it is impossible to speculate on the reason for the discrepancy between this value and that obtained in this study (1.35). The temperature difference alone would account for only about 0.16 pK_a units[7] of the disagreement.

Acidity Functions. Acidity functions in aqueous organic systems have usually been related to an ideal solution in water (the infinitely dilute solution) as the standard state. However, it is preferable[10] to refer the acidity function scale in an aqueous alcohol solvent to the ideal solution in the same solvent as the standard state. Correlation of reaction rates with H_0 then relate those rates to the standard state in that solvent system. In this study, the acidity functions were referred to infinitely dilute solutions in 50% v/v aqueous ethanol by use of the pK_a values defined for this medium.

Values of the acidity function were obtained from the experimentally determined ionization ratios of the indicators, their pK_a's estimated by the stepwise procedure, and the relation

$$H_0 = pK_{BH} - \log (BH^+)/(B)$$

Values in the overlap regions were averaged to obtain the final H_0 for a particular acid concentration. Interpolation of these results provided the data in Table III. The actual acid concentrations utilized covered the ranges of 0.000969–5.26 M H_2SO_4, 0.00115–2.30 M $HClO_4$, and 0.00108–6.77 M HCl. The concentration increments were chosen so that the measured differences in H_0 between consecutive concentrations were usually less than 0.2 units and never more than 0.3 units.

Inspection of the results for the various acids in Table III yields some interesting comparisons. H_0 values for HCl and $HClO_4$ are almost identical in the region from 0.001 M to 0.10 M as might be anticipated for strong acids behaving independently of the nature of their anions at low concentrations. In this same range, the H_0 values for the H_2SO_4 solutions are less than those for $HClO_4$ and HCl solutions at equivalent molar concentrations. This is undoubtedly due to the second dissociation of H_2SO_4 (i.e., ionization of HSO_4^-) which increases the acidity of the medium. At concentrations above 0.10 M, the H_0 values of $HClO_4$ and H_2SO_4 solutions are similar while those for HCl solutions at the same concentrations are higher. Apparently, the dissociation of HSO_4^- in this region becomes unimportant so that the two strong oxygen acids behave nearly the same. The measurements for $HClO_4$ have probably not been carried to sufficiently high concentrations so that specific ion effects of ClO_4^- vis-à-vis HSO_4^- become obvious, although the small change in the difference between H_0 values of $HClO_4$ and H_2SO_4 over the range from 0.2 to 2.4 M may be a harbinger of a more pronounced effect of this type at higher molarities. The lower acidity of HCl solutions as compared to $HClO_4$ and H_2SO_4 solutions of the

Table III. H_0 Values[a] in 50% v/v Aqueous Ethanol at 30.0 °C

	H_0				H_0		
M	HCl	$HClO_4$	H_2SO_4	M	HCl	$HClO_4$	H_2SO_4
0.001	3.11	3.01	2.78	1.4	−0.59	−0.90	−0.91
0.002	2.77	2.71	2.53	1.6	−0.71	−1.06	−1.07
0.003	2.57	2.53	2.39	1.8	−0.82	−1.22	−1.20
0.004	2.43	2.40	2.27	2.0	−0.94	−1.37	−1.33
0.005	2.32	2.31	2.18	2.2	−1.04	−1.52	−1.46
0.006	2.23	2.22	2.11	2.4	−1.15	−1.66	−1.59
0.007	2.16	2.15	2.05	2.6	−1.25		−1.74
0.008	2.10	2.09	1.99	2.8	−1.36		−1.88
0.009	2.04	2.04	1.94	3.0	−1.46		−2.04
0.01	1.99	1.99	1.90	3.2	−1.57		−2.19
0.02	1.67	1.67	1.60	3.4	−1.67		−2.35
0.03	1.49	1.49	1.43	3.6	−1.79		−2.51
0.04	1.36	1.35	1.31	3.8	−1.90		−2.66
0.05	1.26	1.25	1.20	4.0	−2.01		−2.83
0.06	1.18	1.17	1.11	4.2	−2.12		−3.00
0.07	1.11	1.09	1.03	4.4	−2.24		−3.18
0.08	1.05	1.03	0.96	4.6	−2.35		−3.35
0.09	1.00	0.97	0.90	4.8	−2.45		−3.52
0.10	0.95	0.92	0.84	5.0	−2.56		−3.70
0.2	0.62	0.56	0.46	5.2	−2.67		−3.86
0.3	0.42	0.34	0.23	5.4	−2.78		−4.03
0.4	0.26	0.17	0.05	5.6	−2.88		−4.20
0.5	0.13	0.02	−0.09	5.8	−2.99		−4.36
0.6	0.02	−0.11	−0.21	6.0	−3.20		−4.69
0.7	−0.09	−0.23	−0.32	6.4	−3.30		−4.86
0.8	−0.18	−0.34	−0.42	6.6	−3.40		−5.02
0.9	−0.25	−0.44	−0.51	6.8	−3.49		−5.19
1.0	−0.33	−0.54	−0.60				
1.2	−0.46	−0.73	−0.76				

[a] Interpolated from experimental results.

same molarity at medium and high concentrations observed in this study is also apparent in aqueous solutions.[11] This may result from incomplete ionization of HCl at higher concentrations.[12]

These trends in relative acidity function values for 50% v/v aqueous ethanol are also obvious, although at different concentrations, for these same acids in aqueous solutions.[11] At low acid concentrations (less than 0.10 M), the H_0 values for the various acids in 50% v/v aqueous ethanol and in water are almost identical. However, at higher acid concentrations, the acidity functions in the mixed solvent become more negative than those in water—at equal acid concentrations the aqueous ethanol solutions have a greater acidity than the aqueous solutions. This is undoubtedly due to the poorer solvating ability of the partially organic solvent.

It is also useful to compare the results of this investigation with those obtained in studies of similar mixed solvents. Satchell[13] determined the acidity function of HCl (0.05–6.2 M) in 24.4 mol % ethanol–water (52% v/v ethanol in water) using the ideal solution in pure water as the standard state. His H_0 values should therefore differ from the ones in the present paper by about 1.14 units [the difference between the pK_a of *p*-nitroaniline in water (0.99) and in 50% v/v aqueous ethanol (−0.15)]. In fact, they do differ by 1.14 ± 0.02. Vecera and his collaborators[9,14] measured H_0 for $HClO_4$ in 50% v/v aqueous ethanol at concentrations from 0.1 to 7.5 M. Using buffer solutions in the mixed solvent, they assigned a pK_a of 1.81 to *m*-nitroaniline as opposed to 1.33 found in this study. Thus, their H_0 values at low acid concentrations where *m*- and *p*-nitroanilines were used as indicators should differ from those found here by 0.48 units. The correlation between the two scales is actually rather poor since the actual difference in the short range between 0.10 and 1.0 M is 0.39 ± 0.04 units. It is unlikely that this discrepancy is due to the temperature difference of the two studies (10 °C). Above 1.0 M $HClO_4$, substituted *o*-hydroxyazobenzenes were used to establish the acidity functions. Thus, it is not surprising that the results of the two studies differ even more radically at the higher acidities.

This investigation has therefore led to pK_a values of a series of weakly basic primary aromatic amines in 50% v/v aqueous ethanol and the establishment of acidity functions in this medium for hydrochloric, perchloric, and sulfuric acids.

Registry No.—Sulfuric acid, 7664-93-9; hydrochloric acid, 7647-01-0; perchloric acid, 7601-90-3.

References and Notes

(1) This work was supported in part by the National Science Foundation (Grants GP-8996 and GP-1970).
(2) See, for example, R. Curci, F. DiFuria, A. Levi, V. Lucchini, and G. Scorrano, *J. Chem. Soc., Perkin Trans. 2*, 341 (1975); A. Levi, G. Modena, and G. Scorrano, *J. Am. Chem. Soc.*, **96**, 6586 (1974); and references cited therein.
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(10) C. H. Rochester, "Acidity Functions", Academic Press, New York, N.Y., 1970, p 219.
(11) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).
(12) HCl is predicted to have a pK_a of −7 in aqueous solution (F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 3d ed, Interscience, New York, N.Y., 1972, p 169) while $HClO_4$ has an estimated pK_a of about −10 (J. E. Huheey, "Inorganic Chemistry, Principles of Structure and Reactivity", Harper and Row, New York, N.Y., 1972, p 213) and H_2SO_4 is probably of intermediate acid strength.
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Products of Rearrangement of *m*-Chloro-*N*-nitro-*N*-methylaniline[1]

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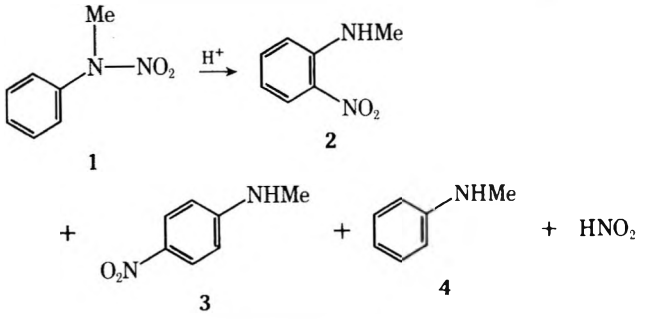
The rearrangement of aromatic nitramines is exemplified by the isomerization of *N*-nitro-*N*-methylaniline[3] (**1**). The



reaction has been found to be at least partially intramolecular.[4] In spite of the apparent simplicity of this reaction, there is considerable disagreement regarding its intimate nature. Three different mechanisms have been proposed by different research groups to account for the results (Chart I). (1) The "cartwheel" mechanism[5] supposes that the protonated nitramine isomerizes to a nitritoamine (>NON=O) which then undergoes a Claisen-like rearrangement to an ortho *C*-nitrite intermediate. The latter can undergo further rearrangement to a para *C*-nitrite intermediate. It is suggested that either of the *C*-nitrites can isomerize to *C*-nitro compounds identical with those expected in nitration. (2) The π complex mechanism[6,7] proposes that the protonated nitramine breaks down to form a π complex of the type postulated in aromatic nitration. The remaining steps to product are analogous to those suggested for the latter reaction. (3) The cation radical mechanism[8,9] involves symmetrical N–N bond scission in the protonated nitramine to yield a pair of radicals—anilinium cation radical and nitrogen dioxide—which can recombine at the ortho and para positions of the ring to form the same nitration intermediates common to the other two mechanisms.

Because of the proposed similarity between the "cartwheel" mechanism and the Claisen rearrangement, it was anticipated that similar factors should control the product distribution in both migrations, if this mechanism was valid. On the other hand, the other two mechanisms would predict a more or less statistical distribution of products depending on the strength of binding between the ring and the dissociated nitro group. Since the product distribution in the Claisen rearrangement of allyl *m*-chlorophenyl ether (**4**) has been accurately determined,[10] it was decided to investigate the products formed in acid-catalyzed reaction of *m*-chloro-*N*-nitro-*N*-methylaniline (**5**) and compare the results with those from the Claisen rearrangement.

Results and Discussion

The products of acid-catalyzed rearrangement of *m*-chloro-*N*-nitro-*N*-methylaniline (**5**) were determined by isotope dilution analysis with the results shown in Table I. This analysis accounts for about 98% of the aromatic portion of the original nitramine and for about 85% of the nitro group. Nitrous acid was detected in the reaction mixture but its concentration was not determined; it probably is the principal form in which the remainder of the nitro group appears in the product. About 50% of the product corresponds to ortho rearrangement (**8** + **11**), 35% to para migration (**9**), and 13% to denitration (**6**). These figures are surprisingly close to those obtained for *N*-nitro-*N*-methylaniline,[3] for which there was about 49% ortho rearrangement, 32% of para isomerization, and 10% of denitration. It is especially noteworthy that there is no evidence for meta rearrangement in either case, which implies that the intermediates in the rearrangement process do not resemble those in direct nitration and that the rearrangement mechanism must specifically prohibit meta nitro compound formation.

As mentioned above, the "cartwheel" mechanism bears a superficial resemblance to the Claisen rearrangement. However, the product distribution from the nitramine (**5**) does not at all resemble that from rearrangement of the allyl ether (**4**).[10] The allyl ether provides no para-substituted isomer as does the nitramine. Furthermore, the ratio of the ortho products formed in the two processes is quite different. The nitramine rearrangement gives a ratio of 2 substitution to 6 substitution of 0.57 while the Claisen rearrangement yields the two isomers in a ratio of 1.92. Thus, any relation between the Claisen and nitramine rearrangements must not extend to product determination.

The distribution of isomers resulting from the acid-catalyzed reaction of **5** is approximately that expected from a model in which the nitro group is relatively unrestricted by the aromatic portion of the system. If it is assumed that the variations in percentages of position isomers produced in the

Chart I

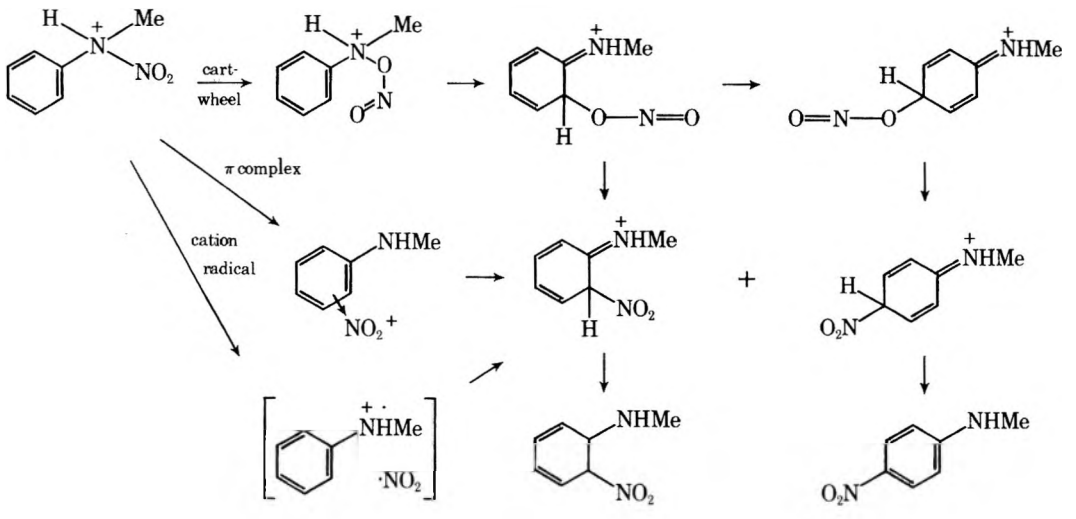


Table I. Rearrangement Products of *m*-Chloro-*N*-nitro-*N*-methylaniline (5)[a]

Product	% yield
3-Chloro-*N*-methylaniline (6)	13.4 ± 0.4
3-Nitro-*N*-methylaniline (7)	0.0 ± 0.0
3-Chloro-2-nitro-*N*-methylaniline (8)	18.1 ± 0.4
3-Chloro-4-nitro-*N*-methylaniline (9)	34.8 ± 0.1
3-Chloro-5-nitro-*N*-methylaniline (10)	0.0 ± 0.0
3-Chloro-6-nitro-*N*-methylaniline[b] (11)	31.6 ± 0.7

[a] Catalyzed by 0.501 M $HClO_4$ in 1:50 dioxane–water, temperature 55 °C. [b] More properly this is named 5-chloro-2-nitro-*N*-methylaniline. However, the name used in this table emphasizes the interrelations between the isomers.

rearrangements of *N*-nitro-*N*-methylaniline and **5** are due only to the steric effects of the methylamino and chloro groups interfering with an incoming nitro group, it is possible to assign parameters that permit the estimation of the amount of each isomer formed. Thus, the amount of substitution at one ortho position in the *N*-methylaniline moiety (in the rearrangement of *N*-nitro-*N*-methylaniline) is 0.77 (½ of 49%/32%) of that at the unencumbered para position. If this same figure applies to substitution at the 6 position in the *m*-chloro-*N*-methylaniline fragment, the observed product distribution requires 0.84 (0.77 × 35%/32%) for the 4 position (this represents the steric effect for substitution ortho to a chloro group as compared to an unhindered position). The 2 position in the *m*-chloro-*N*-methylaniline system is flanked by both a methylamino and a chloro group so the steric factor for this site should be the product of 0.77 and 0.84 (or 0.65). The numbers lead to the prediction that the *nitrated product* formed in the isomerization of **5** should consist of 29% of the 2 isomer, 37% of the 4 isomer, and 34% of the 6 isomer (100% total). The actual experimental values are 21, 41, and 38%, respectively. Better agreement would be obtained if the entirely reasonable assumption was made that the combined steric effects of the methylamino and chloro groups acting in concert on the 2 position were greater in magnitude than that predicted by taking the product of the steric effects of the groups acting separately on the 6 and the 4 positions, respectively (in fact, exact reproduction of the experimental data is possible if it is assumed that when both groups are simultaneously involved, their individual steric effects are 25% greater than when they function separately). In any case, the predicted and experimental values are in sufficient agreement to support the contention that, at some point in the reaction, the nitro group is weakly bound, if at all, to the anilino system so that its subsequent attachment to the ring at the ortho and para positions must be relatively random.

The "cartwheel" mechanism of the nitramine rearrangement involves firm attachment of the nitro group first to the ortho position(s) and then to the para position. Unless the three isomeric intermediates are in equilibrium, which seems unlikely because of their chemical fragility, the "cartwheel" mechanism is not capable of accommodating the experimental information that isomer formation, except for a small steric effect and the requirement for ortho, para substitution, is random. On the other hand, these findings can be interpreted in terms of either the π-complex or radical cation mechanisms since in either of these pathways the nitro group is probably rather loosely associated with the ring system.

Experimental Section

Preparation of *m*-Chloro-*N*-nitro-*N*-methylaniline-^{14}C. A. *m*-Dinitrobenzene-^{14}C. A cold solution of 45.0 ml of concentrated sulfuric acid and 45.0 ml of concentrated nitric acid was added in small portions with swirling and intermittent cooling to 17.25 g (0.221 mol) of benzene-^{14}C. Then 90 ml of concentrated sulfuric acid was added in small portions. The mixture was heated to 120 °C, cooled to 80 °C, and poured into 1500 ml of cold water. The product was collected by suction filtration, washed three times with cold water, and air dried to give 33.7 g (91%) of *m*-dinitrobenzene-^{14}C, mp 87–89 °C (lit.[11] mp 89.0–89.5 °C).

B. *m*-Nitroaniline-^{14}C. To a solution of 33.7 g (0.201 mol) of *m*-dinitrobenzene-^{14}C in 600 ml of ethanol was added 300 ml of 20% ammonium sulfide solution. The mixture was stirred at reflux for 2 h, cooled to room temperature, and then poured into 1500 ml of cold water. The precipitate was collected by suction filtration. The mother liquor was extracted four times with ether. The combined ether solutions were dried over anhydrous magnesium sulfate and then evaporated to dryness. This residue and the precipitate were combined and crystallized from water to give 16.5 g (60%) of *m*-nitroaniline-^{14}C, mp 110–111 °C (lit.[12] mp 112.5 °C).

C. *m*-Chloronitrobenzene-^{14}C. *m*-Nitroaniline-^{14}C (16.5 g, 0.120 mol) was dissolved in a hot solution of 48 ml of concentrated hydrochloric acid in 30 ml of water, and the resulting liquid was cooled to 0 °C in an ice–salt bath. A solution of 9.12 g (0.132 mol) of sodium nitrite in 30 ml of water was added dropwise with continuous stirring and cooling. The cold solution was filtered and then added slowly to a solution of 15.0 g (0.152 mol) of cuprous chloride in 45 ml of concentrated hydrochloric acid while keeping the temperature at 25–30 °C. The resulting mixture was refluxed for 10 min and then steam distilled until about 3 l. of distillate had been collected. The distillate was extracted with ether and the combined ether solutions were washed once with water, dried over anhydrous potassium carbonate, and then evaporated to dryness to give 13.7 g (80%) of yellowish solid, mp 46–48 °C (lit.[13] mp 46 °C).

D. *m*-Chloroaniline-^{14}C. A warm solution of 13.7 g (0.0874 mol) of *m*-chloronitrobenzene-^{14}C in 20 ml of glacial acetic acid was added slowly to a refluxing solution of 68.8 g (0.305 mol) of stannous chloride dihydrate in 115 ml of concentrated hydrochloric acid and 165 ml of methanol. The resulting mixture was concentrated over a period of 1 h to approximately 130 ml and then cooled and stirred into a solution of 136.5 g of sodium hydroxide in 875 ml of ice–water. The mixture was then extracted twice with 150-ml portions of ether. The combined extracts were dried over anhydrous potassium carbonate and the ether distilled. Distillation of the residual oil gave 10.2 g (92%) of *m*-chloroaniline-^{14}C, bp 113–116 °C (19 mm) [lit.[14] bp 118.5 °C (21 mm)].

E. *m*-Chloro-*N*-nitro-*N*-methylaniline-^{14}C. This compound was obtained by a procedure described previously[15] and crystallized from petroleum ether (bp 35–60 °C) to give a 24.5% yield of colorless crystals, mp 48.5–49.2 °C.

Anal. Calcd for $C_7H_7N_2O_2Cl$: C, 45.05; H, 3.78; N, 15.01. Found: C, 45.29; H, 3.74; N, 14.99.

3-Chloro-2-nitroaniline. To a stirred mixture of 90 ml of concentrated sulfuric acid and 24 ml of fuming (30%) sulfuric acid was added 10.75 g (0.050 mol) of 3-chloro-2-nitrobenzoic acid. After several minutes and with intermittent cooling to keep the temperature below 40 °C, 8.15 g (0.125 mol) of sodium azide was added in small portions. The mixture was stirred at 46–48 °C for 3.5 h and then cooled and poured slowly over cracked ice. The resulting mixture was neutralized with 40% sodium hydroxide and the product collected by suction filtration. Crystallization from a mixed solvent of benzene and ligroin (bp 65–90 °C) gave 8.36 g (91%) of orange needles, mp 108–109 °C (lit.[16] mp 108–108.5 °C).

3-Chloro-4-nitroaniline. *m*-Chloroacetanilide was nitrated with concentrated nitric acid in a mixture of concentrated sulfuric acid and glacial acetic acid by the procedure of Mayes and Turner.[17] The desired 3-chloro-4-nitroacetanilide was separated from the 3-chloro-6-nitroacetanilide by dissolving the mixture (65.5 g, 0.305 mol) in 2300 ml of boiling benzene. The solution was allowed to cool whereupon 3-chloro-4-nitroacetanilide crystallized. The solid was collected by suction filtration and then recrystallized from aqueous ethanol to give 37.6 g (58%) of 3-chloro-4-nitroacetanilide, mp 144.5–145.0 °C (lit.[18] mp 145 °C). The acetanilide was then hydrolyzed by heating at 110 °C for 10 min with 150 g of concentrated sulfuric acid. The solution was cooled and poured slowly over ice. The solid was collected by suction filtration, washed once with water, and then crystallized from aqeuous ethanol. Two additional crystallizations from benzene gave 17.3 g (59%) of 3-chloro-4-nitroaniline, mp 161–162 ° (lit.[18] mp 158.4 °C).

3-Chloro-5-nitroaniline. A. 3,5-Dinitrochlorobenzene. A solution of 9.76 g (0.14 mol) of sodium nitrite in 32 ml of water was slowly stirred into an ice-cold solution of 22.0 g (0.12 mol) of 3,5-dinitroaniline in 55 ml of concentrated hydrochloric acid and 20 ml of water. The temperature was maintained at 0–5 °C by addition of ice. The resulting mixture was poured slowly and with intermittent cooling into 16 g of cuprous chloride dissolved in 48 ml of concentrated

Table II. Derivatives of *m*-Chloroaniline[f]

Ring substn[g]	Solvent[a]	%[b]	Mp, °C	Registry no.
		N-*p*-Toluenesulfonyl		
3-Cl	Et–HA	99	136.5–137.5[c]	19377-04-9
3-Cl-2-NO_2	Et–W	22	143.5–144.3	60498-60-4
3-Cl-4-NO_2	HA–W	73	120.5–121.5	60498-61-5
3-Cl-5-NO_2	Et–W	89	137.0–138.0	60498-62-6
		N-Methyl-*N*-*p*-toluenesulfonyl		
3-Cl	Pet.	97	78.0–78.5	35462-50-1
3-Cl-2-NO_2	Et–W	96	135.0–136.0	60498-63-7
3-Cl-4-NO_2	Me	85	99.0–100.0	60498-64-8
3-Cl-5-NO_2	Me	96	148.0–149.0	60498-65-9
		N-Methyl		
3-Cl		93	*d,e*	
3-Cl-2-NO_2	Pet.	87	65.5–66.5	
3-Cl-4-NO_2	HA	65	107.0–108.0	
3-Cl-5-NO_2	Et–W	92	117.0–118.0	

[a] Et = ethanol, Me = methanol, W = water, HA = acetic acid, Pet. = petroleum ether (bp 35–60 °C). [b] Percent yield. [c] Lit. mp 134 °C [F. E. King, T. J. King, and I. H. M. Muir, *J. Chem. Soc.*, 5 (1946)]. [d] Bp of 89–90 °C (1.8 mm) compares with lit. bp 235 °C [J. von Braun and O. Kruber, *Ber.*, **46**, 3470 (1913)]. [e] Mp of *N*-acetyl derivative of 91.5–92.5 °C compares with reported mp of 92.5 °C [W. Staedel, *Ber.*, **19**, 1947 (1886)]. [f] Satisfactory combustion analytical data for C, H, N (±0.4%) were provided for these compounds. Ed. [g] Registry no. are, respectively, 108-42-9, 59483-54-4, 825-41-2, 5344-44-5.

hydrochloric acid. The mixture was refluxed for 10 min and then steam distilled until approximately 5.5 l. of distillate had passed over. The product was collected by suction filtration. The filtrate was extracted with methylene chloride and the solution was dried over anhydrous potassium carbonate and evaporated. Crystallization of the combined fractions from ethanol gave 14.8 g (61%) of 3,5-dinitrochlorobenzene, mp 51–52 °C (lit.[19] mp 53 °C).

B. 3-Chloro-5-nitroaniline. A mixture of 14.7 g (0.0726 mol) of 3,5-dinitrochlorobenzene, 200 ml of ethanol, and 110 ml of 20% ammonium sulfide solution was refluxed with stirring for 1 h. After cooling to room temperature, the mixture was filtered. The filtrate was poured into 800 ml of cold water and the solid was filtered off. This filtrate was extracted three times with 200-ml portions of ether. The combined ether solutions were dried over anhydrous potassium carbonate and then evaporated to dryness. The residue was combined with the previous solid and extracted once with boiling water. The aqueous solution was cooled and gave 3.28 g (26%) of 3-chloro-5-nitroaniline, mp 132–133 °C (lit.[20] mp 133–134 °C).

Preparation of Substituted *N*-Methylanilines from Substituted Anilines. The substituted aniline was treated with *p*-toluenesulfonyl chloride in pyridine to convert to the *N*-*p*-toluenesulfonyl derivative. The latter was alkylated with methyl sulfate in an aqueous dioxane solution of sodium hydroxide. The toluenesulfonyl group was then removed from the amino group by heating the *N*-methyl-*N*-*p*-toluenesulfonyl compound with an acetic acid solution of sulfuric acid. The details of this procedure have been described.[8] The intermediates and products from this sequence of steps are listed in Table II.

5-Chloro-2-nitro-*N*-methylaniline. Into a heavy-walled glass tube were placed 3.84 g (0.02 mol) of 2,4-dichloronitrobenzene, 22 ml of ethanol, and 5.0 ml of 6.0 N methylamine solution. The tube was sealed and heated in a steam bath for 20.5 h. The contents were removed and filtered by suction. The product was washed with water and then crystallized from ethanol to give 2.04 g (55%) of amine, mp 104.5–105.5 °C. A second fraction, 0.22 g (6%), mp 88–90 °C, was also isolated. Repetition of this experiment with 7.68 g (0.04 mol) of 2,4-dichloronitrobenzene gave 4.89 g (65%) of the nitroaniline, mp 99–102 °C. All fractions were combined and recrystallized from ethanol to give 6.22 g of orange needles, mp 106–107 °C (lit.[21] mp 106–107 °C).

Isotope Dilution Analysis of Rearrangement Products of *m*-Chloro-*N*-nitro-*N*-methylaniline. A. Rearrangement. A solution of 933.0 mg (5.00 mmol) of *m*-chloro-*N*-nitro-*N*-methylaniline-^{14}C in 80.0 ml of dioxane in a 2000-ml volumetric flask was diluted very rapidly with sufficient aqueous perchloric acid–sodium perchlorate solution (0.501 M-$HClO_4$, 0.501 M $NaClO_4$), which had previously been thermostated at 55 °C, to bring the volume of the solution to the mark. The flask was shaken by inversion several times and placed in a constant temperature bath at 55.0 °C for 2 h. Then 5.00 g of sulfamic acid was added and heating continued for an additional 30 min. The mixture was then cooled rapidly to room temperature and the volume adjusted to the mark by the addition of dioxane. After the contents were mixed thoroughly, aliquots were removed and treated as described below.

Table III. Yields of Products from the Rearrangement of *m*-Chloro-*N*-nitro-*N*-methylaniline

Ring substn[a]	Mp,[b] °C	% yield sample 1[c]	% yield sample 2[d]	% yield average[e]
3-Cl	92.5–93.5[f]	13.0	13.7	13.4 ± 0.4
3-NO_2	64.6–66.0	0.0	0.0	0.0 ± 0.0
3-Cl-2-NO_2	67.0–67.5	18.5	17.7	18.1 ± 0.4
3-Cl-4-NO_2	107.2–107.8	34.7	34.8	34.8 ± 0.1
3-Cl-5-NO_2	117.1–117.9	0.0	0.0	0.0 ± 0.0
5-Cl-2-NO_2	106.5–107.2	30.9	32.2	31.6 ± 0.7

[a] Substitution in the ring of *N*-methylaniline. [b] Melting points of compounds analyzed, can be compared with similar data in previous parts of Experimental Section. [c] Sample recrystallized four times. [d] Sample recrystallized seven times. [e] Assays of samples 1 and 2 showed that they had constant activity and so they were averaged. [f] Melting point of *N*-acetyl derivative.

B. Dilution and Isolation of 3-Chloro-x-nitro-*N*-methylanilines and *m*-Nitro-*N*-methylaniline. An aliquot (300.0 or 350.0 ml) of the above reaction mixture was thoroughly mixed with an excess (2.50 or 5.00 mmol) of inactive 3-chloro-x-nitro-*N*-methylaniline or *m*-nitro-*N*-methylaniline dissolved in 50.0 ml of dioxane. The solution was made basic with 10% aqueous sodium hydroxide and then extracted with one 100-ml portion and three 50-ml portions of ether. After the combined ether solutions were dried over anhydrous magnesium sulfate, they were evaporated to dryness. The residue was dissolved in ether and chromatographed on an alumina column using ether as the eluent. The fraction containing the desired nitro compound was evaporated and the remaining solid was crystallized four times from a suitable solvent (see Table II). The activity of the product was determined and it was then recrystallized three more times and analyzed again.

C. Dilution and Isolation of a Derivative of *m*-Chloro-*N*-methylaniline. The dilution of the reaction product with *m*-chloro-*N*-methylaniline and the isolation of this substance was carried out as described in B above. The oil remaining after evaporation of the ether extracts was treated with 2.0 ml of acetic anhydride and 2 drops of concentrated sulfuric acid and heated on a steam bath for 5 min. After the addition of 15 ml of methanol, the mixture was again heated on the steam bath and evaporated to dryness under aspirator vacuum.

D. Determination of Activities. The substances to be analyzed for carbon-14 content were dried in a vacuum desiccator over potassium hydroxide and paraffin chips for at least 24 h. Their activities were determined by "burning" carefully weighed samples to carbon dioxide with Van Slyke–Folch solution,[22] collecting the carbon dioxide in an ionization chamber, and measuring four or five "rates of drift" by means of a Cary Model 31 vibrating reed electrometer. This procedure has been described in detail.[23]

E. Calculation of Percentages of Products. The following equation was used to calculate percentages from the averaged rates of drift for each compound.

$$\% = \frac{M_0 M' V_0 w (a - b)}{M V w_0 [S_0 w' - M' (a - b)]}$$

M = mol wt of reactant
M_0 = mol wt of product
M' = mol wt of assayed derivative of product
w_0 = mg of reactant reacted
w = mg of inactive diluent used
V_0 = ml of original reaction solution
V = ml of aliquot of reaction solution
a = rate of drift (mV/min) from CO_2 from w' mg.
b = rate of drift (mV/min) from inactive CO_2
S_0 = specific activity (mV min^{-1} $mmol^{-1}$) of reactant

The last quantity, S_0, is available from

$$S_0 = M_0(a_0 - b)/W'_0$$

W'_0 = mg of pure reactant combusted
a_0 = rate of drift (mV/min) from CO_2 from W'_0 mg.

The value of S_0 used in the computation of percentages was the average of four separate determinations. The results of these calculations are set forth in Table III.

Registry No.—**5**, 23042-41-3; **6**, 7006-52-2; **7**, 619-26-1; **8**, 60498-57-9; **9**, 60498-58-0; **10**, 60498-59-1; **11**, 35966-84-8.

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Synthesis and Chemistry of Some 2-Aminoethenesulfonyl Fluorides. An Unusual Manganese Dioxide Oxidation

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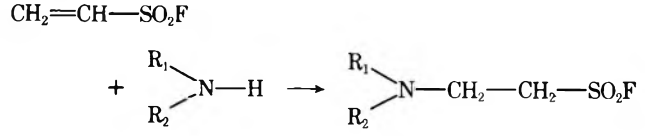
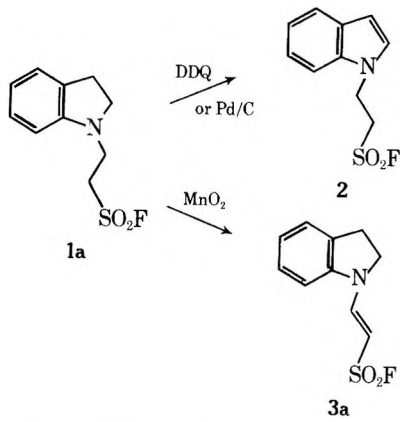
Some recent work in this laboratory demonstrated the facile fluorosulfonylethylation of various amines with vinylsulfonyl fluoride.[1] We wish to report that 3-fluorosulfonylethylamines **1** are dehydrogenated by active manganese dioxide to afford novel 2-aminoethenesulfonyl fluorides.

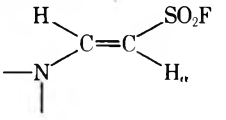


1

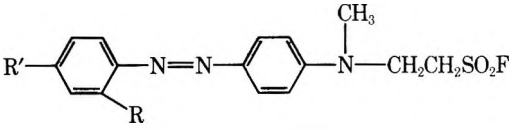
R = H, alkyl, or aryl

Jansen and co-workers have described the dehydrogenation of indolines with active manganese dioxide.[2] We found that, although indole **2** could be prepared from indoline **1a** by using dichlorodicyanobenzoquinone or palladium on carbon, reaction of **1a** with active MnO_2 afforded a new substance, **3a**, which was isomeric with **2**. Compound **3a** was assigned the enaminosulfonyl fluoride structure shown on the basis of its empirical formula and spectral properties (see Experimental Section). In particular, the ^1H NMR spectrum of **3a** points to the presence of a highly polarized olefinic system, wherein H_α is coupled with the fluorine atom.

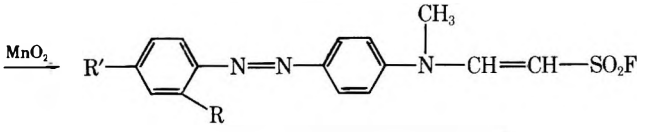




In view of the unusual course of this oxidation, the reaction of a series of substituted 2-aminoethanesulfonyl fluorides with MnO_2 was carried out; Table I gives the structures and yields. Two additional examples were provided by the preparation of dyes **3g** and **3h**. Further experiments delineated the scope

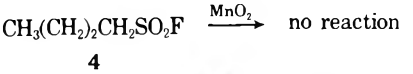


1g, R = SO_2CH_3; R' = NO_2
1h, R = H; R' = SO_2F

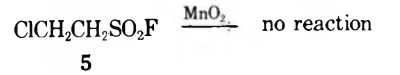


3g, R = SO_2CH_3; R' = NO_2 (56%)
3h, R = H; R' = SO_2F (59%)

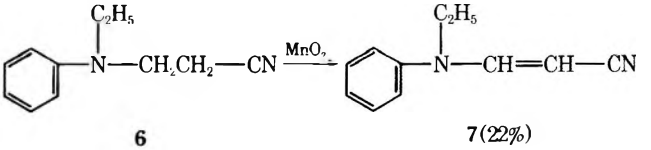
of the oxidation. Sulfonyl fluorides **4** and **5** did not react with MnO_2, and β-cyanoethylamine **6** was converted to enamine **7** very slowly and in poor yield.



4



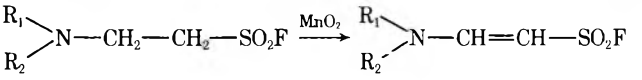
5



6 **7** (22%)

Henbest and co-workers[3,4] have reported the isolation of low yields of enamines as intermediates in the MnO_2 dealkylation of tertiary amines; the enamines were generally unstable in the presence of MnO_2. In the case at hand, the stability of enaminosulfonyl fluorides (vide infra) could account for the good yields obtained. One possible mechanism for the oxidation involves the following electron-transfer process. That electron transfer from β-fluorosulfonylethylamines does indeed lead to the observed products was demonstrated by uv irradiation of **1b** in the presence of benzophenone; **3b** was

Table I.[a] MnO_2 Oxidation of Substituted 2-Aminoethanesulfonyl Fluorides

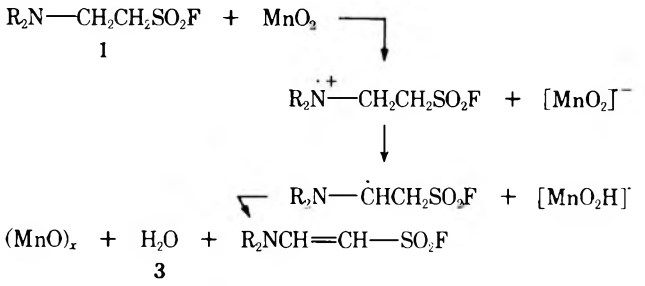


1a-f 3a-f

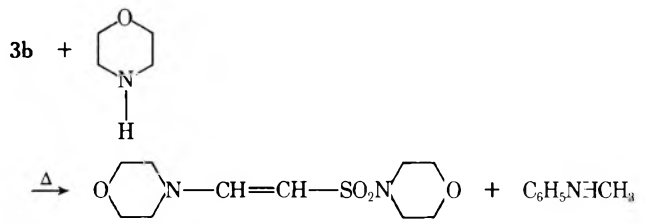
	Starting material		Product			
	R_1	R_2	R_1	R_2	Yield, %	Mp, °C
1a	(1-indolinyl)		3a (1-indolinyl)		95	142.5–143.5
1b	C_6H_5	CH_3	3b C_6H_5	CH_3	84	52.5–53.5
1c	C_6H_5	C_2H_5	3c C_6H_5	C_2H_5	96[b]	Oil
1d	CH_3	CH_3	3d CH_3	CH_3	33[b]	Oil
1e	C_6H_5	H	3e C_6H_5	H	42	115–117
1f	C_6H_5	$CH_2CH_2SO_2F$	3f C_6H_5	$CH_2CH_2SO_2F$	86	96–97.5

[a] Yields are based on isolated products; all compounds gave satisfactory elemental and spectral analyses unless otherwise noted. [b] Satisfactory combustion analysis not obtained; ir, NMR, mass, and uv spectra in agreement with assigned structure.

produced cleanly. Previous work[5-7] has established the electron-transfer mechanism in amine–benzophenone photochemical redox systems.



Aminoethenesulfonyl fluorides **3a–h** were found to be very stable, and selective reactions of the enamine or sulfonyl fluoride functions were not observed. Compound **3b**, for example, reacted with morpholine only at reflux to give 8 and *N*-



8

methylaniline as the sole products. Compound **3b** did not react with cyclopentadiene and was not reduced to **1b** even under forcing conditions.[8]

In summary, it has been found that β-fluorosulfonylethylamines undergo facile dehydrogenation by active MnO_2 to afford novel enaminosulfonyl fluorides, probably via an electron-transfer mechanism.[11] The product enamines are resonance stabilized and react with nucleophiles only under forcing conditions.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 137 instrument; NMR spectra were obtained with Varian EM-360 and JEOLCO MH-100 spectrometers. Mass spectra were taken with a Consolidated Electrodynamics Corp. Model 21-110B spectrometer system.

Starting Materials. The substituted 2-aminoethanesulfonyl fluorides **1a–h** were prepared from vinylsulfonyl fluoride and the appropriate amine in ether solution according to the general procedure described previously.[1] Active manganese dioxide was prepared by the procedure of Attenburrow et al.,[9] or by air oxidation of ammoniacal manganese salts.[10]

General Procedure for MnO_2 Oxidation. The preparation of **3a** serves as a typical example. A solution of 10.6 g (0.046 mol) of 2-(2,3-dihydro-1*H*-indol-1-yl)ethanesulfonyl fluoride (**1a**) in 300 ml of chloroform was treated with 100 g of active MnO_2 and stirred vigorously for 2 h at 27 °C. The mixture was then filtered (Celite, $CHCl_3$ wash), and the filtrate stripped in vacuo to afford 10.1 g (95%) of 2-(2,3-dihydro-1*H*-indol-1-yl)ethenesulfonyl fluoride (**3a**) as an odorless, tan solid. The analytical sample was thrice recrystallized from ethanol and had mp 142.5–143.5 °C; ir (mull) 6.16, 6.28, 7.27, 8.42, and 11.03 μ; NMR (acetone-d_6) δ 8.30 (d, J = 13 Hz, 1 H), 7.38 (m, 4 H), 5.58 (d of d, J = 3.5, 13 Hz, 1 H), 4.0 (m, 2 H), and 3.37 (m, 2 H); uv (EtOH) λ_{max} (ε) 313 nm (24 078), 279 (21 655); mass spectrum *m/e* 227 (P).

Anal. Calcd for $C_{10}H_{10}FNO_2S$: C, 52.83; H, 4.44; N, 6.17. Found: C, 52.92; H, 4.60; N, 6.10.

Photochemical Preparation of 3b from 1b. A solution of 0.10 g of **1b** and 0.20 g of benzophenone in 30 ml of acetonitrile was irradiated with a bank of 16 Rayonet 3200-Å lamps for 16 h. Careful thin layer chromatography (TLC) analysis (two solvent systems) of the light brown reaction mixture disclosed the presence of **1b** and **3b** in ca. 1/1 ratio, in addition to benzophenone and benzpinacol.

4-{[2-(4-Morpholinyl)ethenyl]sulfonyl}morpholine (8). A mixture of 1.0 g of **3b** and 10 g of morpholine was refluxed for 4.0 h, at which time TLC analysis showed loss of **3b** and formation of *N*-methylaniline and a new, more polar, product. The reaction mixture was stripped in vacuo and the brown semisolid residue chromatographed on silica gel 1.5-mm plates (3% CH_3OH in $CHCl_3$ elution). Isolation of the (polar) product band gave 0.67 g (55%) of **8** as an oil which crystallized when scratched. An analytical sample was recrystallized from ethanol: mp 120.5–121.5 °C; ir (mull) 6.20, 6.80, 7.58, 8.78, 8.98 (br), 9.39, 10.70, 11.26, 11.48, 11.77, 12.56, and 13.8 μ (br); NMR ($CDCl_3$) δ 7.08 (d, J = 13 Hz, 1 H), 4.84 (d, J = 13 Hz, 1 H), 3.80 (m, 8 H), 3.29 (m, 4 H), 3.06 (m, 4 H); mass spectrum *m/e* 262 (P).

Anal. Calcd for $C_{10}H_{18}N_2O_4S$: C, 45.78; H, 6.92; N, 10.68. Found: C, 45.93; H, 6.78; N, 10.82.

Acknowledgment. The authors are grateful to Dr. J. G. Pacifici for helpful discussions.

Registry No.—**1a**, 60538-03-6; **1b**, 60353-82-4; **1c**, 60353-81-3; **1d**, 660-13-9; **1e**, 60353-00-6; **1f**, 60353-09-5; **3a**, 60538-04-7; **3b**, 60538-05-8; **3c**, 60538-06-9; **3d**, 60538-07-0; **3e**, 60538-08-1; **3f**, 60538-09-2; **8**, 60538-10-5; vinylsulfonyl fluoride, 677-25-8; R_1R_2NH (R_1R_2 = 1-indolinyl), 120-72-9; R_1R_2NH (R_1 = Ph; R_2 = Me), 100-61-8; R_1R_2NH (R_1 = Ph; R_2 = Et), 103-69-5; R_1R_2NH (R_1 = Me; R_2 = Me), 124-40-3; R_1R_2NH (R_1 = Ph; R_2 = H), 62-53-3; MnO_2, 1313-13-9; morpholine, 110-91-8.

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Photochemical Oxidation of Alcohols Using Ferric Chloride

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We wish to report quantitative measurements on the formation of aldehydes and ketones during the photochemical oxidation of alcohols by ferric chloride.[1] From the standpoint of organic chemistry, the quantitative information and the knowledge that primary alcohols do not form acids during the oxidation are useful. It is evident that the ferric ion in the excited state is a much stronger oxidizing agent than in the ground state. The emphasis of earlier studies[2-6] has been mainly on the ferric chloride participation, the quantum yields, the effect of acid, and the influence of excess chloride ion on the reaction. The irradiation of an ethanolic ferric chloride solution at 77 K yields the $CH_3\dot{C}HOH$ radical as observed by EPR spectra.[7,8] Methanolic and ethanolic solutions of ferric perchlorate also show the same oxidation–reduction phenomena when irradiated at 365 nm.[5,9,10] Ketyl radicals are also found in these irradiation solutions.

The oxidation of primary and secondary alcohols to the corresponding aldehydes or ketones was achieved by irradiation in a Rayonet photochemical reactor for 5–10 h using the 350-nm lamps in a nitrogen atmosphere. The presence of ferric chloride (0.15 M) was found to be essential for the photochemical oxidation. The isolation and characterization of dimedone and 2,4-dinitrophenylhydrazone derivatives established the formation of the aldehydes and ketones. This was confirmed by comparing the retention times of the aldehydes and ketones on GLC and comparing them with those of the authentic samples. The completion of the reaction was marked by the disappearance of the yellow color of ferric chloride, a positive test for the ferrous ion in the irradiated solutions, and the formation of an intense blue precipitate (Turnbull's blue) with potassium hexacyanoferrate(III). The concentrations of the aldehydes and ketones formed were determined by GLC and their percentages are reported in Table I. The reaction mixtures with primary alcohols were devoid of the corresponding acids indicating that the reaction proceeded only up to the aldehyde stage. The reactions were unsuccessful in the presence of air.

From the data of Table I, several generalizations can be made. The yields decrease with increasing chain length for both primary and secondary alcohols, and secondary alcohols are more dependent on chain length than are the primary ones. A suggested reason for this behavior is that, for the longer chain length compounds, there are competing radical–hydrocarbon reactions which occur at the expense of the alcohol reaction.

Experimental Section

All melting points were taken on a Fisher-Johns melting point apparatus and are corrected. All the alcohols and their corresponding aldehydes/ketones were purchased from Aldrich Chemical Co., Milwaukee, Wis. Anhydrous, sublimed ferric chloride was purchased from Fisher Scientific Co., Fair Lawn, N.J. Alcohols and carbonyl compounds were distilled and their purity was checked by GLC.

Irradiation of Alcohols. The irradiations were carried out in a Rayonet photochemical reactor using 350-nm lamps under a nitrogen atmosphere. Ferric chloride (0.15 M) was dissolved in 20 ml of an appropriate alcohol and the solution was placed in a Pyrex vessel. The irradiation was stopped when the reaction solution became colorless. The photochemical reduction of ferric ion into ferrous ion was substantiated by the formation of a characteristic blue precipitate (Turnbull's blue) by adding potassium hexacyanoferrate(III) to a portion of the irradiated solution.

The 2,4-dinitrophenylhydrazone and dimedone derivatives of aldehyde and ketone products were prepared from the reaction solution by usual methods[11] after removing ferric chloride. The melting points of these derivatives are recorded in Table I. The GLC analyses were performed on a Varian Aerograph Model 90-P instrument equipped with a 20 m × 4 mm column containing 20% Carbowax on 60/80 Chromosorb W.

Table I. Photochemical Oxidation[a] of Aliphatic Alcohols in Presence of Ferric Chloride

Alcohol	Registry no.	Irradiation time, h	2,4-DNP mp, °C	Registry no.	Dimedone, mp, °C	Registry no.	Yield, %[b]
Methanol[c]	67-56-1	5	161	1081-15-8	185	2181-22-8	
Ethanol	64-17-5	5	144	1019-57-4	140	3316-11-8	86.8
1-Propanol	71-23-8	5	152	725-00-8	151	19419-21-7	52.5
2-Methylpropanol	78-83-1	5	186–188	2057-82-1	150	3316-12-9	70.5
1-Butanol	71-36-3	5	119	1527-98-6	140	19419-22-8	60
2-Propanol	67-63-0	10	126	1567-89-1			100
2-Butanol	78-92-2	10	112–113	958-60-1			74.5
2-Pentanol	6032-29-7	10	141	1636-82-4			45.2
2-Hexanol	626-93-7	10	105	2348-17-6			35.5

[a] Photochemical oxidation was carried out under nitrogen atmosphere. The Rayonet photochemical reactor equipped with 350-nm lamps was used. [b] Represents yields of the respective aldehyde or ketone formed during photochemical oxidation. [c] Owing to difficulty in preparing the formaldehyde solution, the percentage yield of formaldehyde could not be determined accurately.

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Registry No.—Ferric chloride, 7705-08-0.

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Stabilization of Singlet Oxygen in Solution. Catalysis of the Thia-allylic Rearrangement by Various Oxygen Species

Summary: All sources of $^3O_2$ and both photochemical and endoperoxide sources of $^1O_2$ show strong catalysis of the thia-allylic rearrangement of phenylallyl sulfides at temperatures in the range of 140–200 °C where, normally, $^1O_2$ is rapidly quenched.

Sir: A long-lived singlet oxygen species has been identified in CS_2 solution by Foote, Peterson, and Lee.[1] This could be correlated with the fact that sulfides form adducts[2] with $^1O_2$, thioanisole forming phenylmethyl persulfoxide. In the course of studies of catalysis in the thermal rearrangement of phenylallyl sulfides[3] singlet oxygen has now been found to form reversibly an adduct which remarkably prevents its conversion to the more stable $^3O_2$ even at elevated temperatures in the range 140–200 °C.

The sources of $^1O_2$ showing this behavior are the usual dye-sensitized preparations[4] as well as certain endoperoxides such as rubrene peroxide, **1**. This latter substance is known[5] to evolve molecular oxygen rapidly and quantitatively at ~140 °C. When **1** is mixed with aliphatic sulfides and the thoroughly degassed solution is heated in a sealed tube to this temperature, the red color of rubrene (**2**) rapidly emerges, and the reaction forming aliphatic sulfoxide appears to be completed in a short time. This is one of several indications that the initial product of decomposition of **1** is $^1O_2$, which eagerly complexes with sulfides prior to sulfoxide formation.[2] Ordinary $^3O_2$ does not produce sulfoxides under these conditions.

When **1** was added to the deuterated phenylallyl sulfide, **3**, and the solution heated, the isomerization to **3a** was greatly accelerated (Table I). The rate of thia-allylic rearrangement[3] of α-methylallyl (**4**) to crotylphenyl sulfide (**4a**) was also strongly enhanced by the presence of **1** (Table II); the catalyzed reaction, k_c, required nearly 7 *kcal* less activation than the unimolecular isomerization, k_1. Apparently, the catalytic species remained at constant concentration and the effective concentration of $^1O_2$ was not diminished by the reaction. The kinetics were cleanly pseudounimolecular for the entire course of reaction pursuit (~80% completion), and no products indicative of oxidation by $^1O_2$ could be found despite the presence of an olefin in the allyl substrate. Moreover, neither the sulfoxide nor the sulfone, possible oxidation products of the sulfide moiety, showed any catalytic activity of the nature displayed by the $^1O_2$.

Atmospheric oxygen saturating a solution of **3** appeared to have even greater catalytic activity than $^1O_2$. Measured amounts of $^3O_2$ could be introduced via the (in situ) thermal decomposition of a mixture of *tert*-butyl hydroperoxide (TOOH) and di-*tert*-butyl peroxide (TOOT) which is known[6] to give rise to molecular oxygen according to the equation $2(TOOH) \rightarrow 2(TOH) + O_2$, when heated in the chlorobenzene solution. Though the k_c for the $^3O_2$-catalyzed isomerization at 160 °C appears to be ~10^3 times as great as that for $^1O_2$ (see Table I), this comparison is meaningless since it was not possible to estimate what proportion of the singlet oxygen formed from rubrene peroxide decomposition was initially quenched and what fraction remained to function as an effective catalyst.

Further proof, however, that catalysis by **1** involves an entirely different species ($^1O_2$) than took part in the molecular oxygen process could be obtained through studying the effect of added rubrene. By itself **2** has no influence on the rate of isomerization, but, in the presence of $^3O_2$, a small quantity of rubrene (~2×10^{-3} mol/l.) in a 0.03 M solution of **4** retards the isomerization rate nearly 55-fold. On the other hand the results of rate studies in which varying amounts of **2** are added to the isomerization reaction of **4** in the presence of **1** afford a very different picture. Only a 25% rate retardation is experienced upon addition of the same amount of rubrene; i.e., rubrene competes with the phenylallyl sulfide substrate for $^3O_2$ in reversible complex formation some 200 times as effectively as it does for $^1O_2$. The rapid absorption of oxygen by rubrene solutions which has been observed here prior to conversion to peroxide **2** under the influence of light suggests

$$2 + {}^3O_2 \rightleftharpoons \underset{\text{rubrene–oxygen triplet complex}}{[\cdot 2\text{-}C_2\cdot]} \overset{h\nu}{\rightleftharpoons} \underset{\text{singlet endoperoxide}}{1} \xrightarrow{\Delta} 2 + {}^1O_2$$

the possibility that a relatively stable Rubrene-oxygen triplet intermediate can form under these circumstances. This would also explain the effectiveness of rubrene inhibition of $^3O_2$ catalysis.

The unusual stabilization of $^1O_2$ by phenylallyl sulfides is also confirmed in studies of the oxidation of thioanisole to its sulfoxide by endoperoxide sources of $^1O_2$. For example, ru-

Table I. Catalysis of the Rearrangement $C_6H_5SCH_2CH{=}CD_2$ (3) ⇌ $C_6H_5SCD_2CH{=}CH_2$ (3a) at 160 °C in *o*-Dichlorobenzene at 0.954 mol/l.[a]

k_{obsd} (10^4) sec^{-1}	Rubrene peroxide (10^2), mol/l.	TOOH[b] in TOOT (10^4), mol/l.	k_{obsd}[b] (10^4), sec^{-1}
0.162	0	0	0.162
0.585	1.65	0.151	0.430
0.690	2.19	1.27	2.94
0.980	3.37	1.94	4.33
1.225	4.18	3.02	6.75

[a] Rubrene peroxide, $k_c = 2.5 \times 10^{-3}$ M^{-1} sec^{-1}; TOOH/TOOT, $k_c{}^b = 2.2$ M^{-1} sec^{-1}; $k_{obsc} = k_1 + k_c[c]^{1.0}$, where [c] is the catalyst concentration. [b] Estimated concentration of TOOH in the TOOT: this estimate could be in error by as much as a factor of two, but the percent error in the [TOOH] is identical in all the entries. Thus, both the k_{obsd} and the k_c here are considered only *apparent* values.

Table II. Kinetics of the Rearrangement (0.03 mol/l.) α-Methylallyl (4) ⇌ Crotylphenyl (4a) Sulfide in the Presence of Rubrene Peroxide (0.025 mol/l.) in *o*-Dichlorobenzene Solution[a]

Temp, °C	k_{obsd} (10^6), sec^{-1}	k_1 (10^6), sec^{-1}	$[k_{obsd} - k_1]$ (10^6), sec^{-1}	k_c (10^4), M^{-1} sec^{-1}
170.0	24.9	1.50	23.4	9.36
160.0	13.7	0.70	13.0	5.20
150.0	6.99	0.29	6.7	2.68
140.0	3.37	0.12	3.25	1.30

[a] $k_1 = (2.78 \times 10^9) \exp(-30{,}800/RT)$; $k_c = (6.34 \times 10^8) \exp(-23{,}900/RT)$.

Table III. Kinetics of Decomposition of Rubrene Peroxide (1) at 1.5 mol/l. in Benzene Solution[a]

Reagents added	Concn (10^4), mol/l.	10^6k (temp, °C), sec^{-1}	Reagents added	Concn (10^4), mol/l.	10^6k (temp, °C), sec^{-1}
None	1.5	4.5 (100), 33 (120), 176 (140)	Thioanisole in decalin	3.0	6.1 (100)
Thioanisole	3.0	5.5 (100), 36 (120)	Thioanisole	30	31 (120), 171 (140)
Thioanisole Phenylallyl sulfide	3.0 3.0	5.9 (100), 36 (120)	Phenylallyl sulfide	12	32.5 (120), 160 (140)
Thioanisole Phenylallyl sulfide	3.0 3.0	5.9 (100), 36 (120)			

[a] Computed: log A = 10.1; correlation coefficient = 0.999; E_a = 26.2 ± 0.12 kcal/mol.

brene peroxide (0.85 g, 1.5 mmol) and thioanisole (0.16 g, 1.26 mmol) were combined in benzene (3.1 ml) and the thoroughly degassed, pressure tubes with such solutions were heated at 140° for 72 h. Other tubes, the same in every respect but containing in addition phenylallyl sulfide (0.15 g, 1.0 mmol), were subjected to identical reaction conditions. The yield (9 ± 1%) of phenylmethyl sulfoxide realized in the absence of **3** was nearly doubled (17%) in the presence of the allylic sulfide; yet no phenylallyl sulfoxide could be detected by NMR, GLC, or other chromatographic means. Comparable results were obtained using diphenylanthracene peroxide (0.545 g, 1.4 mmol) with thioanisole (0.15 g, 1.24 mmol) in benzene (2.5 ml) solution heated for 17 h at ~95 °C. The yield of thioanisole sulfoxide again was more than doubled when the oxidation took place in the presence of phenyllyl sulfide (0.15 g, 1.0 mmol). Replacement of **3** by β-phenyl-*p*-nitrophenylallyl sulfide produced further increases in the yield of sulfoxide and sulfone.

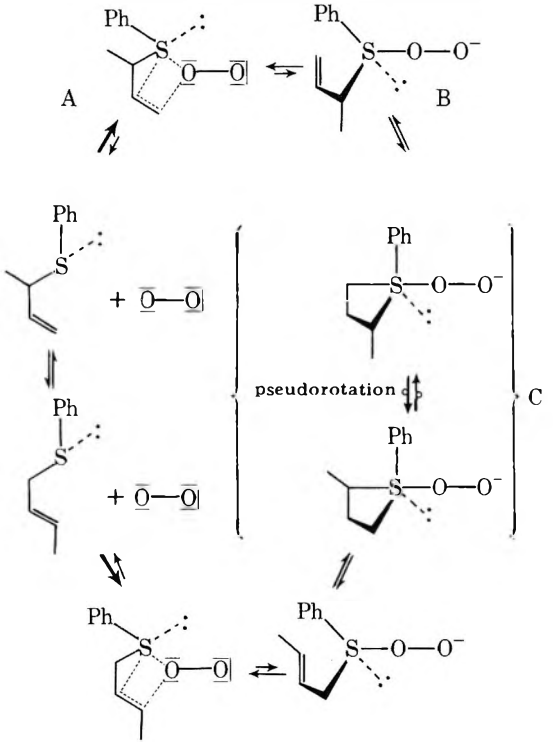
Photogeneration of $^1O_2$ during 8 h of uv irradiation of an eosin-phase transfer agent–benzene solution of thioanisole continuously saturated with oxygen gave ~2.1% sulfoxide, but in the presence of an equimolar amount of phenylallyl sulfide the yield was more than doubled (4.5% thioanisole sulfoxide, 0.5% sulfone with no phenylallyl sulfoxide to be found).

The kinetics of decomposition of **1**, pursued spectrophotometrically in solution in sealed cuvettes, were studied over a 40 °C temperature range. The data (Table III) show that **1** forms **2** and $^1O_2$ unimolecularly and that the rate is almost totally unaffected by the presence of thioanisole, phenylallyl sulfide, or a combination of these reagents. This indicates that there is no induced decomposition of the transannular peroxide involved in the catalysis of thia-allylic rearrangement by $^1O_2$. Moreover, since there is no evidence that $^3O_2$ is present or has been formed during the course of kinetic study with **1**, it can be said the $^1O_2$ is not quenched at the elevated temperatures because it is very rapidly and reversibly sequestered in the form of a phenylallyl sulfide complex of persulfoxide nature. In other words, the $^1O_2$ is surrendered in bimolecular complex formation with phenylallyl sulfides without ever experiencing any freedom as such in the high temperature medium. In this type of complex it is held more tightly than with ordinary sulfides or CS_2.[1,2] In the presence of a large excess of **3** or **4** it appears to be bound and prevented from quenching even at temperatures in excess of 140 °C where there is little tendency for complexing between $^1O_2$ and rubrene.

The simplest explanation of the role of electrophilic catalysts such as $^3O_2$, $^1O_2$, and others[7] in bringing about acceleration of thia-allylic rearrangement must encompass some common features in the catalytic action of all of these reagents. Fortunately it does not seem necessary to devise a uniquely different catalytic mechanism for each recognized catalyst.[8] This is deducible from the previously established fact[3] that the thia-allylic rearrangement involves octet expansion with formation of a trigonal bipyramid (TBP) intermediate which undergoes permutational isomerism[9-11] in the rate-determining step. Thus, the role of catalysts seems most likely to involve lowering of the pseudorotation barrier. It has been anticipated[12] that the higher the hypervalency of the central atom the lower the barrier to permutational isomerism among 3rd row elements. In the case of sulfur this has already been verified experimentally, wherein it has been found in these laboratories[13] that the rearrangement occurs with allylic sulfoxides and sulfones with considerably greater ease than in the case of divalent sulfur, but with very similar reactivity patterns (solvent effects, substituent effects, and isotope effects). Consequently, the most reasonable deduction is that electrophilic catalysts, which can coordinate one of the unshared pairs of the allylic sulfur and thereby effect some increase in its valency, speed up the process of permutational isomerism and thus the thia-allylic rearrangement rate.

Since there are no products formed from direct covalent bonding of $^1O_2$ to either the S or C centers of the substrate, it must be assumed that its preservation against quenching must be the result of a reversible donor–acceptor complex which is considerably more stable than that formed with (say) thioanisole. Scheme I is presented as a rationalization of the

Scheme I. Thia-allylic Catalysis by Singlet Oxygen[a]



[a] A, donor–acceptor complex stabilizing $^1O_2$; B, rearrangement of complex with octet expansion and TBP formation; C, TBP with weak axial bond in the persulfide.

facts discussed above. A similar scheme can also be applied for $^3O_2$ catalysis.

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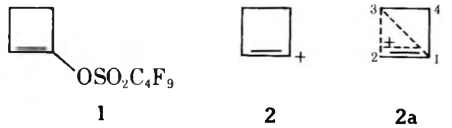
Vinyl Cations. 25.[1] Solvolysis of Cyclobuten-1-yl Nonaflate. Evidence for a Cyclic Vinyl Cation Intermediate

Summary: Cyclobuten-1-yl nonaflate (1) solvolyzes in absolute trifluoroethanol via a cyclic vinyl cation intermediate giving rearranged products. Other probable solvolysis mechanisms were experimentally excluded.

Sir: Compared to other ring vinyl derivatives cyclobuten-1-yl nonaflate (1) solvolyzes with an exceptionally high reaction rate.[2] This was explained by postulating a cationic intermediate (**2a**) in which the positive charge is stabilized by nonclassical interaction.[3] Earlier MO calculations[4] supported the view that the σ-bond orbitals of C_2–C_3 came into overlap with the vacant p orbital of the cation at C_1 (**2a**). Recent ab initio



calculations are in agreement.[5] (At the completely optimized RHF/STO 3G level, **2a** is 2 kcal/mol less stable than the cyclopropylidene cation, **9**.) To obtain an unambiguous insight into the mechanism of the solvolysis of **1**, we have now carried out several experiments which clearly point out a cyclic vinylic cation intermediate.

Beside the vinyl cation mechanism, other compatible pathways in the solvolysis reactions of cyclobuten-1-yl nonaflate (**1**) are the oxygen–sulfur cleavage and electrophilic/nucleophilic addition–elimination reactions.[2] They have, however, been ruled out by kinetic studies which showed that the solvolysis rate of **1** was independent of the pH in the range of 3.2–9.2.[3] An experiment to exclude the oxygen–sulfur cleavage by conducting the solvolysis of **1** in EtOH–$H_2{}^{18}O$ failed owing to the incorporation of ^{18}O into the cyclobutanone oxygen in a blank experiment. The solvolyses of **1** are always carried out at lower temperatures (~75 °C), while an oxygen–sulfur cleavage, including a nucleophilic attack of the solvent at sulfur as in the case of phenyl triflates, occurs only at higher temperatures.[6]

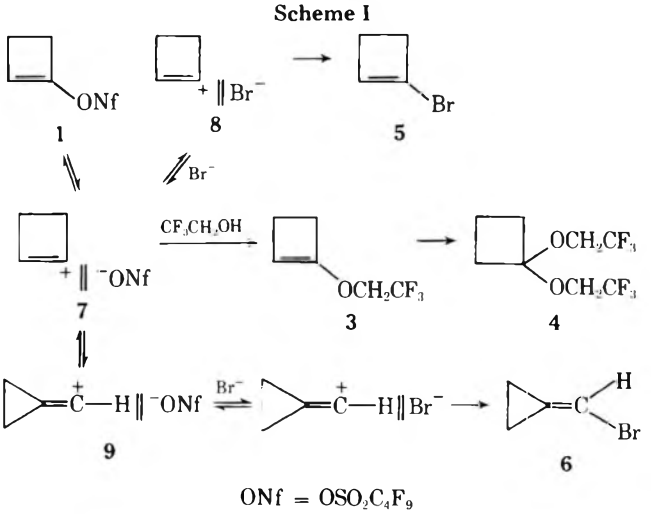
In order to capture the intermediate cyclobuten-1-yl cation, we have now carried out the solvolysis of **1** in absolute trifluoroethanol (TFE) buffered with triethylamine at 75 °C for 10 days. Cyclobuten-1-yl trifluoroethyl ether (**3**) and the ketal (**4**) which were formed[7] in the ratio of 10:1 were isolated by preparative gas chromatography and identified. **3**: NMR δ 4.61 (s, 1 H), 4.18 (q, 2 H), 2.64 (m, 2 H), 2.13 (m, 2 H) ppm; MS *m/e* (rel intensity) 153 (5.5), 152 (61.4, M^+), 151 (6.4), 53 (74.3, cyclobuten-1-ium ion), 39 (base peak, cyclopropenium ion). **4**: NMR δ 3.78 (q, 4 H), 1.6–2.5 (m, 6 H). The formation of the enol ether **3** can be explained only by postulating an intermediate cyclobuten-1-yl cation **2**. The ketal **4** is formed by the addition of TFE to **3**.

An addition–elimination mechanism for the solvolysis of cyclobutenyl nonaflate (**1**) in TFE was excluded unequivocally by carrying out the solvolysis of **1** in absolute CF_3CH_2OD under the conditions mentioned above. The enol ether **3** obtained was examined by GC–MS and found not to contain any deuterium. **3** was separated by preparative gas chromatography and its NMR analysis also showed the complete absence of any deuterium incorporation. The fact that no deuterium was incorporated in **3** rules out an addition–elimination mechanism in the solvolysis of **1**.

A conclusive experiment to prove the intermediate formation of the four-membered cyclic vinyl cation was made as follows. The solvolysis of **1** was carried out in absolute TFE buffered with triethylamine and containing a tenfold excess of tetraethylammonium bromide at 75 °C for 10 days. The product analysis showed that cyclobuten-1-yl bromide (**5**) and cyclopropylidenemethyl bromide (**6**) were formed (53.3% in total) in a ratio of 85:15, along with 34% **3** and 0.9% **4**. The compounds **5** and **6** were identified by GC–MS and NMR spectra, respectively, which were compared with those of authentic samples.[8]

The formation of the bromide **5** and the rearranged cyclopropylidenemethyl bromide (**6**), along with **3** and **4**, are explained as shown in Scheme I, involving ion pairs. In the solvolysis reaction the solvation of the leaving group leads to the solvent separated ion pair **7**. From **7** both the product **3** or the intermediate ion pair **8** are formed which react either with the

Scheme I



solvent or with the nucleophilic bromide leading to **3** and **5**. The rearrangement to form the cyclopropylidenemethyl bromide (**6**) occurs in the solvent separated ion pair **7**. The addition of the excess of tetraethylammonium bromide made the special salt effect possible and the cation **7** had enough time to rearrange and capture the more nucleophilic bromide. This result is in agreement with our earlier work in the solvolysis reactions of other substituted cyclopropylidenemethyl bromides and homopropargyl sulfonates.[9] **5** and **6** are stable under the conditions of solvolysis (75 °C). To bring them to solvolysis, higher temperatures than 75 °C are required.[9]

The next higher homologue of **1**, cyclopenten-1-yl nonaflate and also cyclopenten-1-yl triflate, were recovered practically unchanged even after heating them in an ampule with absolute TFE containing triethylamine as buffer at 100 °C for 10 days. Apparently, cyclopenten-1-yl nonaflate and triflate do not solvolyze with formation of a vinyl cation in TFE, but with an oxygen–sulfur cleavage in the more nucleophilic ethanol/water system.[6]

Acknowledgment. We thank Deutsche Forschungsgemeinschaft for the financial support of this work and the Bayer AG, Leverkusen, for a generous supply of nonafluorobutanesulfonyl fluoride.

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(8) Solvolysis of **1** in 80% TFE buffered with TEA containing a tenfold excess of tetraethylammonium bromide gave identical products except for the formation of more cyclobutanone and less of the trifluoroethyl ketal. The other rearranged product, $HC{\equiv}CCH_2CF_2Br$, could not be detected by GC.
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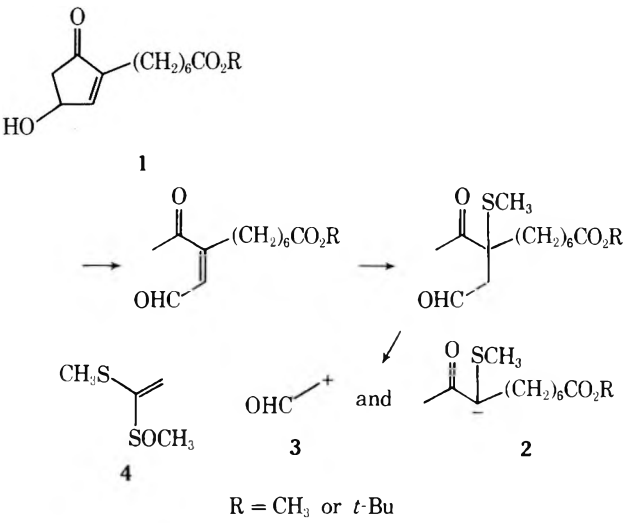
Prostaglandins. An Efficient Synthesis of a 2-Alkyl-4-hydroxycyclopentenone

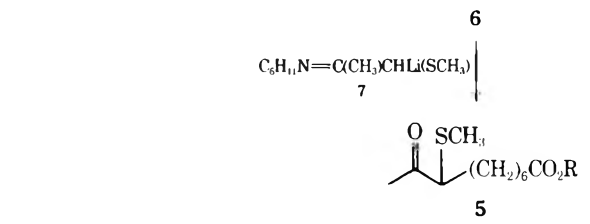
Summary: The preparation of a 2-alkyl-4-hydroxycyclopentenone precursor to PGE_1 is described. This construction is technically simple to achieve and proceeds in good overall yield.

Sir: Hydroxycyclopentenones of type **1** have been shown to be among the most useful of prostaglandin intermediates.[1] We outline here a method for synthesis of **1**, an intermediate leading to PGE_1 and derivatives thereof.

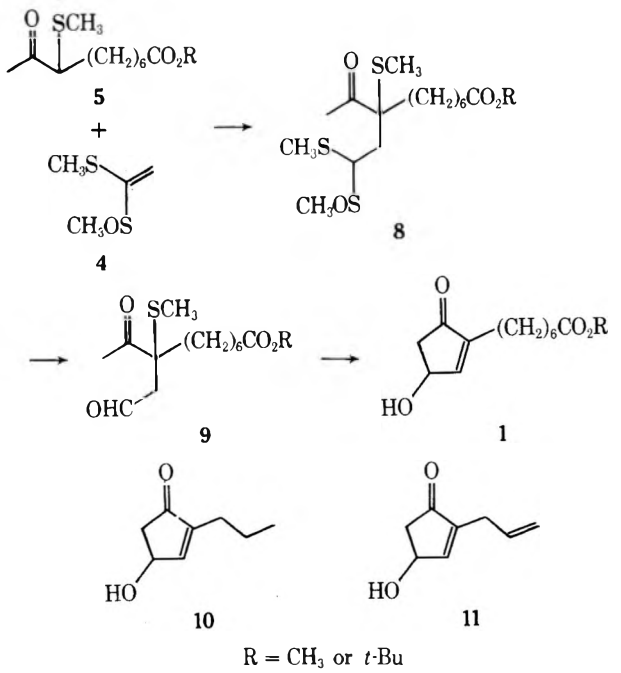
Our construction of **1** arose from the following retro-synthetic consideration which ultimately led to the ketone enolate **2** and the enolonium ion **3**.[2] Efficacy with this scheme has been achieved using the ketene thioacetal monoxide **4**, an experimentally viable equivalent form of enolonium ion **3**.[3]



The synthesis of **1** (R = CH_3 or *t*-Bu) starts with the ketone ester **5** (R = CH_3 or *t*-Bu) which was conveniently prepared in the following manner. Lithium *tert*-butyl acetate (1 equiv, 1 M in THF, −78 °C)[4] was treated with 1,5-dibromopentane (2 equiv) followed immediately by hexamethylphosphoramide (HMPA, 2 equiv). After the mixture was stirred for 10 min at −78 °C, the temperature of the reaction was raised to 0 °C over 2 h and then quenched with saturated ammonium chloride solution. Standard workup followed by distillation from calcium metal gave the bromo ester **6** (X = Br, bp 80 °C at 0.15 Torr) in 65% yield. This material was converted into the corresponding iodide **6** (X = I, bp 65 °C at 5×10^{-4} Torr) in 97% yield using standard methods.[5] Reaction of **6** (X = I, 0.9 equiv) with the lithium imine salt **7**[6] (1 equiv, 1 M in THF) at −78 °C for 10 h followed by hydrolysis with a mixture of sodium acetate, acetic acid, and water at 25 °C for 45 min gave the ketone ester **5** (R = *t*-Bu) in 86% distilled yield (bp 85 °C at 5×10^{-4} Torr). Treatment of this material with thionyl chloride in THF/CH_3OH solution (1:1) afforded the ketone ester **5** (R = CH_3, bp 65 °C at 5×10^{-4} Torr) in essentially quantitative yield.



The conversion of **5** into the hydroxycyclopentenone **1** was accomplished by the three-step reaction sequence outlined below. Compound **5** (R = CH_3, 1 equiv) was added to a 1 M solution of *tert*-butyl alcohol containing potassium *tert*-butoxide (0.1 equiv). After the mixture was stirred for 10 min at 25 °C, the ketene thioacetal monoxide **4** (1.06 equiv) was added and the resulting mixture stirred for 1 h at 25 °C. Workup with saturated ammonium chloride solution gave the adduct **8** (R = CH_3) in quantitative crude yield.[7] Without purification, **8** (1 equiv) was treated with 48% HBF_4 (0.025 equiv) dissolved in acetonitrile (0.76 M with respect to **8**) at 21–22 °C for 2 h. The reaction mixture was quenched at 0 °C with saturated sodium bicarbonate and the resultant keto aldehyde **9** (R = CH_3) was isolated, again in essentially quantitative yield.[7] The crude keto aldehyde was then cyclized into the hydroxycyclopentenone **1** (R = CH_3) using a phase-transfer technique.[8] Thus, compound **9** (1 equiv) dissolved in benzene (1×10^{-2} M) was treated with a mixture of saturated



R = CH_3 or *t*-Bu

lithium hydroxide (2 equiv) and Adogen 464 (1 equiv)[9] at 40 °C for 20 min. Evaporation of the benzene solution gave a colorless oil which on vaccum filtration through silica gel followed by crystallization from ether/petroleum ether afforded pure **1** (R = CH_3, mp 45.5–47.5 °C)[10] in 55% overall yield from **5**.[11] The identical reaction sequence gives an overall yield of 50% for **1** where R = *t*-Bu (oil). In addition, the hydroxycyclopentenones **10** and **11** have been prepared by this method in overall yields of 70 and 50%, respectively.

We intend to prepare other hydroxycyclopentenones related to **1** using this technically simple reaction sequence.

Acknowledgment. We thank the National Institutes of Health and the Hoffmann La-Roche Corporation for support of this work.

Supplementary Material Available: Experimental procedures for reactions described (6 pages). Ordering information is given on any current masthead page.

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(11) We thank Dr. K. G. Untch of the Syntex Research Institute for a generous sample of racemic compound **1** (R = CH_3).
(12) Sherman-Clarke fellow of the University of Rochester and Hooker fellow of the University of Rochester.
(13) Postdoctorate associate supported by NIH grant HL 17341.
(14) Hooker fellow of the University of Rochester.

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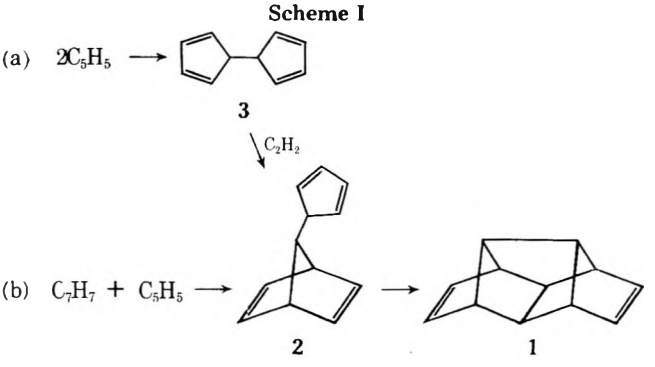
The Reaction of 7-Chloronorbornadiene with Thallium Cyclopentadienide. A Convenient One-Step Synthesis of Hexahydro-3,4,7-methenocyclopenta[*a*]pentalene[1]

Summary: The thermally promoted reaction of thallium cyclopentadienide with 7-chloronorbornadiene provides a convenient, single-stage, preparative route to the title hydrocarbon (**1**) accompanied by minor amounts of dihydro-*as*-indacenes **7–9.**

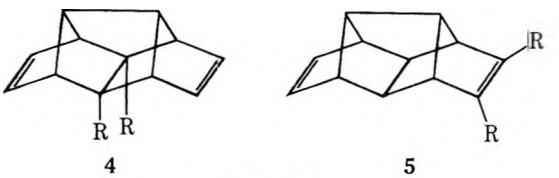
Sir: The novel $C_{12}H_{12}$ hydrocarbon, hexahydro-3,4,7-methenocyclopenta[*a*]pentalene (**1**),[2] may be formally considered to derive from the combination of two cyclopentadienyl (C_5H_5) residues with acetylene (C_2H_2) or alternatively from the coupling of 7-norbornadienyl (C_7H_7) and cyclopentadienyl (C_5H_5) residues as depicted in Scheme I. Critical to the success

Scheme I



of either pathway is the rapid intramolecular [4 + 2] cycloaddition of the intermediate 7-(5-cyclopentadienyl)norbornadiene (**2**).

In practice the synthetic feasibility of path a has been demonstrated recently by Paquette[2] and Hedaya[3] and their co-workers employing a reactive acetylenic dienophile. Thus, the reaction of preformed 9,10-dihydrofulvalene (**3**) with dimethyl acetylenedicarboxylate afforded the 1:1 cycloadducts **4** and **5** in 23.2 and 16.8% yield, respectively. By a sequence



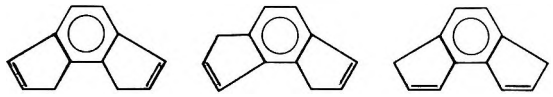
R = CO_2Me

of reduction, hydrolysis, and oxidative decarboxylation the minor adduct **5** was subsequently converted[2] to the parent diene **1** in an overall yield of 7.3%.[4] In an effort to expedite the synthesis of **1** for further synthetic and mechanistic studies

of polyfused cyclopentanoid systems we have examined the preparative value of path b in Scheme I and now wish to report our preliminary findings which detail a convenient one-step synthesis of **1** in 8–12% yield from commercially available starting materials.

Generation of tetraene **2** by path b would appear to require a reaction between 7-norbornadienyl cation and cyclopentadienyl anion; however, for convenience we favored the in situ formation of these reactive partners from appropriately stabilized precursors in a moderately polar aprotic solvent. Thallium cyclopentadienide (TlCp) was chosen as the cyclopentadienyl anion precursor on the basis of thermal stability and possible catalytic role of the metal ion on ionization of a suitable 7-norbornadienyl substrate, e.g., 7-norbornadienyl chloride (**6**-Cl). Accordingly, solutions of **6**-Cl in dry diglyme containing 10–80% molar excess of suspended TlCp were heated at 150 °C for 3–4 h under nitrogen and the reaction products separated from the thallium salts. Chromatography of the crude reaction product on silica gel with pentane afforded an initial fraction containing only diene **1** and dicyclopentadiene, a side product from decomposition of TlCp. Preparative GLC separation afforded pure **1**: ^{1}H NMR ($CDCl_3$) δ 5.79 (t, 4 H, J = 2.0 Hz), 2.85 (q, 4 H, J = 2 Hz), 2.43 (m, 2 H), and 1.80 (t, 2 H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$) 49.08, 60.58, 61.64, and 132.51 ppm from TMS; mass spectrum (70 eV) *m/e* (rel intensity) 156 (16.4), 155 (28.6), 154 (4.8), 152 (16.7), 141 (22.2), 128 (20.6), 115 (29.7), 91 (100), and 78 (21.5). The mass spectrum of **1** was unusual in that it indicated successive loss of one, two, and four hydrogen atoms from the parent ion to form a $C_{12}H_8$ ion (accurate mass) which most reasonably has the acenaphthylene structure.

The later pentane fractions from the original silica gel chromatography contained a third material along with minor contaminants which were removed by preparative GLC separation. Analysis of the separated material on a capillary column revealed at least two incompletely separated components in ~1:1 ratio. The proton spectrum ($CDCl_3$) showed an aromatic two proton singlet at δ 7.16, a set of complex, but sharply defined, two-proton olefinic multiplets at 6.7–7.0 and 6.2–6.6, and a pair of allylic triplets (J = 1.7 Hz) at 3.35 and 3.24 integrating for a total of four protons. This spectrum compares favorably with the published[5] spectrum for a mixture of dihydro-*as*-indacenes **7** and **8** (and possibly **9**). The



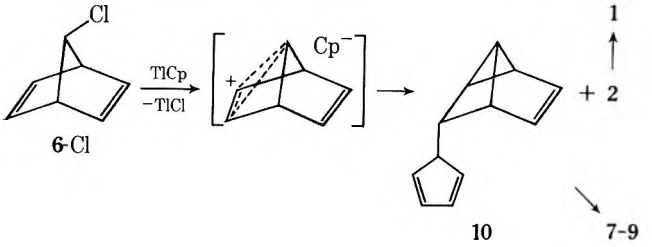
7 **8** **9**

mass spectrum [70 eV, *m/e* (rel intensity) 154 (82.5), 153 (100), 152 (45.4), 77 (10.8), 76.5 (8.4), and 76 (31.6)] is entirely consistent with this assignment.

Altogether some six–eight reactions were carried out in diglyme (150 °C) according to the described procedure and employing 0.5 g, 1.0 g, or 2.0 g of **6**-Cl. Despite variations in the workup procedure the yield of diene **1** after silica gel chromatography consistently averaged ~100 mg/g of **6**-Cl (NMR or GLC analysis).[6] Thus the preparation of **1** on the gram scale by this method is entirely feasible. Furthermore, if analytical grade **1** is not required, material of at least 90–95% purity can be obtained by careful chromatography on silica gel with pentane, **1** eluting just prior to dicyclopentadiene.

Although the yield of diene **1** was consistent in the above reactions the total number of hydrocarbon products and the yield of the dihydro-*as*-indacenes appeared to vary with the age and quality of the TlCp reagent. With aged and slightly discolored samples of TlCp the ratio (NMR) of **1** to **7**, **8**, or **9** in the crude hydrocarbon product was 3–4:1. In experiments using freshly obtained TlCp[7] the yield of **7–9** was considerably reduced and a new hydrocarbon component, tentatively identified as a tetrahydro-*as*-indacene isomer, was detected by GLC and NMR.

The formation of diene **1**, together with the dihydro-*as*-indacenes **7–9**, may be satisfactorily rationalized by invoking initial generation of an intimate 7-norbornadienyl cation–cyclopentadienyl anion ion pair which suffers immediate and stereospecific ion collapse at either the C-7 or C-2 positions of the cation skeleton to afford **2** and the tricyclic hydrocarbon **10**. The latter hydrocarbon should undergo a cascading series



of sigmatropic rearrangements to eventually afford an isomeric mixture of tetrahydro-*as*-indacenes which may be expected to at least partially dehydrogenate under the reaction conditions to give **7–9**.

Further exploration of this facile route into a complex series of C_{12} hydrocarbons is planned with particular emphasis on the reaction of preformed 7-norbornadienyl cations with cyclopentadienyl metal derivatives.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this work.

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(7) Commercial grade TlCp was employed as received from Aldrich Chemical Co.

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Novel Substitution Reactions of 4-Chloro-4*H*-pyrazole Derivatives[1]

Summary: 4-Chloro-4*H*-pyrazoles and their mono and di-*N*-oxides have been prepared by treatment of the parent pyrazole with *tert*-butyl hypochlorite or chlorine. Treatment of these chlorides with methanolic base yields 4-methoxymethyl- or 3-methoxymethylpyrazoles, depending upon the structure of the starting materials.

Sir: Recently the synthesis of a 4-chloro-4*H*-pyrazole 1-oxide was reported.[2] We now have prepared the corresponding 4*H*-pyrazole and 4*H*-pyrazole 1,2-dioxide as well as some homologues and have observed some interesting substitution reactions of these compounds.

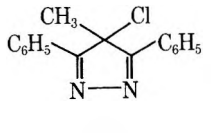
The series, 3,5-diphenyl-4-methyl-4-chloropyrazole (**1**)[3] and the corresponding 1-oxide (**2**) and 1,2-dioxide (**3**), has been

Table I. Elemental Analyses[a]

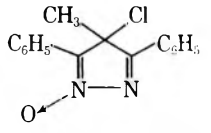
Compd	Calcd, %				Found, %			
	C	H	N	Cl	C	H	N	Cl
1	71.51	4.88	10.42	13.19	71.38	4.91	10.60	13.11
2	67.49	4.60	9.84		67.52	4.72	10.10	
3	63.90	4.36	9.31	11.79	65.70	4.47	9.36	11.98
4	77.25	6.10	10.60		77.25	6.22	10.68	
5	72.84	5.75	9.99		72.73	5.94	9.97	
6	68.91	5.44	9.45		68.62	5.38	9.60	
8	64.87	4.80	8.90	11.26	64.66	4.86	8.89	11.54
9	63.90	4.36	9.31	11.79	63.70	4.47	9.36	11.98

[a] Compounds 10 and 11 were analyzed by mass spectrometer peak matching because only small amounts were available. Calcd for $C_{18}H_{18}N_2O_3$ (10): 310.1318. Found: 310.1283. Calcd for $C_{17}H_{10}N_2O_3$ (11): 296.1162. Found: 296.1122.

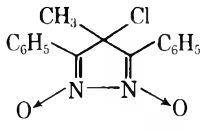
obtained by the action of *tert*-butyl hypochlorite or gaseous chlorine on the parent heterocycle.[4] All react with methanolic



1, mp 115–117 °C

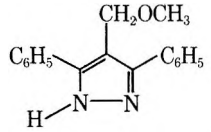


2, mp 109–111 °C

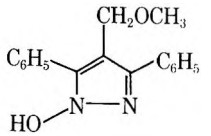


3, mp 140–142 °C

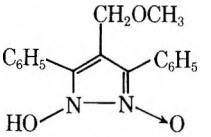
sodium hydroxide[5] to produce the corresponding 4-methoxymethylpyrazole derivatives, **4**, **5**, and **6**,[6] in yields of



4, mp 181–183 °C



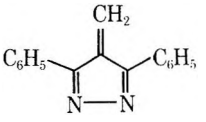
5, mp 157–158 °C



6, mp 183–184 °C

80–95%. These transformations are accompanied by the disappearance of the CCH_3 (δ 2.00–2.18) groups from the NMR spectra, the appearance of OCH_3 (3.42) groups, and the appearance of the low field NH and OH resonances (13.1).

It seems likely that these reactions proceed by an elimination–addition mechanism with the diazafulvene **7** (and its *N*-oxide derivatives) as an intermediate. Burgess and Sanchez have reported the synthesis of the diphenylmethylene analogue of **7** and its reaction with methanol to yield the 4-methoxydiphenylmethylpyrazole.[7]



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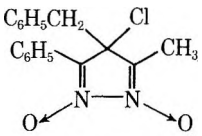
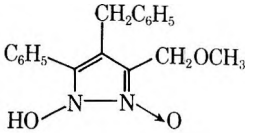
In a somewhat more unusual reaction, treatment of chlorides **8** and **9** in the same manner led to side-chain substitution in the 3-methyl group yielding compounds **10** and **11**. This



8, mp 126–127 °C



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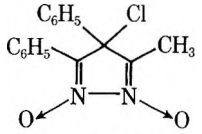
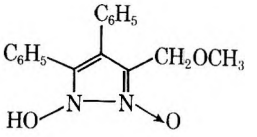


9, mp 127–128 °C



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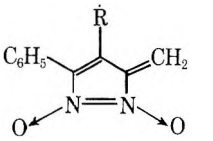
result suggests that the enhanced acidity of these methyl groups leads to the formation of the 3-methylene derivative **12** in these cases.[8] The yields were much lower in these two



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examples and it is apparent that other destructive base-catalyzed reactions operate concurrently. Elemental analyses are given in Table I.

References and Notes

(1) This research was supported in part by a grant from the National Cancer Institute, National Institutes of Health, Grant No. CA-10742.
(2) J. P. Freeman and E. Janica, *J. Org. Chem.*, **39**, 2663 (1974).
(3) A series of unstable 4-bromo-4*H*-pyrazoles has been reported: P. Bouchet, J. Elguero, R. Jacquier, and F. Frissier, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **269**, 570 (1969).
(4) 1-Hydroxypyrazoles and 1-hydroxypyrazole 2-oxides have been reported: J. P. Freeman and J. J. Gannon. *J. Org. Chem.*, **34**, 194 (1969).
(5) Compound 3 gave the corresponding ethyl ether when ethanolic NaOH was used.
(6) Treatment of 3,4,5-trimethylpyrazole with bromine in methanol produces 3-methoxy-3,4,5-trimethyl-3*H*-pyrazole: G. L. Closs and H. Heyn, *Tetrahedron*, **22**, 463 (1966).
(7) E. M. Burgess and J. P. Sanchez, *J. Org. Chem.*, **39**, 940 (1974).
(8) Steric factors also must be involved in the case of compound **8**, since its 4-methyl analogue undergoes the normal reaction leading to the 4-methoxymethyl derivative.

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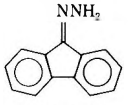
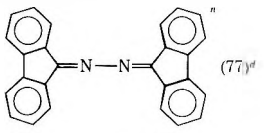
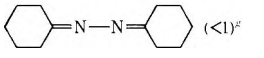
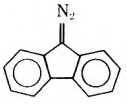
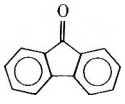
The Reaction of Superoxide with Hydrazines, Hydrazones, and Related Compounds[1]

Summary. Potassium superoxide reacts with various hydrazo compounds and certain related substances in a variety of ways: monosubstituted arylhydrazines are readily oxidized in a reaction which appears to involve free aryl radicals; 1,2-diarylhydrazines are converted to the corresponding azo compound; certain 1,1-disubstituted hydrazines are oxidized to *N*-nitroso amines; and certain hydrazones are converted into the corresponding azine.

Sir: The autoxidation of hydrazines and certain related substances is a well-known but little understood reaction.[2] The redox nature of such processes suggests the possibility that superoxide may be involved.[3,4] In an effort to define the potential role of superoxide in these reactions we have examined

Table I. Reaction of Hydrazines, Hydrazones and Related Compounds with Superoxide[a]

Entry	Substrate	Solvent	Reaction time, h	Product yields (%)[b,c]
1	$C_6H_5NHNH_2$	$C_6H_5CH_3$	16	C_6H_6 (81)
		C_6H_6	16	$(C_6H_5)_2$ (16)
		Me_2SO	16	C_6H_6 (85)
2	p-$CH_3C_6H_4NHNH_2$	C_6H_6	18	$C_6H_5CH_3$ (61) p-$CH_3C_6H_4C_6H_5$ (22)[d]
3	p-$ClC_6H_4NHNH_2$	C_6H_6	18	C_6H_5Cl (48) p-$ClC_6H_4C_6H_5$ (38)[c]
4	$C_6H_5CH_2NHNH_2$	C_6H_6	24	$C_6H_5CH_3$ (54) $C_6H_5CO_2H$ (15)[d] C_6H_5CHO (6) $C_6H_5CH_2OH$ (8)
5	n-$C_8H_{17}NHNH_2$[e]	C_6H_6	24	n-C_8H_{18} (32)
6	$C_6H_5NHNHC_6H_5$	C_6H_6	24	$C_6H_5N{=}NC_6H_5$ (98)
7	(o-$CH_3C_6H_4$)NHNH($C_6H_4CH_3$-o)	C_6H_6	8	(o-$CH_3C_6H_4$)N=N($C_6H_4CH_3$-o) (85)[d]
8	(n-C_4H_9)NHNH(n-C_4H_9)[f]	C_6H_6	24	(n-C_4H_9)N=N(n-C_4H_9) (<1)[g]
			144	(n-C_4H_9)N=N(n-C_4H_9) (<1)
9	$(C_6H_5)_2NNH_2$	C_6H_6	24	$(C_6H_5)_2NNO$[h] (50)
10	$(C_6H_5)(CH_3)NNH_2$	C_6H_6	6	$(C_6H_5)(CH_3)NNO$[i] (33) $(C_6H_5)(CH_3)NH$ (59)
11	$C_6H_5NHNHC(O)NH_2$	C_6H_6	2	$C_6H_5N{=}NC(O)NH_2$[j] (80)[d]
12	$C_6H_5C(=NNH_2)CH_3$	C_6H_6	24	$C_6H_5(CH_3)C{=}NN{=}C(CH_3)C_6H_5$[k] (91)[d]
13	$C_6H_5C(=NNH_2)C_6H_5$[l]	C_6H_6	19	$(C_6H_5)_2C{=}NN{=}C(C_6H_5)_2$[m] (83)[d]
14		C_6H_6	2	 (77)[n]
15		C_6H_6	144	 (<1)[o]
16		C_6H_6	4	 (86)[n]
17	$C_6H_5C(=N_2)C_6H_5$	C_6H_6	30	$C_6H_5C(O)C_6H_5$ (<1)[g]

[a] Reaction carried out at 25 °C. Unless otherwise indicated, a substrate concentration of 0.25 M and a molar ratio of KO_2/substrate = 3 was employed. [b] Yields were determined by GLC unless otherwise stated. [c] Products were identified by comparison of their IR and mass spectra with those of authentic samples as well as GLC retention times and melting points, where applicable. [d] Values based on isolated yield. [e] O. Westphal, *Chem. Ber.*, 74, 759 (1941). [f] H. Feuer, G. B. Silvermann, H. P. Angstadt, and A. R. Fauke, *J. Org. Chem.*, 27, 2081 (1962). [g] A substantial fraction (>90%) of unreacted starting substrate was recovered. [h] Mp 65–66 °C (lit. mp 65–66 °C: M. M. Chen, A. F. D'Adamo, Jr., and R. I. Walter, *J. Org. Chem.*, 26, 2721 (1961). [i] "Organic Syntheses", Collect. Vol. II., Wiley, New York, N.Y., 1955, p 460. [j] Mp 112–114 °C (lit. mp 113–115 °C): H. Beck, E. Baltin, and J. Froner, *Chem. Ber.*, 99, 3337 (1966). [k] Mp 119–121 °C (lit. mp 121.5 °C): U.S. Patent 3 153 089 (Oct 13, 1964); from *Chem. Abstr.*, 62, 490b (1965). [l] R. Baltzly, N. B. Mehta, P. B. Russel, R. E. Brooks, E. M. Grivsky, and A. M. Steinbert, *J. Org. Chem.*, 26, 3669 (1961). [m] Mp 162.5–3.5 °C (lit. mp 162.8–3.8 °C): S. S. Hirsch, *ibid.*, 32, 3433 (1967). [n] Mp 263–268 °C (lit. 262–267 °C): J. Weisburger and P. H. Grandham, *ibid.*, 21, 1160 (1956). [o] A. Pross and S. Sternhall, *Aust. J. Chem.*, 23, 989 (1970).

and report here the reactivity of various hydrazo compounds towards superoxide.

The experimental procedures employed are typified by the following description of the reaction of potassium superoxide with 1,2-diphenylhydrazine. 1,2-Diphenylhydrazine (0.921 g, 5.00 mmol) was added in one portion to a mixture of 18-crown-6 ether[5a] (0.528 g, 2.00 mmol) and powdered potassium superoxide[5b] (1.42 g, 20.0 mmol) in dry benzene (20 ml) at 25 °C contained in a 50-ml flask equipped with a Teflon-coated stirring bar. The subsequent reaction was initially accompanied by a moderate evolution of oxygen; the resulting mixture was stirred vigorously for 24 h and then cautiously poured into 20-ml of water. This mixture was extracted with two 20-ml portions of benzene. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude azobenzene, which was obtained in virtually quantitative yield, was recrystallized from 30% aqueous ethanol. Results obtained on similar treatment of other representative substrates are given in Table I.

These observations reveal that a variety of hydrazo compounds are readily oxidized by superoxide. Taken together, they suggest a picture of the reactivity of hydrazo compounds with superoxide. For example, the reaction of monosubstituted hydrazines (entries 1–5, Table I) with superoxide results in their overall conversion to nitrogen-free products. The fact that the autoxidation of monosubstituted hydrazines results in the same products[2–4] suggests that both processes may be proceeding through a similar mechanistic sequence.

1,2-Disubstituted *aryl*hydrazines and certain related hydrazo compounds (entries 6, 7, and 11) react with superoxide to produce the corresponding azo compound. By comparison, 1,2-disubstituted *dialkyl*hydrazines (as suggested by entry 8) are unaffected by treatment with superoxide under these conditions.[6] In contrast, treatment of several 1,1-disubstituted hydrazines (entries 9 and 10) with superoxide produced, inter alia, significant yields of the corresponding *N*-nitroso amine.

Finally, we have observed that superoxide reacts with certain hydrazones. Thus, a comparison of entries reveals that the hydrazones of acetophenone, benzophenone, and fluorenone (and by extension those of other *aryl* ketones and aldehydes) are converted by treatment with superoxide into the corresponding azine in high yield. However, the hydrazone of a simple representative *alkyl* ketone, viz., cyclohexanone, is unaffected by similar treatment with superoxide (cf. entry

15).[6] The fact that azines are the principal side product produced in the oxidation of unsubstituted hydrazones to diazoalkanes by such agents as mercury(II),[7] silver(I),[8] or manganese(IV) oxide[9] prompted us to briefly examine the reaction of several diazoalkanes with superoxide. Diphenyldiazomethane was recovered unchanged after treatment with superoxide. By comparison, the reaction of superoxide with diazofluorene produces fluorenone in high yield. The reason for this difference in reactivity is not obvious.

Our understanding of the detailed course of these reactions is still incomplete; however, several observations concerning the reaction of monosubstituted aryl hydrazines permit a description of the general features of its reaction with superoxide. First, oxidation of phenylhydrazine in benzene-d_6 produced biphenyl-d_5 (16%), and no observable biphenyl-d_0 or -d_{10} equivalent; benzene isolated from the oxidation of phenylhydrazine in toluene-d_8 showed no deuterium incorporation. Second, oxidation of a 1:1 mixture of 4-methylphenyl- and 4-chlorophenylhydrazine in benzene yielded only two coupling products: 4-methylbiphenyl (10%) and 4-chlorobiphenyl (12%). No other biphenyls were observed. Third, the reaction of 4-chlorophenylhydrazine with potassium superoxide in chlorobenzene produced the following mixture of coupling products: 2,4′-dichlorobiphenyl (8%), 3,4′-dichlorobiphenyl (4%), and 4,4′-dichlorobiphenyl (trace). Finally, the analogous oxidation of 4-methylphenylhydrazine in chlorobenzene yielded 2-chloro-4′-methylbiphenyl (9%), 3-chloro-4′-methylbiphenyl (4%), and 4-chloro-4′-methylbiphenyl (0.5%). Again, no other biphenyls were observed. These results are consistent with the intermediacy of free phenyl radicals in the oxidation of phenyl hydrazines by superoxide. Specifically, (i) the observed coupling products are all solvent derived and (ii) the relative biphenyl isomer distributions produced in chlorobenzene parallel those observed in established phenylation reactions.[10] In light of these arguments, a reasonable mechanism for the reaction of *aryl*hydrazines with superoxide would seem to involve its initial oxidation by superoxide to an aryldiazene (diimide) by an as yet undetermined pathway (eq 1).[11] Autoxidation of diazenes is rapid.[2,12] The subsequent oxidation of this intermediate by a radical chain reaction, in which the initial generation of a phenyl radical by a process whose precise nature need not be specified in detail (eq 2), would be followed by a hydrogen atom transfer from diazene followed by the unimolecular decomposition of the resulting arylazo radical (eq 3–4) to aryl radical and nitrogen. Attack of the aryl radical on the aromatic solvent (eq 5) leads to the observed coupling products.

$$\mathrm{ArNHNH_2} \xrightarrow{O_2^-} \mathrm{ArN{=}NH} \quad (1)$$

$$\mathrm{ArN{=}NH} \rightarrow \mathrm{Ar}\cdot \quad (2)$$

$$\mathrm{Ar}\cdot + \mathrm{ArN{=}NH} \rightarrow \mathrm{ArH} + \mathrm{ArN{=}N}\cdot \quad (3)$$

$$\mathrm{ArN{=}N}\cdot \rightarrow \mathrm{Ar}\cdot + \mathrm{N_2} \quad (4)$$

$$\mathrm{Ar}\cdot + \mathrm{Ar'H} \rightarrow [\mathrm{Ar\text{-}Ar'H}]\cdot \xrightarrow{S\cdot} \mathrm{Ar\text{-}Ar'} + \mathrm{SH} \quad (5)$$

The significance of the observations described here is twofold. First, accepting the limitations on the generality of the reaction, the oxidation of arylhydrazines by superoxide provides a convenient nonphotochemical method for generating free aryl radicals at low temperatures under mild condition. As such, the reaction merits further development as a probe for the study of radical reactions. Second, hydrazo and related azo and azoxy compounds are concerned with a number of important biological reactions[4] including, for example, carcinogenesis[13] and monoamine oxidase inhibitation.[14] In view of the ubiquitous nature of superoxide in aerobic organisms, the results presented here may also provide some insight into the possible metabolic reactions of hydrazo compounds.

Further observations relevant to the mechanisms of these reactions will be reported in later papers.

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References and Notes

(1) Supported by the National Institutes of Health (AM-18713-01).
(2) (a) E. T. Newbold in "The Chemistry of the Hydrazo, Azo and Azoxy Groups", S. Pati, Ed., Wiley, New York, N.Y., 1975, Chapter 14; (b) E. M. Kosower, *Acc. Chem. Res.*, **4**, 193 (1971); (c) P. A. S. Smith, "Open Chain Nitrogen Compounds", Vol. 2, W. A. Benjamin, New York, N.Y., 1966, Chapter 9.
(3) Two of the earliest reports of the autoxidation of hydrazines are to be found in (a) O. Widman, *Ber.*, **28**, 1925 (1895), and (b) F. S. Chattaway, *J. Chem. Soc.*, 1323 (1907).
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(5) (a) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974). (b) Working in a glovebag, lumps of potassium superoxide, purchased from K and K Chemicals, were ground to a fine consistency in a mortar and pestle.
(6) A substantial fraction (>90%) of this substrate and potassium superoxide were recovered unreacted after several days of mixing. The failure to observe an appreciable reaction between 1,2-di-*n*-butylhydrazine or cyclohexylhydrazone and superoxide may reflect the fact that the pK_a of alkylhydrazines and -hydrazones is significantly higher than that of arylhydrazines and -hydrazones (cf. P. A. S. Smith, "Open-Chain Nitrogen Compounds", Vol. II, W. A. Benjamin, New York, N.Y., 1966, pp 150, 151). If, as this observation suggests, the ability of O_2^- to effect the oxidation of these substrates is related to their acidity, it follows that proton abstraction is a necessary step in the oxidation of these substances by superoxide.
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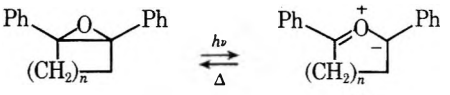
New Photochromic Oxiranes. A Potential Precursor for 2,3-Diphenyloxirene

Summary. A pair of heterobicyclic oxides has been synthesized which undergoes photolysis to give stable cyclic carbonyl ylides; these ylides are highly colored, stable in the solid state as well as in fluid solution at low temperature, and bleach upon exposure to visible light; the photochemistry of epoxydiphenylmaleic anhydride in solution is described.

Sir: The thermal[1] and photoinduced[2] interconversion of three-membered heterocycles into singlet and triplet heterotrimethylene systems or ylides has evoked widespread theoretical[3] and synthetic interest.[1c–e,2] It has been established that stabilization of carbonyl ylides may be achieved by in-

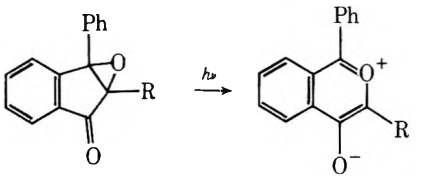
corporation of this moiety into a cyclic structure such as **2a–2c**, where ground-state recyclization of these 4n systems is con-



1a, $n = 1$
b, $n = 2$
c, $n = 3$

2

strained to occur in a disrotatory ("thermally forbidden") manner.[2a,b,g,4] Stable ylides including **4a** and **4b** also have been generated from substrates incorporating aryl-substituted cyclopentadienone or indenone oxide entities such as those present in **3a** and **3b**, respectively.[5]

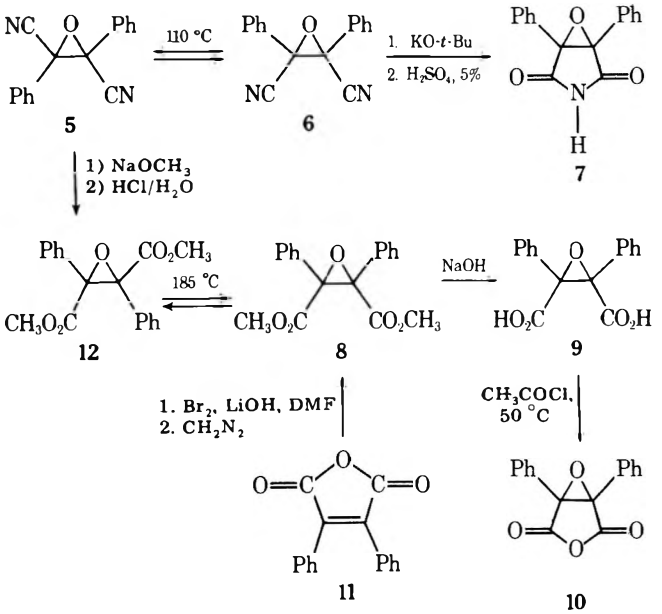


3a, R = Ph
b, R = CH_3

4

We wish to report at this time the results of a recent study in which a new class of stable cyclic carbonyl ylides has been synthesized (Scheme I) and the chemistry investigated. *cis*-

Scheme I

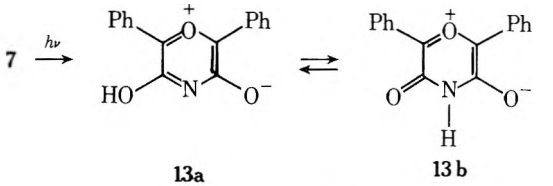


2,3-Dicyanostilbene oxide (**6**, mp 146–147 °C) was prepared by thermal equilibration of the trans isomer **5** (toluene, 110 °C),[1c] obtained in turn by reductive condensation of benzoyl cyanide in accordance with the procedure of Mukaiyama and co-workers.[6] The pure cis isomer **6**, separated from its epimer **5** by fractional crystallization, was then treated with potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature (3 h) and quenched with 5% sulfuric acid to give epoxydiphenylsuccinimide (**7**, 74%, mp 157–158 °C).

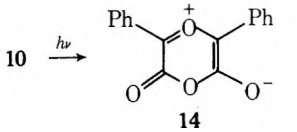
Synthesis of the corresponding anhydride **10** was achieved from *cis*-2,3-dicarbomethoxystilbene oxide (**8**, mp 126–127 °C) which in turn was prepared directly according to the procedure recently developed in these laboratories, which consists of treating methyl phenylglyoxylate with hexamethylphosphorus triamide at room temperature.[8] Hydrolysis of **8** to the dibasic acid **9** (mp 125–126 °C; softens at 98 °C) was accomplished in high yield (97%) by treatment of the diester with aqueous methanolic sodium hydroxide and subsequent acidification with hydrochloric acid (1 N). Dehydration of **9** to diphenylepoxymaleic anhydride (**10**, mp 146–147 °C) occurs smoothly at 50 °C upon treatment with acetyl chloride (>85%).[9] An alternate route for the synthesis of **10** from **5** is depicted in Scheme I, but the overall conversion level is substantially lower. The synthetic details for this process as well as alternate routes to N-substituted analogues of **7** from **10** will be presented in a subsequent full paper on the subject.

The dilithio salt derived in situ from diphenylmaleic anhydride (**11**) was also found to be a convenient precursor for **8** as well as the dibasic acid **9** and epoxy anhydride **10**. To a solution composed of diphenylmaleic anhydride (**11**) dissolved in dimethylformamide, containing lithium hydroxide (10 equiv) and a limited amount of water (10%), was added liquid bromine until an excess was assured. The resulting reaction mixture was stirred for 6 h at room temperature and then quenched with hydrochloric acid (1 N) and ether added. The crude diacid obtained after removal of solvent from the organic layer was heated with pregenerated diazomethane in ether which gave the more tractable diester **8** (41%). The oxide formation is stereoselective if not stereospecific and the trans diester **12** is not formed at least within limits detectable by conventional NMR techniques.

As expected on the basis of previous experience,[2a,b,g] colors are generated when the bicyclic oxides **7** and **10**, which incorporate vicinal diaryl oxirane moieties, are irradiated[10] in rigid matrices such as 2-methyltetrahydrofuran at 77 K (λ_{max} 520 and 541 nm, respectively). To our surprise, however, these colors persist after the matrix is warmed, softens, and appears to become fluid (130–140 K). This represents unique behavior in this series, and suggests that the mesoionic ylides **13** and **14**, presumably responsible for the photochromic behavior,



13a **13b**

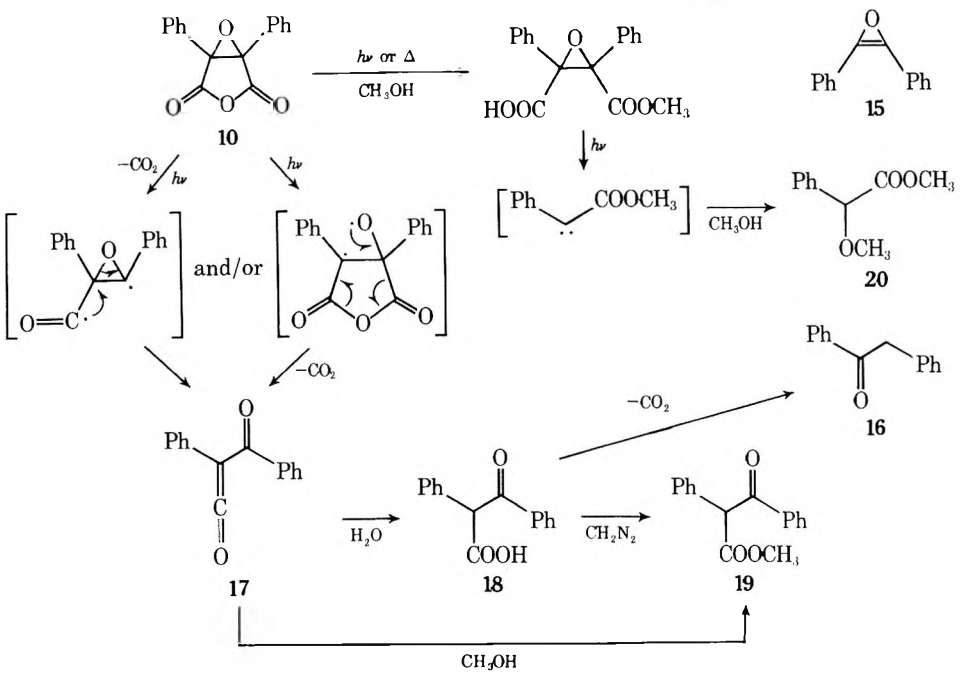


14

are unusually stable relative to their acyclic[2a,b] and monocyclic analogues **2b** and **2c**.[2g,i] As expected, when the matrix contains a dipolarophile such as ethylene (~1:1 by volume), color fading occurs at a significantly faster rate; however, attempts to date to intercept the ylides at ambient temperature with fumaronitrile and 2,3-dimethyl-2-butene proved more complex than observed with **2** and **4** and their acyclic counterparts.[2d,i,j]

That these ylides are stable in the solid state also was readily demonstrated by application of methylene chloride solutions (~0.1 M) of the oxirane **7** (or **10**) to glass slides or paper, evaporation of solvent, and irradiation at 254 nm.[10] Color formation occurs rapidly and, what is more, can be bleached with a 150-W visible flood lamp. In the absence of visible radiation the stability of the colored species may be extended for prolonged periods (2 h), particularly in the case of **7**. Thus it may be concluded that the ylides **13** and **14** are stable in the solid state even at ambient temperature. Unfortunately, color formation is not visually or spectroscopically

Scheme II



detectable upon irradiation of **7** and **10** in fluid solution at ambient temperature in 2-methyltetrahydrofuran.

The anhydride **10** also represents a potential photochemical precursor for 2,3-diphenyloxirene (**15**), a member of an uncharacterized class of compounds.[11,12] Ample precedent exists for the proposed low-temperature photoconversion of **10** to the 4n π-electron system **15**. A variety of cyclobutene-3,4-dicarboxylic acid anhydrides undergo photofragmentation to cyclobutadienes (4n π systems) as well as carbon dioxide and monoxide upon photolysis in rigid matrices at low temperature (77 K).[13]

Preliminary studies of the photochemistry of the anhydride **10** have been conducted in solution at ambient temperature. A major photoproduct detected upon irradiation[10] of **10** in diethyl ether at 40 °C is deoxybenzoin (**16**). Formation of **16** may be rationalized by assuming initial loss of carbon dioxide (Scheme II) to give a diradical (or the cyclic counterpart) in competition with reversible C–C bond cleavage to the ylide followed by electronic reorganization to the ketene **17**. Alternatively, decarboxylation may occur after initial photocleavage of the oxirane C–O bond to give ultimately the same ketene **17**. Hydration of **17** gives the β-keto acid **18**, which is isolable as the methyl ester **19**, and was identified by comparison with an authentic sample. The decarboxylation of **18** provides a rationale for the formation of **16**. The ketene **17** may also be intercepted with methanol to give **19**directly, although competing photocycloelimination of the solvolyzed anhydride to give phenylcarbomethoxycarbene[8] competes effectively. The latter is trapped by methanol to give the methyl ether of methyl mandelate (24%). It is noteworthy that the rearrangement of **9** and/or **10** to **16** in the ground state is catalyzed by trifluoroacetic acid (80 °C) (43 and 27%, respectively).

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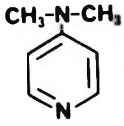
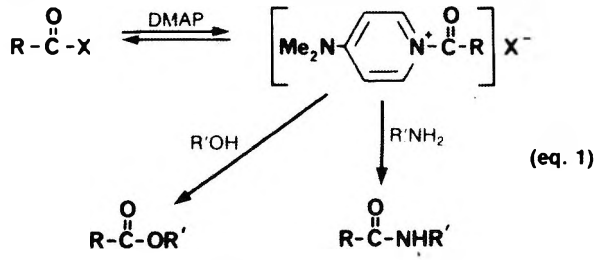


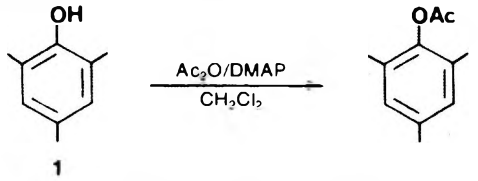
DMAP

The ability of **4-dimethylaminopyridine (DMAP)** to form reactive acylpyridinium intermediates with acid anhydrides and chlorides (eq. 1) enables it to function as a nucleophilic catalyst for the acylation of even highly sterically hindered amines and phenols.



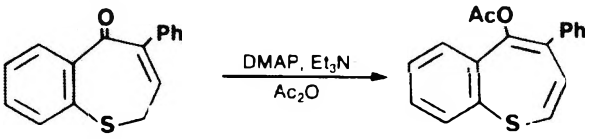
(eq. 1)

This "hypernucleophilic" catalytic activity is a consequence of the combination of the relatively high thermodynamic stability and high kinetic reactivity of the *N*-acylpyridinium intermediate. Thus, mesitol **(1)** is acetylated in nearly quantitative yield in the presence of **DMAP**. Under these conditions pyridine shows negligible catalytic activity.



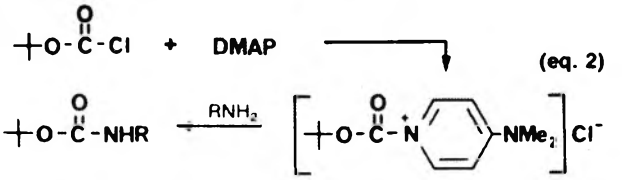
1

Similarly, hydrogen phthalates of hindered alcohols such as *tert*-butyl hydrogen phthalate and (-)-menthyl hydrogen phthalate can be prepared in 97% and 92% yields, respectively. Methyl cholate is acetylated at all three hydroxyl groups in quantitative yield,[1] whereas the use of pyridine as catalyst gives the 3,7-diacetate in 70% yield at room temperature.[2] The benzthiapinone **2** gives the enol acetate **3** when acetylated in the presence of **DMAP**.[3]



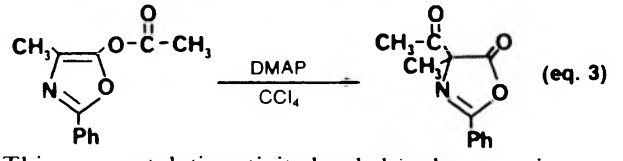
2 3

DMAP reacts with *tert*-butoxycarbonyl chloride to form the *tert*-butoxycarbonyl derivative which is an effective reagent for preparing *t*-BOC amino acids in aqueous solution (eq. 2).[4,5]



(eq. 2)

The "hypernucleophilic" catalytic capability of **DMAP** also enables the facile rearrangement of 5-acyloxyoxazoles to 2- and 4-acyl-5-oxazolinones (eq. 3).[6]



(eq. 3)

This same catalytic activity has led to the extensive use of **DMAP** as a component in the preparation of polyurethanes,[7] polyamides,[8] and polyepoxides.[9]

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