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OCTOBER 8, 1971

Reaction of XeF_2 and Substituted Benzenes. III. Mechanistic Studies[1]

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Received November 30, 1970

The substituent effects, HF catalysis, the products formed, the identification of several radical cations, molecular orbital calculations, a competition study, and the use of HCl and Cl_2 as trapping agents lead us to suggest that xenon difluoride reacts with aromatic compounds to form a complex containing XeF_2, HF, and C_6H_5R which may either collapse to give eventually a fluorobenzene or dissociate to form a radical cation which reacts with starting material to form biphenyls and polyphenyls.

Recently, we reported[2] that xenon difluoride is a useful reagent which effects substitution of fluorine for hydrogen in aromatic compounds to give fluoroaromatics in good yield.[3] It was of interest to examine the mechanism of this reaction. In a number of cases biphenyls, fluorinated biphenyls, and even polyphenyls were found to accompany the major product. Radical cations of benzene and substituted benzenes were proposed as intermediates for both the primary reaction and the formation of by-products.[3] An esr investigation of the reaction of xenon difluoride with substituted benzenes revealed that a variety of 4,4′-disubstituted biphenyl +1 ions were formed.[4] Monocyclic radical cations, however, were not observed.

The purpose of this paper is to present the evidence and to suggest mechanisms for the reactions of XeF_2 with aromatic compounds. In both the fluorination reaction and in the formation of biphenyls, the important intermediates have not been directly observed. The suggested mechanisms are based, therefore, on chemical reasoning, competitive reactions, and analogies and are thus subject to limitations implied by such evidence.

Results

Several important characteristics of the reactions of xenon difluoride with substituted benzenes are summarized.[2-4] (1) Substantial yields of monofluorinated substitution products are observed. (2) The reactions are catalyzed by anhydrous HF and do not proceed without it. (3) Substituent effects are similar to those observed in electrophilic aromatic substitution reactions. (4) Biphenyls and biphenyl radical cations are produced. (5) Fluorine addition products have not been observed.

Catalysis by HF.—The mechanism of fluorination must involve catalysis by HF, since no reaction takes place without it. Only small amounts of HF are necessary for initiation; since about 1.2 mol of HF is generated per mole of XeF_2 added, the reaction is autocatalytic in HF.[2] The oxidation of iodine or sulfur dioxide by XeF_2 is also catalyzed by a trace of HF. These findings were rationalized by assuming that HF facilitates ionization of XeF_2 to XeF^+.[5] However, conductivity measurements of XeF_2 in HF indicate that appreciable ionization does not take place,[6] although fluorine exchange between HF and XeF_2 does occur and is rapid enough to cause coalescence of the separated ^{19}F nmr peaks on warming from −20° to 0°.[7] Infrared measurements have indicated hydrogen bonding between XeF_2 and HF.[8] Thus, the observed acid

(1) Work performed under the auspices of the U. S. Atomic Energy Commission.

(2) M. J. Shaw, H. H. Hyman, and R. Filler, *J. Amer. Chem. Soc.*, **92**, 6498 (1970).

(3) M. J. Shaw, R. Filler, and H. H. Hyman, *ibid.*, **91**, 1563 (1969).

(4) M. J. Shaw, J. Weil, H. H. Hyman, and R. Filler, *ibid.*, **92**, 5096 (1970).

(5) N. Bartlett and F. O. Sladky, *Chem. Commun.*, 1046 (1968).

(6) H. H. Hyman and L. A. Quarterman, "Noble Gas Compounds," H. H. Hyman, Ed., University of Chicago Press, Chicago, Ill., 1963, p 275.

(7) J. C. Hindman and A. Svirmickas, ref 6, p 251.

(8) N. J. Lawrence and G. D. Sturgeon, 157th National Meeting of the American Chemical Society, Division of Inorganic Chemistry, Minneapolis, Minn., April 1969, Abstract 137.

catalysis and the above data may be explained in terms of the equilibrium

$$XeF_2 + HF \rightleftharpoons \overset{\delta+}{F}\text{-}Xe\text{---}\overset{\delta-}{F}HF$$

It might be expected, therefore, that in the presence of HF, xenon difluoride would behave as an electrophile.

Mechanism of Formation of Biphenyls.—Although the formation of biphenyls and polyphenyls represents an unwanted process in the preparation of fluorobenzenes, the mechanism is of obvious interest. Thus, it is possible that the monocyclic precursors to the observed biphenyls and their +1 ions may also be intermediates in the fluorination reaction. Secondly, it has been suggested[9] that benzene radical cations do not react with neutral substituted benzenes (due to a loss in resonance energy), and it was deemed important to determine whether monocyclic radical cations are indeed intermediates in the formation of the biphenyls and their +1 ions.

It seemed possible, *a priori*, that substituted phenyl radicals ($R\text{-}C_6H_4\cdot$), phenyl cations ($R\text{-}C_6H_4^+$), or protonated benzenes ($R\text{-}C_6H_6^+$) could be intermediates in the formation of substituted biphenyls. All of these species are thought to be capable of reacting with benzenes to give biphenyls[10-12] Since a variety of radical cations are observed when XeF_2 reacts with substituted benzenes, monocyclic radical cations were also considered as possible intermediates.

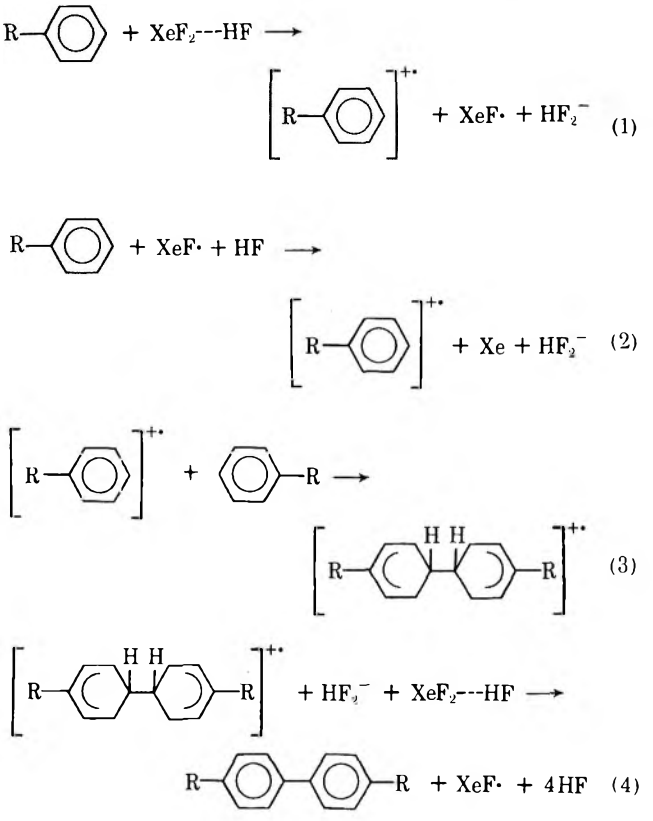
In chlorinated hydrocarbon solvents (*e.g.*, CH_2Cl_2 or CCl_4), chlorine abstraction by the phenyl radical has been observed,[13] but we did not observe any chlorobenzenes among the products of the XeF_2 reaction which casts doubt on the intermediacy of the phenyl radical. Fortunately, the results of competitive reactions are available which provide a chemical test for the presence of the phenyl radical and phenyl cation. The phenyl radical generally exhibits a selectivity of about 4:1 toward nitrobenzene over benzene to produce predominantly 2- and 4-nitrobiphenyl, in preference to biphenyl.[10] The phenyl cation, on the other hand, exhibits a selectivity of about 3:1 toward benzene over nitrobenzene.[11] Of the nitrobiphenyls formed 84% is the meta isomer.[11] Early work in this laboratory has shown that nitrobenzene is soluble in anhydrous HF, is recovered unchanged from HF, and is negligibly protonated in anhydrous HF.[14] Thus, it is unlikely that the chemistry of nitrobenzene would be significantly affected by the presence of small amounts of HF.

Therefore, we conducted a competition experiment using XeF_2 and a 50:50 mixture of benzene and nitrobenzene and have observed that biphenyl and fluorobiphenyl are formed and that nitrobiphenyls are *absent* (see Experimental Section for details and other products). We conclude that it is very unlikely that either the phenyl cation or the phenyl radical is involved in the formation of biphenyls. The absence of nitrobiphenyls also strongly suggests that the monomeric precursor to the observed biphenyls and their +1 ions is an electrophilic species, since it reacts with benzene rather than with the more electron-deficient nitrobenzene ring.

A choice remains between a monomeric radical cation and a protonated benzene. Kovacic, *et al.*,[12] have proposed that protonated benzene is an intermediate in the reaction of benzene with metal chlorides in the presence of aluminum chloride and water. This mechanism seems unlikely when electron-donating substituents are present on the ring, since meta protonation would be required to explain the predominance of 4,4′-disubstituted biphenyls, which we find. In fact, the latter are not found as products in the reaction of metal chlorides and monosubstituted benzenes.[15] Our results are consistent with the formation of benzene radical cations which react as shown in Scheme I.

SCHEME I

SUGGESTED MECHANISM FOR DIMERIZATION



Wexler, *et al.*,[16] have demonstrated that the formation of $C_{12}H_{12}\cdot^+$ is the primary process in the high-pressure gas phase ion–molecule reaction of $C_6H_6\cdot^+$ with benzene. The gas phase reaction of toluene with its radical cation has been shown to yield $C_{14}H_{14}\cdot^+$.[16] Although mass spectrometry does not reveal the structure of these ions, it seems reasonable that these species are the dihydro intermediates proposed in Scheme I, eq 3. These data, combined with our experiments in solution, strongly suggests that benzene and substituted benzene +1 ions do, in fact, react to form biphenyls, which may be further oxidized. It remains to be shown

(9) M. Swarc, *Progr. Phys. Org. Chem.*, **6**, 323 (1968).

(10) (a) D. H. Hey, A. Nechvatal, and T. S. Robinson, *J. Chem. Soc.*, 2892 (1951); (b) D. R. Augood, D. H. Hey, and G. H. Williams, *ibid.*, 2094 (1952).

(11) (a) R. A. Abramovitch and J. G. Saha, *Can. J. Chem.*, **43**, 3269 (1965); (b) J. B. Aylward, *J. Chem. Soc. B*, 1268 (1967).

(12) P. Kovacic and A. Kyriakis, *J. Amer. Chem. Soc.*, **85**, 454 (1963).

(13) D. H. Hey and W. A. Waters, *Chem. Rev.*, **21**, 193 (1937).

(14) H. H. Hyman and L. A. Quarterman, *J. Phys. Chem.* **65**, 123 (1961).

(15) P. Kovacic and R. M. Lange, *J. Org. Chem.*, **30**, 4251 (1965), and references cited therein.

(16) (a) S. Wexler and R. P. Clow, *J. Amer. Chem. Soc.*, **90**, 3940 (1968); (b) S. Wexler and L. G. Pobo, *ibid.*, **91**, 7233 (1969); (c) S. Wexler and L. G. Pobo, *J. Phys. Chem.*, **74**, 257 (1970).

TABLE I

CALCULATED CHARGE DENSITIES FOR SUBSTITUTED BENZENE +1 IONS

	Charge					Convergence
R-C_6H_5	C_1	C_2	C_3	C_4	R	limit
NO_2	+0.192	+0.096	+0.080	+0.088	+0.028	0.031
CF_3	+0.106	+0.082	+0.085	+0.070	+0.214	0.015
H	+0.128	+0.070	+0.090	+0.128	+0.109	0.030
CH_3	+0.130	+0.073	+0.076	+0.064	+0.202	0.021
F	+0.276	+0.131	+0.103	+0.093	−0.176	0.014

whether benzene +1 ions are intermediates in the fluorination reaction.

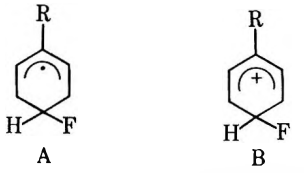
Mechanisms of Fluorination with XeF_2.—Fluorination of aromatic compounds with molecular fluorine in the gas phase yields only fluorine addition products and tars.[17] In view of the large amount of energy released in C–F bond formation, *ca.* 110 kcal/mol^{-1},[18] it is probable that fluorine addition products result from attack of fluorine atoms on the aromatic compound.

Recently, it has been shown that F_2 reacts with aromatic compounds at low temperatures in dilute solutions to give both addition and substitution products.[19] Substituent effects on the formation of substitution product were consistent with an ionic electrophilic substitution reaction. The reaction of benzene and substituted benzenes with XeF_2 bears some resemblance to the above fluorination. However, the absence of fluorine addition products suggests that neither fluorine nor fluorine atoms participate in or are produced during the reaction.

It was suggested that the mechanism of fluorination involves attack of fluoride ion on a benzene radical cation which is formed by oxidation with XeF_2–HF.[3] Perhaps the most important clue to the mechanism of the aromatic fluorination lies in the directional effect of the substituent. For monosubstituted benzene cation radicals, such effects have never been demonstrated.

Since the substituted benzene +1 ions were not observable by esr under the reaction conditions (nor have they ever been observed in solution), it was of interest to calculate the theoretical charge densities as a function of position and substituent in order to determine whether substituents were causing localization of positive charge, which would direct attack by F^- to a particular position on the benzene ring. The Mulliken–Wofsberg–Helmhotz semiempirical method with charge interaction, as described by Carrol, *et al.*,[20] was used. The charge distributions for several positions on the aromatic +1 ions are listed in Table I. It is seen that, within the convergence limit, there does not appear to be any significant variation in charge on carbon atoms 2, 3, and 4 of the benzene ring for a given substituent. Therefore, if it is assumed that a fluoride ion or a polarized segment of a molecule equivalent to F^- would attack the position of highest positive charge, it appears that substituents on these benzene +1 ions do not exert sufficiently strong orientational effects to determine the isomer distribution in the fluorinated products.

It might be postulated that the substituent effects are a function of the stability of the fluorocyclohexadienyl radical produced after attack of F^- on a benzene radical cation. If the incorporation of fluorine into the benzene ring takes place *via* a fluorocyclohexadienyl radical A, substituent effects on this radical should be similar to those observed on homolytic aromatic substitution reactions. Since electron-donating substituents direct substitution predominantly to the ortho and para positions in both homolytic and electrophilic aromatic substitution reactions, the isomer distributions in these fluorinated products, cannot be used to distinguish between species A or B as potential intermediates.



potential intermediate in fluorination

Fortunately, the effect of electron-withdrawing groups on the isomer distribution in the product provides a distinguishing test. The NO_2 substituent is particularly useful in this respect. When nitrobenzene is used, about 90% meta substitution is observed in electrophilic aromatic substitution reactions,[21] whereas less than 10% meta product is formed in homolytic aromatic substitution reactions.[22] When XeF_2 reacts with nitrobenzene, predominantly *m*-fluoronitrobenzene (m/(o + p) ratio = 2.4–3.9) is formed.[2] This is inconsistent with the directive effect of the NO_2 group in the formation of intermediate A. Therefore, it appears that a mechanism of fluorination in which fluorine enters the aromatic molecule by attack of F^- on an aromatic +1 ion does *not* account for the bulk of the fluoro-aromatic compound produced.

Three mechanisms are consistent with the data thus far presented. In the first of these (Scheme II) fluorine atoms are abstracted from XeF_2 by a radical cation which is produced by oxidation of starting materials. The second mechanism (Scheme III) involves the rearrangement of a π complex to a σ complex in the step which determines the final isomer distribution. This mechanism is analogous to the nucleophilic-assisted two-electron transfer mechanism proposed for anodic substitution reactions.[23] On the whole this appears to be the most probable route for the incorporation of fluorine in the molecule.

In the mechanism shown in Scheme IV, a σ complex containing a xenon to carbon bond is implicated. Sta-

(17) N. Fukuhara and L. A. Bigelow, *J. Amer. Chem. Soc.*, **63**, 2792 (1941).

(18) N. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, p 27.

(19) V. Grakauskas, *J. Org. Chem.*, **35**, 723 (1970).

(20) D. G. Carrol, A. T. Armstrong, and S. P. McGlynn, *J. Chem. Phys.*, **44**, 1865 (1966).

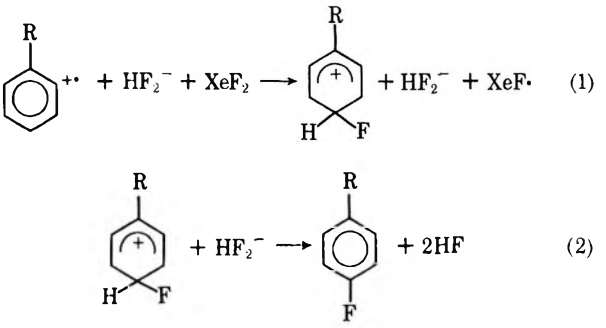
(21) L. M. Stock, "Aromatic Substitution Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1968, p 43.

(22) G. H. Williams, *Int. Ser. Monogr. Org. Chem.*, **4**, 68 (1960).

(23) S. Andreades and E. W. Zahnow, *J. Amer. Chem. Soc.*, **91**, 4181 (1969).

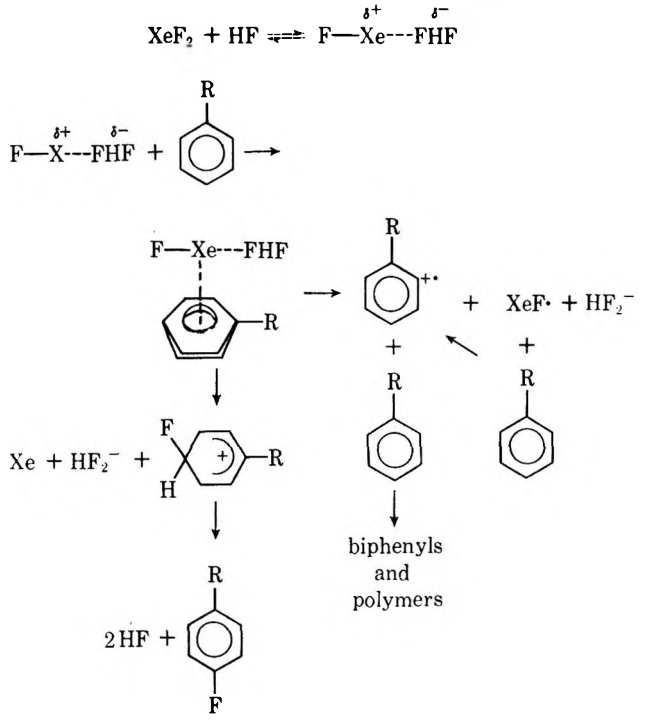
SCHEME II

A RADICAL CATION POTENTIAL MECHANISM FOR THE FLUORINATION OF AROMATIC MOLECULES WITH XeF_2



SCHEME III

A π COMPLEX POTENTIAL MECHANISM FOR THE FLUORINATION OF AROMATIC MOLECULES WITH XeF_2



ble compounds containing xenon to carbon bonds have, as yet, not been prepared by a chemical reaction. However, bombardment of a mixture of xenon and methane with electrons in a mass spectrometer has yielded species containing Xe–C bonds.[24] Nefedov, *et al.*,[25] have observed nonvolatile xenon species to be formed on a tracer scale by the β decay of ^{131}I incorporated into iodobenzene and diphenyliodonium perchlorate, studied the xenon behavior, and concluded that the phenylxenonium ion, $C_6H_5Xe^+$, is formed. Thus, although no compounds of this nature have been reported on a macroscopic scale, compounds with xenon to carbon bonds cannot be entirely dismissed as possible intermediates in the fluorination reaction.

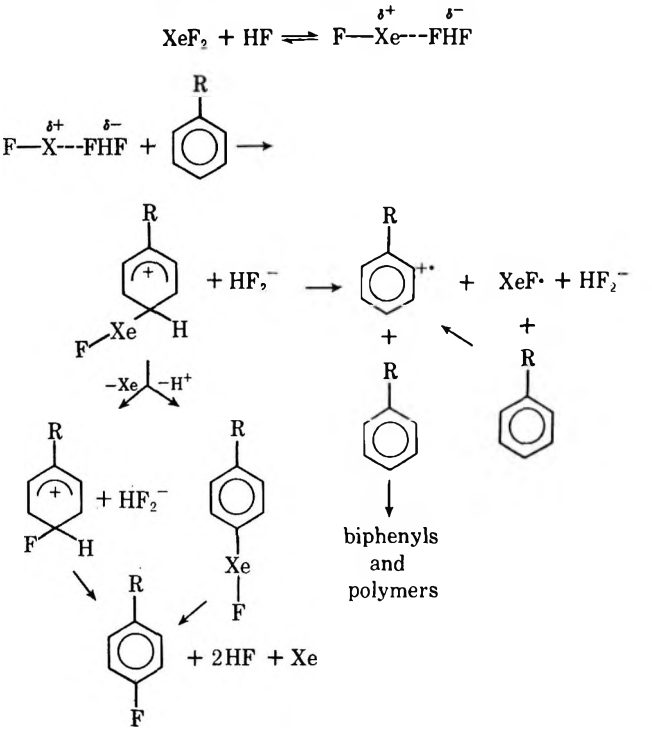
Effect of HCl and Cl_2 on the Fluorination Reaction.—We thought that the effect of hydrochloric acid or chlorine on the fluorination reaction might provide some insight into the mechanism. In a control ex-

(24) J. H. Holloway, "Noble Gas Chemistry," Methuen, London, 1968, p 59.

(25) V. D. Nefedov, M. A. Tropova, A. V. Levchenko, and U. P. Saikov, *Radiokhimiya*, **9**, 138 (1967); **10**, 611, 613, 616 (1968).

SCHEME IV

A Xe BOND POTENTIAL MECHANISM FOR THE FLUORINATION OF AROMATIC MOLECULES WITH XeF_2



periment it was found that above *ca.* −50° HCl is slowly oxidized by XeF_2 to Cl_2. Therefore, when reactions were run in the presence of HCl at 25°, it was also necessary to consider the effect of Cl_2. Benzotrifluoride and nitrobenzene were selected for this study since the CF_3 and NO_2 groups are strongly meta directing in electrophilic aromatic substitution reactions and are ortho–para directing in homolytic aromatic substitution reactions.

Before the results of these experiments are presented it is useful to note that neither benzotrifluoride nor nitrobenzene, themselves, reacted with Cl_2 under any of the experimental conditions employed. Toluene did react with Cl_2 to give substantial amounts of both benzyl chloride and ring chlorinated products and, hence, could not be used. As expected, none of the observed products are isomerized in the reaction medium. The hypothetical compound XeFCl is not formed by an exchange reaction between XeF_2 and HCl at any temperature between −75 and 25°.[26] It was necessary to consider how chlorine atoms, formed during oxidation of HCl, might react with these aromatic compounds. Chlorine atoms react with benzene to give chlorinated addition products as well as substitution products.[27] Since chlorinated addition products were not formed and predominantly meta chlorination is observed (ortho–para chlorine products would be expected for homolytic substitution on nitrobenzene), it is unlikely that reaction of chlorine atoms with nitrobenzene can account for the observed chlorinated products.

The results of these reactions are shown in Tables II and III. Several interesting features are apparent. In the presence of HCl, the formation of chloroben-

(26) M. J. Shaw, J. H. Holloway, and H. H. Hyman, *Inorg. Nucl. Chem. Lett.*, **6**, 321 (1970).

(27) M. L. Poutsma, "Methods in Free Radical Chemistry," E. S. Hayser, Ed., Marcel Dekker, New York, N. Y., 164, p 131.

TABLE II

EFFECT OF CHLORINE ON THE REACTION OF XENON DIFLUORIDE WITH SUBSTITUTED BENZENES[a]

R-C_6H_5	RC_6H_5 added, mmol	XeF_2 added, mmol	HF added, mmol	Cl_2 added, mmol	%[b] RFC_6H_4 formed	Isomer distribution o	m	p	m[c] o + p ratio	%[a] $RClC_6H_4$ formed	Isomer distribution o	m	p	m[c] o + p ratio	% tar	Solvent
NO_2	18.8	6.1	18.0		67.9	14.5	41.8	11.6	2.4						32.1	CCl_4
NO_2	32.8	9.43	31.6	25.2	75.8	16.1	47.8	11.9	2.6	2.7	0.2	1.8	0.7	2.84	21.5	CCl_4
CF_3	23.6	7.8	5.4		79.6	25.0	43.5	11.1	1.8						20.4	CH_2Cl_2
CF_3	10.5	9.3	3.3	3.3	83.6	20.4	53.5	9.7	2.7	8.5	1.0	6.8	0.7	7.2	7.2	CH_2Cl_2
CF_3	36.6	10.6	50.0	50.0	70.5	13.4	46.3	10.8	2.9	18.9	2.5	13.9	2.5	4.2	10.6	CH_2Cl_2

[a] Reaction temperature was 25°. [b] Based on the amount of a starting material that reacted. [c] Corrected for two ortho and two meta positions.

TABLE III

EFFECT OF HCl ON THE REACTION OF XENON DIFLUORIDE WITH SUBSTITUTED BENZENES[a]

R-C_6H_5	RC_6H_5 added, mmol	XeF_2 added, mmol	HCl added, mmol	HF added, mmol	%[b] RFC_6H_4 formed	Isomer distribution o	m	p	m[c] o + p ratio	%[a] $RClC_6H_4$ formed	Isomer distribution o	m	p	m[c] o + p ratio	% tar	Solvent
NO_2	34.2	9.3		14.9	81.2	18.9	50.9	11.4	2.9						22.0	CH_2Cl_2
NO_2	33.7	9.7	16.7		40.1	13.5	23.9	2.7	2.2	31.1	6.9	21.3	3.0	3.2	28.8	CH_2Cl_2
NO_2	18.8	6.1		18.0	67.9	14.5	41.8	11.6	2.4						32.1	CCl_4
NO_2	27.6	8.8	23.7		29.7	9.3	16.3	4.1	1.8	41.5	5.0	34.3	2.2	7.1	29.8	CCl_4
CF_3	23.6	7.8		5.4	79.6	25.0	43.5	11.1	1.8						20.4	CH_2Cl_2
CF_3	60.0	17.3	8.2[d]		48.3	16.8	23.4	8.1	1.4	48.9	9.9	32.4	6.6	2.9	2.8	CH_2Cl_2

[a] Reaction temperature was 25°. [b] Based on the amount of starting material that reacted. [c] Corrected for two ortho and two meta positions. [d] After reaction it was found that 0.2 mmol of Cl_2 was present.

zenes is competitive with the formation of fluorobenzenes. Even when a large excess of Cl_2 is used only low yields of chlorobenzenes are obtained. Thus, it is clear that the significant yields of chlorobenzenes when HCl is used do not arise from a reaction involving Cl_2.

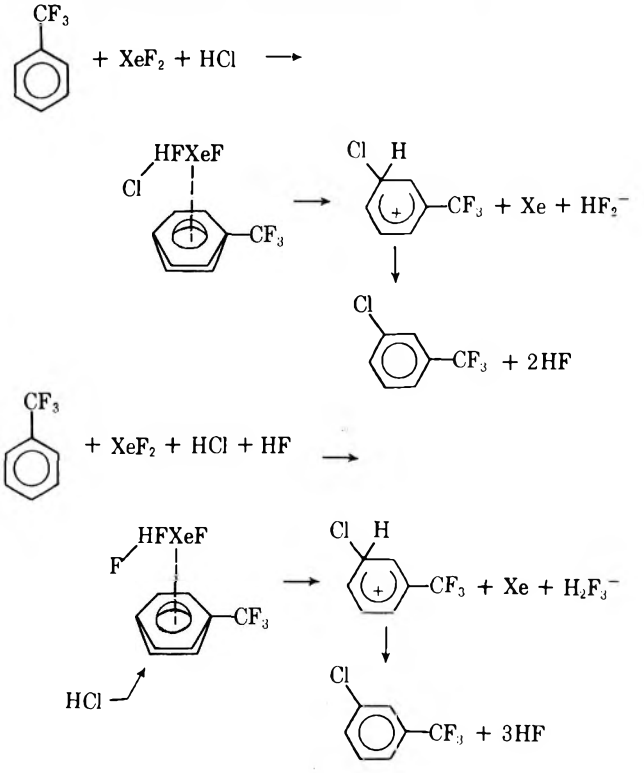
The question then arises, "How are chlorobenzenes produced when HCl instead of HF is added?" Since predominantly meta orientation by the CF_3 and NO_2 groups is observed in both the fluorination and chlorination reactions, the argument used above with reference to reaction of a fluoride ion would be applicable and, thus, it is unlikely that the bulk of the chlorinated product is formed by reaction of a monomeric radical cation with Cl^-. Addition of Cl_2 results in the formation of small amounts of chlorobenzotrifluoride (at the expense of tar formation), without, however, significantly affecting the yield of fluorobenzotrifluoride. This suggests that reaction of a radical cation with Cl_2 may be a side reaction. Reaction of a radical cation with Cl· would be less probable since the concentration of both species would be very low. However, these reactions cannot account for the high yield of chlorobenzotrifluoride when HCl is used. Thus, the formation of a complex between the aromatic and the xenon bearing molecule appears to be an essential part of the reaction mechanism.

In Scheme V we have illustrated two ways in which HCl may be incorporated in that complex. The essential difference between these two possibilities is the function of HCl. In one hypothesis, HCl is both a catalyst, polarizing the XeF bond, and a reagent, serving as a source of Cl^-. In the second HCl is only a source of Cl^-.

We find, however, that HCl is not an effective catalyst for reaction of XeF_2 with the aromatics. Xenon difluoride reacted immediately with benzotrifluoride at −75° when HF was used as a solvent to give a 50% yield of fluorobenzotrifluoride. However, when anhydrous HCl was used as the solvent, no reaction took place at −75° after 2 days. It is therefore clear that

SCHEME V

ROLE OF HCl IN REACTION OF AROMATIC MOLECULES AND XeF_2



HCl does not polarize the Xe–F bond sufficiently to permit reaction with benzotrifluoride. Since HF is produced by oxidation of HCl with XeF_2 at the reaction temperature (25°), HF, not HCl, is the catalyst in these reactions, but HCl may still react with the complex as shown in Scheme V to incorporate chlorine in the aromatic molecule. This suggests that the fluorine, which is incorporated into aromatic compound, is derived from HF, not XeF_2. Summarizing our analysis at this point, the mechanism of fluorination of aromatic compounds with XeF_2 is best described by a pro-

cess which is formally analogous to the nucleophile assisted two-electron transfer mechanism proposed for anodic oxidation substitution reaction, namely the formation of a complex between the aromatic molecule and an XeF_2–HF polarized molecule followed by reaction with HF and elimination of Xe.

Summary.—The products and characteristics of the reactions of xenon difluoride with aromatic compounds are best explained by a mechanism which involves the reaction between a complex of XeF_2 with HF a substituted benzene to yield an intermediate neutral complex molecule which may either react with HF and rearrange to give a fluorobenzene or fragment to give a monocyclic radical cation which then reacts to form a biphenyl. A competition study has provided presumptive evidence for monocyclic radical cations as intermediates in the formation of the observed biphenyls. The effects of HCl and Cl_2 on the reaction are consistent with this mechanism.

Experimental Section

The method of carrying out the reaction of XeF_2 with a number of aromatic molecules while varying solvent, temperature, and other reaction conditions and separating and analyzing the products both qualitatively and quantitatively has been described previously in detail.[2] In brief, purified reagents are handled in polychlorotrifluoroethylene equipment with air rigorously excluded, the rate of reactions controlled by adjusting the temperature or concentration of HF, products separated and quantitatively estimated using a variety of gas chromatographic columns, products characterized largely by ir, mass spectroscopic, and nmr techniques. The results of these experiments are basic to the development of the concepts stated in this paper.

Specific additional experiments carried out for this paper include the competitive reaction between nitrobenzene and benzene and the effect of Cl_2 and HCl on the reaction of XeF_2 with nitrobenzene and benzotrifluoride.

Cl_2 was reagent grade and used as available. Anhydrous HCl was purified in the following manner. A tank containing commercial "anhydrous HCl" was cooled to $-75°$, after which a measured amount was tranferred *in vacuo* to a 120-cc Kel-F tube at $-196°$. The tube, at $-196°$, was then evacuated to 5×10^{-6} Torr to remove O_2. The infrared spectrum of the resulting material revealed only the presence of HCl. These experiments were carried out exactly as described in ref 2, adding either Cl_2 or HCl at the start of the reaction in the amounts shown in Tables II and III, respectively. The competitive reaction experiment was carried out as follows.

Competitive Reaction between Nitrobenzene and Benzene with XeF_2.—A solution of 0.0288 mol of benzene and 0.0195 mol of nitrobenzene in 15.46 g of CH_2Cl_2 in a 29-cc Kel-F tube was degassed by the freeze–thaw technique until the change in pressure upon opening the tube to the pumping manifold was less than 10^{-5} Torr. The solution was then decanted *in vacuo* into another 29-cc Kel-F tube containing 0.019 mol of XeF_2 whose infrared spectrum indicated the absence of HF and XeF_4. The solution was frozen at $-125°$ and *ca.* 0.03 mol of HF was added. Reaction began immediately after removal of the cooling bath as indicated by appearance of a dark green color and evolution of gas into a ballast volume. The reaction mixture was allowed to warm slowly to room temperature with occasional application of a Dry Ice bath to control the rate of gas evolution. The total reaction time was 2 hr. Xe (1 mol) was evolved per mol of XeF_2 used. Mass spectral analysis of the gas phase indicated the presence of *ca.* 5×10^{-6} mol of H_2. The gas phase was condensed into 1.000 *M* NaOH which was back-titrated with 1.000 *M* HCl. In this manner it was determined that *ca.* 0.011 mol of HF was generated in the reaction.

The liquid phase was distilled at 25° *in vacuo* into a 29-cc Kel-F tube by application of a liquid nitrogen bath. Comparison of the infrared spectrum of the distillate with known solutions indicated the presence of benzene and fluorobenzene. Gas chromatographic analysis of the distillate, using a flame ionization detector and a 15 ft $\times$ 0.25 in. column of 8.5% diethylene glycol succinate on Chrom G 70–80 mesh, revealed the presence of 0.74 g of benzene, 0.20 g of fluorobenzene, and a trace of *p*-difluorobenzene.

Fractional sublimation of the nonvolatile products at 225° and 0.4 Torr (conditions under which all nitro dimers would sublime) yielded 0.5 g of residue and 3.15 g of sublimate. Analysis of the sublimate on a 6 ft $\times$ $^1/_8$ in. 3% silicone oil (SF96) on Chrom G 80–100 column at 100° gave 2.11 g of nitrobenzene and 0.84 g of a mixture of biphenyl and fluorobiphenyl and indicated the absence of fluoronitrobenzenes. Mass spectral analysis indicated that the mixture of biphenyl and fluorobiphenyl was predominantly the former. At 175°, the column described above was capable of separating all three isomers and nitrobiphenyl. Chromatography of the sublimate at this temperature revealed the absence of all three nitrobiphenyls. It is estimated that if 1 mg of nitrobiphenyl had been present, it would have been detected. Using a mass spectrometer (Perkin-Elmer 270) as the detector, the presence and absence of the above products was further established, and also, trace amounts of polyfluorobiphenyls and terphenyls were found. Elemental analysis of the polymer gave N, 3.33; C, 77.5; H, 3.99; F, 5.5%. After correction for substituents, a C/H ratio of 1.45 is calculated and comparison of the limiting C/H for polyphenyl of 1.5 with the observed C/H ratio indicates a polyphenyl structure. The absence in the infrared region of the 3035-, 1603-, 1575-, 1190-, and 890-cm^{-1} bands for low-molecular-weight polyphenyls[28] indicates a high-molecular-weight polymer. The 695-cm^{-1} band in high-molecular-weight polyphenyls[28] was observed. The spectrum exhibited a strong C–F band and was further characterized by the complete absence of the characteristic NO_2 absorptions. Thus, it appears that the nitrogen in the polymer arises from a reaction other than ring to ring dimerization. No trace of chlorobenzene or chlorobiphenyl was found.

Mass balance was achieved within experimental error, *i.e.*, 2.39 g of nitrobenzene added and 2.11 g recovered; 2.25 g of benzene added and 0.74 g recovered, plus 0.20 g of fluorobenzene, 0.84 g of a mixture of biphenyl and fluorobiphenyl, and 0.54 g of polymer.

Registry No.—Xenon difluoride, 13709-36-9; nitrobenzene, 98-95-3; benzene, 71-43-2; $CF_3C_6H_5$, 98-08-8; $CH_3C_6H_5$, 108-88-3; FC_6H_5, 462-06-6.

Acknowledgment.—We are grateful for the assistance given us by Drs. L. Kaplan and K. Wilzbach and M. Studier (in the mass spectral identification of compounds) and also to the Argonne analytical group. We also thank Dr. V. Scherr for assistance in the calculation of charge densities.

(28) C. S. Marvell and G. E. Hartzell, *J. Amer. Chem. Soc.*, **81**, 448 (1959).

Ion Radicals. XXII. Reaction of Thianthrenium Perchlorate ($C_{12}H_8S_2^{\cdot+}$ ClO_4^-) with Aromatics[1,2]

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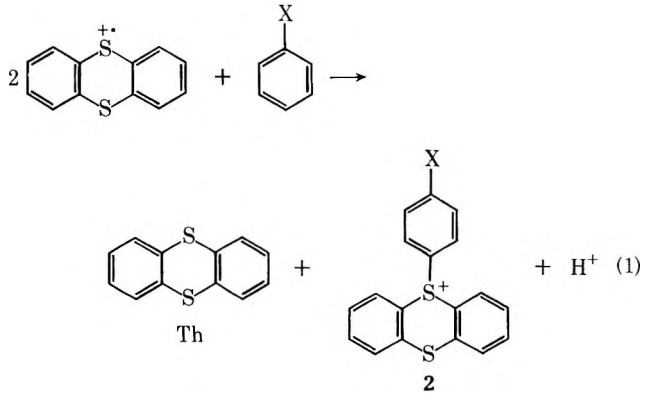
Thianthrenium perchlorate (1) reacts rapidly with C_6H_5X where X is methoxy and slowly where X is methyl. The product is a sulfonium perchlorate, $C_{12}H_8S_2C_6H_4X^+$ ClO_4^-, in which the thianthrene unit is para to X. Kinetic studies with anisole show that reaction is second order in the thianthrene cation radical ($Th^{\cdot+}$). This is interpreted as showing that the reactive agent is the thianthrene dication (Th^{2+}), formed in low concentration in solution by disproportionation of the cation radical. Reaction of 1 with benzene, chlorobenzene, and nitrobenzene was too slow to observe. Reaction with *m*-xylene was slow and gave a sulfonium salt which could not be crystallized.

Few authentic reactions of organosulfur cation radicals (sulfinium ions) are known. Occasionally, cases are to be found in the literature in which sulfinium ion reactions are inferred from the behavior of organosulfur compounds at an anode[4] or in strong acid solutions.[5,6] Recently, it was possible to carry out a kinetic study of the reaction of the thianthrene cation radical ($Th^{\cdot+}$) with water,[7] when the preparation of crystalline thianthrenium perchlorate (1) became available.[8] The availability of 1 has now enabled us to study the reaction of $Th^{\cdot+}$ with aromatic compounds.

Results and Discussion

Products.—Thianthrenium perchlorate reacts with substituted benzenes if the substituents are electron donors (methoxy, methyl). The reactions take place either in solution (acetonitrile or nitromethane) or in the aromatic as solvent. Reaction with neat anisole is fast, while reaction with neat toluene is slow. If the aromatic has an electron-withdrawing group (chloro, nitro), reaction does not occur (or is, at least, too slow to observe at room temperature). Reaction with benzene did not occur either.

The stoichiometry of the reaction is given in eq 1, which shows that equimolar amounts of thianthrene (Th) and a sulfonium salt (2) are formed. Quantitative results with anisole support this stoichiometry. That is, 100% of the anticipated thianthrene and 96% of the anticipated sulfonium salt were obtained.



The structure of the sulfonium salts is deduced from analogy with the literature (see below), nmr spectra, and elemental analysis. The compounds are crystalline solids, readily crystallizable from conventional solvents.

Compound 2 is a triarylsulfonium salt. Analogous salts are described in the literature as resulting from reaction of diaryl sulfoxides with aromatics in concentrated sulfuric acid,[9] in the presence of phosphorous pentoxide,[9] or aluminum chloride.[10] It is noted in these cases also that the aromatic must not carry an electron-withdrawing group. The conditions of McEwen's method (boiling with an excess of aluminum halide)[10] are such, however, that it is possible to prepare a phenylthianthrenonium salt from thianthrene 5-oxide and benzene (X = H)[11] by that method but not by direct reaction of 1 with benzene at room temperature. Reaction of 1 with *m*-xylene occurred very slowly and gave a product which we have not been able to crystallize.

Kinetics and Mechanism.—Mechanistic studies of the formation of triarylsulfonium salts in acid media have never been carried out to our knowledge. Certain diaryl sulfoxides give diarylsulfinium ions in strong acids.[12] The mechanism of formation of the sulfinium ions is not known but has been represented occasionally as the homolysis of the O-protonated sulfoxide (eq 2).[5,6,12,13] Schmidt[6,13] has proposed, therefore,

$$R_2S^+—OH \longrightarrow R_2S^{\cdot+} + \cdot OH \qquad (2)$$

that formation of a sulfonium ion (*e.g.*, 2) from a sulfoxide and an aromatic in strong acid involves reaction of the sulfinium ion (the cation radical) with the aromatic. Some insight into the mechanism of this type of substitution reaction could be obtained if the kinetic order in sulfinium ion were known. We have now been able to follow the kinetics of reaction of a sulfinium ion (*e.g.*, $Th^{\cdot+}$) with anisole and can set out a reasonable mechanism.

Kinetics were carried out by following the disappearance of $Th^{\cdot+}$ spectroscopically at 546 nm. An all-glass, evacuated, sealed apparatus was used. Two methods

(1) Part XX: C. V. Ristagno and H. J. Shine, *J. Amer. Chem. Soc.*, **93**, 1811 (1971). Part XXI: P. D. Sullivan and H. J. Shine, *J. Phys. Chem.*, **75**, 411 (1971).

(2) Supported by the National Science Foundation, Grant No. GP-25989X.

(3) Predoctoral Fellow.

(4) G. Cauquis, *Bull. Soc. Chim. Fr.*, 1618 (1968).

(5) H. J. Shine and L. Piette, *J. Amer. Chem. Soc.*, **84**, 4798 (1962).

(6) U. Schmidt, K. H. Kabitzke, and M. Markau, *Justus Liebigs Ann. Chem.*, **672**, 78 (1964).

(7) Y. Murata and H. J. Shine, *J. Org. Chem.*, **34**, 3368 (1969).

(8) E. A. C. Lucken, *J. Chem. Soc.*, 4963 (1962).

(9) J. Goerdler in "Methoden der Organischen Chemie," Vol. IX, 4th ed, Houben-Weyl, Georg Thieme, Stuttgart, 1955, pp 184, 185.

(10) G. H. Wieland and W. E. McEwen, *J. Org. Chem.*, **33**, 2671 (1968).

(11) The chloride has been prepared by Dr. T. L. Vigo in the laboratories of the U. S. Department of Agriculture, New Orleans, La. We are indebted to Dr. Vigo for sending us details of the method.

(12) H. J. Shine, *Organosulfur Chem.*, 93 (1967).

(13) U. Schmidt, *Angew. Chem., Int. Ed. Engl.*, **3**, 602 (1964).

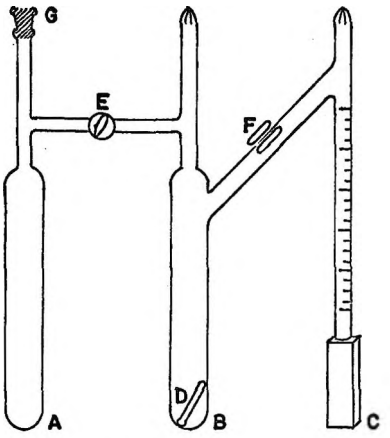


Figure 1.

of obtaining rate data were used. In the first, plots of $1/A$ against time were linear and indicated that reaction was second order in $Th^{\cdot+}$. Log plots for the first-order reactions were definitely not linear.

The reaction that is second order in $Th^{\cdot+}$ is most simply interpreted as involving an initial disproportionation step (eq 3),[7] and a reaction of a dication (Th^{2+}) with anisole (eq 4). By assuming that eq 3 represents

$$2Th^{\cdot+} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Th + Th^{2+} \quad (3)$$

$$Th^{2+} + ArH \xrightarrow{k_3} ThAr^{+} + H^{+} \quad (4)$$

rapidly achieved equilibrium, eq 5 can be written in which K is the equilibrium constant. Integration gives eq 6 and expressing cation radical concentrations as absorbances, A, leads to eq 7. In these equations, C

$$d(Th^{\cdot+})/dt = k_3K[Th^{\cdot+}]^2[ArH]/[Th] \quad (5)$$

$$1/[Th^{\cdot+}] = k_3KCt + 1/[Th^{\cdot+}]_0 \quad (6)$$

$$1/A_t = k_3KCt/\epsilon d + 1/A_0 \quad (7)$$

is $[ArH]/[Th]$, ϵ is the extinction coefficient of $Th^{\cdot+}$ at 546 nm ($9.3 \times 10^3\ M^{-1}\ cm^{-1}$), and d is the cell length. Since both [ArH] and the [Th] change during reaction, the term C must be kept constant during a run to simplify kinetic work, and this was achieved by using an excess of ArH and an excess of Th. The term C, therefore, represents $[ArH]_0/[Th]_0$ in our usage.

The addition of an excess of Th at the start of a run served not only to maintain C as a constant but also to slow down the disappearance of $Th^{\cdot+}$. Without added Th, the reaction of $Th^{\cdot+}$ with anisole was too fast to follow. This in itself is support for the reaction sequence proposed in eq 3 and 4.

By plotting $1/A$ against time, the slope $k_3KC/\epsilon d$ was obtained, and from this the apparent rate constant $k_{app} = k_3K$. Values of k_{app} are given in Tables I and II, for the solvents acetonitrile and nitromethane. The values are reasonably constant with the exception of runs 4–6 and therefore support the application of eq 3–7 to this reaction. Runs 4–6 show high values of k_{app}. These runs were characterized by serious experimental problems. The high initial concentration of $Th^{\cdot+}$ in them caused reaction to be very fast with a half-life comparable with the time of mixing of reactants. The recording of A *vs.* time could begin, therefore, only after at least one half-life, and there is considerable uncertainty about the real time of commencing reaction. The data we present for these runs, however, are compatible with a kinetic order in $Th^{\cdot+}$ close to two rather than equal to one.

TABLE I

KINETIC DATA FOR REACTION OF THIANTHRENIUM PERCHLORATE (1) WITH ANISOLE (ArH) IN ACETONITRILE

Run	$10^4[1]_0$, M	$10^3[Th]_0$, M	$10^3[ArH]_0$, M	k_{app}[a]	Correlation[b] coefficient
1	1.98	1.69	6.52	2.16	0.9998
2	2.25	1.47	7.44	2.21	0.9998
3	1.51	1.48	6.71	2.96	0.9993

[a] $k_{app} = k_3K$ in $M^{-1}\ sec^{-1}$. Values of slope obtained by least-squares treatment. [b] Correlation coefficient for the plot $1/A$ *vs.* t.

TABLE II

KINETIC DATA FOR REACTION OF THIANTHRENIUM PERCHLORATE (1) WITH ANISOLE (ArH) IN NITROMETHANE

Run	$10^5[1]_0$, M	$10^4[Th]_0$, M	$10^3[ArH]_0$, M	k_{app}[a]	Correlation[b] coefficient
4	342	202	10.8	36.36	0.9997
5	240	194	8.66	36.10	0.9999
6	148	141	81.8	29.90	0.9992
7	25.7	26.9	11.4	8.98	0.9993
8	18.3	25.6	11.6	5.73	0.9997
9	20.2	23.9	12.0	6.28	0.9999
10	19.0	21.7	10.8	3.70	0.9996
11	13.8	24.0	7.44	5.99	0.9997
12	2.29	3.28	1.63	5.68	0.9980
13	1.41	7.78	1.13	3.81	0.9989

[a] $k_{app} = k_3K$ in $M^{-1}\ sec^{-1}$. Values of slope obtained by least-squares treatment. [b] Correlation coefficient for the plot $1/A$ *vs.* t.

The kinetic order in $Th^{\cdot+}$ was also obtained by measuring initial rates.[14] Spectrophotometer plots of absorbance at 546 nm against time were extrapolated to zero time, and the tangent to each plot at zero time was drawn. At zero time, the initial rate of reaction, v_0, is given by eq 8, in which n is the order in $Th^{\cdot+}$.

$$v_0 = dA_0/dt = k_3KCA_0^n/\epsilon d \quad (8)$$

Values of v_0 are given in Table III for runs in which $[1]_0$ was varied over 240-fold. Simple inspection of Table III shows that a tenfold increase in $[1]_0$ gave almost a 100-fold increase in v_0/C (*e.g.*, runs 11 and 13, 7 and 12). These results are consistent with a reaction which is second order in $Th^{\cdot+}$. A 100-fold increase in

TABLE III

INITIAL RATE DATA FOR REACTION OF THIANTHRENIUM PERCHLORATE (1) WITH ANISOLE (ArH) IN NITROMETHANE

Run	$10^5[1]_0$, M	C[a]	v_0, min^{-1}	v_0/C
4	342	0.536	11.850	22.100
5	240	0.446	6.040	13.540
6	148	5.76	12.030	2.088
7	25.7	4.24	0.1560	0.0360
8	18.3	4.53	0.0436	0.0097
9	20.2	5.02	0.0738	0.0147
10	19.0	4.97	0.0325	0.0063
11	13.8	3.10	0.0178	0.0056
12	2.29	4.98	0.0013	0.000261
13	1.41	14.6	0.00075	0.000051

[a] $C = [ArH]_0/[Th]_0$.

(14) M. Letort, *Bull. Soc. Chim. Fr.*, 9, 1 (1942).

$[1]_0$ should cause a 10,000-fold increase in v_0/C. The data in Table III show about 40,000-fold (runs 6 and 13) or 50,000-fold (runs 5 and 12) increases. In view of the experimental problems with runs 4–6, these data are not thought to be seriously in error.

A plot of log v_0/C against log A_0 according to eq 9 has

$$\log v_0/C = \log k'_{app} + n \log A_0 \quad (9)$$

a slope n and intercept $k'_{app} = k_3KC/\epsilon d$. Ideally, k'_{app} and k_{app} should be the same. Our results are given in Table IV. Those for runs 7–13 express, we believe,

TABLE IV

KINETIC ORDER (n) AND RATE CONSTANT OBTAINED FROM INITIAL RATE DATA (TABLE III)

Runs	n[a]	k'_{app}, M^{-1} sec^{-1}[b]	Correlation coefficient
4–13	2.35 ± 0.4	4.00	0.991
4–6	2.43 ± 0.1	4.86	0.929
7–13	1.98 ± 0.2	3.86	0.987

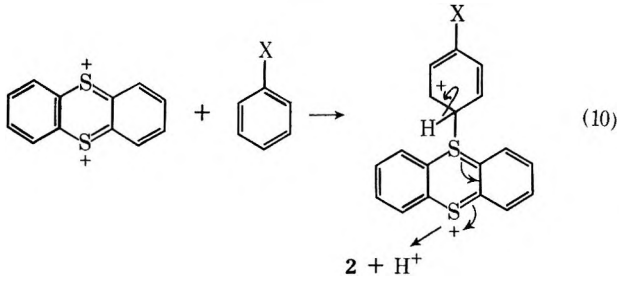
[a] n = slope in plot of log v_0/C *vs.* log A_0. [b] k'_{app} obtained from the intercept of same plot. Slope and intercept are calculated by least-squares treatment.

the true description of the reaction, since these runs were not so susceptible to the experimental error of the faster ones, runs 4–8. Inclusion of runs 4–6 in the calculations gives a value of n somewhat higher than 2. The discrepancy is not serious in our attempt to distinguish between reactions which are first and second order in $Th^{\cdot+}$.

Finally, the intercept value of k'_{app} is considered to be in acceptable agreement with values of k_{app} obtained by the integrated rate method (Table II).

The rate expressions of eq 3–9 include the assumption that eq 3 represents an equilibrium. Similar expressions can be developed, without affecting the end result, for the assumption that Th^{2+} is at a steady-state concentration.

Our kinetic results and interpretation call for electrophilic substitution by Th^{2+} in the aromatic (eq 10).



(10)

The substitution reactions are slow, indicating that the concentration of dication (eq 4, 5) must be quite low. The equilibrium constant (eq 3) calculated from oxidation potentials is approximately 10^{-7}.[15] The effect of substituents is in accord with a cationic reaction rather than a radical reaction, and it is probable that the earlier synthetic methods[9,10] follow the cationic path (eq 4).

We have set out above what we consider to be the simplest interpretation of our results. Another series of steps may be written (eq 11–13) which also suits the stoichiometry of the substitution (eq 1). Equations 11 and 12 are entirely analogous to simple electrophilic

$$Th^{\cdot+} + ArH \underset{k_5}{\overset{k_4}{\rightleftharpoons}} ThArH^{\cdot+} \quad (11)$$

$$ThArH^{\cdot+} \underset{k_7}{\overset{k_6}{\rightleftharpoons}} ThAr\cdot + H^+ \quad (12)$$

$$ThAr\cdot + Th^{\cdot} + \underset{k_9}{\overset{k_8}{\rightleftharpoons}} ThAr^+ + Th \quad (13)$$

substitution. In order for second-order kinetics in $Th^{\cdot+}$ to prevail, the substitution step (k_4) would have to be faster than the electron-transfer step (k_8), a requirement about which we have intuitive doubt. Furthermore, while second-order kinetics requires the electron-transfer step (k_8) to be rate determining, retardation by added thianthrene (Th) requires that step to be reversible. Simple second-order kinetics might be observed, then, if k_9 was very small. Our feeling is that these restrictions make the validity of this series of steps questionable.

Experimental Section

Thianthrenium perchlorate (1) was prepared essentially as described earlier.[7] Only quantities of the order of 50–100 mg were prepared at a time. The solid 1 was filtered through glass fiber paper under a stream of nitrogen, washed with dry carbon tetrachloride, dried under vacuum, and used without long delay.

Warning! Although used without trouble for over 12 months, $Th^{\cdot+}$ ClO_4^- has proved to be extremely hazardous. A freshly made batch of 1–2 g exploded violently after being dried by suction and when being transferred to a petri dish from the sintered-glass filter. Explosion may have been initiated by the friction of transfer or by rubbing with a glass rod.

Preparation of *p*-Anisylthianthrenonium Perchlorate (2a).—To a solution of 117 mg (0.372 mmol) of 1 in *ca.* 10 ml of dry nitromethane was added a sufficient excess of anisole. The solution was stirred until the color of the cation radical had disappeared and was extracted with portions of cyclohexane until tlc of the nitromethane solution no longer showed the presence of thianthrene. The combined cyclohexane solutions which contained both thianthrene and the excess of anisole were evaporated to dryness under reduced pressure. The residue was dissolved in acetonitrile and analyzed spectroscopically (256 nm) for thianthrene, giving 40 mg (100%). The nitromethane solution was treated similarly giving 77 mg (96%) of 2a. Compound 2a was recrystallized from aqueous methanol and had mp 164–165°.

Anal. Calcd for $C_{19}H_{15}ClO_5S_2$: C, 53.86; H, 3.54; Cl, 8.37; S, 15.15. Found: C, 53.76; H, 3.82; Cl, 8.43; S, 15.44.

Compound 2a is white and crystalline, soluble in methanol, acetone, and acetonitrile, and insoluble in cyclohexane and carbon tetrachloride. Its ultraviolet spectrum in acetonitrile had maxima at 310 nm (ϵ 5.36 × 10^3) and 247 (1.60 × 10^4). The nmr spectrum (in dimethyl sulfoxide using TMS as an external standard) had δ 1.9 (s, 3, methoxy group), 7 (m, 4, anisyl ring protons), 7.8 (m, 6, positions 2, 3, 4, 6, 7, 8 of thianthrenonium ring), 8.3 (m, 2, positions 1, 9 of thianthrenonium ring). A similar preparation starting with 109 mg (0.342 mmol) of 1 gave 36.9 mg (100%) of thianthrene.

Preparation of *p*-Tolylthianthrenonium Perchlorate (2b).—The same procedure was used but not carried out quantitatively. Reaction in this case took almost 1 month for completion. The product had mp 208–209° (aqueous methanol).

Anal. Calcd for $C_{19}H_{15}ClO_4S_2$: C, 56.02; H, 3.68; Cl, 8.71; S, 15.76. Found: C, 55.85; H, 3.66; Cl, 8.40; S, 15.90.

Compound 2b had solubility characteristics similar to those of 2a. The ultraviolet spectrum in acetonitrile had maxima at 310 nm (ϵ 6.53 × 10^3) and 227 (3.20 × 10^4). The nmr spectrum had δ 0.5 (s, 3, methyl group), 7.1 (m, 4, tolyl ring protons), 7.8 (m, 6, positions 2, 3, 4, 6, 7, 8 of thianthrenonium ring), 8.3 (m, 2, positions 1, 9 of thianthrenonium ring).

(15) We thank Dr. L. S. Marcoux for this information.

Preparation of Phenylthianthrenonium Chloride (2c).[11]—To a solution of 1.97 g of thianthrene 5-oxide in 100 ml of benzene was added 11.2 g of aluminum chloride. The solution turned dark purple immediately. During 24 hr of boiling the color gradually turned dark brown. The solution was cooled and poured onto a mixture of 100 g of ice and 10 ml of concentrated hydrochloric acid, extracted with benzene until the benzene layer was colorless, and then extracted with chloroform to give 963 mg of 2c, mp 252–253° (benzene–methanol). The ultraviolet spectrum had maxima at 310 nm (ϵ 7.54 × 10^3) and 225 (3.16 × 10^4).

Kinetics of Reaction of 1 with Anisole.—The apparatus in Figure 1 was used. An aliquot of a stock solution of thianthrene was introduced into B, and an aliquot of a stock solution of 1 was introduced into C. A sealed capillary (D) containing a known amount of anisole was placed in B. The chambers B and C were sealed by torch, the solvent was pumped out of B and C, and stopcock E was closed. Dried solvent was distilled into A which contained Linde Molecular Sieve 3A 1/16. The solvent was then degassed by the freeze–thaw technique. After opening stopcock E, solvent was distilled into B, the stopcock was closed, and the apparatus was removed from the vacuum line at G. The capillary was then crushed by the magnet F, after which the solution was poured from B into C, and shaken well to dissolve the 1. The volume was measured and the cell was placed in the spectrophotometer for absorbance measurements at 546 nm.

Kinetic measurements were made with both nitromethane and acetonitrile as solvent. Acetonitrile itself reacts very slowly with 1, whereas nitromethane solutions are stable indefinitely.

Registry No.—1, 21299-20-7; 2a, 30882-98-5; 2b, 30882-99-6; 2c, 30953-02-7.

Basicities of the Individual Amino Groups in ω-Dimethylamino Alkyl Amines[1a]

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The relative basicities of the two different amino groups in the compounds $Me_2N(CH_2)_nNH_2$ where n is 2–5 have been determined by nmr measurements of the chemical shifts of the methyl protons in aqueous solutions containing various amounts of added acid. The primary amino groups were 1.6–3.7 times as basic as the tertiary amino groups. The fact that the chemical shifts of the methyl protons of $Me_2N(CH_2)_2NMe_2$ and $Me_2N(CH_2)_3NMe_2$, which were used as reference compounds, were linear functions of the nunber of equivalents of protons added was taken as evidence against a cyclic hydrogen-bonded structure for the monoprotonated forms of these diamines. The observed relative basicities were combined with overall basicities determined by potentiometric titration to obtain the absolute basicities of the various individual amino groups in water at 35°.

In several cases polyamines, sometimes acting through their monoprotonated forms, have been found to give internal catalysis of various kinds of reactions.[2-4] For a quantitative understanding of such reactions it is desirable to know the basicities of the individual nitrogen atoms of such polyamines. Potentiometric, conductometric, and other standard methods of determining basicity constants, which yield directly only overall values, may be used for this purpose with symmetrical polyamines and are relatively satisfactory if various amino groups differ enough in basicity. However, with simple ω-dimethylamino alkyl amines, where the amino groups are of comparable basicity, it is not obvious how to partition the observed total basicity into that contributed by each of the two different basic centers. We have therefore made proton magnetic resonance measurements, somewhat like those used by Loewenstein and Roberts to determine the relative acidities of the different carboxy groups in citric acid.[5] The results have also shed light on the question of whether the monoprotonated forms of such diamines are stabilized by internal hydrogen bonding.

Results

When the chemical shifts of the methyl protons of compounds of the type $Me_2N(CH_2)_nNH_2$ (where n is 2, 3, 4, and 5) were measured in aqueous solution in the presence of increasing amounts of acid, the downfield shift that accompanied the addition of the first equivalent of acid was less than that which accompanied the addition of the second equivalent. Figure 1 illustrates this for the case of 3-dimethylaminopropylamine. (The experimental points deviate from the idealized line constructed from the initial and final slopes because of overlapping mono- and diprotonation of the amine.) Since the tertiary amino group is thus more affected by the second protonation, it follows that the first protonation takes place largely at the primary amino group. To treat the data quantitatively, let us define f_m as the fraction of the diamine that is monoprotonated, f_d as the fraction diprotonated, f_t as the fraction of monoprotonated diamine that is protonated at the tertiary position, δ_d as the downfield chemical shift of the methyl protons of the diprotonated diamine, δ_t as the shift of the methyl protons of the diamine monoprotonated at the tertiary position, and δ_p as the shift of the methyl protons of the primary-monoprotonated diamine (all chemical shifts relative to that of the methyl group of the unprotonated diamine). It may be shown that if the various differently protonated forms of the diamine are in rapid equilibrium with each other the observed chemical shift of the methyl protons may be expressed as shown in eq 1. The values of

$$\delta_{obsd} - f_d\delta_d = f_m[f_t(\delta_t - \delta_p) + \delta_p] \quad (1)$$

(1) (a) This investigation was supported in part by Public Health Service Grants AM 06829-MCB and AM 10378 from the National Institute of Arthritis and Metabolic Diseases. Abstracted largely from the Ph.D dissertation of F. A. Via, The Ohio State University, 1970. (b) To whom communications should be addressed at The Ohio State University.

(2) J. Hine, F. E. Rogers, and R. E. Notari, *J. Amer. Chem. Soc.*, **90**, 3279 (1968).

(3) W. P. Jencks and K. Salvesen, *Chem. Commun.*, 548 (1970).

(4) J. Hine, M. S. Cholod, and J. H. Jensen, *J. Amer. Chem. Soc.*, **93**, 2321 (1971).

(5) A. Loewenstein and J. D. Roberts, *ibid.*, **82**, 2705 (1960); *cf.* R. B. Martin, *J. Phys. Chem.*, **65**, 2053 (1961).

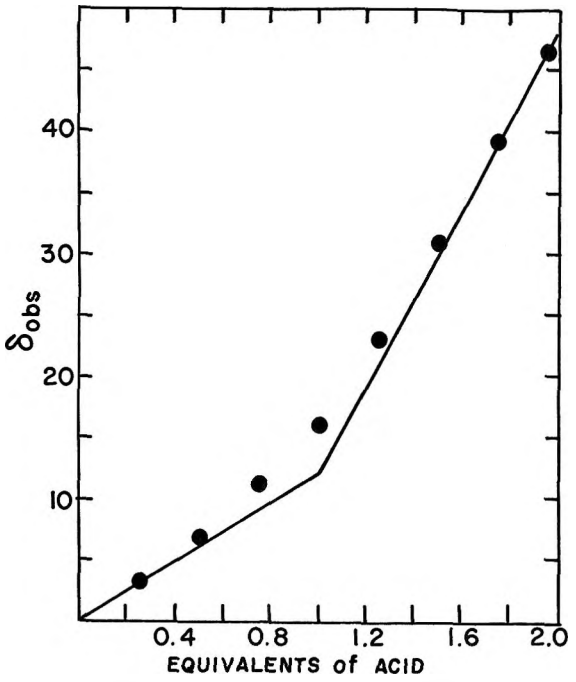


Figure 1.—Plot of the downfield shift of the methyl protons of 3-dimethylaminopropylamine (relative to those of the free base) *vs.* the number of equivalents of added acid.

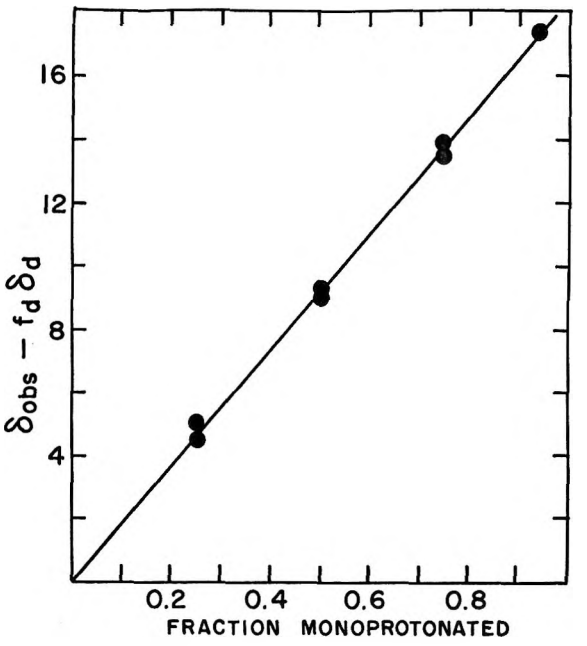


Figure 2.—Plot of chemical shift data for methyl protons of 2-dimethylaminoethylamine using eq 1.

f_d and f_m may be calculated from the two acidity constants of the diamine, and δ_d may be determined from measurements on solutions of diamine containing 2 equiv of strong acid. A plot of the left side of eq 1 *vs.* f_m should give a straight line, as shown in Figure 2 for the case of 2-dimethylaminoethylamine, of slope $[f_t(\delta_t - \delta_p) + \delta_p]$. These slopes and values of δ_d for the four ω-dimethylamino alkyl amines studied are listed in Table I.

TABLE I

PROTON MAGNETIC RESONANCE DETERMINATION OF THE RELATIVE BASICITIES OF THE TWO AMINO GROUPS IN ω-DIMETHYLAMINO ALKYL AMINES IN AQUEOUS SOLUTION AT 35°

Diamine	$f_t(\delta_t - \delta_p) + \delta_p$, Hz	δ_d, Hz	δ_p, Hz	f_t
$Me_2N(CH_2)_2NH_2$	18.4	47.3	2.0	0.38
$Me_2N(CH_2)_3NH_2$	14.7	47.6	0.9	0.30
$Me_2N(CH_2)_4NH_2$	14.0	42.0	0.4	0.33
$Me_2N(CH_2)_5NH_2$	8.9	41.3	0.2	0.21

In order to obtain the desired values of f_t from these slopes, it was necessary to have values for the chemical shifts δ_t and δ_p. These were estimated from data on model compounds. We considered the possibility that the diprotonated diamine might be the best model for a given monoprotonated diamine. If this is true then δ_p, the change in the chemical shift of the methyl protons brought about by protonating the primary amino group of $Me_2N(CH_2)_nNH_2$, will be essentially the same as $\delta_d - \delta_t$, the change brought about by protonating the primary amino group of $Me_2N^+H(CH_2)_nNH_2$. That is, δ_d will be equal to δ_p plus δ_t. The validity of this equation may be tested by using as models symmetrical diamines, such that we know that the two different amino groups are protonated to the same extent. Let us denote the difference in chemical shifts between the boldfaced hydrogen atoms of $(\mathbf{CH_3})_2N(CH_2)_nN(CH_3)_2$ and $(\mathbf{CH_3})_2N^+H(CH_2)_nN(CH_3)_2$, that is, the effect of the first protonation on the shift of the methyl group adjacent to the positive charge, as δ_{a1}, and the differences in shift between $(\mathbf{CH_3})_2N(CH_2)_nN^+H(CH_3)_2$ and $(\mathbf{CH_3})_2N^+H(CH_2)_nN^+H(CH_3)_2$ as δ_{a2}. Analogously, the differences between $(\mathbf{CH_3})_2N(CH_2)_nN(CH_3)_2$ and $(\mathbf{CH_3})_2N(CH_2)_nN^+H(CH_3)_2$ and between $(\mathbf{CH_3})_2N^+H(CH_2)_nN(CH_3)_2$ and $(\mathbf{CH_3})_2N^+H(CH_2)_nN^+H(CH_3)_2$, that is, the effects of remote charges, will be denoted δ_{r1} and δ_{r2}, respectively. Obviously $\delta_{a1} + \delta_{r2}$ is equal to $\delta_{a2} + \delta_{r1}$, since either is equal to δ_d. It may be shown that a plot of δ_{obsd} *vs.* the number of equivalents of protons added to such a symmetrical diamine will be a straight line only if δ_{a1} is equal to δ_{a2} (and hence δ_{r1} equal to δ_{r2}). Figure 3 shows that such plots do give satisfactory straight lines for the cases when n is 2 and 3. Hence $\delta_{a1} + \delta_{r1}$, the equivalent in the symmetrical diamine case of $\delta_p + \delta_t$ in the primary–tertiary diamine case, is equal to δ_d in these cases.

Since the primary amino groups of our ω-dimethylamino alkyl amines are at least three atoms further from the methyl protons than the tertiary amino groups are, δ_p must be much smaller than δ_t. Even if the percentage error in estimating δ_p from data on model compounds is somewhat larger than for δ_t, the absolute error should be much smaller. Therefore, if the equation $\delta_d = \delta_t + \delta_p$ is a good approximation, it is better to estimate δ_p and calculate δ_t than to follow the reverse procedure. Changes in chemical shifts of various protons of several model amines are listed in Table II. The methyl group of 2-methoxyethylamine, separated by an oxygen atom from the $CH_2CH_2NH_2$ group that becomes protonated, provides the best model for δ_p for 2-dimethylaminoethylamine, which relates to a methyl group separated by a nitrogen atom from the $CH_2CH_2NH_2$ group that becomes protonated. Values of δ_p for the other ω-dimethylamino alkyl amines were calculated from this δ_p value by use of a "fall-off factor" of 2.3-fold per additional atom of separation from the primary amino group (an average of the factors ranging from 1.77 to 2.67 that may be

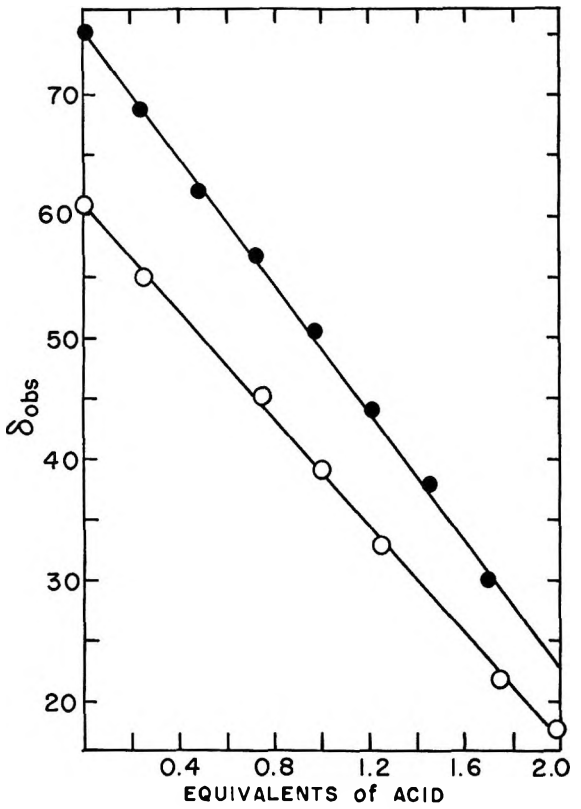


Figure 3.—Plot of chemical shift of methyl protons (upfield from methanol) *vs.* equivalents of added acid: ● for $Me_2N(CH_2)_2NMe_2$; ○ for $Me_2N(CH_2)_3NMe_2$.

calculated from the data in Table II). These values and the resulting values of f_t are listed in Table I. The values of δ_t that may be calculated, ranging from 41.1 to 46.7 Hz, seem plausible in view of the data on reference compounds. If we assume that the equation $\delta_d = \delta_t + \delta_p$ is not necessarily applicable, and that for 2-dimethylaminoethylamine δ_p may be anywhere in the range 0–5 Hz and δ_t anywhere in the range 40–50 Hz, it follows that f_t is in the range 0.30–0.46. The uncertainty in the other f_t values is probably somewhat less because of smaller uncertainties in δ_p.

We shall use the symbol TP for the tertiary–primary diamines studied, HTP^+ for the tertiary monoprotonated and TPH^+ for the primary monoprotonated species, and $HTPH^{2+}$ for the diprotonated species. The value of the acidity constant K_{HTP}, defined by eq 2, may be calculated from the experimentally determined acidity constant of the monoprotonated diamine (K_1) and f_t by use of eq 3, and the value of K_{TPH}, the acidity

$$K_{HTP} = \frac{[H^+][TP]}{[HTP^+]} \quad (2)$$

$$K_{HTP} = K_1/f_t \quad (3)$$

constant of TPH^+, may be calculated similarly. The resulting acidity constants (including K_2, the acidity constant of $HTPH^{2+}$) are listed in Table III.

$$K_2 = \frac{[H^+]([HTP^+] + [TPH^+])}{[HTPH^{2+}]} \quad (4)$$

Discussion

The values of f_t in Table I show that the primary amino groups of our ω-dimethylamino alkyl amines are 1.6–3.7 times as basic as the tertiary amino groups.

Table II

Changes in Chemical Shifts Brought about by Complete Protonation of the Amino Groups in Water at 35°

A	B	C	D	δ_A	δ_B	δ_C	δ_D
$N(CH_3)_3$				41.4			
$N(CH_2CH_3)_3$				43.5	17.5		
H_2NCH_3				19.7			
$H_2NCH_2CH_2CH_3$				24.1	13.6	5.1	
$H_2NCH_2CH_2$–O–CH_3				23.6	11.1		2.0
$[(CH_3)_2NCH_2]_2$				52.6			
$[(CH_3)_2NCH_2]_2CH_2$				44.2			

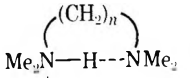
Table III

Acidity Constants of ω-Dimethylamino Alkyl Amines in Water at 35°

Amine	pK_1	pK_{HTP}	pK_{TPH}	pK_2
$Me_2N(CH_2)_2NH_2$	9.30 ± 0.03	8.88	9.09	5.98 ± 0.01
$Me_2N(CH_2)_3NH_2$	9.91 ± 0.02	9.39	9.75	7.67 ± 0.02
$Me_2N(CH_2)_4NH_2$	10.17 ± 0.01	9.69	10.00	8.44 ± 0.02
$Me_2N(CH_2)_5NH_2$	10.44 ± 0.03	9.77	10.34	9.07 ± 0.02

This is not surprising in view of the fact that, for the seven primary R groups for which the basicity of both RNH_2 and $RNMe_2$ is given in Perrin's table of aliphatic amine basicities,[6] the primary amines are 2–13 times as basic as the corresponding tertiary amines.

A cyclic hydrogen-bonded structure such as **1** may be



1

written for the various monoprotonated diamines. If this were the structure of the monoprotonated symmetrical diamines we have studied, then δ_{r1}, the shift produced by a "remote" positive charge, would actually be the result of a rather nearby positive charge and should therefore be larger than δ_{r2}, which should be the result of a truly remote positive charge (since the diprotonated diamine must exist largely in an extended conformation, with the like-charged nitrogen atoms widely separated). The evidence that δ_{r1} is equal to δ_{r2} provided by the plots in Figure 3 is therefore evidence that the monoprotonated amines for which n is 2 or 3 do not exist largely in structures like **1**.

Experimental Section

Reagents.—The methylamine and trimethylamine were Matheson products that were not further purified. All the other amines were commercially available products except for *N*,*N*-dimethyl-1,4-butanediamine and *N*,*N*-dimethylpentane-1,5-diamine, which were prepared by the lithium aluminum hydride reduction of the corresponding nitriles;[7] all were found by glpc, usually on a Carbowax 20M column, to be more than 99% pure, except for the *N*,*N*-dimethyl-1,4-butanediamine, which was more than 95% pure.

Proton Magnetic Resonance Spectrum Measurements on Solutions of Amines.—All pmr measurements were made at 35 ± 1° on a Varian Model A-60 spectrometer, using methanol as an internal reference. Total concentrations of amine around 0.08–0.2 *M* were used with perchloric acid added to neutralize various fractions of the amine. In obtaining the chemical shift of the free amine, a small amount of sodium hydroxide was

(6) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965, pp 13–52.

(7) *Cf.* W. A. Lott and J. Krapcho, U. S. Patent 2,813,904 (1957); *Chem. Abstr.*, **52**, 9197c (1958).

added to suppress ionization. Sodium chloride was added to keep the concentration of anions constant (at 0.40 *M* for *N,N*-dimethylethylene diamine and *N,N*-dimethyl-1,3-propanediamine, and at 0.17 *M* for *N,N*-dimethyl-1,4-butanediamine and *N,N*-dimethyl-1,5-pentanediamine). The chemical shift of 75% neutralized methylamine was found to be unaffected by the addition of 0.5 *M* sodium chloride. All plots of chemical shift *vs.* number of equivalent of acid added for monoamines were linear.

Determinations of pK_a.—Standard aqueous solutions of the diamines were titrated potentiometrically at 35 ± 1° with standard perchloric acid using a Beckman Research pH meter, Model 101900. About 15 pH readings were taken in the range 0.2–0.8 mol of acid per mole of diamine and another 15 in the range 1.2–1.8 mol of acid per mole of diamine. The pH was taken as $-\log a_{H^+}$, and the Davies equation[8] (which becomes eq 5 at 35°) was

$$\log f = -0.52Z^2\left(\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.2\mu\right) \quad (5)$$

used to calculate ionic activity coefficients. Each of the possible pairs of pH values, one from the first and one from the second part of the titration, was used to calculate a value of pK_1 and pK_2, and the results obtained in a given titration were averaged.[9]

(8) C. W. Davies, *J. Chem. Soc.*, 2093 (1938).
(9) *Cf.* D. J. MacDonald, *J. Org. Chem.*, **33**, 4559 (1968).

Considering that the values of pK_1 depend largely on the pH's measured with around 0.5 mol of acid per mole of diamine, and the values of pK_2 depend largely on pH's measured with about 1.5 mol of acid per mole of diamine, the average ionic strengths at which the values of pK_1 were obtained ranged from about 0.014 to 0.19 *M* and those at which pK_2 were obtained ranged from about 0.023 to 0.23 *M*. For each amine the concentration of amine and titrating acid were varied so that the ionic strength at which each pK was determined varied by at least threefold. In no case was any trend noticed in the thermodynamic pK_a values, the overall average values of which are listed with their standard deviations in Table III.

The values of f_m and f_d used in the plots according to eq 1 were calculated from the concentration acidity constants at the appropriate ionics trength which was calculated from the thermodynamic constants and the Davies equation.

Registry No.—$Me_2N(CH_2)_2NH_2$, 108-00-9; $Me_2N(CH_2)_3NH_2$, 109-55-7; $Me_2N(CH_2)_4NH_2$, 3529-10-0; $Me_2N(CH_2)_5NH_2$, 3209-46-9.

Acknowledgment.—We wish to thank Kenneth W. Narducy for the computer calculation of the pK values reported here.

Bicyclo[3.1.0]hexane Conformation. The Crystal Structure of *N-exo*-6-Bicyclo[3.1.0]hexyl-*p*-bromosulfonamide

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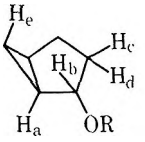
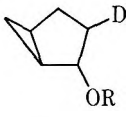
Received January 5, 1971

The crystal structure of the *p*-bromosulfonamide of 6-aminobicyclo[3.1.0]hexane has been determined by single-crystal X-ray diffraction. This structure shows the boat conformation as previously indicated by nuclear magnetic resonance studies.

A nuclear magnetic resonance (nmr) study of compounds I and II indicated that the bicyclo[3.1.0]-hexane system was in the boat conformation.[1] This



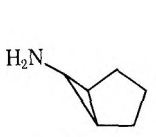
Ia, R = H
b, R = CH_3



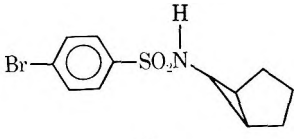
IIa, R = H
b, R = CH_3

conformation explained the unique doublet at τ 6.27 (J = 5.1 cps) in the nmr spectrum of compounds Ia and Ib resulting from the splitting of the absorption of the *cis* C-2 hydrogen (H_b in I) by the *cis* C-3 hydrogen (H_c in I). This was verified by the synthesis of IIb and the presence of a singlet at τ 5.88 in its nmr spectrum. Other nmr studies have also confirmed this boat conformation for the bicyclo[3.1.0]hexane system.[2-6]

The synthesis of 6-aminobicyclo[3.1.0]hexane (III)[7] offered an opportunity to prepare a heavy atom derivative for X-ray crystallographic studies as an



III



IV

independent method of testing the conformation of bicyclo[3.1.0]hexanes. The *p*-bromosulfonamide IV was prepared according to the Hinsberg reaction.[8]

Results and Discussion

Crystallographic Measurements.—The structure of the *p*-bromosulfonamide IV was determined by single-crystal X-ray diffraction using the heavy-atom method. Details of the structure analysis, final atomic coordinates (Table I), and thermal parameters (Table I) are given in the Experimental Section.

Figure 1 is a plot of the X-ray data of the molecule with the hydrogens placed in their calculated rather than observed coordinates. As this figure indicates, the bicyclo[3.1.0]hexane system is in the boat conformation. The four ring atoms, C(8), C(9), C(11), and C(12) are all coplanar with the C(7) and C(10) atoms lying

(1) P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, **30**, 771 (1965).
(2) M. S. Bergqvist and T. Norin, *Ark. Kemi*, **22**, 137 (1964).
(3) K. Tori, *Chem. Pharm. Bull.*, **12**, 1439 (1964).
(4) H. E. Smith, J. C. D. Brand, E. H. Massay, and L. J. Durham, *J. Org. Chem.*, **31**, 690 (1966).
(5) A. Diefferbacker and W. von Philipsborn, *Helv. Chem. Acta*, **49**, 897 (1966).
(6) S. Winstein, E. C. Friedrich, R. Baker, and Y. Lin, *Tetrahedron, Suppl.*, **8**, II, 621 (1966).
(7) The authors wish to thank Dr. Jacob Szmuszkovicz, The Upjohn Co., for this compound.
(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 119.

TABLE I

FINAL ATOMIC COORDINATES AND THERMAL PARAMETERS FOR COMPOUND IV[a]

	X	*Y*	*Z*	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Br	40107 (7)	100785 (16)	23354 (5)	1270 (8)	5119 (40)	645 (4)	−415 (34)	713 (9)	351 (21)
S	−559 (14)	26460 (30)	14252 (8)	913 (15)	3190 (63)	272 (5)	727 (59)	405 (14)	164 (35)
O(1)	−4059 (37)	20261 (70)	6541 (21)	1245 (47)	3557 (180)	287 (15)	1208 (160)	422 (43)	5 (85)
O(2)	3760 (38)	10208 (76)	20194 (22)	264 (49)	3447 (168)	353 (17)	1102 (161)	454 (47)	817 (92)
N	−11926 (42)	37601 (96)	14816 (24)	915 (49)	4481 (222)	250 (17)	370 (190)	367 (48)	−73 (109)
C(1)	10774 (47)	46545 (104)	16599 (28)	794 (51)	3505 (257)	257 (20)	736 (209)	504 (54)	200 (122)
C(2)	20189 (54)	47736 (109)	24028 (31)	022 (61)	3880 (285)	280 (22)	611 (254)	350 (60)	608 (142)
C(3)	29015 (54)	63911 (127)	26012 (34)	867 (62)	4736 (300)	340 (25)	547 (247)	398 (66)	746 (151)
C(4)	28208 (55)	78771 (112)	20593 (37)	941 (62)	3501 (273)	529 (30)	189 (237)	928 (75)	−196 (153)
C(5)	18900 (58)	77747 (110)	13166 (33)	1128 (69)	3366 (274)	325 (24)	695 (249)	422 (66)	437 (142)
C(6)	10254 (54)	61469 (124)	11271 (31)	1000 (64)	4307 (284)	240 (21)	846 (239)	342 (62)	396 (137)
C(7)	−18372 (48)	55544 (103)	9545 (32)	679 (50)	3118 (262)	344 (23)	162 (188)	300 (55)	−316 (121)
C(8)	−27724 (60)	49382 (111)	1664 (36)	1309 (72)	2298 (235)	435 (26)	670 (262)	157 (71)	−218 (150)
C(9)	−31130 (79)	65908 (145)	−4627 (43)	2270 (123)	5116 (369)	477 (35)	2542 (376)	931 (110)	44 (188)
C(10)	−33738 (73)	87061 (139)	−1488 (44)	1576 (93)	4351 (313)	689 (40)	1764 (314)	1126 (104)	895 (197)
C(11)	−37478 (62)	79528 (153)	4422 (43)	1078 (76)	6945 (453)	607 (36)	2007 (322)	633 (85)	−838 (205)
C(12)	−31569 (59)	57497 (138)	7311 (39)	924 (65)	5546 (380)	539 (32)	582 (265)	763 (77)	464 (176)

	X	*Y*	*Z*		*X*	*Y*	*Z*
H(1)	2046 (51)	3723 (98)	2707 (30)	H(8)	−3439 (49)	4886 (91)	991 (30)
H(2)	3587 (49)	6087 (99)	3151 (29)	H(9)	−4773 (50)	7527 (99)	83 (31)
H(3)	1790 (49)	8854 (99)	977 (29)	H(10)	−3952 (49)	8918 (99)	692 (31)
H(4)	494 (51)	6316 (99)	666 (30)	H(11)	−2841 (50)	9354 (95)	−106 (30)
H(5)	−1003 (49)	4081 (96)	1941 (31)	H(12)	−4255 (51)	9788 (89)	−701 (31)
H(6)	−1290 (48)	6982 (95)	1101 (30)	H(13)	−3836 (52)	5895 (99)	−987 (31)
H(7)	−2662 (51)	3686 (99)	69 (30)	H(14)	−2629 (54)	6440 (99)	−720 (30)

[a] × 10^4 for hydrogens, × 10^5 for other atoms. Standard deviations in the last digit are given in parentheses following each parameter.

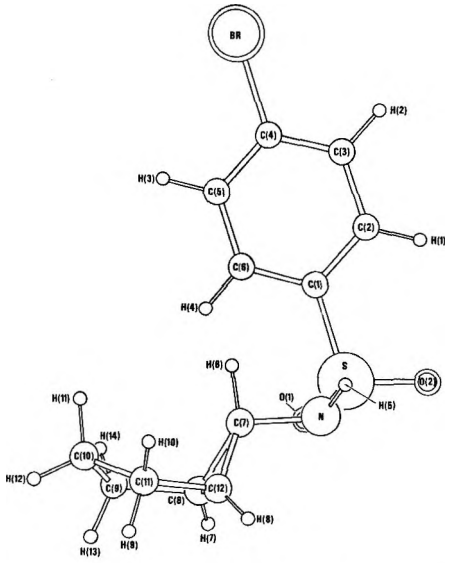


Figure 1.—Plot of compound IV molecule.

above the plane determined by these four ring atoms. Table II lists the best plane calculations from the X-ray data and clearly shows that C(7) and C(10) are on the same side of the determined plane.

TABLE II

BEST PLANE CALCULATIONS FOR CRYSTALLINE COMPOUND IV

Atom	Deviation, Å	Wt
C(8)	0.0000	1.00
C(9)	0.0000	1.00
C(10)	−0.4125	0.0
C(11)	0.0000	1.00
C(12)	0.0000	1.00
C(7)	−1.1974	0.0

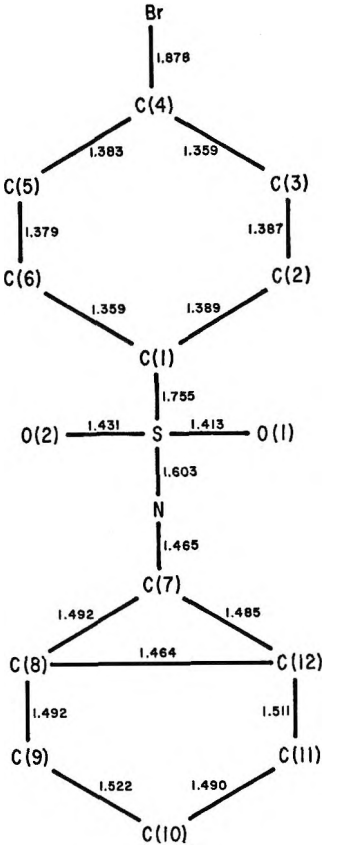


Figure 2.—Observed bond lengths for compound IV.

Figures 2 and 3 show the observed bond lengths and angles for compound IV. These values are within expected values for a compound of this type. Standard deviations are estimated to be 0.01 Å for C–C bonds and 1.0° for C–C–C angles.

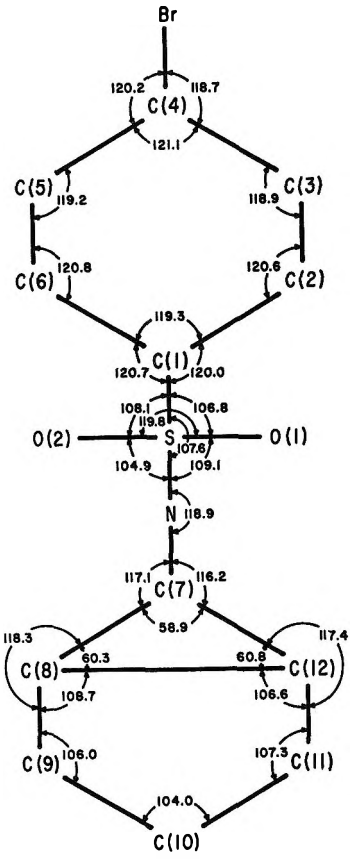


Figure 3.—Observed angles for compound IV.

The dihedral angle calculations were of particular interest in this molecule. Since, in the nmr study of compounds I and II, the dihedral angles were estimated from the coupling constants, it was hoped that the X-ray results would be similar. Figures 4a and 4b show this to be true. Since the hydrogen positions determined in X-ray refinement with heavy atoms present are poor, calculated hydrogen positions (assuming standard geometry) were used in X-ray dihedral angle calculations. The estimated dihedral angles from nmr studies of I were about 20° for the H_b–C–C–H_c angle and about 100° for the H_b–C–C–H_d angle. These correspond to the X-ray results of 26.5 and 95.3°, respectively (Figure 4a), or 26.9 and 94.8° (Figure 4b). Likewise, the H_a–C–C–H_b angle was estimated at about 80° and found by X-ray to be 75.7° [H(7), C(8), C(9), H(14)] and 74.7° [H(8), C(12), C(11), H(10)].

Experimental Section

N-exo-6-Bicyclo[3.1.0]hexyl-*p*-bromosulfonamide.—A mixture of 480 mg of *p*-bromosulfonyl chloride and 360 mg of *exo*-6-aminobicyclo[3.1.0]hexane in 10 ml of dry benzene was allowed to stand for 1 hr at room temperature. The solution was filtered and the filtrate was evaporated. The residue was recrystallized from dilute ethanol and analyzed by infrared and mass spectrometry. Crystals suitable for the X-ray analysis were obtained by crystallization from an acetone–Skellysolve B mixture.

Crystallographic Measurements.—*N-exo*-6-Bicyclo[3.1.0]hexyl-*p*-bromosulfonamide (IV) crystallizes in the monoclinic space group $P2_1/c$ as evidenced by systematic absences of $h0l$ for l odd and $0k0$ for k odd. The unit cell constants are a = 12.31 (±0.02), b = 6.10 (±0.01), and c = 19.45 (±0.03) Å, β = 116.8° (±0.2°). The calculated volume is 1460 Å^3; the calculated density is 1.437 g/cm^3 assuming four molecules per unit cell.

Complete three-dimensional intensity data were measured using a General Electric diffractometer with an Electronics and

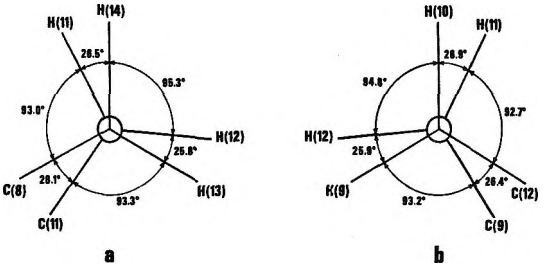


Figure 4.—(a) Dihedral angles along the C(9) (front) and C(10) (back) bond. (b) Dihedral angles along the C(11) (front) and C(10) (back) bond.

Alloys full circle orienter and Datex automation. The crystal was coated by dipping in colloidion. The θ–2θ scan technique with nickel-filtered copper radiation and a scintillation counter were used. The crystal showed significant change during data collection as evidenced by the intensities of the reflections 5,0,2; 0,0,10; and 0,4,0 which were measured periodically during data collection. $I_{final}/I_{initial}$ was 0.76.

Background counts were taken on either side of each peak and averaged, scaled, and subtracted from the cumulative scan count to give the observed intensity for each reflection. If the observed intensity so obtained was negative, it was set equal to zero and assigned zero weight in subsequent calculations. Observed intensities were corrected for Lorenz and polarization effects in the usual way. Intensities were then corrected for crystal deterioration. An absorption correction was applied using the method of Busing and Levy.[9] The linear absorption coefficient is 60.1 cm^{-1} for copper K_α radiation. Each intensity was assigned a standard deviation according to[10]

$$\sigma^2(I) = \sigma^2 \text{ counting} + (0.03)I^2$$

The data were placed on an approximate absolute scale by Wilson statistics. Through all the corrections described above, the assigned standard deviation for each observed intensity was scaled by propagation of error to give a standard deviation for that corrected intensity. The final set of data consisted of 2183 reflections of which 119 were assigned zero weight.

Derivation of a trial structure proceeded by the heavy atom method. Positions for the bromine and sulfur atoms were derived from analysis of a three-dimensional sharpened Patterson map. Structure factors calculated using these two atoms were used to phase a three-dimensional electron density map. From this map positions for the remaining 15 atoms were easily derived.

The structural parameters and the scale factor were refined by multiple-matrix least squares. The function minimized was $\Sigma\omega(|F_o|^2 - |F_c|^2)^2$. The initial weighting function was the Hughes I/F_o type. Scattering factors are those of the "International Tables for X-Ray Crystallography."[11] Several cycles of least squares with isotropic temperature factors were followed by several cycles of least squares with anisotropic thermal parameters according to the expression

$$\exp[-(h^2B_{11} + k^2B_{22} + l^2B_{33} + hkB_{12} + hlB_{13} + klB_{23})]$$

A difference Fourier was then calculated to locate hydrogen atoms. Predicted positions for all hydrogen atoms were also calculated to aid in interpretation of the difference map. All hydrogens were found at positions very close to the calculated positions. No extraneous peaks were observed. Hydrogen coordinates were included in the refinement; all hydrogen atoms were assigned an isotropic temperature factor of 3.5 which was not refined. For the refinements the weighting scheme used was

$$\sqrt{\omega} = \frac{1}{\sigma(F_o^2)}$$

where $\sigma(F_o^2)$ was the one assigned at data reduction time and subsequently scaled.

(9) W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **10**, 180 (1957).
(10) S. W. Peterson and H. A. Levy, *ibid.*, **10**, 70 (1957).
(11) "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1959.

A correction for secondary extinction was applied according to the equation[12]

$$(F_c^*)^2 = \frac{F_c^2}{1 + g\beta F_c^2}$$

The parameter, g, was refined in the least squares. With the hydrogen atoms and secondary extinction factor included, the refinement was continued until shifts in all positional and thermal parameters were less than $^1/_3$ standard deviations. The final R for these refinements was 0.076. The

$$\text{weighted } R = \left\{\frac{\Sigma\omega(|F_o|^2 - |F_c|^2)^2]}{\Sigma\omega|F_o|^4}\right\}^{1/2} = 0.13$$

and the standard deviation of fit =

$$\left\{\frac{\Sigma\omega(|F_o|^2 - |F_c|^2)^2}{m - s}\right\}^{1/2} = 1.90$$

(12) A. C. Larson, *Acta Crystallogr.*, **23**, 664 (1967).

The standard deviation of fit is expected to be 1.0 if the refinement has converged and if the weighting scheme and structural model are adequate.

The final parameters are listed in Table I. The final value of the secondary extinction parameter, g, is 1.041×10^{-5}. A table of observed and calculated structure factors has been deposited with the National Auxiliary Publication Service.[13] All calculations were done on the IBM 360 computer using programs of the CRYM system written by one of the authors (D. J. Duchamp).

Registry No.—IV, 31128-90-2.

(13) Listings of structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Conformation and Reactivity in the *cis,trans*-2,6-Cyclodecadienyl System[1,2]

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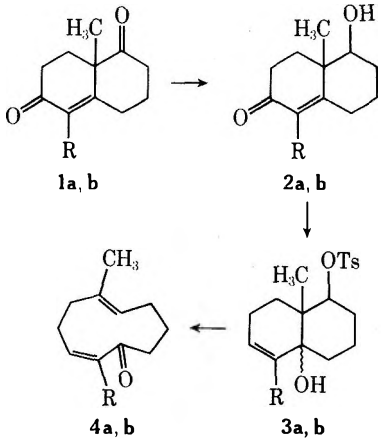
Received February 23, 1971

6-Methyl- and 2,6-dimethyl-*cis,trans*-2,6-cyclodecadienones (**4a** and **4b**) were synthesized by fragmentation of octalin diol monotosylates. They exhibit the properties of twisted α,β-unsaturated ketones. 2,6-Dimethyl-*cis,trans*-2,6-cyclodecadienyl methyl ether exists in two conformations in carbon disulfide (70:30 at −62°). Solvolysis of the corresponding *p*-nitrobenzoate (**5** PNB) in buffered acetic acid at 30° yielded exclusively *trans*-bicyclo[5.3.0] products, and it is tentatively concluded that participation of the C-6,7 double bond contributes significantly to the solvolytic rate.

Ten-membered rings have been of unusual interest with respect to the stereochemisty of transannular reactions.[3] The following study of the *cis,trans*-2,6-cyclodecadienyl system, originally undertaken with thoughts of sesquiterpene synthesis, is exemplary.



6-Methyl-*cis,trans*-2,6-cyclodecadienone (4a) was prepared by fragmenting hydroxy tosylate **3a** with potassium *tert*-butoxide in *tert*-butyl alcohol.[4] Cyclodecadienone **4a** was obtained in 20% overall yield from ketol **2a**[5] by conversion of the ketol to a crystalline tosylate which was then subjected to epoxidation, hydrazine reduction, and fragmentation, without isolation of intermediates.[6] Dienone **4a**, obtained by this method, exhibits the properties of a twisted α,β-unsaturated ketone. The ultraviolet maximum at 228 nm in ethanol is of low intensity, ϵ 4680.[7] The relative nmr shifts of the α and β hydrogens are reversed from normal, with the β hydrogen at τ 4.4 at higher field than the α hydrogen at τ 3.8.[7] The stereochemistry of the double bonds of **4a** must be cis-2 (unchanged during the reaction, with the vinyl hydrogens showing a coupling constant of 11.5 Hz[7]) and trans-6 (determined by the geometrical constraint of the fragmentation step[8]).

2,6-Dimethyl-*cis,trans*-2,6-cyclodecadienone (4b) was then synthesized, without further study of **4a**. It was prepared in 64% overall yield by the procedure already described but starting from ketol **2b**.[9] The new dienone differs from **4a** solely by the presence of a methyl group at C-2, but this additional methyl group greatly facilitated analysis of a reaction described later

(1) This investigation was supported by Public Health Service Research Grants GM 14133 and GM 16338 from the Division of General Medical Sciences, U. S. Public Health Service.

(2) This article is abstracted from the Ph.D. thesis of M. D. B., University of Wisconsin, 1969. The research was carried out in part at Wesleyan University.

(3) For a survey of transannular reactions in medium-sized rings see A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev., Chem. Soc.*, **20**, 119 (1966).

(4) Under similar conditions formation of another 2,6-cyclodecadienone by fragmentation–elimination has been demonstrated by M. Iguchi and A. Nishiyama, *Tetrahedron Lett.*, 4295 (1969).

(5) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2680 (1960).

(6) This sequence is superior to that originally used to prepare 6-methyl-*trans*-5-cyclodecenone, which unnecessarily involved benzoylation of ketol **2a** and subsequent saponification; see P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961).

(7) *cis*-2-Cyclodeeenone exhibits a uv maximum at 227 nm in ethanol with ϵ 3500 and nmr chemical shifts for the α and β protons at τ 3.67 and 4.23, respectively, $J_{2,3}$ = 11.9 Hz. For further comparison the following constants are also noted: *cis*- and *trans*-2-cycloundecenones, $J_{2,3}$ = 12.1 and 16.7 Hz, respectively; *cis*- and *trans*-2-cyclododecenones, $J_{2,3}$ = 11.6 and 15.9 Hz, respectively. See M. Regitz and J. Ruter, *Chem. Ber.*, **102**, 3877 (1969).

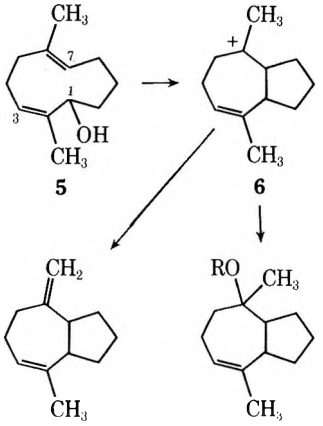
(8) P. S. Wharton and G. A. Hiegel, *J. Org. Chem.*, **30**, 3254 (1965), and references cited therein.

(9) V. F. Kucherov and I. A. Gurvich, *Zh. Obshch. Chim.*, **31**, 796 (1961); *J. Gen. Chem. USSR*, **31**, 731 (1961).

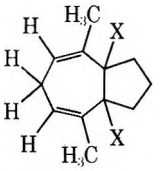
The spectroscopic properties of dienone **4b** were similar to those of **4a**: a low-intensity (ϵ 4200) ultraviolet maximum at 239 nm in ethanol and a high-field chemical shift of τ 4.6 for the β proton of the α,β-unsaturated ketone.

2,6-Dimethyl-*cis,trans*-2,6-cyclodecadienol (5), a solid, mp 79°, was obtained by reduction of the corresponding dienone with lithium aluminum hydride. Certain deuterium-labeled compounds were similarly prepared. Reduction with lithium aluminum deuteride yielded **5**-1-d_1. In addition, by reducing dione **1b** initially with sodium borodeuteride, it was possible to prepare **5**-7-d_1 and **5**-1,7-d_2. Labeling with deuterium established the unrearranged location of the hydroxyl group and enabled straightforward nmr assignments to be made to the three hydrogens at τ 5.84 (C-1), 5.16 (C-7), and 4.84 (C-3).

Dienol **5** was found to be unstable at 150°, affording products apparently derived from cyclization. The corresponding methyl ether and acetate behaved similarly and the acetate also yielded similar products upon solvolysis in buffered acetic acid at room temperature. It was, however, cyclization of the corresponding *p*-nitrobenzoate (**5** PNB), mp 80°, a nicely crystalline derivative, which was most conveniently studied.[10] Solvolysis in buffered acetic acid at room temperature gave a mixture which was separated by a combination of crystallization and thick layer chromatography into olefin (46%), acetate (46%), and PNB (8%) fractions. According to the criteria of glpc, tlc, and various spectroscopic data, each fraction consisted essentially of one component (but the presence in each fraction of small amounts of compounds with similar properties is not excluded). Spectroscopic data characterized the olefin, acetate, and PNB as **7**, **8a**, and **8b**, respectively. Thus

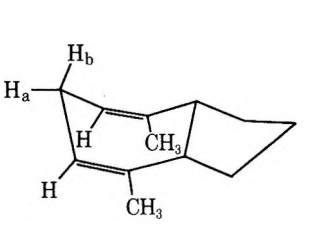


all the products were produced, in a formal sense, by Markovnikov addition of the C-1 carbon of the incipient allyl cation to the C-6,7 double bond, generating ion **6**.[11] The three products were readily shown to have the same stereochemistry of ring fusion: acetate and PNB were interconverted by reduction–esterification and, upon pyrolysis, acetate yielded olefin in 47% yield. The pyrolysis also afforded, in 53% yield, another olefin (**9a**) which made possible the assignment of stereochemistry to the ring fusion. This was accomplished by inspec-



9a, X = H
b, X = D

tion of the nmr spectrum of **9b**, obtained from acetate derived from solvolysis of the PNB of **5**-1,7-d_2. The two doubly allylic methylene protons appeared as a pattern consisting of a triplet of septuplets with J = 5.8 Hz for the coupling with the two vinyl hydrogens and J = 1.3 Hz for the coupling with the six methyl protons. The spectrum of this region was broadened but not grossly changed down to −84°. This pattern is consistent with the equivalence of the methylene protons in a molecule with a trans ring fusion but cannot be explained for the nonequivalent methylene protons of cis-fused diene. In *trans*-diene a very facile wagging motion of the methylene group of the 1,3-cycloheptadiene ring interconverts identical conformations and makes the two protons equivalent. Some extraordinary coincidences would have to occur for the observed pattern to arise from *cis*-diene, and such a possibility can be dismissed as follows. *cis*-Diene can exist in two



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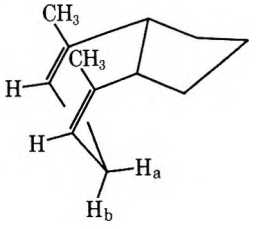


11

conformations, **10** and **11**, also interconvertible by a wagging motion of the methylene group. They are not identical. If *cis*-diene should exist solely in conformation **10** the two methylene protons might have coincidental chemical shifts but they would not be coupled equally to the vinyl[12] or methyl[13] hydrogens (dihedral angles 10 and 130° from models). If *cis*-diene should exist as equal amounts of the two conformations the couplings would be averaged but the two protons could not absorb at the same chemical shift: in conformation **11** H_a lies directly under the cyclopentane ring and should be shielded, relative to H_b in either conformation or H_a in conformation **10**, by *ca.* 24 Hz (at 60 MHz).[14] The averaged shift difference of 12 Hz is more than enough to exclude the possibility in the coupling pattern of a set of simple septuplets with J = 1.3 Hz.

Inspection of Dreiding models reveals no immediately obvious reason why products with a cis ring fusion

(10) A similar cyclization has been reported by J. A. Marshall and W. F. Huffman, *J. Amer. Chem. Soc.*, **92**, 6358 (1970).

(11) Formation of a carbon–carbon bond involving the C-3 carbon of the incipient allylic cation seemed unlikely from inspection of Dreiding models and it was straighforward to show that this mode of cyclization was inconsequential. Solvolysis of **5**-1-d_1 PNB yielded products with nmr absorption corresponding to one vinyl hydrogen at C-3. Dehydrogenation of the total product yielded 4,8-dimethylazulene (one singlet at τ 7.15) with no trace of 1,4-dimethylazulene [two singlets at τ 7.38 and 7.22 reported by D. Mueche and S. Huneck, *Chem. Ber.*, **99**, 2669 (1966)].

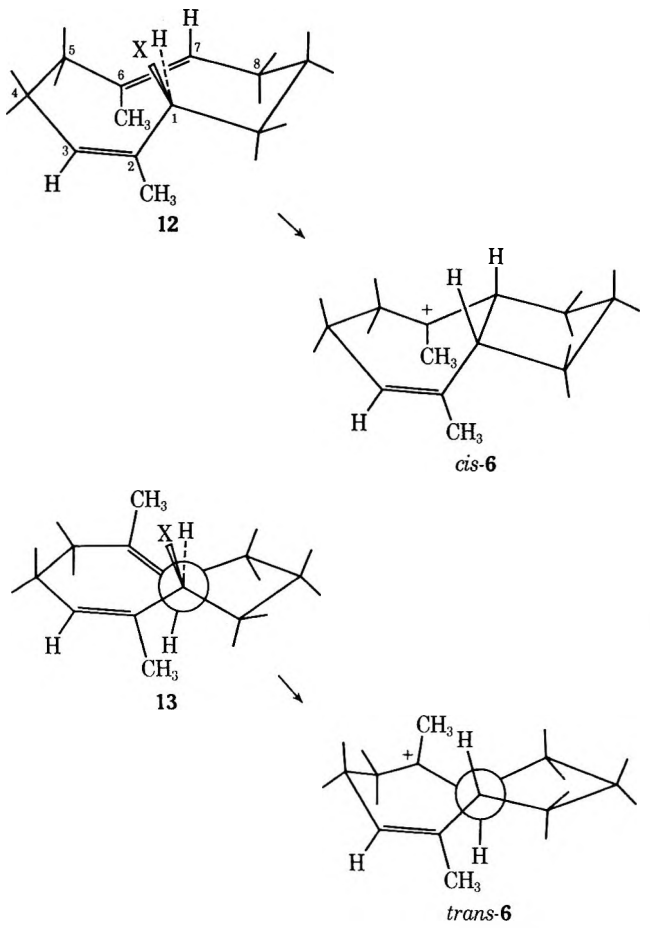
(12) K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

(13) J. T. Pinkey and S. Sternhell, *Tetrahedron Lett.*, 275 (1963).

(14) The calculation employed $\chi_L - \chi_T = 5.5 \times 10^{-30}$ ml molecule^{-1}, and the McConnell equation; see A. A. Bothner-By and C. Naar-Colin, *Ann. N. Y. Acad. Sci.*, **70**, 833 (1958), and H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).

should not form from a process involving simple allylic ionization. Two conformations (or conformational subsets), **12** and **13**, can readily be defined, interconvertible by rotation of the trans double bond through the ring.[15,16] In each case the two assemblies of carbons containing the double bonds, C-1–4 and C-5–8, define two planes which face each other across the ring. The two conformations can be defined by the relation of the methyl groups as syn (**12**) or anti (**13**) with respect to the overall plane of the ring. The two double bonds are approximately parallel in the syn conformation and crossed in the anti conformation. In each conformation the PNB group, which necessarily lies outside, rather than inside, the ring, is favorably aligned for allylic ionization. The syn conformation is geometrically related to cis product, the anti conformation to trans product.

SCHEME I[a]



[a] Note the unorthodox but hopefully not misleading use of a Newman projection in **13** which serves to separate sets of atoms attached to two *nonbonded* carbon atoms coincident in projection. Compare and contrast with the orthodox use in *trans*-**6**.

Nmr temperature-dependent spectra were revealing with respect to the conformational composition of the ground state of the ten-membered ring. Although neither **5** PNB nor **5** acetate yielded useful data because of insolubility and a coincidence of chemical shifts, respectively, interpretable results were obtained with the methyl ether, using deuterium-established nmr assignments for hydrogens at C-1, -3, and -7. Two conformations were well resolved in the ratio 70:30 at −62° in carbon disulfide. They averaged rapidly on the nmr time scale above −20°. It was possible to correlate the major one with the anti conformation on account of the large shift difference for the C-7 proton in the two conformations, arising from the fact that it lies directly above the C-2,3 double bond in the anti conformation.

It would thus appear that both syn and anti conformations are available to **5** PNB in acetic acid but only trans product is formed, presumably solely from the anti conformation.[17] Participation of the C-6,7 double may well provide the required explanation. A more detailed examination shows that, although the C-1,7 distance in undistorted Dreiding models is less than 3 Å for both conformations, the C-6,7 double bond of the anti conformation can initiate and maintain favorable overlap of the developing transannular bond with less geometric restraint or distortion than can the double bond of the syn conformation; and trans product is almost certainly more stable than cis product.[18]

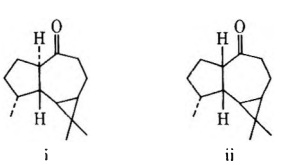
Kinetic data were also suggestive of participation. Solvolysis of **5** PNB in buffered acetic acid at 30° was found to be extremely fast, proceeding with a first-order rate constant of 2×10^{-4} sec^{-1}. This compares with a solvolytic rate constant of 1×10^{-6} sec^{-1} at 100° in 90% aqueous acetone for the similarly substituted PNB of *trans*-α,γ-dimethylallyl alcohol;[19] after allowing for differences of temperature and solvent,[20] **5** PNB is estimated to solvolyze 10^5–10^6 times faster. This is certainly much faster but this fact is unfortunately not immediately interpretable; some relevant comparative rate data are available[21] but until the rate of sol-

(15) This motion in *trans*-cyclodecene, for which E_a = 11 kcal mol^{-1}, has been studied by G. Binsch and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 5157 (1965).

(16) Conformational isomerism has been established by nmr for several 1,5-cyclodecadienes: urospermal, R. K. Bentley, J. G. St. C. Buchanan, T. C. Halsall, and V. Thaller, *Chem. Commun.*, 435 (1970); isabelin, H. Yoshioka, T. J. Mabry, and H. E. Miller, *ibid.*, 1679 (1968); neolinderolactone, K. Tori, I. Horibe, K. Kuriyama, and K. Takeda, *ibid.*, 957 (1970); and hedycaryol and 1,5-dimethyl-*trans*,*trans*-1,5-cyclodecadiene, H. C. Kluender and Y. C. Poon, respectively, Ph.D. theses, Wesleyan University, 1971. Individual conformations have been determined by X-ray for germacatriene, F. H. Allen and D. Rogers, *Chem. Commun.*, 588 (1967); pregeigerene J. McClure, G. A. Sims, P. Coggan, and A. T. McPhail, *ibid.*, 128 (1970); and costunolide, F. Sorm, M. Suchy, M. Holub, A. Link, I. Hadinec, and C. Novak, *Tetrahedron Lett.*, 1893 (1970); and by nuclear Overhauser effects for furanodienone and isofuranodienone, H. Hikino, C. Komo, T. Takemoto, K. Tori, M. Ohtsuru, and I. Horibe, *ibid.*, 662 (1969); dihydrotamaulipin A acetate, N. S. Bhacca and N. H. Fischer, *ibid.*, 68 (1969); zeylanine and zeylanane, K. Tori, M. Ohtsuru, I. Horibe, and K. Takeda, *ibid.*, 943 (1968).

(17) Formation of trans product starting from the syn conformation would involve an unlikely combination of steps: allylic ionization, rotation of the trans double bond through the ring, and addition of the allyl cation to the double bond.

(18) See G. Buchi, S. W. Chow, T. Matsuura, T. L. Popper, H. H. Rennhard, and M. Schach V. Wittenau, *Tetrahedron Lett.*, No. 6, 14 (1959). In particular, it was shown that apoaromadendrone (i) is more stable than α-apoaromadendrone (ii).



(19) H. L. Goering and W. D. Closson, *J. Amer. Chem. Soc.*, **83**, 3511 (1961).

(20) The temperature calculation assumed $\Delta H^{\ddagger}$ = 28 kcal mol^{-1} for solvolysis of the PNB of α,γ-dimethylallyl alcohol; see H. L. Goering and E. F. Silversmith, *J. Amer. Chem. Soc.*, **77**, 6249 (1955), and references cited therein. No solvent calculation was necessary because the *Y* values of acetic acid and 90% aqueous acetone are virtually identical: see A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 45.

(21) The relative rates of solvolysis of PNBs of *trans*-5-cyclodecenol, α,γ-dimethylallyl alcohol, and cyclodecanol in 90% aqueous acetone are approximately 10:1:$<10^{-2}$; see ref 19.

volysis of the PNB of *cis*-2-cyclodecenol has also been determined an estimate of the extent of participation in the solvolysis of **5** PNB is deferred. Participation of this kind is not unknown, occurring, for example, in the solvolytic cyclization of (allylic) esters of linalool and nerol to the terpenyl system.[22]

Experimental Section

Physical Data.—Melting points were determined on a Thomas Unimelt capillary melting point apparatus and are uncorrected. Analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. and Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were obtained using Perkin–Elmer Model 137 Infracord and Beckman IR-8 spectrophotometers. Nmr spectra were recorded on Varian Associates A-60 or A-60A instruments employing tetramethylsilane as an internal reference. A Varian V-6040 nmr variable-temperature controller was used for low-temperature work. Ultraviolet spectra were obtained with Cary Models 11 and 15 recording spectrophotometers. Mass spectra were recorded with a Consolidated Electrodynamics Corp. Type 21-203 C mass spectrometer. Gas–liquid phase chromatography (glpc) was performed on Varian Aerograph, Model A-90-P, and Perkin–Elmer Model F-11, units, using packed and capillary stainless steel columns, respectively. The various columns used for glpc were 5 ft × 0.25 in. (1) 5% Carbowax 20M on Teflon-6; (2) 10% Carbowax 20M on Chromosorb P; (3) 20% SF-96 on 60–80 firebrick; and 150 ft × 0.01 in. (4) Ucon 50 HB 2000 Polar; (5) SF-96; (6) Apiezon L.

Materials and Procedures.—All solvents were dried and distilled with the exception of Merck absolute methanol and Mallinckrodt absolute ether. Magnesium sulfate was used as a drying agent. Pyridine was distilled from barium oxide and stored over barium oxide. *p*-Nitrobenzoyl chloride was recrystallized from hexane. Sodium acetate was dried at 110° for 6 hr. Glacial acetic acid was purified by addition of 1% v/v of acetic anhydride and 2% by weight of chromium trioxide and subsequent distillation (bp 115–116°).[23] Preparative tlc was performed on 20 × 20 cm glass plates covered with a 1.5-mm layer of silica gel (Brinkman PF 254).

6-Methyl-2,6-*cis,trans*-cyclodecadienone (4a).—To a slurry of 0.502 g (1.51 mmol) of **2a** tosylate[24] in 16.5 ml of absolute methanol at 0° was added 0.6 ml (21.8 mmol) of 90% hydrogen peroxide and 0.17 ml of 10 *N* aqueous sodium hydroxide solution. After stirring for 2 hr at 0° the reaction mixture was poured into 60 ml of saturated sodium chloride solution. The resulting mixture was extracted with 100 ml of ether. The organic layers were washed with saturated sodium chloride solution and dried. Filtration and evaporation gave 0.528 g (101%) of white solid: mp 104–130°; nmr ($CDCl_3$) τ 9.27–7.6 (complex, 14.4, with equally intense peaks at 8.88 and 8.81) and equally intense singlets at 7.13 and 6.95. To a slurry of 0.500 g (1.44 mmol) of this solid in 10 ml of absolute methanol was added 0.24 ml of glacial acetic acid. The flask was attached to a gas-measuring buret, and 0.24 ml (4.9 mmol) of hydrazine hydrate (99–100%) was added through a septum. The mixture became warm. Gas evolution indicated that the reaction was nearly complete in 3 min; after stirring for 1 hr the total gas evolution was 28.2 ml (64%). The yellow solution was poured into 100 ml of saturated sodium chloride solution and the mixture was extracted with 200 ml of ether. The organic layer was washed with saturated sodium chloride solution, 1.5 *N* sodium hydroxide solution, and saturated sodium chloride solution until neutral and dried. Filtration and evaporation gave 0.412 g which was dissolved in 16 ml of *tert*-butyl alcohol and treated with 3.7 ml of 1 *N* potassium *tert*-butoxide in *tert*-butyl alcohol. The reaction mixture turned cloudy and dark red immediately. After 25 min 10 ml of water was added and the mixture was extracted with 100 ml of hexane. The organic layer was washed with 100 ml of saturated sodium chloride solution and dried. Filtration and evaporation gave 0.183 g of brown oil, short-path distillation of which gave 0.059 g (22% overall) of a colorless oil at a bath temperature of 37–141° (0.1 mm): glpc analysis on column 1 (127°) revealed the presence of only one component; uv max (95% ethanol) 228 nm (ϵ 4860); ir (film) 5.97, 6.20, 10.0, 12.17 13.05, and 13.5 μ; nmr (CCl_4) τ 8.57 (s, 3), 5.27 (t, 1), 4.4 (d of t, 1), 3.79 (d, 1, J = 11.5 Hz). Preparative glpc yielded a sample which was submitted for analysis.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.23; H, 9.99.

p-Toluenesulfonate of 1,4aβ-Dimethyl-4,4a,5,6,7,8-hexahydronaphth-5β-ol-2(3*H*)-one (2b Tosylate).—To a solution of 99.3 g (0.510 mol) of anhydrous ketol **2b**,[25] bp 150–155° (0.2 mm), in 355 ml of dry pyridine at room temperature was added 198 g (1.04 mol) of tosyl chloride. The reaction mixture was cooled and stirred at 5° for 70 hr. It was then diluted with 2000 ml of water and extracted with four 1000-ml portions of chloroform. The combined chloroform extracts were washed with 2500 ml of 2 *M* hydrochloric acid and 1000 ml of saturated sodium chloride solution and dried. Filtration, evaporation, and crystallization from benzene–hexane gave 146.1 g (82%) of white solid: mp 104–105°: uv max (methanol) 228 nm (ϵ 18,700), 245 (14,500); ir ($CHCl_3$) 6.02 μ; nmr ($CDCl_3$) τ 8.80 (CH_3) and 5.72 (CHOTs). Three recrystallizations from methanol afforded an analytical sample, mp 108–109°.

Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.50; H, 6.94; S, 9.18. Found: C, 65.44; H, 6.89; S, 9.35.

2,6-Dimethyl-2,6-*cis,trans*-cyclodecadienone (4b).—A slurry of 26.4 g (75.8 mmol) of **2b** tosylate in 551 ml of absolute methanol was warmed to 55°, yielding an amber solution. The solution was then cooled to 30° and 39 ml (1.44 mmol) of 90% hydrogen peroxide was added with stirring. Then 9 ml of 10 *N* sodium hydroxide solution was added dropwise over a 5-min period. A white precipitate formed but did not increase in quantity with time. The reaction mixture was stirred at room temperature for 3 hr[26] and was then poured into 1110 ml of saturated sodium chloride solution, diluted with a further 500 ml of water, and extracted with three 1000-ml portions of ether. The combined organic layers were washed with five 500-ml portions of saturated sodium chloride solution and dried. The final washing gave a negative peroxide test with acidic potassium iodide. Filtration and evaporation gave 27.2 g (99%) of white semisolid epoxide: uv max (methanol) 226 nm; ir ($CHCl_3$) 5.89 μ; nmr ($CDCl_3$) two equally intense methyl peaks at τ 8.94 and 8.82 and 5.44 (CHOTs).

Another run yielded 79.9 g of crude epoxide. This was dissolved in 275 ml of methanol containing 0.8 ml of acetic acid. The flask was attached to a gas meter and 39 ml of hydrazine hydrate was added. Gas evolution reached 4100 ml after 30 min and 5600 ml when the reaction was worked up after 7 hr. The methanol was removed from the reaction mixture on a rotary evaporator and the resulting oil was dissolved in 4000 ml of ether. The ether was washed with water until the washings were neutral. Drying, followed by filtration and evaporation, gave 78.0 g of a yellow oil which was dissolved in 330 ml of *tert*-butyl alcohol and heated with 440 ml of 1 *N* potassium *tert*-butoxide in *tert*-butyl alcohol. A further 250 ml of *tert*-butyl alcohol was added to facilitate stirring, which was continued at room temperature under nitrogen for 30 min. The reaction mixture was then poured into 1500 ml of water. The mixture was extracted with three 1000-ml portions of hexane and the combined organic layers were evaporated at 30°, yielding a brown oil which was dissolved in 1000 ml of hexane, washed with two 500-ml portions of saturated sodium chloride solution, and dried. Filtration and evaporation gave 39.1 g of a brown oil; nmr (CCl_4) showed the presence of *ca.* 5% of a tosylate-containing impurity. Short-path distillation gave 28.4 g of a colorless oil at a bath temperature of 85–107° (0.1 mm). The residue of 8.37 g yielded a further 1.0 g of distillate after trituration with hexane and separation of the hexane solution from insoluble gum. The distillate was identical with material collected from another run: ir (film) 5.96 and 6.15 μ; uv max (hexane) 230 nm (ϵ 5070); uv max (methanol) 239 nm (ϵ 4220); nmr (CCl_4) τ 8.55 and 8.1 (CH_3) and 5.22 and 4.67 (vinyl hydrogens). Glpc on column 1 (125°) showed only one component; on column 4 (125°) 10% of another component was observed which may have been due to decomposition on the column. Preparative glpc on column 1 (125°) furnished an analytical sample.

(22) See W. Rittersdorf and F. Cramer, *Tetrahedron*, **24**, 43 (1968), and references cited therein.

(23) K. J. P. Orton and A. E. Bradfield, *J. Chem. Soc.*, 983 (1927).

(24) C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Amer. Chem. Soc.*, **89**, 4133 (1967).

(25) Crystallization from ether gave white crystals, mp 83–87°, possibly hydrated. The melting point reported by Kucherov (ref 9) is 73–74°.

(26) The reaction was monitored by uv and was worked up when the ratio of absorbances at 288 and 245 nm was 9.5:1.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.08; H, 10.16.

2,6-Dimethyl-2,6-*cis*,*trans*-cyclodecadienol (5).—To a slurry of 0.184 g (4.86 mmol) of lithium aluminum hydride in 8 ml of ether was added 1.638 g (9.22 mmol) of dienone **4b** in 6 ml of ether over a 20-min period. The reaction mixture was stirred for a total of 60 min at room temperature under nitrogen and then poured into a beaker. Saturated magnesium sulfate solution was added until hydrogen evolution ceased and then anhydrous magnesium sulfate was added until the solid residue was powdery. The slurry was then filtered and the solid was washed with five 100-ml portions of ether. After drying and evaporation the combined filtrate and washings afforded 1.654 g (99%) of white solid, which was sublimed at 40°, giving 1.459 g (88%): mp 73–78°; mass spectrum (70 eV) *m/e* (rel intensity) 180 (0.3), 162 (35), 91 (100); nmr (CCl_4) τ 8.41 and 8.32 (CH_3 doublets with J = 1.3 and 1.45 Hz, respectively), 5.84 (t, 1, J = 7 Hz), 5.16 (t, 1, J = 7 Hz), and 4.88 (t, J = 7 Hz).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, C, 79.62; H, 10.93.

Another sample after four recrystallizations from pentane gave white crystals, mp 77–79°.

2,6-Dimethyl-2,6-*cis*,*trans*-cyclodecadienyl Methyl Ether.—To a slurry of 0.243 g (10.1 mmol) of pentane-washed sodium hydride oil dispersion in 1 ml of ether was added 0.385 g (2.16 mmol) of dienol **5** in 0.2 ml of ether and 0.31 ml (4.96 mmol) of methyl iodide. After refluxing for 17 hr wet ether and then water were added and the mixture was extracted with three 40-ml portions of ether. The extracts were washed with 150 ml of saturated sodium chloride solution and dried. Filtration and evaporation gave 0.415 g (99%) of a yellow oil which, upon short-path distillation at 0.1 mm and bath temperature 60–70°, gave 0.356 g (85%) of a clear oil which showed only one peak by glpc on column 1 (126°); nmr (CS_2), center of mass of multiplet in hertz downfield from tetramethylsilane (relative area) at 42°, 176 (3.0, OCH_3), 216 (1.0, H_1), 290 (0.9, H_7), 317 (1.0, H_3); at −62°, 176 (3.0, OCH_3), 209 (0.7, $H_1{}^a$), 226 (0.3, $H_1{}^s$), 280 (0.7, $H_7{}^a$), 322 (1.2, $H_3{}^a + H_3{}^s + H_7{}^s$). (Superscripts a and s refer to anti and syn conformations.) Preparative glpc gave a clear oil which, upon distillation, afforded an analytical sample.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 79.95; H, 11.29.

2,6-Dimethyl-2,6-*cis*,*trans*-cyclodecadienyl Esters. A. Acetate.—To a solution of 0.117 g (0.65 mmol) of dienol in 0.45 ml of dry pyridine was added 0.114 ml (1.12 mmol) of acetic anhydride. After standing for 13 hr the reaction mixture was diluted with 1 ml of water and then worked up, yielding 0.126 g (87%) of clear oil. Two successive short-path distillations at a bath temperature of 27–77° (0.1 mm) gave 75 mg of product: nmr (CCl_4) τ 5.20 (t, 1), 4.85 (t, 1, J = 7.5 Hz), and 4.7 (t, 1, J = 7.1 Hz).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.36; H, 10.07.

B. *p*-Nitrobenzoate.—To a solution of 1.475 g (8.18 mmol) of dienol **5** in 18.8 ml of dry pyridine at 0° was added 3.000 g (16.20 mmol) of *p*-nitrobenzoyl chloride. The reaction mixture was stirred for 3 hr at 0° under nitrogen. The excess acid chloride was then destroyed by adding pieces of ice. Then 250 ml of water was added and the reaction mixture was extracted with two 250-ml portions of ether. The organic extracts were washed with two 500-ml portions of 2% hydrochloric acid and 200 ml of 2% potassium carbonate and dried. Filtration and evaporation gave 2.727 g (101%) of a white solid, mp 72–76°. Repeated recrystallizations from acetone gave white crystals: mp 78–80°; nmr (CCl_4) τ 5.13 (t, 1), 4.70 (t, 1), 4.35 (t, 1); uv max (95% ethanol) 259 nm (ϵ 13,800).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.26; H, 6.97; N, 4.26.

Hydrolysis of *p*-nitrobenzoate with 2.5 *N* ethanolic sodium hydroxide for 1 hr at 60° led to the recovery, after sublimation, of 71% of starting alcohol **5**, mp 77–78°.

Solvolysis of 5 *p*-Nitrobenzoate.—To a mixture of 0.810 g (2.39 mmol) of **5** *p*-nitrobenzoate and 0.706 g (8.6 mmol) of anhydrous sodium acetate was added 43.0 ml of glacial acetic acid. The reaction mixture was stirred at 30° under nitrogen for 13 hr. Then 43 ml of water was added and the aqueous phase was extracted with two 200-ml portions of hexane. The organic phase was washed with 50 ml of saturated sodium chloride solution and 100 ml of 2% potassium carbonate solution and dried. Filtration and evaporation gave 0.525 g of oil in which crystals formed on standing. The solid was separated and crystallized twice from ether, giving an analytical sample of **8b**, mp 130.5–131.5°, uv max (95% ethanol) 259 nm (ϵ 13,200).[27]

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.35; H, 7.00; N, 4.26.

A portion (0.218 g) of solid-free oil was separated into two components, with R_f values of 0.4 and 0.7, by preparative tlc using 1:9 (v/v) ether–hexane. Recovery of the faster moving component and short-path distillation from a bath at 30–40° (0.1 mm) yielded an oil, identified as olefin **7**, which was shown to be homogeneous by glpc on column 1 (130°): ir (film) 6.11 and 11.33 μ; nmr (CCl_4) τ 8.30 (CH_3), 5.37 (CH_2=), 4.52 (-CH=); molecular weight by mass spectroscopy, 162.

After recovery, the slower moving component was found to contain about 5 mol % of *p*-nitrobenzoate, which could be almost completely removed by stirring with Norit in 2-methylbutane solution. Short-path distillation from a bath at 65–110° (0.1 mm) gave an oil, identified as acetate **8a**: ir (film) 5.80 and 8.0 μ; nmr (CCl_4) τ 8.59 and 8.35 (CH_3), 8.15 (CH_3CO), and 4.6 (-CH=); molecular weight by mass spectroscopy, 222.

A portion (87 mg) of acetate was reduced with lithium aluminum hydride and the resulting alcohol was acylated with *p*-nitrobenzoyl chloride in pyridine, yielding 117 mg (94%) of crude *p*-nitrobenzoate, mp 122–126°. Crystallization afforded, with 60% recovery, material with mp 128–129°, undepressed upon admixture with *p*-nitrobenzoate isolated from solvolysis, mp 130–131°.

4,8-Dimethylazulene. Dehydrogenation of Solvolysis Products.—The total crude product, obtained from solvolysis of 0.221 g of **5** *p*-nitrobenzoate, was mixed with 0.854 g of sulfur and heated at 222° under nitrogen for 3 min. The product was extracted first with hexane and then with boiling ethanol until the extract was colorless. All solvent was removed and the purple residue was dissolved in ether, washed with three 25-ml portions of 2% aqueous potassium carbonate, and dried. Filtration and evaporation gave 35 mg of a purple solid, which was purified by two preparative tlc treatments, using hexane, which gave 21 mg of purple crystals, mp 68–70° (lit.[28] 69°), nmr (CCl_4) τ 7.15 (CH_3).

Pyrolysis of Acetate 8a.—A solution of 0.946 g (4.24 mmol) of acetate **8a** (purified by tlc) in 11.0 ml of hexane was added dropwise over 1 hr to a 1 × 34 cm tube of $^1/_8$ in. glass helices maintained at 425° and swept by a stream of dry nitrogen (flow rate 240 ml/min). Two 2-ml portions of hexane were then passed through the tube, which was then allowed to cool to 50° and rinsed with 50 ml of hexane. The combined organic fractions were washed with 50 ml of 2% aqueous potassium carbonate and dried. Filtration and evaporation gave 0.570 g (82%) of an oil which was shown to consist of two components, with retention times of 20 (47%) and 23 min (53%).

Preparative glpc afforded two fractions, the first containing 87% of the 20-min component, the second 91% of the 23-min component. Glpc of each fraction on columns 5 and 6 (150°) did not indicate the presence of a third component. The major component in the first fraction was identified as olefin **7** by comparison with solvolysis olefin (nmr spectrum and glpc coinjection). The major component in the second fraction was identified as olefin **9a** on the basis of absorptions in the nmr spectrum (CCl_4) at τ 7.47 (doubly allylic CH_2) and 4.56 (two -CH=).

2,6-Dimethyl-*trans*-bicyclo[5.3.0]deca-2,6-diene-1,7-d_2 (9b).—The preparation of this diene is given briefly as illustrative of the synthesis of deuterated compounds.

Reduction of 30.25 g (0.157 mol) of dione **1b** in ethanol with 1.660 g (0.159 equiv) of sodium borodeuteride gave, after work-up, 3.27 g (76%) of deuterated ketol **2b**, mp 85–87°. Tosylation with 45.24 g (0.238 mol) of tosyl chloride in pyridine yielded 37.42 g (90%) of deuterated keto tosylate, mp 107–109°. Epoxidation in methanol was allowed to proceed until the ratio of absorbances for the uv maxima at 228 and 245 nm was 9.5:1. Work-up gave 40 g (39.1 g theoretical) of white gum which, upon treatment with hydrazine hydrate and acetic acid in methanol, evolved nitrogen (57%) and afforded, after work-up, 38.4 g of product. Fragmentation gave 21 g of oil which was triturated with 2-methylbutane and thereby separated into 3.3 g of gummy solid and 17.7 g of brown oil. Distillation of the oil gave a total of 11.5 g (41%

(27) Based on the given uv max the yield of *p*-nitrobenzoate in the solvolysis product was calculated to be 8%. (A 5% yield of crystalline material, mp 120–125°, was recovered from one run.)

(28) Mueche, ref 11.

based on starting dione **1b**) of **4b**-7-d_1 after triturating the initial residue with 2-methylbutane, separating, distilling, and combining distillates. A 5.03-g portion of deuterated dienone was reduced with lithium aluminum deuteride, using the procedure described for the undeuterated case, and afforded 5.0 g (98%) of **5**-1,7-d_2, mp 75–77.5°. This was converted to 6.4 g (70%) of **5**-1,7-d_2 *p*-nitrobenzoate, mp 73–78°, which was solvolyzed in buffered acetic acid for 19 hr at room temperature. Work-up gave 4.09 g of product which yielded 0.36 g (5.6%) of dideuterated **8b** after addition of 2-methylbutane and filtration. The remaining oil was subjected to preparative tlc (development with 1:9 ether–hexane), giving 1.53 g of dideuterated **7** and 2.20 g of cloudy yellow oil which afforded 2.0 g of dideuterated acetate **8a** as a clear oil after treatment with Norit in 2-methylbutane (<1% *p*-nitrobenzoate present). Pyrolysis of a 0.528-g portion of acetate yielded 0.279 g (72%) of a mixture of dienes which was separated by preparative glpc on column 2 (120°) into two fractions, the second of which (69 mg) was, by analytical glpc, a 90:10 mixture of **9b** and dideuterated **7**, respectively: nmr (CCl_4) τ 7.47 (triplet of septuplets, J = 5.8 and 1.3 Hz) and 4.56 (triplet of quartets, J = 5.8 and 1.4 Hz).

Registry No.—**2b** tosylate, 30783-60-9; **4a**, 30783-61-0; **4b**, 30783-62-1; **5**, 30783-63-2; **5** methyl ether, 30783-64-3; **5** acetate, 30783-65-4; **5** *p*-nitrobenzoate, 30783-66-5; **7**, 30783-67-6; **8a**, 30783-68-7; **8b**, 30783-69-8.

Cyclopropanes. XXX. Haller–Bauer Cleavage of Phenyl Cyclopropyl Ketones[1]

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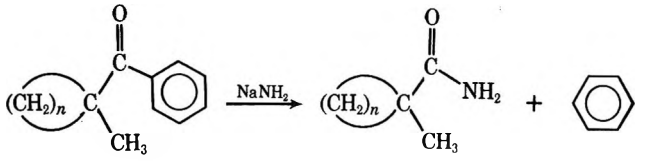
The syntheses and the establishment of the absolute configurations of 1-chloro-, 1-fluoro-, and 1-methoxy-2,2-diphenylcyclopropyl phenyl ketones are described. The optically active ketones were cleaved with sodium amide to yield optically active 1-chloro-, 1-fluoro-, and 1-methoxy-2,2-diphenylcyclopropane, respectively.

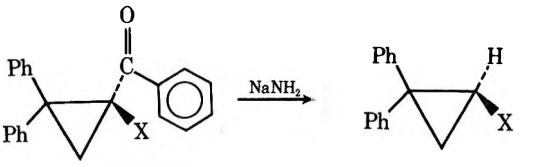
The Haller–Bauer cleavage of nonenolizable ketones such as 1-alkylcyclohexyl phenyl,[3] 1-alkylcyclopentyl phenyl,[3] 1-alkylcyclobutyl phenyl,[3] and 1-alkylcyclopropyl phenyl[4] ketones with sodium amide proceeds in the direction to produce largely the 1-alkylcycloalkanecarboxamide and benzene.



n = 2-5

A notable exception was observed in the case of 1-alkylcyclopropyl phenyl ketones in that certain 2-substituted cyclopropyl ketones such as 1-methyl-2,2-diphenylcyclopropyl phenyl ketone[5] (**1**) and *Z*-2-phenylcyclopropyl phenyl ketone[6] cleaved predominantly in the reverse manner. These observations were rationalized[6] on the basis that relief of steric interaction between the phenyl group in the 2 position and the carbonyl in the 1 position provided the driving force for the reverse cleavage.

Moreover, it was demonstrated that cleavage of **1** was stereospecific in that the hydrocarbon, 1-methyl-2,2-diphenylcyclopropane (**5**) formed by cleavage of optically active **1**, was optically pure and its configuration was retained. In connection with some other work it became necessary to prepare optically active 1-chloro-2,2-diphenylcyclopropane (**6**), 1-fluoro-2,2-diphenylcyclopropane (**7**), and 1-methoxy-2,2-diphenylcyclopropane (**8**). Based on our previous experience, the Haller–Bauer cleavage reaction seemed a promising route for accomplishing this. It was not clear, however, what the effect of an α-halo or methoxyl substituent would have on the course of the reaction.



X = CH_3 = 1-(−)-(*R*) X = CH_3 = 5-(+)-(*S*)
Cl = 2-(+)-(*S*) Cl = 6-(+)-(*S*)
F = 3-(−)-(*S*) F = 7-(−)-(*S*)
CH_3O = 4-(+)-(*S*) CH_3O = 8-(+)-(*S*)

Syntheses and Absolute Configurations.—The synthesis and absolute configuration of (−)-(*R*)-**1** has previously been described.[5] Optically active (+)-(*S*)-**2** was prepared by the addition of phenyllithium to known[7] (+)-(*S*)-1-chloro-2,2-diphenylcyclopropanecarboxylic acid. The syntheses of **3** and **4** were achieved in an analogous manner to that of **1** and **2**. This involved the addition of diazodiphenylmethane to α-fluoro and α-methoxy acrylate, which yielded after saponification the 1-fluoro- and 1-methoxy-2,2-diphenylcyclopropanecarboxylic acids, respectively. The acids were resolved using an appropriate alkaloid and the optically active acids were treated with phenyllithium to obtain **3** and **4** (see Experimental Section).

The absolute configuration of **3** was established by relating its precursor, 1-fluoro-2,2-diphenylcyclopropanecarboxylic acid, to 2,2-diphenylcyclopropanecarboxylic acid. The absolute configuration of the latter

(1) The support of this work by grants from the National Science Foundation and Public Health Service Grant No. 04065 from the National Cancer Institute is gratefully acknowledged.

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(3) K. E. Hamlin and V. Biermacher, *J. Amer. Chem. Soc.*, **77**, 6376 (1955); for a review see K. E. Hamlin and A. W. Weston, *Org. React.*, **9**, 1 (1957).

(4) F. J. Piehl and W. G. Brown, *J. Amer. Chem. Soc.*, **75**, 5023 (1953); C. L. Bumgardner, *J. Org. Chem.*, **29**, 767 (1964).

(5) F. J. Impastato and H. M. Walborsky, *J. Amer. Chem. Soc.*, **84**, 4838 (1962); H. M. Walborsky and F. J. Impastato, *Chem. Ind. (London)*, 1690 (1958).

(6) C. L. Bumgardner and K. G. McDaniel, *J. Amer. Chem. Soc.*, **91**, 6821 (1969).

(7) H. M. Walborsky and A. E. Young, *ibid.*, **86**, 3288 (1964).

acid had previously been established.[8] Of the many methods available for relating configurations one of the most convenient, when applicable, is the infrared analysis of quasiracemates.[7-9] The solid-state (KBr disks) spectrum (Table I) of the equimolar mixture of

TABLE I
THE INFRARED ABSORPTION BANDS (cm^{-1}) ASSOCIATED WITH CARBOXYL GROUP

Compd[a]	Bonded OH	COOH dimer sub-maxima	Carbonyl stretching	Broad in-plane COH	Broad out-of-plane COH
(+)-A	3235		1741, 1708	1226	821
(±)-A		2624	1714		852
		2538			
		2474			
(+)-B	3200		1733, 1696	1163	820
(+)-B		2685	1696		939
		2615			
		2550			
(+)-A–(+)-B	3230		1730, 1696	1153	826
				1169	
(+)-A–(−)-B		2710	1714		946
		2633			
		2573			

[a] A = 1-fluoro-2,2-diphenylcyclopropanecarboxylic acid; B = 2,2-diphenylcyclopropanecarboxylic acid.

(+)-1-fluoro-2,2-diphenylcyclopropanecarboxylic acid and (−)-2,2-diphenylcyclopropanecarboxylic acidshows clearly quasiracemate compound formation and the molecules are therefore of opposite configuration. Moreover, the equimolar mixture of (+)-1-fluoro-2,2-diphenylcyclopropanecarboxylic acid and (+)-2,2-diphenylcyclopropanecarboxylic acid gave a solid solution spectrum.[10] On the basis of these results it can be concluded with confidence that the acids of like sign of rotation have the same configuration. Since the absolute configuration of (+)-2,2-diphenylcyclopropanecarboxylic acid has been established as *S*, then the absolute configuration of (+)-1-fluoro-2,2-diphenylcyclopropanecarboxylic acid is *R* and the (−) enantiomer is *S*.

The method of quasiracemates was not amenable to the determination of the absolute configuration of 1-methoxy-2,2-diphenylcyclopropanecarboxylic acid, since the infrared spectra (KBr disk) of the racemic acid and the optically pure enantiomer were virtually identical.

We had previously shown[10] that optical rotatory dispersion of the aldehydes derived from the configurationally related acids, (+)-2,2-diphenylcyclopropanecarboxylic acid and (−)-1-methyl-2,2-diphenycyclopropanecarboxylic acid, gave similar negative Cotton effects. Optical rotatory dispersion is then another method available for relating configuration.[11]

(+)-(*R*)-1-Fluoro-2,2-diphenylcyclopropanecarboxylic acid was converted to (+)-(*R*)-1-fluoro-2,2-diphenylcyclopropylcarboxaldehyde (see Experimental Section). The aldehyde exhibited the expected negative Cotton effect and thereby provided additional evidence for the assignment of the (+)-(*R*) configuration to its precursor acid.

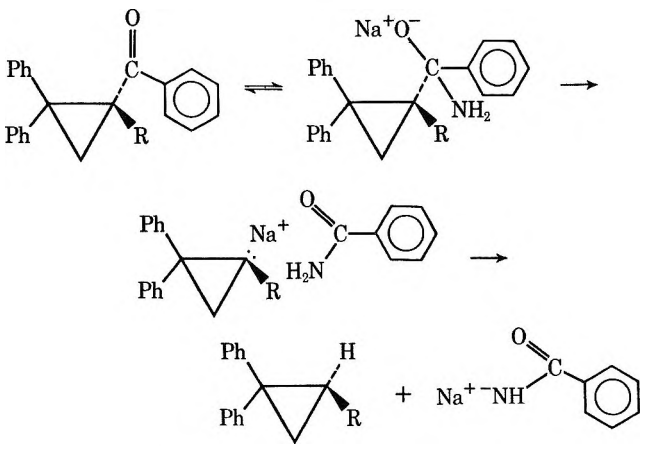
The configuration of (+)-1-methoxy-2,2-diphenylcyclopropanecarboxylic acid was obtained by converting it to the (+)-1-methoxy-2,2-diphenylcyclopropanecarboxaldehyde, which exhibited a negative Cotton effect very similar in shape to the other aldehydes in this series. The dextrorotatory 1-methoxy acid and aldehyde as well as the (−)-phenyl ketone derived from the (+) acid have therefore been assigned the *R* configuration.

Discussion

In our earlier work[5] it was shown that the cleavage of **1** resulted in the formation of **5** in a stereospecific manner. The cleavage of **2**, **3**, and **4** produced the cyclopropyl hydrocarbons **6**, **7**, and **8**, respectively. We have assigned absolute configurations based on the retention of configuration previously demonstrated for this reaction.[5] The optical rotations of the hydrocarbons (**6**, **7**, and **8**), in the absence of authentic samples, can only be viewed as minimum values. Although based on our previous work they would be expected to be of high optical purity.

The results obtained are consistent with the mechanism proposed earlier[5] (Scheme I). Both steric and

SCHEME I



electronic effects would favor the cleavage in the direction shown. Although the electronic effect to be expected is by no means entirely clear,[12] it is felt that the inductive effect of Cl, F, and methoxy groups would facilitate the formation of the carbanion intermediate,[12] since the cyclopropyl anion has been shown to be pyramidal.[13]

Experimental Section[14]

(±)-1-Methoxy-2,2-diphenylcyclopropanecarboxylic Acid.—A solution of 32.0 g (0.25 mol) of ethyl α-methoxy acrylate[15] and

(8) H. M. Walborsky, L. Barash, A. E. Young, and F. J. Impastato, *J. Amer. Chem. Soc.*, **83**, 2517 (1961), and references cited therein.

(9) A. Rosenberg and L. Schotte, *Ark. Kemi*, **7**, 347 (1954).

(10) Thermal analysis (A Fredga, "The Suedberg Anniversary Volume," Almquist and Wiksells, Uppsala, 1945) confirms the observations of the infrared analysis. The phase diagrams of the quasiracemates may be found in the Dissertation of E. J. Powers, Florida State University, June 1969.

(11) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, N. Y., 1960.

(12) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.*, **89**, 5911 (1967); A. Streitwieser, Jr., and F. Mares, *ibid.*, **90**, 2444 (1968).

(13) H. M. Walborsky and J. M. Motes, *ibid.*, **92**, 2445 (1970), and references cited therein.

(14) The infrared spectra were obtained with a Perkin–Elmer infrared spectrophotometer, the nmr spectra with a Varian A-60 analytical spectrometer, and optical rotations with a Bendix automatic polarimeter using a 1.0-cm cell. All melting points are uncorrected.

(15) N. Ogata, S. Nazakura, and S. Murahashi, *Bull Chem. Soc. Jap.*, **43**, 2987 (1970); V. Auwers, *Ber.*, **44**, 3523 (1911).

49.0 g (0.25 mol) of diazodiphenylmethane dissolved in 200 ml of cyclohexane was refluxed until the C=C stretching band at 1628 cm^{-1} was no longer present. The solvent was removed *in vacuo* and the residue was distilled to yield 60.8 g (80%) of ethyl 1-methoxy-2,2-diphenylcyclopropanecarboxylate: bp 146–148° (1 mm); ir (neat) 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.7–7.0 (m, 10, phenyl), 3.8 (q, 2, CH_2O), 3.2 (s, 3, CH_3O), 2.3 (d, 1, J = 6 Hz, ring CH), 1.7 ppm (d, 1, J = 6 Hz, ring CH).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.81; H, 6.97.

Ethyl 1-methoxy-2,2-diphenylcyclopropanecarboxylate (49 g) was added to a solution of 200 ml of 25% aqueous potassium hydroxide and 300 ml of methanol and refluxed for 4 hr. Acidification with 2 *N* hydrochloric acid yielded 36.9 g (85%) of the acid which, after recrystallization from chloroform–hexane (1:1), gave white needles: mp 178–179°; ir 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.5–7.0 (m, 10, phenyl), 3.25 (s, 3, CH_3O), 2.22 (d, 1, ring), 1.80 ppm (d, 1, ring).

Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.21; H, 5.89.

(+)-(*R*) and (−)-(*S*)-1-Methoxy-2,2-diphenylcyclopropanecarboxylic Acid. A.—A mixture of 13.4 g (0.05 mol) of (±) acid and 19.7 g of brucine was added to 500 ml of acetone and the mixture was refluxed for 1 hr. The hot solution was filtered and evaporated to one-half its volume, and water was added until the solution became slightly cloudy. The solution was allowed to remain overnight at ambient temperature. The first crop of crystals (15 g) was dried in a vacuum oven at 50° (12 mm). The dried crystals (12.1 g) were recrystallized twice from acetone to yield 8.1 g of brucine salt.

The brucine salt was dissolved in acetone, acidified with 30 ml of concentrated hydrochloric acid, and diluted with water. The solid was filtered and recrystallized from chloroform–hexane (1:1) to yield 3.3 g of acid: mp 179°; $[\alpha]_{Hg}^{25}$ −84° (c 1.0, $CHCl_3$); ir and nmr were identical with those of (±) acid.

Anal. Calcd for $C_{17}H_{16}O_3$: 76.10; H, 7.31. Found: C, 75.81; H, 6.95.

B.—The combined filtrates from the above resolution were acidified with 30 ml of concentrated hydrochloric acid and diluted with water to yield 9.8 g of acid, $[\alpha]_{Hg}^{25}$ +12°. The partially resolved acid was added to 11.8 g of quinine dissolved in 500 ml of acetone. The solution was filtered and concentrated to one-half its volume, and water was added until the solution was slightly cloudy. After the solution had remained overnight at ambient temperatures, 10.4 g of quinine salt was obtained which after two recrystallizations from acetone and hydrolysis with hydrochloric acid gave 4.3 g of (+)-(*R*)-1-methoxy-2,2-diphenylcyclopropanecarboxylic acid. A further crystallization from chloroform–hexane (1:1) gave mp 179°, $[\alpha]_{Hg}^{25}$ +84.5° (c 1.0, $CHCl_3$).

(+)-(*S*)-1-Benzoyl-1-methoxy-2,2-diphenylcyclopropane.—To a stirred cooled (0°) solution of 1.07 g (0.0025 mol) of (−)-(*S*)-1-methoxy-2,2-diphenylcyclopropanecarboxylic acid, $[\alpha]_{Hg}^{25}$ −84.5°, was added, over a period of 30 min, 6 ml of a 1.35 *M* ethereal solution of phenyllithium. Stirring was continued for an additional 30 min and the mixture was then hydrolyzed with 100 ml of saturated ammonium chloride. The ether solution was washed three times with water and saturated sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was crystallized from methanol to yield 1.2 g (85%) of ketone: mp 154–155°; $[\alpha]_{Hg}^{25}$ +34.2° (c 1.0, $CHCl_3$); ir (CCl_4) 1684 cm^{-1} (s, C=O); nmr ($CDCl_3$) δ 9.0 7.0 (m, 15, phenyl), 3.10 (s, 3, CH_3O), 2.61 (d, 1, ring), 1.72 ppm (d, 1, ring).

Anal. Calcd for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14. Found: C, 84.30; H, 6.02.

(−)-(*R*)-1-Methoxy-2,2-diphenylcyclopropylcarbinol.—To a cooled (0°) solution of 2.68 g (0.01 mol) of (+)-(*R*)-1-methoxy-2,2-diphenylcyclopropanecarboxylic acid ($[\alpha_{Hg}^{25}$ +84°) dissolved in 100 ml of ether was slowly added an ether solution of 0.02 mol of lithium aluminum hydride. After the addition was completed the mixture was refluxed for 1 hr and then hydrolyzed with 20 ml of saturated ammonium chloride. The clear supernatant was filtered from the solids and dried over molecular sieves, and the solvent was removed to yield an oil which crystallized from ether–chloroform (3:1) to give a 75% yield of carbinol: mp 82–83°; $[\alpha]_{Hg}^{25}$ −12.5 (c 1.0, $CHCl_3$); nmr (CCl_4) δ 7.6–7.1 (m, 10, phenyl), 3.7–3.4 (m, 2, CH_2O), 3.18 (s, 3, CH_3O), 2.6–2.5 (s, 1, OH), 1.65 (d, 1, ring), 1.32 ppm (d, 1, ring).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.08. Found: C 80.18; H, 6.95.

(+)-(*R*)-1-Methoxy-2,2-diphenylcyclopropanecarboxaldehyde.—A solution of 2.0 g (0.008 mol) of (−)-(*R*)-1-methoxy-2,2-diphenylcyclopropylcarbinol, $[\alpha]_{Hg}^{25}$ −12.5°, in 11 ml of acetic anhydride and 17 ml of dimethyl sulfoxide was allowed to remain at ambient temperature for 18 hr[16] and then poured onto a mixture of 4.5 g of sodium hydroxide dissolved in 50 ml of water and 200 g of ice. The gummy precipitate was taken up in ether and washed three times with water and saturated sodium chloride, and the ether solution was dried over molecular sieves. The solvent was removed and the residue was crystallized from hexane–chloroform (5:1) to yield 1.2 g (54%) of the aldehyde: mp 128–129°; $[\alpha]_{Hg}^{25}$ +49° (c 5.0, dioxane); uv (dioxane) 304 nm (ϵ_{max} 130); ir 2750 and 1728 cm^{-1} (CHO). A sample, mp 117–118°, $[\alpha]_{Hg}^{26}$ −40° (c 1.0, $CHCl_3$), gave ORD (c 0.011 g/cm^3, dioxane) $[\Phi]_{500}$ −86.1°, $[\Phi]_{450}$ −96.9°, $[\Phi]_{400}$ −161°, $[\Phi]_{375}$ −184°, $[\Phi]_{350}$ −75.1°, $[\Phi]_{340}$ +129°, $[\Phi]_{330}$ +786°, $[\Phi]_{323}$ +852°, $[\Phi]_{320}$ +388°, $[\Phi]_{315}$ −214°, $[\Phi]_{311}$ −1032°, CD (c 0.043 *M*, dioxane) $[\theta]_{340}$ 0, $[\theta]_{306}$ 5500, $[\theta]_{278}$ 0.

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.82; H, 6.26.

(±)-1-Methoxy-2,2-diphenylcyclopropane.—A solution of 19.4 g (0.9 mol) of diazodiphenylmethane in 100 g of methyl vinyl ether was irradiated with a Hannovia medium pressure mercury lamp using a Pyrex filter until the solution was decolorized. The excess ether was removed and the oily residue was distilled to yield 11.2 g (50%) of product, bp 106–108° (0.25 mm). An analytical sample was obtained by vpc using a CES 4-ft column: nmr ($CDCl_3$) δ 7.5–7.1 (m, 10, phenyl), 3.51 (q, 1, Hx), 3.08 (s, 3, CH_3O), 1.60–1.14 ppm (m, 2, H_aH_b).

Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.41; H, 7.29.

Ethyl α-Fluoroacrylate.[17]—Two drops of ethanol and 179 g (1.22 mol) of ethyl oxalate were added to 48 g (1.11 mol) of sodium hydride (56% dispersion in mineral oil) stirred in 1100 ml of benzene. While the reaction temperature was maintained between 40 and 60°, 118 g (1.11 mol) of ethyl fluoroacetate was added over a period of 1 hr. Ethanol was distilled off and after cooling to 40°, 33.5 g (1.12 mol) of trioxymethylene (anhydrous powder) was added to the stirred reaction mixture. After 20 min the benzene solution was decanted from the precipitated solids. This solution was usually submitted to further reaction without separation, hydroquinone being added to retard polymerization. A minimum yield of 75% was obtained based on the formation of 1-fluoro-2,2-diphenylcyclopropanecarboxylic acid from the subsequent addition of diazodiphenylmethane to the benzene solution of acrylate.

To obtain analytical data, a reaction was run in decalin and the product was distilled from the reaction mixture, since in benzene and even in xylene an azeotrope was formed. The reaction in decalin yielded 25% product: ir (neat) 1750 (C=O), 1180 and 1160 (d, CO), 1655 (C=C), 898 (=CH_2), and 1025 cm^{-1} (CF); nmr (benzene) δ 5.66 (dd, 1, J_{FH} = 32, J_{HH} = 3.5 Hz, *trans*-HC=CF), 5.19 (dd, 1, J_{FH} = 7.1 Hz, J_{HH} = 3.5 Hz, *cis*-HC=CF), 4.22 (q, 2, J = 7.2 Hz), and 1.23 (t, 3, J = 7.2 Hz).

Ethyl (±)-1-Fluoro-2,2-diphenylcyclopropanecarboxylate.—A pentane solution (900 ml) containing 0.86 mol of diazodiphenylmethane was added to the above benzene solution of ethyl α-fluoroacrylate and heated to reflux.

After decolorization of the diazodiphenylmethane a sample of the crude ester was precipitated from ether at Dry Ice–acetone temperatures and crystallized from pentane yielding cubic crystals: mp 59–60°; ir (CCl_4) 1750 (C=O), 1140 (CO), 1020 and 1060 cm^{-1}; near ir (CCl_4) 1.627 μ (ring CH_2); nmr (CCl_4) 7.56–7.00 (m, 10, phenyl), 3.85 (q, 2, J = 7.5 Hz, CH_2O), 2.13 (dd, 1, J_{FH} = 11.4, J_{HH} = 6.8 Hz, *trans* ring H), 2.07 (dd, 1, J_{FH} = 38.5, J_{HH} = 6.8 Hz, *cis* ring H), 0.82 (t, 3, = 7.5 Hz).

Anal. Calcd for $C_{18}H_{17}O_2F$: C, 76.04; H, 6.03. Found: C, 75.96; H, 6.11.

(±)-1-Fluoro-2,2-diphenylcyclopropanecarboxylic Acid.—The above ester was saponified with 100 g of potassium hydroxide in 1 l. of aqueous methanol, and the acidified product was taken up in ether after removal of a neutral fraction which was discarded. Crude product was realized in 75% yield based on the starting ethyl α-fluoroacetate. Crystallization from benzene gave fine needles: mp 174–175°; ir (KBr) 1714 (C=O), 2624, 2538, and

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(17) E. D. Bergman and I. Shahak, *J. Chem Soc.*, 4033 (1961).

2475 (OH submaxima), 852 (γ, COOH), and 710 and 695 cm^{-1} (d, phenyl); the ir spectrum was run on a Perkin–Elmer 541 spectrophotometer; near ir ($CHCl_3$) 1.627 μ; nmr ($CDCl_3$) δ 7.6–7.0 (m, 10, phenyl), 2.20 (dd, 1, J_{FH} = 4.2, J_{HH} = 6.6 Hz, *trans* ring CH to F), and 2.13 ppm (dd, 1, J_{FH} = 30.6, J_{HH} = 6.6 Hz, *cis* ring CH to F).

Anal. Calcd for $C_{16}H_{13}FO_2$: C, 74.99; H, 5.11. Found: C, 75.00; H, 5.13.

(+)-(*R*)- and (−)-(*S*)-1-Fluoro-2,2-diphenylcyclopropanecarboxylic Acid.—The salt obtained by adding 52.6 g (0.212 mol) of the above racemic acid to 99.0 g (0.212 mol) of brucine in acetone was crystallized from acetone to constant rotation (six times). Hydrolysis with hydrochloric acid yielded acid, $[\alpha]^{25}_{Hg}$ −155 ± 1° (*c* 1.2, acetone), and an additional crystallization of the acid from dimethylformamide did not change the rotation.

The mother liquors from the first two of the above crystallizations yielded on hydrolysis 39.7 g of acid, $[\alpha]^{25}_{Hg}$ +13°, which was combined with 52 g (0.16 mol) of quinine in acetone. One crystallization of the salt afforded on hydrolysis acid of the above maximum, but opposite, rotation. A second crystallization of the acid from acetone and another from ethanol produced no change in rotation.

The resolved acid crystallized from chloroform as cubes: mp 181–183°; $[\alpha]^{25}_{Hg}$ +155° (*c* 1.0, acetone); ir (KBr) 3235 (ν, OH), 1741, 1708 (d, C=O), 1226 (β, COH), and 821 cm^{-1} (γ, C=OH–); the nmr ($CDCl_3$) was identical with that of the racemic acid.

Anal. Calcd for $C_{16}H_{13}FO_2$: C, 74.99; H, 5.11. Found: C, 75.12; H, 5.25.

(±)-1-Fluoro-2,2-diphenylcyclopropylcarbinol.—A solution of 9.2 g (0.0368 mol) of 1-fluoro-2,2-diphenylcyclopropanecarboxylic acid in 150 ml of anhydrous ether was added slowly to 2.6 g (0.068 mol) in lithium aluminum hydride. After the mixture was stirred for 4.5 hr, 25 ml of saturated ammonium bromide was added.

A clear ether solution was filtered from the coagulated solids, dried over molecular seives, and evaporated to yield 83% product which was crystallized from 25% chloroform in low-boiling petroleum ether: mp 83.5–85.0°; ir (Nujol) 3300 (bonded OH), 1060 (CO), and 762, 748, 735, 708, and 694 cm^{-1} (phenyl); near ir ($CHCl_3$) 1.633 μ; nmr (CCl_4) δ 7.55–7.05 (m, 10, phenyl), 3.82 (s, 1, ½ CH_2O), 3.44 (d, 1, *J* = 5 Hz, ½ CH_2O), 2.58 (s, 1, OH) (the signal shifted upfield on dilution), 1.73 (dd, 1, *J* = 14, *J* = 7 Hz), ring CH), 1.44 ppm (s, 1, ring CH); nmr (benzene) δ 3.83 (s, 1, ½ CH_2O), 3.44 (s, 1, ½ CH_2O), 2.98 (s, 1, OH), 1.79, 1.46, 1.42, and 1.24 (d, ½ H each, *J* = 7 Hz, ring CH_2).

Anal. Calcd for $C_{16}H_{15}OF$: C, 79.32; H, 6.24. Found: C, 79.32; H, 6.19.

(+)-(*R*)-1-Fluoro-2,2-diphenylcyclopropylcarbinol.—The optically active carbinol (85% yield) was prepared from acid of maximum rotation (*i.e.*, $[\alpha]^{25}_{Hg}$ +155°) in a manner similar to the racemic carbinol except for an increase of the reaction period to 7.5 hr. Crystallization from high-boiling petroleum ether gave fine needles: mp 105.2–106.0°; $[\alpha]^{25}_{Hg}$ +146 ± 2° (*c* 0.48, methanol); the ir, near ir, and nmr spectra were identical with those of the racemic material.

Anal. Calcd for $C_{16}H_{15}OF$: C, 79.32; H, 6.24. Found: C, 79.51; H, 6.05.

(±)-1-Fluoro-2,2-diphenylcyclopropanecarboxaldehyde.—To 4.85 g (0.02 mol) of 1-fluoro-2,2-diphenylcyclopropylcarbinol dissolved in 2 ml of dimethyl sulfoxide (stored over molecular sieves) was added 12.3 g (0.06 mol) of dicyclohexylcarbodiimide. After the mixture was cooled to 0°, 3.0 g (0.003 mol) of crystalline orthophosphoric acid was added. The mixture was stirred overnight at room temperature with a calcium chloride drying tube venting the flask.

The reaction mixture was diluted with four volumes of ether and filtered. The ether layer was separated and washed successively with saturated sodium bicarbonate, water, and finally saturated sodium chloride. The ether solution was dried over molecular seives and the solvent was stripped to yield a gummy residue. Triturating with pentane produced 2.1 g (44%) of a granular white solid which crystallized from hexane: mp 96–98.5°; ir (CCl_4) 1735 (C=O), 2780, 2770, 2930 (O=CH), and 1195 and 1205 cm^{-1} (d, CO); near ir 1.631 and 2.229 μ; uv max (CCl_4) 298 mμ; nmr (CCl_4) δ 9.17 (d, 1, *J* = 11 Hz, O=CH), 7.84–7.05 (m, 10, phenyl), 218 (d, 1, *J* = 7 Hz, ½ ring CH_2) and 2.11 ppm (dd, 1, J_{FH} = 26, J_{HH} = 7 Hz, ½ ring CH_2).

Anal. Calcd for $C_{16}H_{13}OF$: C, 79.98; H, 5.45. Found: C, 80.13; H, 5.70.

(+)-(*R*)-1-Fluoro-2,2-diphenylcyclopropanecarboxyladehyde.—In a 50-ml flask, 0.900 g (0.0037 mol) of (+)-1-fluoro-2,2-diphenylcyclopropanecarbinol (maximum rotation), 16 ml of dimethyl sulfoxide, and 10 ml of acetic anhydride were mixed and allowed to stand for 18 hr at room temperature.[16] The reaction mixture was added, with stirring, to 4.5 g of sodium hydroxide in 50 ml of water and 200 g of ice. The gummy precipitate which resulted was dissolved in ether, and the ether solution was washed with water several times, lastly with aqueous sodium chloride, and then dried over molecular sieves. After the solvent was removed on a rotary evaporator, the resulting oil was crystallized from hexane. After three more crystallizations from hexane, 0.150 g (57%) of product was obtained: mp 116–117°; $[\alpha]^{25}_{Hg}$ +164° (*c* 0.56, dioxane); the ir and nmr spectra were identical with those of the racemic material; uv (dioxane) 305 (ϵ_{max} 63); ORD $[\alpha]^{25}_{550}$ +168, $[\alpha]_{400}$ +496, $[\alpha]_{350}$ +638°, $[\alpha]_{332}$ +708°, $[\alpha]_{323}$ +594°, $[\alpha]_{320}$ +673°, $[\alpha]_{315}$ +710°, $[\alpha]_{300}$ +4070°, $[\alpha]_{277.5}$ +11,860°, $[\alpha]_{275}$ +13,100°, $[\alpha]_{272}$ +118,860°, $[\alpha]_{267}$ +13,980°, $[\alpha]_{264}$ +12,730°, and $[\alpha]_{254}$ +17,700° (*c* 0.056, dioxane).

Anal. Calcd for $C_{16}H_{13}OF$: C, 79.98; H, 5.45. Found: C, 79.20; H, 5.30.

(−)-(*S*)-1-Benzoyl-1-fluoro-2,2-diphenylcyclopropane.—To a cooled (0°) and stirred solution of 2.5 g (0.01 mol) of (−)-(*S*)-1-fluoro-2,2-diphenylcyclopropanecarboxylic acid, $[\alpha]^{25}_{Hg}$ − 155°, was added, over a 30-min period, 25 ml of 1.5 *M* phenyllithium solution in ether. Stirring was continued for an additional hour and the reaction mixture was then hydrolyzed with ice water. The ether extract was washed with water and saturated sodium chloride and dried over magnesium sulfate. The solvent was evaporated and the residue was crystallized from ethanol to yield 2.8 g (90%) of ketone: mp 147–148°; $[\alpha]^{25}_{Hg}$ −38° (*c* 1.0, $CHCl_3$); ir (neat) 1683 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.3–7.0 (m, 15, phenyl), 2.72 (q, 1, ring), 2.12 ppm (q, 1, ring).

Anal. Calcd for $C_{22}H_{17}OF$: C, 81.40; H, 6.11; F, 6.77. Found: C, 81.51; H, 5.90; F, 6.4.

(±)-1-Chloro-2,2-diphenylcyclopropanecarboxaldehyde.—To a solution of 5.7 g (0.022 mol) of (±)-1-chloro-2,2-diphenylcyclopropylcarbinol[7] in 95 ml of dimethyl sulfoxide was added to 60 ml of acetic anhydride and allowed to stir at ambient temperature for 16 hr. The solution was poured into a mixture of 200 ml of 15% sodium hydroxide and 100 g of ice and stirred until the oil solidified. The supernatant liquid was decanted and the solid was recrystallized from hexane to give 3.0 g (53%) of crystals: mp 124–125°; ir (CCl_4) 2740 and 2840 (aldehyde CH), 1720 cm^{-1} (C=O); nmr (CCl_4) δ 2.20 (d, 1, *J* = 5 Hz, ring H), 2.66 (d, 1, *J* = 5 Hz, ring H), 7.50 (complex, 10, phenyl), 9.36 (s, 1, aldehyde).

Anal. Calcd for $C_{16}H_{11}ClO$: C, 74.85; H, 5.10; Cl, 13.83. Found: C, 74.95; H, 5.17; Cl, 13.98.

(+)-(*S*)-1-Chloro-2,2-diphenylcyclopropanecarboxyaldehyde.—Optically pure carbinol,[7] $[\alpha]^{24}_{Hg}$ +74.1° (*c* 1.0, $CHCl_3$), prepared from acid, $[\alpha]^{24}_{Hg}$ +87.7° (*c* 1.1, $CHCl_3$), was oxidized by the above procedure to produce aldehyde, mp 106–108°, $[\alpha]^{24}_{Hg}$ +153° (*c* 1.0, $CHCl_3$). The ORD and CD curves were obtained using a sample of aldehyde: $[\alpha]^{24}_{Hg}$ −71° (*c* 1.0, $CHCl_3$); ORD (*c* 0.0096 g/cm^3, dioxane) $[\Phi]_{800}$ −195°, $[\Phi]_{450}$ −268°, $[\Phi]_{400}$ −346°, $[\Phi]_{375}$ −450°, $[\Phi]_{350}$ −651°, $[\Phi]_{340}$ −868°, $[\Phi]_{330}$ −1170°, $[\Phi]_{326}$ −1600°, $[\Phi]_{315}$ −1532°, $[\Phi]_{310}$ −1450°, $[\Phi]_{300}$ −544°, $[\Phi]_{290}$ +1409°; CD (*c* 0.0375 *M*, dioxane) $[\theta]_{343}$ 0°, $[\theta]2_{94}$ −5100°, $[\theta]_{259}$ 0°. The ir, nmr, and uv spectra were identical with those of the racemic aldehyde.

(−)-(*R*)-1-Benzoyl-1-chloro-2,2-diphenylcyclopropane.—To a solution of 1.2 g (4.4 mmol) of (−)-(*R*)-1-chloro-2,2-diphenylcyclopropanecarboxylic acid,[7] $[\alpha]^{24}_{Hg}$ −84° (*c* 0.98, $CHCl_3$), 96% optically pure, in 100 ml of ether was added 17 ml of 1.0 *M* phenyllithium in ether under nitrogen at 0°. The solution was allowed to stir for 40 min while warming to room temperature. The reaction was quenched with ice water and the solution was washed with saturated sodium chloride until the washings were neutral and dried, and the ether removed to give an oil which crystallized upon trituration with hexane. Crystallization from ethanol gave 0.59 g (40%) of white crystals: mp 123–124°; ir (CCl_4) 1680 cm^{-1}; nmr (CCl_4) δ 2.02 (d, 2, *J* = 6.5 Hz, ring), 3.10 (d, 2, *J* = 6.5 Hz, ring), 7.48 (complex, 13, aromatic), 8.24 (complex, 2, benzoyl ortho H); $[\alpha]^{25}D$ −66.1° (*c* 1.0, $CHCCl_3$). The analytical sample had mp 125–127°.

Anal. Calcd for $C_{22}H_{17}ClO$: C, 79.39; H, 5.15; Cl, 10.65. Found: C, 79.12; H, 5.17; Cl, 10.74.

Cleavage of (−)-(*R*)-1-Benzoyl-1-chloro-2,2-diphenylcyclopropane.—A mixture of 231 mg (0.69 mmol) of (−)-(*R*)-1-benzoyl-1-

chloro-2,2-diphenylcyclopropane, $[\alpha]^{25}D$ −64.8° (c 1.0, $CHCl_3$), prepared from acid, $[\alpha]^{25}_{Hg}$ −82.1°, 93.9% optically pure, 150 mg of sodium amide, and 9 ml of benzene was stirred at reflux under nitrogen for 20 hr. Ice water was added and the solution was washed with water until the washings were neutral, dried, concentrated, and subjected to preparative tlc on silica gel using benzene–hexane (1:1). The band with the highest R_f value weighed 18 mg and proved to be (−)-(*R*)-1-chloro-2,2-diphenylcyclopropane based on nmr spectrum and elemental analysis: $[\alpha]^{23}_{Hg}$ −202° (c 0.16, $CHCl_3$); nmr (CCl_4) δ 1.71 (d, 2, *J* = 6 Hz, $-CH_2-$), 3.70 (t, 1, *J* = 6 Hz, −CHCl−), 7.37 (m, 10, phenyl).

Anal. Calcd for $C_{15}H_{13}Cl$: C, 78.80; H, 5.73. Found: C, 78.69; H, 5.69.

Cleavage of (−)-(*S*)-1-Benzoyl-1-fluoro-2,2-diphenylcyclopropane.—A mixture of 1.65 g (0.005 mol) of (−)-(*S*)-1-benzoyl-1-fluoro-2,2-diphenylcyclopropane ($[\alpha]^{25}_{Hg}$ −38°), 1 g of sodium amide, and 50 ml of toluene was stirred and refluxed for 12 hr. The reaction mixture was hydrolyzed by pouring onto ice water and the organic layer was washed with water and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was distilled to yield 580 mg (55%) of 1-fluoro-2,2-diphenylcyclopropane whose ir and nmr spectra were identical with those of an authentic sample.[18]

Cleavage of (+)-(*S*)-1-Benzoyl-1-methoxy-2,2-diphenylcyclopropane.—A mixture of 1.1 g (0.03 mol) of ketone, 1.2 g of sodium amide, and 100 ml of xylene was stirred and refluxed for 12 hr. The reaction mixture was hydrolyzed by pouring onto ice, the organic layer was separated, washed with water, and dried over molecular sieves, and the solvent removed *in vacuo*. The residue (0.95 g) was distilled to yield 0.37 g (40%) of 1-methoxy-2,2-diphenylcyclopropane, $[\alpha]^{25}_{Hg}$ +75°. Ir and nmr spectra were identical with those of the racemic sample synthesized.

(18) C.-J. Chen, Ph.D. Dissertation, Florida State University, 1969.

Registry No.—(−)-(*R*)-2, 30724-74-4; (−)-(*S*)-3, 30724-75-5; (+)-(*S*)-4, 30724-76-6; (−)-(*R*)-6, 30724-77-7; (±)-8, 30724-78-8; (±)-A, 30788-13-7; (+)-(*R*)-A, 30724-79-9; (−)-(*S*)-A, 30745-01-8; (±)-1-methoxy-2,2-diphenylcarboxylic acid, 30724-80-2, 30724-81-3 [(±)-(*R*) isomer], 30745-02-9 [(−)-(*S*) isomer]; ethyl 1-methoxy-2,2-diphenylcyclopropanecarboxylate, 30724-82-4; (−)-(*R*)-1-methoxy-2,2-diphenylcyclopropylcarbinol, 30724-83-5; (+)-(*R*)-1-methoxy-2,2-diphenylcyclopropanecarboxaldehyde, 3074 5-03-0; ethyl (±)-1-fluoro-2,2-diphenylcyclopropanecarboxylate, 30724-84-6; (±)-1-fluoro-2,2-diphenylcyclopropanecarbinol, 30724-85-7, 30745-04-1 [(+)-(*R*) isomer]; (±)-1-fluoro-2,2-diphenylcyclopropanecarboxaldehyde, 30788-14-8; 30788-15-9 [(+)-(*R*) isomer]; (±)-1-chloro-2,2-dephenylcyclopropanecarboxladehyde, 30724-86-8, 30724-87-9 [(+)-(*S*) isomer].

The Tricyclo[5.1.0.0^{3,5}]octan-2-ols

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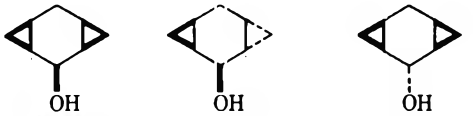
The cis,cis-, *cis,trans-*, and *trans,trans*-tricyclo[5.1.0.0^{3,5}]octan-2-ols have been prepared and the structures assigned by chemical correlations and nmr spectroscopy. Solvolysis of the *p*-nitrobenzoate of the cis,cis isomer has been carried out in formic acid, acetic acid, and aqueous 1,4-dioxane (85%) for kinetic and product studies. The latter two solvents produce only isomers of the starting material, but formic acid produces a complex reaction mixture that arises from cyclopropyl participation. Some solvolytic studies of the cis,trans *p*-nitrobenzoate in aqueous dioxane have been carried out.

Tricyclo[5.1.0.0^{3,5}]octan-2-ol may exist in three isomeric forms, *cis,cis*-**1** (*cc*-**1**), *cis,trans*-**1** (*ct*-**1**), and

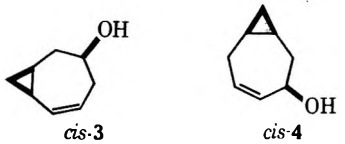


cis,cis-**1** *cis,trans*-**1** *trans,trans*-**1**

trans,trans-**1** (*tt*-**1**), from which are derived only two ketones, *cis*-**2** and *trans*-**2**. We became interested in

cis-**2** *trans*-**2**

the various isomers of **1** as solvolytic models for the related *cis*-bicyclo[5.1.0]oct-5-en-3-ol (*cis*-**3**) and *cis*-bicyclo[5.1.0]oct-4-en-3-ol (*cis*-**4**).[2] The carbonium ions from the sulfonic or carboxylic esters of **1**, **3**, and **4** are

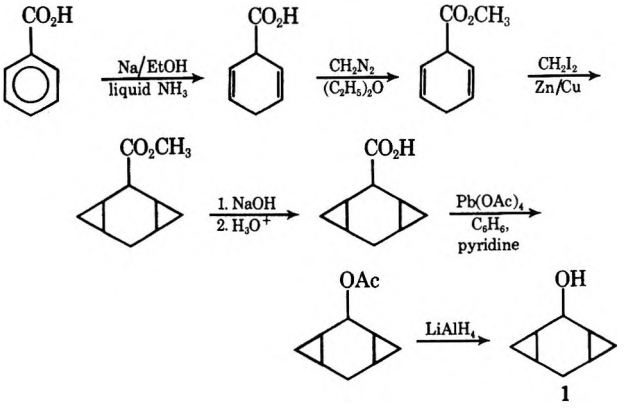


cis-**3** *cis*-**4**

valence tautomeric. We have consequently prepared each of the isomers of **1**, proved their structures, and examined the solvolytic behavior of the *p*-nitrobenzoates of *cc*-**1** and *ct*-**1**.

Synthesis and Structure.—The synthesis of *cis,cis*-**1** followed the procedures developed by Sims[3] and Winstein[4,5] (Scheme I). The stereochemistry of the Sim-

SCHEME I



(1) National Institutes of Health Predoctoral Fellow, 1968–1970.

(2) J. B. Lambert, J. W. Hamersma, A. P. Jovanovich, F. R. Koeng, S. A. Sweet, and P. J. Kucinski, *J. Amer. Chem. Soc.*, **92**, 6372 (1970).

(3) J. J. Sims, *ibid.*, **87**, 3511 (1965).

(4) T. Hanafusa, L. Birladeanu, and S. Winstein, *ibid.*, **87**, 3510 (1965).

(5) L. Birladeanu, T. Hanafusa, B. Johnson, and S. Winstein, *ibid.*, **88**, 2316 (1966).

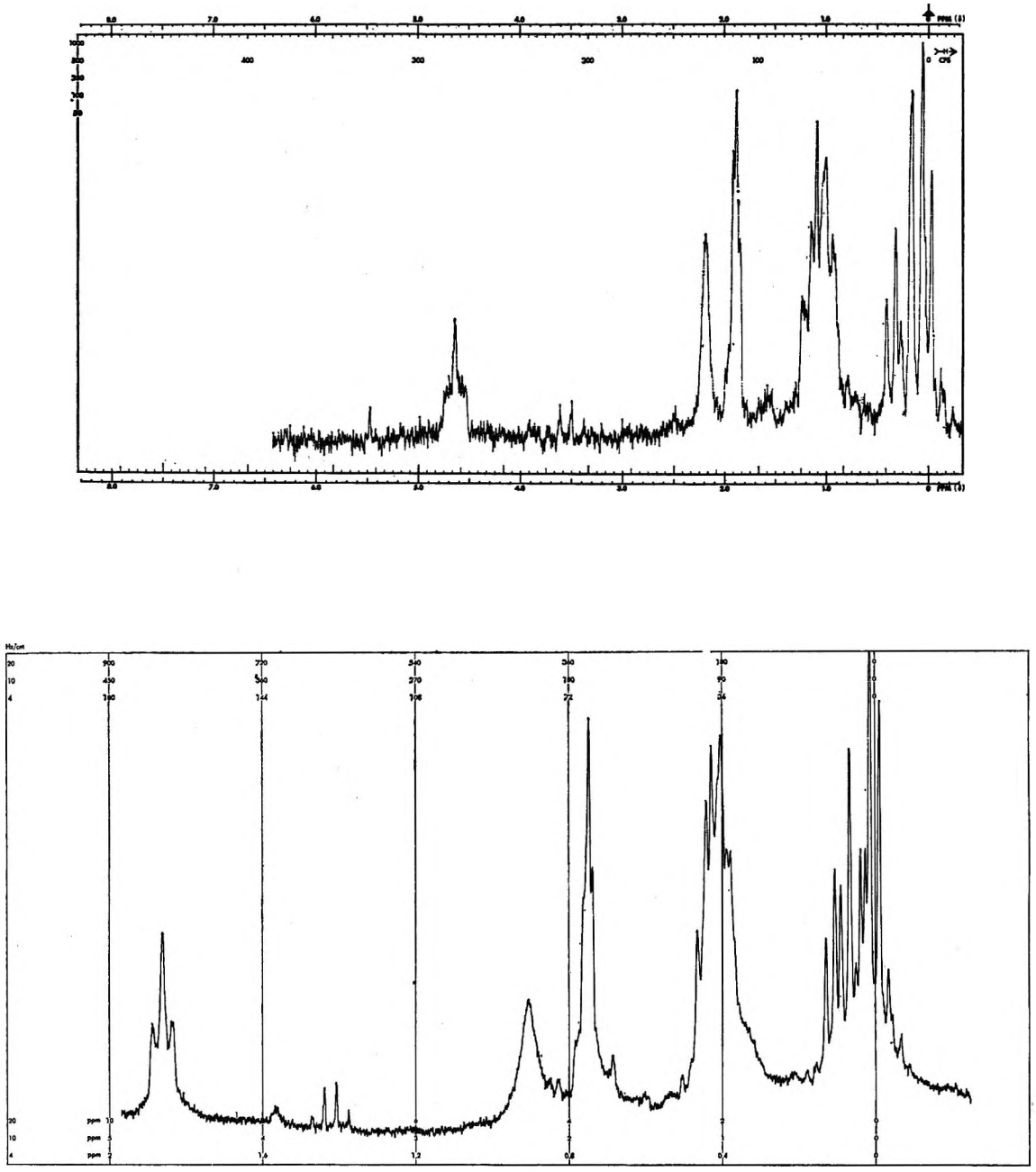


Figure 1.—The 60- (upper) and 90-MHz (lower) proton spectra of *cis,cis*-tricyclo[5.1.0.0^{3,5}]octan-2-ol in $CDCl_3$. The small quartet at δ 3.6 is due to an ethyl ether impurity. The 90-MHz spectrum is on the 10 Hz/cm scale.

mons–Smith reaction is thought to produce the cis,cis carboxylate. The corresponding acid was purified by recrystallization and converted by treatment with lead tetraacetate ultimately to the cis,cis alcohol,[3-5] which is a white, crystalline solid, mp 50–51°. Oxidation of this alcohol to the ketone *cis*-**2** and reduction with lithium aluminum hydride produced both the original alcohol, and a new alcohol, assigned the structure *tt*-**1**.

The mother liquor from purification of the cis,cis carboxylic acid was found to contain a significant amount of an isomeric acid. This mixture was carried through the reaction sequence to the alcohols **1** and thence by Jones oxidation to a mixture of two ketones **2**. These materials were separated by vpc and the new ketone was assigned the structure *trans*-**2**. Reduction of this new ketone with lithium aluminum hydride produced a single alcohol, thought to be *ct*-**1**.

The mass spectra and analytical data for *cc*-**1** and its derivatives indicate that a molecule with the correct formula is obtained from the above synthetic sequence. Although cis addition is fully expected for the Simmons–Smith reaction,[3,4,6] the stereochemistry of the lead tetraacetate oxidation is less well established. The structure of *ct*-**1** is firm, since it is the only alcohol produced from the ketone *trans*-**2**, whereas *cis*-**2** produces two alcohols, *cc*-**1** and *tt*-**1**. Stronger evidence is therefore required for differentiating the two alcohols with cis cyclopropane rings.

For further structural information we have examined the nmr spectra of the three isomers. Figure 1 shows the 60- and 90-MHz proton spectra of *cc*-**1**, and Table I summarizes the observed resonance positions of the 2 hydrogens for the three alcohols and the two *p*-nitrobenzoates.

For each isomer there are two conformational forms, given in Chart I. For *cc*-**1** and *tt*-**1**, the series B con-

(6) C. D. Poulter, E. C. Friedrich, and S. Winstein, *J. Amer. Chem. Soc.*, **91**, 6892 (1969); *ibid.*, **92**, 4274 (1970).

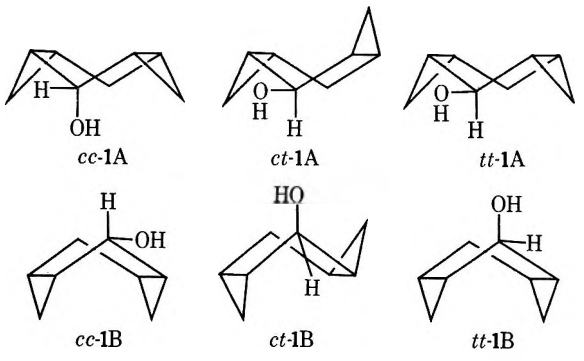
TABLE I

NMR SPECTRAL PARAMETERS

Compd	δ, ppm[a]	J, Hz[b]
cc-1	4.65 (t)	6.0
ct-1	4.14 (d of d)	6.5
		2.3
tt-1	3.92 (broad s)	
cc-1-OPNB	6.15 (t)	6.5
ct-1-OPNB	5.48 (d of d)	6.0
		2.3

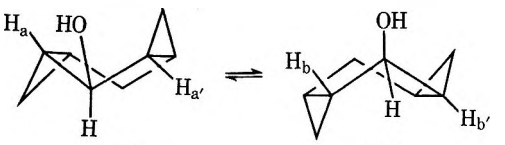
[a] The chemical shift of the 2 proton downfield from TMS. [b] The coupling constant between the 2 proton and the protons on adjacent carbon atoms.

CHART I



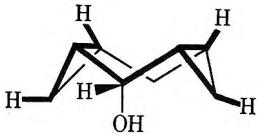
formers are clearly less stable than the series A conformers, because of nonbonded repulsions between the opposed cyclopropane hydrogens. The series B conformer of *ct*-1 is also probably the less stable because it would place the hydroxyl group in the very crowded "flagpole" position. An examination of the more stable A conformers indicates that the 2 hydrogen should be increasingly shielded by the cyclopropane rings in the order *cc*, *ct*, *tt*. In *cc*-1, this proton is directed away from both cyclopropane rings and is therefore least affected. In *ct*-1 the 2 proton is situated over the face of one cyclopropane ring, and in *tt*-1 this proton is over both rings. The region in space above a cyclopropane ring is well known to be shielding.[7] The alcohol with the most shielded proton, resonating at δ 3.92, must therefore be *tt*-1. Similarly, the δ 4.65 isomer must be *cc*-1, and the δ 4.14 isomer *ct*-1. These assignments are in accord with the chemical evidence presented above.

Further structural verification may be obtained from the vicinal coupling constants of the proton at the 2 position. The isomer *ct*-1 (δ 4.14) is easily identified by the four-line pattern of the 2 proton coupled to nonequivalent vicinal protons. In *cc*-1 and *tt*-1, the vicinal couplings must be equal because of the plane of symmetry passing through C-2 and C-6. In conformer B of *ct*-1, the larger coupling (6.5 Hz) is most likely associated with the adjacent proton that is almost eclipsed ($H_{b'}$) and the smaller coupling (2.3 Hz) with the staggered proton (H_b). Similar values are expected from conformer A. If A and B were present equally, averaging



of the couplings would result in a simple triplet splitting. The observed four-line pattern indicates that one conformer, presumably A, must predominate.

The 2 proton in *cc*-1 (δ 4.65) is equivalently coupled to the two vicinal protons to give a triplet (^3J = 6.0 Hz). This coupling corresponds to the larger coupling constant in *ct*-1, since the coupled protons are nearly eclipsed in conformer A. The observed components of the triplet in *cc*-1 are considerably broadened with respect to the *ct*-1 peaks, most likely because of four W-path couplings over four bonds. Finally, the coupling in *tt*-1 (δ 3.92) corresponds to the smaller coupling in *ct*-1, as expected for the staggered arrangement in conformer A. The small magnitude of this coupling gives rise to only a single, broad line. The chemical evidence, the shielding of the 2 proton, and the vicinal couplings of the 2 proton thus all give identical structural assignments.



Solvolysis Results.—Although the tosylate of *cc*-1 could not be prepared by either of the most common methods,[8,9] no problems were encountered in obtaining the *p*-nitrobenzoate. The crowded environment about the hydroxyl group may preclude introduction of the tetrahedral sulfonate group but still permit the trigonal carboxylate group.

Titrimetric solvolysis rates for *cc*-1-OPNB were measured in 85% (by volume) aqueous 1,4-dioxane by the aliquot method. Infinity titers agreed well with the calculated values, so that internal return to a less reactive species is ruled out. The kinetic data are given in Table II and the activation parameters in Table III.[10]

TABLE II

KINETIC DATA FOR THE HYDROLYSIS OF *cis,cis*-1 *p*-NITROBENZOATE IN 85% DIOXANE–WATER

Temp, °C	k, sec^{-1} × 10^5	Correlation coeff
25.15	2.89	0.997
	2.62	0.998
32.25	6.43	0.998
	6.04	0.997
40.35	15.0	0.997
	14.5	0.999

TABLE III

ACTIVATION PARAMETERS (25°) FOR THE HYDROLYSIS OF *cis,cis*-1 *p*-NITROBENZOATE

E_a	20.5 ± 0.5[a]
Log A	10.5 ± 0.4[a]
$\Delta H^{\pm}$	19.9 ± 0.5[a]
$\Delta S^{\pm}$	−12.6 ± 1.7 eu
$\Delta G^{\pm}$	23.7 ± 0.7[a]
Correlation coefficient	0.999

[a] Kcal/mol.

Solvolysis products were examined after 5 half-lives in dioxane–water. For the reactions in acetic acid and

(7) J. B. Lambert, J. L. Gosnell, Jr., D. S. Bailey, and L. G. Greifenstein, *Chem. Commun.*, 1004 (1970).

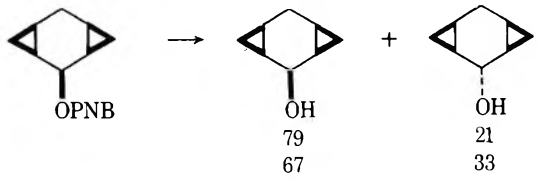
(8) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(9) R. M. Coates and J. P. Chen, *Tetrahedron Lett.*, 2705 (1969).

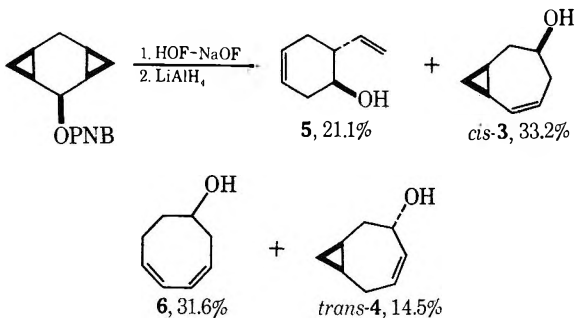
(10) A rate constant of 2.4 × 10^{-4} sec^{-1} at 25° has been quoted for the solvolysis of *cc*-1-OPNB in 80% aqueous acetone; see ref 5.

formic acid, 1.1 equiv of sodium acetate and sodium formate, respectively, were added for product studies. Completion of reaction was ascertained by infrared analysis of the product mixture for absence of nitro and benzoate bands. All the products were subjected to the reaction conditions and found to be stable. In formolysis and acetolysis, the esters products were reduced to the alcohols for analysis. The three alcohols **1** are destroyed under most gas chromatographic conditions but survive a 6 ft × 1/8 in. 10% SE-30 column without alteration, eluting in the order *ct*, *tt*, *cc*. The alcohol products were oxidized by the Jones procedure as a cross check, and the ketones were analyzed by gas chromatography, with *trans*-**2** at the shorter retention time.

The only products from the hydrolysis and the acetolysis of *cc*-**1**-OPNB were *cc*-**1** and *tt*-**1** in slightly differing



proportions. Four products were obtained from solvolysis in the less nucleophilic formic acid: *trans*-2-vinylcyclohex-4-enol (**5**), *cis*-bicyclo[5.1.0]oct-5-en-3-ol

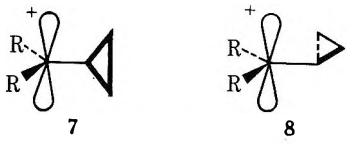


(*cis*-**3**), cycloocta-3,5-dienol (**6**), and *trans*-bicyclo[5.1.0]oct-4-en-3-ol (*trans*-**4**). The structure proofs are given in the Experimental Section. Specifically excluded as formolysis products by comparison of vpc retention times with those of authentic materials were all the tricyclic alcohols **1**, as well as *trans*-**3** and *cis*-**4**. The vinylcyclohexenol **5** is the end product under isomerizing conditions (trifluoroacetolysis or unbuffered formalysis after extended reaction times).

The *p*-nitrobenzoate of *ct*-**1** was solvolyzed in 85% dioxane–water and found to yield only *ct*-**1**. Formolysis gave several products, none of which were **1**, **3**, or **4**. These reactions were not examined further.

Discussion

The ability of a cyclopropane ring to conjugate with a developing positive charge is critically dependent on the geometry of the system. The interaction is maximized in the bisected geometry (**7**) and reduced in the parallel geometry (**8**).[11] The geometrical requirement for

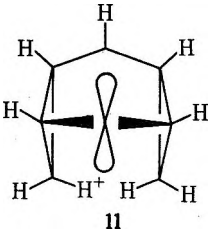


cyclopropylcarbinyl participation is that one cyclopropyl carbon–carbon bond be anti periplanar to the leaving group. Under these conditions the bisected structure is easily obtained. The adamantane system **9** is an example of a molecule in which there is no cyclopropyl bond anti periplanar to the tosylate group; so an ion of the type **8** results.[12] As a consequence, **9** solvolyzes

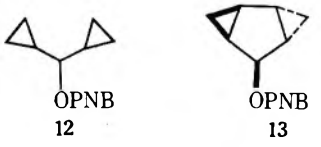
over a thousand times as slowly as **10**. Thus, in the absence of conjugative assistance, a cyclopropane ring can severely retard the rate of solvolysis.

Examination of molecular models shows that the stable conformer of *cc*-**1**-OPNB (A in Chart I) does not contain the requisite anti-periplanar arrangement for participation. The less stable conformer (B), however, contains one such bond in each cyclopropane ring. This conformer is therefore expected to be solvolytically more reactive. Similar analysis shows that *tt*-**1**-OPNB and *ct*-**1**-OPNB have anti-periplanar arrangements with both cyclopropane rings in the more stable conformer (A) and should therefore be able to react without a prior conformational interconversion.

The ion that results from the solvolysis of *cc*-**1**-OPNB might have the structure **11**, in which both cyclopropane



rings enjoy the bisected geometry. The hydrolysis reaction occurs some 20–30 times as rapidly as that of dicyclopropylcarbinyl *p*-nitrobenzoate (**12**),[13] which is



conformationally much more flexible and which cannot attain the ideal geometry of **11** because of steric factors. The five-membered analog **13** furnishes an interesting contrast to **1**. The cyclopropyl bonds are no longer anti periplanar to the leaving group because of the constraints of the cyclopentane ring; so this molecule hydrolyzes considerably more slowly than **12**.[14]

(11) C. V. Pittman, Jr., and G. Olah, *J. Amer. Chem. Soc.*, **87**, 2998 (1966).

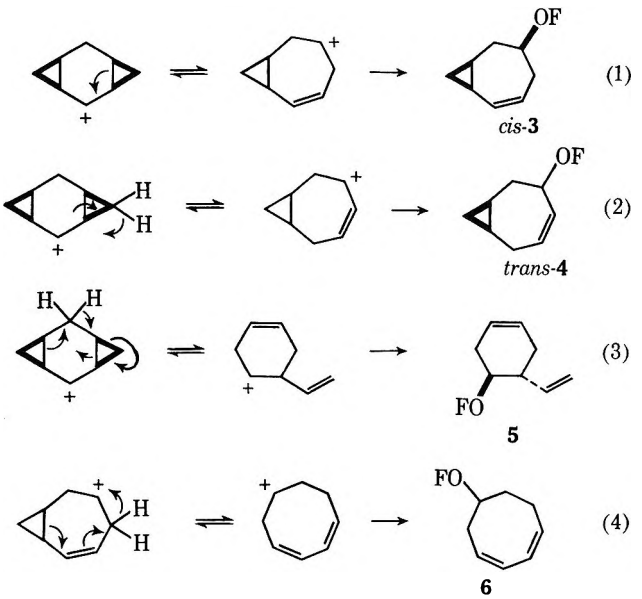
(12) B. R. Ree and J. C. Martin, *ibid.*, **92**, 1660 (1970).

(13) A. P. Krapcho, R. C. H. Peters, and J.-M. Conia, *Tetrahedron Lett.*, 4827 (1968).

(14) J. J. Gajewski and C. N. Shih, *ibid.*, 2967 (1970).

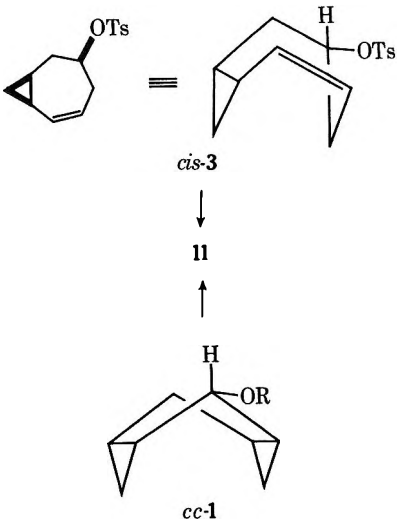
Although the large rate acceleration in *cc*-1-OPNB is indicative of significant cyclopropyl participation, the stereochemistry of the products is less easy to interpret. The major product of both hydrolysis and acetolysis is cc-1, the starting material with retained stereochemistry. In addition, both reactions produce some of the inverted isomer, *tt*-1. It is not possible to decide if this latter material arises from a k_s (nucleophilic displacement by solvent) component of the rate or if the ion **11** gives both products. The similarity of isomer ratios in acetic acid and dioxane–water, solvents of extremely different nucleophilicities, suggests that the k_s interpretation is unlikely.

In the more strongly ionizing, less nucleophilic medium offered by formic acid, carbonium ion intermediates are longer lived and hence more prone to rearrange. Thus, formolysis yields a complex reaction mixture. The major product (*cis*-**3**) is the result of a cyclopropylcarbinyl–allylcarbinyl rearrangement (eq 1). The remaining products probably arise from hydride-shift processes, as suggested in eq 2–4, which are by no means intended to be definitive mechanisms. Vinyl products analogous to **5** have been observed in other cyclopropylcarbinyl systems.[15]



Solvolysis of *cis*-**3**-OTs with double bond participation can lead to the same ion as from *cc*-**1**, since the two materials are conformationally identical (eq 5). In the illustrated conformation of *cis*-**3** (eq 5), the cyclopropane ring is incorrectly oriented for participation, but the double bond is correctly oriented.[2] Formolysis of *cis*-**3**-OTs produces[2] *cis*-**3**, *trans*-**4**, **5**, and **6** in almost the same proportions as does *cc*-**1**-OPNB. All evidence points to a near identity of ions from the two sources.

In summary, we have prepared the three isomers of tricyclo[5.1.0.0^{3,5}]octan-2-ol (**1**) and proved their structures. Hydrolysis and acetolysis of the *p*-nitrobenzoate of the cis,cis isomer produce only the two isomers of **1** in which the cyclopropane rings remain cis. Intermediate carbonium ions do not therefore undergo conformational or geometrical isomerization to an arrangement with the cyclopropane rings trans. Furthermore, hydrolysis of the cis,trans *p*-nitrobenzoate yields only



(5)

material with the rings still trans to each other. The kinetics of hydrolysis of *cis,cis*-**1**-OPNB implicate strong anchimeric assistance from at least one of the cyclopropane rings. Examination of the two available conformations indicates that solvolysis occurs from the less stable form. This conformation is expected to give an ion very similar to that produced by double bond participation in *cis*-bicyclo[5.1.0]oct-5-en-3-yl tosylate (*cis*-**3**-OTs). In fact, formolysis of *cis*-**3**-OTs gives all the products observed in the formolysis of *cis,cis*-**1**-OPNB, and in the same proportion. This similarity of product distribution is taken as evidence that the intermediate carbonium ions have similar or even identical structures.

Experimental Section

All melting points were measured on a Fisher-Johns apparatus and have been left uncorrected. The infrared spectra were measured on a Beckman IR-5 infrared spectrometer. Ultraviolet spectra were measured on a Cary 14 recording spectrophotometer. Routine nmr spectra were taken on Varian Associates A-60 and T-60 spectrometers. The nmr spectrum of *cc*-**1** was also measured on a Bruker HFX-10 90-MHz spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Coupling constants are reported in hertz. A Consolidated Electrodynamics Corp. 21-104 mass spectrometer was used for the mass spectral work. Analytical vapor phase chromatography data were obtained with either a Hewlett-Packard Model 700 chromatograph or a Varian Associates Aerograph Series 1520B. Preparative vpc work was performed on the Hewlett-Packard chromatograph. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

1,4-Dihydrobenzoic Acid.—To a 5-l., three-necked flask, equipped with a mechanical stirrer, a Dry Ice–acetone condenser, and a gas-inlet tube, was added 500 ml of anhydrous ethanol and 60 g (0.49 mol) of benzoic acid. Approximately 3 l. of ammonia was distilled into the flask. While the solution was being stirred, 37 g (1.6 g-atoms) of sodium was added gradually. The blue color of the sodium–ammonia solution was allowed to disappear before each new addition of sodium. When all of the sodium had been consumed, 87.5 g (1.65 mol) of NH_4Cl was added. The mixture was stirred and then allowed to stand until the ammonia had evaporated. The reaction mixture was worked up by dissolving the contents of the flask in ice water and acidifying the solution with concentrated HCl. The aqueous solution was extracted five times with 200-ml portions of ether. The extracts were combined and dried over $MgSO_4$, filtered, and stripped of solvent, to give 57.4 g of the acid.

Methyl 1,4-Dihydrobenzoate.—Diazomethane was prepared by the gradual addition of 75.6 g (0.73 mol) of *N*-methyl-*N*-nitrosourea[16] to a stirred system of 330 g of 40% potassium hy-

(15) K. B. Wiberg and J. G. Pfeiffer, *J. Amer. Chem. Soc.*, **92**, 553 (1970).

(16) F. Arndt, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 461.

TABLE IV

NUCLEAR MAGNETIC RESONANCE DATA

Compd	Cyclopropane ring	$-CH_2-$	CH–O	OH	Aromatic
cis-2	1.56 (m, 4), 0.80 (m, 4)	2.08 (m, 2)			
cis,cis-1	1.07 (m, 4), 0.16 (m, 4)	1.90 (m, 2)	4.65 (t, 1, J = 6.0 Hz)	2.20 (s, 1)	
cis,cis-1-OPNB	1.40 (m, 4), 0.55 (m, 4)	2.13 (m, 2)	6.15 (t, 1, J = 6.5 Hz)		8.18 (m, 4)
trans-2	1.50 (m, 6), 0.82 (m, 2)	2.32 (m, 2)			
cis,trans-1	0.60 (m, 7), −0.12 (m, 1)	1.63 (m, 2)	4.14 (q, 1, J = 6.5, J = 2.3 Hz)	3.06 (s, 1)	
cis,trans-1-OPNB	0.60 (m, 8)	1.80 (m, 2)	5.48 (q, 1, J = 6.0, J = 2.3 Hz)		8.17 (m, 4)

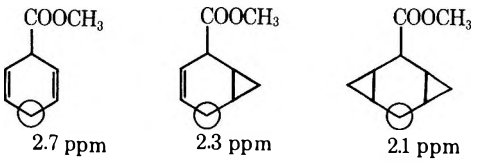
droxide under 1200 ml of ether at 0°. The development of a yellow color in the ether layer indicated the presence of diazomethane. The mixture was stirred for 1.5 hr and then the ether layer was decanted. The ether–diazomethane solution was dried 1 hr over KOH before use.

An ether solution of 1,4-dihydrobenzoic acid was prepared by dissolving 57.5 g (0.46 mol) of the acid in 1 l. of ether, drying the solution over $MgSO_4$, and filtering. The ether–diazomethane solution was added to the filtered solution of the acid until the yellow color of diazomethane persisted. The excess was destroyed by the addition of acetic acid. The ether was removed and the product distilled under vacuum to give 56.4 g of product or 82% from benzoic acid, bp 33° (0.5 mm).

Zinc–Copper Couple.—Zinc dust (50 g) was placed in a sintered-glass funnel. The zinc dust was slurried with and then filtered from each of the following solutions: four times with 40-ml portions of 3% HCl solution, five times with 100-ml portions of water, two times with 75-ml portions of 2% copper sulfate solution, five times with 100-ml portions of water, and five times with 100-ml portions of anhydrous ether. The zinc–copper couple was air-dried a few minutes in the funnel and then dried overnight in a vacuum desiccator.

Methyl Tricyclo[5.1.0.0^{3,5}]octyl-2-carboxylate.—To a 2-l., three-necked flask equipped with a mechanical stirrer, an addition funnel, and a condenser, were added 93.5 g (1.4 mol) of zinc–copper couple, 750 ml of ether, and approximately 1/2 of 344 g (1.3 mol) of methylene iodide. This solution was brought to reflux with stirring in order to initiate the formation of the Simmons–Smith reagent. When the solution was refluxing gently with no further heating, the remainder of the methylene iodide was added in order to maintain the reflux action. The solution was allowed to reflux for 1 hr after the complete addition of the methylene iodide. At this time 55.7 g (0.40 mol) of methyl 1,4-dihydrobenzoate was added slowly. Refluxing was continued for 8 hr. The reaction mixture was cooled, filtered, and worked up by washing with the following solutions: three times with 100-ml portions of saturated NH_4Cl solution, three times with 100-ml portions of saturated $NaHCO_3$ solution, and three times with 100-ml portions of saturated NaCl solution. The ether solution was dried over $MgSO_4$, filtered, and stripped of solvent. The residue was used directly in the repeated treatments with Simmons–Smith reagent.

The above reaction was repeated two additional times using 250 g of methylene iodide and 75 g of zinc–copper couple to ensure diaddition of the Simmons–Smith reagent. After the third Simmons–Smith treatment, the product was distilled under vacuum. Careful distillation of the product and examination of the fractions by nmr made it possible to obtain a fairly pure diaddition product. The distinguishing nmr data are given.



The optimum yield of nearly pure diaddition product was 27.0 g (40%), bp 45° (0.5 mm).

Tricyclo[5.1.0.0^{3,5}]octyl-2-carboxylic acid was prepared by refluxing 27.0 g (0.16 mol) of the above ester with 575 g of 10% aqueous NaOH solution for 3 hr. The aqueous solution was cooled, acidified with concentrated HCl, and extracted with ether. The ether solution was dried over $MgSO_4$ and filtered, and the ether was removed to give 18.5 g (75%) of the acid. The crude acid was recrystallized from pentane to give 11.4 g of pure cis,cis acid, mp 105–106° (lit.[3] mp 106–107°).

***cis,cis*-Tricyclo[5.1.0.0^{3,5}]oct-2-yl Acetate** (*cis,cis*-1-OAc).—In a three-necked, 500-ml flask equipped with a condenser, a nitrogen-inlet tube, and a stirrer, were placed 11.3 g of the cis,cis acid (0.073 mol), 9 ml of dry pyridine (distilled first from tosyl chloride, then from calcium hydride, and stored over molecular sieves), and 230 ml of dry benzene. The system was flushed with nitrogen. Lead tetraacetate (50 g) was stirred into the mixture, which was slowly brought up to reflux and kept there for 1 hr. A heavy white precipitate of lead diacetate formed during the reaction. The reaction mixture was cooled and filtered. The benzene filtrate was washed with water, 1 N NaOH solution, water, 1 N HCl solution, and water. The organic phase was dried over $MgSO_4$, filtered, and distilled to give 9 g (73%) of *cis,cis*-1-OAc: bp 55° (0.1 mm); ir 3100 (w), 3030 (m), 2820 (m), 2720 (w), 1735 (s), 1375 (s), 1250 (s), 1030 (s), 1005 (s), 957 (s), 870 (m), 845 (w), and 780 cm^{-1} (w); nmr δ 5.8 (t, 1, CHOAc), 2.0 (s, 3, CH_3), 1.1 (six-membered-ring protons), and 0.3 (m, 4, cyclopropane ring CH_2).

***cis,cis*-Tricyclo[5.1.0.0^{3,5}]octan-2-ol** (*cis,cis*-1).—To a 200-ml three-necked flask equipped with a condenser, an addition funnel, and a stirrer was added 1.3 g (33 mmol) of lithium aluminum hydride and 100 ml of anhydrous ether. To this stirred solution was added 5.3 g (33 mmol) of *cis,cis*-1-OAc in 50 ml of ether at a rate suitable to maintain reflux. At the end of the addition the solution was heated and held at reflux temperature for 30 min. The reaction mixture was hydrolyzed by the careful addition of 4.9 ml of 5% sodium hydroxide solution. When the solids in the flask had turned white, the mixture was filtered. The solids were returned to the flask and boiled with tetrahydrofuran. Again the solution was filtered, and the tetrahydrofuran treatment repeated. The filtrates were combined, dried over $MgSO_4$, filtered, and stripped of solvent. The yield of crude product was 3.5 g (90%). The product was recrystallized from pentane to give a white crystalline material, mp 50–51°. Table IV summarizes the nmr spectral data for *cis,cis*-1 and its derivatives: ir (CCl_4) 3400 (s), 3080 (m), 2980 (s), 2790 (s), and 2680 cm^{-1} (s). *Anal.* Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74; O, 12.88. Found: C, 77.23; H, 9.45; O, 12.66.

***cis,trans*-Tricyclo[5.1.0.0^{3,5}]octan-2-ol** (*cis,trans*-1).—The crude acid remaining after recrystallization of the cis,cis acid was oxidized with lead tetraacetate, as described in the preparation of *cis,cis*-1-OAc. The crude acid (11.3 g) gave 5.2 g of 1-OAc (mixture of cis,cis and cis,trans). This mixture was reduced with lithium aluminum hydride by the usual procedure to give the alcohols. The alcohol mixture was oxidized in acetone by adding Jones reagent until an excess was noted by the persistence of the yellow color. The excess was destroyed by the addition of isopropyl alcohol. Water was added to the reaction mixture to dissolve all the inorganic precipitate and the resulting aqueous solution was extracted five times with ether. The ether extracts were combined, dried over $MgSO_4$, filtered, and stripped of solvent. The resulting mixture of ketones was found to be approximately 75% *cis*-2 and 26% *trans*-2 by vpc (6 ft × 1/8 in. 10% silicone rubber on Chromosorb W column at 100°, 30 ml/min). Some of the cis ketone was removed by recrystallization

from pentane. The remaining 50–50 mixture of ketones was separated by preparative vpc (10 ft × 0.5 in. 10% SE-30 silicone rubber on Chromosorb G). The yield of *trans*-**2** was 175 mg.

The *trans*-**2** was reduced with lithium aluminum hydride by the usual procedure to give *cis,trans*-**1**. Compound *cis*-**2** was also reduced to give a mixture of 45% *trans,trans*-**1** and 55% *cis,cis*-**1**. The carbonyl absorption bands for *cis*-**2** and *trans*-**2** were 1670 and 1690 cm^{-1}, respectively. *Anal.* Calcd for $C_8H_{10}O$ (*cis*-**2**): C, 78.65; H, 8.25; O, 13.10. Found: C, 78.50; H, 8.26; O, 13.18.

***cis,cis*-Tricyclo[5.1.0.0^{3,5}]oct-2-yl *p*-Nitrobenzoate (*cis,cis*-1-OPNB).**—A sample of *cis,cis*-**1** (2.28 g, 18 mmol) in 10 ml of dry pyridine was added to a solution of 4.0 g (22 mmol) of *p*-nitrobenzoyl chloride in 40 ml of pyridine. The reaction mixture was cooled in an ice bath and stirred for 2 hr. The mixture was poured into ice water and the aqueous phase was extracted with pentane. The pentane extracts were combined and dried over $MgSO_4$, filtered, and stripped of solvent. The residue was recrystallized from pentane to give 3.9 g (80%) of product: mp 45–47°; ir (CCl_4) 3100 (w), 2940 (w), 2880 (w), 2760 (w), 1725 (s), 1615 (m), and 1275 cm^{-1} (m). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; O, 23.42. Found: C, 66.10; H, 5.53; O, 23.39.

Solvolysis of Tricyclo[5.1.0.0^{3,5}]oct-2-yl *p*-Nitrobenzoate. Kinetic Studies.—The rate of solvolysis of *cis,cis*-**1**-*p*-nitrobenzoate was measured in 85% dioxane–water (by volume). The 1,4-dioxane was refluxed over sodium for 24 hr and then distilled before use. The solvolysis solvent was prepared by diluting the dioxane with water that had been deionized and distilled through a glass apparatus. A standard solution of *cis,cis*-**1**-*p*-nitrobenzoate (0.01 *M*) in the solvolysis solvent was prepared for each kinetic run and equilibrated in a constant temperature bath. Aliquots were withdrawn at intervals, quenched in dioxane, and titrated with 0.01 *M* aqueous NaOH to the bromthymol blue end point (yellow to blue).

Product Studies.—For product studies, 0.1 *M* solutions of *cis,cis*-**1**-*p*-nitrobenzoate were prepared and stirred at a predetermined temperature for various time periods. The acetolysis and formolysis reactions contained 1.1 equiv of sodium acetate and sodium formate, respectively. The solvolysis mixture was then poured into ice water and extracted several times with ether. The ether extracts were combined, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and stripped of solvent. Recovered ester after 1 half-life contained only *cis,cis*-**1**-*p*-nitrobenzoate.

The aqueous dioxane solvolysis products were analyzed directly on a 10% SE-30 silicone rubber on Chromosorb W column (6 ft × 1/8 in.). The alcohols were oxidized to a single ketone (*cis*-**2**) with Jones reagent.

The acetolysis products were reduced with lithium aluminum hydride and then analyzed by the same procedure used in the hydrolysis experiments. A single ketone (*cis*-**2**) was formed on oxidation.

The formolysis products were reduced with lithium aluminum hydride, hydrogenated over platinum catalyst at atmospheric pressure, and then oxidized with Jones reagent. Each step was followed by vpc analysis using a 20 ft × 1/8 in. 12% Carbowax on Chromosorb G column at 170° (30 ml/min flow rate).

Structure Proofs of Formolysis Products.—Four products were obtained from the formolysis of *cis,cis*-**1**-OPNB. Each could be obtained in a pure state by preparative vpc.

First Component.—Hydrogenation of the alcohol took up 2 mol of H_2 and produced *trans*-2-ethylcyclohexanol, which was identified by comparison with authentic samples. The nmr spectrum of the original material contained five alkenic protons and no ethyl resonances. A vinyl group is therefore present, plus one endocyclic double bond. The latter functionality was placed in the 4 position on the basis of the nmr spectrum. This component therefore has the structure *trans*-2-vinylcyclohex-4-enol.

Second Component.—An nmr spectrum of this material was identical with an authentic sample of *cis*-bicyclo[5.1.0]oct-5-en-3-ol.[17] A sample of the trans isomer was available for comparison; the reaction mixture contained only *cis*-**3**.

Third Component.—Hydrogenation of the alcohol produced cyclooctanol, with an uptake of 2 mol of H_2. The formate had an ultraviolet absorption at 225 nm (ϵ 2800), so the double bonds must be conjugated. The alcohol was oxidized to the corresponding cyclooctadienone, which had no new uv absorptions. The ketone is therefore not α,β unsaturated. Only cycloocta-3,5-dienol (**6**) has these properties.

Fourth Component.—Hydrogenation and Jones oxidation produced bicyclo[5.1.0]octan-3-one.[17] The intermediate saturated alcohol was not identical with the saturated cis alcohol from *cis*-**3**; so the stereochemistry must be trans. Furthermore, this component was different from *trans*-**3** but produced the same saturated alcohol on hydrogenation. The alkenic region of the nmr spectrum contained a two-proton AB quartet with further fine structure. The spectrum and the chemical evidence are only consistent with *trans*-bicyclo[5.1.0]oct-4-en-3-ol (*trans*-**4**).

Registry No.—*cis,cis*-**1**, 30953-03-8; *cis,cis*-**1**-OAc, 30953-05-0; *cis,cis*-**1**-OPNB, 30953-04-9; *cis,trans*-**1**, 30953-06-1; *cis,trans*-**1**-OPNB, 30883-12-6; *trans,trans*-**1**, 30889-17-9; *cis*-**2**, 30889-18-0; *trans*-**2**, 30889-19-1; methyl 1,4-dihydrobenzoate, 30889-20-4; methyl ticyclo[5.1.0.0^{3,5}]octyl-2-carboxylate, 30889-21-5.

Acknowledgments.—This work was supported by the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-AC4, 5), and by the National Science Foundation (Grants GP-9257 and GP-22942).

(17) Authentic samples of this material were made available by Dr. A. P. Jovanovich.[2]

C-Alkylation of Active Methylene Compounds by Means of Alcohols. VI. A Facile Monoalkylation of Phenylacetonitrile[1]

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Alkylation of phenylacetonitrile by means of aliphatic primary alcohols (from ethyl to decyl and lauryl) and secondary alcohols (isopropyl, *sec*-butyl, and cyclohexyl) in the presence of sodium leads to the corresponding monoalkyl phenylacetonitriles in good to excellent yields. Addition of an equimolar amount of the ester of acetic acid and the alcohol to be used in alkylation is made as a means to decrease or avoid hydrolysis of phenylacetonitrile. A mechanism is proposed. Since the method involves simple manipulation and the use of alcohols as reagents, it can be recommended as a method superior to that previously used.

Preliminary reports[2] from this laboratory revealed that phenylacetonitrile is readily monoalkylated by means of higher boiling aliphatic alcohols (from *n*-heptyl to *n*-decyl and lauryl) and metallic sodium, whereas the conventional method[3] consists in heating under reflux the nitrile and alkyl halide in the presence of sodium amide in an inert solvent.

The research has now been extended to the study of lower molecular weight aliphatic alcohols.

The C-alkylation of active methylene groups by means of an aliphatic alcohol and sodium has been reported in only one case, namely the alkylation of fluorene.[4,5] The application of this procedure to a wide variety of active methylene compounds has failed. The water formed in the reaction causes hydrolysis of the cyano or ester group of the active methylene compounds with consequent loss of reactivity. In the previous communications, benzylation[1] and alkylation[2] of phenylacetonitrile were effected by addition to the reaction mixture of equimolar amounts of various esters, which reacted with the water formed.

With this device to protect the cyano group from hydrolysis, monoalkylation of phenylacetonitrile with a series of aliphatic alcohols has been achieved.

$$C_6H_5CH_2CN + ROH \xrightarrow[\substack{C_6H_5COOCH_3 \text{ (method A)}\\ CH_3COOR \text{ (method B)}}]{Na} C_6H_5\underset{\displaystyle R}{\underset{|}{C}}H{-}CN$$

The reactions were conducted at 210–220° (bath temperature) throughout. With the alcohols higher than *n*-heptyl (bp 176°) alkylation proceeded in good yield (61–74%). Higher temperatures did not result in an appreciable change in yield. On the other hand, the yield of *n*-hexylated phenylacetonitrile dropped to 27% (average of two runs), suggesting that the required reaction temperature is well above the boiling point (157°) of *n*-hexyl alcohol. Consequently, with the low-boiling aliphatic alcohols the use of an autoclave is essential.

The study of the addition of esters to the reaction mixtures in order to control hydrolysis was confined to two, methyl benzoate (method A) and an acetic acid ester involving the alcohol to be used for alkylation (method B). A comparison of the yields by the two methods in the alkylation of phenylacetonitrile by higher boiling alcohols is shown in Table I.

TABLE I[a]

α-ALKYLPHENYLACETONITRILES, $C_6H_5\underset{\displaystyle R}{\underset{|}{C}}HCN$

Compd	R	Bp, °C (mm)[b]	Yield, %[c] (method)	$n^{25}D$[d]
1	*n*-Heptyl[e]	128–130 (1.5)	73.4 (A) 78.3 (B)	1.4939
2	*n*-Octyl[f]	149–151 (2)	74.1 (A) 85.5 (B)	1.4907
3	2-Ethylhexyl[g]	138–140 (2)	61.0 (A) 76.7 (B)	1.4968
4	*n*-Nonyl[h]	157–159 (2)	86.1 (A) 76.6 (B)	1.4901
5	3,5,5-Trimethylhexyl[h]	139–141 (2)	73.2 (A) 80.0 (B)	1.4918
6	*n*-Decyl[h]	169–171 (2)	70.3 (A) 72.8 (B)	1.4882
7	Lauryl[h,i]	184–186 (2)	64.0 (A) 71.9 (B)	

[a] All compounds in Tables I–III gave satisfactory (±0.3) C, H, and N analyses. The data were made available to the Editor and the referees. [b] Boiling points of the redistilled products. [c] Based on phenylacetonitrile. [d] $n^{25}D$ of analytical samples. [e] Bp 139° (1.5 mm), $n^{20}D$ 1.4953: M. Makosza and B. Serafin, *Rocz. Chem.*, **39** (10), 140 (1965). [f] $n^{25}D$ 1.4932: D. Zavoianu and Fl. Cocu, *Rev. Chim. (Bucharest)*, **18** (1), 2 (1967). [g] Bp 175–178° (12 mm): Kali-Chemie A.-G., British Patent 748,064 (1956). [h] New compounds. [i] Mp 25–25.5°, colorless needles (from petroleum ether).

In the alkylation with the higher boiling alcohols that do not require an autoclave, the procedure consists in adding[6] the mixture of phenylacetonitrile and methyl benzoate to the preheated (200–210°) solution of sodium in 3–4 times the equivalent amount of alcohol and then raising the temperature of the mixture to 210–220°.

Method A offers the advantage of the ready availability of methyl benzoate. In three examples, however, *n*-heptylation, *n*-octylation, and 2-ethylhexylation, when equimolar amounts of methyl benzoate and nitrile were employed, some ester interchange occurred that led to the presence of traces of alkyl benzoate produced from the methyl benzoate and the alkylation alcohol. This interchange was detected in an ir analysis of the products[7] (ester carbonyl at 1718–1720 cm^{-1}). If 0.9

(1) Paper V: S. Miyano and N. Abe, *Chem. Pharm. Bull.*, **18**, 550 (1970).

(2) S. Miyano and N. Abe, *ibid.*, **15**, 1811 (1967).

(3) K. Ziegler, *Justus Liebigs Ann. Chem.*, **498**, 84 (1932); F. W. Bergstrom and W. C. Fernelius, *Chem. Rev.*, **12**, 135 (1933); **20**, 451 (1937); A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957); H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 184.

(4) K. L. Shoen and E. I. Becker, *J. Amer. Chem. Soc.*, **77**, 6030 (1955).

(5) D. N. Matthews and E. I. Becker, *J. Org. Chem.*, **21**, 1317 (1956).

(6) Addition should be made dropwise in order to keep a higher ratio of alcohol in the reaction medium and thus avoid a Thorpe type of self-condensation of the phenylacetonitrile.

(7) Usually two distillations resulted in products adequately pure to give correct analytical values.

TABLE II

PREPARATION OF α-ALKYLPHENYLACETONITRILES, $C_6H_5\underset{\displaystyle R}{\underset{|}{C}}HCN$, ACCORDING TO METHOD B

Compd	R	Bp, °C (mm)	Yield, %[a]	$n^{25}D$
8	Ethyl	120–126 (19)	62.5	1.5067[b]
9	*n*-Propyl	132–138 (19)	71.7	1.5029[c]
10	Isopropyl	127–134 (20)	56.6	1.5039[d]
11	*n*-Butyl	138–143 (16)	74.8	1.5003[e]
12	Isobutyl	134–139 (16)	68.0	1.4981[f]
13	*sec*-Butyl	103–105 (2)[g]	38.0	1.5038
14	*n*-Amyl	152–160 (13)[h]	66.5	1.4970[h]
15	Isoamyl	147–152 (18)[i]	72.2	1.4967
16	*n*-hexyl	161–166 (12)[j]	70.1	1.4949
17	Cyclohexyl	137–140 (3)[k]	56.5	

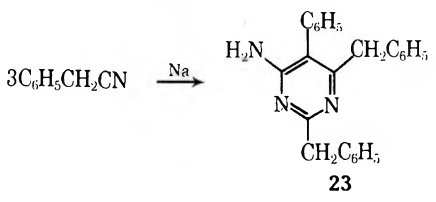
[a] Based on phenylacetonitrile. [b] $n^{25}D$ 1.5070: D. J. Cram and J. Allinger, *J. Amer. Chem. Soc.*, **76**, 4516 (1954). [c] $n^{25}D$ 1.5033: K. Mislow and C. M. Hamermesh, *ibid.*, **77**, 1590 (1955). [d] $n^{25}D$ 1.5032: D. J. Cram, F. A. A. Elhafez, and H. L. Niquist, *ibid.*, **76**, 22 (1954). [e] $n^{25}D$ 1.5003: K. Mislow and C. M. Hamermesh, *ibid.*, **77**, 1590 (1955). [f] $n^{25}D$ 1.4978–1.4985: A. W. Ruddy and T. J. Becker, British Patent 682,261 (1952); *Chem. Abstr.*, **48**, 740 (1954). [g] Bp 130–133° (12 mm): Kali-Chemie A.-G., British Patent 748,064 (1956); *Chem. Abstr.*, **52**, 12913 (1958). [h] Bp 150–152° (20 mm), $n^{25}D$ 1.5007: L. H. Boldinger and J. A. Nieuland, *J. Amer. Chem. Soc.*, **55**, 2851 (1933). [i] Bp 276°: A. Rossolymo, *Ber.*, **22**, 1237 (1889). [j] Bp 327°: A. Rossolymo, *ibid.*, **22**, 1237 (1889). [k] Mp 56–58° (from pentane): E. M. Hancock and A. C. Cope, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 219.

times the equivalent amount of methyl benzoate was employed, no ester carbonyl band appeared in the product. However, the very weak band of an amide carbonyl[8] at 1686 cm^{-1} was present instead. By one distillation this amide is readily removed.

When method B was used, the yields were improved in all examples (Table I) and one distillation of the products served to give pure material that showed in the infrared no ester or amide groups. The advantage of method B over method A is thus obvious in both purity and yield of product.

Method B was used exclusively in alkylation of phenylacetonitrile with low-boiling alcohols (ethyl to *n*-hexyl) in an autoclave. The results are shown in Table II. The only poor yield was in the alkylation with *sec*-butyl alcohol.

Alkylation with methanol, however, failed; 4-amino-2,6-dibenzyl-5-phenylpyrimidine (**23**),[9,10] a cyclic trimer



23

of phenylacetonitrile in 34.8% yield, was the resulting product.

The formation of compound **23** takes place exclusively. This may be due to the fact that methanol does not tend to dehydrogenate to formaldehyde in the presence of sodium under the conditions used. Moreover, methanol and sodium are incapable of reducing the expected unsaturated intermediates, as exemplified by the failure to reduce α-cyclohexylidenephenylacetonitrile with methanol and sodium.

It is noteworthy that secondary alcohols such as isopropyl, *sec*-butyl, and cyclohexyl alcohols are also reactive in this type of alkylation, but the yields are somewhat lower (Table II).

Other nitriles that were alkylated by this procedure are *o*- and *p*-chlorophenyl-, α- and β-naphthyl-, and α-pyridylacetonitriles (Table III). The reaction thus appears to be of quite general application.

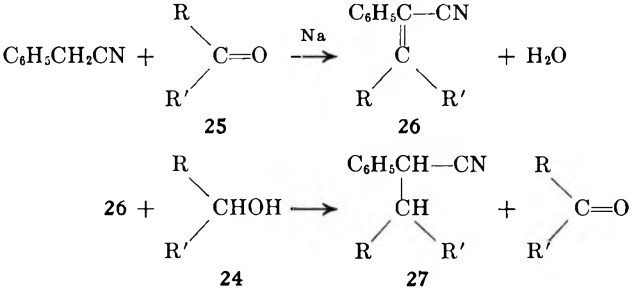
TABLE III

α-OCTYLNITRILE, $NC\underset{\displaystyle R}{\underset{|}{C}}H(CH_2)_7CH_3$

Compd	R	Bp, °C (mm)	Yield, %	$n^{25}D$
18	*o*-Chlorophenyl	157–162 (2)	65.4	1.5031
19	*p*-Chlorophenyl	165–170 (2)	79.7	1.5031
20	α-Naphthyl	200–203 (2)	67.4	1.5489
21	β-Naphthyl	200–205 (2)	85.3	1.5484
22	α-Pyridyl	147–153 (3)	83.5	1.4873

The mechanism of this general reaction is the same as that proposed for the C-benzylation of phenylacetonitrile and involves the two consecutive reactions shown in Scheme I.

SCHEME I



Weizmann and coworkers, in the study of the Guerbet condensation,[11] demonstrated that aliphatic alcohols in the presence of sodium at higher temperatures were dehydrated to aldehydes (**24** → **25**), which underwent the expected condensation with the active methylene compound. Moreover, the alcohols in the presence of sodium at temperatures over 200° are capable of reducing double bonds (**26** → **27**). Our experiments demonstrated that the product from the condensation of phenylacetonitrile and cyclohexanone was readily reduced with cyclohexanol and sodium to α-cyclohexylphenylacetonitrile (**27**). In a one-step reaction at a temperature of 135° only the unsaturated nitrile **26** could be isolated.

The alkylation procedure with higher boiling alcohols (heptyl and higher) consisted in the dropwise addition of a mixture of the phenylacetonitrile and alkyl acetate to a preheated (200–210°) solution of sodium in the appropriate alcohol.

On the other hand, the alkylation with lower boiling alcohols was carried out by heating gradually in an autoclave to 210–220° a mixture of phenylacetonitrile,

(8) The infrared value suggests that the phenylacetonitrile and/or the product was hydrolyzed to amide. However, the contaminant is so small in amount that there is no difficulty in its removal.

(9) E. F. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **89**, 1915 (1906).

(10) G. A. Reynolds, W. J. Humphlett, F. W. Swamer, and C. R. Hauser, *J. Org. Chem.*, **16**, 165 (1951).

(11) Ch. Weizmann, E. Bergmann, and L. Haskelberg, *Chem. Ind. (London)*, **56**, 587 (1937).

alkyl acetate, the appropriate alcohol, and sodium. Under these conditions, the condensation of alkyl acetate and phenylacetonitrile probably takes place first to afford α-phenylacetoacetonitrile (**28**) as an intermediate, which then undergoes alcoholysis. This was established by keeping the reaction mixture using cyclohexyl acetate and cyclohexanol at 150–155° and isolating the intermediate compound **28** in 56.5% yield.[12]

$$C_6H_5CH_2CN + CH_3COOR \xrightarrow{Na} C_6H_5\underset{\underset{\underset{CH_3}{|}}{CO}}{\overset{|}{C}}HCN + ROH$$

28

The procedure just described has a great advantage over the one previously used in that it employs alcohols in place of halides and sodium in place of sodium amide and gives much more consistent results.

Experimental Section

Commercial aliphatic alcohols were purified by distillation before use. *o*-[13] and *p*-chlorophenyl-,[13] α-[14] and β-naphthyl-,[15] and α-pyridylacetonitriles[16] were prepared according to known methods.

Alkylation of Phenylacetonitrile with the Alcohols (*n*-Heptyl to *n*-Decyl and Lauryl) (Table I, 1–7). Method A.—In a typical example, 3.5 g (0.15 mol) of sodium was added portionwise to 65 g (0.5 mol) of *n*-octyl alcohol and the mixture was heated until all the sodium was in solution. To the preheated solution (200–210°) was added dropwise with stirring a mixture of 17.6 g (0.15 mol) of phenylacetonitrile and 18.4 g (0.135 mol) of methyl benzoate. In less than 5 min methanol started to distil briskly. The temperature was maintained at 210–220°. After the methanol was all distilled off the remaining mixture solidified to a pale-yellow cake. This was heated for an additional 10 min. The cooled mixture was dissolved in water, the oily layer was taken up in ether, and the ethereal extract was washed with water, dried (K_2CO_3), and distilled to give α-*n*-octylphenylacetonitrile: bp 145–150° (2 mm); yield 25.5 g (74.1% based on phenylacetonitrile); ir bands at 2242 (C≡N) and 1686 cm^{-1} ($CONH_2$, weak). The latter band disappeared completely after distillation.

Method B.—The procedure differs from method A merely in the use of the appropriate alkyl acetate in place of methyl benzoate. In a typical example, 17.6 g (0.15 mol) of phenylacetonitrile, 3.5 g (0.15 mol) of sodium, and 75 g (0.65 mol) of *n*-heptyl alcohol in the presence of 23.7 g (0.15 mol) of *n*-heptyl acetate gave 25.3 g (78.3%) of α-*n*-heptylphenylacetonitrile, ir band at 2242 cm^{-1} (C≡N).

α-Alkylphenylacetonitriles (Alkyl Is Ethyl to *n*-Hexyl) (Table II, 8–17).—α-Ethylphenylacetonitrile was prepared following method B. To a refluxing solution of 6.9 g (0.3 mol) of sodium in 80 g (100 ml, 1.74 mol) of absolute ethanol was added dropwise under stirring a mixture of 35.1 g (0.3 mol) of phenylacetonitrile and 26.4 g (0.3 mol) of ethyl acetate. The resulting suspension was placed in an autoclave and heated at 210–220° for 1.5 hr. The contents of the autoclave were filtered to remove crystals that had separated. The filtrate was freed from ethanol and the residue was dissolved in ether and dried (K_2CO_3). Evaporation of the ether followed by vacuum distillation of the residue gave 27.2 g (62.5%) of α-ethylphenylacetonitrile, bp 120–126° (19 mm).

The amounts of alcohols employed for 6.9 g (0.3 mol) of sodium are 100 ml for ethyl, *n*-propyl, and isopropyl alcohols; 120 ml for *n*-butyl, isobutyl, and *sec*-butyl alcohols; 130 ml for *n*-amyl and isoamyl alcohols; and 150 ml for cyclohexyl and *n*-hexyl alcohols. These amounts have been selected on the basis of the solubility of the sodium.

Experiments Supporting the Proposed Mechanism of Formation of Alkylphenylacetonitriles. α-Cyclohexylidenephenylacetonitrile.—To a solution of 2.8 g (0.12 mol) of sodium in 100 g (1 mol) of cyclohexanol was added dropwise a mixture of 14 g (0.12 mol) of phenylacetonitrile, 9.8 g (0.1 mol) of cyclohexanone, and 17 g (0.12 mol) of cyclohexyl acetate. The mixture was heated at 130–135° for 45 min. After cooling, water was added and the resulting oil extracted with ether. The ethereal extract was washed with water, dried (K_2CO_3), concentrated, and distilled to give 17.5 g (88.8%) of α-cyclohexylidenephenylacetonitrile, bp 140–143° (2 mm),[17] $n^{25}D$ 1.5635.

Anal. Calcd for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N, 7.10. Found: C, 85.48; H, 7.59; N, 7.29.

Reduction of α-Cyclohexylidenephenylacetonitrile with Cyclohexanol to α-Cyclohexylphenylacetonitrile.—To a solution of 4.6 g (0.2 mol) of sodium in 100 g (1 mol) of cyclohexanol was added a mixture of 29.6 g (0.15 mol) of α-cyclohexylidenephenylacetonitrile and 28.4 g (0.32 mol) of cyclohexyl acetate. The mixture was heated with stirring in an autoclave at 210–220° for 1.5 hr and worked up as in the preparation of α-alkylphenylacetonitriles. A yield of 24.9 g of α-cyclohexylphenylacetonitrile, bp 135–140° (2 mm), was obtained. After one redistillation it boiled at 137–140° (2 mm) and solidified to colorless needles. The yield was 22.2 g (74%). One recrystallization from pentane gave crystals, mp 56–58°.

***n*-Octylation of *o*-Chlorophenylacetonitrile and Related Nitriles (Table III, 18–22).**—Preparation of α-*n*-octyl-*o*-chlorophenylacetonitrile **18** is illustrative. To a stirred solution of sodium octoxide prepared from 2.3 g (0.1 mol) of sodium and 80 ml of *n*-octyl alcohol was added dropwise a mixture of 15.2 g (0.1 mol) of *o*-chlorophenylacetonitrile and 17.2 g (0.1 mol) of *n*-octyl acetate at 215°. The mixture was stirred for 1.5 hr at the same temperature. After cooling, water was added and the oily layer was extracted with ether. The ethereal solution was dried (K_2CO_3), the ether removed, and the product distilled; 17.3 g (65.4%) of α-*n*-octyl-*o*-chlorophenylacetonitrile resulted.

Attempted Methylation of Phenylacetonitrile.—To a methanolic solution of sodium methoxide prepared from 6.9 g (0.3 mol) of sodium in 100 ml of methanol was added 35.1 g (0.3 mol) of phenylacetonitrile and 22.2 g (0.3 mol) of methyl acetate. The mixture was heated at 210–220° in an autoclave for 1.5 hr. After cooling, the crystalline substance was filtered off, washed with ether, and recrystallized from isopropyl ether to give 4 g of 4-amino-2,6-dibenzyl-5-phenylpyrimidine (**23**) as colorless needles, mp 106–107°.[18] The filtrate combined with washings was freed from solvent, mixed with water, and extracted with ether and the ethereal extract was dried (K_2CO_3). Distillation gave 12.2 g (34.8%) of unreacted phenylacetonitrile.

Attempted Methanol Reductions.—To a solution of 2.3 g (0.1 mol) of sodium in 50 ml of methanol was added a mixture of 19.7 g (0.1 mol) of α-cyclohexylidenephenylacetonitrile and 7.4 g (0.1 mol) of methyl acetate. The resulting mixture was heated with stirring at 210–220° in an autoclave for 1.5 hr. Methanol was distilled off and the residue was extracted with ether. The ethereal extract was dried (K_2CO_3), concentrated, and distilled. Only starting material was obtained.

Separation of Intermediary Phenylacetoacetonitrile 28.—To a solution of 2.8 g (0.12 mol) of sodium in 100 ml of cyclohexanol was added dropwise a mixture of 11.7 g (0.1 mol) of phenylacetonitrile and 17 g (0.12 mol) of cyclohexyl acetate at 150–155° and heated at the same temperature for 1 hr. After cooling, 100 ml of ether was added and the mixture was shaken with three 40-ml portions of water. The combined aqueous layer was cooled in a freezing mixture to −5° and neutralized with acetic acid to afford 9 g (56.5%) of phenylacetoacetonitrile **28**, which after crystallization from methanol gave needles, mp 88.5–89.5°.

Alcoholysis of α-Phenylacetoacetonitrile (28) by Cyclohexanol to α-Cyclohexylphenylacetonitrile (17).—A mixed slurry of 54.3 g (0.3 mol) of α-phenylacetoacetonitrile sodium salt and 150 g

(12) α-Phenylacetoacetonitrile (**28**) is usually prepared by condensation of phenylacetonitrile with ethyl acetate in the presence of sodium ethoxide: P. L. Jurian, J. J. Oliver, R. H. Kimball, A. B. Pike, and G. D. Jefferson, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1957, p 487.

(13) R. von Walther and L. H. Hirschberg, *J. Prakt. Chem.*, [2] **67**, 377 (1903).

(14) L. H. Briggs and J. M. Wilson, *J. Chem. Soc.*, 500 (1941).

(15) M. S. Newmann, *J. Org. Chem.*, **9**, 518 (1944).

(16) K. Winterfield and K. Flick, *Arch. Pharm. (Weinheim)*, **26**, 448 (1956).

(17) Bp 125–131° (0.7 mm): S. Archer and A. W. Rudd, British Patent 674,246 (1956); *Chem. Abstr.*, **47**, 7538 (1953).

(18) Mp 106–107°: ref 7.

(1.5 mol) of cyclohexanol was heated with stirring in an autoclave at 210–220° for 1.5 hr. After cooling, water was added and the oily layer that separated was extracted with ether. The ethereal extract was washed with water and dried (K_2CO_3), the ether was removed, and the residue was distilled; 35.5 g (59.5%) of α-cyclohexylphenylacetonitrile[19] resulted which soon solidified to light-yellow prisms. After two recrystallizations from methanol the product melted at 56–58°.

Registry No.—1, 5558-36-1; 2, 15601-30-6; 3, 17178-81-3; 4, 17179-16-7; 5, 30889-57-7; 6, 17179-17-8; 7, 17179-18-9; 8, 769-68-6; 9, 5558-78-1; 10, 5558-29-2; 11, 3508-98-3; 12, 5558-31-6; 13, 5558-32-7; 14, 5558-33-8; 15, 5558-34-9; 16, 5558-35-0; 17, 3893-23-0; 18, 21764-73-8; 19, 21764-74-9; 20, 21764-71-6; 21, 30878-93-4; 22, 21764-72-7; 28, 4468-48-8; α-cyclohexylidenephenylacetonitrile, 10461-98-0; phenylacetonitrile, 140-29-4.

(19) See footnote *k*, Table II.

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Behavior of Tungsten Hexachloride and Ethylaluminum Dichloride Cocatalyst System in Alkylation and Metathesis Reactions[1]

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Received September 22, 1970

We have discovered a novel behavior of the WCl_6–$C_2H_5AlCl_2$ when this cocatalyst was preformed in toluene. When this catalyst was treated with 2-pentene, instead of the expected metathesis of 2-pentene, a very rapid Friedel–Crafts alkylation of toluene was encountered. With benzene, the alkylation proceeded at a somewhat slower rate and was accompanied by an even slower 2-pentene metathesis reaction. Thus, in addition to phenylpentane, phenylbutane and phenylhexane were also formed. This is the first observance of metathesis during Friedel–Crafts alkylation. The behavior of the WCl_6–$C_2H_5AlCl_2$ catalyst system with pyridine or triphenylphosphine added as the ligand was also briefly studied. When either was added to the preformed WCl_6–$C_2H_5AlCl_2$, the alkylation was completely inhibited and a slow metathesis of olefin was observed. Alkylation of benzene with 1-dodecene gave the expected isomeric mixture of phenyldodecanes.

The use of WCl_6–$C_2H_5AlCl_2$ or RLi cocatalyst system *in situ* for olefin metathesis, sometimes also designated olefin dismutation or disproportionation, has been investigated by several workers.[2–4] The coordination mechanism for olefin metathesis has been proposed by Kothari[5] in which the reduced tungsten compound is coordinated to two olefin molecules *via* a four-centered "quasicyclobutane" type complex intermediate. This mechanism also applies to the reactions catalyzed by oxides of tungsten, molybdenum, or rhenium and soluble complexes of tungsten and molybdenum.[6,7]

The past investigations on the use of WCl_6–$C_2H_5AlCl_2$ cocatalyst were concerned with the fundamental aspects of the metathesis reaction as applied to linear vinylenic olefins[2,3,7] and the ring-opening polymerization of a variety of cyclo olefins.[8] However, these studies did not disclose the behavior of this catalyst when preformed in aromatic solvents. In toluene, this catalyst promoted a rapid Friedel–Crafts alkylation of toluene, whereas, in the case of benzene, both alkylation and metathesis reactions were observed. This behavior of the preformed catalyst system prompted us to carry out a more detailed investigation.

(1) (a) Presented in part at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970; (b) abstracted in *Chem. Eng. News*, **48**, 39 (1970).

(2) N. Calderon, H. Y. Chen, and K. W. Scott, *Tetrahedron Lett.*, 3327 (1967).

(3) N. Calderon, E. A. Ofstead, J. P. Ward, W. A. Judy, and K. W. Scott, *J. Amer. Chem. Soc.*, **90**, 4133 (1968).

(4) J. Wang and H. R. Menapace, *J. Org. Chem.*, **33**, 3794 (1968).

(5) Reference 4, footnote 6.

(6) C. P. C. Bradshaw, E. J. Howman, and L. Turner, *J. Catal.*, **7**, 269 (1967).

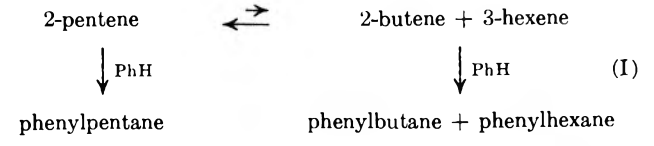
(7) G. C. Bailey, *Catal. Rev.*, **3** (1), 37 (1969), and references cited therein.

(8) N. Calderon, E. A. Ofstead, and W. A. Judy, *J. Polym. Sci., Part A-1*, **5**, 2209 (1967).

Results

Alkylation by 2-Pentene.—When WCl_6–$C_2H_5AlCl_2$ cocatalyst is preformed in toluene and treated with 2-pentene, an almost exclusive and very rapid alkylation of toluene is encountered in contrast to the metathesis of 2-pentene when this cocatalyst is prepared *in situ*. The term *in situ*, as employed in this discussion, pertains to the formation of a cocatalyst in the presence of the olefin. The isomer distribution for pentyltoluenes, based on infrared spectra, is para > ortho > meta. The isomer distribution was determined by comparing their band strengths in 700–800-cm^{-1} region. Due to many inherent differences in Friedel–Crafts catalyst systems, a quantitative comparison between catalysts is difficult. However, the high activity of the WCl_6–$C_2H_5AlCl_2$ case is indicated by the alkylation of nearly 1500 mol of toluene per mole of catalyst after 1 hr at 25°.

We have observed that, when WCl_6–$C_2H_5AlCl_2$ cocatalyst is preformed in benzene and added to a solution of 2-pentene in benzene, a reaction occurs which gives rise to phenylpentane, phenylbutane, and phenylhexane (I). The latter two products which account for about 10% of the products (Table I) are clearly the result of a 2-pentene metathesis reaction (eq I).



(I)

The small amount of these products formed indicates that under these conditions the rate of alkylation is

TABLE I

WCl_6–$C_2H_5AlCl_2$ PREFORMED CATALYZED REACTIONS OF 2-PENTENE AT 25°

Run	WCl_6, mmol	$C_2H_5AlCl_2$, mmol	2-Pentene, mmol	Solvent	Ratio, Al/W	Reaction time, min	% convn of olefin	Products
1	0.1	0.1	43	Toluene	1	10	100	
2	0.05	0.1	50	Toluene	2	10	100	Pentyltoluenes
3	0.05	0.2	43	Toluene	4	10	100	
4	0.05	0.1	45	Benzene	2	10–15	100	Phenylpentane Phenylbutane Phenylhexane

much faster than that of metathesis. Although the alkylation of benzene by cyclooctene and cyclooctadiene has been observed in a trace amount during their polymerization with WCl_6–C_2H_5OH–$C_2H_5AlCl_2$ catalyst system,[9] this is the first example of the observance of metathesis during alkylation giving rise to the disproportionated alkylated products.

The catalysis of both metathesis and alkylation reactions raises certain questions as to the nature of the intermediate responsible for each of these reactions. The simultaneous occurrence may require the formation of two different cocatalyst intermediates. The mechanism of metathesis reaction in which WCl_6 reduced by $C_2H_5AlCl_2$ interacts with two olefin molecules to form a "quasicyclobutane" type complex intermediate has been postulated and supported by several investigators.[3,5,7] The inability of the metathesis reaction to compete when the cocatalyst is preformed does suggest that the prior coordination of the reduced tungsten with olefins apparently is necessary for the formation of the active metathesis intermediate. In the benzene case, a small amount of the metathesis catalyst survives and competes with the alkylation catalyst. The inability of metathesis to compete with alkylation is probably due to the coordination of the catalyst to the aromatic ring to give the alkylation intermediate, thus interfering with coordination to the olefin. The alkylation activity of this catalyst produced from the reaction of $C_2H_5AlCl_2$ with WCl_6 is quite similar to that of aluminum chloride.

The results of the alkylation reactions of 2-pentene (Table II) further indicate that at higher temperature and higher $C_2H_5AlCl_2$–WCl_6 ratio the monoalkylated intermediate reacts faster than the starting compound. The molar ratio of mono- to dialkyl derivatives was established by weighing the distilled fractions.

Ligand Effects.—The behavior of WCl_6–$C_2H_5AlCl_2$ cocatalyst system upon treatment with ligands pyridine and triphenylphosphine was investigated briefly (Table III).

With the *in situ* catalyst, pyridine inhibited the metathesis reaction while its presence in the preformed system suppressed the Friedel–Crafts alkylation reaction but allowed a 4% conversion to metathesis products. Pyridine has been found to reduce tungsten and form a brown precipitate which is $[WCl_4(pyridine)_2]$.[10] The formation of such an intermediate may explain the suppression of alkylation and greatly reduced metathesis activity.

On the other hand, the triphenylphosphine *in situ* system slowed the metathesis reaction so that about 2–3 hr was required to reach equilibrium which is contrasted with the few minutes needed with the *in situ* catalyst. $P(C_6H_5)_3$ hinders the metathesis of 2-pentene to some extent perhaps by forming a labile complex with reduced tungsten and thus slowing down the rapid interaction of reduced tungsten with olefin. We believe that the competition of phosphine with olefin for reduced tugsten provides an explanation for slower metathesis reaction (eq II). The presence of triphenylphosphine in the preformed catalyst suppressed the alkylation but permitted a slow metathesis process.

$$WCl_4 \cdot 2P(Ph)_3 \overset{\text{olefin}}{\rightleftharpoons} WCl_4 \cdot P(Ph)_3 \cdot \text{olefin} \overset{\text{olefin}}{\rightleftharpoons} WCl_4 \cdot (\text{olefin})_2 \quad \text{(II)}$$

The inability of the alkylation reaction to proceed when pyridine or triphenylphosphine is added to a preformed catalyst may be due to the neutralization of the active intermediate by ligand which acts more or less as a base. The alternate explanation, for the suppression of alkylation, is the possibility of $(C_6H_5)_3P \rightarrow Al$ interaction and the formation of a pyridine$\rightarrow$Al adduct.

Alkylation by 1-Dodecene.—The use of the preformed WCl_6–$C_2H_5AlCl_2$ catalyst system has been extended to the alkylation of 1-dodecene.

The reaction of 1-dodecene with benzene was investigated in order to obtain an indication of the relative rates of isomerization and alkylation. The results summarized in Table IV show that the isomerization occurs during alkylation and that all the possible phenyldodecanes are obtained except the 1-phenyl isomer. This is similar to the results obtained by others in the Friedel–Crafts alkylation reactions of 1-dodecene and

TABLE II

DISTRIBUTION OF ALKYLATED AROMATICS IN REACTIONS WITH 2-PENTENE

Aromatic	Ratio, Al/W	Temp, °C	Products (%)
Benzene	2	50	Phenylpentane (55) Phenylbutane and phenylhexane (10) Dialkylbenzene (30) Higher alkylated (5)
Benzene	2	25	Phenylpentane (85) Phenylbutane and phenylhexane (10) Dialkylbenzene (5)
Benzene	4	30	Phenylpentane (42) Phenylbutane and phenylhexane (9) Dialkylbenzene (43) Higher alkylated (6)
Toluene	2	50	Monoalkyl/dialkyl = 2.5
Toluene	2	25	Monoalkyl/dialkyl = 5

(9) K. W. Scott, N. Calderon, E. A. Ofstead, W. A. Judy, and J. P. Ward, *Advan. Chem. Ser.*, **91**, 399 (1969).

(10) R. E. McCarley and T. M. Brown, *Inorg. Chem.*, **3**, 1232 (1964).

TABLE III

LIGAND EFFECTS IN THE PREFORMED AND THE *in Situ* CATALYST SYSTEMS

Run	WCl_6, mmol	$C_2H_5AlCl_2$, mmol	Ligand, mmol	2-Pentene, mmol	Reaction time	% convn of olefin	Products
1[a]	0.05	0.1		45	10 min	50	3-Hexene 2-Butene
2	0.06	0.24	0.06 (TPP)[b]	45	10 hr	47	3-Hexene 2-Butene
3[a]	0.06	0.24	0.06 (TPP)	45	2 hr	46	3-Hexene 2-Butene
4[a]	0.24	0.48	0.24 (Py)[c]	90	2 hr	None	
5	0.24	0.48	0.24 (Py)	45	5 hr	4	3-Hexene 2-Butene

[a] Run with *in situ* catalyst. [b] TPP, triphenylphosphine. [c] Py, pyridine.

TABLE IV

ALKYLATION OF BENZENE WITH WCl_6–$C_2H_5AlCl_2$ COCATALYST SYSTEM

$$\frac{\text{benzene}}{WCl_6} \sim 1000, \frac{C_2H_5AlCl_2}{WCl_6} \sim 2, \frac{\text{olefin}}{WCl_6} \sim 200$$

Compd	—% alkylation by olefin 1-dodecene— 5–10°	40–45°	55–60°
2-Phenyl	38.4	29.3	26.1
3-Phenyl	14.4	12.7	11.4
4-Phenyl	6.8	9.3	10.3
5- and 6-phenyl	11.2	16.9	18.0
Polyalkylated and polymers	29.2	31.8	34.2
Conversion based on olefin	98.7	80.0	73.5

other olefins[11,12] employing $AlCl_3$. In contrast to $AlCl_3$, the isomerization of pure 3-phenyldodecane was, however, not observed with WCl_6–$C_2H_5AlCl_2$ catalyst.

Three common features are found with regard to these results (Table IV) and those reported by Alul[13] using the HCl–$AlCl_3$ catalyst. These are (1) the high formation of 2-phenyldodecane; (2) the increase in this isomer as the reaction temperature is lowered; (3) the high yield of polyalkylated products.

Again, we believe that the active intermediate derived from WCl_6–$C_2H_5AlCl_2$ behaves similarly to aluminum chloride. However, unlike aluminum chloride, this catalyst is soluble, can be employed in a low concentration, and does not isomerize phenyldodecane under the alkylating condition.

Experimental Section

Materials.—Benzene, toluene, and pyridine were distilled in nitrogen atmosphere and kept over Drierite. Mixed 2-pentene (99%, trans/cis = 0.85) from Chemical Samples Co., Columbus, Ohio, was distilled from sodium bisulfite under N_2. Dodecene-1, from Gulf Oil Co., was distilled in nitrogen atmosphere. Tungsten hexachloride, ethylaluminum dichloride (25% in hexane or heptane), and triphenylphosphine were used as received without further purification. Tungsten hexachloride, when found contaminated with impurities (yellow-orange WO_2Cl_2 and $WOCl_4$), was purified by sublimation of the more volatile $WOCl_4$ and WO_2Cl_2 under nitrogen at about 200°.

Alkylation by 2-Pentene.—The alkylation reactions of benzene and toluene with 2-pentene (Table I, II) were carried out in flask (by the procedure employed in the alkylation of benzene with 1-dodecene) and in 4-oz screwcap bottles flushed with nitrogen and sealed with rubber and teflon gaskets. Injections of chemical reagents were done by means of hypodermic syringes from which air and moisture were carefully excluded. The WCl_6–$C_2H_5AlCl_2$ cocatalyst was preformed to give a cherry-red solution in benzene or toluene and 2-pentene was added to it. In some cases, a third component (ligand), triphenylphosphine or pyridine, was added to the preformed catalyst system before adding olefin. In *in situ* systems (Table III), the reagents WCl_6, ligand, and $C_2H_5AlCl_2$ were injected into a mixture of benzene and olefin. The reaction mixtures were distilled, where necessary, and analyzed by gas chromatography.

Alkylation by 1-Dodecene.—In a three-neck 250-cc flask equipped with a stirrer, thermometer, dropping funnel, condenser, and nitrogen inlet was placed the solution of 0.5 g of WCl_6 dissolved in 100 cc of dry benzene (1.25 mmol of WCl_6) and 2 cc of 1.55 *M* $C_2H_5AlCl_2$ in heptane (2.90 mmol of $C_2H_5AlCl_2$) in nitrogen atmosphere. To the resultant deep red-brown solution of the cocatalyst was added with stirring over a 20-min period, 38.0 g of 1-dodecene (226 mmol) at 40–45°. The reaction is exothermic and the temperature was maintained in the 40–45° region with ice–water bath. After the addition of 1-dodecene was completed, the reaction mixture was stirred for an additional 0.5 hr. After filtering the solid residue and removing heptane and benzene by distillation, the reaction mixture contained unreacted 1-dodecene, phenyldodecane isomers, and polyalkylated materials. The mixture containing these products then was analyzed by gas chromatography using mesitylene as an internal standard.

Two more alkylation reactions of benzene with 1-dodecene at 5–10 and 55–60° were also carried out employing the same molar quantities of each reagent as described above.

Vpc Analysis.—The analyses of alkylated products were done with an Aerograph and Hewlett-Packard F & M 700 thermal conductivity chromatographs using 20 ft × 0.25 in. SE-30 and 12 ft × 1/8 in. Apiezon L columns. The relative retention volumes of phenyldodecanes were determined using 3-phenyldodecane as the standard and were found to compare well with data reported in the literature[14] when recalculated using 3-phenyldodecane as the standard. The identity of the metathesized alkylated products of the 2-pentene reaction with benzene was determined by employing reagent grade 2-phenylbutane, 2- and 3-phenylpentanes, and 3-phenylhexane from Chemical Samples Co.

Infrared Spectra.—The infrared spectra on the alkylated products were carried out with a Perkin-Elmer 137 recording spectrophotometer using sodium chloride cells in a neat liquid phase. The assignment of bands for pentyltoluene isomers in 700–800-cm^{-1} region was done by using bands for isopropyltoluenes.[15]

	Para	Meta	Ortho
Isopropyltoluene	816, 721	783, 703	757, 727
Pentyltoluene	819 vs, 723 sh	787 m, 702 m	759 s, 730 ms

Registry No.—Tungsten hexachloride, 13283-01-7; ethylaluminum dichloride, 563-43-9; 2-pentene, 109-68-2; toluene, 108-88-3; benzene, 71-43-2; 1-dodecene, 112-41-4.

Acknowledgment.—The authors wish to thank The Goodyear Tire and Rubber Co. for granting the permission to publish this paper.

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(12) A. C. Olson, *Ind. Eng. Chem.*, **52**, 833 (1960).
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(14) J. M. Blackway and D. B. Thomas, *J. Chromatogr.*, **6**, 74 (1961).
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The Preparation and Reaction of *tert*-Butyl Trimethylsilyl Carbonate and Related Compounds[1]

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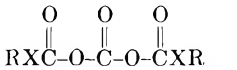
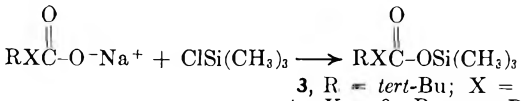
tert-Butyl trimethylsilyl carbonate (**4a**) and the thiol analog **3** have been prepared from the corresponding *tert*-butyl carbonate salts and chlorotrimethylsilane. Similar compounds were prepared with primary and secondary alkyl groups; the *n*-butyl compound proved to be too unstable to isolate, but the ethyl analog was obtained pure. The compounds **3** and **4** react with a variety of secondary and primary amines to form the silylcarbamates **5**. Action of butyl trimethylsilylcarbonate (**4a**) and acetyl chloride gives the *tert*-butyl acetic anhydride **7**, which was also prepared by the standard procedure. *tert*-Butyl ethyl dicarbonate was obtained by the action of ethyl chlorocarbonate on *tert*-butyl trimethylsilyl carbonate.

Recent work has shown that di-*tert*-butyl tricarbonates **1** and **2** can be readily prepared as crystalline compounds,[2-4] the kinetics and mechanisms of decomposition of these compounds have been examined,[4] and reactions of some nucleophiles with these tricarbonates have been studied.[5]



1, X = O; R = *tert*-Bu
2, X = S; R = *tert*-Bu

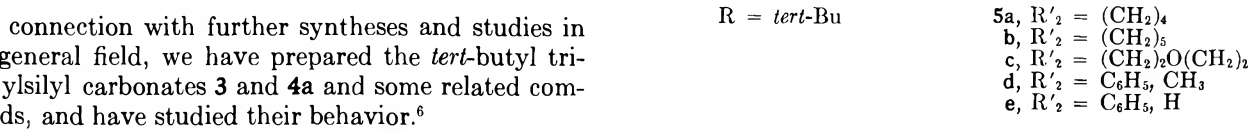
In connection with further syntheses and studies in this general field, we have prepared the *tert*-butyl trimethylsilyl carbonates **3** and **4a** and some related compounds, and have studied their behavior.[6]



3, R = *tert*-Bu; X = S
4a, X = O; R = *tert*-Bu
4b, X = O; R = *i*-Pr
4c, X = O; R = 2,4-dimethyl-3-pentyl
4d, X = O; R = *n*-Bu (unstable)
4e, X = O; R = Et

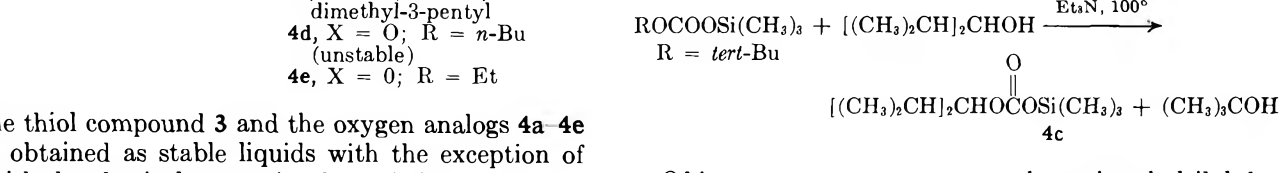
The thiol compound **3** and the oxygen analogs **4a**–**4e** were obtained as stable liquids with the exception of **4d**, with the physical properties shown in Table I.[7] Attempts to prepare the *n*-butyl analog led to CO_2 evolution below room temperature, and distillation yielded n-$C_4H_9OSi(CH_3)_3$, which was identical with a sample prepared from sodium *n*-butoxide and chlorotrimethylsilane. The formation and existence of the *n*-butyl analog at low temperatures is supported by two strong bands at 1760 and 1725 cm^{-1}, similar to those of the other compounds in Table I; these bands gradually disappeared at room temperature, and also when distillation was attempted at room temperature.

The *tert*-butyl compound **4a** reacted with a variety of secondary amines to form the silylcarbamates[8] indicated in Table II, and a similar reaction was given by the thiol compound **3**. The *i*-Pr compound **4b** and the

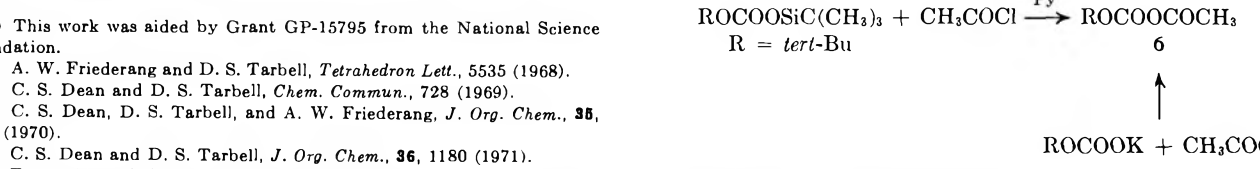


tert-Bu compound **4a** yielded **5e** with aniline, and the same compound was prepared from the thiol compound **3** (mixture melting point) The physical properties of the silylcarbamates are given in Table II.

An ester interchange took place as follows.



Of interest to us were reports that trimethylsilyl derivatives reacted with acyl halides.[9] We have prepared the mixed carboxylic carbonic anhydride **6** as below; the product was identical with that prepared by the usual method.



Treatment of *tert*-butyl trimethylsilyl carbonate with ethyl chlorocarbonate in the presence of a trace of pyridine yielded *tert*-butyl ethyl dicarbonate **7**, previously

(1) This work was aided by Grant GP-15795 from the National Science Foundation.

(2) A. W. Friederang and D. S. Tarbell, *Tetrahedron Lett.*, 5535 (1968).

(3) C. S. Dean and D. S. Tarbell, *Chem. Commun.*, 728 (1969).

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(6) For reviews of the use of silyl compounds as synthetic reagents, see among others (a) L. Birkofer and A. Ritter, *Angew. Chem.*, **77**, 414 (1965); (b) "Organosilicon Chemistry," IUPAC Symposium, Prague, 1965, particularly paper by R. C. Mehrotra, p 111 ff; (c) V. Bayant, V. Chvalvosky, and J. Rathovsky, "Organosilicon Compounds," Academic Press, New York, N. Y., 1965; (d) R. J. H. Voorhoeve, "Organohalosilanes; Precursors to Silicones," Elsevier, Amsterdam 1967; (e) L. F. Fieser and M. Fieser, "Reagents for Organic Syntheses," Vol. 2, Wiley, New York, N. Y., 1969, p 435 ff; (f) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966), and accompanying papers; (g) C. A. Buehler and D. E. Pearson, "Survey of Organic Syntheses," Wiley, New York, N. Y., passim; (h) Y. K. Yur'ev and Z. V. Belyakova, *Russ. Chem. Rev.*, 383 (1960); (i) J. F. Klebe, *Accounts Chem. Res.*, **3**, 299 (1970); G. Urry, *ibid.*, **3**, 306 (1970).

(7) Compounds of type $R_3MSCOOEt$, where M = Si, Ge, Sn, Pb, have been made from KSCOOEt + R_3MX by M. Schmidt, *et al.*, *J. Organometal. Chem.*, **17**, 277 (1969). The Si compound is very unstable.

(8) Several groups have prepared silylcarbamates by action of CO_2 or CS_2 as follows: $R_2NSi(CH_3)_3 + CO_2 \rightarrow R_2NCOOSi(CH_3)_3$ [G. Oertel, H. Malz, and H. Holtschmidt, *Chem. Ber.*, **97**, 891 (1964); R. H. Cragg and M. F. Lappert, *J. Chem. Soc., A*, 82 (1966); J. F. Klebe, J. B. Bush, Jr., and J. E. Lyons, *J. Amer. Chem. Soc.*, **86**, 4400 (1964), using phenyl isocyanate; S. S. Washburn and W. R. Peterson, Jr., *J. Organometal. Chem.*, **21**, 59 (1970)]; E. A. V. Ebsworth, *et al.*, *J. Chem. Soc. A*, 362 (1967); H. Breederveld, *Recl. Trav. Chim. Pays-Bas*, **81**, 276 (1962).

(9) F. H. Pinkerton and S. F. Thames, *J. Organometal. Chem.*, **24**, 623 (1970); L. Birkofer, A. Ritter, and P. Neuhausen, *Justus Liebigs Ann. Chem.*, **659**, 190 (1962).

Table I

Physical Properties of $RXCOOSi(CH_3)_2$

R	X	Bp, °C (mm)	Yield, %	Ir,[a] ν (C=O)	Nmr[b,c]
tert-Bu	O	71–72 (22)	60	1755, 1720	0.30 (9 H, s) 1.48 (9 H, s)
i-Pr	O	66–67 (28)	53	1760, 1720	0.31 (9 H, s) 1.08 (6 H, d, J = 6.5 Hz) 4.85 (1 H, quintet, J = 6.5 Hz)
2,4-Dimethyl-3-pentyl	O	59 (2)	39	1755, 1720	0.33 (9 H, s) 0.91 (12 H, d, J = 6.5 Hz) 1.6–2.2 (2 H, m) 4.36 (1 H, t, J = 6.5 Hz)
Et	O	42–43 (11)	62	1760, 1725	0.30 (9 H, s) 1.31 (3 H, t, J = 7 Hz) 4.16 (2 H, q, J = 7 Hz)
tert-Bu	S	47–49 (3.5)	47	1690	0.31 (9 H, s) 1.45 (9 H, s)

[a] In cm^{-1} in liquid film. [b] In parts per million from $(CH_3)_4Si$ in $CDCl_3$: s = singlet, d = doublet, t = triplet, q = quartet. [c] All compounds gave C and H analyses within 0.4% of the calculated values. The data were made available to the editors.

Table II

Physical Properties of Silylcarbamates[a]

R_2NCOOR' [R' = $Si(CH_3)_3$]

Compd[a]	Bp, °C (mm)	Yield, %	Ir, ν (C=O), in CCl_4
R_2 = $(CH_2)_4$	79–80 (6)	55	1680 (liquid film) 1680
R_2 = $(CH_2)_5$	64–65 (2)	70	1675 (liquid film)
R_2 = $(CH_2)_2O(CH_2)_2$	Mp 44–46	57	1670 (in $CHCl_3$)
R_2 = CH_3 and C_6H_5	70.5–72 (1)	77	1682
R_2 = H and C_6H_5	Mp 134–136	64	1720

[a] All compounds gave C and H analyses within 0.4% of the calculated values. The analytical data were made available to the editors.

obtained by action of ethanol on di-*tert*-butyl tricarbonate.[5]

$$(CH_3)_3COC(=O)-O-C(=O)OC_2H_5$$

7

Further investigations of carbonate syntheses *via* silicon-containing intermediates are under way.

Experimental Section[10]

***tert*-Butyl Trimethylsilylcarbonate (4a).**—Dry carbon dioxide was passed into a solution of 20 g of potassium *tert*-butoxide to 250 ml of THF at −10–0° over a period of 30 min with stirring, and 50 ml of THF was added to dilute the thick gel. To the mixture was added 20 g of chlorotrimethylsilane in 50 ml of THF over a period of 30 min. The thick gel changed to a white slurry. The mixture was stirred and chilled with ice-salt bath for an additional hour. The mixture was centrifuged to separate it into an organic layer and a semisolid material. The semisolid was washed with 100 ml of THF and centrifuged, and the organic layer was combined with the washing. Solvent was removed at ambient temperature under reduced pressure by an aspirator, and the residue was distilled and had the recorded boiling point (Table I).

Anal. Calcd for $C_8H_{18}O_3Si$: C, 50.49; H, 9.58; Si, 14.76. Found: C, 50.44; H, 9.37; Si, 14.57.

***tert*-Butylthiol trimethylsilylcarbonate (3)** was prepared by carbonation of sodium *tert*-butyl mercaptide[4] followed by treatment with chlorotrimethylsilane as described above.

Anal. Calcd for $C_8H_{18}O_2SSi$: C, 46.60; H, 8.73. Found: C, 46.82; H, 8.42.

(10) Analyses and instrumentation were as previously described.[4] Glass apparatus was dried under a nitrogen stream with a heating mantle, and THF was distilled from $LiAlH_4$ directly before use.

The other compounds in Table I were made by similar procedures and had similarly acceptable carbon and hydrogen analyses.

Trimethylsilyl 1-Pyrrolidinocarbamate (5a).—A solution of 3 g of *tert*-butyl trimethylsilyl carbonate (**4a**) and 1.1 g of pyrrolidine was refluxed in 15 ml of dry ether for 1 hr, the solvent was removed, and the product obtained by distillation had the properties given in Table II.

Anal. Calcd for $C_8H_{17}NO_2Si$: C, 51.83; H, 9.15. Found: C, 51.65; H, 9.19.

The other compounds in Table II were prepared similarly except that the solids were purified by crystallization.

The aniline derivative **5e** was prepared from both the *tert*-butyl and isopropyl compounds **4a** and **4b**.

***tert*-Butylcarbonic Acetic Anhydride (6).** **A.**—To a solution of 2.5 g of *tert*-butyl trimethylsilylcarbonate and 1.25 g of pyridine in 5 ml of THF was added dropwise 1.25 g of acetyl chloride in 45 ml of THF at room temperature with stirring over a period of 3.5 hr. The reaction mixture was evaporated under reduced pressure, pentane was added, the suspension was filtered, and the filtrate was evaporated under reduced pressure. Distillation of the residual liquid gave two fractions: (1) a mixture of *tert*-butyl trimethylsilyl carbonate and *tert*-butylcarbonic acetic anhydride (in an approximate ratio of 2:1), 0.3 g, bp 57–58° (9 mm); (2) *tert*-butylcarbonic acetic anhydride, **6**, 0.5 g (24%), bp 60–62° (9 mm).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.50; H, 7.50. Found: C, 52.55; H, 7.58.

The ir spectra in both liquid film and CCl_4 solution showed a broad carbonyl band at 1760–1830 cm^{-1} and the nmr ($CDCl_3$) showed two singlets at 1.55 (9 H) and 2.18 (3 H). These ir and nmr spectra were identical in all respects with those of an authentic sample, prepared as below.

B.—Potassium *tert*-butoxide (5.6 g) was carbonated in 100 ml of THF in an ice–salt bath in the usual way,[4] and 3.9 g of acetyl chloride in 10 ml of THF was added dropwise. The mixture yielded, after usual work-up, two centrifugations, and washings, 3.3 g (41%) of *tert*-butylcarbonic acetic anhydride (**6**), bp 63–64° (10 mm).

***tert*-Butyl Ethyl Dicarbonate (7).**—A mixture of 2.85 g of *tert*-butyl trimethylsilyl carbonate, 1.78 g of ethyl chlorocarbonate, and about 0.05 g of pyridine in 10 ml of $CHCl_3$ (alcohol free) was stirred for 30 min at room temperature. An additional 0.95 g of *tert*-butyl trimethylsilyl carbonate in 5 ml of $CHCl_3$ was added. Stirring was continued for 15 min. The reaction mixture was evaporated under aspirator pressure. The residue was washed with dry ether and the solid was filtered off. The ether layer was evaporated and the residue gave after distillation 0.65 g of *tert*-butyl ethyl dicarbonate, bp 38° (0.2 mm). The ir spectrum (liquid film) was identical in all respects with that of the authentic sample.[5]

***n*-Butyl trimethylsilylcarbonate** was found to liberate CO_2 even below room temperature, and was found in two runs to be much less stable than the corresponding ethyl compound **4e**. Distillation of the supposed *n*-butyl compound gave complete loss of

CO_2, forming the known *n*-butoxytrimethylsilane, whose boiling point and ir and nmr properties agreed completely with those of an authentic sample.[11]

(11) J. Fertig, W. Gerrard, and H. Herbst, *J. Chem. Soc.*, 1488 (1957).

Registry No.—**3**, 30882-86-1; **4a**, 30882-87-2; **4b**, 30882-88-3; **4c**, 30882-89-4; **4e**, 30882-90-7; **5a**, 30882-91-8; **5b**, 30882-92-9; **5c**, 30882-93-0; **5d**, 30882-94-1; **5e**, 30882-95-2; **6**, 30882-96-3.

Preparation, Characterization, and Photofragmentation of the Isomeric 1,4-Bis(2,3-diphenyloxiranyl)benzenes

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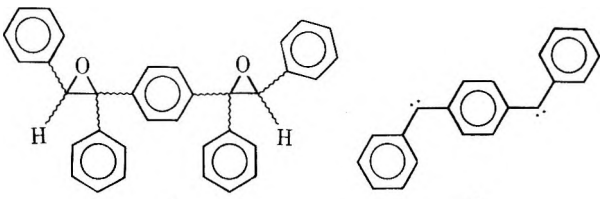
The preparation and separation of the three isomeric 1,4-bis(1,2-diphenylvinyl)benzenes and their epoxidation to give the six diastereoisomeric 1,4-bis(2,3-diphenyloxiranyl)benzenes are described. One of the dialkenes and the two bisoxiranes derived from it are unambiguously assigned cis–trans geometry on the basis of pmr data. Tentative structural assignments for the remaining cis–cis and trans–trans isomers in the alkene and oxirane series are made on the basis of the ultraviolet spectra of the respective dialkenes. The photofragmentation of the bisoxiranes in solution has been studied and the primary mode of cleavage determined.

Previous studies have demonstrated that aryl-substituted oxiranes fragment photochemically yielding aryl carbenes and carbonyl compounds.[2-6] Esr and optical spectral investigations have provided direct evidence for the formation of diphenylmethylene upon photofragmentation of tri- and tetraphenyloxirane.[7] More recently optical spectroscopic evidence for the formation of phenylmethylene upon photolysis of the isomeric 2,3-diphenyloxiranes also has been obtained.[6] In independent studies Trozzolo and coworkers have observed the esr spectra of two dicarbenes, namely *m*- and *p*-phenylenebis(phenylmethylene), upon irradiation of 1,3- and 1,4-bis(α-diazobenzyl)benzene, respectively, in rigid matrices.[8,9] The esr spectra of quintet *m*-phenylenebis(phenylmethylene) was independently reported by Itoh[10] who oriented the diazo precursor in a single crystal of benzophenone.

The observation that the unsymmetrical oxirane, triphenyloxirane, fragments preferentially (85%) to give diphenylmethylene and benzaldehyde[6] suggested that the isomeric 1,4-bis(2,3-diphenyloxiranyl)benzenes (**1**) would fragment in a similar manner and perhaps provide additional precursors for *p*-phenylenebis(phenylmethylene) (**2**), a transient of considerable theoretical as well as potential practical interest as a cross-linking agent for a broad variety of polymers having functionality known to react with carbenes. Observation of the dicarbene *per se* will undoubtedly require low temperature rigid matrices, a stepwise fragmentation of the bisoxiranes in solution being likely.



1 **2**

The bisoxiranes **1** in principle may exist in six diastereoisomeric forms and we were also interested in the possibility that the mode of fragmentation might vary as a function of the stereochemistry of the precursor. Therefore we have prepared, separated, and characterized the three isomeric 1,4-bis(1,2-diphenylvinyl)benzenes and the six diastereoisomeric 1,4-bis(2,3-diphenyloxiranyl)benzenes derived from them by peracid oxidation and studied the fragmentation pattern of the latter in methanol.

Results and Discussion

1,4-Bis(1,2-diphenylvinyl)benzenes.—A mixture of the three isomeric alkenes was prepared from *p*-dibenzoylbenzene *via* a Grignard addition–dehydration sequence previously described by Buu-Hoi and coworkers.[11] These authors report the preparation of "α"-distilbenzylbenzene, mp 74°, a substance characterized only by elemental analyses. No structural assignment or mention of the other potential isomers was made. Microscopic examination revealed that amorphous materials were obtained in our attempts to repeat the earlier work and to crystallize the product from ethanol as described. Neither heating under reflux in ethanol containing a trace of iodine nor in toluene containing *p*-toluenesulfonic acid converted the mixture to a single, stable isomer. One of the isomers, mp 172–174°, eventually crystallized from *n*-heptane

(1) (a) Taken from the dissertation submitted by N. R. B. in partial fulfillment of the Ph.D. requirements, Louisiana State University in New Orleans, New Orleans, La. (b) Author to whom inquiries regarding this communication should be directed, Louisiana State University in New Orleans. (c) One of the laboratories of the Southern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) H. Kristinnsson and G. W. Griffin, *Angew. Chem., Int. Ed. Engl.*, **4**, 868 (1965).

(3) H. Kristinnsson and G. W. Griffin, *J. Amer. Chem. Soc.*, **85**, 1579 (1966).

(4) H. Kristinnsson, *Tetrahedron Lett.*, 2343 (1966).

(5) P. C. Petrellis, H. Dietrich, E. Meyer, and G. W. Griffin, *J. Amer. Chem. Soc.*, **89**, 1967 (1967).

(6) R. S. Becker, R. O. Bost, J. Kole, N. R. Bertoniere, R. L. Smith, and G. W. Griffin, *ibid.*, **92**, 1302 (1970).

(7) A. M. Trozzolo, W. A. Yager, G. W. Griffin, H. Kristinnsson, and I. Sarkar, *ibid.*, **89**, 3357 (1967).

(8) A. M. Trozzolo, R. W. Murray, G. Smolinsky, W. A. Yager, and E. Wasserman, *ibid.*, **85**, 2526 (1963).

(9) E. Wasserman, R. W. Murray, W. A. Yager, A. M. Trozzolo, and G. Smolinsky, *ibid.*, **89**, 5076 (1967).

(10) K. Itoh, *Chem. Phys. Lett.*, **1**, 235 (1967).

(11) N. P. Buu-Hoi, T. B. Loo, and N. D. Xuong, *J. Chem. Soc.*, 3964 (1957).

after preliminary purification of the crude reaction mixture by passage through an acidic alumina column with benzene as the eluent. The other two isomers, mp 145–146 and 109–110°, then deposited in succession in crystalline form from the solution. After the initial crystallizations subsequent batches of solid deposited as mixtures which we found necessary to separate by fractional crystallization from 2-propanol and/or diethyl ether (more an art than a science). In our experience *n*-heptane remains the only solvent discovered from which a freshly prepared mixture would crystallize. Repeated attempts to separate these isomers using glc, tlc, and column chromatography proved unsuccessful.

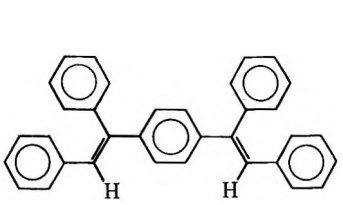
The gross structural features of the 1,4-bis(1,2-diphenylvinyl)benzenes were confirmed by the following data. (a) The mass spectra of all three isomers exhibit the expected parent peak at *m/e* 434 and the combustion analytical data are consistent with the proposed structures. (b) Significant absorption bands at 3050 cm^{-1} with a weak shoulder at 2900 cm^{-1} are apparent and are compatible with a phenyl-substituted ethylenic structure. (c) The pmr spectra of these dienes confirm the presence of 2 vinyl and 24 aromatic protons, although in one case (for example, the cis–trans[12] isomer **4**) one of the vinyl protons is obscured by the aromatic multiplet. The pmr data for the isomeric 1,4-bis(1,2-diphenylvinyl)benzenes are summarized in Table I. While chemical and spectroscopic data con-

Table I

Pmr Data for the Isomeric 1,4-Bis(1,2-diphenylvinyl)benzenes

Mp of isomer, °C	Vinyl protons, τ	Aromatic protons (major peaks), τ
172–174	2.95 (2 H)	2.88, 2.67 (24 H)
109–110	?, 3.02 (1 H)	2.94, 2.90, 2.87, 2.78, 2.74, 2.68 (25 H)
145–146	2.95 (2 H)	2.96, 2.77, 2.69 (24 H)

firm the gross structural features of **3**, **4**, and **5**, no distinction between the cis–cis and trans–trans isomers **3** and **5**, respectively, could be made by pmr spec-



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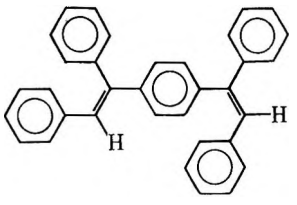

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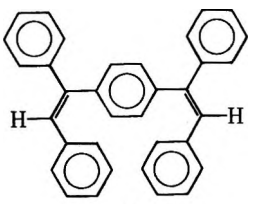
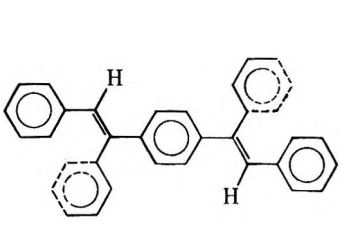


5

troscopy since the vinyl protons in each isomer are equivalent. The fortuitous overlap of the aromatic protons of **4** with one of the nonequivalent vinyl protons renders the assignment of structure solely by pmr tenuous even in this case. That the 1,4-bis(1,2-diphenylvinyl)benzene isomer melting at 109–110° does indeed possess the cis–trans geometry is apparent from the pmr spectra of the pair of bisoxiranes derived from **4** which also exhibit two singlet signals for the oxiranyl hydrogens (*vide infra*).

The ultraviolet absorption spectral data for the three isomeric 1,4-bis(1,2-diphenylvinyl)benzenes proved useful and are summarized in Chart I along with data for several related systems. The structural feature of primary significance in determining the position of the long wavelength band in the ultraviolet spectra of these systems is the extent of coplanarity which may be achieved along the linear molecular skeleton. Structural features, such as cis double bonds and branching phenyl groups, which cause deviations from planarity result in the expected hypsochromic shifts.[13] The absorption at longer wavelengths observed in the 1,4-bis(2-phenylvinyl)benzenes (*p*-distyrylbenzenes) relative to the 1,4-bis(1,2-diphenylvinyl)benzene system is therefore expected. *A priori* one would predict that, in either series, the isomer with the longest trans linear backbone should absorb at the longest wavelength.

A study of molecular models reveals that a completely planar conformation is not possible in the case of the three isomeric 1,4-bis(1,2-diphenylvinyl)benzenes. However, it is apparent that maximum conjugation and thus minimum steric interaction is achieved in the case of the cis–cis isomer if the 1- and 1′-phenyl substituents are rotated perpendicular to the plane of the *trans,trans*-1,4-bis(2-phenylvinyl)benzene chromophore present in conformer **6**. The corresponding conformation **7** for the trans–trans isomer is inaccessible because of the interference encountered between the ortho hydrogens of the cis coplanar phenyl groups. A more stable conformation **8** for this isomer possesses two planar trans stilbene-like structures rotated slightly with respect to the phenylene group in such a manner that the adverse steric interactions existing in **7** are reduced at the expense of coplanarity.



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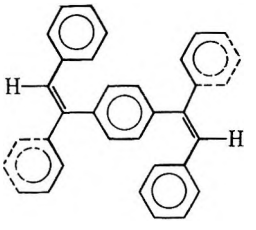

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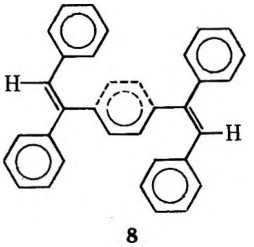


8

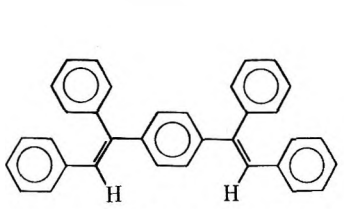
On the basis of these considerations the following structural assignments are proposed. That isomer melting at 172–174° (λ_{max} 333 nm) is assigned structure **3** while that isomer of melting point 145–146° (λ_{max}

(12) This and subsequent designations of this type refer to the relationship of the monosubstituted phenyl groups to each other in the respective stilbenyl substituents.

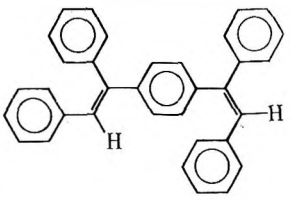
(13) R. N. Jones, *J. Amer. Chem. Soc.*, **65**, 1818 (1943).

CHART I

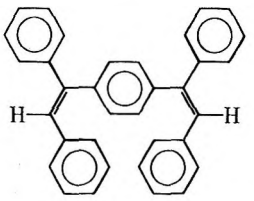
ULTRAVIOLET ABSORPTION MAXIMA OF THE ISOMERIC 1,4-BIS(1,2-DIPHENYLVINYL)BENZENES AND RELATED SYSTEMS



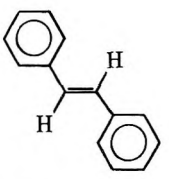
mp 172–174°: λ_{max} 333 nm (ϵ 35,500) (benzene)



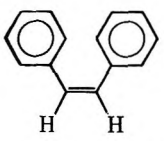
mp 109–110°; λ_{max} 330 nm (ϵ 24,000) 301 (33,000) (hexane)



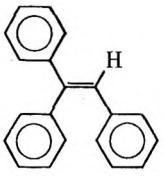
mp 145–146°; λ_{max} 295 nm (ϵ 36,000) (hexane)



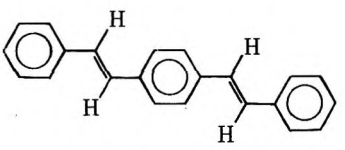
λ_{max} 295 nm (ϵ 27,000)[a]



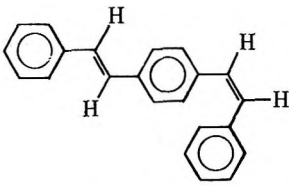
λ_{max} 280 nm (ϵ 10,450)[a]



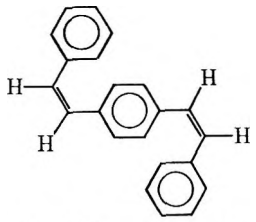
λ_{max} 299 nm (ϵ 18,200)[c]



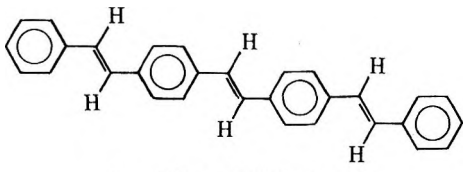
λ_{max} 350 nm (ϵ 57,000)[a]



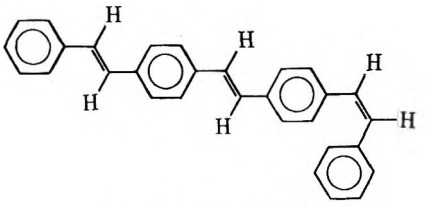
λ_{max} 331 nm (ϵ 36,500)[d]



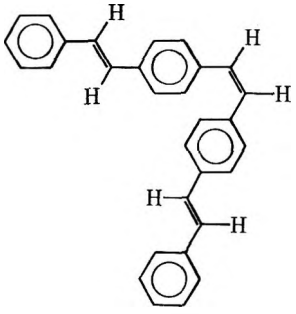
λ_{max} 314 nm (ϵ 17,700)[a]



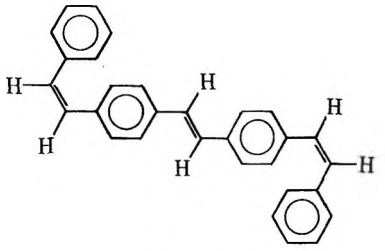
λ_{max} 384 nm (ϵ 89,300)[a]



λ_{max} 372 nm (ϵ 68,100)[a]



λ_{max} 316 nm (ϵ 52,100), 353 (41,000)[a]



λ_{max} 359 nm (ϵ 48,800)[a]

[a] S. Misumi, M. Kuwana, and M. Nakagawa, *Bull. Chem. Soc. Jap.*, **35**, 143 (1962). [b] R. N. Beal and E. M. F. Roe, *J. Chem. Soc.*, 2755 (1953). [c] H. Suzuki, *Bull. Chem. Soc. Jap.*, **33**, 389 (1960). [d] S. Misumi, M. Kuwana, K. Murashima, and M. Nakagawa, *ibid.*, **34**, 1833 (1961).

295 nm; approximately the same wavelength as triphenylethylene but with twice the molar extinction coefficient) is assigned the trans–trans structure **5**.

1,4-Bis(2,3-diphenyloxiranyl)benzenes.—The bisoxiranes (Chart II) were prepared from the three isomeric 1,4-bis(1,2-diphenylvinyl)benzenes by epoxidation with *m*-chloroperoxybenzoic acid.[14] The literature confirms that such oxidations invariably result in stereospecific cis addition to the olefin.[15] Epoxidation of the 1,4-bis(1,2-diphenylvinyl)benzenes **3**, **4**, and **5**, however, may give rise to two isomeric bisoxiranes since attack at the two vulnerable sites may occur on the same or alternate sides of the molecule. The symmetrical diolefins **3** and **5** each may give rise to a *dl* and *meso* mixture of bisoxiranes, whereas in the unsymmetrical case of **4** two *dl* pairs may in principle be formed.

(14) N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).

(15) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 112.

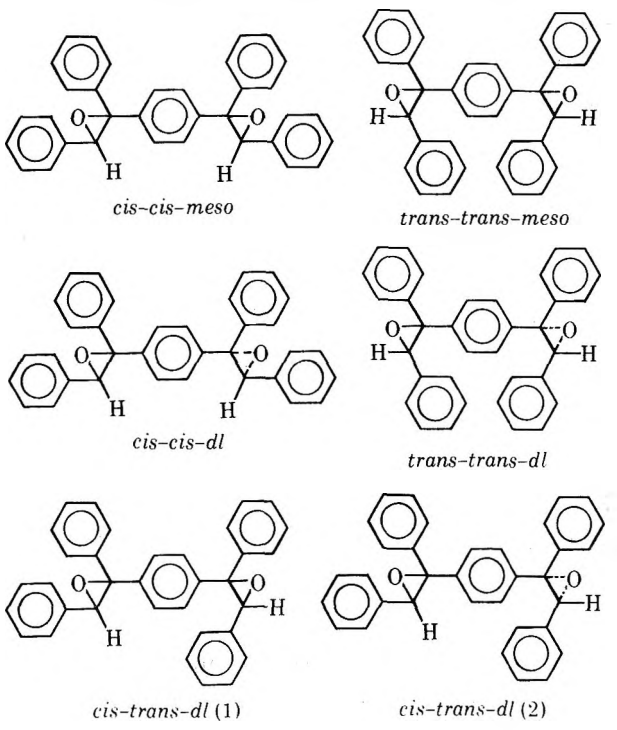
As expected, a total of six bisepoxy derivatives were obtained—two from each bisalkene—and their melting points are tabulated along with the data for the precursors.

	Cis–cis	Cis–trans	Trans–trans
Alkenes	172–174°	109–110°	145–146°
	(**3**)	(**4**)	(**5**)
Oxiranes	258–260°	189–190°	150–152°
	(**9**)	(**11**)	(**13**)
	200–206°	149–151°	111–113°
	(**10**)	(**12**)	(**14**)

The separation of the oxiranes **9** and **10** obtained from the common precursor **3** was achieved by taking advantage of their relative solubilities in chloroform. The residue **9** remaining after extraction of the more soluble isomer **10** was recrystallized by dissolution in boiling chloroform and subsequently adding methanol. Final purification of **10** may be accomplished by recrystallization from 2-propanol. The mixture of **11** and **12** obtained from **4** was separated by fractional

Chart II

Diastereoisomers of 1,4-Bis(2,3-diphenyloxiranyl)benzene



crystallization from 2-propanol. The mixture of **13** and **14** obtained upon oxidation of **5** was dissolved in boiling 2-propanol. After collection of **13** the solvent was removed and the residue dissolved in methanol from which **14** crystallized.

The wavelength of the bands in the ultraviolet spectra of the bisoxiranes vary with skeletal geometry; however, they are essentially identical for pairs derived from common precursors. The extinction coefficients of all six isomers are essentially the same at the wavelength of maximum absorption but differ markedly at 2537 Å, the accessible wavelength required to effect fragmentation (Table II).

Table II

Ultraviolet Absorption Maxima of the Diastereoisomeric 1,4-Bis(2,3-diphenyloxiranyl)benzenes

Isomer	Skeletal geometry	λ_{max}, nm	ϵ at λ_{max}, ϵ	ϵ at 253.7 nm	Solvent
9	Cis–cis[a]	241	39,500	21,600	Heptane–THF
10	Cis–cis	241	44,600	23,500	Heptane
11	Cis–trans	231	39,200	5,600	Heptane
12	Cis–trans	231	43,600	6,200	Heptane
13	Trans–trans[a]	225	42,000	2,600	Heptane
14	Trans–trans	225	43,700	2,500	Heptane

[a] Suggested by the ultraviolet spectra of the parent diolefins.

The pmr spectra of the isomeric bisoxiranes **9**–**14** are consistent with the proposed 1,4-bis(2,3-diphenyloxiranyl)benzene structures. Complex multiplet signals due to the aromatic protons are apparent in the pmr spectra and also are characteristic for isomer pairs derived from common precursors. In fact, the overall spectra of the bisoxiranes derived from each isomer of 1,4-bis(1,2-diphenylvinyl)benzene are strikingly similar. As indicated earlier the presence of two oxiranyl singlet signals in the spectra of **11** and **12** demonstrates that these bisoxiranes, and therefore the parent 1,4-bis(1,2-diphenylvinyl)benzene (mp 109–110°), have cis–trans geometry. The pmr spectra of **9** and **10** as well as **13** and **14** are not helpful in distinguishing between the cis–cis and trans–trans precursors **3** and **5** or between *dl* and *meso* bisoxiranes because of the symmetry and resulting magnetic equivalency of the pertinent protons. The pmr spectral data are summarized in Table III.

Table III

Pmr Data for the Six Diastereoisomers of 1,4-Bis(2,3-diphenyloxiranyl)benzene

Isomer	Oxirane protons, τ	Aromatic protons (major peaks), τ
9	5.71 (2 H)	2.91, 2.89, 2.82, 2.67 (24 H)
10	5.65 (2 H)	2.88, 2.83, 2.76, 2.60 (24 H)
11	5.74 (1 H) 5.67 (1 H)	2.90, 2.83, 2.80, 2.66 (24 H)
12	5.75 (1 H) 5.68 (1 H)	2.92, 2.83, 2.80, 2.67 (24 H)
13	5.67 (2 H)	2.91, 2.68 (24 H)
14	5.73 (2 H)	2.94, 2.71 (24 H)

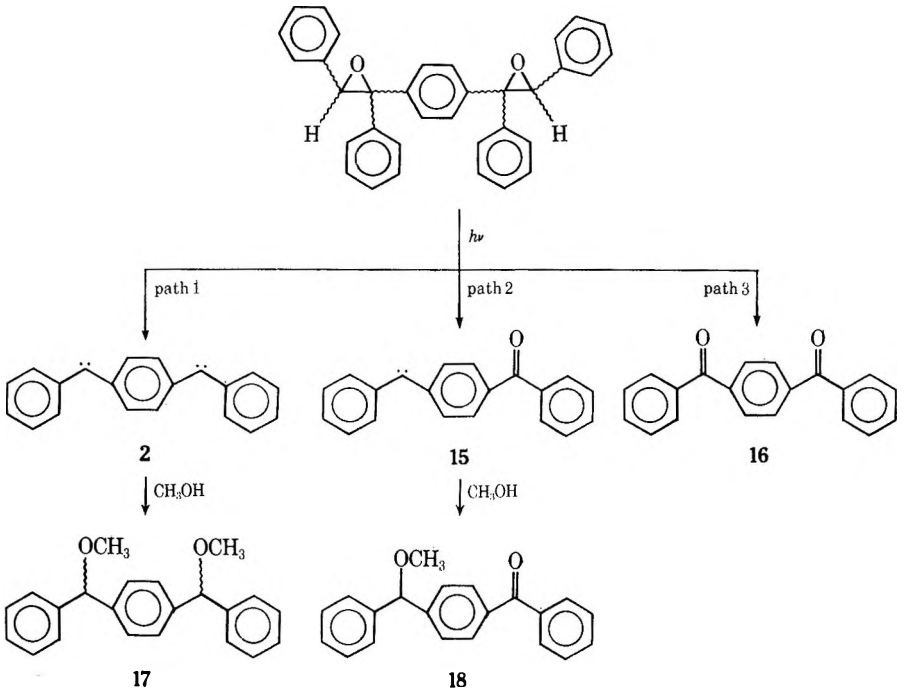
The existence of polymorphic pairs appears unlikely because repeated recrystallization of the individual bisoxiranes from a variety of solvents produces no change in the melting points.[16]

Photofragmentation in Methanol.—Theoretically three fragmentation patterns are possible for the 1,4-bis(2,3-diphenyloxiranyl)benzenes as shown in eq 1. In order to determine the extent to which each of the reaction paths is followed, methanol solutions of each of the six isomeric 1,4-bis(2,3-diphenyloxiranyl)benzenes were irradiated with 2537-Å light, the carbenes being trapped as their methyl ethers.[17] Thus *p*-phenylenebis(phenylmethylene) (**2**) is trapped as 1,4-bis(α-methoxybenzyl)benzene (**17**) and 1-benzoyl-4-(phenylmethylene)benzene (**15**) as 1-benzoyl-4-(α-methoxybenzyl)benzene (**18**). The extent to which paths 1, 2, and 3 were followed was ascertained by determining the relative amounts of the high-molecular-weight fragments **17**, **18**, and **16** formed upon irradiation. Conclusions drawn from the low-molecular-weight fragments, benzyl methyl ether (from phenylcarbene) and benzaldehyde, would be ambiguous as both are formed by more than one pathway.

An irradiation period of 3 min (low conversion) was used as both 1-benzoyl-4-(α-methoxybenzyl)benzene and *p*-dibenzoylbenzene are photolabile. Their destruction, however, is only detectable if the irradiation period exceeds 5 min. *p*-Dibenzoylbenzene was not detected and experiments in which it was added to the

(16) A close similarity of the pmr, ir, and uv spectra of pairs of bisoxiranes from common precursors was also observed with the related 1,4-bis(3-phenyl-2-oxiranyl)benzene system. That the suspected compounds are indeed diastereoisomers was demonstrated by determining the pmr spectra of the two *trans,trans*-1,4-bis(3-phenyl-2-oxiranyl)benzenes obtained from *trans,trans*-*p*-distyrylbenzene in deuteriochloroform containing tris(dipivalomethanato)europium(III), the "shift reagent" reported recently [C. C. Hinkley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969)]. In both cases substantial downfield shifts in the resonance peaks are observed and the aromatic signals, which are normally broad singlets, are split into complex multiplets. Distinct oxiranyl and aromatic signals in the pmr spectrum of a mixture of the europium complexes of the two compounds demonstrate that they are not polymorphic modifications of a single isomer.

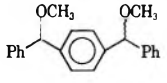
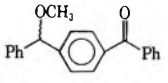
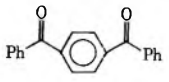
(17) W. Kirmse, L. Horner, and H. Hoffman, *Justus Liebigs Ann. Chem.*, **614**, 19 (1958).



(1)

irradiated solutions indicated that it could be detected in quantities representing only 2% of the total area. Although 1,4-bis(α-methoxybenzyl)benzene exists in two diastereoisomeric forms, their separation could not be effected *via* glc and therefore *dl*/*meso* ratios could not be determined. The results are given in Table IV.

TABLE IV
RELATIVE DIRECTIONS OF PHOTOFRAGMENTATION OF THE SIX DIASTEREOISOMERIC 1,4-BIS(2,3-DIPHENYLOXIRANYL)BENZENES IN METHANOL

Isomer	 %	 %	 %
9	74	26	—
10	75	25	—
11	73	27	—
12	74	26	—
13	70	30	—
14	69	31	—

The geometry of the bisoxirane precursor had little effect on the relative direction of fragmentation.

Triphenyloxirane has been shown to fragment preferentially (85%) to give diphenylcarbene.[6] Thus, on a statistical basis one would predict probabilities for paths 1, 2, and 3 of 72, 26, and 2% assuming that the oxirane rings react independently of each other. This is very close to what is actually observed (Table IV). Thus, it seems unlikely that a dicarbene, *per se*, ever actually existed in solution but that the oxirane rings fragmented in sequence, the second not reacting until the first had been converted to the methyl ether. This does not, however, exclude the possibility that the dicarbene can exist in an unreactive rigid matrix at −196° where bimolecular reactions are excluded. The methanol trapping data indicate that it is highly probable that the dicarbene would be formed upon irradiation of the bisoxiranes in rigid matrices provided the lifetime of the initially formed carbene is sufficiently long.

Experimental Section

General.—Melting points were determined on a Thomas-Hoover capillary melting point apparatus[18] and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 137 and 337 spectrophotometers. The ultraviolet absorption spectra were run on a Beckman DB spectrophotometer. The pmr spectra were taken on a Varian A-60 nmr spectrometer using $CDCl_3$ as the solvent with tetramethylsilane as an internal standard unless otherwise specified. The mass spectra were determined on a Perkin-Elmer MS 270. An F & M model dual column programmed temperature gas chromatograph equipped with a 3-ft OV-1 (3% on Chromsorb G HP) column was used for glc determinations. The instrument was operated isothermally at 220°. Silica gel G layers on glass plates were used in thin layer chromatographic separations. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Photofragmentation in Methanol.—Methanol solutions ($1\text{–}6 \times 10^{-3}$ *M*) of the six 1,4-bis(2,3-diphenyloxiranyl)benzenes were irradiated for 3 min in a Rayonet photochemical reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) equipped with sixteen 2537-Å lamps. The product distribution was calculated from glc peak areas (measured on a Du Pont 310 curve resolver) which were corrected for detector response [1,4-bis(α-methoxybenzyl)benzene–1-benzoyl-4-(α-methoxybenzyl)benzene–*p*-dibenzoylbenzene, 1:0.813:0.704, w:w:w].

Preparation of the Isomeric 1,4-Bis(1,2-diphenylvinyl)benzenes (3–5).—A mixture of the three isomers was prepared in 96% yield employing the procedure described by Buu-Hoi[11] with the exception that tetrahydrofuran rather than diethyl ether was used as the solvent for *p*-dibenzoylbenzene. The resulting oily mixture was decolorized by passage through three acidic alumina columns with benzene as the solvent. Approximately 60% of the clear residue obtained after removal of the benzene under vacuum was crystallized from *n*-heptane upon standing over a 3-week period. The three individual isomers were then separated by fractional crystallization from 2-propanol. Frequently a virtually inseparable mixture, mp 122–132°, of the two higher melting isomers was obtained. It was found that separation could usually be achieved with difficulty if the recrystallizing solvent was changed to diethyl ether. The three isomers thus obtained were *cis*,*cis*-**3**, mp 172–174° (*Anal.* Calcd for $C_{34}H_{26}$: C, 93.97; H, 6.03. Found: C, 94.07; H, 6.09); *cis*,*trans*-**4**, mp 109–110° (Found: C, 93.88; H, 5.98); *trans*,*trans*-**5**, mp 145–146° (Found: C, 93.84; H, 6.13).

Preparation of the Isomeric 1,4-Bis(2,3-diphenyloxiranyl)benzenes (9–14).—In a typical experiment 0.43 g (1.0 mmol) of the

(18) Use of a company or product name by the Department does not imply approval or recommendation of the product to the exclusion of others which may also be suitable.

1,4-bis(1,2-diphenylvinyl)benzene was dissolved in approximately 15 ml of chloroform and 0.45 g (2.2 mmol) of solid *m*-chloroperoxybenzoic acid (85%) (Aldrich Chemical Co., Milwaukee, Wis.) added slowly with stirring. The reaction mixture was then stirred at room temperature overnight. The progress of the reaction was followed by tlc [R_f 0.6 (diolefin), 0.42 (monoepoxides), and 0.26 (bisepoxides)] using silica gel G plates which were developed with benzene–Skelly B (1:1, v/v). Spots were located by spraying with 5% sulfuric acid in ethanol followed by charring. After the reaction was complete (~20 hr) the excess peracid was destroyed by the addition of a sodium sulfite solution, the reaction mixture washed with aqueous sodium bicarbonate (10%), the organic phase separated and dried over anhydrous sodium sulfate, and the volatile solvent removed under vacuum. The residue (0.45 g, 97%) was further purified by thick layer chromatography on 1-mm silica gel G plates. Pairs of isomers were separated by fractional crystallization as already described. The isomers thus obtained were **9**, mp 258–260° (*Anal.* Calcd for $C_{34}H_{26}O_2$: C, 87.52; H, 5.62. Found: C, 87.22; H, 5.62); **10**, mp 200–206° (Found: C, 87.21; H, 5.58); **11**, mp 189–191° (Found: C, 87.65; H, 5.58); **12**, mp 149–151° (Found: C, 87.61; H, 5.66); **13**, mp 150–152° (Found: C, 87.44; H, 5.44); **14**, mp 111–113° (Found: C, 87.26; H, 5.76).

Preparation of 1-Benzoyl-4-(α-hydroxybenzyl)benzene.—To 5 g (17.5 mmol) of *p*-dibenzoylbenzene in tetrahydrofuran was added 0.5 g of sodium borohydride (Alfa Inorganics, Beverly, Mass.). The mixture was stirred at room temperature for 4 hr after which the excess $NaBH_4$ was destroyed by the slow addition of a 5% solution of sulfuric acid. The products were extracted with chloroform, the organic phase was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. The desired product was separated from the totally reduced 1,4-bis(α-hydroxybenzyl)benzene and the unreacted *p*-dibenzoylbenzene on 1-mm silica gel G plates which were developed with benzene–methanol (9:1, v/v) [R_f 1.0 (*p*-dibenzoylbenzene), 0.43 (1-benzoyl-4-(α-hydroxybenzyl)benzene), and 0.29 (1,4-bis(α-hydroxybenzyl)benzene)]. The residue (0.25 g, 50%) was recrystallized from benzene–hexane to give pure 1-benzoyl-4-(α-hydroxybenzyl)benzene: mp 93–95°; infrared (KBr) 1600 (C=O), 3500 cm^{-1} (OH); pmr τ ~2.2 (m, 14, aromatic), 4.0 (s, 1, methine), 6.7 (s, 1, hydroxyl).

Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.30; H, 5.60. Found: C, 83.36, H, 5.60.

Preparation of 1-Benzoyl-4-(α-methoxybenzyl)benzene (18).—The ether was prepared from 1-benzoyl-4-(α-hydroxybenzyl)-benzene according to the procedure described by Gillis.[19] To 3.4 g (12 mmol) of 1-benzoyl-4-(α-hydroxybenzyl)benzene in approximately 50 ml of dimethyl sulfoxide was added 4 g of powdered sodium hydroxide and 8.5 g (60 mmol) of methyl iodide. The mixture was stirred at room temperature overnight. The reaction mixture was then poured into water, the product extracted with chloroform, the organic phase washed with water, dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residue (3.7 g, 100%) was further purified by passage through a neutral alumina column using benzene as the solvent. The residue after the benzene had been removed under vacuum crystallized slowly upon standing at ~5°. Recrystallization from methanol at ~5° gave pure 1-benzoyl-4-(α-methoxybenzyl)benzene: mp 46–48°; infrared 1620 cm^{-1} (C=O); pmr τ ~2.2 (m, 14, aromatic), 4.52 (s, 1, methine), 6.5 (s, 3, methoxyl).

Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.50; H, 6.01. Found: C, 83.27; H, 5.86.

Preparation of 1,4-Bis(α-hydroxybenzyl)benzene.—*p*-Dibenzoylbenzene (11.4 g, 4 mmol) in approximately 300 ml of tetrahydrofuran was added slowly to a stirred suspension of 2 g of lithium aluminum hydride (Alfa Inorganics, Beverly, Mass.) in 100 ml of tetrahydrofuran. The reaction mixture was refluxed for 1 hr. The excess $LiAlH_4$ was then destroyed by cautiously adding 30 ml of water in 100 ml of tetrahydrofuran. The reaction mixture was poured into 1 l. of cold 10% sulfuric acid and stirred 30 min. The product was extracted with chloroform, the organic phase washed with water and 10% sodium bicarbonate solution and dried over anhydrous sodium sulfate, and the solvent removed under vacuum. The crystalline residue (11.2 g, 97%) was dissolved in ethanol from which the two diastereoisomers were obtained by fractional crystallization. Two isomers were thus obtained (A and B).

A: mp 170–172°; infrared (KBr) 3250 cm^{-1} (OH); pmr (acetone-d_6, 45°) τ 2.68 (s, 14, aromatic), 4.20 (d, 2, methine), 5.88 (d, 2, hydroxyl).

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.32; H, 6.25.

B: mp 141–143°; infrared (KBr) 3300 cm^{-1} (OH); pmr (acetone-d_6, 25°) τ 2.69 (s, 14, aromatic), 4.25 (d, 2, methine), 5.40 (d, 2, hydroxyl).

Anal. Found: C, 82.67; H, 6.25.

Preparation of 1,4-Bis(α-methoxybenzyl)benzenes (17).—The methylation technique described by Gillis[19] was applied individually to the two isomers of 1,4-bis(α-hydroxybenzyl)-benzene. To 4.5 g of powdered sodium hydroxide in approximately 65 ml of dimethyl sulfoxide was added 3.6 g (12.4 mmol) of the diol and then 45 g (317 mmol) of methyl iodide. The mixture was stirred at room temperature for 1 hr. It was then poured into water, the product extracted with chloroform, the organic phase washed with water and dried over anhydrous sodium sulfate, and the solvent removed under vacuum. The 4-g residue (~100%) crystallized on standing overnight. Recrystallization from 2-propanol yielded two diols (C and D).

C from A, mp 170–172°: mp 98–100°; pmr τ 3.7 (s, 14, aromatic), 4.78 (s, 2, methine), 6.66 (s, 6, methoxyl).

Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.98; H, 6.97. Found: C, 82.83; H, 6.93.

D from B, mp 141–143°: mp 65–67°; pmr τ 2.7 (s, 14, aromatic), 4.78 (s, 2, methine), 6.66 (s, 6, methoxyl).

Anal. Found: C, 82.83; H, 7.02.

Registry No.—**3**, 31020-17-4; **4**, 31020-18-5; **5**, 31024-80-3; **9**, 31024-81-4; **10**, 31024-82-5; **11**, 31024-83-6; **12**, 31024-84-7; **13**, 31024-85-8; **14**, 31024-86-9; (±)-**17**, 31024-87-0; *meso*-**17**, 31024-88-1; **18**, 31020-19-6; 1-benzoyl-4-(α-hydroxybenzyl)benzene, 31020-20-9; (±)-1,4-bis(α-hydroxybenzyl)benzene, 31024-89-2; *meso*-1,4-bis(α-hydroxybenzyl)benzene, 31024-90-5.

(19) R. G. Gillis, *Tetrahedron Lett.*, 1413 (1968).

Photochemical Synthesis of 1,2-Diazepines. V.[1] Synthesis and Rearrangements of 1,2-Diazepines

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A large-scale synthesis of 1-isopropoxycarbonyl-1,2-diazepine (**17**) was performed using a thin film ultraviolet reactor. 1,5-Disubstituted diazepines **10** and **12** and 1,3,7-trisubstituted 1,2-diazepine **14** have been prepared. Iron tricarbonyl complexes could be obtained only with diazepines which are unsubstituted on the butadiene moiety. Photosensitization of a 1-iminopyridinium ylide of type **1**, using triplet sensitizers, dramatically increased the photolytic N–N bond cleavage, a process which is in competition with the photoisomerization to 1,2-diazepines. A singlet excited state is postulated for the formation of 1,2-diazepines of type **3**. Base-induced ring opening of diazepine **17** led to the cis–cis dienaminonitrile **18** in good yield, whereas its pyrolysis led only to trace amounts of the isomeric dienaminonitriles **19** and **20**. Thermal rearrangement of **17** in *o*-xylene and in acetic acid solution gave 2-isopropoxycarbonylaminopyridine (**21**) and 1-isopropoxycarbonyliminopyridinium ylide (**15**), respectively, and suggests the existence of an equilibrium between diazepine **17** and its valence tautomer **16**. 2,3-Diaza-2-isopropoxycarbonyl[3.2.0]bicyloheptadiene (**22**) was obtained by a photoinduced disrotatory electrocyclic reaction of diazepine **17**.

1,2-Diazepines **3** can be obtained photochemically from 1-iminopyridinium ylides **1** on a preparative scale.[2–5] Several authors have postulated the heteroatomic norcaradienes, 1,7-diaza[4.1.0]bicycloheptadienes (**2**), as intermediates during these photoinduced rearrangements.

According to orbital symmetry conservation rules, 4-π-electron 1,3 dipoles of type A should undergo both thermal and photochemical intramolecular ring closure to the corresponding three-membered ring isomers of type B (see Scheme I). It can be seen that there are two possible modes for both ring closure and ring opening. Since thermodynamic parameters play no role in the Hoffmann–Woodward rules,[6] the direction of the equilibrium cannot be predicted by orbital symmetry considerations. The following examples serve to illustrate this point. Type I: Huisgen[7] showed that the aziridine **4** is much more stable than its isomeric azomethine ylide **5** which can only be formed and trapped when **4** is being heated above 100°. Type II: On the other hand, the dipolar nitrones **6** are much more stable than their isomeric oxaziridine counterparts **7**; thermally it is therefore impossible to ring close nitrones **6** into oxaziridines **7**; only the photoinduced ring closure operates, a reaction which has been discovered by Calvin.[8]

Greene[9] has given a brief account of the relative stability of 1,3-dipolar systems and of their three-membered carbon-, nitrogen-, and oxygen-containing analogs. 1-Iminopyridinium ylides **1**, being aromatic 1,3 dipoles,[10] belong to type II since their photoisomers **2** have no aromatic character and are thermally less stable compounds (*vide infra*). As a matter of fact, refluxing 1-iminopyridinium ylides **1** in solvents of any kind does not lead to the diazepines **3**.

We describe in this paper the synthesis of several 1,2-diazepines as well as a procedure for a large-scale synthesis of such a diazepine. Thermally and photochemically induced, as well as base-catalyzed, rearrangements of 1,2-diazepines reflect the peculiar reactivity of their seven-membered ring.

Synthesis of 1,2-Diazepines.—Although quite a few ring-substituted 1-iminopyridinium ylides have been investigated by Sasaki[3] and by Snieckus[4] since our original findings,[2] it seemed worthwhile to investigate the effect of the nature of the substituent in position 4 upon the photochemical reactivity of the corresponding pyridinium ylide. Unfortunately, the majority of C-4 substituted pyridines do not give the corresponding 1-iminopyridinium ylides. The 4-(4′-chloro)benzoyl-1-carbethoxyiminopyridinium ylide **8** does not lead to the corresponding 1,2-diazepine; instead, one gets photolytic cleavage of the N–N bond. 4-Methyl- and 4-phenylcarbethoxyiminopyridinium ylides **9** and **11** rearrange photochemically in good yields to the corresponding diazepines **10** and **12**; compound **10** has already been synthesized by Sasaki[3b] and by Snieckus.[4b] The iron tricarbonyl complexes, which we had obtained easily with unsubstituted 1,2-diazepines,[2,11] failed to form with **10** and **12**. Apparently substituents attached to the butadiene moiety prevent the formation of such complexes. For example, 1-acetyl-3-methyl-1,2-diazepine (**13**) leads to a tricarbonyl iron complex, whereas 1,7-dimethyl-1,2-diazepine (**14**) does not.

A large-scale synthesis of 1,2-diazepine **17** could be achieved by irradiation of **15** in thiophene-free benzene during 22 hr at 15–18° in a nitrogen atmosphere using a Pyrex circular-irradiating apparatus and high-pressure mercury lamps.[5] After evaporation of the solvent and chromatography on silica gel, a 90.3% yield of crystalline **17**, mp 54–56°, was obtained.

Triplet Photosensitization and Quenching of 1-Iminopyridinium Ylide 15.—In all photoinduced 1,2-diaze-

(1) Presented at the Spring Meeting of the Société Chimique de France, Organic Chemistry Section, Paris, March 13, 1971. Part IV: R. Gleiter, D. Schmidt, and J. Streith, *Helv. Chim. Acta*, in press.

(2) (a) J. Streith and J. M. Cassal, *Angew. Chem.*, **80**, 117 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 129 (1968); (b) J. Strieth and J. M. Cassal, *Tetrahedron Lett.*, 4541 (1968); (c) J. Streith and J. M. Cassal, *Bull. Soc. Chim. Fr.*, 2175 (1969).

(3) (a) T. Sasaki, K. Kanematsu, and A. Kakehi, *Chem. Commun.*, 432 (1969); (b) T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *J. Org. Chem.*, **35**, 426 (Z970).

(4) (a) V. Snieckus, *Chem. Commun.*, 831 (1969); (b) A. Balasubramanian, J. M. McIntosh, and V. Snieckus, *J. Org. Chem.*, **35**, 433 (1970).

(5) British Patent 1,212,330; Swiss patent 493,268.

(6) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

(7) R. Huisgen, W. Scheer, G. Szeimies, and R. H. Huber, *Tetrahedron Lett.*, 397 (1966); R. Huisgen, W. Scheer, and R. H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

(8) J. S. Splitter and M. Calvin, *J. Org. Chem.*, **23**, 651 (1958).

(9) F. D. Greene and S. S. Hecht, *ibid.*, **35**, 2482 (1970).

(10) R. Huisgen, *Proc. Chem. Soc.*, 365 (1961).

(11) R. Allmann, *Angew. Chem.*, **82**, 982 (1970).

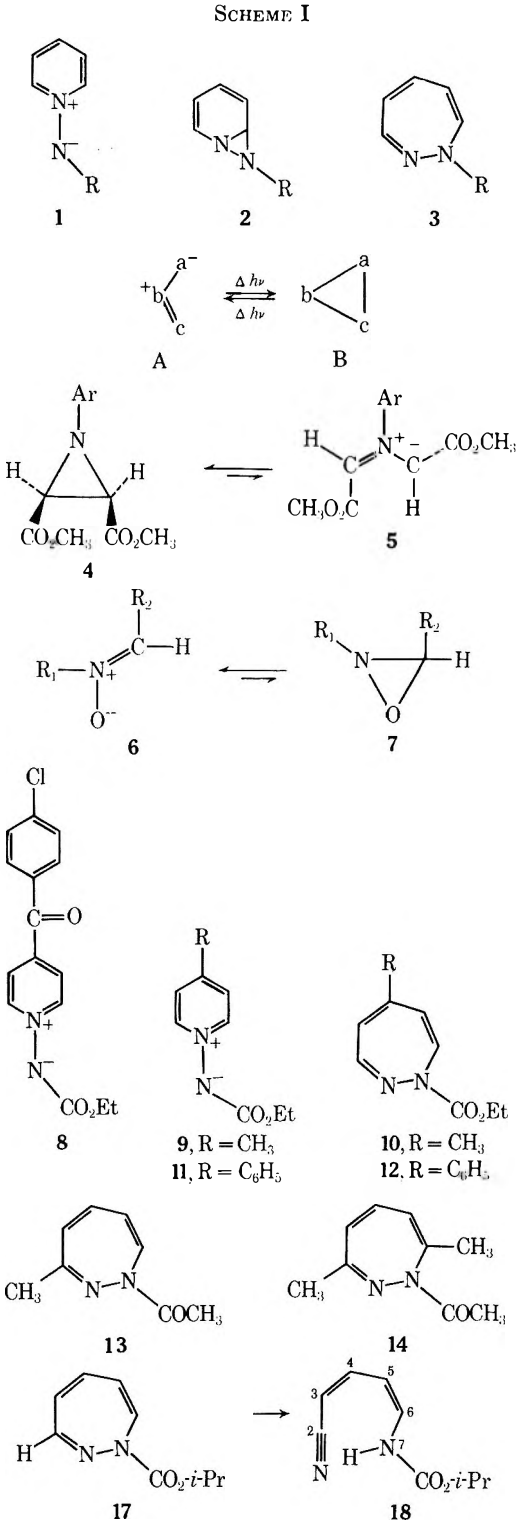
TABLE I

SENSITIZATION EXPERIMENTS OF IMINOPYRIDINIUM YLIDE 15[a]

Tube	Solvent	Sensitizer	λ_{max}, sens	ϵ, sens	E_T, sens	Filter	Atm	Pyridine formed, %
1	CH_2Cl_2					Pyrex	N_2	3.0
2	CH_2Cl_2					Pyrex	O_2	0.5
3	Acetone					Pyrex	N_2	5.0
4	Acetone	Eosine, 50 mg	538	67,000	43	GWV	N_2	58.0
5	CH_2Cl_2	3,4-Benzopyrene, 600 mg	296 320	5,800 2,800	42	Corex	N_2	33.0

[a] Experimental data obtained with a merry-go-round multitube reactor: λ_{max} in nm; E_T values expressed in kcal/mol; 25 mg of iminopyridinium ylide 15 in 15 ml of solvent for each tube.

SCHEME I



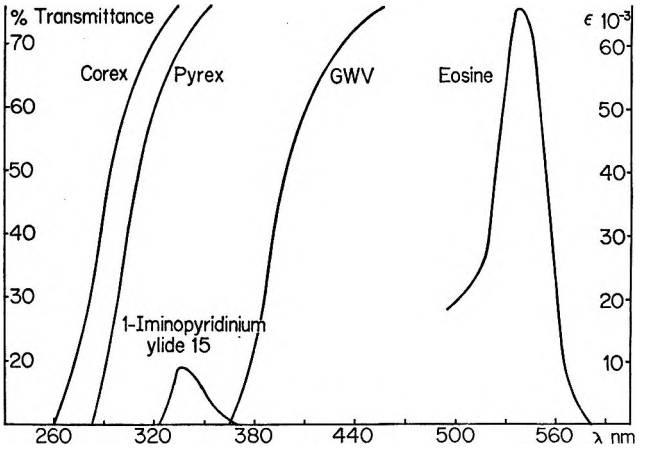


Figure 1.—Transmittance curves of some cut-off glass filters and absorption spectra of pyridinium ylide 15 and of eosine.

pine synthesis, we observed a minor competing process, namely photolytic N–N bond cleavage which gave the parent pyridines and led to nitrenes which reacted further with solvent molecules. When benzene was used as the solvent, formation of 1-substituted azepines had previously been observed.[2] These two competing processes have also been observed with pyridine *N*-oxides and with pyridinium dicyanomethylide.[12] We have recently demonstrated, through sensitization experiments, that photochemical-induced oxygen transfer from pyridine *N*-oxides toward solvent molecules occurs *via* an excited triplet state.[13] Analogously, photolysis of 1-iminopyridinium ylides in the presence of triplet sensitizers led to a notable increase of N–N bond cleavage (see Table I). Experiments have been conducted in a merry-go-round multitube photoreactor[14] under inert atmosphere until complete consumption of the starting material; formation of pyridine has been monitored by vpc. The most extensive cleavage was observed when eosine was used as a sensitizer. In this case the ylide was not excited directly, since a GWV glass cut-off filter was used (see Figure 1 for transmission curves of the various cut-off glass filters used).[15] In the presence of eosine, photolytic bond cleavage played the dominant

(12) J. Streith, A. Blind, J. M. Cassal, and C. Sigwalt, *Bull. Soc. Chim. Fr.*, 948 (1969).

(13) F. Bellamy, L. G. Ruiz-Barragan, and J. Streith, *Chem. Commun.*, 456 (1971).

(14) A Sem-Bruckl photochemical reactor of type PR-20 has been used. The original apparatus has been slightly modified in order to have all tubes under controlled atmosphere.

(15) The GWV cylindrical cut-off glass filter (Glaswerk, Wertheim, Germany) has been kindly provided by Dr. G. Pfundt of The Max Planck Institut für Kohlenforschung, Abteilung Strahlenchemie, Mülheim/Ruhr, Germany.

TABLE II

NMR SPECTRAL DATA OF ISOMERIC DIENAMINONITRILES 18, 19, AND 20 ($CDCl_3$)[a]

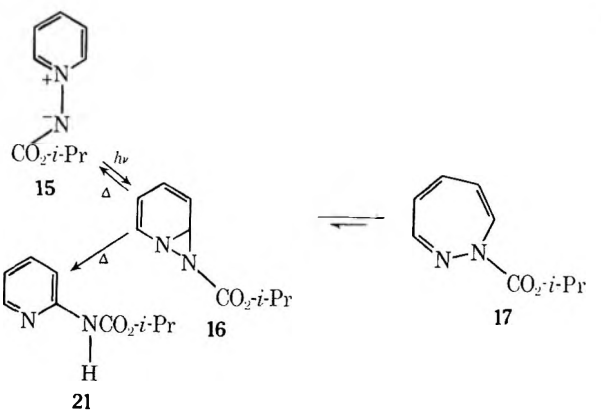
	H-2, τ	H-3, τ	H-4, τ	H-5, τ	H-6, τ
18 (cis–cis), mp 85–90°	4.94 ($J_{2,3}$ = 11.0)[b]	2.88 ($J_{2,3}$ = 11.0, $J_{3,4}$ = 12.0)	4.33 ($J_{4,3}$ = 12.0, $J_{4,5}$ = 9.0)	3.18 ($J_{5,4}$ = 9.0, $J_{5,6}$ = 11.5)	2.29 ($J_{5,6}$ = 11.5)
19 (cis–trans), mp 94–95°	5.0 ($J_{2,3}$ = 10.5)	3.08 ($J_{3,2}$ = 10.5, $J_{3,4}$ = 12)	3.75 ($J_{4,3}$ = 12, $J_{4,5}$ = 13)	2.73 ($J_{5,4}$ = 13, $J_{5,6}$ = 11)	2.3
20 (tran–trans), mp 113–114°	4.73 ($J_{2,3}$ = 16)	2.82 ($J_{3,2}$ = 16, $J_{3,4}$ = 11.5)	4.03 ($J_{4,3}$ = 11.5, $J_{4,5}$ = 14)	2.6 ($J_{5,4}$ = 14)	2.5

[a] Proton H-6 disappears after deuterium exchange. [b] J values in hertz.

role, whereas in the presence of oxygen it was almost totally suppressed. From these data we conclude that a triplet state of somewhat lower energy than 43 Kcal/mol is operative for the photolytic bond cleavage. Therefore, we assume that an excited singlet state gives rise to the isomerization process. A Pariser–Parr–Pople calculation, along with measurements of the absorption spectra of preoriented 1-iminopyridinium ylides **1** in polarized uv light, point to a π–π^* transition for the photoactive absorption band.[1]

Base-Catalyzed and Thermally Induced Rearrangements of Diazepine 17.—As pointed out previously the photochemical synthesis of diazepine **17**, starting with the pyridinium ylide **15**, was supposed to proceed *via* the bicyclic diaziridine **16**. Since valence tautomeric equilibria of, *e.g.*, epoxybenzene–oxepin, have been reported by various groups,[16] it seemed appropriate to investigate whether or not a valence tautomeric equilibrium occurred between diazepine **17** and diaziridine **16** (Scheme II). Nmr spectra taken at

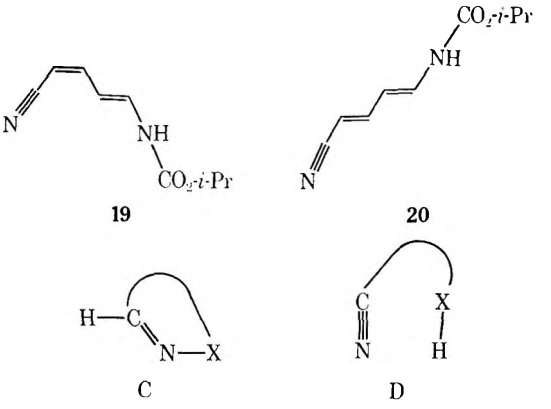
SCHEME II



various temperatures and concentrations of **17** did not permit us to detect the bicyclic tautomer **16**. Potassium hydroxide treatment of **17** led to the formation of 2-aminopyridine, a product which was initially thought to derive directly from the bicyclic diaziridine **16**. The following experiments disprove that hypothesis. Treatment of diazepine **17** in 2-propanol solution with sodium isopropoxide at 20° led, in a few minutes, to the formation of the isomeric dienaminonitrile **18** in 60% yield. The structure of **18** and its cis–cis geometry rest on the nmr data as indicated in Table II, as well as on its ir and uv spectra [ir ($CHCl_3$) ν 3420 (NH), 2210 (C=N), 1730 (C=O), 1640 and 1590 (C=C), and δ (CH) out of plane at 690 cm^{-1}; uv (Et_2O) λ_{max} 298 nm (ϵ 29,500)].

The facile base-catalyzed ring opening of 1,2-diazepines which bear a hydrogen atom in the C-3 position should be expected, since many heterocyclic systems, having an sp^2 nitrogen attached to an electron-withdrawing heteroatom or group of the type C, open up with base to give nitriles of type D (see Scheme III).[17]

SCHEME III



The presence of a hydrogen atom in position 3 is mandatory. Treatment of 1-acetyl-3-methyl-1,2-diazepine (**13**) with sodium isopropoxide does not lead to any nitrile isomer. Nevertheless, H-3 atoms do not have a pronounced acidic character since no deuterium exchange could be detected by nmr spectroscopy after a prolonged treatment in heavy water. The cis–cis nitrile **18**, when treated once more with sodium isopropoxide for a longer period, gave 2-aminopyridine in good yield. When the diazepine **17** was refluxed in *o*-xylene at 140°, the geometric isomers cis–trans **19** [for nmr data see Table II; ir ν 3420 (NH), 2210 (C≡N), 1730 (C=O), 1640 and 1600 (C=C), δ 985 and 690 cm^{-1} (CH); uv (Et_2O) λ_{max} 290 nm (ϵ 36,700)] and trans–trans **20** [for nmr data see Table II; ir ν 3420 (NH), 2210 (C≡N), 1730 (C=O), δ 985 cm^{-1} (CH); uv (Et_2O) λ_{max} 289 nm (ϵ 27,000)] were obtained in poor yield,

(16) E. Vogel and H. Günther, *Angew. Chem.*, **79**, 429 (1967); *ibid.*, *Int. Ed. Engl.*, **6**, 385 (1967); H. Prinzbach, D. Stusche, and R. Kitzing, *Angew. Chem.*, **82**, 393 (1970); G. Maier, *ibid.*, **79**, 446 (1967); *ibid.*, *Int. Ed. Engl.*, **6**, 402 (1967); M. Görlitz and H. Günther, *Tetrahedron*, **25**, 4467 (1969).

(17) (a) For isoxazoles see R. B. Woodward and R. A. Olofson, *ibid.*, *Suppl.*, **7**, 415 (1966); (b) for isoxazolium salts see R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **88**, 3169 (1966); (c) for isoxazolines see G. W. Moersch, E. L. Wittle, and W. A. Neuklis, *J. Org. Chem.*, **30**, 1272 (1965); (d) for pyrazoles see R. Fusco, V. Rosnati, and G. Pagani, *Tetrahedron Lett.*, 1739 (1966); (e) for pyrazolines see G. L. Closs and H. Heyn, *Tetrahedron*, **22**, 463 (1966); (f) for triazoles see R. M. Carmann, D. J. Brecknell, and H. C. Deeth, *Tetrahedron Lett.*, 4387 (1966).

along with trace amounts of the 2-isopropoxycarbonylaminopyridine (**21**). Pyrolysis of **17**, at 170° under nitrogen atmosphere, led mainly to tar formation. Careful chromatography of the reaction mixture led to the isolation of isomer **21** in 10% yield.

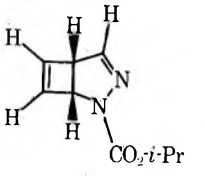
A definite proof for the existence of the diaziridine **16** has been found by refluxing diazepine **17** in acetic acid, a reaction which led to the parent 1-iminopyridinium ylide **15** in 55% yield (see also ref 2c). Thermal rearrangement of diazepine **17** to 2-isopropoxycarbonylaminopyridine (**21**), and even more interestingly to the parent pyridinium ylide **15**, is in good agreement with the 1,7-diaza[4.1.0]bicycloheptadiene intermediate **16** and fits with the original reaction scheme as depicted in Scheme I. For the time being we do not have any rational explanation for the two different pathways when using acetic acid instead of *o*-xylene. The base-catalyzed ring closure of the cis–cis dienaminonitrile **18**, followed by the saponification of the carbamoyl ester which led to the formation of 2-aminopyridine, cannot occur with the isomers **19** and **20** because of their cis–trans and trans–trans geometry, respectively.

Photochemical Isomerization of Diazepine 17.—In view of the thermal rearrangements of 1,2-diazepines which we have just described, it seemed of interest to test whether a photochemically induced rearrangement would also take place. Photoinduced electrocyclic reactions of seven-membered trienes are well known and proceed by a disrotatory course, leading to [3.2.0] bicycloheptadienes. For example, cycloheptatriene, tropones, and tropolones give [3.2.0] bicycloheptatrienes,[18] 2,7-dimethyloxepine gives 1,5-dimethyl-2-oxa[3.2.0]bicycloheptadiene,[18] and 1-carbethoxyazepine leads to 2-carbethoxy-2-aza[3.2.0]bicycloheptadiene.[19] Although earlier attempts to effect photocyclization of diazepine **17** in benzene solution did not succeed, ultraviolet irradiation of **17** in methylene chloride under nitrogen atmosphere, using a high-pressure mercury lamp in a Pyrex reactor, led to a slow disappearance of the starting material and to the formation of a major product. Column chromatography followed by vacuum distillation led to the isolation of a pale yellow photoisomer in 40% yield. The structure of this compound, 2,3-diaza-2-isopropoxycarbonyl[3.2.0]bicycloheptadiene (**22**), has been deduced from its uv, ir, and nmr spectra. The uv spectrum of this photoisomer shows two absorption bands [λ_{max} (EtOH) 249 nm (ϵ 6450) and 316 (25)] tailing out in the visible region. The infrared spectrum agrees with the proposed structure **22**: ν 1720 (C=O), 1680 (C=N), and 1580 cm^{-1} (C=C); δ (CH) out of plane at 730 cm^{-1} characteristic of a cis-disubstituted double bond in a strained ring. Making use of Paquette's interpretation of some [3.2.0] bicycloheptadiene nmr spectra[19,20] and applying the double resonance technique, we could ascertain structure **22** unambiguously (Table III). In a preceding paper we made the statement that the bicyclic photoisomer **22** could not be obtained;[2] as a matter of fact irradiation of **17** in benzene led only to trace amounts of compound **22** which could not be isolated for analytical purposes. Methylene chloride is the solvent of choice in order to obtain photoisomer **22**.

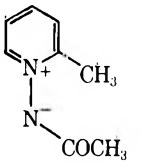
TABLE III

NMR SPECTRUM OF COMPOUND **22** RING PROTONS ($CDCl_3$)

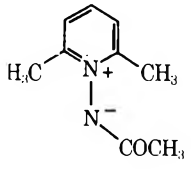
Hydrogen atoms	Chemical shifts in τ units, ppm	Coupling constants, Hz
H-1	5.0	$J_{1,5} = 4.0$, $J_{1,6} = 2.0$
H-4	3.1	$J_{4,5} = 1.4$
H-5	5.92	$J_{5,1} = 4.0$, $J_{5,4} = 1.4$, $J_{5,7} = 1.0$, $J_{5,6} = 0.5$
H-6	3.68	$J_{6,7} = 2.8$, $J_{6,1} = 2.0$, $J_{6,5} = 0.5$
H-7	3.93	$J_{7,6} = 2.8$, $J_{7,5} = 1.0$



22



23



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In addition to the five ring protons reported in Table III, the typical isopropyl bands appear at τ 8.68 (doublet; 6 protons, J = 7 Hz) and 4.95 (multiplet, 1 proton, J = 7 Hz). Compound **22** is thermally stable up to 150°; when heated in diphenyl ether at 170° it reverts quantitatively back to the parent 1,2-diazepine **17**. Since the electrocyclic thermal ring opening of a substituted cyclobutene proceeds by a conrotatory mode, the first diazepine to be formed by such a process should have the enormously strained cis–cis–trans or the cis–trans–cis geometry; such geometries would immediately isomerize to the *all-cis*-diazepine.

Experimental Section

Microanalysis were performed by the Service Central de Microanalyse du C.N.R.S., divisions of Strasbourg and Lyon. Melting points were measured on a Leitz apparatus and are uncorrected. Infrared spectra were determined with Beckman IR-5 A and IR-12 instruments in chloroform solution, unless otherwise indicated. Ultraviolet spectra were recorded on a Beckman DB spectrophotometer. Nuclear magnetic resonance spectra were obtained with Varian A-60A and T-60 spectrometers in deuteriochloroform solution using tetramethylsilane as an internal standard (d = doublet; t = triplet; q = quartet; o = octet; m = multiplet; chemical shifts are given in τ values). Column, thin, and thick layer chromatographies were carried out with silica gel (Merck, Darmstatt). Gas–liquid chromatography was performed with a Carlo-Erba Fractovap apparatus, using a flame ionization detector. Solvents were reagent grade and distilled before use. Photochemical reactions were carried out in a Pyrex glass vessel unless otherwise indicated, reactors being of the Hanovia internal cooling finger type.

Synthesis of 1-Iminopyridinium Ylides. Method A.[21] **Synthesis of *N*-Isopropoxycarbonyliminopyridinium Ylide (15).**—A solution of 19 g of isopropyl azidoformate in 40 g of pyridine was heated for 70 hr at 100°, the nitrogen evolution being measured with a gas buret. Excess pyridine was removed *in vacuo* and the dark residue was taken up in 1 l. of boiling methanol and treated several times with charcoal. The filtrate was evaporated to dryness and the solid material recrystallized three times from benzene–hexane to yield 16 g of ylide **15**, mp 96°. This procedure was repeated five times in order to get 80 g of ylide **15**: nmr 1.14 (q, 2 H, J = 2 and 7 Hz), 2.34 (m, 3 H, J = 2 and 7 Hz); ir ν 1640 cm^{-1} (C=O); uv (C_6H_6) λ_{max} 344 nm (ϵ 11,600) and 282 (2900).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.2; H, 6.6; N, 15.3.

(18) O. L. Chapman, *Advan. Photochem.*, **1**, 323 (1963).

(19) L. A. Paquette and J. L. Barrett, *J. Amer. Chem. Soc.*, **88**, 1718 (1966).

(20) L. A. Paquette, J. H. Barrett, R. P. Spitz, and R. Pitcher, *ibid.*, **87**, 3417 (1965).

(21) T. Curtius and G. Kraemer, *J. Prakt. Chem.*, **125**, 303 (1930); K. Hafner, D. Zinser, and K. L. Moritz, *Tetrahedron Lett.*, 1733 (1964).

Synthesis of 4-(4′-Chloro)benzoyl-1-carbethoxyiminopyridinium Ylide (8).—Method A was used. A solution of 16 g of ethyl azidoformate in 63 g of 4-(4′-chloro)benzoylpyridine (mp 110°) was heated at 120° for 92 hr. Excess solid 4-(4′-chloro)benzoylpyridine was removed by dissolving it in hexane. After the standard treatment with charcoal, recrystallization from acetone gave 1.3 g of ylide 8 (pale yellow crystals): mp 203–204°; nmr 0.86 (d, 2 H, J = 7 Hz), 2.40 (d, 2 H, J = 7 Hz), 2.4 (m, 4 H); ir ν 1650 cm^{-1} (C=O); uv (C_6H_6) λ_{max} 395 nm (ϵ 17,900).

Anal. Calcd for $C_{15}H_{13}O_3N_2Cl$: C, 59.12; H, 4.30; N, 9.19; Cl, 11.64. Found: C, 59.1; H, 4.3; N, 9.2; Cl, 12.1.

Synthesis of 4-Methyl-1-ethoxycarbonyliminopyridinium Ylide (9).—Method A was used by replacing pyridine with 4-picoline. Three recrystallizations from benzene–hexane gave ylide 9 as colorless crystals: mp 150° (lit.[4b] 151.5–152.5°); uv (EtOH) λ_{max} 243 nm (ϵ 5600) and 314 (5400); uv (C_6H_6) λ_{max} 341 nm (ϵ 9400); yield 6%.

Synthesis of 4-Phenyl-1-ethoxycarbonyliminopyridinium Ylide (11).—Method A was used by replacing pyridine with 4-phenylpyridine. Three recrystallizations from acetone–hexane gave colorless crystals: yield 9%; mp 163° (ylide 11); nmr 1.28 (d, 2 H, J = 7.5 Hz), 2.36 (d, 2 H, J = 7.5 Hz), 2.5 (m, 5 H); ir ν 1640 cm^{-1} (C=O); uv (C_6H_6) λ_{max} 370 nm (ϵ 19,000).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.36; H, 5.76; N, 11.57.

Method B.[22,23] Synthesis of 2-Methyl-1-acetyliminopyridinium Ylide (23).—A stirred solution of 25 g (0.106 mol) of 1-amino-2-picolinium iodide in 250 ml of acetic anhydride was heated for 2 hr at 95°. After 2 days at normal temperature, yellow crystals had formed which were filtered off and washed with diethyl ether. Yield of acetylamino-2-picolinium iodide so obtained was 85%, mp 187°.

A solution of 7 g of iodide in 500 ml of ethanol was run through an ion exchange column IRA 410 which had been pretreated with sodium hydroxide. After removal of ethanol under vacuum and chromatography over silica gel, one obtained 3.4 g of 2-methyl-1-acetyliminopyridinium ylide as hygroscopic needles: yield 90%; uv (C_6H_6) λ_{max} 336 nm (ϵ 5600); picrate mp 166–167° (lit. 167°).

Synthesis of 2,6-Dimethyl-1-acetyliminopyridinium Ylide (24).—Method B was used. Purification was achieved by *in vacuo* sublimation and yielded colorless and hygroscopic crystals, mp 65°, for which no good microanalytical values could be obtained: nmr 2.3 (m, 3 H), 7.33 (s, 6 H), 7.88 (s, 3 H); ir ν 1574 cm^{-1} (C=O); uv (C_6H_6) λ_{max} 280 nm (ϵ 5800) and a shoulder at 340 (1800); mass spectrum m/e 164 (parent ion).

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.7; H, 7.5; N, 17.2.

Photochemical Synthesis of 1-Isopropoxycarbonyl-1,2-diazepine (17). Standard Procedure.—A solution of 3.44 g (0.019 mol) of pyridinium ylide 15 in 900 ml of benzene was irradiated under nitrogen with a Philips HPK 125 mercury high-pressure lamp until the photoactive absorption band of 15 had disappeared. After 12 hr the solvent was removed *in vacuo* and the oily residue was chromatographed over 300 g of silica gel with cyclohexane–ethyl acetate 6:4; 3.1 g of the crystalline diazepine 17 was obtained: mp 55°; yield 90%; nmr 2.60 (q, 1 H, J = 1 and 3 Hz), 3.6 (m, 3 H), 4.30 (m, 1 H); ir ν 1700 (C=O), and 1640 cm^{-1} (C=N); uv (C_6H_6) λ_{max} 370 nm (ϵ 230) and 278 (530).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.2; H, 6.6; N, 15.3.

Large-Scale Synthesis Using a Pyrex Circular-Irradiating Apparatus.—A solution of 27.0 g (0.147 mol) of pyridinium ylide 15 in 6 l. of thiophene-free benzene was irradiated under nitrogen atmosphere during 22 hr at 15–16° in a Pyrex circular-irradiating apparatus with two 2000-W mercury high-pressure lamps. The reaction was followed spectrophotometrically. The dark red solution was evaporated to dryness under reduced pressure at 15–20°. The brown and slowly crystallizing residue weighed 30.3 g. This crude product was filtered over a 10 times excess of silica gel (deactivated by addition of 5% water) using cyclohexane–ethyl acetate 7:3; 24.4 g of the crystalline diazepine 17 was obtained, mp 54–56° (yield 90.3%). This latter procedure was performed at the CIBA-Basel plant by Dr. N. Tarkoy and C. Campana.

Iron Tricarbonyl Complex of Diazepine 17.—To a solution of 500 mg of diazepine 17 (2.8 mmol) in 100 ml of benzene, 1.5 g of $Fe_2(CO)_9$ was added and the resulting suspension was stirred under nitrogen for 4 hr at normal temperature. After filtration of the excess iron carbonyl reagent, the solvent was evaporated *in vacuo*. From the brown residue 400 mg of yellow crystals was isolated by preparative thick layer chromatography (elution with cyclohexane–ethyl acetate 6:4), followed by a vacuum sublimation: mp 106°; yield 45%; nmr 2.99 (d, 1 H, J = 6.5 Hz, H_3), 3.69 (q, 1 H, J = 7 and 2 Hz, H_7), 4.9 (m, 1 H, J = 7 and 2 Hz, H_5), 5.4 (m, 1 H, J = 7 Hz, H_6), 6.65 (q, 1 H, J = 6.5 and 7 Hz, H_4); ir ν 2060, 1990, and 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{12}N_2O_5Fe$: C, 45.03; H, 3.78; N, 8.75; Fe, 17.45. Found: C, 45.1; H, 3.8; N, 8.8; Fe, 17.6.

Photochemical Synthesis of 1-Acetyl-3-methyl-1,2-diazepine (13).—The standard procedure was repeated with a solution of 3.5 g of pyridinium ylide 23 (0.023 mol) in 2.6 l. of benzene with a Hanovia 450-W mercury high-pressure lamp. After 12 hr all starting material had disappeared and the solution was evaporated to dryness. The only residue was chromatographed over 300 g of silica gel with cyclohexane–ethyl acetate 6:4 and yielded 2.8 g of diazepine 13 (yield 80%) as an orange oil: nmr 3.53 (m, 3 H), 4.23 (m, 1 H), 7.78 (s, 3 H), 7.86 (s, 3 H); ir ν 1650 cm^{-1} (C=O); uv (C_6H_6) λ_{max} 368 nm (ϵ 270) and 279 (2700); mass spectrum m/e 150 (parent ion).

Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.1; H, 6.8; N, 18.8.

Iron Tricarbonyl Complex of Diazepine 13.—The same procedure as above was used with 500 mg of diazepine 13. Yellow crystals were obtained after chromatography and *in vacuo* sublimation: mp 110°; yield 92%; nmr 3.51 (q, 1 H, J = 6.5 and 2 Hz, H_7), 4.82 (o, 1 H), J = 7, 4.5, and 2 Hz, H_5), 5.32 (o, 1 H, J = 6.5, 4.5, and 1.5, H_6), 6.77 (q, 1 H, J = 7 and 1.5 Hz, H_4); ir ν 2060 and 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{10}N_2O_4Fe$: C, 45.50; H, 3.47; N, 9.66; Fe, 19.25. Found: C, 45.8; H, 3.5; N, 9.6; Fe, 19.4.

Photochemical Synthesis of 1-Acetyl-3,7-dimethyl-1,2-diazepine (14).—The standard procedure was repeated with 1.5 g of pyridinium ylide 24 in 2.75 l. of benzene using a Hanovia 450-W mercury high-pressure lamp for 3 hr and yielded 312 mg of diazepine 14 as a red oil: yield 21%; nmr 3.5 (m, 2 H), 4.0 (m, 1 H), 7.78 (s, 3 H), 7.80 (s, 3 H), 7.82 (s, 3 H); ir ν 1660 cm^{-1} (C=O); uv (C_6H_6) λ_{max} 356 nm (ϵ 350) and 279 (1900).

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.6; H, 7.4; N, 16.7.

Photochemical Synthesis of 1-Carbethoxy-5-methyl-1,2-diazepine (10).—The standard procedure was repeated with 1 g of pyridinium ylide 9 (5.6 mmol) in 1.4 l. of benzene using a Hanovia 450-W mercury high-pressure lamp for 6 hr. Diazepine 10 (750 mg) was isolated as yellow crystals, mp 52° (lit.[3b,4b] 51–53°).

Photochemical Synthesis of 1-Carbethoxy-5-phenyl-1,2-diazepine (12).—The standard procedure was repeated with 190 mg (0.78 mmol) of pyridinium ylide 11 in 25 ml of benzene, using a Philips HPK 125 mercury high-pressure lamp for 10 hr, and yielded 171 mg of diazepine 12 as orange crystals after chromatography and recrystallization: mp 86–87°; nmr 2.43 (d, 1 H, J = 4 Hz), 2.50 (s, 5 H), 3.43 (q, 1 H, J = 4 and 2 Hz), 3.51 (d, 1 H, J = 7 Hz), 3.97 (q, 1 H, 7 and 2 Hz); ir ν 1715 cm^{-1} (C=O); uv (C_6H_6) λ_{max} 375 nm (ϵ 510) and 279 (12,000); mass spectrum m/e 242 (parent ion).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.5; H, 5.9; N, 11.4.

Thermal Rearrangements of 1-Isopropoxycarbonyl-1,2-diazepine (17). Reflux in *o*-Xylene.—A 2-g solution of diazepine 17 (11.1 mmol) in 50 ml of *o*-xylene was refluxed for 17 hr at 144°. The reaction was followed by tlc. After removal of the solvent *in vacuo*, chromatography of the residue over 350 g of silica gel (elution with cyclohexane–ethyl acetate 5:5) led to the isolation of products with the following order of elution: 1.2 g of diazepine 17; 500 mg of a mixture of nonidentified compounds; 120 mg of a colorless compound A, mp 94–95°; 60 mg of a colorless compound B, mp 113–114°; 40 mg of a third colorless compound C, mp 80–81°.

Compound A was identified as cis–trans dienaminonitrile 19. For spectral data see Table II and data previously given for 19; mass spectrum m/e 180 (parent ion).

Anal. Calcd for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.0; H, 6.7; N, 15.3.

(22) R. Gösl and A. Meuwsen, *Chem. Ber.*, **92**, 2521 (1959).

(23) (a) T. Okamoto, M. Hirobe, C. Mizushima, and A. Ohsawa, *Yakugaku Zasshi*, **83**, 308 (1963); *Chem. Abstr.*, **59**, 5103*b* (1963); (b) T. Okamoto, M. Hirobe, and A. Osawa, *Chem. Pharm. Bull. Jap.*, **14**, 518 (1966).

Compound B was identified as trans–trans dienaminonitrile **20**. For spectral data see Table II and data previously given for **20**; mass spectrum *m/e* 180 (parent ion).

Anal. Calcd for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.5; H, 6.7; N, 15.2.

Compound C was identified with 2-isopropoxycarbonylaminopyridine (**21**). **21** was synthesized as follows. To a solution of 2 g of 2-aminopyridine (0.021 mol) in 100 ml of isopropyl alcohol, 4 g of sodium bicarbonate (0.048 mol) and 3.7 g of isopropyl chloroformate were added successively. Once the CO_2 evolution had ceased the solution was refluxed for 16 hr. Evaporation to dryness followed by a chromatography over silica gel with cyclohexane–ethyl acetate 4:1 led to the isolation of 1.6 g of crystals identical in all respects with compound C (melting point, mixture melting point, and ir and uv spectra).

Anal. Calcd for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.3; H, 6.7; N, 15.6.

Reflux in Acetic Acid.—A solution of 300 mg of diazepine **17** (1.67 mmol) in 5 ml of acetic acid was refluxed for 1 hr under nitrogen. After evaporation to dryness the residue was treated several times with ether in order to eliminate the remaining diazepine. Thick layer chromatography over neutral alumina with ethyl acetate yielded pyridinium ylide **15** (165 mg, yield 55%), mp 96°.

Pyrolysis at 170°.—A 2-g batch of diazepine **17** was pyrolyzed under nitrogen for 20 min at 170°. The black residue was chromatographed over silica gel thick layer; 206 mg of 2-isopropoxycarbonylaminopyridine (**21**) was obtained (yield 10%).

Treatment of 1-Isopropoxycarbonyl-1,2-diazepine (17) with Sodium Isopropoxide.—To a solution of 3 g (16.7 mmol) of diazepine **17** in 60 ml of isopropyl alcohol was slowly added a solution of sodium isopropoxide (30 mmol) in 150 ml of isopropyl alcohol at room temperature. After a few minutes a change in color had occurred and aqueous hydrochloric acid was added until neutralization. The solvent was removed *in vacuo* at a temperature not exceeding 45° after the usual extraction procedure, and the residue was chromatographed over 300 g of neutral alumina with cyclohexane–ethyl acetate 4:1. Besides 157 mg of 2-aminopyridine, mp 57°, 1.8 g of colorless crystals (yield 60%) was isolated and identified as cis–cis dienaminonitrile **18**, mp 85–90°. For spectral data see data previously given for **18**; mass spectrum *m/e* 180 (parent ion).

Anal. Calcd for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.9; H, 6.4; N, 15.5.

Base-Induced Ring Closure of Cis–Cis Dienaminonitrile 18.—To a solution of 200 mg of dienaminonitrile **18** (1.11 mmol) in 20 ml of isopropyl alcohol, a solution of sodium isopropoxide (2 mmol) in isopropyl alcohol was added. After 15 min at room temperature the starting material had disappeared. Removal of the solvent *in vacuo* and thick layer chromatography over neutral alumina yielded 57 mg of 2-aminopyridine (yield 55%).

Sensitization and Quenching of the 1-Iminopyridinium Ylide 15 Triplet State.—A Sem-Bruckl merry-go-round multitube photoreactor was used.[14] The 15-ml quartz tubes were surrounded by various cylindrical cut-off glass filters. A Philips HPK 125 mercury high-pressure lamp, placed into a water-cooled quartz jacket, was positioned along the rotation axis of the apparatus. Each tube was placed under controlled atmosphere and was stirred magnetically. Acetone and methylene chloride were used as solvents, tubes being irradiated until complete disappearance of the starting material (control by tlc). Pyridine formation was determined quantitatively by vpc (Carbowax 20M on 10% Chromosorb W). For quantitative results see Table I.

Electrocyclic Photoisomerization of 1-Isopropoxycarbonyl-1,2-diazepine (17) into 2-Isopropoxycarbonyl-2,3-diaza[3.2.0]bicycloheptadiene (22).—A 2-g solution of diazepine **17** (11 mmol) in 1 l. of methylene chloride was irradiated according to the standard procedure under nitrogen atmosphere using a Hanovia 450-W mercury high-pressure lamp. After 92 hr diazepine **17** had disappeared; formation of a major product was detected by tlc. Evaporation of the solvent *in vacuo*, followed by a chromatography of the residue over 200 g of silica gel with cyclohexane–ethyl acetate 1:1, yielded a yellow liquid which was distilled under vacuum (70°, 0.2 mm), overall yield 40%. This yellow and viscous oil was identified as being 2-isopropoxycarbonyl-1,2-diaza[3.2.0]bicycloheptadiene (**22**). For spectroscopic data see Table III and the data previously given for **22**; mass spectrum *m/e* 180 (parent ion).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.1; H, 6.7; N, 15.4.

Thermal Rearrangement of 2-Isopropoxycarbonyl-2,3-diaza-[3.2.0]bicycloheptadiene (22) into 1-Isopropoxycarbonyl-1,2-diazepine (17).—A solution of 50 mg of photoisomer **22** in 10 ml of diphenyl ether was heated during 18 hr under nitrogen at 135°; no reaction occurred. At 180° a quantitative reaction leading to a single product occurred after 2 hr. Chromatography of the preceding solution over silica gel with cyclohexane–ethyl acetate 1:1 yielded 45 mg of 1-isopropoxycarbonyl-1,2-diazepine (**17**) (melting point, mixture melting point; ir and tlc data identical with an authentic sample of **17**).

Registry No.—**8**, 31020-21-0; **9**, 22928-85-4; **11**, 31020-23-2; **12**, 31020-24-3; **13**, 23882-04-4; **13** iron tricarbonyl complex, 12524-67-3; **14**, 23922-05-6; **15**, 31020-27-6; **17**, 31020-28-7; **17** iron tricarbonyl complex, 12524-66-2; **18**, 31020-29-8; **19**, 31020-30-1; **20**, 31020-31-2; **21**, 31020-32-3; **22**, 31020-33-4; **23**, 7584-27-2; **24**, 31020-35-6; acetylamino-2-picolinium iodide, 7583-98-4; 2-aminopyridine, 504-29-0.

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Quinazolines and 1,4-Benzodiazepines. LIII.[1] Ring Expansion of Some Chloromethylpyrazolo[1,5-c]quinazolines and a 1,2,4-Benzothiadiazine 1,1-Dioxide

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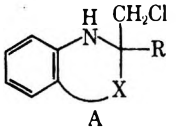
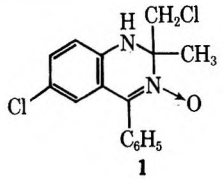
Reaction of the pyrazoloquinazoline **8** with potassium *tert*-butoxide gives the aziridine **10** which on treatment with base and methanol is transformed into the 1,4-benzodiazepine **11**. The dichloromethyl analog **7** undergoes a similar reaction to form **9**. The chloromethylbenzothiadiazine 1,1-dioxide **16** undergoes ring expansion in a different manner to form the 1,2,5-benzothiadiazepine **14**. This divergence is explained by the existence of two different types of anions.

Treatment of chloromethyl dihydro heterocycles of the general type A with base frequently gives rearrangement reactions in which the heterocyclic ring is expanded by incorporation into the ring of a methylene group derived from the chloromethyl group. However, whether this methylene group becomes attached to the nitrogen or to group X in A is not completely predictable. Specifically, reaction of the quinazoline **1** with

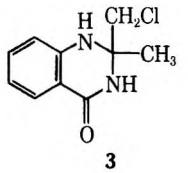


A

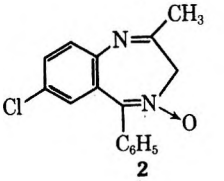
potassium *tert*-butoxide in tetrahydrofuran[2] gives mainly **2** while, under approximately the same conditions, reaction of the quinazolone **3** gives mainly **4**.[3] In the products **2** and **4**, the methyl group clearly tags the carbon atom which was in the 2 position of the starting material.



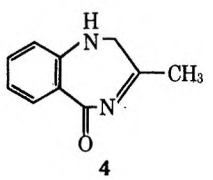
1



3

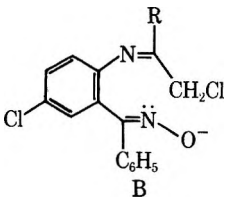


2

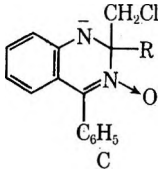


4

Previously, we discussed[2] both the effect of the solvent and the effect of the replacement of the methyl group by other groups, on the type of product obtained. We postulated two anions, *e.g.*, C, in which the charge is relatively concentrated on N-1, and B, in which the heterocyclic ring has been disrupted. Products related to **4** would be formed from an anion of type C, whereas products related to **2** would result from the cyclization of anion B. Products which can be considered to be derived from anion C are favored if R is a group which is less electron releasing than methyl, or if nonpolar solvents are used.[2]



B



C

It appears from the structure of the products **2** and **4** that the end product is usually derived from the more stable of the anions analogous to B and C. That is, if the conjugate acid of B has the lower pK_a, products corresponding to **2** would be favored. However, if the tautomeric conjugate acid C has a lower pK_a, the anion analogous to C should predominate and products of type **4** would result.

Here we describe two additional heterocyclic systems which illustrate this hypothesis. The first system is exemplified by the pyrazolo[1,3-*c*]quinazolines **7** and **8** (Chart I). These compounds are readily prepared from the hydroxyquinoline **5**[4] and hydrazine[5] followed by condensation of the intermediate **6**[6] with the appropriate chloro ketone. Treatment of **8** with potassium *tert*-butoxide in tetrahydrofuran gave the aziridine **10**, whose structure was assigned on the basis of its nmr spectrum. Particularly, the unique appearance of two singlets at δ 1.85 and 2.73 ppm for the protons of the methylene group supports the assignment of an aziridine structure.[2] Reduction of **10** with lithium aluminum hydride disrupted the center rings to give an isopropyl derivative **12**. The structure of **12** is supported by spectral data. The nmr spectrum reveals clearly the attachment of the isopropyl chain to the aniline nitrogen. The proton of the aniline nitrogen appears as a broadened doublet (J = 7 Hz) at δ 7.8 ppm, the proton on the pyrazole nitrogen as a broad singlet at δ 12.7 ppm. In addition, the compound did not form a dye upon diazotization and coupling with β-naphthol. Treatment of **10** with sodium borohydride in methanol did not result in reduction, as expected, but led only to the methoxy derivative **11** containing a seven-membered ring as evidenced by its nmr spectrum (see Experimental Section) and hydrolysis. The same compound could also be obtained directly from **8** by the action of sodium methoxide in methanol. Hydrolysis of **11** with acid opened the seven-membered ring to give

(1) Part LII: A. Walser, G. Silverman, J. F. Blount, R. I. Fryer, and L. H. Sternbach, *J. Org. Chem.*, **36**, 1465 (1971).

(2) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Amer. Chem., Soc.*, **89**, 332 (1967).

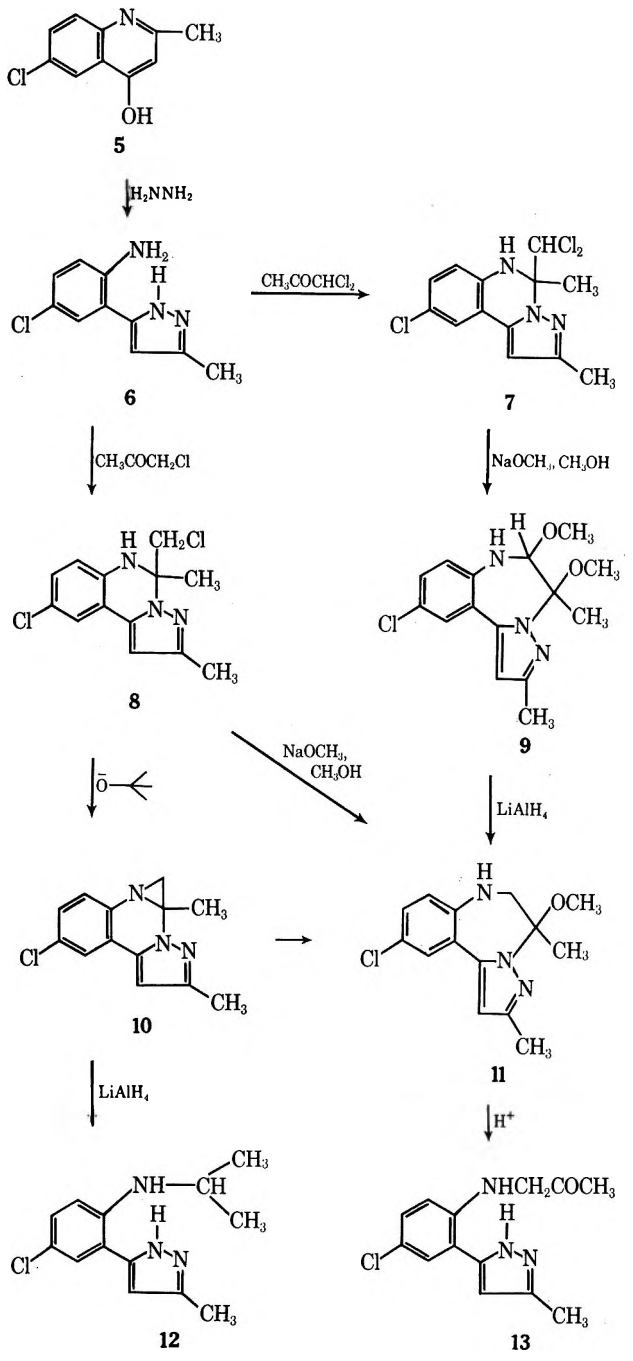
(3) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **36**, 777 (1971).

(4) C. R. Hauser and G. A. Reynolds, *J. Amer. Chem. Soc.*, **70**, 2402 (1948).

(5) G. Alberti, *Gazz. Chim. Ital.*, **87**, 772 (1957).

(6) G. DeStevens, A. Halamandaris, M. Bernier, and H. M. Blatter, *J. Org. Chem.*, **28**, 1336 (1963).

CHART I



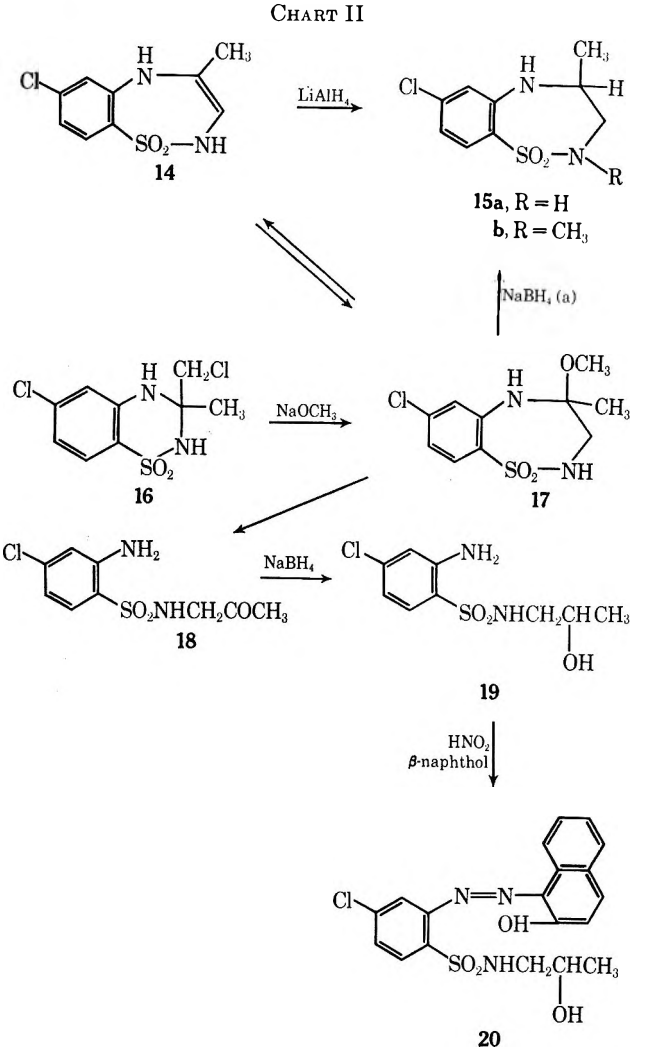
the acetonyl derivative **13**. The attachment of the acetonyl group to the anilino nitrogen was again evident from the nmr spectrum. The proton of the pyrazole nitrogen appears at δ 12.72 ppm, the proton of the aniline nitrogen as a triplet (J = 5 Hz) at δ 8.27. Similarly, reaction of the dichloromethyl derivative **7** with sodium methoxide in methanol gave the dimethoxy derivative **9**, again with ring expansion. Reduction of **9** with lithium aluminum hydride resulted in the formation of **11**, thus confirming the presence of the seven-membered ring.[7]

(7) The preferential reduction of the methoxy group in position 2 is in good agreement with the structures assigned to **9** and **11**. An analogous case is the lability of a similarly situated carbinolamine ether in anthramycin methyl ether described by Leimgruber and coworkers [W. Leimgruber, V. Stefanović, F. Schenker, A. Karr, and J. Berger, *J. Amer. Chem. Soc.*, **87**, 5791 (1965); W. Leimgruber, A. D. Batcho, and F. Schenker, *ibid.*, **87**, 5703 (1965)]. The factor responsible for the preferential elimination of the 2-methoxy group is probably the presence of an NH group, since in compound **22** of ref 3 where two methoxy groups are adjacent to an NH group both are removed with lithium aluminum hydride.

In compounds **7** and **8** it is, therefore, the nitrogen in position 1 which is alkylated by the chloromethyl or dichloromethyl group, respectively, rather than the one at position 3 of the quinazoline ring. This suggests that the intermediates are of the C type.

The second system is exemplified by the 2*H*-1,2,4-benzothiadiazine 1,1-dioxide **16** (Chart II). The

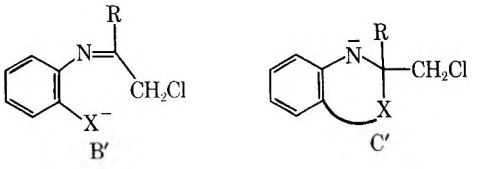
CHART II



starting material **16** was prepared from 2-amino-4-chlorobenzenesulfonamide and chloroacetone with azeotropic removal of the water formed in the reaction. Treatment of this compound with sodium methoxide in methanol gave **17**, which on heating with benzene yielded **14**. Compound **14** could be reconverted into **17** by repeated recrystallization from methanol. These compounds were characterized by their nmr spectra and interrelated by reduction to **15a**. Hydrolysis of **17** gave the open acetonyl derivative **18**. Reduction of **18** with lithium aluminum hydride gave **19**, which was diazotized and coupled with β-naphthol to give the dye **20**. This reaction demonstrates the presence of a primary aromatic amino group in **18** and consequently the position of the methyl group in **17**. Therefore in this compound it is not the anilino nitrogen but the sulfonamido nitrogen which is alkylated by the chloromethyl group.

Discussion

The divergent structures of the products obtained in the two systems discussed above can again be explained on the basis of the existence of two anions, which are ring–chain tautomers, represented in general form by anions B′ and C′. The pyrazolo compounds shown in Chart I are formed from anion C′ (X = 3-methyl-5-pyrazolyl) and the ring-expansion products of the type obtained in the sulfonamide series in Chart II are de-



rived from anion B′ (X = $-SO_2NH_2$). However, we cannot exclude the possibility that the sulfonamides do not fit into this general scheme, since the formation of the anion C′ might not be the first step in this case.[8]

Considerable additional work will be needed in order to fully elucidate the effects of the various factors which might influence the course of this ring enlargement.

Experimental Section[9]

5-(2-Amino-5-chlorophenyl)-3-methylpyrazole (6).—A mixture of 50 g of 6-chloro-4-hydroxy-2-methylquinoline, 27.1 g of hydrazine dihydrochloride, 66 ml of hydrazine, and 150 ml of ethylene glycol was heated in an oil bath at 200° for 3 hr. The reaction mixture was then cooled and diluted with 300 ml of water to precipitate 40.5 g of product, mp 123–127°. Recrystallization from ethyl acetate–hexane gave colorless needles: mp 134–136°; uv max 217 mμ (ε 25,000), 230 (24,000), 259 (10,000), and 325 (5000).

Anal. Calcd for $C_{10}H_{10}ClN_3$: C, 57.84; H, 4.85. Found: C, 57.73; H, 4.87.

9-Chloro-5-dichloromethyl-5,6-dihydro-2,5-dimethylpyrazolo[1,5-*c*]quinazoline (7).—A mixture of 70.6 g of 5-(2-amino-5-chlorophenyl)-3-methylpyrazole, 70.6 ml of 1,1-dichloro-2-propanone, and 1.7 l. of benzene was heated under reflux for 18 hr. The water which separated was collected in a Dean–Stark trap. The reaction mixture was then cooled, treated with charcoal, filtered, and concentrated to dryness *in vacuo*. The residue was crystallized from petroleum ether to give 94.3 g of crude product, mp 112–119°. Recrystallization from hexane gave colorless needles: mp 120–123°; uv max 230 mμ (ε 26,000), 243 (26,000), 271 (7600), and 343 (5700).

Anal. Calcd for $C_{13}H_{12}Cl_3N_3$: C, 49.31; H, 3.82. Found: C, 48.93; H, 3.80.

9-Chloro-5-chloromethyl-5,6-dihydro-2,5-dimethylpyrazolo[1,5-c]quinazoline (8).—A mixture of 20.45 g of 6, 20.45 ml of chloroacetone, and 500 ml of benzene was heated under reflux for 5 hr. The water which separated was collected in a Dean–Stark trap. The reaction mixture was then cooled and the benzene layer decanted from the tars and concentrated *in vacuo*. Crystallization of the residue from petroleum ether gave 22.9 g of crude product, mp 111–115°. Recrystallization from hexane gave colorless prisms: mp 121–124°; uv max 230 mμ (ε 24,000), 243 (23,000), 273 (7500), and 345 (5000).

Anal. Calcd for $C_{13}H_{13}Cl_2N_3$: C, 55.35; H, 4.64. Found: C, 55.06; H, 4.76.

10-Chloro-6,7-dihydro-5,6-dimethoxy-2,5-dimethyl-5*H*-pyrazolo[1,5-*d*][1,4]benzodiazepine (9).—To a solution of 6.33 g of 7 dissolved in 100 ml of methanol cooled in an ice bath was added 2.16 g of sodium methoxide. The reaction mixture was then stirred overnight at room temperature. The precipitated solids were filtered and the filtrate was concentrated *in vacuo*. The residue was crystallized from hexane to give 5.3 g of crude product, mp 130–140°. Recrystallization from ether–hexane gave 4.1 g of white needles, mp 135–140°. Further recrystallization from ether–hexane gave colorless prisms: mp 144–147°; ir 3450 cm^{-1}; uv max 228 mμ (ε 22,000), 233 (21,000), 265 (13,000), and 335 (6800); nmr (DMSO) δ 2.00 (s, 3, $-CH_3$), 2.25 (s, 3, $-CH_3$), 2.91 (s, 3, $-OCH_3$), 3.20 (2, 3, $-OCH_3$), 4.59 ppm (d, 1, J = 6 Hz, $-NHCH$), 6.63 (s, 1, C_1 H), 6.95 (d, 1, J = 9 Hz, C_8 H), 7.2 (q, 1, J_{AB} = 9 Hz, J_{AX} = 2 Hz, C_9 H), 7.63 (d, 1, J = 2 Hz, C_{11} H), 7.66 (d, 1, J = 6 Hz, NH).

Anal. Calcd for $C_{15}H_{18}ClN_3O_2$: C, 58.53; H, 5.89. Found: C, 58.43; H, 5.86.

10-Chloro-5,6-dihydro-2,5-dimethylazirino[α]pyrazolo[1,5-*c*]quinazoline (10).—To a solution of 12 g of 8 in 100 ml of tetrahydrofuran was added 1.7 g of potassium *tert*-butoxide and the mixture was stirred at room temperature for 3 hr. It was then filtered through Celite and concentrated *in vacuo*. The residue was crystallized from petroleum ether to give 2.3 g of crude product, mp 109–111°. Recrystallization from petroleum ether gave colorless prisms: mp 107–109°; uv max 235 mμ (ε 25,000), 270 (sh) (11,000), 320 (2500), and 343 (2400); nmr (DMSO) δ 1.85 (s, 4, CCH_3 and NCH), 2.25 (s, 3, $=CCH_3$), 2.73 (s, 1, NCH), 6.61 (s, 1), 7.3 (m, 2), and 7.7 ppm (m, 1).

Anal. Calcd for $C_{13}H_{12}ClN_3$: C, 63.54; H, 4.92. Found: C, 63.34; H, 5.19.

10-Chloro-6,7-dihydro-5-methoxy-2,5-dimethyl-5*H*-pyrazolo[1,5-*d*][1,4]benzodiazepine (11). **A. From 8.**—To a solution of 28.2 g of 8 in 500 ml of methanol was added 21.6 g of sodium methoxide and the mixture was stirred at room temperature overnight. It was then neutralized with methanolic hydrogen chloride, filtered, and concentrated to dryness *in vacuo*. The residue was crystallized from ether–hexane to give 30.3 g of crude product, mp 127–132°. Recrystallization from 2-propanol–water and then from cyclohexane gave colorless prisms: mp 128–131°; ir 3450 cm^{-1}; uv max 230 (ε 19,000), 245 (19,500), 270 (11,000) and 340 (5600); nmr (DMSO) δ 1.82 (s, 3, $-CH_3$), 2.21 (s, 3, $-CCH_3$), 3.02 (s, 3, $-OCH_3$), 3.41 (m, → AB on exchange, 2, $-NHCH_2$), 6.6 (m, 2, C_1 H and NH), 6.87 (d, 1, J = 9 Hz, C_8 H), 7.13 (q, 1, J_{AB} = 9 Hz, J_{AX} = 2 Hz, C_9 H), 7.68 (d, 1, J = 2 Hz, C_{11} H).

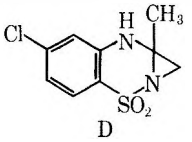
Anal. Calcd for $C_{14}H_{16}ClN_3O$: C, 60.54; H, 5.81. Found: C, 60.35; H, 5.81.

B. From 10.—To a solution of 4 g of 10 in 175 ml of methanol cooled in an ice bath was added 4 g of sodium borohydride and the reaction mixture was stored in a refrigerator for 2 days. It was then neutralized with saturated sodium bicarbonate solution, concentrated *in vacuo*, and diluted with water. The mixture was extracted with methylene chloride in three portions. The methylene chloride extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from hexane to give 3.5 g of crude 11, mp 100–120°. Recrystallization from 2-propanol gave white prisms, mp 124–128°. The infrared spectrum was superimposable with that obtained from material described in the previous experiment.

C. From 9.—A solution of 3.1 g (10 mmol) of 9 in 30 ml of dry tetrahydrofuran was added to a solution of 0.84 g (22 mmol) of lithium aluminum hydride in 270 ml of tetrahydrofuran, and the mixture was stirred and heated under reflux for 3 hr. The reaction mixture was cooled, treated with ethyl acetate and water to destroy excess lithium aluminum hydride, and extracted with methylene chloride in four portions. The extracts were dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was crystallized from hexane to give 1 g of 11, mp 125–130°, identified by mixture melting point and infrared spectrum.

5-[2-(Isopropylamino)-5-chlorophenyl]-3-methylpyrazole (12).—To a suspension of 1 g of lithium aluminum hydride in 100 ml of ether was added a solution of 4.9 g of 10 in 100 ml of ether. The reaction mixture was then stirred for 24 hr at room temperature and cooled on ice, and the excess lithium aluminum hydride

(8) As suggested by the referees, the intermediacy of a compound of type D in this sequence of reactions leading to **17** cannot be excluded. In that case the cyclic sulfonamido nitrogen would undergo alkylation.



(9) Melting points were determined on a Thomas–Hoover capillary melting point apparatus. Nmr spectra were obtained on a Varian A-60 instrument. Petroleum ether refers to a fraction of bp 40–60°. Alumina refers to Woelm grade I. The ir spectra were determined in chloroform unless otherwise specified. The ultraviolet spectra were taken in 2-propanol.

was decomposed by addition of 30 ml of ethyl acetate followed by 50 ml of 10% sodium bicarbonate solution. The reaction mixture was then filtered through Celite and separated, and the organic phase was dried over sodium sulfate. It was then concentrated *in vacuo* and the residue was crystallized from hexane to give 4 g of crude product, mp 125–133°. Recrystallization from ethanol–water gave colorless needles: mp 131–135°; ir 3450 cm^{-1}; uv max 225 mμ (ε 19,400), 235 (21,000) 270 (9500), and 340 (4500); nmr ($CDCl_3$) δ 1.15 [d, 6, J = 6 Hz, $-CH(CH_3)_2$], 2.02 (s, 3, $-CH_3$), and 3.6 ppm [m, 1, $-CH(CH_3)_2$], 6.54 (s, 1, C_4 H), 6.67 (d, 1, J = 9 Hz, C_3 H), 7.1 (q, 1, J_{AB} = 9, J_{AX} = 2 Hz, C_4, H), 7.51 (d, 1, J = 2 Hz, C_6, H), 7.8 (d, 1, J = 7 Hz, NHCH), 12.7 (broad s, 1, NH pyrazole).

Anal. Calcd for $C_{13}H_{16}ClN_3$: C, 62.51; H, 6.37. Found: C, 62.63; H, 6.45.

5-[5-Chloro-2-(2-oxopropylamino)phenyl]-3-methylpyrazole (13).—A mixture of 4 g of **11** and 80 ml of hydrochloric acid was heated on the steam bath for 5 min. The reaction mixture was then neutralized with saturated sodium bicarbonate solution and the precipitated solid was collected. The aqueous phase was extracted with methylene chloride in four portions. The methylene chloride extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate to give 1.8 g of crude product, mp 175–178°. Recrystallization from benzene gave white needles: mp 175–177°; ir (KBr) 3270 and 1710 cm^{-1}; uv max 220 mμ (ε 23,000), 233 (24,000), 263 (13,000), and 335 (5500); nmr (DMSO) 2.17 (s, 3, CH_3), 2.32 (s, 3, CH_3), 4.16 (d, 2, J = 5 Hz, $NHCH_2$–), 6.45 (s, 1, C_4 H), 6.48 (d, 1, J = 9 Hz, C_3, H) 7.08 (q, 1, J_{AB} = 9 Hz, J_{AX} = 2 Hz, C_4, H), 7.48 (d, 1, J = 2 Hz, C_6, H), 8.27 (t, 1, J = 5 Hz, $NHCH_2$), 12.73 (broad s, 1, NH pyrazole).

Anal. Calcd for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35. Found: C, 59.53; H, 5.27.

7-Chloro-2,5-dihydro-4-methyl-1,2,5-benzothiadiazepine 1,1-Dioxide (14).—A solution of 5.6 g (0.02 mol) of **17** in a mixture of 20 ml of tetrahydrofuran and 75 ml of benzene was boiled for 30 min and then concentrated to one-third volume. The hot solution was diluted with an equal volume of hexane and chilled on ice; the solids were collected to give 4.5 g (92% yield) of the crude product, mp 165–167°. Recrystallization from tetrahydrofuran–hexane gave colorless needles: mp 175–178°; uv max 220 mμ (ε 19,500) and 285 (6100); nmr (DMSO) δ 1.83 (s, 3, $-CH_3$), 4.96 (s, 1 =CH), 8.17 (s, 1, NH), and 8.54 ppm (s, 1, NH).

Anal. Calcd for $C_9H_9ClN_2O_2S$: C, 44.17; H, 3.71. Found: C, 44.30; H, 4.31.

Five recrystallizations of 1 g of **14** from methanol gave 0.1 g of **17**, mp 133–136°.

7-Chloro-2,3,4,5-tetrahydro-4-methyl-1,2,5-benzothiadiazepine 1,1-Dioxide (15a). A. By Reduction with Lithium Aluminum Hydride of 14.—To a suspension of 1.5 g (40 mmol) of lithium aluminum hydride in 150 ml of dry ether was added 4.9 g (0.02 mol) of **14**, and the mixture was stirred and heated under reflux for 2.5 hr. It was then cooled and the excess lithium aluminum hydride was decomposed by the addition of ethyl acetate and water. The reaction mixture was then filtered through Celite and the filter was washed with tetrahydrofuran. The aqueous phase was separated and extracted with ether. The combined organic extracts were dried over sodium sulfate and concentrated to dryness *in vacuo* to give 2.5 g of crude product, mp 190–195° dec. Recrystallization from 2-propanol gave colorless prisms: mp 221–225° dec; uv max 220 mμ (ε 31,000), 257 (8400), and 309 (2700).

Anal. Calcd for $C_9H_{11}ClN_2O_2S$: C, 43.81; H, 4.49. Found: C, 43.82; H, 4.41.

B. By Reduction of 17 with Sodium Borohydride.—To a solution of 50 g of **17** in 1 l. of dry 1,2-dimethoxyethane was added 10 g of sodium borohydride and the mixture was stirred under reflux for 18 hr. The reaction mixture was then cooled and the excess borohydride was decomposed with acetic acid and water. It was then diluted with water and extracted with methylene chloride in four portions. The organic extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from hexane to give 33.5 g (67%) of crude product, mp 208–221° dec.

7-Chloro-2,3,4,5-tetrahydro-2,4-dimethyl-1,2,5-benzothiadiazepine 1,1-Dioxide (15b).—A solution of 5 g (20 mmol) of **15a** in 250 ml of 1,2-dimethoxyethane was stirred and heated under reflux for 30 min with 1.2 g (25 mmol) of a 50% dispersion of sodium hydride in mineral oil. To the cooled reaction mixture was then added 3.5 g (25 mmol) of methyl iodide dropwise with stirring. The reaction mixture was then stirred under reflux for 1 hr, filtered, and concentrated to dryness *in vacuo*. The residue was then dissolved in tetrahydrofuran and filtered through alumina using more tetrahydrofuran to wash the alumina. The eluates were concentrated to dryness *in vacuo*, and the residue was crystallized from ether to give 3.5 g of crude product, mp 140–150°. Recrystallization from 2-propanol gave off-white prisms: mp 148–150°; ir (KBr) 3380 cm^{-1}; uv max 220 mμ (ε 29,000), 258 (8900), and 310 (3100); nmr ($CDCl_3$) δ 1.3 (d, 3, J = 6 Hz, CH_3), 2.86 (s, 3, NCH_3), and 4.28 ppm (s, 1, NH).

Anal. Calcd for $C_{10}H_{13}ClN_2O_2S$: C, 46.06; H, 5.03. Found: C, 45.97; H, 5.10.

6-Chloro-3-chloromethyl-3,4-dihydro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (16).—A mixture of 206.6 g (1 mol) of 2-amino-4-chlorobenzenesulfonamide, 118.5 ml (1.5 mol) of chloroacetone, 1 g of *p*-toluenesulfonic acid, and 3 l. of toluene was stirred and heated under reflux for 2.5 hr. The water which separated was collected in a Dean–Stark trap. The reaction mixture was then filtered and the insoluble material was discarded. To the filtrate was added 1 l. of hexane and after standing overnight 252.5 g (89%) of crude product, mp 160–163°, was collected. Recrystallization from ethanol–water with charcoal gave colorless prisms: mp 171–173°; uv max 216 mμ (ε 36,000), 253 (12,500), and 315 (3500).

Anal. Calcd for $C_9H_{10}Cl_2N_2O_2S$: C, 38.45; H, 3.58. Found: C, 38.25; H, 3.71.

7-Chloro-2,3,4,5-tetrahydro-4-methoxy-4-methyl-1,2,5-benzol thiadiazepine 1,1-Dioxide (17).—To a stirred solution of 28.1 g (0.1 mol) of **16** in 150 ml of methanol, prechilled to an internatemperature of 10°, was added 6.0 g (0.11 mol) of sodium methoxide. The solution was stirred at 10° for 15 min and then at room temperature overnight. The precipitated solid was filtered off and discarded. The filtrate was concentrated to dryness *in vacuo*. The residue was crystallized from 100 ml of ether to give 14.4 g (52%) of crude **17**, mp 130–134°. Recrystallization from methanol gave colorless prisms: mp 134–137°; uv max 220 mμ (ε 36,000), 250 (8300), and 300 (2800); nmr (DMSO) δ 1.43 (s, 3, $-CCH_3$), 3.03 (s, 3, $-OCH_3$), and 3.3 ppm (m, 3, NH and CH_2).

Anal. Calcd for $C_{10}H_{13}ClN_2O_3S$: C, 43.40; H, 4.37. Found: C, 43.72; H, 4.91.

***N*-Acetonyl-2-amino-4-chlorobenzenesulfonamide (18).**—A solution of 15 g of **17** in 500 ml of tetrahydrofuran and 120 ml of water was allowed to stand for 3 days at room temperature in an open beaker while the tetrahydrofuran evaporated slowly. The solid which separated was collected and washed with water to give 11 g of crude **18**, mp 115–119°. Recrystallization from tetrahydrofuran–hexane gave colorless plates: mp 116–118°; ir (KBr) 3450, 3360, 3340, and 1730 cm^{-1}; uv max 217 mμ (ε 36,600), 250 (9200), and 315 (4500); nmr (DMSO) δ 2.07 (s, 3, $-CH_3$), 3.73 (d, 2, J = 6 Hz, $-CH_2$), and 7.86 ppm (t, 1, J = 6 Hz, –NH–).

Anal. Calcd for $C_9H_{11}ClN_2O_3S$: C, 41.15; H, 4.22. Found: C, 41.07; H, 4.38.

2-Amino-4-chloro-*N*-(2-hydroxypropyl)benzenesulfonamide (19).—To a solution of 5 g of **18** in 200 ml of methanol cooled in an ice bath was added 5 g of sodium borohydride and the mixture was stored in a refrigerator overnight. It was then diluted to 2 l. with ice, neutralized with glacial acetic acid, and extracted with methylene chloride in five portions. The organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give 5.5 g of residue, which was crystallized from ethyl acetate–petroleum ether to give 3.5 g of crude product, mp 91–97°. Recrystallization from benzene gave colorless prisms, mp 103–105°.

Anal. Calcd for $C_9H_{13}ClN_2O_3S$: C, 40.83; H, 4.95; N, 10.58. Found: C, 40.80; H, 5.22; N, 10.72.

***N*-(2-Hydroxypropyl)-4-chloro-2-(2-hydroxy-1-naphthyl)azobenzenesulfonamide (20).**—A solution of 1 g of **19** in 3 ml of concentrated HCl was diluted with 5 ml of water and treated with several drops of a solution of 1 g of sodium nitrite in 5 ml of water until the mixture gave a positive starch iodide test. This solution was then added to a solution of 0.1 g of β-naphthol in 2 ml of 10% aqueous sodium hydroxide in 5 ml of water. The orange solids which precipitated on standing were collected and recrystallized twice from ethanol to give 0.1 g of orange-red needles, mp 233–236°.

Anal. Calcd for $C_{19}H_{18}ClN_3O_4S$: C, 54.34; H, 4.32; N, 10.01; S, 7.63. Found: C, 54.46; H, 4.22; N, 9.83; S, 7.94.

Registry No.—**6**, 30855-63-1; **7**, 30855-64-2; **8**, 30855-65-3; **9**, 30855-66-4; **10**, 30855-67-5; **11**, 30855-68-6; **12**, 30855-69-7; **13**, 30855-70-0; **14**, 30855-71-1; **15a**, 30855-72-2; **15b**, 30855-73-3; **16**, 30855-74-4; **17**, 30855-75-5; **18**, 30855-76-6; **19**, 30855-77-7; **20**, 30855-78-8.

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Pyrazolotriazines from Condensation of Nitro with Amino Groups

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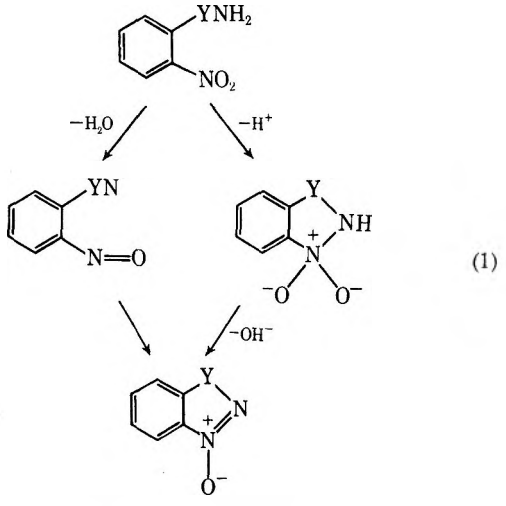
The *o*-nitrophenylhydrazones and 2,4-dinitrophenylhydrazones of α-cyanophenylacetaldehyde and its *p*-chloro and *p*-methoxy derivatives were isomerized to the corresponding 1-*o*-nitroaryl-5-aminopyrazoles. These were converted to 3-arylpyrazolo[5,1-*c*]benzo-1,2,4-triazine 5-oxides with potassium hydroxide. The expected interference if a nitroso nitrene intermediate were involved could not be detected. The 3-phenyl and 3-*p*-methoxyphenyl analogs were deoxygenated to the corresponding 3-arylpyrazolobenzotriazines by catalytic hydrogenation. 3-Phenylpyrazolo[5,1-*c*]benzo-1,2,4-triazine was also prepared by cyclization of the diazonium salt of 5-amino-1,4-diphenylpyrazole.

Various heterocyclic structures having a cyclic azoxy group can be prepared by base-catalyzed reaction of nitro and primary amino groups in the same molecule.[3] The mechanism has been assumed to be nucleophilic attack by the amino group on the nitro nitrogen, analogous to the aldol condensation,[3,4] but the assumption has never been questioned and the mechanism has never been investigated. A plausible alternative mechanism is internal oxidation of the amino group by the nitro group, with expulsion of water and formation of a nitroso nitrene as an intermediate (eq 1). Oxidation of



(1)

Y = bridge of 1 or 2 atoms

amino groups to give products that might have arisen from a nitrene has been reported,[5] and there is precedent for reaction of a nitrene with a nitroso group in the recent report that *o*-azido-*o'*-nitrosobiphenyl is converted to benzocinnoline oxide by heat.[6] The fact that this product is also formed by the base-catalyzed cyclization of *o*-nitro-*o'*-aminobiphenyl[7] is suggestive (eq 1, Y = *o*-C_6H_4).

We had in our hands a way to test whether the cyclization of nitro and amino groups to form an azoxy function involves a nitrene intermediate. The test is based on the fact that reactions that should produce 5-nitrenopyrazoles in fact produce the isomeric fragmentation products, azoacrylonitriles.[8] A 1-*o*-nitrophenyl-5-aminopyrazole, therefore, should produce some fragmentation product when exposed to cyclizing conditions, if it passes through a nitrene stage (Scheme I). This would be a significant limitation on the synthetic use of this cyclization.

A group of 1-(*o*-nitrophenyl)-5-aminopyrazoles were prepared by treating arylcyanoacetaldehydes (I) with 2-nitro- or 2,4-dinitrophenylhydrazine. When carried out in benzene without any added catalyst but with continuous removal of water, the reaction generally yielded the corresponding hydrazones II, which were readily cyclized by exposure to acid to form the isomeric 5-aminopyrazoles (Table I). The uncyclized hydrazones more or less readily assumed a red tint on long exposure in solution to air. The parent compound, α-cyanophenylacetaldehyde phenylhydrazone, eventually produced small amounts of α-phenyl-β-phenylazoacrylonitrile; deliberate oxidation with permanganate gave this product in 95.4% yield.

The 1-(*o*-nitrophenyl)-5-aminopyrazoles were warmed with potassium hydroxide in aqueous pyridine and were thereby converted to orange-red, crystalline products. No infrared absorption could be detected in the region for C≡N stretching, although their color while somewhat light was not inconsistent with the highly conjugated arylazoacrylonitrile structure. These substances, which were obtained pure in very high yields

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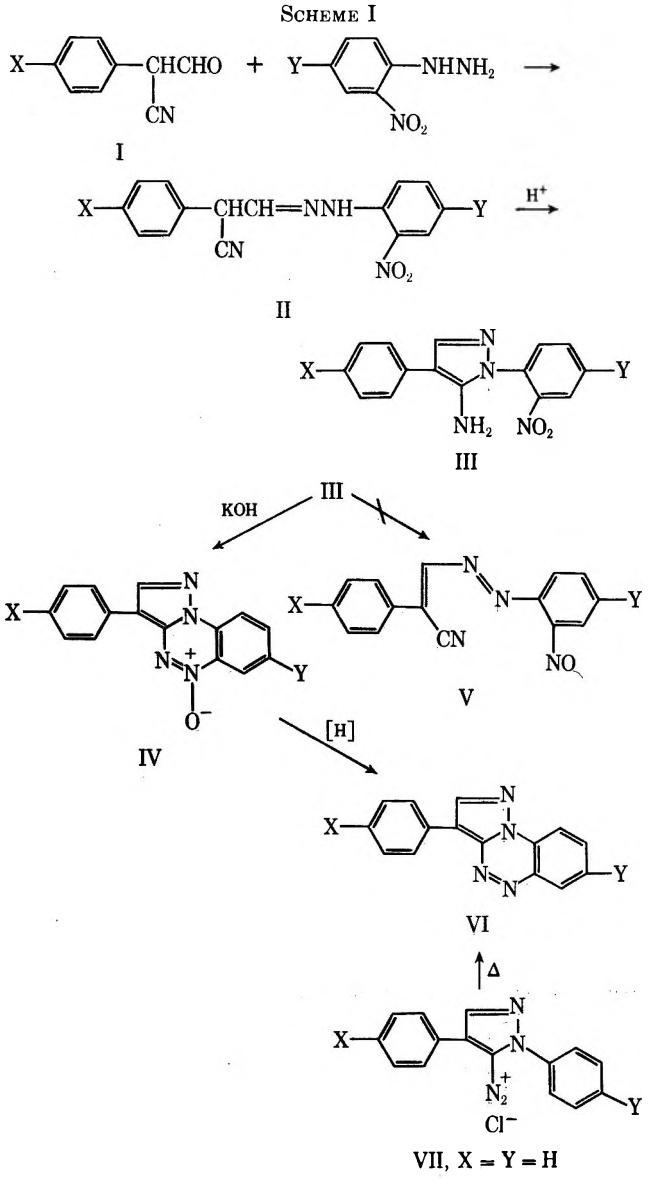
TABLE I

ARYL-α-CYANOACETALDEHYDE o-NITROPHENYLHYDRAZONES (II), 1,4-DIARYL-5-AMINOPYRAZOLES (III), AND 3-ARYLPYRAZOLO[5,1-c]BENZO-1,2,4-TRIAZINE 5-OXIDES (IV)[a]

		II		III			IV		
X	Y	Yield, %	Mp, °C	Yield, %	Mp, °C	Color[b]	Yield, %	Mp, °C	Color[b]
H	H	85	139–140	80	153–155	Y	92	213–214	BO
Cl	H	92	164–165	91	154–155	Y	94	236–237	BO
CH_3O	H	89	133–134	86	135.5–136.5	O	87	218–219	OR
H	NO_2	90	163–164	89	188–189	Y	91	262–263	DR
Cl	NO_2	93	180 dec	93	201–202	OBr	93	286–287	DR
CH_3O	NO_2	85	163–164	84	160–161	YO	73	257–258	DR

[a] Satisfactory analyses (±0.2% for C, H, and N) were obtained for all compounds reported here: Ed. [b] O = orange, R = red, Y = yellow, Br = brown, B = bright, D = dark.

SCHEME I



(Table I), appeared to be the isomeric pyrazolo[5,1-c]-benzo-1,2,4-triazine 5-oxides (IV), but infrared identification of the azoxy function was too ambiguous to be decisive.

The structures of two of them were confirmed by reduction in good yield to the corresponding pyrazolobenzotriazines (VI) with hydrazine and palladium (the other examples too easily suffered dehalogenation or reduction of a nitro group). The isomeric 3-[α-cyanobenzyl]benzo-1,2,4-triazine structure was ruled out by the lack of a C≡N stretching band in the infrared. The spectra of the deoxygenation products were also simpler than those of the 5-oxides in the 1200–1350-cm^{-1} region, where azoxy compounds generally absorb;[9] bands at 1222–1225 and 1337–1340 cm^{-1} were present in the spectra of IV (except that IVc lacked the latter) but not VI. Furthermore, simple deoxygenation, without concomitant addition of hydrogen, is a reaction only to be expected of an *N*-oxide function and not of the nitrosophenylazoacrylonitrile structure.

The only previously reported example of the pyrazolo[5,1-*c*]benzo-1,2,4-triazine system is the 2,3-dimethyl compound, which was prepared by cyclization of diazotized 5-amino-3,4-dimethyl-1-phenylpyrazole.[10] The structure of one of our deoxygenation products was confirmed by the analogous synthesis from 5-amino-1,4-diphenylpyrazole, which produced VIIa identical with that obtained by deoxygenation.

Our results thus uphold the putative aldol-type mechanism (although without strictly proving it) and demonstrate that synthesis of diazine *N*-oxide analogs can be accomplished without interference arising out of possible nitrene intermediates.

Experimental Section

α-Cyanoarylacetaldehyde Arylhydrazones (II).—These compounds were prepared from the α-cyanoarylacetaldehyde (11 mmol) and the arylhydrazine (10 mmol) by refluxing them in about 100 ml of benzene in an apparatus fitted with a Dean-Stark trap to remove water. The reactions appeared to be essentially complete in about 3 hr, but refluxing was continued for 16 hr, after which most of the solvent was removed *in vacuo*, and the products were precipitated in an essentially pure state by addition of ligroin. Analytical samples were obtained by recrystallization from ethyl acetate, alone or mixed with ligroin. The results are summarized in Table I. All samples showed consistent infrared spectra, including absorption at 2180–2200 cm^{-1} (C≡N stretching).

The unsubstituted compound, α-cyanophenylacetaldehyde phenylhydrazone, was isolated after only a 2-hr reflux period: yield 80%; white micro needles; mp 112–113°; infrared (Nujol) 3350 (w, NH), 2180 cm^{-1} (s, C≡N); nmr ($CDCl_3$) δ 6.06 (s, 1 H), 6.66–7.4 (m, 12 H). The nmr signal at δ 6.06 disappeared upon addition of D_2O.

Anal. Calcd for $C_{15}H_{13}H_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.45; H, 5.52; N, 17.86.

Prolonged warming of the foregoing phenylhydrazone in ethanol converted it into the isomeric 5-amino-1,4-diphenylpyrazole, mp 138–140° (lit.[11] 140–141°). Repetition of the procedure of Rupe and Grünholz,[12] reported to produce the phenylhydrazone with mp 155–156°, in our hands produced only the foregoing pyrazole.

α-Phenyl-β-phenylazoacrylonitrile.—A solution of 235 mg of α-cyanophenylacetaldehyde phenylhydrazone in 50 ml of benzene

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was stirred vigorously at room temperature with 25 ml of a 1% solution of potassium permanganate in water for 3 hr. Evaporation of the dried benzene layer left 220 mg (94.4%) of dark red α-phenyl-β-phenylazoacrylonitrile, identical (infrared, mixture melting point) with the substance obtained[8] by thermolysis of 5-azido-1,4-diphenylpyrazole. The same product was formed in traces upon long exposure to the air of solutions of the phenylhydrazone in organic solvents and could be isolated by careful concentration, mp 95–96°.

5-Amino-1-(*o*-nitrophenyl)-4-arylpyrazoles (III).—The corresponding *o*-nitrophenylhydrazones (II) (generally 10 mmol) were boiled for 3 hr in 20 ml of glacial acetic acid containing 2 drops of concentrated sulfuric acid. The solvent was then removed *in vacuo*, the residue was triturated with ice water until it solidified, and a few drops of aqueous ammonia were added. The yellow solids so produced were washed with water, dried, and recrystallized from ethyl acetate. The results are collected in Table I. All of the substances so obtained were free of infrared absorption in the 2100–2300-cm^{-1} region, and all showed absorption at 3248–3300 and 3370–3410 cm^{-1} attributable to NH.

Some of the pyrazoles were also prepared directly from the aldehyde and arylhydrazine by refluxing them in ethanol solution for 48 hr, and in some cases ethanol was used as the recrystallizing solvent; yields were similar. When refluxing of the ethanolic reaction mixtures was discontinued as soon as clear solutions were obtained, the products were found to be the arylhydrazones contaminated with only small amounts of the isomeric pyrazoles.

Pyrazolo[5,1-*c*]benzo-1,2,4-triazine 5-Oxides (IV).—Solutions of the 5-aminopyrazoles (III, 5 mmol) in 10 ml of pyridine were mixed with 10 ml of 5% aqueous potassium hydroxide at room temperature; the mixtures soon became deep red. After heating on a steam bath for 3 hr, the mixtures were poured on ice slurried with enough dilute sulfuric acid to make the resulting mixture slightly acidic. The orange precipitates that separated were collected, washed with cold water, and dried. Analytical samples were obtained by recrystallization from ethyl acetate or dimethylformamide. The results are collected in Table I. None of the examples had infrared absorption above 3200 cm^{-1}, and all of them had a strong absorption peak at 1222–1226 cm^{-1}.

Pyrazolo[5,1-*c*]benzo-1,2,4-triazines (VI).—Compounds VIa and VIc were obtained by adding 1 ml of 90% hydrazine hydrate to a hot solution of 5 mmol of IVa or IVc in 200 ml of ethanol to which 100 mg of 5% palladium on charcoal had been added. After 16 hr of refluxing, the catalyst was filtered off, the filtrate was evaporated *in vacuo*, and the residue was recrystallized from ethyl acetate. When the foregoing procedure was applied to IVb, the unsubstituted product VIa was obtained in 69% yield.

3-Phenylpyrazolo[5,1-*c*]benzo-1,2,4-triazine (VIa) was obtained in 73% yield, mp 166–167°, yellow-orange.

Anal. Calcd for $C_{15}H_{10}N_4$: C, 73.15; H, 4.09; N, 22.75. Found: C, 73.22; H, 4.13; N, 22.86.

3-*p*-Methoxyphenylpyrazolo[5,1-*c*]benzo-1,2,4-triazine (VIc) was obtained in 76% yield, mp 152–153°, orange-red.

Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.53; H, 4.23; N, 20.32.

Preparation of VIa from VII.—A solution of 0.52 g (7.5 mmol) of sodium nitrite in 10 ml of water was added dropwise to a stirred and chilled solution of 1.18 g (5 mmol) of 5-amino-1,4-diphenylpyrazole (VII)[8] in 50 ml of 10% hydrochloric acid. After 15 min, 0.2 g of urea was added, and the mixture was allowed to stand in an ice bath for 3 hr and at room temperature overnight. The mixture was then brought to a boil, whereupon the flocculent, yellow precipitate coagulated to a brown mass. The product was filtered off, washed with cold water, and repeatedly recrystallized from ethanol with the aid of charcoal. A final recrystallization from ethyl acetate gave 0.40 g (32.5%) of yellow needles, mp 166–167°, identical in infrared spectrum and mixture melting point with VIa prepared from IVa.

Registry No.—IIa, 30953-09-4; IIb, 30885-17-7; IIc, 30885-18-8; IId, 30885-19-9; IIe, 30885-20-2; IIf, 30885-21-3; IIIa, 30885-22-4; IIIb, 30885-23-5; IIIc, 30885-24-6; IIId, 30885-25-7; IIIe, 30885-26-8; IIIf, 30885-27-9; IVa, 30885-28-0; IVb, 30885-29-1; IVc, 30885-30-4; IVd, 30885-31-5; IVe, 30885-32-6; IVf, 30885-33-7; VIa, 30885-34-8; VIc, 30885-35-9; α-cyanophenylacetaldehyde phenylhydrazone, 30885-36-0; α-phenyl-β-phenylazoacrylonitrile, 30885-37-1.

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Pyrimido[5,4-*e*]-*as*-triazines. V. The Preparation of Alkyl 6-Amino-*as*-triazine-5-carboxylates from Some 5-Chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazines[1]

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The reaction of 5-amino-4-chloro-6-hydrazinopyrimidine (**1**) with ethyl ortho(methoxy)acetate, ethyl ortho(chloromethyl)acetate, and ethyl ortho(ethoxycarbonyl)acetate gave, respectively, the corresponding 3-substituted 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazines (**3–5**). Oxidative 5-methoxydechlorination of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (**2**), **3**, and **4** with silver oxide in MeOH gave the heteroaromatic 5-methoxy compounds **7–9**. The pyrimidine ring of **7** was opened with methanolic HCl to give methyl 6-amino-*as*-triazine-5-carboxylate (**17**). The formation of **17** and some 3-substituted derivatives was also effected by treatment of **2–5** with Br_2 in alcohol.

In previous papers, we described some replacement reactions of the chloro group of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (**2**) with various nucleophiles.[2,3] We now report the preparation and conversion of this and related type compounds to the esters of 6-amino-*as*-triazine-5-carboxylate (*i.e.*, **17**). Previously, the preparation of derivatives of **17** from simple reactants was unsuccessful.[4]

The condensation of **1** with ethyl orthoformate in the presence of hydrochloric acid was shown to give **2**.[5] Similarly, the reaction of **1** with ethyl ortho(methoxy)-acetate,[6] ethyl ortho(chloromethyl)acetate,[7] and ethyl

(1) This investigation was supported by funds from the C. F. Kettering Foundation and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract NIH-71-2021.

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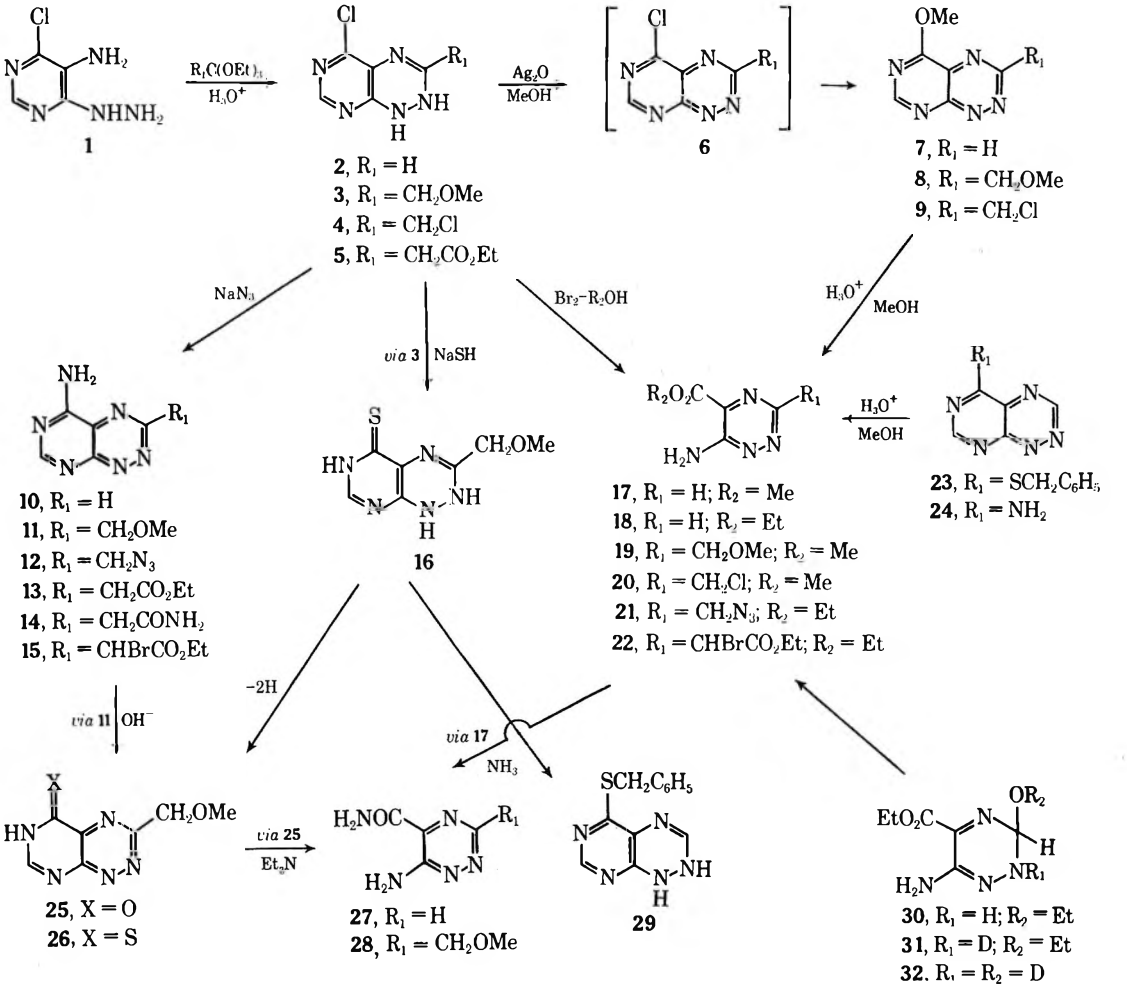

ortho(ethoxycarbonyl)acetate[8] gave, respectively, **3**, **4**, and **5**. Recently the oxidative 5-methoxylation of 1,2-dihydropyrimido[5,4-*e*]-*as*-triazine and its *C*-methyl derivatives with silver oxide in MeOH gave the corresponding 5-methoxypyrimido[5,4-*e*]-*as*-triazines (two oxidation steps).[9] Treatment of **2** with the reagent at room temperature resulted in oxidative 5-methoxydechlorination to give **7**. Similarly, treatment of the dihydro compounds **3** and **4** gave, respectively, the 3-methoxymethyl- and 3-chloromethyl-5-methoxy compounds **8** and **9**. Apparently the pyrimidotriazine **6** is an intermediate in which the reactivity of the chloro group is increased by the increase in the electron-withdrawing ability of the heteroaromatic *as*-triazine ring. The pyrimidine ring of **7** was opened in methanolic HCl to give the triazine-5-carboxylate **17**, presumably formed *via* an imino ether intermediate. Similarly, the pyrimidine ring of the heteroaromatic 5-benzylthio[2] and 5-amino[3] compounds **23** and **24** was opened in hot methanolic HCl to give **17**. The preparation of **17** was also effected by treatment of a methanolic solution of **2** with Br_2. Presumably **7** is an intermediate, which undergoes acidic ring cleavage by the HBr generated in the oxidation step. In the reaction of **2** with Br_2 in EtOH, the product was identified as the hydrobromide of either the 3-ethoxy-2,3-dihydro-*as*-triazine **30** or the corresponding 5-ethoxy-4,5-dihydro compound by its pmr spectrum in deuterated DMSO. This spectrum also showed that the product disassociated with time to give **18**, and the addition of D_2O to this solution gave another form, presumably (from **30**) either **31** or **32**. Structure **30** is favored by steric considerations but protonation of **18** might result in addition across the 4,5[10a] double bond. The corresponding 3-ethoxy-3,4-dihydro-*as*-triazine is a possible addition product, but this compound is probably less stable than **30**.[10b]

The uv spectrum of **17** in HCl changed with time from three peaks to one peak, indicating that this compound also undergoes covalent hydration readily. Neutralization of an aqueous solution of **30** not only removed the HBr but also the covalently bound EtOH to give **18**. Proof of the structure of the latter was provided by its reaction with refluxing NH_3 to give the known amide **27**.[3] These and previous results indicate that in an acidic medium the triazine ring of a dihydropyrimidotriazine is opened to give a pyrimidine, whereas the pyrimidine ring of a heteroaromatic pyrimidotriazine is opened to give an *as*-triazine.[2,3,11]

The dihydropyrimidotriazines **3**–**5** were also treated with Br_2 in MeOH. Compound **3** gave **19**, **4** gave a 4:1 mixture of **20** and the corresponding 3-bromomethyl compound, and **5** gave the 3-bromoacetic acid derivative **22**. The mixture of **20** and the bromomethyl compound was identified by elemental analyses, by its pmr spectrum and by reaction with NaN_3 in EtOH to give **21**, transesterification occurring during the reaction.

(8) S. M. McElvain and J. P. Schroeder, *J. Amer. Chem. Soc.*, **71**, 40 (1949).
(9) M. E. C. Biffin, D. J. Brown, and T. Sugimoto, *J. Chem. Soc. C*, 139 (1970).
(10) (a) W. P. Paudler and T.-K. Chen, *J. Heterocycl. Chem.*, **7**, 767 (1970); (b) A. Maccoll, *J. Chem. Soc. C*, 670 (1946).
(11) (a) P. A. Van Damme, A. G. Johannes, H. C. Cox, and W. Berends, *Recl. Trav. Chim. Pays-Bas*, **79**, 255 (1960); (b) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Amer. Chem. Soc.*, **84**, 1724 (1962).

Previously, the reaction of **2** with NaN_3 gave directly the heteroaromatic 5-aminopyrimidotriazine **10**.[3] Similarly, **3**–**5** gave **11**–**13**. In **4** azidodechlorination of both the 5-chloro- and 3-chloromethyl groups occurred, but only the 5-azido group was converted to an amino group. Treatment of **13** with refluxing NH_3, and Br_2 in $CHCl_3$, gave the acetamide **14** and the α-bromoacetate **15**, respectively. Reaction of **11** with aqueous NaOH gave **25**, and reaction of **3** with hydrated NaSH gave **16**. The latter was oxidized with diethyl azodicarboxylate to give **26** and alkylated with benzyl chloride to give **29**. The pyrimidine ring of **25** was opened with aqueous ethanolic triethylamine to give **28**.

Experimental Section

Melting points were determined on a Kofler–Heizbank apparatus. The uv absorption spectra of solutions were determined with Cary Model 14 and 17 spectrophotometers, whereas the ir absorption spectra were determined in pressed KBr disks with Perkin–Elmer Models 521 and 621 spectrophotometers. The pmr spectra were obtained on DMSO-d_6 solutions (5–10% w/v) with a Varian A-60A spectrometer at a probe temperature of about 37° with tetramethylsilane as an internal reference. Chemical shifts quoted in the case of multiplets are measured from the approximate center, and the relative peak areas are given to the nearest whole number.

Condensation of Ortho Esters with 5-Amino-4-chloro-6-hydrazinopyrimidine (1).—Ethyl ortho(chloro)acetate (50 ml)[7] was added with vigorous stirring to a mixture of **1** (5.0 g) and concentrated HCl (2.5 ml). After 1.5 hr, the hydrochloride of **4** was collected by filtration, washed with EtOAc (800 ml), and dried *in vacuo* over P_2O_5: yield 6.1 g (76%); mp 180–181° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12a] 0.1 *N* HCl, 335 (5.50); pmr δ 3.87 (2, CH_2), 7.46 (1, CH), ~9.3 (NH, HCl, H_2O).

Anal. Calcd for $C_6H_5Cl_2N_5 \cdot HCl$: C, 28.32; H, 2.38; N, 27.82. Found: C, 28.52; H, 2.53; N, 27.87.

Similarly, ethyl ortho(methoxy)acetate[6] was added with stirring to a mixture of **1** (5.0 g) and concentrated HCl (3.0 ml). After 2 hr, the resulting solution deposited a mixture of **3** and its hydrochloride, which was collected by filtration and washed with petroleum ether, yield 4.5 g. The combined filtrate and wash deposited an additional 1.4 g. The total yield was 5.9 g (75%), mp 143–145° with presoftening. Recrystallization of this material from THF gave the hygroscopic hydrochloride salt of **3**: yield 2.9 g; mp 147–149° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] 0.1 *N* HCl, 224 (14.4), 337 (5.03).

Anal. Calcd for $C_7H_8ClN_5O \cdot HCl$: C, 33.62; H, 3.63; N, 28.00. Found: C, 33.61; H, 4.43; N, 27.96.

The filtrate from above was evaporated to dryness *in vacuo*, and the resulting residue was recrystallized from petroleum ether (bp 85–105°) to give **3**: yield 0.84 g; mp 148–150° dec; pmr δ 3.27 (3, CH_3), 3.59 (2, CH_2), 7.43 (1, CH), ~7.6, ~9.2 (1, 1, NH).

Anal. Calcd for $C_7H_8ClN_5O$: C, 39.36; H, 3.77; Cl, 16.6; N, 32.78. Found: C, 39.53; H, 3.68; Cl, 16.7; N, 32.84.

Similarly, a mixture of **1** (18.5 g), concentrated HCl (9.8 ml), and ethyl ortho(ethoxycarbonyl)acetate (93 ml)[8] was stirred with cooling for 45 min. The solid (30.9 g) was collected by filtration and added with stirring to a 4.2% (w/v) solution of $NaHCO_3$ (310 ml) to give **5**: yield 17 g (57%); mp 177° dec with presoftening from 171° (recrystallization from petroleum ether did not change the melting point); λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] 0.1 *N* HCl, 224 (15.5), 337 (5.49); ν_{max}, cm^{-1}, 1735, 1710 (CO); pmr δ 1.21 (t, 3, CH_3), 3.98 (2, CH_2CO_2), 4.12 (q, 2, CH_2O), 7.45 (1, CH), 7.88, 9.13 (1, 1, NH).

Anal. Calcd for $C_9H_{10}ClN_5O_2$: C, 42.28; H, 3.94; N, 27.39. Found: C, 42.49; H, 4.10; N, 27.21.

Preparation of 5-Methoxypyrimido[5,4-*e*]-*as*-triazines (7–9).—A mixture of **2** (2.0 g)[5] and Ag_2O (5.4 g) in MeOH (400 ml) was stirred at room temperature for 40 hr. The residue was removed by filtration, the filtrate was evaporated to dryness, and the resulting product was recrystallized from petroleum ether to give **7**: yield 0.82 g (43%); mp 99–100° (lit.[9] mp 100°); λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] pH 7, 227 (16.4),255 sh (2.12), 326 (5.72).

Similarly, treatment of **3**·HCl (2.0 g) gave a solid that was recrystallized from hexane to give **8**: yield 0.84 g (51%); mp 91°; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12a] pH 7, 257 sh (3.12), 332 (5.68); pmr δ 3.45 (3, 3-CH_3O), 4.25 (3, 5-CH_3O), 5.10 (2, CH_2), 9.12 (1, CH).

Anal. Calcd for $C_8H_9N_5O_2$: C, 46.38; H, 4.38; N, 33.80. Found: C, 46.20; H, 4.69; N, 33.95.

Similarly, treatment of **4**·HCl (5.0 g) gave a residue that was extracted with ether. Removal of ether *in vacuo* gave an oil that was triturated with H_2O to give solid **9**, yield 2.1 g, mp ~67°. Recrystallization of this sample from hexane gave pure **9**: yield 0.70 g (17%); mp 79–81°; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12a] pH 7, 258 sh (3.35), 332 (5.73); pmr δ 4.25 (3, CH_3), 5.38 (2, CH_2), 9.18 (1, CH).

Anal. Calcd for $C_7H_6ClN_5O$: C, 39.73; H, 2.86; N, 33.10. Found: C, 39.69; H, 2.92; N, 33.32.

The hexane and H_2O filtrates from above gave an additional 1.5 g of crude **9**, mp ~69° with presoftening. The infrared spectrum (ν_{max} 1710 cm^{-1}) indicated that this material was contaminated with the corresponding 5(6H)-oxy compound.

5-Amino-3-methoxymethylpyrimido[5,4-*e*]-*as*-triazine (11).—A mixture of **3** HCl (5.0 g) and NaN_3 (3.3 g) in 1:1 EtOH–H_2O (100 ml) was refluxed for 2 hr. The resulting solution was evaporated to dryness *in vacuo*, and the residue was extracted with hot THF. Removal of the solvent gave a solid which was recrystallized from EtOAc to give **11** in two crops: yield 3.0 g (78%); mp 178–180°; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] pH 7, 222 (11.1), 253 (12.3), 283 sh (2.35), 373 (5.33); pmr δ 3.52 (3, CH_3), 5.05 (2, CH_2), 8.70, ~8.8 (3, CH, NH_2).

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 43.77; H, 4.16; N, 43.90.

5-Amino-3-azidomethylpyrimido[5,4-*e*]-*as*-triazine (12).—A solution of NaN_3 (4.0 g) in H_2O (40 ml) was added to a solution of **4** HCl (2.0 g) in EtOH (130 ml). The mixture was stirred at room temperature for 18 hr and evaporated to dryness *in vacuo* at ~50°. The resulting residue was extracted with $CHCl_3$ (three 200-ml portions), and the combined extracts were evaporated to dryness, yield 1.2 g (75%), mp 177° dec. Recrystallization of a portion of this sample (0.2 g) from C_6H_6 gave pure **12**: yield 0.1 g; mp 179–180° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12a] pH 7, 254 (13.0), 284 sh (2.78), 376 (5.44); ν_{max}, cm^{-1}, 2110 (N_3); pmr δ 5.05 (2, CH_2), 8.67, ~8.7 (3, CH, NH_2).

Anal. Calcd for $C_6H_5N_9$: C, 35.47; H, 2.48; N, 62.05. Found: C, 35.63; H, 2.56; N, 62.03.

Ethyl 5-Aminopyrimido[5,4-*e*]-*as*-triazine-3-acetate (13).—A mixture of **5** (1.0 g) and NaN_3 (0.6 g) in 1:1 EtOH–H_2O (40 ml) was stirred at room temperature for 18 hr and evaporated to dryness *in vacuo*. The residue was extracted with THF, the extract was evaporated to dryness, and the resulting solid was recrystallized from C_6H_6: yield 0.43 g (47%); mp 175°; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] pH 7, 218 (11.0), 255 (13.5), 284 sh (3.05), 374 (5.48); ν_{max}, cm^{-1}, 1730 (CO); pmr δ 1.22 (t, 3, CH_3), 4.20 (q, 2, CH_2O), 4.46 (2, CH_2CO_2), 8.68, ~8.8 (3, CH, NH_2).

Anal. Calcd for $C_9H_{10}N_6O_2$: C, 46.15; H, 4.30; N, 35.89. Found: C, 46.27; H, 4.40; N, 35.68.

5-Aminopyrimido[5,4-*e*]-*as*-triazine-3-acetamide (14).—A mixture of **13** (0.90 g) and liquid NH_3 (~30 ml) was confined in a Parr bomb for 18 hr at room temperature. The contents of the bomb were evaporated to dryness, and the residue was recrystallized from H_2O: yield 0.24 g (30%); mp >264°; λ_{max}, nm,[12a] pH 7, 263, 395 unstable; ν_{max}, cm^{-1}, 1670 sh (CO), 1615 (NH_2).

Anal. Calcd for $C_7H_7N_7O$: C, 40.97; H, 3.44; N, 47.79. Found: C, 40.87; H, 3.45; N, 47.49.

An additional amount of crude **14** (0.4 g) was obtained from H_2O filtrate. The total yield was 0.64 g (81%).

Ethyl α-Bromo-5-aminopyrimido[5,4-*e*]-*as*-triazine-3-acetate Hydrobromide (15).—A mixture of **13** (400 mg) and Br_2 (0.1 ml) in $CHCl_3$ (70 ml) was stirred at room temperature for 24 hr followed by the addition of a solution of Br_2 (0.1 ml) in $CHCl_3$ (10 ml). After 90 hr, the solid was collected by filtration and recrystallized from CH_3CN: yield 81 mg (12%); mp ~187° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] pH 7, 260 (13.0), 294 sh (3.51), 379 (5.45); ν_{max}, cm^{-1}, 1740 (CO); pmr δ 1.20 (t, 3, CH_3), 4.25 (q, 2, CH_2), 6.53 (1, CHBr), 8.82 (1, CH), ~7.2, ~9.7 (3, NH_2, HBr).

Anal. Calcd for $C_9H_9BrN_6O_2 \cdot HBr$: C, 27.43; H, 2.56; N, 21.33. Found: C, 27.61; H, 2.55; N, 21.44.

(12) Each solution contains 10% dissolving solvent and 90% appropriate aqueous solvent: (a) 8% methanolic DMSO; (b) MeOH; (c) 0.1 *N* NaOH.

Concentration of recrystallization filtrate deposited an additional amount (292 mg) of crude **15**. The total yield was 373 mg (55%).

1,2-Dihydro-3-methoxymethylpyrimido[5,4-*e*]-*as*-triazine-5-(6*H*)-thione (16).—A mixture of **3** (5.2 g), EtOH (650 ml), and hydrated NaSH (26 g) was refluxed for 1 hr, cooled to room temperature, and filtered. The filtrate was evaporated to dryness *in vacuo*, and the residue was dissolved in H_2O and acidified with HOAc. The solid that deposited was collected by filtration, washed with C_6H_6, and reprecipitated from a dilute NaOH solution by the addition of dilute HCl: yield 3.3 g (64%); mp ~253–254° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12c] 0.1 *N* HCl, 234 (7.04), 260 (5.68), 336 (2.94), 406 (2.15); pmr δ 3.25 (3, CH_3), 3.68 (2, CH_2), 6.20, 8.95, ~12.7 (1, 1, 1, NH), 7.57 (1, CH).

Anal. Calcd for $C_7H_9N_5OS$: C, 39.79; H, 4.30; N, 33.15; S, 15.18. Found: C, 39.90; H, 4.31; N, 33.10; S, 15.05.

Methyl 6-Amino-*as*-triazine-5-carboxylate (17). Acidic Cleavage of 7.—A solution of **7** (300 mg) in MeOH (10 ml) containing 1 *N* HCl (2.0 ml) was stirred at room temperature for 18 hr. The product that deposited was collected by filtration: yield 127 mg (45%); mp 186–187° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] 0.1 *N* HCl, 233, 282, 366 changing to 282 (4.36), pH 7, 240 (10.8), 363 (4.17); ν_{max}, cm^{-1}, 1710 (CO); pmr δ 3.90 (3, CH_3), ~7.5 (2, NH_2), 9.15 (1, CH).

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.84; H, 4.12; N, 36.38.

The MeOH filtrate was evaporated to dryness *in vacuo*, and the resulting residue was extracted with $CHCl_3$ to give an additional 79 mg of **17**. The total yield was 206 mg (73%).

Similarly, a solution of **23**[2] was heated at 60° for 2 hr to give a 90% crude yield of **17**. Also, treatment of **24**[3] at 75° for 5 hr gave a 29% crude yield of **17**.

Oxidation and Ring Opening of 5-Chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazines (2–5).—A solution of Br_2 (6.1 ml) in MeOH (100 ml) was added slowly with stirring to a suspension of **2**[5] (10 g) in MeOH (100 ml). After 15 min, the resulting warm solution was diluted with H_2O (10 ml), stirred at room temperature for an additional 3 hr, and evaporated to dryness *in vacuo*. The residue was dissolved in H_2O (300 ml); the solution was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (three 1000-ml portions). The extracts were dried ($MgSO_4$) and evaporated to dryness to give **17**, yield 4.3 g (47%), mp 181° dec. Recrystallization of a small sample from hexane gave a product identical with that described above, mp 185–186° dec.

Similarly, **3** (2.0 g) and Br_2 (0.82 ml) in MeOH (40 ml) and H_2O (2.0 ml) gave **19**, yield 0.93 g (59%), mp 144–145°. Recrystallization of a sample (0.20 g) from C_6H_6 gave the analytical sample (0.13 g): mp 149–150°; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] pH 7, 245 (14.1), 368 (4.2); ν_{max}, cm^{-1}, 1715 (CO); pmr δ 3.33 (3, CH_3O), 3.91 (3, CH_3O_2C), 4.58 (2, CH_2), 7.5 (2, NH_2).

Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.45; H, 4.91; N, 28.11.

In the reaction of **4** (1.0 g) with Br_2 in MeOH (20 ml) and H_2O (1.0 ml), the residue obtained by evaporation of the reaction mixture was dissolved in H_2O (20 ml) and neutralized with $NaHCO_3$ to deposit a 4:1 mixture of **20** and the corresponding 3-bromomethyl compound: yield 0.58 g (70%); mp ~163° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12a,13] pH 7, 252 (14.0), 370 (3.99); ν_{max}, cm^{-1}, 1715 (CO); pmr δ 3.94 (3, CH_3), 4.83, 4.93 (2, CH_2Cl, CH_2Br), ~7.7 (2, NH_2).

Anal. Calcd for $(C_6H_7ClN_4O_2)_4 \cdot C_6H_7BrN_4O_2$: C, 34.29; H, 3.35; N, 26.65. Found: C, 33.97; H, 3.30; N, 26.30.

Similarly, **5** (1.0 g) and Br_2 (0.40 ml) in EtOH (20 ml) and H_2O (1.0 ml) gave an H_2O-insoluble residue that was extracted into $CHCl_3$. The residue obtained from the dried extract ($MgSO_4$) was washed with hexane to give **22**: yield 0.34 g (26%); mp ~115° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12a] pH 7, 254 (9.75), 366 (3.13); ν_{max}, cm^{-1}, 1740, 1710 (CO); pmr (DMSO-d_6–D_2O), δ 1.27 (m, CH_3), 4.32 (m, CH_2), 6.24 (CHBr).

Anal. Calcd for $C_{10}H_{13}BrN_4O_4$: C, 36.05; H, 3.93; Br, 23.99; N, 16.82. Found: C, 35.93; H, 4.00; Br, 24.26; N, 17.09.

Ethyl 6-Amino-*as*-triazine-5-carboxylate (18) and Ethyl 6-Amino-3-ethoxy-2,3-dihydro-*as*-triazine-5-carboxylate Hydrobromide (30).—A solution of Br_2 (0.61 ml) in EtOH (50 ml) was added with stirring over a 10-min period to a suspension of **2**[5] (2.0 g) in EtOH (120 ml). After 1 hr, this solution was concentrated *in vacuo* to half-volume and allowed to stand at room temperature for 18 hr. The solid that deposited was collected by filtration, washed with Et_2O, and recrystallized from ethanol to give **30**: yield 1.3 g (37%); mp 191° dec with presublimation; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] 0.1 *N* HCl, 284 (4.72), pH 7, 241 (11.5), 364 (4.58); ν_{max} cm^{-1}, 1760 (CO); pmr δ 1.20 (m, CH_3 of **30**, **18**, and EtOH), 3.44, 4.32 (m, CH_2 of **30**, **18**, and EtOH), ~8.6 (br, CH of **30**), 9.16 (CH of **18**), ~7.7, ~11 (NH, HBr, OH). Addition of D_2O gave a new peak at δ 8.45 (CH).

Anal. Calcd for $C_6H_8N_4O_2 \cdot C_2H_6O \cdot HBr$: C, 32.56; H, 5.12; N, 18.98. Found: C, 32.67; H, 5.08; N, 19.18.

A sample of **30** (200 mg) was dissolved in H_2O (10 ml); this solution was neutralized with NaOAc (56 mg) and evaporated to dryness. The residue was extracted with hot petroleum ether, and the extract was cooled to deposit **18**: yield 63 mg (55%); mp 119°; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] 0.1 *N* HCl, 237, 282, 364 unstable; pH 7, 241 (11.3), 363 (4.48); ν_{max}, cm^{-1}, 1705; pmr δ 1.33 (t, 3, CH_3), 4.38 (q, 2, CH_2), 7.5 (2, NH_2), 9.17 (1, CH).

Anal. Calcd for $C_6H_8N_4O_2$: C, 42.86; H, 4.80; N, 33.32. Found: C, 42.87; H, 4.85; N, 33.19.

Ethyl 6-Amino-3-azidomethyl-*as*-triazine-5-carboxylate (21).—A suspension of a 4:1 mixture of **20** and the corresponding 3-bromomethyl compound (0.40 g) and NaN_3 (1.0 g) in 5:2 EtOH–H_2O (35 ml) was stirred at room temperature for 20 hr and evaporated to dryness *in vacuo*. The residue was washed with H_2O and dissolved in ether ($MgSO_4$), and the resulting solution was evaporated to dryness *in vacuo*: yield 0.22 g (56%); mp 134–135°; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12a] pH 7, 246 (14.8), 368 (4.15); ν_{max}, cm^{-1}, 2130, 2095 (N_3), 1710 (CO); pmr δ 1.35 (t, 3, CH_3), 4.41 (q, 2, CH_2), 4.67 (2, CH_2), ~7.6 (2, NH_2).

Anal. Calcd for $C_7H_9N_7O_2$: C, 37.67; H, 4.06; N, 43.93. Found: C, 37.62; H, 3.82; N, 43.61.

3-Methoxymethylpyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (25).—A suspension of **11** (1.0 g) in H_2O (10 ml) containing 1 *N* NaOH (5.3 ml) was stirred at room temperature for 2 hr. The resulting solution was acidified with 1 *N* HCl (11 ml), and the yellow solid that deposited was collected by filtration and dried *in vacuo* over P_2O_5 at 78°: yield 0.75 g (75%); mp ~175° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] 0.1 *N* NaOH, 251 (14.7), 282 sh (3.18), 372 (4.58); ν_{max}, cm^{-1}, 1715, 1700 (CO).

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.52; H, 3.66; N, 36.27. Found: C, 43.78; H, 3.72; N, 36.28.

3-Methoxymethylpyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione Hemihydrate (26).—A mixture of **16** (1.0 g), diethyl azodicarboxylate (1.5 ml), and $CHCl_3$ (100 ml) in a flask protected from light with aluminum foil was stirred at room temperature for 20 hr, then evaporated to dryness *in vacuo*. The solid was washed with MeOH (100 ml) and dried *in vacuo* over P_2O_5 to give mainly **26**, yield 0.84 g (85%), mp ~226° dec (taken rapidly). A solution of the product (0.17 g) in H_2O containing 1 *N* NaOH (0.9 ml) was neutralized with 1 *N* HCl (0.9 ml) to deposit the hemihydrate (0.07 g): mp 160–161° dec with presoftening; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12c] 0.1 *N* NaOH, 254 (11.3), 375 (2.18), 455 (2.77); pmr δ 3.58 (CH_3), 5.27 (CH_2), 9.33 (CH), ~13 (NH).

Anal. Calcd for $C_7H_7N_5OS \cdot {}^1/_2H_2O$: C, 38.51; H, 3.69; N, 32.09. Found: C, 38.43; H, 4.05; N, 32.09.

6-Amino-*as*-triazine-5-carboxamide (27).—A mixture of **18** (200 mg) and liquid NH_3 was refluxed under a Dry Ice–acetone condenser for 8 hr. The ammonia was allowed to evaporate, and the practically pure product (156 mg) was recrystallized from MeOH, yield 47 mg (28%), mp 253° (lit.[3] mp 253–254°).

6-Amino-3-methoxymethyl-*as*-triazine-5-carboxamide (28).—A mixture of **25** (4.4 g), EtOH (90 ml), H_2O (9.0 ml), and Et_3N (9.0 ml) was refluxed for 22 hr. The solid that deposited was collected by filtration and dried *in vacuo* over P_2O_5: yield 2.1 g (50%); mp 206–207°; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] pH 7, 243 (14.2), 362 (3.91); ν_{max}, cm^{-1}, 1700 (CO).

Anal. Calcd for $C_6H_9N_5O_2$: C, 39.34; H, 4.95; N, 38.24. Found: C, 39.36; H, 5.04; N, 38.19.

5-(Benzylthio)-1,2-dihydro-3-methoxymethylpyrimido[5,4-*e*]-*as*-triazine (29).—A solution of **16** (1.0 g) in H_2O (25 ml) containing benzyl chloride (0.6 ml) and 1 *N* NaOH (5.0 ml) was stirred at room temperature for 5 hr. The solid that deposited (1.2 g) was extracted with hot C_6H_6, the extract was evaporated to dryness, and the resulting residue (0.91 g) was recrystallized from petroleum ether: yield 0.34 g; mp 134–135°; λ_{max}, nm ($\epsilon \times 10^{-3}$),[12b] pH 7, 242 (13.8), 265 sh (6.90), 392 (8.07); pmr δ 3.25 (3, CH_3), 3.61 (2, CH_2O), 4.33 (2, CH_2S), 7.05, 8.83 (1, 1, NH), 7.35 (5, C_6H_5), 7.71 (1, CH).

(13) The ϵ values were calculated from the molecular weight of the mixture.

Anal. Calcd for $C_{14}H_{15}N_5OS$: C, 55.79; H, 5.05; N, 23.24. Found: C, 55.84; H, 5.04; N, 23.20.

Registry No.—**3**, 30855-40-4; **3** HCl, 30855-41-5; **4** HCl, 30855-42-6; **5**, 30855-43-7; **8**, 30855-44-8; **9**, 30855-45-9; **11**, 30855-46-0; **12**, 30855-47-1; **13**, 30855-48-2; **14**, 30855-49-3; **15**, 30936-92-6; **16**, 30855-50-6; **17**, 30855-51-7; **18**, 30855-52-8; **19**, 30855-53-9; **20**, 30855-54-0; **20** (R_1 = CH_2Br), 30855-55-1; **21**, 30855-56-2; **22**, 30855-57-3; **25**, 30855-58-4; **26**, 30855-59-5; **28**, 30855-60-8; **29**, 30855-61-9; **30**, 30855-62-0.

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

The Facile Isomerization in the 1,3-Dipolar Addition Reactions of Substituted 1-Alkoxycarbonyliminopyridinium Ylides with Dimethyl Acetylenedicarboxylate[1]

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Received August 25, 1970

The 1,3-dipolar cycloaddition of substituted 1-alkoxycarbonyliminopyridinium ylides (**1**, **2**, **6**, **7**, **10–14**, and **32–34**) with dimethyl acetylenedicarboxylate in the absence and the presence of tetracyanoethylene produced pyrazolo[1,5-*a*]pyridines (**3–5**, **8**, **9**, and **39**), dihydropyrazolo[1,5-*a*]pyridines (**15–19**), vinylpyridines (**20–24** **35–37**), and cycloadducts (**25**, **26**, and **29–31**). The dihydro compounds **22** and **23** were easily transformed into the vinylpyridines **41** and **42**. Structural elucidation of the cycloadducts and the rearranged products was accomplished by spectral means, while the structures of **45** and **46** were established by chemical degradation. Some mechanisms for the rearranged products are also discussed.

Although 1,3-dipolar cycloaddition reactions of zwitterionic ylides have been extensively studied,[2] the addition of 1-alkoxycarbonyliminopyridinium ylides (pyridinium *N*-betaines) to dipolarophiles have not yet been reported. Okamoto, *et al.*,[3] observed that *N*-iminopyridinium ylides reacted with nucleophilic reagents, but the reactions of *N*-methylimino- and *N*-acetyliminopyridinium ylides with a dipolarophile such as acetonitrile did not afford 1,3-dipolar cycloadducts; the contrasting reactivity of these compounds was attributed to the difference in basicity. The mechanism of 1,3-dipolar cycloaddition reactions of the heteroaromatic nitrogen ylides with dipolarophiles has been discussed,[3] but information concerning the detailed mechanisms and, in particular, convincing evidence for dihydro-type intermediates have not been presented. In continuation of work in this area,[4] this paper deals with the 1,3-dipolar cycloaddition of substituted 1-alkoxycarbonyliminopyridinium ylides with dimethyl acetylenedicarboxylate (DAC) in the presence and the absence of tetracyanoethylene (TCNE).

Results and Discussion

Several ring-substituted 1-alkoxycarbonyliminopyridinium ylides **1**, **2**, **6**, **10–14**, and **32–34** were prepared by the modified Gösl method.[4] The ylide **7**[5] was obtained by the modified Hafner method described by Snieckus, *et al.*, and the yield was increased to 40%.

1,3-Dipolar Cycloaddition of Substituted Pyridinium Ylides with DAC.—The 1,3-dipolar cycloaddition reactions of the 1-alkoxycarbonyliminopyridinium ylides with dimethyl acetylenedicarboxylate (DAC) were carried out both in the absence and the presence of tetracyanoethylene (TCNE) in benzene or acetonitrile. These results are summarized in Tables I and II.

TABLE I

1,3-DIPOLAR CYCLOADDITION OF THE YLIDES AND DAC IN THE ABSENCE OF TCNE

	Yields of reaction products[a]					
	Dihydropyrazolopyridine derivatives		Vinylpyridine derivatives		Pyrazolopyridine derivatives	
Ylide	Yield, %	Compd no.	Yield, %	Compd no.	Yield, %	Compd no.
1					*Ca.* 1	**3**
2					Trace	**4** + **5**
6					27	**8**
7					28	**9**
10	12	**15**	22	**20**		
11	11	**16**	24	**21**		
12	80	**17**	3	**22**		
13	68	**18**	17	**23**		
14	56	**19**	44	**24**		
32			43	**35**		
33			27	**36**		
34			5	**37**		

[a] C, H, and N analyses within ±0.35% for all products: Ed.

The reactions of **1** and **2** with DAC in the presence of TCNE gave the pyrazolopyridine derivative **3**[2] and an isomeric mixture of **4** and **5** (on the basis of the nmr inspection), respectively, in very low yields. In the reactions in the absence of TCNE, the pyrazolopyridine derivatives were formed in only trace amounts. On similar treatment of γ-substituted pyridinium ylides

(1) Part LI: Studies of Heteroaromaticity. For part L of this series, see T. Sasaki, T. Yoshioka, and Y. Suzuki, *J. Syn. Org. Chem. Jap.*, **28**, 1054 (1970).

(2) For leading references, see (a) R. Huisgen, R. Grashey, and J. Sauer, "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, Chapter 11, p 739; (b) V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **33**, 2062 (1968).

(3) T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *Chem. Pharm. Bull.*, **14**, 506 (1966).

(4) (a) T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc. C*, 481 (1970); (b) T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *J. Org. Chem.*, **35**, 426 (1970).

(5) This ylide could not be synthesized by the Gösl method. Although 4-ethoxyearbonyl-1-ethoxycarbonyliminopyridinium ylide was prepared by the Hafner method, the yield was reported as only 1%; see A. Balasubramanian, J. M. McItosh, and V. Snieckus, *ibid.*, **35**, 433 (1970).

TABLE II

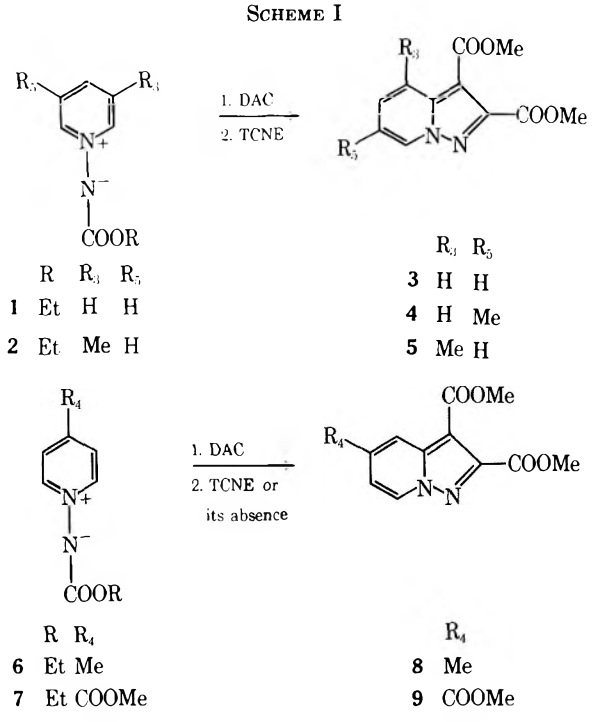
1,3-DIPOLAR CYCLOADDITION OF THE YLIDES AND DAC IN THE PRESENCE OF TCNE

	Yields of reaction products[a]			
	Diels–Alder adduct		Pyrazolopyridine derivatives	
Ylide	Yield, %	Compd no.	Yield, %	Compd no.
1	0		5	3
2	0		1	4 + 5
6	0		44	8
7			45	9
10	12	25	40	28
11	15	26	51	28
12	75	29		
13	62	30		
14	67	31		
32	0		0	(38)
33	0		46	39
34	0		0	(40)

[a] C, H, and N analyses within ±0.35% for all products: Ed.

6 and 7 with DAC in the presence or the absence of TCNE, the products were characterized by nmr spectral data as the corresponding pyrazolopyridine derivatives 8 and 9, the normal products as suggested by Huisgen and others,[2] as shown in Scheme I. The structures of 3–5, 8, and 9 were elucidated by the unequivocal independent synthesis (see Experimental Section). These nmr data are shown in Table III. The formation of these pyrazolopyridines involves aromatization of the initial unstable adducts with loss of the ethoxycarbonyl group and hydrogen. TCNE has been found to function as a dehydrogenating agent in analogous reactions,[6] although in the present case a less common elimination by loss of alkyl formate is observed.[7]

SCHEME I



	R	R_3	R_5
1	Et	H	H
2	Et	Me	H

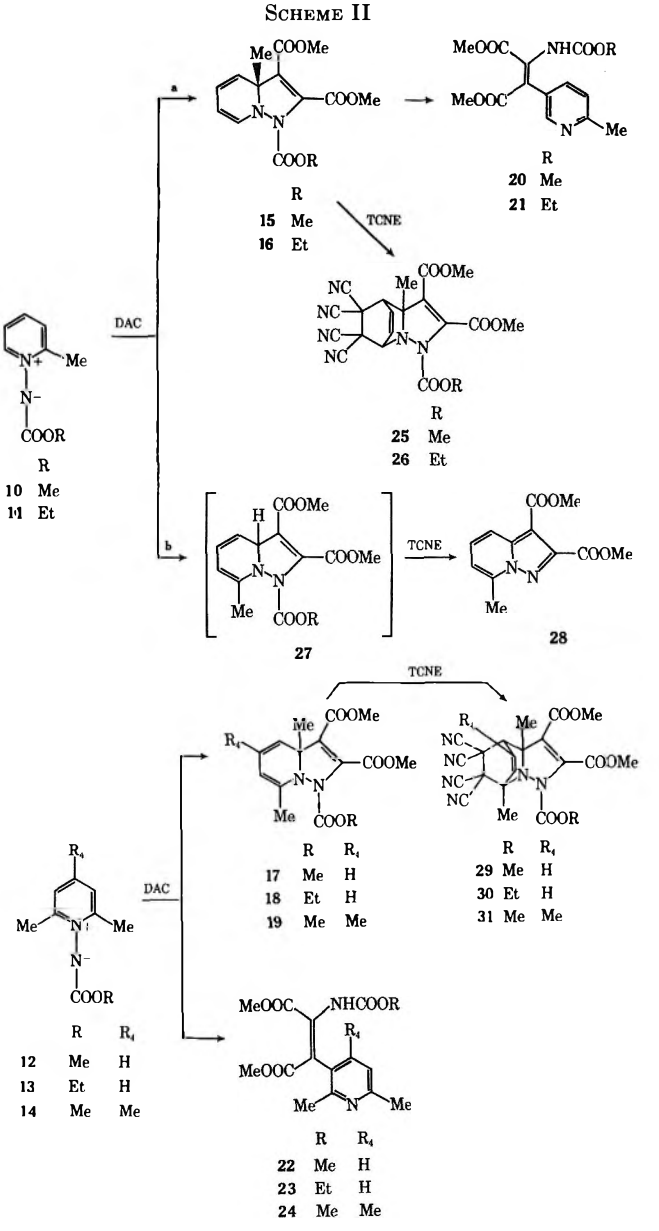
	R_3	R_5
3	H	H
4	H	Me
5	Me	H

	R	R_4
6	Et	Me
7	Et	COOMe

	R_4
8	Me
9	COOMe

On the other hand, the reactions of the ylides 10–14 and DAC proceeded rapidly even at room temperature, as detected by immediate disappearance of the deep color of the solution, to give the relatively unstable 1:1 adducts 15–19, together with the corresponding stable products 20–24, respectively. Since the ethoxycarbonyl ylides are colorless, the deep color is probably associated with a charge-transfer complex of DAC plus ylide. This point should be noted, because the N-unsubstituted imine itself is blue.[2b] Intractable tarry material always accompanied these products. When the former oily, unstable products were allowed to stand at room temperature, they were easily transformed after 3 days into the latter crystalline stable products. The unstable 1:1 adducts 15 and 16 reacted readily with TCNE in benzene even at room temperature to give the crystalline Diels–Alder adducts 25 and 26, respectively, in *ca.* 70% yields. When an equimolar amount of TCNE was added to the reaction solution of the ylides 10 and 11 with DAC after disappearance of the deep blue color, compound 28, together with the corresponding cycloadducts 25 and 26, was isolated alternatively. In the reactions of 12, 13, and 14 with DAC in the presence of TCNE, the cycloadducts 29, 30, and 31 were obtained in 62–75% yields, but pyrazolopyridine derivatives could not be detected. These results are summarized in Scheme II.

SCHEME II



	R
10	Me
11	Et

	R
15	Me
16	Et

	R
20	Me
21	Et

	R
25	Me
26	Et

27

28

	R	R_4
12	Me	H
13	Et	H
14	Me	Me

	R	R_4
17	Me	H
18	Et	H
19	Me	Me

	R	R_4
29	Me	H
30	Et	H
31	Me	Me

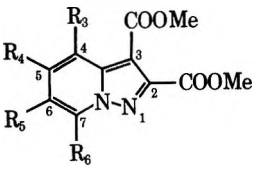
	R	R_4
22	Me	H
23	Et	H
24	Me	Me

(6) V. Boekelheide and N. A. Fedoruk, *J. Amer. Chem. Soc.*, **90**, 3830 (1968).

(7) T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *J. Org. Chem.*, **36**, 813 (1971).

TABLE III

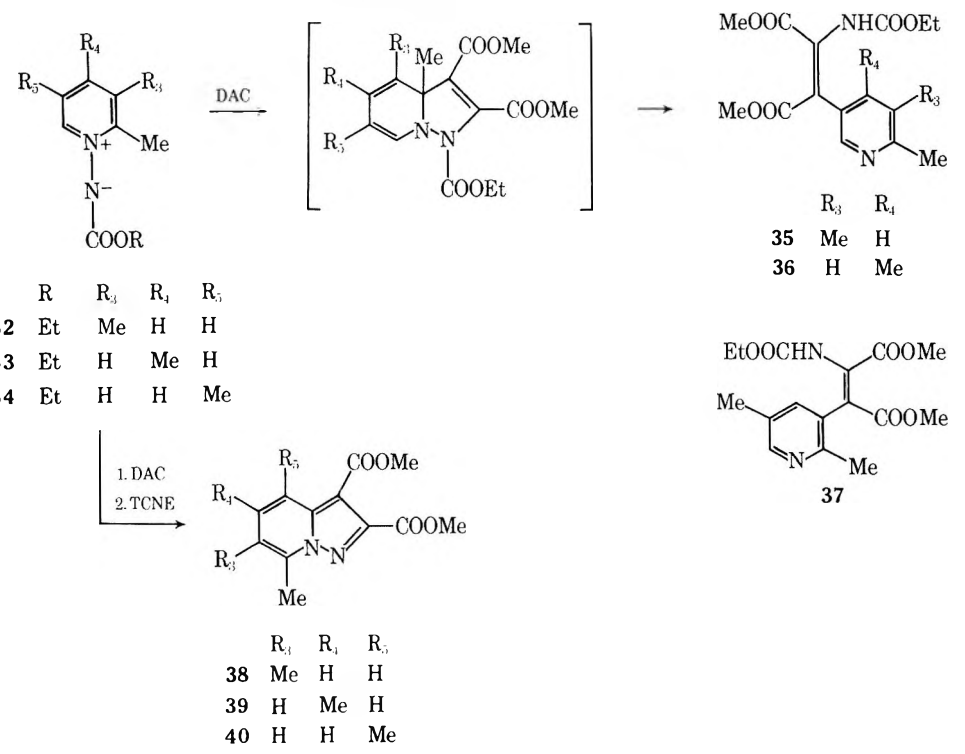
NMR DATA OF PYRAZOLO[1,5-a]PYRIDINE DERIVATIVES[a]



Compd no.	Ring protons and ring methyl protons				Coupling constant, Hz
	R_3	R_4	R_5	R_6	
3	1.82 (dd, 1 H)	2.55 (br t, 1 H)	2.97 (dt, 1 H)	1.44 (dd, 1 H)	$J_{4,5} = 9.0$, $J_{5,6} = 7.0$, $J_{6,7} = 7.0$
4	1.93 (d, 1 H)	2.70 (dd, 1 H)	7.63 (s, 3 H)	1.67 (br s, 1 H)	$J_{4,5} = 9.0$, $J_{5,7} = 1.5$
5	7.43 (s, 1 H)	2.96 (br d, 1 H)	3.19 (t, 1 H)	1.62 (dd, 1 H)	$J_{5,6} = 7.0$, $J_{5,7} = 1.0$, $J_{6,7} = 7.0$
8	2.15 (br s, 1 H)	7.55 (s, 3 H)	3.17 (br d, 1 H)	1.66 (d, 1 H)	$J_{4,5} = 1.5$, $J_{6,7} = 7.0$
9	1.17 (br s, 1 H)	6.02 (s, 3 H)	2.43 (dd, 1 H)	1.45 (dd, 1 H)	$J_{4,6} = 2.0$, $J_{6,7} = 7.5$
28	1.97 (br d, 1 H)	2.67 (q, 1 H)	3.17 (br d, 1 H)	7.24 (s, 3 H)	$J_{4,5} = 9.0$, $J_{5,6} = 7.0$
39	2.20 (br s, 1 H)	7.57 (s, 3 H)	3.33 (br s, 1 H)	7.27 (s, 3 H)	

[a] The methyl protons of 2,3-dimethoxycarbonyl groups appear at τ 5.97–6.14 as each singlet.

SCHEME III



	R	R_3	R_4	R_5
32	Et	Me	H	H
33	Et	H	Me	H
34	Et	H	H	Me

	R_3	R_4
35	Me	H
36	H	Me

37

	R_3	R_4	R_5
38	Me	H	H
39	H	Me	H
40	H	H	Me

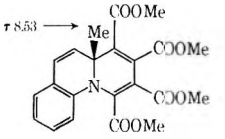
In the similar reactions of **32**, **33**, and **34**, with DAC, only the corresponding stable products **35** (43%), **36** (27%), and **37** (5%) were produced, respectively, suggesting the intermediacy of the dihydropyrazolopyridine derivatives which rapidly rearranged into the stable compounds. However, in the presence of TCNE, only **39** was obtained in 46% yield together with considerable amounts of intractable tarry compounds, and neither Diels–Alder adducts nor pyrazolopyridine derivatives such as **38** and **40** could be detected. These are summarized in Scheme III.

Structural Elucidation of 1,3-Dipolar Cycloadducts.— Structural elucidation of 1,3-dipolar cycloadducts **15–19** was accomplished by their nmr spectral analysis. The spectral patterns of these products are grossly similar to each other, as shown in Table IV.

The spectrum of **17** exhibits signals at τ 4.21, 4.53, and 5.08 with relative intensities of 1:1:1 attributable to the ring protons and at τ 6.10, 6.15, 6.24, 8.13, and 8.54 with relative intensities of each three protons. In particular, a singlet at τ 8.54 clearly arises from a methyl group at C-3a, since methyl protons attached to a fully substituted carbon atom should appear further upfield, as given in a literature.[8]

For further structural elucidation, the spectral data of the TCNE adducts **25**, **26**, and **29–31** were analyzed; spectral assignments were derived by comparison with those of ethoxycarbonylazepine–,[9] ethoxycarbonyldi-

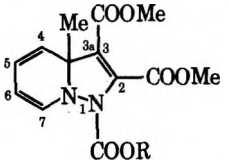
(8) A. Crabtree, L. M. Jackman, and A. W. Johnson, *J. Chem. Soc.*, 4417 (1962); for example



(9) T. Sasaki, K. Kanematsu, and A. Kakehi, *Bull. Chem. Soc. Jap.*, **43**, 2893 (1970), and references cited therein.

TABLE IV

NMR DATA[a] OF COMPOUNDS 15–19[b]



Compd no.	Ring protons and ring methyl protons, τ (CCl4)
15	3.97 (br d, 1 H, H_7, $J_{7,6}$ = 7.5 Hz), 4.35 (m, 2 H, H_4 and H_5), 5.10 (m, 1 H, H_6), 8.57 (s, 3 H, C_{3a}-CH_3)
16	3.86 (br d, 1 H, H_7, $J_{7,6}$ = 8.0 Hz), 4.31 (m, 2 H, H_4 and H_5), 4.98 (m, 1 H, H_6), 8.56 (s, 3 H, C_{3a}-CH_3)
17	4.21 (q, 1 H, H_5, $J_{5,4}$ = 10 Hz, $J_{5,6}$ = 5.0 Hz), 4.53 (br d, 1 H, $J_{4,5}$ 10 Hz), 5.08 (br d, 1 H, H_6, $J_{6,5}$ = 5.0 Hz), 8.13 (br s, 3 H, C_7-CH_3), 8.54 (s, 3 H, C_{3a}-CH_3)
18	4.26 (q, 1 H, H_5, $J_{5,4}$ = 10, $J_{5,6}$ = 5.0 Hz), 4.60 (br d, 1 H, $J_{5,4}$ = 10 Hz), 5.17 (br d, 1 H, H_6, $J_{6,5}$ = 5.0 Hz), 8.15 (br s, 3 H, C_6-CH_3), 8.57 (s, 3 H, C_{3a}-CH_3)
19	5.01 (br s, 1 H, H_4), 5.41 (br s, 1 H, H_6), 8.21 (s, 3 H, C_7-CH_3), 8.39 (d, 3 H, C_6-CH_3, J = 1.5 Hz), 8.65 (s, 3 H, C_{3a}-CH_3)

[a] Multiplicity is indicated as follows: s, singlet; d, doublet; dd, double doublet; m, multiplet; t, triplet; q, quartet; br, broad. [b] The methyl proton signals of the 2,3-dimethoxycarbonyl and 1-methoxycarbonyl groups appear at τ 6.10 ~ 6.36 as each singlet, and the proton signals of the 1-ethoxycarbonyl group at τ 5.75 (q, J = 7.0 Hz) and 8.70 (t, J = 7.0 Hz), respectively.

azepine–,[4b] and ethoxycarbonyl-2,3,-homoazepine–TCNE adducts.[10] Each adduct displayed characteristic ir bands for C=O (1700–1770 cm^{-1}), C≡N (2280 cm^{-1}), and C=C (1620–1650 cm^{-1}).

The nmr spectral patterns of the adducts are grossly similar as seen in Table V. From these data, the structures of the adducts were concluded to be normal $_{\pi}4_s + _{\pi}2_s$ cycloadducts, having 1-alkoxycarbonyl-2,3-dimethoxycarbonyl-3a-methyl-1,3a(1*H*)-dihydropyrazolo-[1,5-*a*]pyridine structures **25**, **26**, and **29–31**.

Structural Elucidation of the Rearranged Products by Spectra.—Structural elucidation of the rearranged products **20–24** and **35–37** was based on the spectra, since attempted hydrogenation and oxidation with ozone or potassium permanganate of the rearranged products were unsuccessful. The assignments of the methyl and ring proton signals could be correlated with those of the corresponding α-, β-, and γ-substituted pyridine derivatives;[11] the methyl protons appear at τ 7.44–7.57 (attached to C_2), 7.70–7.73 (to C_3), 7.85 (to C_4), and 7.65–7.68 (to C_6) as each singlet with relative intensity of three, respectively. The spectra of compounds **15–19** changed after 3 days standing at room temperature, and the methyl proton signals were shifted to lower field regions, arising from the protons attached to the pyridine skeleton. These spectral patterns are completely identical with those of compounds **20–24** and **35–37** (Table VI).

Interestingly, when the nmr of **17** was taken in carbon tetrachloride at 68 and 100°, the signals appeared at τ 2.73 (d, 1 H, J = 7.5 Hz) and 3.07 (d, 1 H, J = 7.5 Hz), indicating obviously the presence of the trisubstituted pyridine ring, and τ 3.50 (br s, 1 H, NH, exchanged by D_2O) and 7.55 and 7.75 as each singlet with relative intensities of 3:3 attributable to methyl protons attached to pyridine ring (*cf.* Figure 1). From the results, it was concluded that **17** rearranged to the vinylpyridine derivative **22**. In addition, heating of **22** and **23** without solvent at 120° in a sealed tube afforded **41** and **42**, respectively, in quantitative yields. The nmr spectra of **41** and **42** exhibit signals at τ −0.50 ~ −0.55 (br s, exchanged by D_2O) due to a hydrogen bonding amino group as shown in Figure 1, suggesting that the thermal cis–trans isomerization has occurred (Scheme IV).

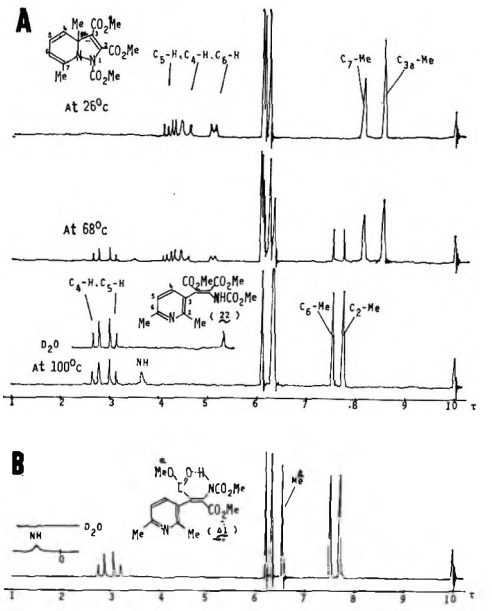
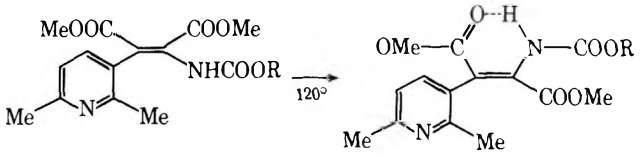


Figure 1.—A, observed nmr spectra of **17** in carbon tetrachloride at 26, 68, and 100°; B, nmr spectrum of isomerization product **41** in CCl_4.

SCHEME IV



	R
22	Me
23	Et

	R
41	Me
42	Et

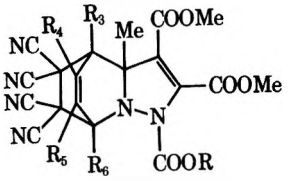
On the basis of the nmr assignments, it appears that the migration group attacked on the pyridine ring at the R_5 position to give **20–24**, **35**, and **36**, respectively, with the exception of **37**. Since the R_5 position in **37** is occupied with methyl group, the migration group (ethoxycarbonylethenyl diester group) is forced to attack at R_3 position, although the yield was quite low. The facts that the rearrangement products **20–24**, **35**, and **36** were obtained by the cycloaddition reactions of the ylides, whose α, α,α′, α,β, and α,γ positions are occupied with methyl groups, with DAC would give more information of the reaction mechanism. Whereas, mechanistic speculation for the rearranged products also leads to consideration of the alternate pathway by either a concerted 1,4- or stepwise two 1,2-methyl migrations rather than that of the alkoxycarbonylethenyl diester group. With one exception, iden-

(10) T. Sasaki, K. Kanematsu, and A. Kakehi, *Chem. Commun.*, 1030 (1970).

(11) *Cf.* F. A. Bovey, "Nmr Data for Organic Compounds," Vol. 1, Interscience, New York, N. Y., 1967.

TABLE V

NMR DATA OF THE DIELS–ALDER ADDUCTS[a]

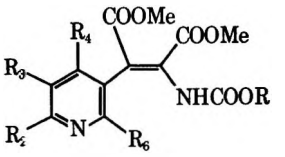


Adduct	Ring protons and ring methyl protons, τ (CDCl3)				
	R3	R4	R5	R6	Me
25	5.83 (m, 1 H)	3.23 (m, 2 H)		4.83 (m, 1 H)	8.52 (s, 3 H)
26	5.81 (m, 1 H)	3.21 (m, 2 H)		4.75 (m, 1 H)	8.52 (s, 3 H)
29	5.83 (dd, 1 H)	3.16 (q, 1 H, J = 8.0, J = 6.5)	3.46 (dd, 1 H, J = 8.0, J = 1.5)	7.89 (s, 3 H)	8.53 (s, 3 H)
30	5.82 (dd, 1 H, J = 6.5, J = 1.5)	3.16 (q, 1 H, J = 8.0, J = 6.5)	3.46 (dd, 1 H, J = 8.0, J = 1.5)	7.99 (s, 3 H)	8.53 (s, 3 H)
31	6.13 (1 H, overlapping with methyl protons of methoxycarbonyl group)	7.83 (d, 3 H, J = 1.5)	3.94 (br s, 1 H)	8.06 (s, 3 H)	8.56 (s, 3 H)

[a] Coupling constant J given in hertz.

TABLE VI

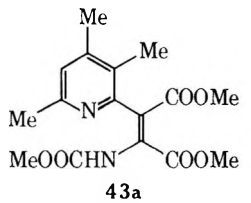
NMR DATA OF THE REARRANGEMENT PRODUCTS[a]



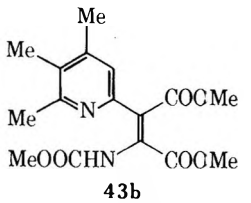
Compd no.	τ (CDCl3)					Coupling constant, Hz
	R2	R3	R4	R6	NH[b]	
20	7.50 (s, 3 H)	2.80 (br d, 1 H)	2.50 (dd, 1 H)	1.64 (d, 1 H)	2.73 (br s)	$J_{3,4}$ = 8.0, $J_{4,6}$ = 2.0
21	7.45 (s, 3 H)	2.83 (br d, 1 H)	2.54 (dd, 1 H)	1.66 (d, 1 H)	3.25 (br s)	$J_{3,4}$ = 7.5, $J_{4,6}$ = 2.0
22[c]	7.44 (s, 3 H)	2.93 (d, 1 H)	2.60 (d, 1 H)	7.65 (s, 3 H)	3.34 (br s)	$J_{3,4}$ = 7.5
23	7.47 (s, 3 H)	2.96 (d, 1 H)	2.63 (d, 1 H)	7.65 (s, 3 H)	3.50 (br s)	$J_{3,4}$ = 7.5
24	7.50 (s, 3 H)	3.05 (br s, 1 H)	7.85 (s, 3 H)	7.68 (s, 3 H)	3.50 (br s)	
35	7.55 (s, 3 H)	7.73 (s, 3 H)	2.75 (br s, 1 H)	1.84 (d, 1 H)	3.03 (br s)	$J_{4,6}$ = 2.0
36	7.57 (s, 3 H)	3.03 (br s, 1 H)	7.86 (s, 3 H)	1.94 (br s, 1 H)	3.20 (br s)	
37	1.66 (br s, 3 H)	7.70 (s, 3 H)	2.74 (br s, 1 H)	7.66 (s, 3 H)	3.70 (br s)	

[a] The methyl proton signals of the 2,3-dimethoxycarbonyl and 1-methoxycarbonyl groups appear at τ 6.03 ~ 6.35 as each singlet, and the protons of the 1-ethoxycarbonyl group at τ 5.79 ~ 5.90 (q, J = 7.0 Hz) and 8.79 ~ 8.80 (t, J = 7.0 Hz), respectively. [b] Disappeared by shaking with D_2O. [c] In CCl_4, the signals appear at τ 7.55 (s, 3 H), 3.07 (d, J = 7.5 Hz, 1 H), 2.73 (d, J = 7.5 Hz, 1 H), 7.75 (s, 3 H), and 3.50 (br s, NH).

tical mechanisms can be proposed for all other dihydropyrazolo[1,5-*a*]pyridine derivatives and the possible structures resulting from 1,4-methyl migration would have to be considered. The exception involves the transformation of **19** to **43a** or **43b**. In these cases, information available from the nmr spectra of these pyridines is limited to provide a proof of the structures.



43a



43b

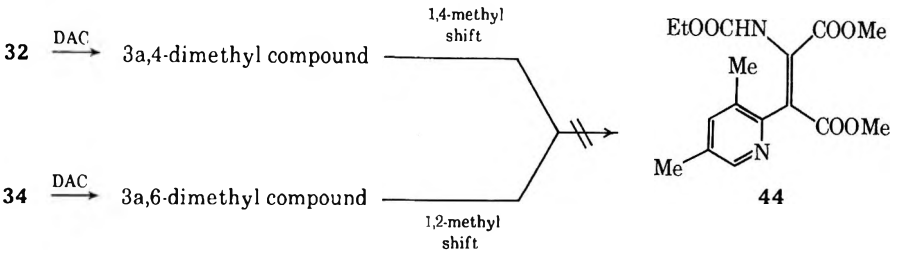
However, in the case of the reactions of **32** or **34** with DAC, the same rearrangement product **44** might be obtained *via* the 1,4- and 1,2-methyl migration process, but actually the rearranged products **35**, mp 144–146°, and **37**, mp 158–161°, were obtained, respectively, as shown in Scheme III. Therefore, **44** can be ruled out as a structural possibility as shown in Scheme V.

Structural Elucidation of the Rearranged Products by Chemical Degradation.—Final structural elucidation of these rearranged compounds was accomplished by chemical degradation.

The rearranged products **20–24** and **35–37** resisted ozonolysis because of the presence of the bulky tetrasubstituted olefinic moiety. Accordingly, we prepared the trisubstituted rearranged products **45** and **46**, which were synthesized by the reaction of **12** or **13** with ethyl propiolate followed by rearrangement (Scheme VI).

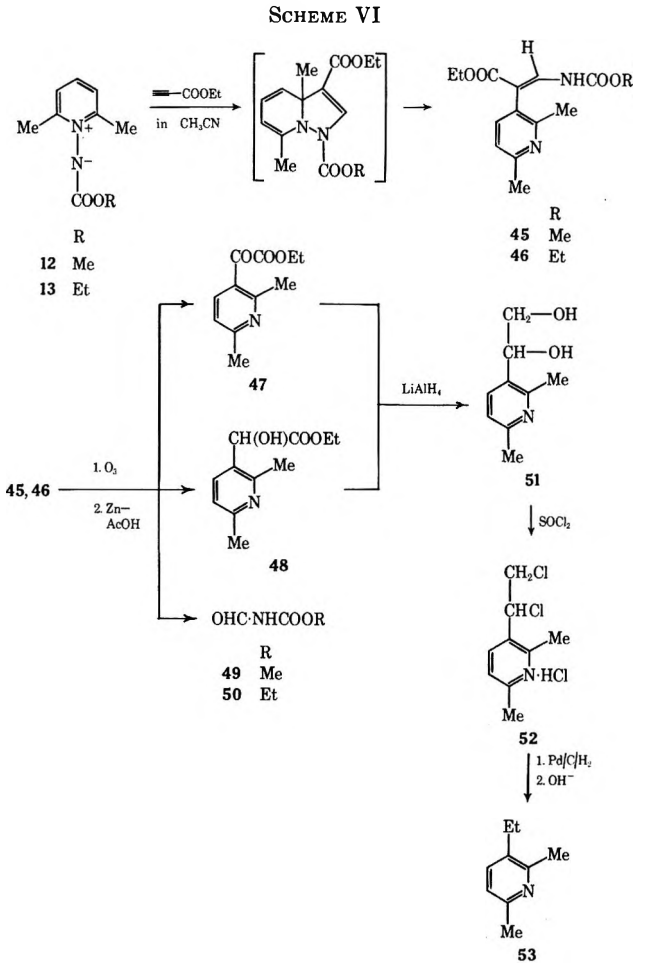
Ozonolysis of **45** or **46** followed by treatment of zinc in acetic acid gave three products, **47–49** (or **50**). Chromatography of the mixture over silica gel afforded an crystalline product **49** (or **50**) and oily products, **47** and **48**. These compounds were elucidated on the basis of the nmr spectral inspection. A mixture of compounds **47** and **48** was reduced by lithium aluminium hydride in tetrahydrofuran under refluxing condition to give a diol (**51**). Treatment of **51** with thionyl chloride followed by catalytic hydrogenation (10% Pd/C) gave **53**, which was found to be identical with the known

SCHEME V



2,6-dimethyl-3-ethylpyridine[12] by mixed glpc and by comparisons of their ir and nmr spectra (see Experimental Section).

SCHEME VI



Mechanisms for the Rearranged Products.—Considering the results, we proposed the reaction mechanisms for the rearranged products **20**–**24**, **35**–**37**, **45**, and **46**, as shown in Scheme VII. Thus, the relief of highly strained 3a-methyl-1,3a(1*H*)-dihydropyrazolopyridine ring systems, followed by the migration of the nucleophilic alkoxycarbonylethenyl diester group to give R_5-substituted pyridine derivatives, which involve the initial N–N bonding fission rather than the attack at the sterically hindered R_3 position, might be the driving force for the rearrangement in the facile isomerization of the 1,3-dipolar cycloadducts. In conclusion, when there is no 2 substitution in pyridine ring, the net result of reaction with DAC is dehydrogenation and the intermediate dihydro derivative cannot be isolated. On the other hand, when there is a 2 substituent, the intermediate can be isolated but undergoes facile rearrangement to a vinylpyridine derivative.

(12) T. Omae, H. Yamamoto, T. Motoda, and Y. Yoshie, *Kogyo Kagaku Zasshi*, **65**, 354 (1962).

Experimental Section[13]

4-Methoxycarbonyl-1-ethoxycarbonyliminopyridinium Ylide (7).—Ethyl azidoformate (3.2 g, 0.028 mol) and excess methyl isonicotinate (10 g) were placed in a sealed tube and heated in an oil bath at 90° for 12 hr. The reaction mixture was evaporated *in vacuo*, and the residue was recrystallized from benzene to give pale yellow crystals (2.5 g, 40%), mp 152–154°.

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.46; H, 5.30; N, 12.55.

1,3-Dipolar Cycloaddition Reactions of the Ylides with DAC. General Method.—To a benzene or acetonitrile solution of DAC an equimolar amount of the ylides was added under stirring at room temperature. After disappearance (about 5–30 min) of the deep color of the solution, the solvent was removed *in vacuo*, and the oily mixture was separated by column chromatography (silica gel) using chloroform as eluent. The yields of these products were summarized in Table I.

Reaction of 1 with DAC.—From 0.72 g of **1** and 0.62 g of DAC there was obtained **3** (*ca.* 1%) as pale yellow crystals: mp 70–72°; ν_{max}^{KBr} 1727, 1683, 1630 cm^{-1}; λ_{max}^{EtOH} 223 nm (ϵ 2.34 × 10^4), 300 (5.85 × 10^3); identical with a material prepared by the reaction of pyridinium *N*-imine (0.4 g, 4.3 mmol) and DAC (0.6 g).[14]

Reaction of 2 with DAC.—From 0.54 g (3 mmol) of **2** and 0.43 g of DAC there was obtained 6-methyl- and 4-methyl-2,3-dimethoxycarbonylpyrazolo[1,5-*a*]pyridines (**4** and **5**) as a mixture in only 0.5% yield. The mixture could not be separated by column chromatography.

Reaction of 6 with DAC.—From 0.54 g of **6** and 0.43 g of DAC there was obtained 5-methyl-2,3-dimethoxycarbonylpyrazolo-[1,5-*a*]pyridine (**8**) (0.20 g, 27%) as pale yellow crystals: mp 119–120°; ν_{max}^{KBr} 1742, 1702, 1640 cm^{-1}; λ_{max}^{EtOH} 224 nm (ϵ 3.11 × 10^4), 293 (8.06 × 10^3).

Reaction of 7 with DAC.—From 0.45 g (2 mmol) of **7** and 0.28 g of DAC there was obtained 2,3,5-trimethoxycarbonylpyrazolo-[1,5-*a*]pyridine (**9**) (0.16 g, 28%) as yellow crystals: mp 141–143°; ν_{max}^{KBr} 1724, 1700, 1638 cm^{-1}; λ_{max}^{EtOH} 232 nm (ϵ 2.32 × 10^4), 329 (5.29 × 10^3).

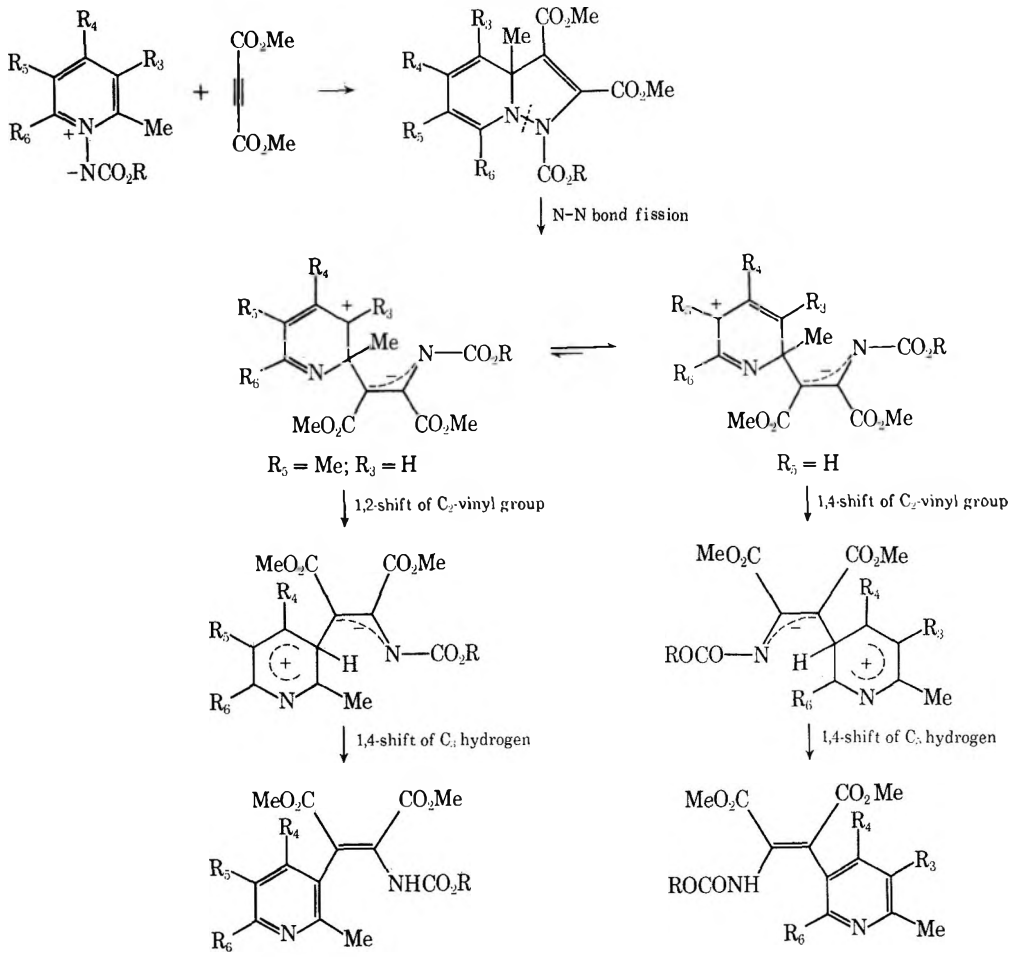
Reaction of 10 with DAC.—From 0.5 g (3 mmol) of **10** and 0.43 g (3 mmol) of DAC there was obtained 1,2,3-trimethoxycarbonyl-3a-methyl-1,3a-dihydropyrazolo[1,5-*a*]pyridine (**15**) (0.11 g, 12%) as a pale yellow oil (ν_{max}^{neat} 1745, 1713, 1631, 1589 cm^{-1}), and 2-methyl-5-(*cis*-1,2-dimethoxycarbonyl-2-methoxycarbonyl-aminoethenylpyridine (**20**) (0.20 g, 22%) as colorless crystals [mp 144–146°; ν_{max}^{KBr} 1740, 1708, 1610, 1600 cm^{-1}; λ_{max}^{EtOH} 275 nm (ϵ 1.9 × 10^4)].

Reaction of 11 with DAC.—From 0.54 g (3 mmol) of **11** and 0.43 g (3 mmol) of DAC there was obtained 1-ethoxycarbonyl-2,3-dimethoxycarbonyl-3a-methyldihydropyrazolo[1,5-*a*]pyridine

(13) The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 elemental analyzer. The uv spectra were determined with a JASCO Model ORD/UV-5 recorder. The nmr spectra were taken with a Japan Electric Optics Laboratory Co., Ltd., Model C-60-XL, nmr spectrometer and with a Varian A-60 recording spectrometer with tetramethylsilane as an internal standard. The chemical shifts are expressed in τ values. The ir spectra were taken with a JASCO Model IR-S spectrophotometer.

(14) 2,3-Dimethoxycarbonylpyrazolo[1,5-*a*]pyridine **3** was obtained in 22% yield by the reaction of *N*-iminopyridinium ylides and DAC but without detail: R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Lett.*, 387 (1962).

SCHEME VII



(16) (0.11 g, 11%) as a pale yellow oil (ν_{max}^{neat} 1755, 1711, 1634, 1592 cm^{-1}), and 2-methyl-5-(*cis*-1,2-dimethoxycarbonyl-2-ethoxycarbonylamino)ethenylpyridine (**21**) (0.23 g, 24%) as colorless crystals [mp 134–136°; ν_{max}^{KBr} 1732, 1703, 1613, 1600 cm^{-1}; λ_{max}^{EtOH} 275 nm (ϵ 1.14 × 10^4)].

Reaction of 12 with DAC.—From 0.54 g of **12** and 0.43 g of DAC there was obtained 1,2,3-trimethoxycarbonyl-3a,7-dimethyl-1,3a-dihydropyrazolo[1,5-*a*]pyridine (**17**) (0.78 g, 80%) as a pale yellow oil (ν_{max}^{neat} 1744, 1718, 1659, 1639, 1608 cm^{-1}), and 2,6-dimethyl-3-(*cis*-1,2-dimethoxycarbonyl-2-methoxycarbonylamino)ethenylpyridine (**22**) (0.03 g, 3%) as colorless crystals [mp mp 185–188°; ν_{max}^{KBr} 1743, 1708, 1618, 1597 cm^{-1}; λ_{max}^{EtOH} 269 nm (ϵ 1.53 × 10^4)]. However, when **17** was allowed to stand at room temperature, **22** was obtained after 3 days in quantitative yield.

Reaction of 13 with DAC.—From 0.58 g of **13** and 0.43 g of DAC there was obtained 1-ethoxycarbonyl-2,3-dimethoxycarbonyl-3a,7-dimethyl-1,3a-dihydropyrazolo[1,5-*a*]pyridine (**18**) (0.69 g, 68%) as a pale yellow oil (ν_{max}^{neat} 1760, 1710, 1669, 1640, 1607 cm^{-1}) and 2,6-dimethyl-3-(*cis*-1,2-dimethoxycarbonyl-2-ethoxycarbonylamino)ethylpyridine (**23**) (0.17 g, 17%) as pale yellow crystals [mp 152–154°; ν_{max}^{KBr} 1735, 1710, 1614, 1595 cm^{-1}; λ_{max}^{EtOH} 270 nm (ϵ 1.74 × 10^4)].

Reaction of 14 with DAC.—From 0.39 g (2 mmol) of **14** and 0.28 g of DAC there was obtained 1,2,3-trimethoxycarbonyl-3a,5,7-trimethyl-1,3a-dihydropyrazolo[1,5-*a*]pyridine (**19**) (0.38 g, 56%) as a pale yellow oil (ν_{max}^{neat} 1750, 1720, 1675, 1640, 1620 cm^{-1}) and 2,4,6-trimethyl-3-(*cis*-1,2-dimethoxycarbonyl-2-methoxycarbonylamino)ethenylpyridine (**24**) (0.29 g, 44%) as colorless crystals [mp 145–146°; ν_{max}^{KBr} 1750, 1720, 1620, 1600 cm^{-1}; λ_{max}^{EtOH} 268 nm (ϵ 7.64 × 10^3)].

Reaction of 32 with DAC.—From 0.58 g (3 mmol) of **32** and 0.43 g of DAC there was obtained 2,3-dimethyl-5-(*cis*-1,2-dimethoxycarbonyl-2-ethoxycarbonylamino)ethenylpyridine (**35**) (0.44 g, 43%) as colorless crystals [mp 144–146°; ν_{max}^{KBr} 1733, 1703, 1608 cm^{-1}; λ_{max}^{EtOH} 277 nm (ϵ 9.60 × 10^3)].

Reaction of 33 with DAC.—From 0.58 g of **33** and 0.43 g of DAC there was obtained 2,4-dimethyl-5-(*cis*-1,2-dimethoxycarbonyl-2-ethoxycarbonylamino)ethenylpyridine (**36**) (0.28 g, 27%) as colorless crystals: mp 144–146°; ν_{max}^{KBr} 1735, 1715, 1700, 1610 cm^{-1}; λ_{max}^{EtOH} 272 nm (ϵ 1.39 × 10^4).

Reaction of 34 with DAC.—From 0.58 g of **34** and 0.43 g of DAC there was obtained 2,5-dimethyl-3-(*cis*-1,2-dimethoxycarbonyl-2-ethoxycarbonylamino)ethenylpyridine (**37**) (0.05 g, 5%) as colorless crystals: mp 158–161°; ν_{max}^{KBr} 1732, 1704, 1614 cm^{-1}; λ_{max}^{EtOH} 270 nm (ϵ 1.40 × 10^4). The reaction was carried out under the refluxing temperature conditions.

Thermal Cis–Trans Isomerization Reactions of the Vinylpyridine Derivatives.—Heating of **22** and **23** (each 50 mg) without solvent at 120° in a sealed tube for 10 hr afforded **41** and **42**, respectively, in quantitative yields.

2,6-Dimethyl-3-(*trans*-1,2-dimethoxycarbonyl-2-methoxycarbonylamino)ethenylpyridine (**41**): mp 93–95°; pale yellow prisms; λ_{max}^{MeOH} 269 nm (ϵ 1.60 × 10^4); ν_{max}^{KBr} 3260, 1735, 1677, 1615, 1603 cm^{-1}; τ (CCl_4) −0.50 (br s, 1 H), 2.83 (d, 1 H, J = 7.5 Hz), 3.16 (d, 1 H, J = 7.5 Hz), 6.20 (s, 3 H, $NCOOCH_3$), 6.33 (s, 3 H, $COOH_3$), 6.54 (s, 3 H, $COOCH_3$), 7.51 (s, 3 H, CH_3), 7.70 (s, 3 H, CH_3).

Anal. Calcd for $C_{15}H_{18}N_2O_6$: 55.89; H, 5.63; N, 8.69. Found: C, 56.04; H, 5.71; N, 8.47.

2,6-Dimethyl-3-(*trans*-1,2-dimethoxycarbonyl-2-ethoxycarbonylamino)ethenylpyridine (**42**): mp 110–112°; ν_{max}^{KBr} 3260, 1735, 1677, 1616, 1598 cm^{-1}; λ_{max}^{MeOH} 271 nm (ϵ 2.05 × 10^4); τ (CCl_4) −0.55 (br s, NH), 2.79 (d, 1 H, J = 7.5 Hz), 3.14 (d, 1 H, J = 7.5 Hz), 5.76 (q, 2 H, $NCOOCH_2$), 6.31 (s, 3 H, CH_3), 6.54 (s, 3 H, CH_3), 7.51 (s, 3 H, CH_3), 7.68 (s, 3 H, CH_3), 8.66 (t, 3 H, $NCOOCH_2CH_3$, J = 7.0 Hz).

Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.13; H, 5.99; N, 8.33. Found: C, 57.09; H, 6.01; N, 8.40.

1,3-Dipolar Cycloaddition Reactions of the Ylides and DAC in the Presence of TCNE. General Method.—To a dry benzene or acetonitrile solution of DAC and the ylides an equimolar amount of TCNE was added under stirring at room temperature, and then the reaction solution turned a black color. After the precipitated tarry substance was decanted, the solvent was removed *in vacuo*, and the residue was purified by column chromatography

(silica gel) using chloroform as eluent. The pyrazolo[1,5-*a*]-pyridine derivatives were eluted from the first fraction and the recrystallized from chloroform–*n*-hexane or carbon tetrachloride–*n*-hexane. These data are summarized in Table II.

Reaction of 1 and DAC in the Presence of TCNE.—From 0.17 g (1 mmol) of **1**, 0.14 g of DAC, and 0.13 g of TCNE there was obtained 2,3-dimethoxycarbonylpyrazolo[1,5-*a*]pyridine (**3**) (0.01 g, 5%), identical in all respects with that formed from the reaction of pyridinium *N*-imine and DAC.[13]

Reaction of 6 and DAC in the Presence of TCNE.—From 0.18 g of **6** and each equimolar of DAC and TCNE there was obtained 2,3-dimethoxycarbonyl-5-methylpyrazolo[1,5-*a*]pyridine (**8**) (0.1 g, 44%) as pale yellow crystals, mp 119–120°.

Reaction of 7 and DAC in the Presence of TCNE.—From 0.22 g of **7** and each equimolar amount of DAC and TCNE there was obtained 2,3,5-trimethoxycarbonylpyrazolo[1,5-*a*]pyridine (**9**) (0.13 g, 45%) as pale yellow crystals, mp 141–143°.

Reaction of 10 and DAC in the Presence of TCNE.—From 0.17 g of **10** and each equimolar amount of TCNE there was obtained 2,3-dimethoxycarbonyl-7-methylpyrazolo[1,5-*a*]pyridine (**28**) (0.09 g, 40%) as pale yellow crystals: mp 99–100°; ν_{max}^{KBr} 1738, 1693, 1640 cm^{-1}; λ_{max}^{EtOH} 222 nm (ϵ 2.78 × 10^4), 300 (9.47 × 10^3), and **25** (0.05 g, 12%) as a colorless crystals, mp 170° dec.

Reaction of 11 and DAC in the Presence of TCNE.—From 0.18 g of **11** and each equimolar amount of DAC and TCNE there was obtained **28** (0.13 g, 51%) as pale yellow crystals, mp 99–100°, and **26** (0.13 g, 15%) as colorless crystals, mp 170° dec.

Reaction of 33 and DAC in the Presence of TCNE.—From 0.19 g of **33** and each equimolar amount of DAC and TCNE there was obtained 2,3-dimethoxycarbonyl-5,7-dimethylpyrazolo-[1,5-*a*]pyridine (**39**) (0.12 g, 46%) as pale yellow crystals: mp 124–126°; ν_{max}^{KBr} 1740, 1700, 1641 cm^{-1}; λ_{max}^{EtOH} 223 nm (ϵ 3.34 × 10^4), 297 (1.16 × 10^4).

Preparation of the Adducts 25 and 26. Method A.—The reactions of dihydropyrazolopyridine derivatives and TCNE were carried out in dry benzene under stirring at room temperature. Then the cycloadducts were precipitated and filtered. The crude adducts were recrystallized from chloroform–*n*-hexane to give colorless crystals.

Reaction of 15 with TCNE.—From 0.11 g (0.36 mmol) of **15** and 0.05 g of TCNE there was obtained cycloadducts **25** (0.11 g, 71%) as colorless crystals: mp 170° dec; ν_{max}^{KBr} 2280, 1743, 1697, 1630 cm^{-1}; λ_{max}^{EtOH} 312 nm (ϵ 6.67 × 10^3).

Reaction of 16 with TCNE.—From 0.09 g (0.28 mmol) of **16** and 0.04 g of TCNE there was obtained **26** (0.09 g, 68%) as colorless crystals: mp 170° dec; ν_{max}^{KBr} 2280, 1755, 1730, 1710, 1627 cm^{-1}; λ_{max}^{EtOH} 312 nm (ϵ 7.61 × 10^3).

Preparation of the Adducts 29–31. Method B.—In benzene solution of the ylides **12**, **13**, and **14** with DAC, an equimolar amount of TCNE was added under stirring at room temperature. Then the precipitated cycloadducts were filtered and recrystallized from benzene.

Reaction of 12 and DAC in the Presence of TCNE.—From 0.18 g (1 mmol) of **12**, DAC (0.14 g), and TCNE (0.13 g) there was obtained **29** (0.34 g, 75%) as colorless crystals: mp 150° dec; ν_{max}^{KBr} 2280, 1770, 1746, 1713, 1630 cm^{-1}.

Reaction of 13 and DAC in the Presence of TCNE.—From 0.19 g (1 mmol) of **13** and equimolar amounts of DAC and TCNE there was obtained **30** (0.29 g, 62%) as colorless crystals: mp 150° dec; ν_{max}^{KBr} 2280, 1770, 1750, 1703, 1629 cm^{-1}.

Reaction of 14 and DAC in the Presence of TCNE.—From 0.19 g (1 mmol) of **14** and equimolar amounts DAC and TCNE there was obtained **31** (0.31 g, 67%) as colorless crystals: mp 150° dec; ν_{max}^{KBr} 2280, 1768, 1737, 1705, 1643, 1632 cm^{-1}.

Reaction of 12 with Ethyl Propiolate.—From 0.54 g of **12** and 0.40 g of ethyl propiolate there was obtained 2,6-dimethyl-3-(1-ethoxycarbonyl-2-methoxycarbonylamino)ethenylpyridine (**45**) (0.48 g, 58%), as colorless crystals: mp 174–177°; ν_{max}^{KBr} 1729, 1700, 1632, 1595 cm^{-1}; λ_{max}^{EtOH} 263 nm (ϵ 1.64 × 10^4); τ ($CDCl_3$) 1.92 (d, 1 H, J = 13.0 Hz, vinyl proton), 2.70 (d, 1 H, J = 7.5 Hz, ring proton), 3.03 (d, 1 H, J = 7.5 Hz, ring proton), 3.15 (br d, 1 H, J = 13 Hz, NH), 5.81 (q, 2 H, J = 7.0 Hz, OCH_2), 6.25 (s, 3 H, OCH_3), 7.51 (s, 3 H, CH_3), 7.65 (s, 3 H, CH_3), 8.76 (s, 3 H, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.30; H, 5.55; N, 9.86.

Reaction of 13 with Ethyl Propiolate.—From 0.58 g of **13** and 0.40 g of ethyl propiolate there was obtained 2,6-dimethyl-3-(1-ethoxycarbonyl-2-ethoxycarbonylamino)ethenylpyridine (**46**) (0.39 g, 45%), as colorless crystals: mp 137–139°; ν_{max}^{KBr} 1726, 1690, 1645, 1602 cm^{-1}; λ_{max}^{EtOH} 263 nm (ϵ 1.75 × 10^4); τ ($CDCl_3$) 1.92 (d, 1 H, J = 13.0 Hz, vinyl proton), 2.74 (d, 1 H, J = 7.5 Hz, ring proton), 3.04 (d, 1 H, J = 7.5 Hz, ring proton), 3.27 (br d, 1 H, J = 13.0 Hz, NH), 5.82 (q, 4 H, J = 7.0 Hz, $2OCH_2$), 7.51 (s, 3 H, CH_3), 7.65 (s, 3 H, CH_3), 8.75 (t, 6 H, J = 7.0 Hz, $2CH_2CH_3$).

Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.96; N, 9.58. Found: C, 61.68; H, 6.87; N, 9.51.

Ozonolysis of 45 and 46. 1.—A solution of 0.2 g of **45** in 30 ml of methylene chloride was treated with ozone at a rate of 40 l./hr, at 0° for 3 hr. After flushing with dry oxygen, the reaction mixture was evaporated to dryness under reduced pressure. The oily residue was poured into 20 ml of acetic acid, suspended with 1 g of zinc powder. After the solution was kept at room temperature overnight, the reaction mixture was filtered to remove syrupy zinc powder. This filtrate was evaporated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel) using benzene as eluent to give **47** (colorless oil, n^{19}D 1.5174), **48** (colorless oil, n^{20}D 1.5255), and **49** (colorless crystals, mp 88–89°, 40–60 mg).

47: ν^{neat} 1729, 1684, 1590, 1567 cm^{-1}; τ (CDCl) 2.11 (d, 1 H, J = 8.0 Hz, ring proton), 2.91 (d, 1 H, J = 8.0 Hz, ring proton), 5.62 (q, 2 H, J = 7.0 Hz, OCH_2), 7.25 (s, 3 H, CH_3), 7.42 (s, 3 H, CH_3), 8.60 (t, 3 H, J = 7.0 Hz, OCH_2), 7.25 (s, 3 H, CH_3), 7.42 (s, 3 H, CH_3), 8.60 (t, 3 H, J = 7.0 Hz, CH_2CH_3)

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.50; H, 6.22; N, 6.76.

48: ν^{neat} 3140, 1735, 1596, 1584 cm^{-1}; τ ($CDCl_3$) 2.45 (d, 1 H, J = 7.5 Hz, ring proton), 3.02 (d, 1 H, J = 7.5 Hz, ring proton), 4.70 (s, 1 H, =CH), 5.50 (br s, 1 H, OH), 5.82 (q, 2 H, J = 7.0 Hz, OCH_2), 7.40 (s, 3 H, CH_3), 7.50 (s, 3 H, CH_3), 8.80 (t, 3 H, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.10; H, 7.11; N, 6.43.

The total yield of two pyridine derivatives **47** and **48** was 40–60%.

49: mp 88–89°; ν_{max}^{KBr} 1759, 1684 cm^{-1}.

Anal. Calcd for $C_3H_5NO_3$: C, 34.95; H, 4.89; N, 13.59. Found: C, 35.18; H, 4.78; N, 13.47.

2.—From 0.3 g of **46**, there was obtained a mixture of **45** and **46**, and **50** (colorless crystals: mp 81–83°; ν_{max}^{KBr} 1759, 1693 cm^{-1}.

Anal. Calcd for $C_4H_7NO_3$: C, 41.02; H, 6.03; N, 11.96. Found: C, 41.20; H, 6.22; N, 11.90.

Lithium Aluminum Hydride Reduction of 47 and 48.—To a solution of 0.1 g of a mixture of **47** and **48** in 10 ml of absolute tetrahydrofuran was added 0.1 g of $LiAlH_4$ with stirring at 5° and the reaction mixture was stirred at 70° for 5 hr. The mixture was added with 2 ml of water and filtrated. The solution was evaporated *in vacuo* and the residue was recrystallized from benzene to give **51** as colorless crystals: mp 130–132° (70–80%); ν_{max}^{KBr} 3290, 1601, 1581 cm^{-1}.

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.70; H, 7.90; N, 8.43.

2,6-Dimethyl-3-ethylpyridine (53).—A mixture of 0.1 g of **51** and 1 ml of thionyl chloride was heated at 60–80° for 12 hr. The reaction mixture was evaporated *in vacuo*, and the residue (**52**) was reduced by hydrogen over 10% Pd/C (200 mg) in methanol at room temperature for 2 days. The reaction mixture was filtered and evaporated *in vacuo*. The residue was then neutralized with 10% NaOH and extracted with ether. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to give a colorless oil (**53**) (25–30%): ν_{max}^{neat} 1597, 1580 cm^{-1}; τ (CCl_4) 2.89 (d, 1 H, J = 7.0 Hz, ring proton), 3.29 (d, 1 H, J = 7.0 Hz, ring proton), 7.47 (q, 2 H, J = 7.0 Hz, CH_2), 7.60 (s, 6 H, $2CH_3$), 8.82 (t, 3 H, J = 7.0 Hz, CH_2CH_3). Compound **53** was found to be identical with 2,6-dimethyl-3-ethylpyridine[12] by comparison of their ir and nmr spectra as described above and by mixed glpc.

Registry No.—DAC, 762-42-5; **3**, 5825-71-8; **4**, 30689-96-4; **5**, 30758-64-6; **7**, 30689-97-5; **8**, 30689-98-6; **9**, 30689-99-7; **15**, 30690-00-7; **16**, 30758-65-7; **17**, 30690-01-8; **18**, 30758-66-8; **19**, 30690-02-9; **20**, 30690-03-0; **21**, 30690-04-1; **22**, 30690-05-2; **23**,

30690-06-3; **24**, 30690-07-4; **25**, 30690-08-5; **26**, 30690-09-6; **28**, 30758-67-9; **29**, 30758-68-0; **30**, 30690-10-9; **31**, 30758-69-1; **35**, 30690-11-0; **36**, 30690-12-1; **37**, 30758-70-4; **39**, 30758-71-5; **41**, 30690-13-2; **42**, 30690-14-3; **45**, 30690-15-4; **46**, 30690-16-5; **47**, 30690-17-6; **48**, 30690-18-7; **49**, 30690-19-8; **50**, 18804-91-6; **51**, 30690-20-1; **53**, 23580-52-1.

Overcrowded Molecules. I. Substituted 8-*tert*-Butyl-1-(2-pyridyl)naphthalenes, Including a Thermodynamically Stable Ketonic Tautomer

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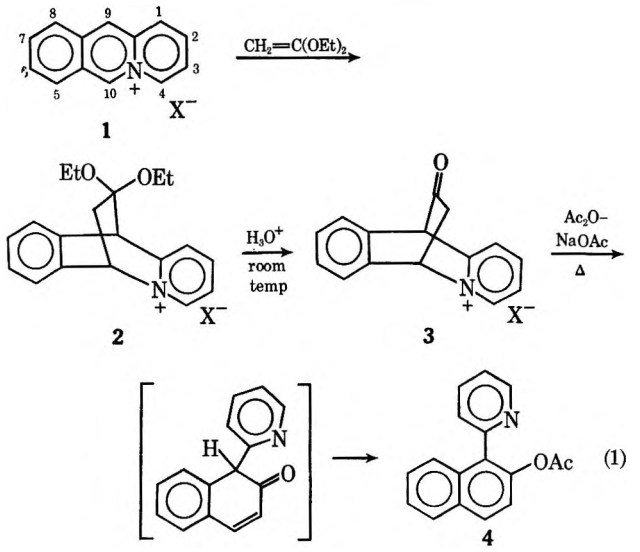
Condensation of appropriately substituted 4a-azoniaanthracene salts with ketene diethyl acetal followed by mild hydrolysis and then thermolysis in acetic anhydride has given several 8-*tert*-butyl-1-(2-pyridyl)naphthalenes. Their spectral properties and reactivity are adduced to indicate the high degree of steric strain present. Low-temperature nmr spectra of the *N*-methyl quaternary salt of 6-substituted 2,5-diacetoxy-8-*tert*-butyl-1-(2-pyridyl)naphthalenes indicate the existence of two isomers and are interpreted in terms of skewing of the naphthalene framework. 8-*tert*-Butyl-1-(2-pyridyl)naphthalenediol **13** is shown to exist exclusively as the thermodynamically stable keto tautomer **14**. 5-Acetoxy-8-*tert*-butyl-1-(2-pyridyl)-2-naphthol (**11**) has been oxidized (by Cu^{2+}) to give a novel intramolecular cyclization product formed by attack by N at the peri position to displace the *tert*-butyl group.

1-(2-Pyridyl)-2-naphthyl acetate (**4**) has recently been obtained by a three-step synthesis outlined in eq 1 involving the stereospecific 4 + 2 cycloaddition of ketene diethyl acetal to 4a-azoniaanthracene **1**, controlled hydrolysis of the resulting adduct (**2**) to ketone **3**, and sequential elimination, enolization, and acetylation reactions which occur as **3** is heated in acetic anhydride in the presence of sodium acetate.[1] Owing to the easy



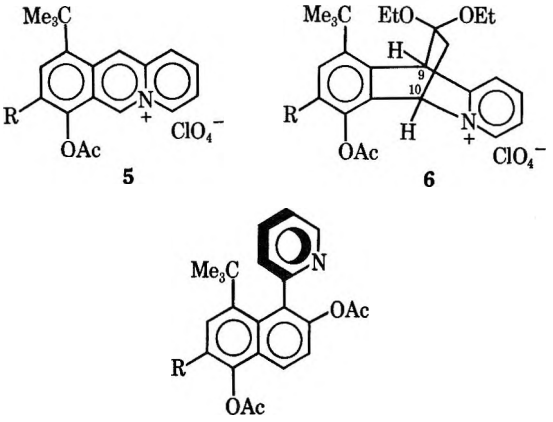
(1)

availability of a variety of types of substituted 4a-azoniaanthracene salts, especially those having substituents on the C_5–C_8 positions, this synthesis offers convenient access to 8-substituted 1-(2-pyridyl)naphthalenes, certain ones of which are of interest for peri-interaction studies. In succeeding papers we will describe some highly overcrowded pyridyl-substituted phenanthrenes and pentaphenes whose syntheses are based on this general approach. In this paper we report the synthesis of 8-*tert*-butyl-1-(2-pyridyl)naphthalenes and our observations of the consequences of steric strain on their physical and chemical properties.

(1) D. L. Fields and T. H. Regan, *J. Org. Chem.*, **35**, 1870 (1970).

Results and Discussion

The feasibility of the synthesis outlined in eq 1 to yield highly overcrowded naphthalenes was readily confirmed by the preparation of 8-*tert*-butyl-1-(2-pyridyl)naphthalenes **7a–c**. Some feeling for the high



a, R = H; **b**, R = Br; **c**, R = OAc

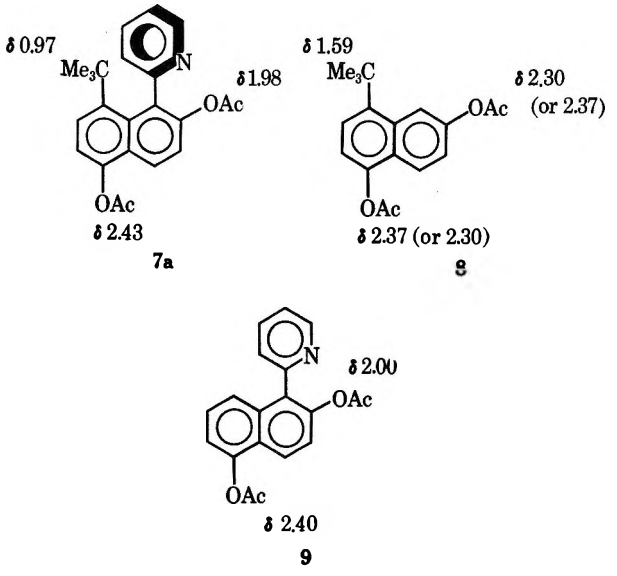
degree of overcrowding inherent in these compounds follows from the knowledge that even with the much less crowded 1,8-dimethylnaphthalene, peri interaction between the methyls is sufficient to cause distortion of the naphthalene skeleton as well as considerable bond-angle deformation.[2] Nonetheless, the syntheses of **7a–c** proved to be quite straightforward and free of complications.

As an example, adduct **6a** was obtained in quantitative yield following treatment of **5a** with an excess of ketene diethyl acetal for 10 min at room temperature. The stereochemistry of the addition was confirmed by

(2) A single-crystal X-ray analysis of 3-bromo-1,8-dimethylnaphthalene showed the normal C_1–C_8 distance in naphthalene of 2.44 Å extended to 2.56 Å, the methyls constrained to a 2.92-Å separation, a distance much less than the sum of their van der Waal's radii (4.0 Å) accompanied by some departure from planarity within the aromatic rings: M. D. Jameson and B. R. Penfold, *J. Chem. Soc.*, 528 (1965). The strain energy of 1,8-dimethylnaphthalene has been estimated at 7.9 kcal: J. Parker, J. Vaughan, and E. Wong, *J. Org. Chem.*, **23**, 1373 (1958).

nmr analysis, based on the multiplicities of the bridgehead hydrogens, *i.e.*, H_9 a singlet at δ 6.05 and H_{10} a broadened triplet at δ 6.67 (DMSO-d_6). Mild acid hydrolysis of **6a** afforded the corresponding bicyclic ketone which, in turn, was heated for 5 min in refluxing acetic anhydride in the presence of anhydrous sodium acetate. Work-up of the reaction mixture gave crystalline **7a** in 79% overall yield from **5a**.

The elemental analysis and molecular weight (mass spectrometry) of this product were satisfactory, and its infrared spectrum was consistent with the assigned structure. The salient features of its nmr spectrum include two AB quartets (3,4- and 6,7-naphthalene protons) in the aromatic region superimposed on the pyridyl proton absorptions, and the unusually high-field positions for the *tert*-butyl and one of the two acetoxymethyl signals (0.6 and 0.3 ppm higher field, respectively, than those of analogous groups in model compound **8**[3]). Such upfield shifts would result if the gross overcrowding is accommodated by bond-angle deformations so that the *tert*-butyl and pyridyl groups are bent away from one another above and below the naphthalene ring, with the pyridine rotated further out



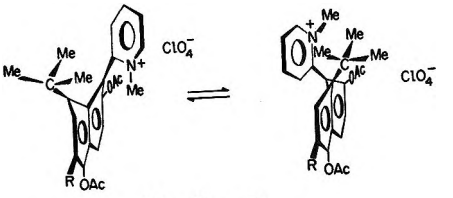
of the plane to a degree that helps minimize its interaction with the *tert*-butyl as well as the 2-acetoxy groups. In this conformation, the *tert*-butyl group would lie outside the zone of maximum deshielding of the naphthalene, and both it and the 2-acetoxy group would reside in the shielding zone of the pyridine as well.

The syntheses of **7b** and **7c** were accomplished in like manner, and analytical and spectral data for both were consistent with their assigned structures.

Low-temperature nmr spectra of **7** were examined with the expectation that the high degree of steric interference would lead to restricted rotation of the *tert*-butyl group, a phenomenon which has been observed in considerably less sterically crowded molecules.[4] At −86°, the absorption of the *tert*-butyl group of **7a** had broadened considerably ($W_{1/2}$ = 13 Hz compared to $W_{1/2}$ = 0.8 Hz for TMS at −100°) but was still symmetrical; *i.e.*, it showed no evidence for nonequivalence of the methyl groups. This was true also for **7b** and **7c**. That at least part of the broadening was due to restricted motion of the *tert*-butyl group was indicated by the fact that the acetate methyls were broadened only approximately one-third as much as the *tert*-butyl peak.

Careful examination of Dreiding models of compounds **7** shows that, while there is a very high degree of interference at the 1,8 positions, the methyls of the *tert*-butyl do not pass through an obvious energy minimum in the course of rotating past the face of the pyridyl ring. Thus, there is no energy well corresponding to a frozen position of the *tert*-butyl rotation, and, therefore, no preferred conformation in which the methyls would be nonequivalent.

Alkylation of **7a–c** with iodomethane followed by anion exchange produced the methyl quaternary salts **10a–c**. The nmr spectrum of **10a** again showed disproportionate broadening (symmetrical) of the *tert*-butyl signal with respect to the two acetate methyls as the temperature was lowered to −100°. Interestingly, the *N*-methyl signal showed the most broadening. This broadening was even more dramatic for **10b** and **10c** (their *N*-methyl signals collapsed and actually split into two peaks of unequal intensity below −53 and −86°, respectively). The appearance of two *N*-methyl signals is interpreted in terms of the previously mentioned ring deformation of the naphthalene system as depicted below. While the two conformational isomers are in rapid equilibrium above −50°, the rate of ring inversion slows sufficiently below this to allow the separate *N*-methyl resonances to be observed. An attempted line-shape analysis[5] of the *N*-methyl signal of **10b** over the range −80 to −40° was complicated, apparently by viscosity broadening below −65°. However, over the temperature range near coalescence (−64 to −40°), a constant $\Delta G^{\pm}$ = 12.0 ± 1.0 kcal/mol was obtained, and, from a plot of log k/T) *vs.* $1/T$, $\Delta H^{\pm}$ was found to be 19.5 ± 1.0 kcal/mol. The two configurations differ by only 220 cal/mol.



10a, R = H
b, R = Br
c, R = OAc

Ultraviolet and mass spectral data obtained for **7a–c** when compared with like data of several related compounds, **8**, **9**, and 1,6-diacetoxynaphthalene, also show abnormalities which are considered to be manifestations of ring strain. The uv spectrum of **7a** in such a comparison (Figure 1) shows pronounced bathochromic and hyperchromic shifts in its long-wavelength absorptions accompanied by loss of vibrational structure, which is indicative of the large perturbation present in its aromatic system. Analogous spectral characteristics for a number of other overcrowded

(3) D. L. Fields, *J. Org. Chem.*, **36**, 3002 (1971).

(4) As examples, see J. P. N. Brewer, H. Heaney, and B. A. Marples, *Chem. Commun.*, 27 (1967); F. A. L. Anet, M. St. Jacques, and G. N. Chmurny, *J. Amer. Chem. Soc.*, **90**, 5243 (1968); W. F. Heyd and C. A. Cupas, *ibid.*, **91**, 1559 (1969).

(5) A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *ibid.*, **88**, 3185 (1966); J. Jonas, A. Allerhand, and H. S. Gutowsky, *J. Chem. Phys.*, **42**, 3396 (1965).

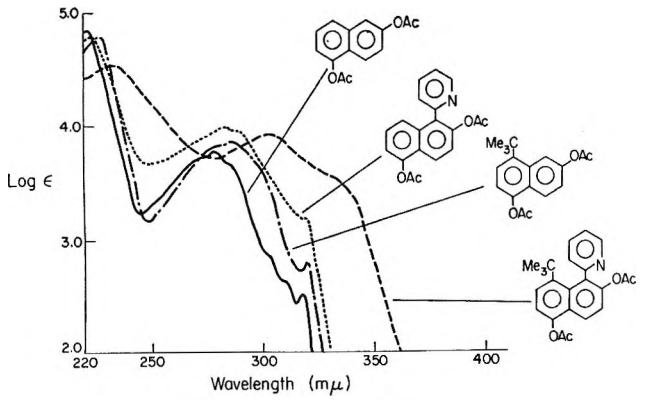


Figure 1.—Ultraviolet spectra of **7a**, **8**, **9**, and 1,6-diacetoxynaphthalene.

aromatic compounds have been documented in the literature and are usually attributed to a convergence of excited- and ground-state energy levels, the ground state having been destabilized by overcrowding.[6]

Low-resolution mass spectral data for **7a** and **8** are compared in Table I. The strongest signal displayed

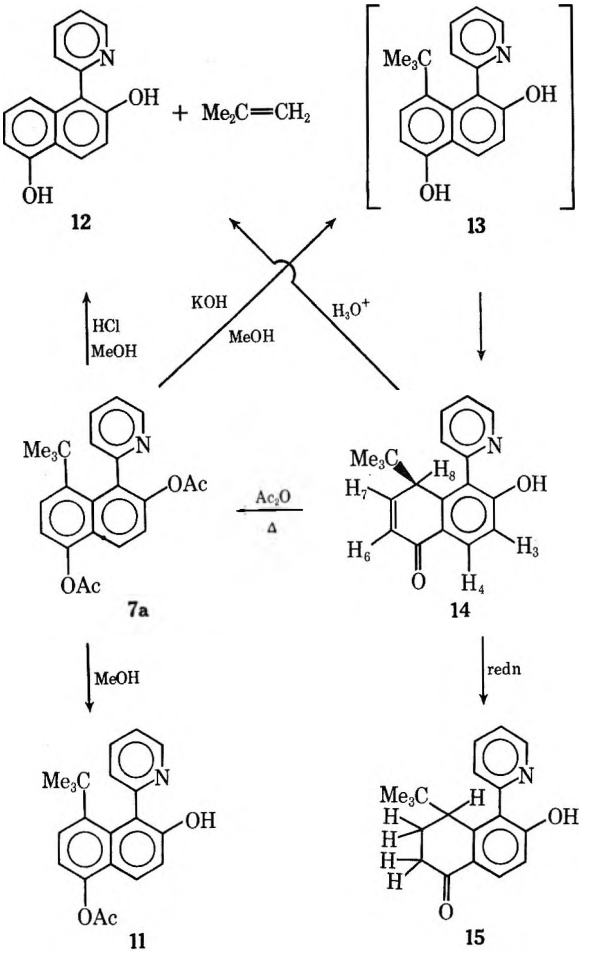
TABLE I
MASS SPECTRAL DATA (70 eV)

Fragment	Assignment	% abundance 7a	% abundance 8
M	M	0.1	43
M − 42	M − CH_2CO	0.2	86
M − 84	M − $2CH_2CO$	0.05	67
M − 57	M − C_4H_9	63	19
M − 97	M − (CH_2CO + C_4H_9)	44	0
M − 141	M − ($2CH_2CO$ + C_4H_9)	100	100

by both compounds is a M − 141 peak, representing the parent ion minus the *tert*-butyl and two ketene fragments. The data indicate that, for the most part, the succession of fragmentations leading to the M − 141 species differs for **7a** and **8** in that **7a**, upon electron impact, expels the *tert*-butyl radical before, rather than after, ester fragmentation–rearrangement (-CH_2CO). We assume that relief of peri strain is responsible for this behavior.

One property of **7**, of a chemical nature, is particularly indicative of the high degree of resonance destabilization which characterizes these naphthalene derivatives. This was encountered during our attempt to deacetylate **7a** to the corresponding naphthalenediol **13** (Scheme I). In refluxing methanol, **7a** lost an acetyl group, presumably as a consequence of neighboring pyridyl group participation, to give naphthol **11**. When **7a** was treated with methanolic HCl under conditions permitting complete deacetylation, the *tert*-butyl group was lost as isobutylene in the process,[7] yielding diol **12**. On the other hand, deacetylation without accompanying loss of the *tert*-butyl substituent was easily achieved under basic conditions, and from a reaction of **7a** with methanolic KOH, we isolated a crystalline product which was analyzed satisfactorily as **13** and whose mass spectrum showed the

SCHEME I



correct parent ion at *m/e* 293, as well as strong signals at 257 (M − C_4H_8) and 256 (M − C_4H_9). However, other more meaningful spectral (ir, uv, nmr) and chemical evidence negates this structural assignment in favor of the tautomeric structure **14**. Its uv spectrum showed maxima at $\lambda_{max}^{CH_3CN}$ 213 nm (ε 15,800), 244 (17,000), and 283 (15,200), and its ir spectrum had a strong carbonyl absorption at 1661 cm^{-1}, both pieces of data consistent for structure **14** rather than **13**. More definitive is the spectral evidence derived from 90-MHz nmr measurements. The *tert*-butyl signal was observed as a sharp singlet at 0.55 ppm, a field position more in keeping with a *tert*-butyl group attached to an sp^3 than an sp^2 carbon. The remaining absorptions, completely consistent for **14**, were observed at δ 4.36 (d, 1 H, J = 5.5 Hz, H_8), 6.47 (d, 1 H, J = 10 Hz, H_6), 7.03 (d, 1 H, J = 8.5 Hz, H_3), 7.21 and 7.27 (d of d, J = 5.5, 10 Hz, H_7) superimposed on the H_5 pyridyl proton multiplet, two multiplets at 7.50 and 7.85 (2 H, H_3 and H_4 pyridyl protons, respectively), 8.15 (d, 1 H, J = 8.5 Hz, H_4), and 8.67 ppm (d of m, 1, H_6 pyridyl proton). The coupling assignments for H_6, H_7, and H_8 were confirmed by double irradiation experiments. Coupling between H_8 and H_6 is so small as to be barely observable.

Supporting chemical evidence for this structural assignment includes the rearomatization of **14** to **7a** when treated at reflux temperature with acetic anhydride, and to **12** (plus isobutylene) when heated with 6 *N* HCl. Its reduction, either chemically ($LiAlH_4$ in ether) or catalytically (Pd/C, 40 psi of H_2), gave

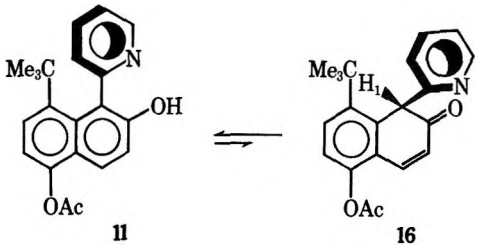
(6) See V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966), for leading references.

(7) This is not an uncommon phenomenon for strained *tert*-butyl aromatic compounds. For a recent example, see R. W. Franck and E. G. Leser, *J. Amer. Chem. Soc.*, **91**, 1577 (1969).

phenol **15**: $\nu_{C=O}$ 1671 cm^{-1}; partial nmr, four-proton multiplet centered at δ 2.52.

There is, of course, abundant evidence that, if a reagent requires it, certain phenolic substances react as if they existed in equilibrium with the keto form. Furthermore, isolable keto tautomers of several highly substituted phenols have been reported.[8] They were formed under kinetically controlled conditions, albeit by several different types of reactions, *i.e.*, thermal rearrangements,[8a,b] electrophilic substitution,[8c] and photochemical[8d,e,f] and oxidative coupling;[8g] with one exception,[9] each proved to be more or less labile, ultimately tautomerizing to the thermodynamically more stable phenol. In related naphthol systems, although a few rare examples of thermodynamically stable keto tautomers of naphthols are known,[10] the case under discussion is certainly a striking example of this phenomenon. Even the expected solution equilibrium between **14** and **13** is very slow to be established, since H_8 of **14** does not undergo detectable deuterium exchange over a 2-hr period in the presence of D_2O or D_2O plus a few drops of either 35% DCl or 40% KOD in D_2O (by nmr in DMSO-d_6).

Let us contrast these results with the behavior of naphthol **11**, which on first inspection might be expected to relieve *tert*-butyl–pyridine overcrowding by isomerizing to **16**. We found, however, that such a tautomerization does not occur to a measurable extent,

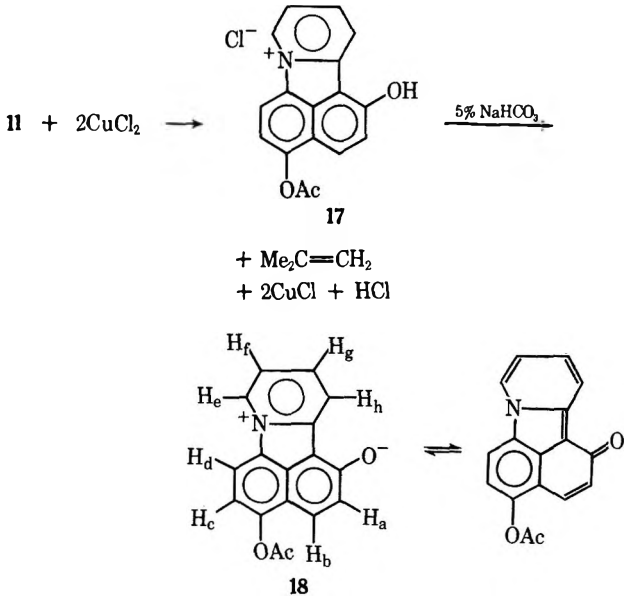


in that the amount of **16** present upon dissolution of **11** in $CDCl_3$ or DMSO-d_6 is less than that detectable by nmr means.

Examination of molecular models of **14** and **16** suggests a rationale for this marked difference in behavior. For the equilibrium between **13** and **14** to lie far toward **14** means that the energy gained in relief of steric strain must greatly overbalance the loss of naphthalene resonance energy associated with **13**; and indeed there appears to be a complete absence of steric interaction between the *tert*-butyl, pyridine, and H_8 substituents when **14** assumes a conformation having the *tert*-butyl in a quasiaxial position.

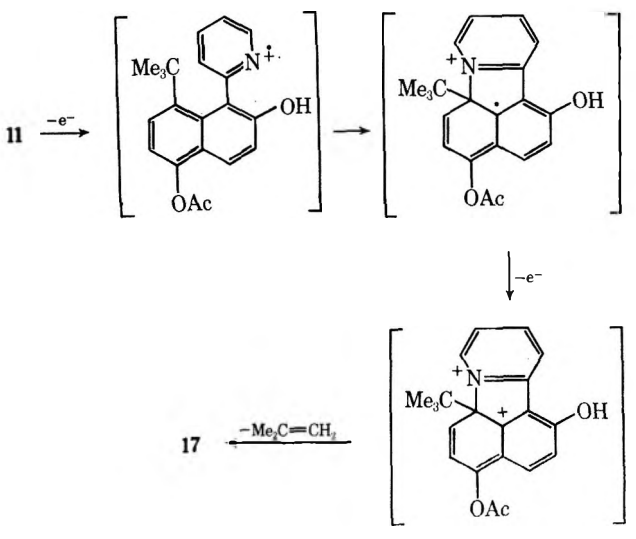
Such is not the case for the tautomerization of **11** to **16**. While the pyridine of **16**, in a quasiaxial conformation, is removed from interacting with the *tert*-butyl group, H_1 finds itself thrust directly into it. Ketonization of **11** to **16** thus produces at best only a partial relief of steric strain at the expense of resonance energy, evidently insufficient to make ketonization an energetically preferred process.

One other interesting point related to **11** concerns its behavior upon oxidation. Naphthol **11** in solution is fairly labile to oxidation, as substantiated by a polarographic study which showed that it undergoes a facile one-electron oxidation at $E_{1/2}$ = 1.00 V. When **11** was treated with anhydrous $CuCl_2$ in refluxing ethanol, a yellow crystalline chloride salt separated from solution, and isobutylene collected as a gaseous by-product within 15 min. Basification of the chloride salt with 5% sodium bicarbonate gave a red crystalline diamagnetic zwitterion, which was purified by Florisil chromatography. Elemental, nmr, and mass spectral analyses support the assigned structures as **17** and **18** for the chloride salt and zwitterion, respectively. The overall reaction is a two-electron oxidation process involving a novel intramolecular naphthalene peri



cyclization. A reasonable mechanism for this transformation is suggested in Scheme II. The oxidative

SCHEME II



(8) (a) B. Miller, *ibid.*, **89**, 1685 (1967); (b) J. C. Floyd, D. A. Plank, and W. H. Starnes, Jr., *Chem. Commun.*, 1237 (1969); (c) V. V. Ershov and A. A. Volod'kin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 680 (1962); *Chem. Abstr.*, **57**, 12337*c* (1962); (d) T. Matsuura and K. Ogura, *J. Amer. Chem. Soc.*, **89**, 3846 (1967); (e) *Tetrahedron*, **24**, 6167 (1968); (f) *ibid.*, **24**, 6157 (1968); (g) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1439 (1957).

(9) Major amounts of both 2,4,6-tri-*tert*-butylresorcinol and its diketo tautomer are present at solution equilibrium; see ref 8b.

(10) Certain dihydroxynaphthalenes have been partly isomerized in the molten state to the corresponding diketone form: D. B. Bruce and R. H. Thomson, *J. Chem. Soc.*, 2759 (1962). The monoanion of 1,3-naphthalenediol exists as a keto tautomer: E. S. Hand and R. M. Horowitz, *J. Org. Chem.*, **29**, 3088 (1964).

coupling of a pyridyl radical through N rather than C is, to our knowledge, unprecedented in the literature. We have examined its occurrence in a different system, which we shall describe in a future paper.

Experimental Section[11]

5-Acetoxy-8-*tert*-butyl-4a-azoniaanthracene–Ketene Diethyl Acetal Adducts 6a–c.—These adducts were isolated in quantitative yields following a procedure described previously[12] involving cycloaddition of ketene diethyl acetal to 4a-azoniaanthracene perchlorates **5a–c**,[13] respectively.

Adduct **6a** had mp 219–221° dec after one recrystallization from acetonitrile–ether.

Anal. Calcd for $C_{25}H_{32}ClNO_8$: C, 58.9; H, 6.3; N, 2.8. Found: C, 58.6; H, 6.0; N, 2.6.

Adducts **6b** and **6c** were isolated as amorphous white powders.

2,5-Diacetoxy-8-*tert*-butyl-1-(2-pyridyl)naphthalenes 7a–c.—As a representative example, a suspension of adduct **6a** (2.00 g, 3.9 mmol) in 10 ml of 12 *N* hydrochloric acid was shaken on a wrist-action shaker for 2 hr at room temperature.[14] The resulting heterogeneous mixture was diluted with 5 ml of cold water and then treated with sodium perchlorate to complete the crystallization of the desired bicyclic ketone, 8-*tert*-butyl-9,10-dihydro-5-hydroxy-12-oxo-4a-azonia-9,10-ethanoanthracene perchlorate, 1.30 g (84%). An analytical sample, crystallized as white needles from acetonitrile–ether, had mp 170–174° dec, ir 1750 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{20}ClNO_6$: C, 57.9; H, 5.1; Cl, 9.0; N, 3.6. Found: C, 57.5; H, 5.0; Cl, 9.2; N, 3.7.

A mixture of 0.90 g (2.3 mmol) of this product, 0.30 g of anhydrous sodium acetate, and 20 ml of acetic anhydride was heated under reflux for 5 min and concentrated to a syrup; the syrup was triturated in 75 ml of 5% aqueous sodium bicarbonate solution, giving 0.81 g (94%) of crude **7a**. One recrystallization from methylcyclohexane gave analytically pure **7a** as white plates: mp 182–184°; nmr ($CDCl_3$) δ 0.97 (s, 9, *tert*-butyl), 1.98 (s, 3, 2-acetoxy), 2.43 (s, 3, 5-acetoxy), doublets at 7.20 (H_3) and 8.01 (H_4), J = 9 Hz, and 7.20 (H_7) and 7.70 (H_6), J = 8 Hz, superimposed on H_3, H_4, and H_5 pyridyl multiplets, 8.73 ppm (d of m, 1, H_6 pyridyl proton).

Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.2; H, 6.1; N, 3.7. Found: C, 73.1; H, 6.2; N, 3.7.

Pyridinium perchlorate **10a**, prepared by treating **7a** with excess iodomethane for 18 hr at 40° followed by anion exchange, had mp 111–113°.

Anal. Calcd for $C_{24}H_{26}ClNO_8$: C, 58.6; H, 5.3; Cl, 7.2. Found: C, 58.4; H, 5.5; Cl, 7.0.

Naphthalenes **7b**, mp 154–156°, and **7c**, mp 198–200°, and their respective *N*-methyl derivatives **10b**, mp 134–137°, and **10c**, mp 237–238°, were prepared in a similar manner.

Anal. Calcd for $C_{23}H_{22}BrNO_4$ (**7b**): C, 60.6; H, 4.8; N, 3.1. Found: C, 60.6; H, 5.1; N, 3.1.

Anal. Calcd for $C_{25}H_{25}NO_6$ (**7c**): C, 69.0; H, 5.7. Found: C, 69.3; H, 6.0.

Anal. Calcd for $C_{24}H_{25}BrClNO_8$ (**10b**): C, 50.5; H, 4.4. Found: C, 50.6; H, 4.7.

Anal. Calcd for $C_{26}H_{28}ClNO_{10}$ (**10c**): C, 56.7; H, 5.1; N, 2.5. Found: C, 56.7; H, 5.1; N, 2.5.

5-Acetoxy-8-*tert*-butyl-1-(2-pyridyl)-2-naphthol (11).—A mixture of **7a** (5.00 g, 0.0133 mol) and 100 ml of methanol was refluxed for 3 hr. Naphthol **11** (4.04 g, 91%) crystallized from solution during this period and was collected after refrigerating the mixture for 2 hr at 5°. The product had mp 194–195° after one recrystallization from methylcyclohexane; nmr ($CDCl_3$) δ 1.15 (s, 9, *tert*-C_4H_9), 2.55 (s, 3, OAc), 6.22–7.17 (2 AB quartets, J = 8 and 9 Hz, superimposed on multiplets, 7, H_3, H_4, H_6, H_7 of naphthalene and H_3, H_4, H_5 of pyridine), 8.60 ppm (d of m, 1, H_6 of pyridine).

Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.3; H, 6.3; N, 4.2. Found: C, 74.9; H, 6.3; N, 4.4.

5-(2-Pyridyl)naphthalene-1,6-diol (12).—The yellow crystalline hydrochloride salt of **12** separated from solution and isobutylene evolved as an off-gas (identified by mass spectrometry) when a mixture of **7a** (0.60 g, 1.6 mmol) in 12 ml of 6 *N* hydrochloride acid was heated for 30 min at reflux temperature. The chloride salt was collected after being refrigerated at 5° for 2 hr and converted directly into its diacetyl derivative **9** (0.44 g, 88%): mp 145–147° (from methylcyclohexane); nmr ($CDCl_3$) δ 2.00 (s, 3, 2-acetoxy), 2.40 (s, 3, 5-acetoxy), 7.17–7.50 (m, 6), 7.70 (d of d, 1, H_8), 8.00 (d, 1, J = 8 Hz, H_4), 8.78 ppm (d of m, 1, H_6 of pyridine).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.1; H, 4.7; N, 4.4. Found: C, 70.7; H, 5.1; N, 4.1.

Ketonic Tautomer 14.—A mixture of **7a** (1.50 g, 4.0 mmol) and potassium hydroxide (0.40 g) in 20 ml of 50% aqueous methanol was stirred at room temperature for 10 min. The solution was diluted with 40 ml of water and then 5% HCl solution until the resulting amphoteric precipitate began to redissolve. The mixture was made alkaline with 5% aqueous sodium bicarbonate solution, and the product was collected, dried, and recrystallized as white needles (0.70 g, 60%) from methylcyclohexane, mp 194–196°; see text for spectral data.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.9; H, 6.5; N, 4.8. Found: C, 77.6; H, 6.5; N, 4.9.

Phenol 15.—A mixture of 0.60 g of **14**, 0.20 g of 10% palladium on charcoal, and 100 ml of ethanol was hydrogenated at 40 psi (initial pressure) for 3 hr in a Parr shaker, giving (after work-up of the reaction mixture) 0.54 g (90%) of **15** as white needles (from methylcyclohexane): mp 205–206°; nmr ($CDCl_3$) δ 0.62 (s, 9), 2.27–2.77 (m, 4), 3.50 (m, 1), 6.98 (d, 1, J = 9 Hz), 7.10–7.90 (m, 3), 8.09 (d, 1, J = 9 Hz), 8.67 ppm (d of m, 1).

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.3; H, 7.1; N, 4.7. Found: C, 77.0; H, 7.2; N, 4.6.

The same product was obtained from a $LiAlH_4$ reduction of **14** in ether.

Zwitterion 18.—A solution of **11** (0.67 g, 2.0 mmol) and 0.67 g of anhydrous cupric chloride in 20 ml of ethanol was refluxed for 15 min, during which time isobutylene gas was evolved (identified by mass spectrometry) and **17** (0.45 g, 73%) crystallized from solution.

The zwitterion **18** was prepared by dissolving **17** in 10 ml of DMSO and basifying with 50 ml of 5% aqueous sodium bicarbonate solution. The resulting orange crystals were collected, dried, dissolved in a minimum amount of acetone, and introduced onto a column of Florisil magnesium silicate. The chromatogram was developed with acetone–ethanol (10:1 v/v) and the eluted product recovered and crystallized as red needles from ethanol–ligroin (bp 30–60°): mp 212–215° dec; uv max (CH_3CN) 242 nm (log ϵ 4.62), 264 (4.42), 330 (3.97), 345 (3.94), 410 (3.66), 431 (3.98), 457 (4.31), 489 (4.38); nmr (DMSO-d_6) δ 2.50 (s, 3, acetoxymethyl), 6.75 (d, 1, J = 10 Hz, H_a), 7.60 (d, J = 9 Hz, H_c), 7.60 (m, H_f or H_g), 7.80 (d, J = 10 Hz, H_b), 7.81 (m, H_f or H_g), 8.38 (d of m, H_h), 8.37 (d, J = 9 Hz, H_d), 9.22 ppm (d of m, 1, H_e); mass spectrum (70 eV) m/e (rel intensity) of major peaks 277 (32) (M^+), 235 (100) ($M - CH_2CO$).

Anal. Calcd for $C_{17}H_{11}NO_3$: C, 73.7; H, 4.0; N, 5.1. Found: C, 73.4; H, 4.0; N, 5.2.

Registry No.—**6a**, 30319-50-7; **7a**, 30310-01-1; **7b**, 30310-02-2; **7c**, 30310-03-3; **8**, 30310-04-4; **9**, 30310-05-5; **10a**, 30275-77-5; **10b**, 30275-78-6; **10c**, 30310-06-6; **11**, 30310-07-7; **14**, 30310-08-8; **15**, 30310-09-9; **18**, 30310-10-2; 8-*tert*-butyl-9,10-dihydro-5-hydroxy-12-oxo-4a-azonia-9,10-ethanoanthracene perchlorate, 30310-11-3.

Acknowledgment.—We are indebted to Mr. R. L. Graves, of this laboratory, who wrote the computer program for the line-shape calculations and provided invaluable guidance in its implementation. We also wish to thank Mr. D. P. Maier and Dr. J. C. Chang for supplying the mass spectral and electrochemical data, respectively.

(11) Melting points (uncorrected) were determined on a Thomas-Hoover apparatus. Ultraviolet absorption spectra were recorded on a Cary Model 14 spectrophotometer. Infrared spectra were obtained with either a Beckman IR-12 or a Perkin-Elmer Infracord spectrometer. Nmr spectra were determined with either a Varian A-60 or Bruker HX-90 spectrometer. Peak positions are reported in parts per million downfield from tetramethylsilane, followed by (in parenthesis) multiplicity, relative area, and assignment.

(12) D. L. Fields, T. H. Regan, and J. C. Dignan, *J. Org. Chem.*, **33**, 390 (1968).

(13) D. L. Fields and J. B. Miller, *J. Heterocycl. Chem.*, **7**, 91 (1970).

(14) More stringent conditions, using elevated temperatures, will degrade ketone-**3**-type intermediates; see ref 1.

Overcrowded Molecules. II. 4,5-Bis(2-pyridyl)phenanthrene-3,6-diols

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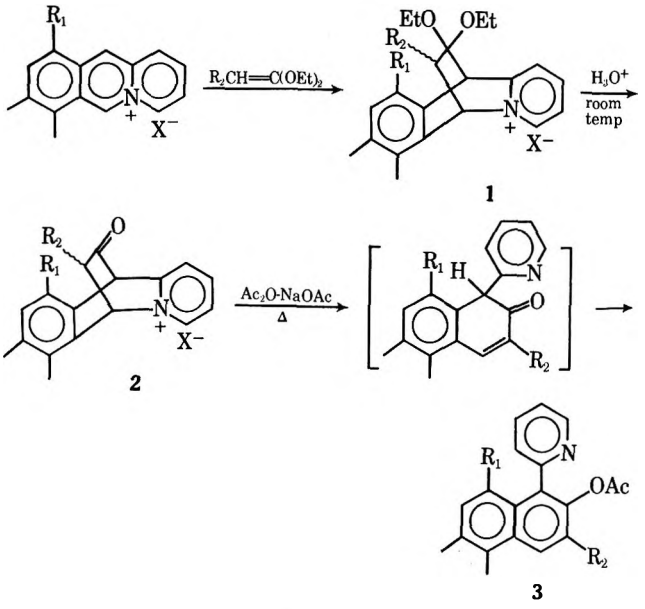
The ketene acetal adducts of several azoniaanthracene, azoniabenzanthracene, and diazoniapentaphene salts were used to prepare (2-pyridyl)naphthols **5**, (2-pyridyl)phenanthrols **7** and **9**, and bis(2-pyridyl)phenanthrenediols **11**, **13**, and **15**, respectively, by a modification of a known procedure. The phenanthrene-3,6-diols having pyridine substituents at the 4,5 positions (11) show a high degree of steric strain which strongly influences their uv, mass, and nmr spectra.

The synthetic route to 1-(2-pyridyl)-2-naphthols *via* the three-step process outlined in Scheme I has

SCHEME I



been utilized for the preparation of two new classes of molecules with exceedingly high steric strain. One set, the 8-*tert*-butyl-1-(2-pyridyl)naphthalenes, has already been described.[1]

In this paper, some further observations on the synthetic pathway are noted, and the synthesis and basic spectral properties of the second class of sterically hindered compounds, the 4,5-bis(2-pyridyl)phenanthrene-3,6-diols, are described. An X-ray crystallographic structure determination of one of these compounds was undertaken by Smith and is discussed elsewhere.[2] The pyridine rings in these nonplanar, and therefore chiral, phenanthrenes have a spatial relationship similar to that of the phenyl groups in [2.2]-metacyclophanes,[3] being almost coplanar and held in face-to-face proximity. The combination of severe ring strain and unusual geometry has pronounced effects on their physical and chemical properties, some aspects of which are reported here; certain others are under current investigation.

Results and Discussion

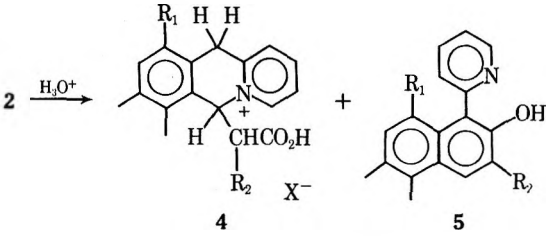
Synthesis.—Prior to this study, our envisioned adaptation of Scheme I to the synthesis of more complex polycyclic compounds was clouded by the knowledge that ketones **2**, generated from ketal precursors by acid treatment, are themselves acid labile, readily degrading to a mixture of **4** and **5**, with **4** often predominating.[4]

Accordingly, the success of this synthesis was thought to depend on the isolation of these rather elusive intermediate ketones in useful yields. Fortunately, however, the hydrolytic cleavage product **4** readily reverts to **2** in high yield on treatment with acetic anhydride–sodium acetate at room temperature. More importantly, this reagent at reflux temperature converts **4**, *via* **2**, to the desired product **3**, exclusively. Thus the initial hydrolysis of ketal **1** may be carried out in refluxing 6 *N* HCl without concern for the nature of the products, be they **2**, **4**, or **5**, since treatment of the resulting mixture with acetic anhydride–sodium acetate at reflux temperature will convert each of them to the same final product, **3**.[5]

Application of this modified synthesis (eq 1) to the previously described azoniapolycyclic ketene acetal

$$1 \xrightarrow[\Delta]{H_3O^+} [2 \text{ and/or } 4 + 5] \xrightarrow[\Delta]{Ac_2O\text{-}NaOAc} 3 \xrightarrow{H_3O^+} 5 \qquad (1)$$

adducts[6] shown in Scheme II has provided the indicated naphthols and phenanthrols in 85–90% yields. In like manner, bis adducts **10a–e**, **12**, and **14** (Scheme III), obtained from stereoselective[7] cycloadditions of ketene diethyl acetals to 4a,8a-, 4a,12a-, and 12a,14a-diazoniapentaphene salts, were converted without difficulty to the desired phenanthrenediols **11a–e**, **13**, and **15**, respectively. The structural assignments of the new products were supported by elemental analyses



(1) D. L. Fields and T. H. Regan, *J. Org. Chem.*, **36**, 2986 (1971).

(2) D. L. Smith and E. K. Barrett, *Acta Crystallogr., Sect. B*, **27**, 419 (1971).

(3) C. J. Brown, *J. Chem. Soc.*, 3278 (1953).

(4) (a) D. L. Fields and T. H. Regan, *J. Org. Chem.*, **35**, 1870 (1970). (b) For example, **1** (R_1, R_2 = H; X^- = ClO_4^-) gives on treatment with 6 *N* hydrochloric acid at 90° for 0.5 hr a mixture of **4** (84%) and **5** (9%); no **2** could be isolated.

(5) A minor limitation to this procedure exists when **4** possesses a 5-hydroxyl substituent, in that O-acylation–elimination leading to a coumarin by-product competes favorably with the desired C-acylation–elimination.

(6) D. L. Fields, T. H. Regan, and J. C. Dignan, *J. Org. Chem.*, **33**, 390 (1968).

(7) Adducts **10a–e**, **12**, and **14** each are believed to be a mixture of geometric isomers formed from bis cycloadditions in which the ketene acetal had added both to the same side and from opposite sides of the diazoniapentaphene ring (see ref 6) in a stereoselective or, when R_2 = H, a stereospecific manner. This is inconsequential in the preparation of **11**, **13**, and **15**.

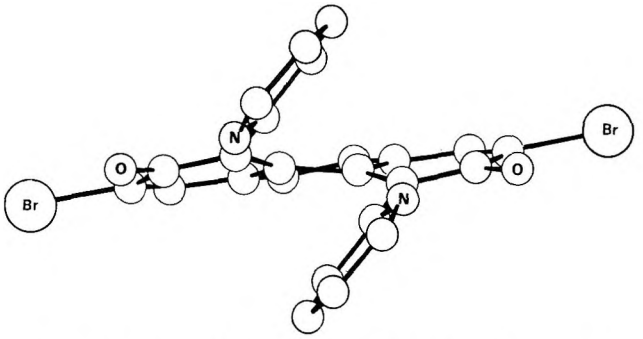
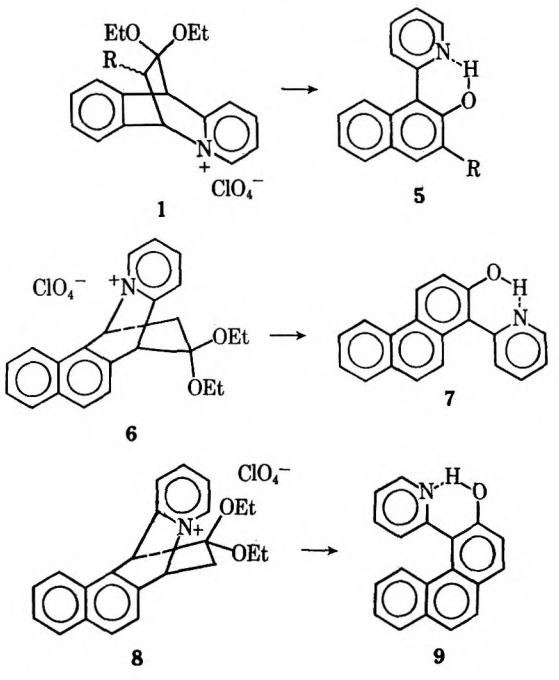


Figure 1.—View of **11b** along the twofold symmetry axis.

SCHEME II



a, R = H; **b**, R = CH_3; **c**, R = C_6H_5; **d**, R = Br

(Table III and IV, Experimental Section) and by the usual spectral means, selected results of which will be discussed in the following sections.

Molecular Structure of 11b.—The compounds of prime interest are, of course, the 4,5-dipyridyl derivatives **11a–e**, products which if completely planar and free of angle and bond deformations would have the two pyridyl rings occupying the same space. Obviously considerable altering of normal bond angles and lengths is necessary for **11** to have even the minimum-allowed ~3-Å separation between their pyridine rings.[8] The nature and extent of the deviations have been clarified through a single-crystal X-ray analysis of a representative member, **11b**. Although the details of this structure determination are being reported elsewhere,[2] a brief qualitative description of the results is warranted here.

In agreement with conclusions drawn from nmr data that will be commented on later, each pyridine of **11b** is found to be intramolecularly hydrogen bonded to the neighboring hydroxyl group, creating a twofold axis of

(8) When aromatic rings are held face to face and are not constrained, they have a normal "van der Waal" separation of ~3.4 Å; see J. M. Robertson, "Organic Crystals and Molecules," Cornell University Press, Ithaca, N. Y., 1953, pp 157, 174, 206, 270.

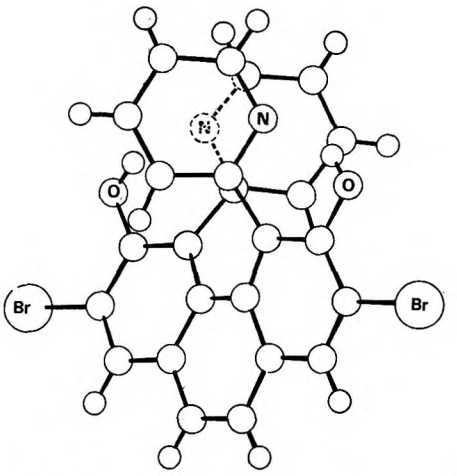
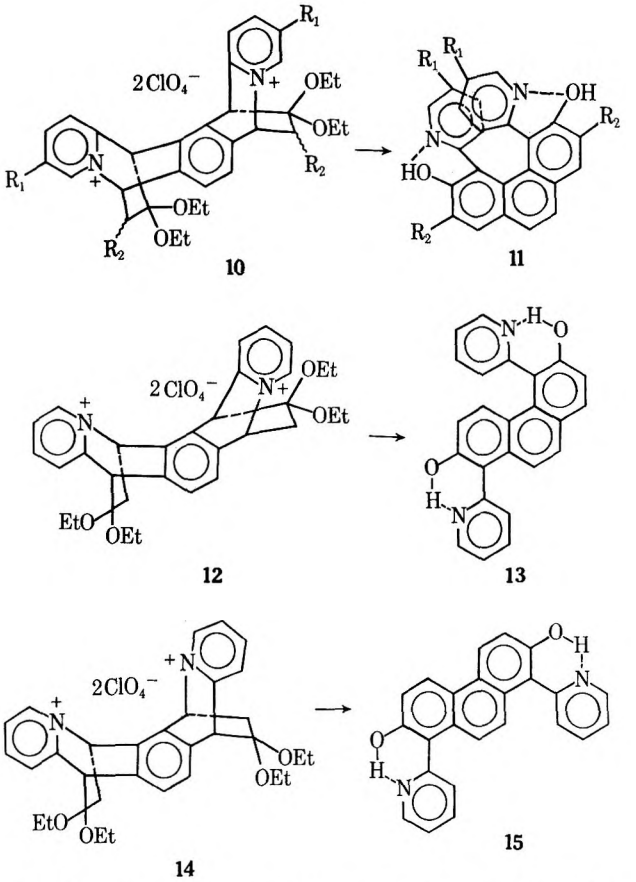


Figure 2.—Projection of **11b** normal to one of the pyridyl rings.

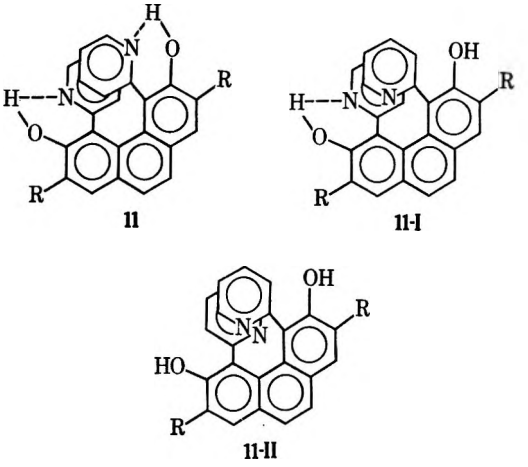
SCHEME III



a, R_1, R_2 = H; **b**, R_1 = H, R_2 = Br; **c**, R_1 = H, R_2 = CH_3; **d**, R_1 = CH_3, R_2 = H; **e**, R_1 = CH_3, R_2 = CH_3

symmetry. As can be inferred from Figure 1, the distortion is distributed over the entire framework of the molecule in such a way that the trigonal symmetry of the bonds around any particular carbon bond is not greatly disturbed. No major segment of the molecule is truly planar; yet all individual rings are approximately planar. The pyridyl rings have a stair-step relationship to one another (Figure 2) and are almost parallel, being inclined 11° to each other. The distance between vicinal nonbonded pyridyl carbon atoms varies from an extraordinary close 2.81 Å between C_2 of one pyridine and $C_{2'}$ of the second pyridine, to a more normal 3.34 at C_6–$C_{6'}$.

Under such steric constraint, it seems reasonable that the pyridines would suffer restricted rotation, making possible two diastereoisomers other than that known from the X-ray study. The three isomers would differ solely in the orientation of the pyridines with respect to one another as indicated for **11**, **11-I** and **11-II**. However, we have no experimental evidence



suggesting the presence of the latter two possibilities. Each of **11a–e** appeared homogeneous based on melting point behavior and tlc analysis. More significant is the fact that the position of the hydroxyl proton signals in their nmr spectrum ($CDCl_3$) was concentration independent, located as a two-proton broadened singlet at a low-field position (~12.5 ppm). This result is only consistent for the energetically preferred, intramolecularly hydrogen-bonded isomer **11**.

Spectral Properties.—Some effects of overcrowding on the spectral properties of **11** are easily recognized through a comparison of uv and mass spectral data of **11a** with like data obtained for the lesser strained isomeric phenanthrenediols **13** and **15**.

Perturbations resulting from distortion of the phenanthrene nucleus are known to produce bathochromic and hyperchromic shifts of the longer wavelength absorptions,[9] and such shifts are apparent in comparison with the uv spectra of the diacetyl derivatives of **11a**, **13**, **15**, and the parent 3,6-dihydroxyphenanthrene (Figure 3). Spectra of the diacetates rather than the parent diols are compared to eliminate unknown contributions resulting from hydroxyl–pyridine hydrogen bonding.

The mass spectral fragmentation of **11a** also shows abnormalities attributable to overcrowding. The initial and major fragmentation of **11a** involves loss of a pyridyl group, a fragmentation of minor importance in the lesser strained **13** and **15** (Table I). This mode of

TABLE I

IMPORTANT IONS IN THE MASS SPECTRA OF **11a**, **13**, AND **15**

		Rel intensity, %		
m/e	Assignment	**11a**	**13**	**15**
364	M	21.0	65.0	100.0
363	M − 1	0.6	100.0	96.0
286	M − Py	100.0	1.7	8.6

(9) For example, see G. M. Badger, J. E. Campbell, J. W. Cook, R. A. Raphael, and A. I. Scott, *J. Chem. Soc.*, 2326 (1950); H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, pp 384–449.

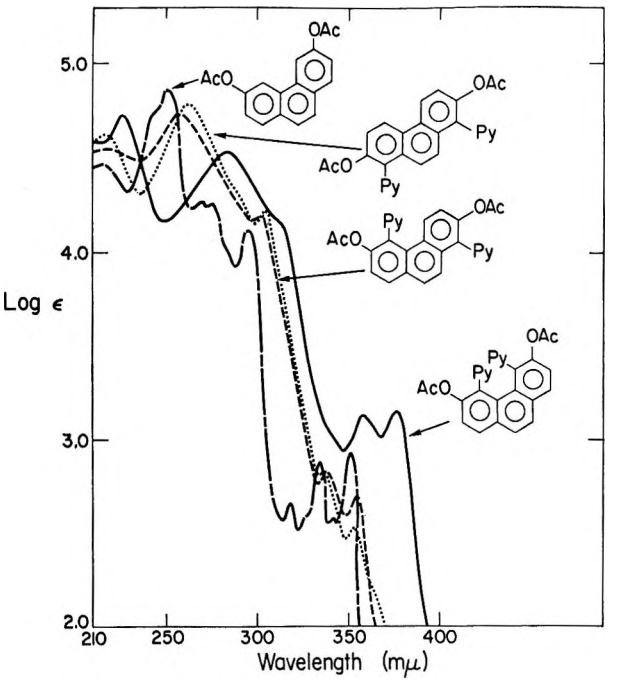


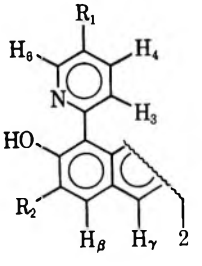
Figure 3.—Ultraviolet spectra of the diacetyl derivatives of **11a**, **13**, **15**, and phenanthrene-3,6-diol.

cleavage appears to be characteristic of these 4,5-dipyridylphenanthrene derivatives and has proved valuable in structure elucidation of reaction products derived from free radical oxidation processes which will be reported at a later time.

The nmr data are contained in Table II. The individual absorptions in the spectrum of **11e** were unambiguously assignable since the positions of the methyl substituents were unequivocal from the synthesis, and the "apparent" coupling constants in this and the other compounds ($|J_{34}| \simeq 8$–9 Hz, $|J_{45}| \simeq 7.5$ Hz, and $|J_{46}| \simeq 2$ Hz) defined the positions of the protons with respect to one another. Using these assignments, absorptions of the remaining compounds could be readily identified, since the chemical shifts were such that no serious second-order perturbations appeared to be present.

TABLE II

NMR CHEMICAL SHIFTS[a] OF 4,5-BIS(2-PYRIDYL)PHENANTHRENE-3,6-DIOLS



	R_1	R_2
11a	H_5	H_α
11b	H_5	Br
11c	H_5	CH_3
11d	CH_3	H_α
11e	CH_3	CH_3

Compd	R_2	H_β	H_γ	H_3	H_4	R_1	H_6	OH
11a	7.24	7.77	7.54	6.83	7.39	6.97	8.03	12.5
11b		8.06	7.48	6.85	7.47	7.04	8.04[b]	
11c	2.42	7.63	7.49	6.84	7.39	6.96	8.01	13.0
11d	7.18	7.74	7.52	6.72	7.22	2.26	7.84	12.5
11e	2.29	7.59	7.46	6.74	7.20	2.23	7.82	12.6

[a] δ values in ppm downfield from internal TMS. Obtained with a Varian HA-100 spectrometer using 1–4% solutions in $CDCl_3$. Accuracy ±0.01 ppm. [b] Partially obscured by H_β.

TABLE III

PYRIDYL-SUBSTITUTED 2-NAPHTHOLS AND PHENANTHROLS

Compd	Yield, %	Mp, °C	Uv, $\lambda_{max}^{CH_3CN}$ (log ε)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
5a[a]	91								
5b[a]	95								
5c[a]	87								
5d[b]	93	98–100	232 (4.67) 250 (4.38) 318 (3.98) 351 (3.90)	60.1	3.3	4.7	59.8	3.1	4.6
7[b]	86	194–195	259 (4.69), 315 (4.00) 353 (3.50), 367 (3.48)	84.1	4.8	5.2	84.5	5.0	5.2
9[b]	88	126–127	226 (4.59), 246 sh (4.44) 281 (4.31), 361 (3.49) 383 (3.46)	84.1	4.8	5.2	84.2	4.9	5.1

[a] Reference 4. [b] Recrystallized from methylcyclohexane.

TABLE IV

DIPYRIDYL-SUBSTITUTED PHENANTHRENEDIOLS

Compd	Yield, %	Mp, °C	Uv, $\lambda_{max}^{CH_3CN}$ (log ε)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11a[a,b]	88	221–223	239 (4.66), 295 (4.49), 312 sh (4.40) 402 (3.60), 420 (3.63)	79.1	4.4	7.7	78.8	4.7	7.7
11b[c]		290 dec		55.2	2.7	5.4	55.1	2.8	5.2
11c[d]	86	274–277 (with dec)		78.7	5.2	7.1	78.9	5.4	7.2
11d		231–233		79.6	5.1	7.1	79.4	5.0	7.2
11e		267–269 (with dec)		80.0	5.7	6.7	79.6	5.7	6.7
13[a,e]	70	134–135	239 (4.59), 321 (4.39), 390 sh (3.45)	79.1	4.4	7.7	78.8	4.5	7.6
15[a,f]	92	236–237	241 (4.46), 273 (4.62), 310 (4.35), 380 (3.73)	79.1	4.4	7.7	78.7	4.8	7.9

[a] Recrystallized from methylcyclohexane. [b] Diacetyl derivative, mp 237–241°. [c] Recrystallized from CH_2Cl_2–ligroin (bp 30–60°). [d] Solvated: $0.25H_2O$. Recrystallized from ethanol–H_2O. [e] Diacetyl derivative, mp 176–179°. [f] Diacetyl derivative, mp 254–256°.

The nmr data combined with the nonbonded internuclear distances from the X-ray data provide an unusual opportunity to test the widely used "ring current" model for diamagnetic anistropy of aromatic compounds. This material is discussed in detail in another report.[10] The results show good agreement between the experimentally observed shifts and those calculated from theory.

Experimental Section[11]

Azoniapolycyclic Ketene Acetal Adducts.—Adducts **1a–d**, **6**, **8**, and **10a** have been described previously.[5] The following new adducts were prepared by the same general procedure. In each case the nmr spectrum was consistent with the assigned structure.

Adducts 10b and 10c were isolated as amorphous white powders in quantitative yields following treatment of 4a,8a-diazoniapentaphene diperchlorate[12] with 1-bromo-2,2-diethoxyethylene[13] and with 1,1-diethoxypropene,[14] respectively.

The synthesis of **10d** and of **10e** necessitated beginning with rudimentary starting materials. 2,5-Lutidine was converted by known procedures[15] to 5-methyl-2-(1,3-dioxolan-2-yl)pyridine [bp 55° (110 mm), $n^{25}D$ 1.5215], which was further characterized as its methoperchlorate, mp 107–109°.

Anal. Calcd for $C_{10}H_{14}ClNO_6$: C, 42.8; H, 5.0; N, 5.0. Found: C, 42.8; H, 5.4; N, 5.3.

This pyridine acetal was then employed in the Bradsher diazoniapentaphene synthesis[11] to give 3,10-dimethyl-4a,8a-diazoniapentaphene diperchlorate: uv max (CH_3CN) 217 nm (log ε 4.69), 253 (4.02), 256 sh (4.01), 286 (4.24), 298 (4.32), 340 (4.51), 353 (4.56), 364 (4.38), 384 (4.51), 418 (3.66), 444 (3.61).

Its reaction with excess 1,1-diethoxyethylene[16] and 1,1-diethoxypropene[14] afforded **10d** and **10e**, respectively, as amorphous white solids. Adducts **10b–e** were not fully characterized other than to establish in each case the absence of absorbances longer than 270 nm in their uv spectra.

Adduct 12, mp 217° (with dec), and **adduct 14**, mp 270° dec, were obtained as crystalline solids from bis cycloadditions of 1,1-diethoxyethylene with 4a,12a- and 12a,14a-diazoniapentaphene perchlorates,[12] respectively.

Anal. Calcd for $C_{32}H_{38}Cl_2N_2O_{12}$: C, 53.8; H, 5.3; N, 3.9. Found (for **12**): C, 53.4; H, 5.3; N, 4.0. Found (for **14**): C, 53.6; H, 5.3; N, 3.9.

Naphthol–Phenanthrol Synthesis.—The following procedure for the preparation of 4,5-bis(2-pyridyl)phenanthrene-3,6-diol (**11a**) is typical of that used in the syntheses of the products listed in Tables III and IV.

A solution of **10a**[5] (23.9 g, 0.032 mol) in 100 ml of 6 *N* hydrochloric acid was heated under reflux for 1 hr and then concentrated on a rotary evaporator to a viscous syrup. A mixture of this syrup, 10 g of anhydrous sodium acetate, and 200 ml of acetic

(10) P. I. Rose, unpublished results.

(11) Melting points (uncorrected) were determined on a Thomas–Hoover apparatus. Ultraviolet absorption spectra were recorded by a Cary Model 14 recording spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrometer. Nmr spectra were determined at ambient probe temperature with either a Varian A-60 or HA-100 spectrometer. Peak positions are reported in parts per million downfield from internal tetramethylsilane. In a few cases $CHCl_3$ was used as a secondary reference. The mass spectra were determined on a Consolidated 21-110 instrument operating at nominal resolution.

(12) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **29**, 856 (1964).

(13) F. Beyersted and S. M. McElvain, *J. Amer. Chem. Soc.*, **72**, 1661 (1950).

(14) S. M. McElvain and W. R. Davie, *ibid.*, **73**, 1400 (1951).

(15) V. Boekelheide and W. J. Linn, *ibid.*, **76**, 1286 (1954); C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).

(16) S. M. McElvain, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 506.

anhydride was refluxed for 1 hr. The residue obtained upon concentrating the reaction mixture was triturated in 250 ml of 5% sodium bicarbonate solution, giving 14.3 g of the diacetyl derivative of **11a**, as light tan crystals.

An analytical sample had mp 237–241° after two recrystallizations from methylcyclohexane; uv, Figure 3; nmr δ 1.88 (s, 6 H, $COCH_3$), 6.35 (d of m, 2, two pyridine H), 6.90–8.20 (m, 12, H_α, H_β, H_γ, and remaining pyridine H with H_γ appearing as a singlet at 7.80; H_β, d, J = 9 Hz at 7.98; H_α, d, J = 9 Hz at 7.30); mass spectrum (70 eV) m/e 448 (M^+), 406, 370, 364, 328, 286.

Anal. Calcd for $C_{28}H_{20}N_2O_4$: C, 75.0; H, 4.5; N, 6.2. Found: C, 75.0; H, 4.9; N, 6.3.

The above product was deacetylated by heating a solution of it in 100 ml of 6 *N* hydrochloric acid for 0.5 hr at reflux temperature. The resulting crystalline dihydrochloride was isolated after concentrating the reaction mixture to dryness; its neutralization with 5% sodium bicarbonate solution gave 10.2 g (88%) of essentially pure (tlc) **11a** as fine yellow needles.

Registry No.—**5d**, 30309-81-0; **7**, 30309-82-1; **9**, 30309-83-2; **11a**, 26244-86-0; **11a** diacetyl derivative, 26244-85-9; **11b**, 30309-86-5; **11c**, 30309-87-6; **11d**, 30309-88-7; **11e**, 30309-89-8; **12**, 30259-90-6; **13** diacetyl derivative, 30309-90-1; **14**, 30259-91-7; **15** diacetyl derivative, 30309-91-2; 3,6-diacetylphenanthrene, 30309-92-3; 5-methyl-2-(1,3-dioxolan-2-yl)pyridine, 30309-93-4, 30309-94-5 (methoperchlorate); 3,10-dimethyl-4a,8a-diazoniapentaphene diperchlorate, 30309-95-6.

Acknowledgment.—We wish to thank Mr. D. P. Maier for supplying the mass spectral data and Dr. P. I. Rose for technical assistance in recording some of the nmr spectra and for helpful discussions regarding their interpretation.

Overcrowded Molecules. III. 13,14-Bis(2-pyridyl)pentaphene and Related Compounds

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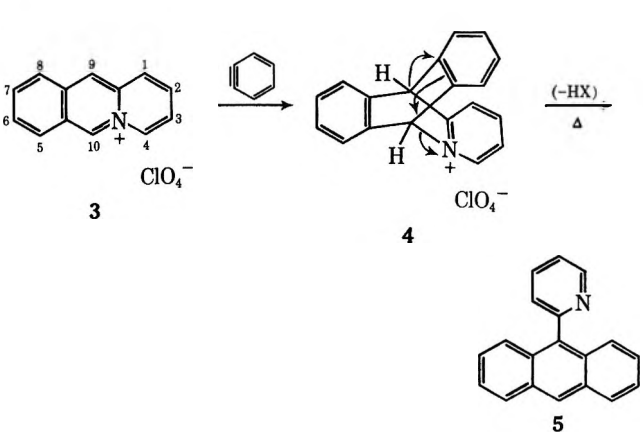
Received January 6, 1971

The reaction of benzyne with 4a-azoniaanthracene and 4a,8a- and 4a,12a-diazoniapentaphene salts produces, in good yields, azoniatriptycene-type adducts, which are thermolyzed in boiling acetic anhydride to 9-(2-pyridyl)-anthracene (**5**), 5,13- (**15**), and 13,14-bis(2-pyridyl)pentaphenes (**18**), respectively. The nmr spectrum of **19**, the bis-*N*-methyl quaternary salt of **15**, displays each of its *N*-methyl resonances as two sharp peaks of equal intensity up to 130°, indicative that both pyridine rings are suffering restricted rotation giving rise to a pair of geometric isomers. The nmr spectrum of the mono-*N*-methyl quaternary salt of **18** shows the presence of at least two of the four possible geometrical isomers; these, however, begin to interconvert at room temperature and are equilibrated above 80° ($\Delta F^\ddagger \sim 17$ kcal/mol). The bis-*N*-methyl quaternary salt of **18** shows its *N*-methyl absorptions as two singlets (2:1 area ratio) at 70°. The major peak is temperature independent, whereas the minor peak broadens as the temperature is lowered, finally separating into two singlets of equal area at 20°. These results are interpreted in terms of an unexpectedly facile pentaphene ring inversion accompanied by a synchronous rotation of both pyridines.

Previously it has been shown that, in marked contrast to the low order of reactivity that azonia polycyclic aromatic compounds display toward conventional electrophilic dienophiles, a variety of these compounds will readily undergo stereoselective 4 + 2 cycloadditions with nucleophilic olefins including enamines and ketene acetals to give adducts in high yields.[1] The ketene diethyl acetal adduct of 5-acetoxy-8-*tert*-butyl-4a-azoniaanthracene perchlorate and the bis adduct of 4a,8a-diazoniapentaphene diperchlorate have been particularly useful, serving as precursors to the interesting, highly overcrowded naphthalene **1**[2] and phenanthrene **2**,[3] respectively, *via* the synthesis shown in Scheme I.

Benzyne is considered to be an electrophilic reagent. Nevertheless, we have now found that it too will undergo cycloaddition efficiently with azonia polycyclics to afford azoniatriptycene-type adducts (**4**). Our interest in these types of compounds has been twofold. First, they serve as precursors to substituted anthracenes and related hydrocarbons in a synthesis to be described in a separate publication. Second, and relevant to this paper, is the discovery that their thermolysis usually leads to pyridyl-substituted polycyclic aromatic hydrocarbons, the simplest of these being 9-(2-pyridyl)anthracene (**5**). Exploitation of this reaction sequence as a new synthetic approach to overcrowded molecules has been profitably investigated



3 **4** **5**

in the synthesis of highly strained nonplanar, and therefore chiral, 13,14-bis(2-pyridyl)pentaphene. Manifestations of the ring strain and unusual geometry associated with this compound parallel those previously observed with 4,5-dipyridylphenanthrene **2** in several ways. One interesting and distinctive difference is discussed, related to conformational isomerism.

(1) D. L. Fields, T. H. Regan, and J. C. Dignan, *J. Org. Chem.*, **33**, 390 (1968).
(2) D. L. Fields and T. H. Regan, *ibid.*, **36**, 2986 (1971).
(3) D. L. Fields and T. H. Regan, *ibid.*, **36**, 2991 (1971).

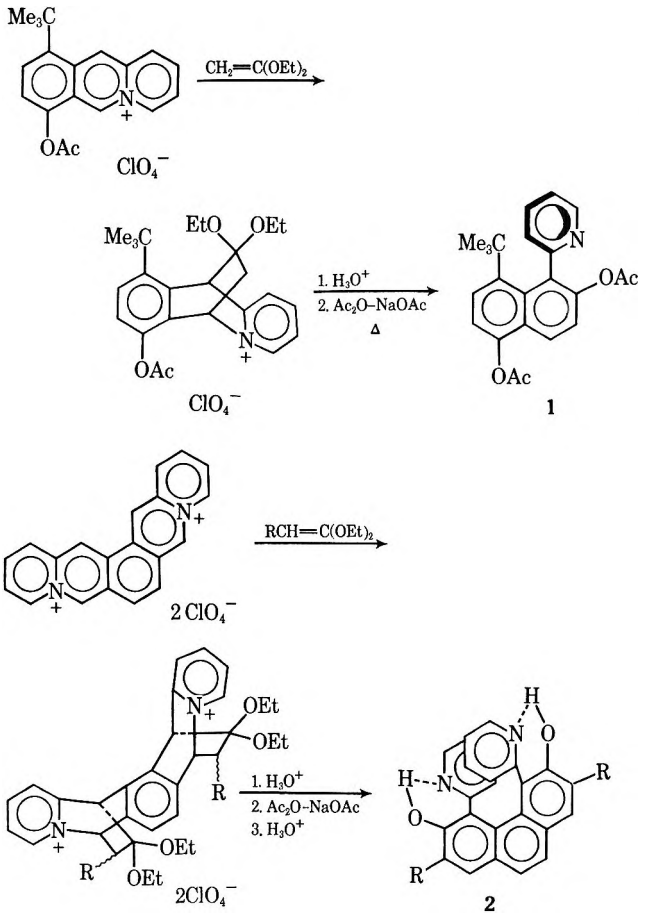
TABLE I

AZONIATRIPTYCENE PERCHLORATES (4)

No.	Starting azoniaanthracene (3)	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
4a	Unsubstituted[a]	78	64.1	3.9	3.9	64.2	4.1	3.9
4b	5,6-Diacetoxy-8-phenyl[b]	67	63.8	4.0	2.6	63.4	3.9	2.4
4c	5-Acetoxy-8-*tert*-butyl[c]	75	63.9	5.2	3.0	63.5	5.3	2.9
4d	5-Methyl[a]	75	65.0	4.3	3.7	64.8	4.4	3.7
4e	7-Methyl[a]	72	65.0	4.3	3.7	64.9	4.7	3.6
4f	9-Phenyl[d]	59	67.7	4.4	3.4	68.1	4.8	3.2
4g	5-Nitro[e]	55	56.8	3.2	8.8	56.5	3.2	8.7

[a] C. K. Bradsher and L. E. Beavers, *J. Amer. Chem. Soc.*, **77**, 4812 (1955). [b] D. L. Fields, J. B. Miller, and D. D. Reynolds, *J. Org. Chem.*, **30**, 252 (1965). [c] D. L. Fields and J. B. Miller, *J. Heterocycl. Chem.*, **7**, 91 (1970). [d] C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **28**, 78 (1963). [e] C. K. Bradsher and J. C. Parham, *J. Heterocycl. Chem.*, **1**, 30 (1964).

SCHEME I



Results and Discussion

Azoniatriptycenes (4).—While the triptycene synthesis developed by Friedman and Logullo,[4] involving the reaction of anthracene with benzyne generated from anthranilic acid, diazotized *in situ*, is suitable for converting azoniapolycyclics to azoniatriptycene-type adducts *per se*, this procedure was modified slightly to make it more compatible with our ionic starting materials. Thus, concurrent additions of acetonitrile solutions of approximately equimolar quantities (twofold excess) of anthranilic acid and isoamyl nitrite to a refluxing mixture of 0.1 mol of **3** in the same solvent is completed within 15 min, and the reaction mixture is worked up immediately. The isolation and purification of the desired product generally is easier than that encountered in the analogous triptycene preparation in that the azoniatriptycene salt can be precipitated by addition of ether, leaving the usual benzyne by-products in solution. Thus, a considerable excess of benzyne reagents can be used without unduly complicating the isolation–purification steps, thereby eliminating the usual product contamination by unreacted **3**. In Table I are listed azoniatriptycene perchlorates prepared in this manner. No attempt was made to optimize the reaction conditions and the reported yields generally represent the results of single experiments. Support for the structural assignment for these adducts was by elemental analysis, spectral evidence, and in several cases by their behavior upon thermolysis, as discussed later.

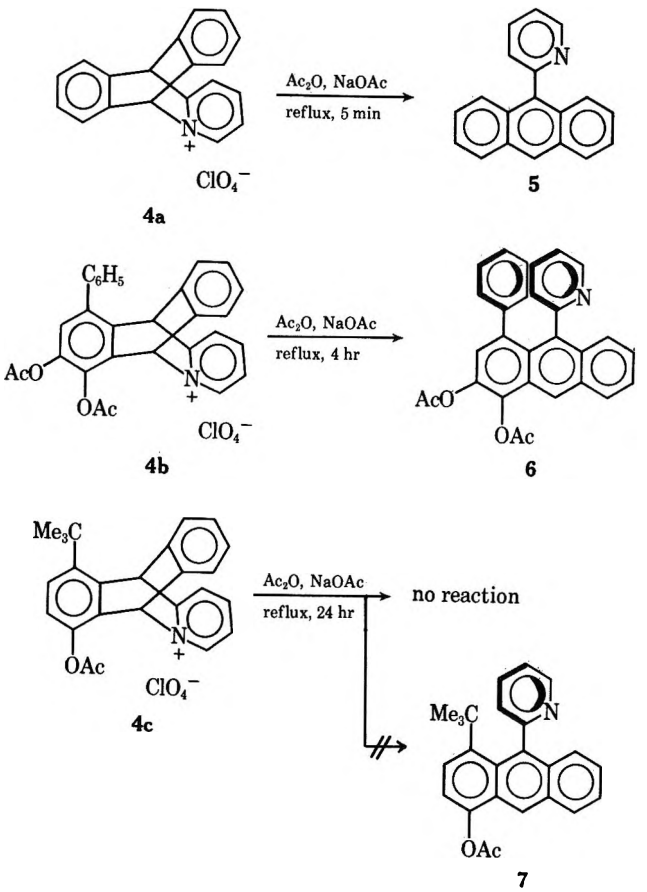
9-(2-Pyridyl)anthracenes.—To effect the conversion of an azoniatriptycene (**4**) to the corresponding 9-(2-pyridyl)anthracene, the adduct is heated in a high-boiling solvent such as acetic anhydride or diglyme, in the presence of sodium acetate, and the ensuing elimination reaction monitored by following the appearance and increase in the characteristic anthracene absorptions in the 320–390-nm region. Since aromatization to an anthracene provides a major driving force for this reaction, the facility with which the elimination occurs is influenced by the size of the R group on C_8; that is, the more bulky the C_8 substituent, the more destabilized the final product owing to adverse peri interaction with the 9-pyridyl group, and the less energetically favorable the reaction. This was borne out by qualitative observations made on the relative rates of anthracene formation starting with **4a**, **4b**, and **4c**, where R_8 = H, C_6H_5, and *tert*-C_4H_9, respectively (Scheme IIA). In refluxing acetic anhydride–sodium acetate the maximum concentrations of anthracenes **5** and **6** were formed within 5 min and 4 hr, respectively, and were isolated at the end of these periods in 86 and 62% yields. The 8-*tert*-butyl adduct **4c**, on the other hand, was recovered quantitatively after a 24-hr reaction period under the same conditions, was unchanged after 4 hr at 160° in diglyme, and slowly decomposed at 290° neat (10° above its melting point) with no indication of anthracene generation in the process.

After recognizing the relative inertness of **4c** to thermolysis, we also examined the 5-hydroxy derivative **8** (Scheme IIB) since the hydroxyl function could allow the formation of the much less sterically strained ketone **10**[5] as well as provide an alternate elimination route *via* ketomethine **9**. However, heating a mixture of **8** and sodium acetate in diglyme, varying

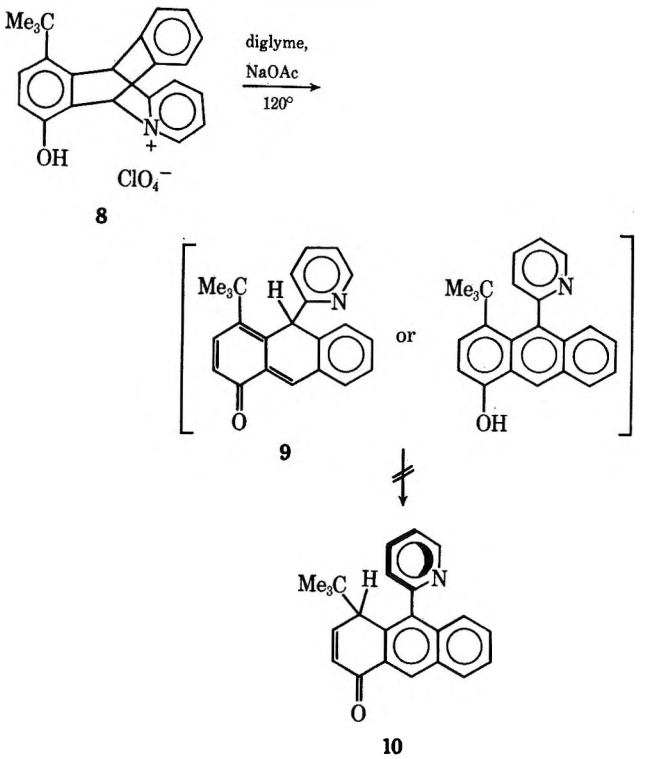
(4) L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963).

(5) Naphthalenediol **11**, for example, avoids a similar peri interaction by existing exclusively in the tautomeric keto form, **12**; see ref 2.

SCHEME IIA

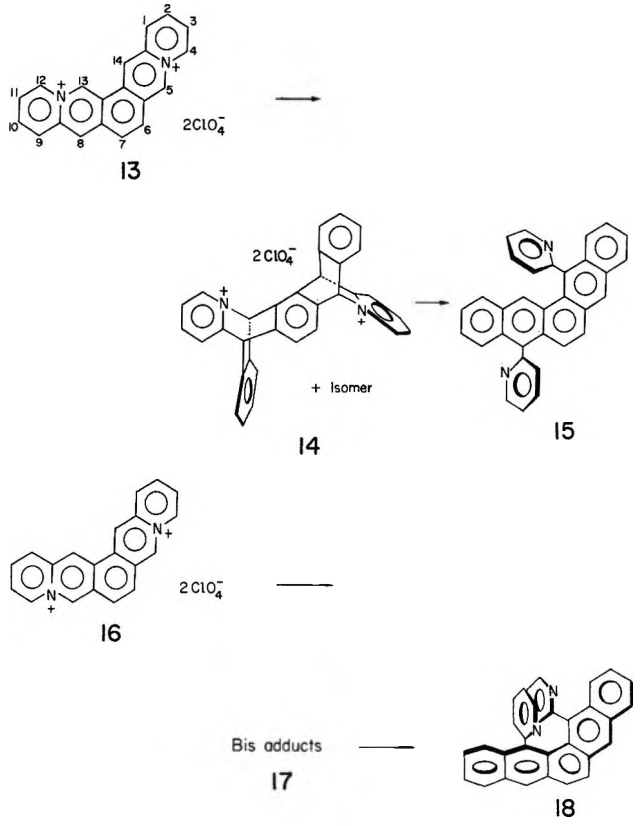


SCHEME IIB



the temperature and time, resulted only in the eventual nondescript decomposition of the starting material.

Bis(2-pyridyl)pentaphenes.—Based on the known sites of cycloaddition of ketene diethyl acetal to 4a,12a- and 4a,8a-diazoniapentaphene diperchlorates,[1,3] benzyne should cycloadd twice in each case, across the 5,14 and 8,13 positions, to give a mixture of two isomers resulting from attack by the second benzyne from the same or the opposite side of the pentaphene ring. Thermolysis of bis adducts **14** and **17**, regardless of their stereochemistry, should, and in fact did, give pentaphenes **15** and **18**, respectively.



As an example of the rather simple synthetic technique required, crude amorphous adduct **14**, isolated following treatment of **13** in the usual way with a threefold molar excess of benzyne reagents, was neither purified nor characterized other than to establish the absence of unreacted **13** (by uv), but was heated for 2 hr in refluxing acetic anhydride in the presence of sodium acetate. Florisil chromatography of the syrup obtained after removing solvent and neutralizing the residue with aqueous sodium carbonate solution gave the desired crystalline **15** in 26% overall yield. The structural assignments of it and its bis-*N*-methyl perchlorate derivative (**19**) were supported by elemental analyses and by the spectral evidence cited below.

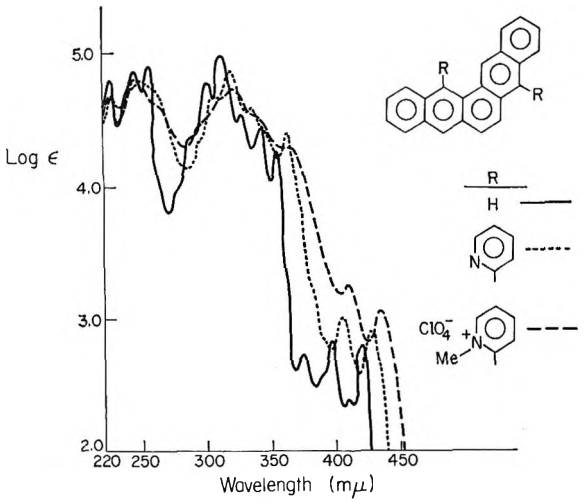


Figure 1.—Ultraviolet spectra of **15**, **19**, and pentaphene.

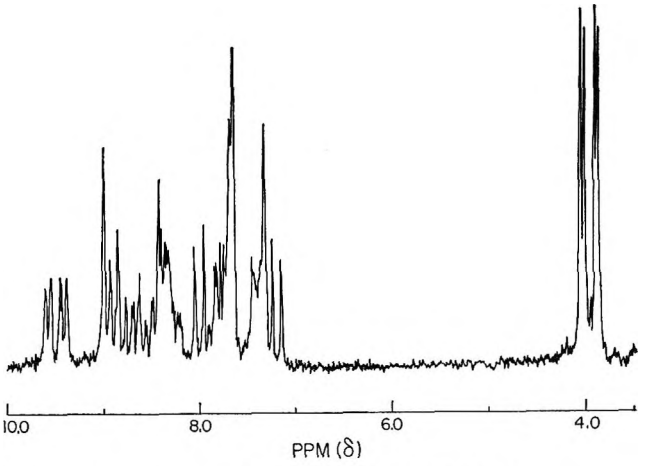
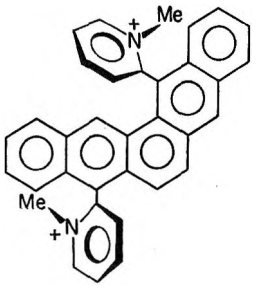


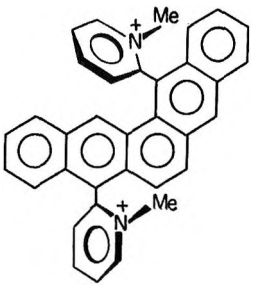
Figure 2.—Nmr spectrum of pentaphene **19a,b**.

The two important peaks in the mass spectrum of **15** occur at *m/e* 432 (100%) M^+ and 431 (92%). A comparison of the ultraviolet spectra of **15**, **19**, and pentaphene itself (Figure 1) shows them to be very similar, in keeping with the expectation that, owing to potential steric interaction with the 7,9- and 1,13-pentaphene hydrogens, the pyridines are nonplanar with respect to the pentaphene moiety and thus do not significantly perturb the pentaphene chromophore.

The presence of the methyl groups found in bispyridinium salt **19** greatly accentuates the degree of interaction with these same pentaphene hydrogens, and should further discourage rotational freedom of both pyridines. An examination of the aliphatic region in the nmr spectrum of **19** is quite informative on this point (Figure 2), showing each of the methyls as a pair of sharp singlets up to at least 130° with no hint of peak coalescence. This indicates that, at least on the nmr time scale, **19** is actually a mixture of two noninterconverting geometric isomers, **19a** and **19b**. It is not known whether parent **15** also exists in two analogously stable isomeric forms.



19a

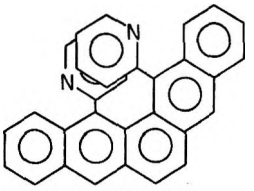


19b

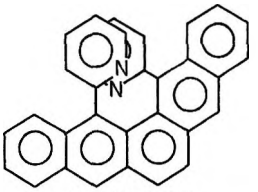
The synthetic procedure just described proved equally applicable to converting diazoniapentaphene **16** to dipyridylpentaphene **18**. The overcrowding found in this compound is probably quite similar to that being experienced by the 4,5-bis(2-pyridyl)-phenanthrene-3,6-diols (**2**),[3] a class of compounds we have studied previously in some detail. For example, we know by a single-crystal X-ray analysis[6] that **2** (R = Br) is distorted from a planar configuration (see Figure 3). The two pyridines have a stair-step relationship to one another, are almost parallel, and are extremely close, having a nonbonded intramolecular contact of 2.81 Å. In all likelihood **18** will be similarly distorted, and, indeed, abnormalities we have noted in some of the spectral properties of **2** as a result of overcrowding are equally evident for **18**.

Its mass spectrum shows *m/e* 432 (14%) M^+, 431 (0.3%), and 354 (100%) M − pyridyl. The predominant and unusual loss of a pyridyl group, an insignificant fragmentation (5%) in the less strained isomeric **15**, is also the major mass spectral fragmentation path taken by **2**, and is attributed in both instances to a drive toward strain relief. Likewise, perturbations in the π system of **18** owing to overcrowding are prominently displayed in its uv spectrum (Figure 4) in the form of bathochromic and hyperchromic shifts and loss of fine structure in the long-wave absorptions when compared with the spectrum of **15** (Figure 2). The uv spectrum of **2** was previously characterized by analogous spectral shifts.[3]

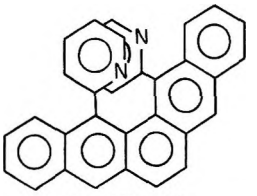
There is one interesting dissimilarity in these two types of compounds. In the di-ring-opening reactions leading to **2** and **18**, we had assumed earlier that once aromatization to the phenanthrene or pentaphene was complete, the pyridines would suffer restricted rotation, thus giving rise to three possible geometrical isomers differing solely in the conformational relationship of the pyridines to one another, *i.e.*, **18a–c**. In our study of **2**, only one of these types of isomers was recognized, that one having both pyridine nitrogens oriented toward their respective neighboring hydroxyls, thus permitting intramolecular hydrogen bonding to prevail.



18a (*dl* pair)



18b (*dl* pair)



18c (*dl* pair)

(6) D. L. Smith and E. K. Barrett, *Acta Crystallogr., Sect. B*, **27**, 419 (1971).

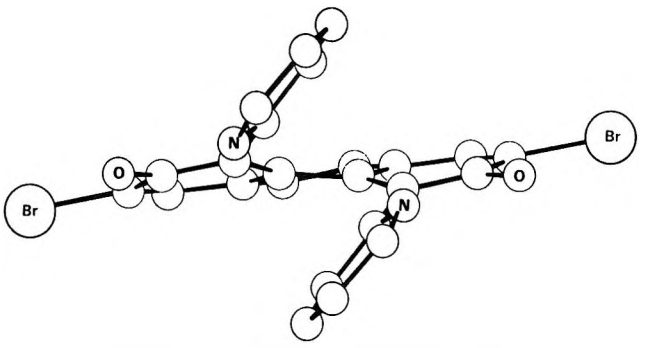
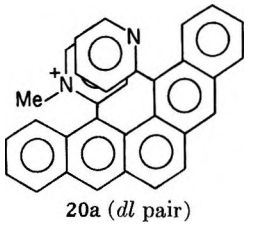


Figure 3.—View of **2** (R = Br) along the twofold symmetry axis.

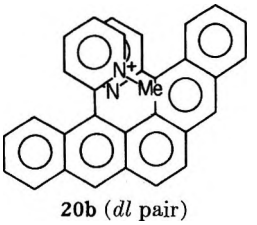
However, in the thermolysis of **17** to produce **18**, there is no obvious influence which would similarly dictate the orientation of the pyridines prior to complete aromatization. Therefore it would be reasonable to expect **18** to be a mixture of the three diastereoisomers shown.

In hope of shedding light on this possibility through nmr techniques, both mono- and bis-*N*-methylpyridinium derivatives were prepared. The mono derivative **20** was formed quantitatively by allowing a solution of **18** in methyl iodide to stand at room temperature for 6 hr. Prolonged treatment (18 hr) at reflux temperature (42°) failed to effect the alkylation of the second pyridine, reflecting the fact that the bis derivative must necessarily have two positive charges very close to one another. Bisquaternary salt **21** was obtained in good yield, but only by using much more drastic conditions, *i.e.*, boiling methyl *p*-toluenesulfonate.

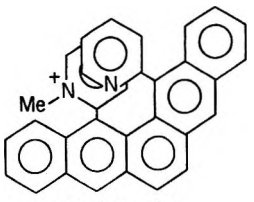
Considering first the monopyridinium derivatives, if one assumes **18** to be a mixture of **a**, **b**, and **c** isomers, then their mono-N-methylation could give a total of four diastereoisomers, **20a–d** (each as a *dl* pair), wherein **18a** and **18b** yield **20a** and **20b**, respectively, while **18c** gives both **20c** and **20d**. *A priori*, the chemical shifts of the methyls of **20a** and **20c** should be sufficiently different from those of **20b** and **20d** to make the two pairs distinguishable even though the methyl environments of **20a** and **20c**, or **20b** and **20d**, are similar enough to probably make their respective chemical shifts coincidental.



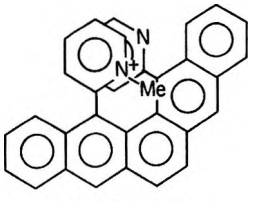
20a (*dl* pair)



20b (*dl* pair)



20c (*dl* pair)



20d (*dl* pair)

In the nmr spectrum of **20** dissolved in DMSO-d_6–CD_3CN (1:1 v/v) the line shape of the methyl resonance was found to be a function of temperature (Figure 5). At 5° two distinct peaks at δ 2.89 and 3.01 were

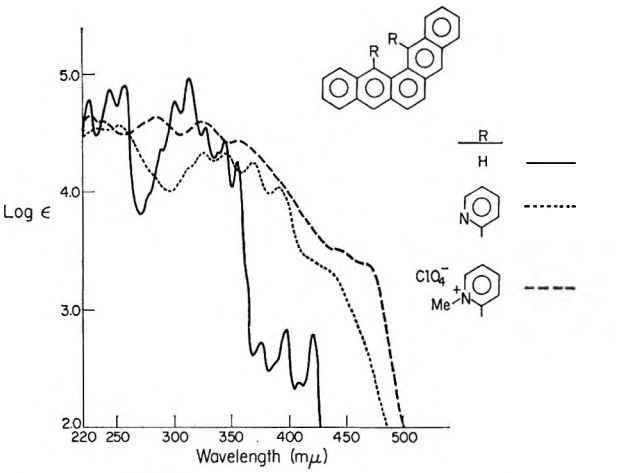
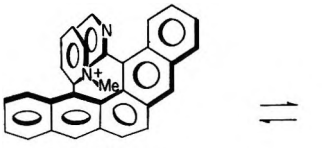


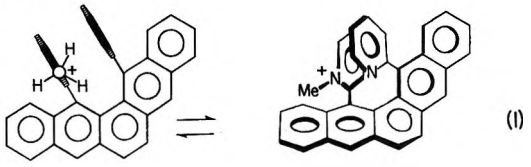
Figure 4.—Ultraviolet spectra of **18**, **21**, and pentaphene.

seen, which are due to conformers **20a,c** and **20b,d**. As the temperature was raised, the two lines coalesced and became a sharp singlet above 80°. A line-shape analysis[7a] of the methyl signal of **20** dissolved in a mixture of DMSO-d_6–acetone-d_6 (3:7 v/v) yielded a free energy of activation of 16.6 ± 0.1 kcal at 30° and a $\Delta H^{\pm}$ of 10.0 ± 0.1 kcal.[7b] Changing the solvent to hexafluoroacetone increased the temperature at which coalescence occurs to ~45°.

The only reasonable explanation for these results is that our original assumption that the pyridines are locked into a rigid conformation is incorrect. Instead it appears that at room temperature, the twisted pentaphene is undergoing ring inversion accompanied by a *synchronous* rotation of both pyridines so that **20a** and **20b** are interconverting as are **20c** and **20d** (for example, eq 1).



20d (*dl* pair)



20c (*dl* pair) (1)

At elevated temperatures the two types of *N*-methyls are interchanging environments sufficiently rapidly by this process so that the resulting spectrum shows a single sharp line. The ring inversion is slowed as the temperature is lowered to the point where the two types of unequally populated conformers can be observed.

Further support for this rationale comes from examination of the nmr spectrum of the bis-*N*-methylpyridinium derivative **21**. For the bis-*N*-methyl-

(7) (a) A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, **88**, 3185 (1966); J. Jonas, A. Allerhand, and H. S. Gutowsky, *J. Chem. Phys.*, **42**, 3396 (1965). (b) On the basis of the above figures one can estimate a value of $\Delta S^{\pm}$ that is $\sim -20 \pm 10$ eu. However, there was no attempt made to estimate the size of the temperature dependent part of $\Delta H^{\pm}$ which may be fairly large: G. Govil and H. J. Bernstein, *ibid.*, **48**, 285 (1968).

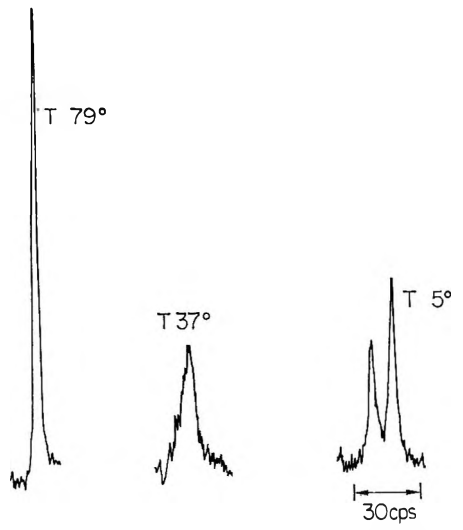


Figure 5.—The temperature dependence of the N–CH_3 resonances of pentaphenes **20a–d** (100 MHz).

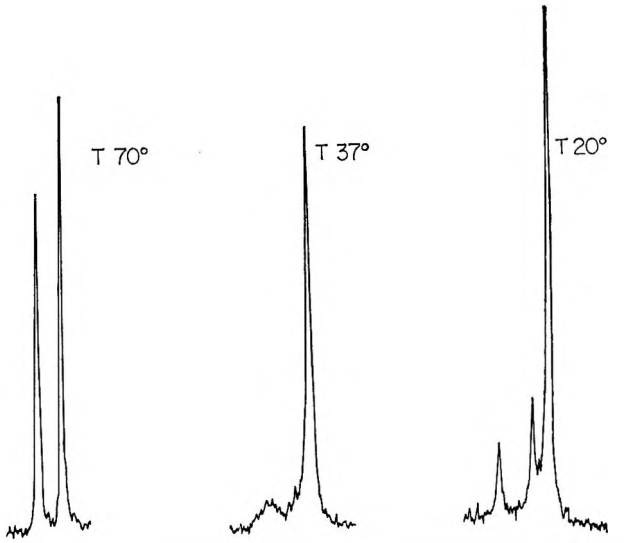
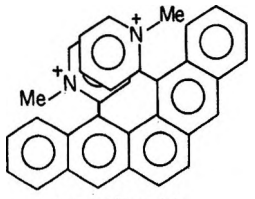
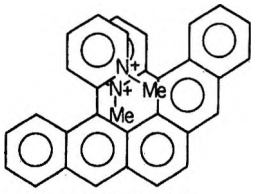


Figure 6.—The N–CH_3 resonances of pentaphenes **21a–c** at different temperatures.

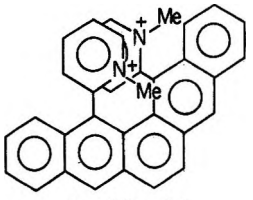
pyridinium derivative there are three diastereoisomers possible, **21a**, **21b**, and **21c**, each again existing as a *dl* pair. Isomers **21a** and **21b**, each have a twofold axis



21a (*dl* pair)



21b (*dl* pair)



21c (*dl* pair)

of symmetry, making their respective methyls magnetically equivalent. If our interpretation of the ring inversion with synchronous pyridyl rotation is correct, they will equilibrate in solution, allowing one isomer, that one having the largest N^+–N^+ charge separation, to strongly dominate, and its *N*-methyl absorption would be observed as a temperature-independent singlet. The preferred conformer would probably be **21b**, based on analogy with the known distances found in **2** by X-ray analysis. On the other hand, ring inversion of **21c** simply results in an equilibration of its two enantiomeric forms with no net ground-state energy change, and its nmr spectrum should reveal this fact by a temperature dependency. The nmr results (Figure 6) are completely consistent with this concept. At 70°, the methyls are observed as two sharp singlets having an area ratio of 2:1. The major peak (**21b**) was temperature independent, whereas the lesser singlet (**20c**) broadened upon cooling and at 20° appeared as two singlets (area ratio ~1:1).

One of the intriguing aspects of these results comes from the realization that ring inversion involves a *planar* pentaphene transition-state conformation which must still accommodate a 2.8–3.0-Å separation between the two pyridine rings. The strain energy of such a conformer must be extraordinarily high owing to large distortions of bond angles (up to 30° each), particularly those associated with the bonds attaching the pentaphene to the pyridines and to H_1 and H_{12}. However, the free energy barrier for ring inversion, at least for the mono-*N*-methyl derivatives, is less than 17 kcal/mol. Since this value represents the difference in energy between the lowest energy ground state and the planar transition state, it serves to emphasize the high energy of the ground state caused by steric strain.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover apparatus. Ultraviolet absorption spectra were recorded on a Cary Model 14 spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrometer. The mass spectral data were obtained using a CEC 21-110B mass spectrometer, with the samples analyzed *via* the direct inlet system. Nmr spectra were determined with either a Varian A-60 or HA-100 instrument. Chemical shifts are recorded as parts per million to lower field from TMS ($\delta = 0$), followed by (in parenthesis) multiplicity, relative area, and assignment. The nmr spectra used for the line-shape analysis were recorded on a Varian HA-100 spectrometer equipped with a V-4343 temperature controller. The temperature of the sample was checked by use of the chemical shift of the water resonance in the sample. Temperatures were measured to an accuracy of $\pm 1°$ and were determined to better than $\pm 0.5°$. The sample used for the line-shape analysis was prepared on a vacuum line and sealed following several freeze–pump–thaw cycles. The solvent consisted of ~30% DMSO-d_6, ~70% acetone-d_6, and less than 1% TMS. The concentration of the solute was 5×10^{-2} *M*.

4a-Azoniatriptycene Perchlorates (see Table I).—The following synthesis of azoniatriptycene **4a** is representative of the procedure used for preparing the benzyne adducts of Table I.

9,10-Dihydro-4a-azonia-9,10-*o*-benzenoanthracene Perchlorate, *i.e.*, 4a-Azoniatriptycene Perchlorate (4a).—To a refluxing solution of 4a-azoniaanthracene perchlorate (**3a**) (28.0 g, 0.10 mol) in 150 ml of acetonitrile were concurrently added, *via* two dropping funnels, over a 15-min period, solutions of isoamyl nitrite (23.0 g, 0.2 mol) and anthranilic acid (24.7 g, 0.18 mol), each in 250 ml of acetonitrile. The resulting solution was concentrated to one-quarter volume and the product precipitated by the addition of ether–ligroin (bp 30–60°) (2:1 v/v), as an oil which subsequently crystallized. The uv spectrum of this product showed no absorptions at wavelengths longer than 270 nm, establishing the absence of **3a**. One recrystallization from methanol (Darco)–ether gave 27.7 g (78%) of **4a** as stubby white needles: nmr

(DMSO-d_6) δ 6.61 (s, 1), 7.23–8.00 (m, 10), 8.45 (m, 2), 9.47 (d of m, 1).

Azoniatriptycene Perchlorate 8.—A sample of **4c** was deacetylated with methanolic potassium hydroxide solution; the solution was acidified with 6 *N* hydrochloric acid and treated with dilute sodium perchlorate solution to yield **8** as a white crystalline precipitate. This product was recrystallized as white needles from CH_3CN, mp 230–250° dec. Its nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{23}H_{22}ClNO_5$: C, 64.5; H, 5.1; N, 3.3. Found: C, 64.2; H, 5.3; N, 3.5.

Pyridylanthracenes and -pentaphenes (Table II). 9-(2-Pyridyl)anthracene (5).—A mixture of **4a** (2.00 g, 0.056 mol), anhydrous sodium acetate (1.0 g), and 25 ml of acetic anhydride was refluxed for 5 min, cooled, and diluted with 100 ml of water. The resulting crystals were collected, dried, and recrystallized as thick yellow needles (1.24 g, 86%) from methylcyclohexane: uv max (CH_3CN) 223 nm (log ε 4.08), 253 (5.13), 316 (3.08), 328 (3.49), 345 (3.81), 363 (4.00), 382 (3.97).

TABLE II

PYRIDYLANTHRACENES AND -PENTAPHENES

Compd	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
5	155–156	89.5	5.1	5.5	89.2	5.1	5.6
6	187–191	78.0	4.7	3.1	78.4	5.2	3.1
15	217–219	89.0	4.6	6.5	89.0	4.4	6.1
18	293–294	89.0	4.6	6.5	89.1	4.6	6.4

Anthracene **6** was similarly prepared, but required a 4-hr reflux period to maximize the yield (62%): uv max (CH_3CN) 225 nm (log ε 4.34), 259 (4.97), 338 sh (3.52), 356 (3.78), 371 (3.92), 391 (3.90).

Bis(2-pyridyl)pentaphenes 15 and 18.—As a representative example, crude bisbenzyne adduct **17** was prepared by the general procedure described above for the synthesis of **4a**. Thus, solutions of anthranilic acid (41.1 g, 0.30 mol) and isoamyl nitrite (41.0 g, 0.35 mol), each in 250 ml of acetonitrile, were concurrently added over a 15-min period to a refluxing solution of **16**[8] (24.0 g, 0.05 mol) in 500 ml of acetonitrile. The resulting dark solution was concentrated to a syrup, which in turn was triturated in 300 ml of acetone and filtered, leaving 2.35 g of orange, crystalline acridone as a residue.

The acetone filtrate was concentrated to a syrup which was partially dissolved in 200 ml of methanol and reprecipitated as a tan amorphous solid (**17**, 45.0 g) by the addition of 500 ml of ether. Its uv spectrum showed no absorptions at wavelengths longer than 265 nm.

A mixture of 45.0 g of this product, 20.0 g of sodium acetate, and 400 ml of acetic anhydride was heated at reflux for 2 hr, and then concentrated to a dark syrup. The syrup was freed of residual acetic acid and anhydride by trituration in 400 ml of water containing an excess of sodium carbonate, and was extracted into 400 ml of methylene chloride and clarified by passing through a Florisil magnesium silicate bed disposed in a 600-ml, coarse, sintered-glass Büchner funnel. The eluate was concentrated to *ca.* 100 ml and introduced onto the top of a Florisil column (4.5 × 56 cm) and chromatographed, 4 l. of methylene chloride–ethyl acetate (4:1 v/v) being used as a developer. Fifteen 250-ml fractions of eluate were collected. Analysis by tlc[9] showed the desired product to be in fractions 9–13. These were combined and concentrated giving 5.0 g (23% from **13**) of essentially pure crystalline pentaphene **18**. The analytical sample was recrystallized as thick yellow needles from benzene.

Bis(pyridinium) Salts 19 and 21.—The procedure used in preparing both of these compounds consisted in heating on a hot plate a mixture of 0.5 g of **15** or **18** in 10 ml of methyl *p*-toluenesulfonate to the boiling point. The solution was cooled and the product precipitated as a yellow solid by the addition of ether. This product was converted to its bisperchlorate salt by ion exchange and was recrystallized from acetonitrile–ether. Melting points of **19** and **21** were >300°.

Anal. Calcd for $C_{34}H_{26}Cl_2N_2O_8$: N, 4.2; Cl, 10.7. Found for **19**: N, 4.3; Cl, 10.6. Found for **21**: N, 4.5; Cl, 10.4.

Mono(pyridinium) Salts 20.—A solution of **18** (0.40 g, 0.9 mmol) in 30 ml of methyl iodide and 15 ml of methylene chloride was allowed to stand at room temperature for 18 hr. Tlc analysis of the mixture during this period indicated the absence of starting **18** by the end of the first 6 hr. The solution was concentrated to a crystalline solid, which was dissolved in warm water–methanol (4:1 v/v) and treated with sodium perchlorate. The resulting yellow crystalline perchlorate **20** was recrystallized from pyridine–ether as fine yellow needles, mp 185–187°.

Anal. Calcd for $C_{33}H_{23}ClN_2O_4$: C, 72.4; H, 4.0. Found: C, 72.0; H, 4.1.

Registry No.—**5**, 20308-96-7; **6**, 30318-88-8; **8**, 30318-86-6; **15**, 30318-87-7; **18a**, 30319-26-7; **18b**, 30319-27-8; **18c**, 30319-28-9; **19a**, 30319-29-0; **19b**, 30319-30-3; **20a**, 30344-36-6; **20b**, 30275-72-0; **20c**, 30319-31-4; **20d**, 30344-37-7; **21a**, 30319-32-5; **21b**, 30319-33-6; **21c**, 30319-34-7.

Acknowledgments.—The authors wish to thank Mrs. Jean C. Dignan and Mr. David White for technical assistance and Mr. D. P. Maier for mass spectral interpretations.

(8) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **29**, 856 (1964).

(9) Thin layer chromatographies (tlc) were performed employing precoated silica gel F-254 tlc plates, containing a fluorescent indicator, distributed by Brinkmann Instruments Inc., Westbury, N. Y. Development was achieved with methylene chloride.

A Novel Synthesis of 2-Naphthols, Phenanthrols, Anthracenes, and Other Polycyclic Aromatic Products

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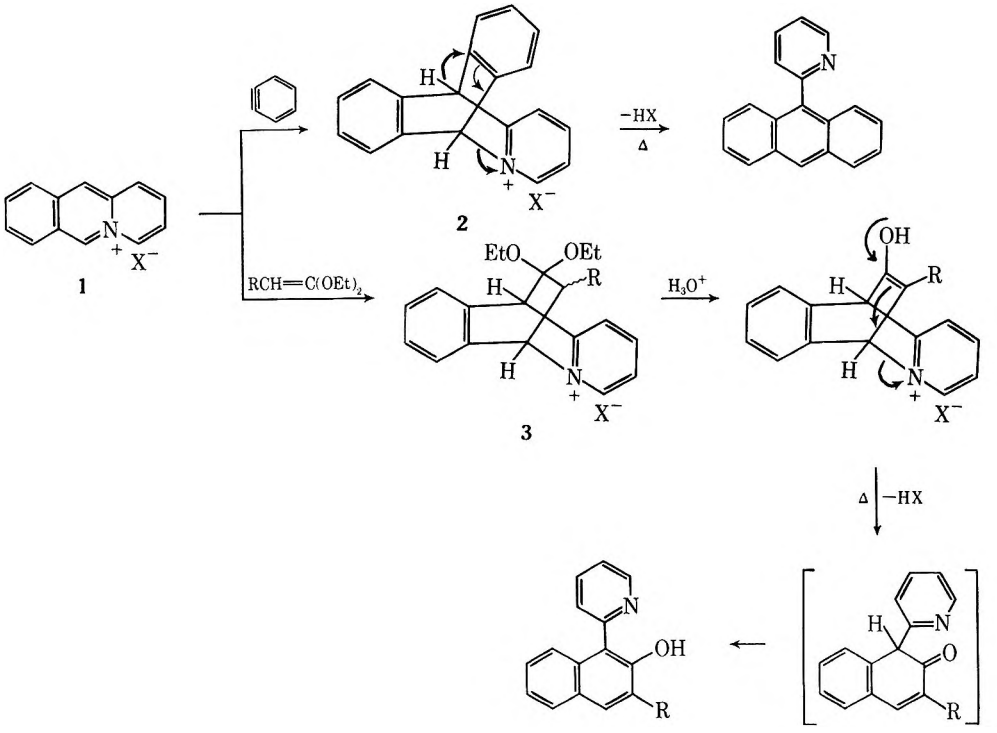
A simple and convenient synthesis of a number of new, or difficultly accessible, substituted 2-naphthols, phenanthrols, and related compounds is described, consisting of catalytic or chemical reduction of the appropriate ketene acetal–azoniapolycyclic adduct followed by a retrograde Diels–Alder reaction, which occurs upon heating of the reduction product in the presence of 6 *N* hydrochloric acid. Several substituted anthracenes and pentaphene were prepared similarly by sequential reduction and thermolysis of benzyne adducts of 4a-azoniaanthracene perchlorates and of 4a,8a-diazoniapentaphene diperchlorate, respectively. The scope and limitations of these syntheses are discussed.

In several of our recent publications we have dealt with the syntheses and properties of novel compounds derived from 4 + 2 cycloadducts of various azoniapolycyclic aromatic compounds with benzyne[1] and with ketene acetals.[2] The thermolysis of benzyne adducts such as **2**[1] and the hydrolysis followed by thermolysis of ketene acetal adducts such as **3** were shown to give (2-pyridyl)-substituted aromatic products according to eq 1 and 2, respectively.



(1)

(2)

If the pyridinium moiety of either of these two types of adducts is reduced prior to the hydrolysis and/or thermolysis steps, an alternate course of reaction will become available, specifically, a retrograde Diels–Alder reaction, which ultimately yields the same parent hydrocarbons as above, minus the pyridyl substituent (eq 3 and 4).

In this paper we report the results of our investigation of the applicability of these two reaction sequences as new general methods for preparing the title compounds. We have found that these syntheses do show considerable promise for providing research quantities of a variety of substituted 2-naphthols, anthracenes, etc., which are difficult to prepare, if not inaccessible, by other routes now known.

Naphthols and Phenanthrols—As a way of elaborating on the scope of these syntheses, we shall first consider details relevant to the step-by-step construction of a multisubstituted 2-naphthol, **4** (Scheme I). Azoniaanthracene salts (**1**) generally are prepared in good to excellent yields by allowing a 2-formyl-[3] [or preferably 2-(1,3-dioxolan-2-yl)-],[4] 2-acetyl-,[5] or 2-benzoylpyridine[5] to react with the appropriate benzyl halide, the resulting quaternary salt being cyclodehydrated by acid treatment. Although R_1 in azoniaanthracenes thus far described has been limited to H, CH_3, and C_6H_5, the availability of a variety of types of substituted benzyl halides gives one considerable latitude in the choice of R_5–R_8 substituents.

The R_3 substituent is established through selection of the ketene acetal to be used in preparing the inter-

(1) D. L. Fields, T. H. Regan, and R. E. Graves, *J. Org. Chem.*, **36**, 2995 (1971).

(2) (a) D. L. Fields, T. H. Regan, and J. C. Dignan, *ibid.*, **33**, 390 (1968); (b) D. L. Fields and T. H. Regan, *ibid.*, **35**, 1870 (1970); (c) **36**, 2986 (1971); (d) **36**, 2991 (1971).

(3) C. K. Bradsher and L. E. Beavers, *J. Amer. Chem. Soc.*, **77**, 4812 (1955).

(4) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).

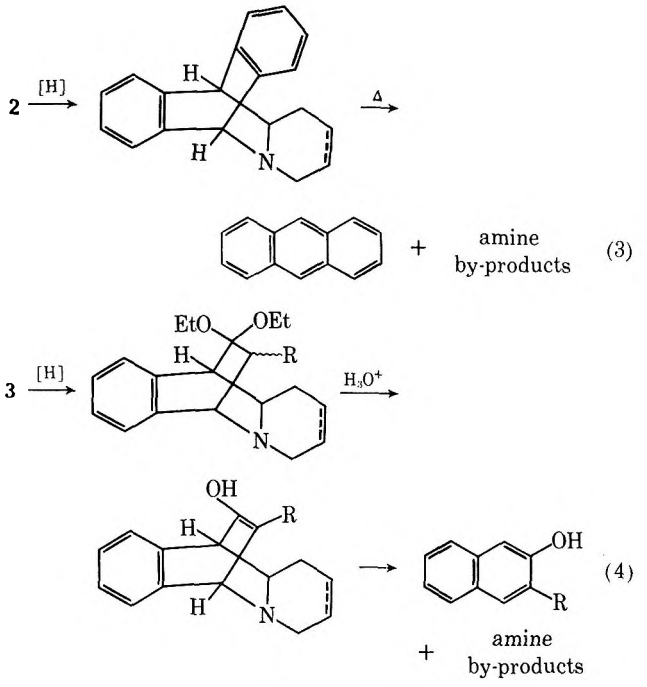
(5) C. K. Bradsher and T. W. G. Solomons, *J. Amer. Chem. Soc.*, **81**, 2550 (1959).

Table I

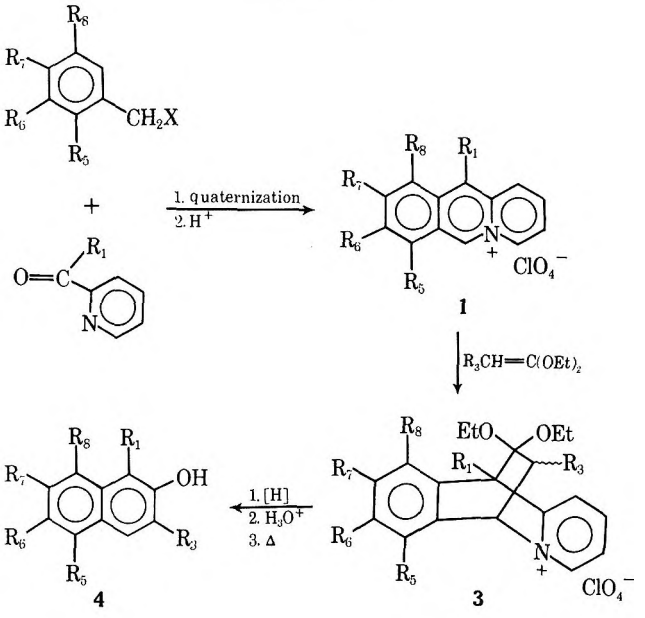
Naphthalenes Prepared from Ketene Acetal–Azoniaanthracene Adducts

Precursor	Product	Mp, °C	Yield, %	—Calcd, %— C	H	—Found, %— C	H
3a[a]	2-Naphthol		83				
3b[b]	1-Phenyl-2-naphthol[c]		71				
3c[a]	3-Methyl-2-naphthol[d]		96				
3d[a]	3-Phenyl-2-naphthol	117–118	92	87.3	5.5	87.3	5.7
3e[a]	3-Bromo-2-naphthol[e]		45				
3f[b]	3,5-Dimethyl-2-naphthol	126–127	83	83.7	7.0	83.5	7.3
3g[b]	3,5,8-Trimethyl-2-naphthol	126–127	90	83.9	7.5	84.3	7.7
3h[b]	5-Nitro-2-naphthol[f]		91				
3i[b]	7-Methyl-2-naphthol[g]		89				
3j[h]	1,6-Diacetoxy-4-*tert*-butylnaphthalene	101–103	47	72.0	6.7	71.6	7.1
3k[h]	1,2,6-Triacetoxy-4-phenylnaphthalene	137–143	54	69.8	4.8	69.8	5.1

[a] Reference 2a. [b] New adduct. See Experimental Section. [c] W. Henderson and E. Ullman, *J. Amer. Chem. Soc.*, **87**, 5424 (1965). [d] J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 817 (1937). [e] C. Marschalk, *Bull Soc. Chim. Fr.*, **43**, 1361 (1928). [f] A. Cohen, J. W. Cook, C. L. Hewett, and A. Girard, *J. Chem. Soc.*, 653 (1934). [g] Reference 8. [h] Reference 2c.



Scheme I



mediary cycloadduct **3**. The experimental details related to cycloaddition reactions of ketene acetals to azoniaanthracene salts have been adequately described in earlier papers,[2] and it will suffice to say that such additions generally occur rapidly and regiospecifically,[6] and provide good to quantitative yields of adduct.

The reduction of the pyridinium moiety in the next step is accomplished by either catalytic or chemical means. Hydrogenation of adducts to give piperidino products has been effected in a Parr hydrogenation apparatus using H_2 at 60 psi over PtO_2. Alternatively, pyridinium ring reduction can be achieved within minutes by employing excess sodium borohydride in methanolic sodium methoxide solution. Whether the pyridinium ring is completely or only partly reduced apparently is unimportant.

Except for the more acid-sensitive products,[7] the final two steps, hydrolysis of the ketal and thermolysis, can be conducted simultaneously by simply heating the reduction product in refluxing 6 *N* hydrochloric acid. These steps are conveniently carried out in a two-phase system consisting of 6 *N* hydrochloric acid and an organic solvent such as toluene, so that the naphthol formed during the thermolysis is extracted into the toluene, effectively separating it from the amine hydrochloride by-product which remains in the aqueous phase. After 0.5–1-hr reflux, the toluene layer is separated and concentrated, yielding the naphthol in a good state of purity.

In Table I are listed 2-naphthols that have been prepared by this procedure and in Table II are shown the products derived from ketene acetal adducts of more complex starting azoniapolycyclics. The reported yields are based on single experiments run on a 1–10-g scale. The structural assignments for all new products were supported by elemental analysis and the usual (uv, ir, nmr) spectral means.

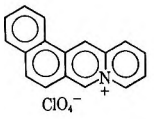
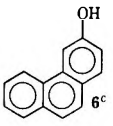
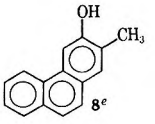
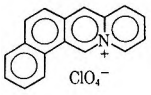
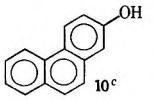
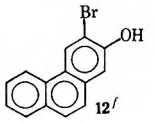
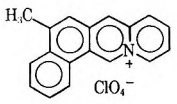
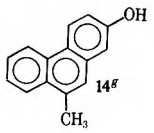
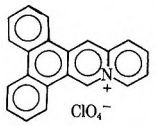
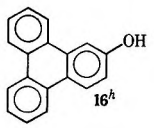
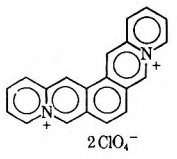
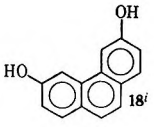
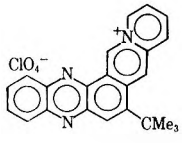
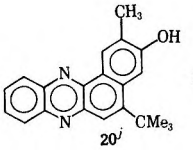
Anthracenes.—In light of the previous discussions, the synthesis of anthracenes *via* adducts of benzyne and substituted 4a-azoniaanthracenes, *i.e.*, 4a-azoniatriptycenes (eq 3), is straightforward and needs little clarification. Anthracenes that we have prepared by

(6) A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

(7) For example, 8-*tert*-butylnaphthalenes are prone to de-*tert*-butylate in the presence of strong acid, especially at elevated temperatures. Therefore, in the synthesis of 1,6-diacetoxy-4-*tert*-butylnaphthalene, Table I, the ketal hydrolysis step was carried out at room temperature, and the resulting ketone was isolated and then thermolyzed in acetic anhydride–sodium acetate at reflux temperature. 1,2,6-Triacetoxy-4-phenylnaphthalene was prepared similarly.

TABLE II

PRODUCTS DERIVED FROM VARIOUS KETENE ACETAL–AZONIAPOLYCYCLIC ADDUCTS

Starting azoniapolycyclic	$RCH{=}C(OEt)_2$ R	Adduct	Product	Yield,[a] %
	H	5[b]	 6[c]	95
	CH_3	7[d]	 8[e]	77
	H	9[b]	 10[c]	92
	Br	11[d]	 12[f]	73
	H	13[d]	 14[g]	97
	H	15[b]	 16[h]	83
	H	17[b]	 18[i]	45
	CH_3	19[d]	 20[j]	16

[a] Based on adduct. [b] Reference 2a. [c] A. Werner, *Justus Liebigs Ann. Chem.*, **321**, 248 (1902). [d] New adduct. See Experimental Section. [e] Mp 159–161°. *Anal.* Calcd for $C_{15}H_{12}O$: C, 86.6; H, 5.8. Found: C, 86.4; H, 5.9. [f] Mp 150–154°. *Anal.* Calcd for $C_{14}H_9BrO$: C, 61.5; H, 3.3. Found: C, 61.6; H, 3.4. [g] Mp 178–180°. *Anal.* Calcd for $C_{15}H_{12}O$: C, 86.6; H, 5.8. Found: C, 86.5; H, 6.0. [h] W. S. Rapson, *J. Chem. Soc.*, 14 (1941). [i] I. F. Fieser, *J. Amer. Chem. Soc.*, **51**, 2471 (1929). [j] Mp 262–264°. *Anal.* Calcd for $C_{21}H_{20}N_2O \cdot {}^1/_4H_2O$: C, 78.7; H, 6.4; N, 8.7. Found: C, 78.8; H, 6.4; N, 8.8.

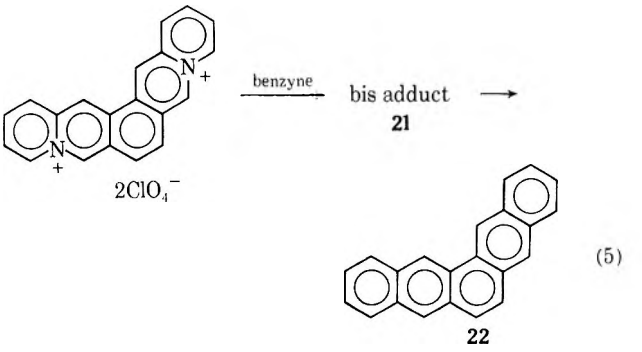
this procedure are listed in Table III. The intermediary 4a-azoniatriptycene perchlorates (2) have been described previously[1] and were obtained in 60–78% yields by thermal decomposition of anthranilic acid diazotized *in situ* in the presence of the appropriate 4a-azoniaanthracene perchlorate. Sodium borohydride proved to be the best reagent for the reduction step in that several attempts to catalytically hydrogenate 4a-azoniatriptycene perchlorate over PtO_2 led to a rather indiscriminate reduction of one of the benzene moieties in addition to the pyridinium ring. The thermolysis step was satisfactorily accomplished at reflux temperature in any one of several solvents, including acetic acid, acetic anhydride, and a toluene–6 *N* hydrochloric acid mixture.

TABLE III

ANTHRACENES PREPARED FROM BENZYNE–AZONIAANTHRACENE ADDUCTS

Product	Yield, %
Anthracene	93
1-Methylanthracene	94
2-Methylanthracene	87
1-Nitroanthracene	61
1-Acetoxy-4-*tert*-butylanthracene	91
1,2-Diacetoxy-4-phenylanthracene	59
9-Phenylanthracene	90

There are a number of obvious extensions of this synthesis that should be of interest, in particular the use of some of the more complex azoniapolycyclics in combinations with benzyne, substituted benzynes, other arynes, and perhaps even heteroarynes, and, in this regard, we have synthesized pentaphene from 4a,8a-diazoniapentaphene diperchlorate and benzyne (eq 5) in 31%



(5)

overall yield. However, a complication in the use of substituted benzynes is anticipated, owing to a probable lack of regiospecificity[6] in a cycloaddition reaction involving a substituted benzyne with a substituted azoniaanthracene salt. It is likely that, where possible, not one but rather a mixture of two isomeric adducts will be produced, thus necessitating a separation step either at the adduct stage or after final production of the two-component anthracene mixture.

Experimental Section

Melting points (uncorrected) were determined on a Thomas–Hoover apparatus. Ultraviolet absorption spectra were recorded by a Cary Model 14 recording spectrophotometer. Nmr spectra were determined at ambient probe temperature with a Varian A-60 spectrometer. Peak positions are reported in parts per million downfield from tetramethylsilane.

New Ketene Diethyl Acetal–Azoniapolycyclic Adducts.—The new crystalline adducts tabulated in Table IV were prepared following previously described procedures.[2a]

Naphthol–Phenanthrol Synthesis. A. *Via* $NaBH_4$ Reduction.—The following example is representative of the procedure used to prepare the products listed in Tables I and II, with the exception of 1,6-diacetoxy-4-*tert*-butylnaphthalene and 1,2,6-triacetoxy-4-phenylnaphthalene. Adduct **3d** (R_3 = C_6H_5) (5.00 g, 0.011 mol) was added to a mixture of 1.50 g of sodium methoxide and 1.00 g of sodium borohydride in 50 ml of methanol in a 500-ml separatory funnel. The resulting mixture was swirled intermittently over a 5-min period and diluted with 200

Table IV

Ketene Acetal-Azoniapolycyclic Adducts

Adduct	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3b (R_1 = C_6H_5)	160–180 dec	89	63.7	5.5	3.0	63.4	5.2	3.3
3f (R_3, R_5 = CH_3)	189–198	94	59.6	6.1	3.3	59.4	6.1	3.5
3g (R_3, R_5, R_8 = CH_3)	192–197	86	60.4	6.4	3.2	60.5	6.4	3.2
3h (R_5 = NO_2)	230 dec	93	51.3	5.1	6.3	51.7	4.8	6.3
3i (R_7 = CH_3)	133–134	94	58.6	5.9	3.4	58.6	6.0	3.5
7	199–201 dec	65	62.7	5.7	3.0	62.5	5.5	3.0
11	210–250 dec	65	52.7	4.4	2.7	52.5	4.4	2.5
13	250–290 dec	94	62.6	5.7	3.0	62.4	5.8	3.1
19	240–275 dec	73	63.4	6.0	7.4	63.3	5.8	7.5

ml of water, and the reduction product was extracted with three 50-ml portions of toluene. A mixture of the toluene extract and 50 ml of 6 *N* hydrochloric acid was refluxed for 1 hr and cooled, and the toluene layer was separated and concentrated to dryness, yielding a crystalline residue (one spot on tlc analysis). One recrystallization from methylcyclohexane afforded 2.13 g (93%) of analytically pure 3-phenyl-2-naphthol.

1,6-Diacetoxy-4-*tert*-butylnaphthalene and 1,2,6-triacetoxy-4-phenylnaphthalene were prepared by a variation of the above synthesis. As an example, adduct **3j** (R_5 = OAc, R_8 = *tert*-C_4H_9) (1.50 g, 3.2 mmol) was treated for 5 min with 0.75 g of sodium borohydride and 0.50 g of sodium methoxide in 50 ml of methanol as described above. After dilution of the reaction mixture with 200 ml of water, the solution was acidified with concentrated hydrochloric acid and then neutralized with sodium bicarbonate. The resulting precipitate was extracted with three 100-ml portions of ether and the combined extracts were concentrated to dryness, leaving a syrupy residue. This syrup was dissolved in 30 ml of 10 *N* hydrochloric acid, allowed to stand for 30 min at room temperature, and then diluted with 150 ml of water and neutralized with sodium bicarbonate. The resulting tan, amorphous solid was collected by filtration, dried, and then treated with 25 ml of acetic anhydride and 0.5 g of sodium acetate for 0.5 hr at reflux temperature. The reaction mixture was concentrated free of solvent and the residue was triturated in water, yielding a syrup. The syrup was dissolved in methylene chloride and chromatographed on a Florisil column using methylene chloride as eluent. The early fractions of eluate collected yielded the desired crystalline product, 1,6-diacetoxy-4-*tert*-butylnaphthalene, which was recrystallized as white needles (0.45 g, 47%) from ligroin (bp 60–90°): mp 101–102.5°; nmr ($CDCl_3$) δ 1.59 (s, 9, *tert*-C_4H_9), 2.30 (s, 3, OAc), 2.37 (s, 3, OAc), 7.22–8.23 (m, 5, aromatic).

B. *Via* Catalytic Reduction.—A mixture of **3i** (R_7 = CH_3) (25.0 g, 0.061 mol) in methanol (150 ml) was hydrogenated at room temperature and 66-psi initial hydrogen pressure, with PtO_2 (1.0 g) catalyst. After the consumption of 3 molar equiv of hydrogen (8 hr), when the uptake ceased, the catalyst was removed by filtration and washed with acetonitrile, and the combined filtrates were evaporated to afford 23.5 g (93%) of the crystalline perchloric acid salt of the desired reduction product. A solution of this product in 100 ml of 6 *N* hydrochloric acid was refluxed for 2 min, during which time a clear oil separated from solution. Upon cooling, the oil crystallized and was collected, recrystallized as white needles (9.50 g, 89%) from methylcyclohexane, and identified as 7-methyl-2-naphthol, mp 117–118° (lit.[8] mp 118°).

Anthracene–Pentaphene Synthesis.—With the exceptions of 1-acetoxy-4-*tert*-butylanthracene and 1,2-diacetoxy-4-phenylanthracene, the anthracenes listed in Table III were prepared following a procedure identical with that described in procedure A (*via* $NaBH_4$ reduction) of the naphthol–phenanthrol synthesis.

(8) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2564 (1956).

1-Acetoxy-4-*tert*-butylanthracene.—The sodium borohydride reduction was carried out in the usual manner. However, after dilution with 200 ml of water, the reaction mixture was acidified with concentrated hydrochloric acid and neutralized with sodium carbonate; the resulting precipitate was extracted with ether.

The syrup obtained by concentrating the ether extract was dissolved in 100 ml of acetic anhydride, sodium acetate (2.5 g) was introduced, and the mixture was heated for 30 min at reflux temperature. It was concentrated to a syrup, which crystallized after trituration in 100 ml of water. One recrystallization from methanol yielded the title compound as white plates (91% yield): mp 140–141°; nmr ($CDCl_3$) δ 1.65 (s, 9, *tert*-C_4H_9), 2.45 (s, 3, OAc), 7.00–8.01 (m, 6, aromatic), 8.47 (s, 1, H_9 or H_{10}), 9.00 (s, 1, H_9 or H_{10}); uv max (CH_3CN) 217 nm (log ϵ 4.07), 220 (4.06), 253 (5.16), 315 (3.08), 328 (3.46), 344 (3.76), 361 (3.94), 381 (3.89).

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.2; H, 6.8. Found: C, 81.8; H, 6.9.

1,2-Diacetoxy-4-phenylanthracene, prepared in analogous fashion, had mp 216–217°.

Anal. Calcd for $C_{24}H_{18}O_4$: C, 77.8; H, 4.9. Found: C, 77.5; H, 5.2.

Pentaphene (22).—Crude adduct **21**[1] (5.00 g, 0.0079 mol) was introduced into a solution of sodium borohydride (3.0 g) and sodium methoxide (3.00 g) in 100 ml of methanol. After standing at autogenous temperature for 30 min, the mixture was diluted with 300 ml of water and the precipitated reduction product was extracted with two 200-ml portions of ether. The syrup obtained after concentration of the combined ether extracts was dissolved in 50 ml of acetic acid and the mixture was refluxed for 15 min, during which time golden yellow crystals separated from solution. The mixture was cooled and the product (0.68 g, 31%) collected, washed with ether, and identified as pentaphene by comparison of its melting point and spectral properties with those of an authentic sample.

Registry No.—**3b** (R_1 = C_6H_5), 30889-35-1; **3f** (R_3, R_5 = CH_3), 30889-36-2; **3g** (R_3, R_5, R_8 = CH_3), 30889-37-3; **3h** (R_5 = NO_2), 30889-38-4; **3i** (R_7 = CH_3), 30889-39-5; **7**, 30889-40-8; **8**, 30953-11-8; **11**, 30953-12-9; **12**, 18894-71-8; **13**, 30889-42-0; **14**, 30889-43-1; **18**, 30309-92-3; **19**, 31002-85-4; **22**, 222-93-5; 1-acetoxy-4-*tert*-butylanthracene, 30889-46-4; 1,2-diacetoxy-4-phenylnaphthalene, 30889-47-5; 3-phenyl-2-naphthol, 30889-48-6; 3,5-dimethyl-2-naphthol, 30889-49-7; 3,5,8-trimethyl-2-naphthol, 30889-50-0; 1,6-diacetoxy-4-*tert*-butylnaphthalene, 30310-04-40; 1,2,6-triacetoxy-4-phenylnaphthalene, 30889-52-2.

Acknowledgment.—The author is indebted to Mrs. Jean C. Dignan for her laboratory assistance.

Electrochemistry of Natural Products. II. Electrolytic Oxidation of Some Simple 1,2,3,4-Tetrahydroisoquinoline Phenols[1]

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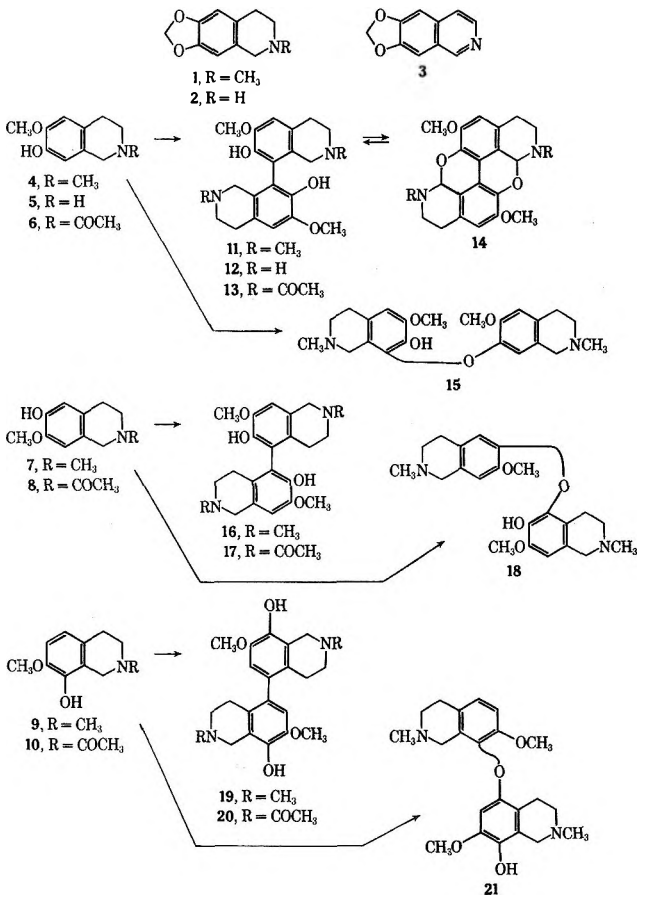
A series of derivatives of 1,2,3,4-tetrahydroisoquinoline has been oxidized electrolytically. Those containing phenol groups were dimerized to yield carbon–carbon dimers and carbon–oxygen–carbon dimers. Some of the variables such as the nature of the anode, the cell design, the solvent, the pH, and the reaction time were considered. The optimum conditions for the coupling of these phenols would seem to be oxidation of their sodium salts in CH_3CN using tetraethylammonium perchlorate as supporting electrolyte and a graphite felt anode. The results of a number of experiments are presented. The products of the reactions depend strongly upon the relative location of the phenol group in the aromatic ring and the nitrogen in the heterocyclic ring. An explanation for this phenomenon is proposed.

We have been interested in the electrolytic oxidations of phenolic tetrahydroisoquinolines[3] as model compounds for some of the more important biosynthetic oxidation reactions. In the previous paper of this series,[1] we studied the ratio of C–C dimers to C–O–C dimers as a function of the steric hindrance around the incipient bond between the isoquinolines. In this paper, we would like to present a more general and random study of some simple compounds.

The compounds oxidized fell into several groups. Compounds **1–3** were nonphenolic and were examined to see how easily the various forms of the nitrogen ring were oxidized. Three oxygenation patterns were examined for the phenols themselves. The pattern in **4–6** is the most common one in nature.[4] The isomeric patterns in **7** and **8** and in **9** and **10** were chosen for comparison. Three possible nitrogen functions, **4–6**, were studied for the natural system, and two were studied for the others. Compound **4**, the alkaloid, corypalline,[5] has been the starting point of several of our investigations[6] (Scheme I).

SCHEME I



Reaction Conditions. The Working Electrode.—The oxidation of **4** was studied in a two-compartment cell in aqueous systems with five different working electrodes. The results are given in Table I. The best yields at the lowest voltages were given on the Hg pool and graphite anodes. However, Hg failed to yield *any* product with the other phenols and was, itself, attacked in CH_3CN solutions. Graphite felt was chosen as the anode for most of our work because of its high surface area and its low cost.

Cell Design.—Two different cell designs were used. One was a two-compartment system and has been described.[6b] The other was a simple one-compartment system as described in the Experimental Section. Both worked well. However, when limited amounts of base were used, the base tended to concentrate in the cathode chamber of a two-compartment system and change the nature of the oxidation. This was avoided in the one-compartment system. These particular oxidations could be carried out in such a system because they seem to be irreversible.

Anode Potential.—In all of the experiments presented, the anode potential was the minimum (as measured against sce and controlled with a potentiostat) which would produce a current flow of 20–30 mA (in solutions about 10^{-2} *M* in substrate and 10^{-1}*M* in supporting electrolyte). In a preliminary study of the potentials necessary to cause reactions in the various media, we were able to make some generalizations. The various phenols (**4** through **10**) were oxidizable at potentials of about +0.35 V in aqueous $Na_2B_4O_7$ solutions, at +0.7 to 0.8 V in aqueous HCl solutions and at −0.1 to +0.2 V in basic CH_3CN systems. A more detailed study of the voltammetric curves of some of the

(1) (a) Paper I: J. M. Bobbitt, K. H. Weisgraber, A. S. Steinfeld, and S. G. Weiss, *J. Org. Chem.*, **35**, 2884 (1970). Paper I was numbered as part of another series but should now be considered as beginning a new one. (b) This work was sponsored, in part, by Grants CA-10494 from the National Cancer Institute of the National Institutes of Health and GP-7601 from the National Science Foundation.

(2) On leave from Tohoku University, Sendai, Japan.

(3) See paper I for pertinent background references and history.

(4) A. R. Battersby, "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1967, p 119.

(5) R. H. F. Manske, *Can. J. Res., Sect. B*, **15**, 159 (1937).

(6) (a) J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind. (London)*, 2127 (1966); (b) G. F. Kirkbright, J. T. Stock, R. D. Pugliese, and J. M. Bobbitt, *J. Electrochem. Soc.*, **116**, 219 (1969); (c) paper I of this series.

Table I
Oxidation of 4 to 11 Using Various Working Electrodes

Medium	Anodes[a] and yields, % Pt gauze	Hg pool	Pt fuel cell[b]	Graphite cloth[c]	Graphite felt[c]
0.1 *M* $Na_2B_4O_7$	50–55[d] (0.35 V)	70 (0.3 V)	50 (0.4 V)	82 (0.35 V)	85 (0.35 V)
0.1 *N* HCl	10–20 (0.78 V)	*e*	10–15 (0.78 V)	40 (0.8 V)	35–40 (0.8 V)

[a] The cathode was platinum. The anode potentials were measured against a standard calomel electrode (sce). [b] Fuel-cell electrode (Pt powder on tantalum backing), type LAA-25, Commercial Developments Dept., American Cyanamide Co., Wayne, N. J. [c] WCB graphite cloth and WDF graphite felt, Carbon Products Division, Union Carbide Corp., New York, N. Y. [d] Reference 6b. [e] Mercury electrodes are unstable in the presence of chloride.

phenols has been published[6b] or will appear elsewhere.[7,8]

Solvent Systems.—Two solvent systems were studied, water and CH_3CN. In water, the supporting electrolytes were $Na_2B_4O_7$ for basic experiments and HCl for the acid reactions. In CH_3CN, the electrolyte was tetraethylammonium perchlorate. Aqueous systems were used exclusively in the initial phases of this work. While they give excellent results with **4** and some of its derivatives,[1] poor results were obtained with other compounds due to electrode coating and appreciable decomposition. Acetonitrile, frequently used in partially aqueous solutions but never especially dried, alleviated the coating problem and is now the solvent of choice.

pH.—Both acidic and basic systems were investigated. However, oxidations took place at lower potentials in base. This should minimize side reactions and was generally used. This is in agreement with Vermillion and Pearl.[9] In fact, the most satisfactory reactions were carried out on the sodium salts of the phenols in an essentially neutral medium.

Reaction Times.—These were especially difficult to determine since most of the products of the oxidations undergo further reaction to polymeric products. The current was highest at the beginning of the reaction and dropped slowly. However, it rarely returned to zero. Two general conditions were used. The first was the reaction time in which the theoretical electricity was passed to achieve a one-electron oxidation (coulometric control). This was estimated from the current and time but was not precisely measured. Alternatively, electrolysis was carried out until no starting material could be seen in the reaction mixture by tlc (tlc control). In general, the first condition produced the best results.

Oxidation Products.—The starting materials were prepared by methods previously reported from this laboratory[10,11] except for the amides (**6**, **8**, and **10**) which were prepared from the appropriate secondary amines by selective acetylation. Compound **3** was prepared by dehydrogenation of **2** over Pd on carbon.

Of the products of these reactions, only three, **11**,[1] **15**,[1] and **14**,[12] have been reported. The compounds were mostly crystalline and fall into two classes, the carbon–carbon dimers (**11**–**13**, **16**, **17**, **19**, and **20**) and the carbon–oxygen dimers (**15**, **18**, and **21**). Both classes are completely characterized by their nmr[1a,13,14] and mass spectra. The carbon–carbon dimers show a sharp singlet at about δ 6.6 in their nmr spectra, and the carbon–oxygen dimers, **15** and **18**, show three aromatic singlets in the region δ 6.3–6.7. The dimer **21** shows a singlet at δ 6.39 and an AB pattern, J = 9 Hz, at δ 6.6 and 6.25.

None of the dimers contain any open ortho or para positions in respect to the phenol, and all should give negative tests with diazotized sulfanilic acid.[15] All gave negative tests except **17** and **18** which were questionable and **16** which gave a positive test. However, when these three compounds were investigated for ortho, meta, and para protons (to the phenol) by the nmr procedure of Highet and Highet,[16] the shifts observed in the aromatic protons between the free bases and the sodium salts, as measured in dimethyl sulfoxide-d_6, were well within the range for meta protons. Specifically, the shifts for **16**, **17**, and **18** were 0.24 for **16**, 0.16 for **17**, and 0.08 ppm (one proton only) for **18**. The ranges quoted[16] are 0.42–0.59, ortho; 0.19–0.38, meta; and 0.71–0.79, para.

Discussion of Results

Compounds **1**–**3** were unchanged after attempted electrolysis at +1.0 V in H_2O or CH_3CN solutions for 2 hr. This potential is well above that necessary for phenol coupling reactions in any system we have investigated and makes possible the desired, selective coupling reaction in isoquinoline alkaloids. This is in accord with our earlier work[1a] and the literature concerning the oxidizability of amine functions.[17] One exception to this has been noted, the facile oxidation of **11** to **14**. This does involve the oxidation of the nitrogen ring and takes place under normal coupling reaction conditions. It is probably best explained by the proximity of a radical generated from the phenol of **11** and the 1 position of the neighboring ring system. In fact, **11** was frequently isolated as **14** and regenerated from it with $NaBH_4$.

The results of the oxidations in aqueous systems are given in Table II, and those in CH_3CN are given in Table III. The most remarkable aspect of the data in-

(7) J. T. Stock, *Microchem. J.*, **15**, 564 (1970).
(8) When the preparative reactions were correlated with voltammetric data, the oxidations were carried out at potentials slightly more positive than the foot of the wave.
(9) F. J. Vermillion, Jr., and I. A. Pearl, *J. Electrochem. Soc.*, **111**, 1392 (1964).
(10) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).
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(12) T. Kametani and H. Yagi, *J. Chem. Soc. C*, 2182 (1967).
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TABLE II

OXIDATIONS IN AQUEOUS SYSTEMS ON A PLATINUM ANODE

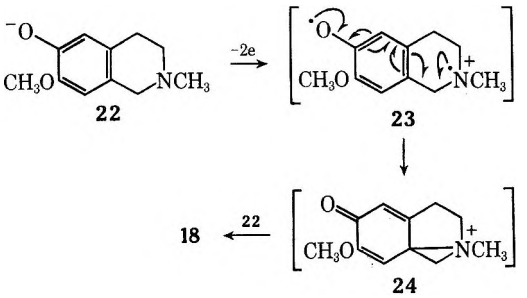
Compd	Products (%): 0.1 *N* HCl, +0.7–0.8 V	0.1 *M* $Na_2B_4O_7$, +0.3–0.4 V
4	11 (20)	11 (50–55), 15[a] (3–5)
5	12[b] (48)	12[c] (39)
7	16[d] (15)	No products
9	19[e] (24)	No products
10		20[f] (56)
		20 (40)

[a] Reference 1a. [b] Oxidation on graphite felt; 12 isolated by methylation to 11. [c] Oxidation on graphite felt; 12 isolated as 13. [d] Isolated as the hydrochloride. [e] Isolated as the acetate. [f] In 0.05 *M* $Na_2B_4O_7$–CH_3CN (2:1) using a graphite felt electrode.

volves the different types of products obtained when the sodium salts of **4**, **5**, **7**, and **9** were oxidized in CH_3CN. Compounds **4** and **5** yielded mainly the carbon–carbon dimers **11** and **12**, but **7** and **9** yielded the carbon–oxygen dimers **18** and **21**. When the electron pair of the nitrogen is less available as in acid reactions (Table II) or in the *N*-acetyl compounds **6**, **8**, and **10**, the products were all carbon–carbon dimers. From these results and the literature,[9,18] it would appear that carbon–carbon dimers are normal for this oxygenation system (without serious steric effects[1a]) and that compounds **7** and **9** are unique.

The reasons for the unique behavior of **7** and **9** are not clear. Since the *N*-acetyl derivatives yield normal carbon–carbon dimers, the electron pair of the nitrogen would seem to be involved. In **7** and **9**, the phenol is ortho–para to the benzylamine portion while, in **4** and **5**, it is meta. If these reactions take place by a radical-coupling mechanism[18a] this relationship in **7** and **9** must give rise to an enhanced stability of the oxygen radical. This is understandable, assuming that the CH_2N group is an electron-feeding group.[18a] However, the sharp differences in behavior between the phenols do not seem explainable by such a subtle effect.

An alternate argument could be made involving a two-electron oxidation of one molecule followed by an addition of phenolate ion. This type of mechanism is an alternate to radical coupling.[18a] It could be visualized as shown in **22**–**24**.



The simultaneous oxidation of nitrogen and oxygen has been observed in the enzymatic oxidation[19] and electrolytic[20] oxidation of 1-(*p*-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinolines. This mechanism is impossible in acid or when the nitrogens are acetylated.

From a synthetic viewpoint, all of the skeletal types except **15** are now available selectively. Compound **15** can be isolated in small quantity only.

(18) (a) H. Musso in ref 4, p 1; (b) reference 15, p 486.

(19) Y. Inubushi, Y. Aoyagi, and M. Matsuo, *Tetrahedrom Lett.*, 2363 (1969).

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Experimental Section[21]

Oxidations in Aqueous Media.—These were carried out in a two-compartment system[6b] using a platinum gauze working anode (50 × 75 mm) separated from the platinum cathode by a porous glass disk. The tip of the sce was placed just over the top of the anode. The cell was covered with a piece of rubber dental dam, and a stream of N_2 was passed in through a capillary.

The acidic oxidations were carried out in 150 ml of 0.1 *N* HCl on samples of base hydrochlorides ranging from 300 to 500 mg. The reactions were carried out in an ice bath at temperatures between 5 and 10°. In general, the cell was set up; the anode potential was set at the estimated value; the circuit was opened and the system was allowed to equilibrate for a few minutes; and the sample was added in one portion. The potential was adjusted if necessary to give a current of about 20–40 mA. After the reaction was finished, the electrodes were removed and the anode was washed with CH_3OH. The reaction mixture was basified with NH_4OH and extracted with three 50-ml portions of $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4), combined with the CH_3OH wash, and evaporated to a residue which was treated as described for the specific compounds.

The basic oxidations were carried out in 150 ml of 0.1 *M* $Na_2B_4O_7$ (pH 9) using essentially the same set of operations. The reaction mixture, however, was not treated with NH_4OH before extraction.

Oxidations in CH_3CN.—These were carried out on a graphite felt anode (60 × 60 mm) in a two-compartment system as described above and in a one-compartment system. In the one-compartment cell, the sce tip[22] was adjacent to the anode, and the platinum gauze cathode was located approximately 2 cm from the anode.

The oxidations were carried out in media consisting of 150 ml of CH_3CN, 5 ml of H_2O, and 3.45 g of tetraethylammonium perchlorate. The sodium salts were prepared by treating 300–500-mg samples of the phenols with 1 molar equiv of $NaOCH_3$ in CH_3OH. The solutions were warmed for 30 min and evaporated to dryness. The sample was dissolved in 10 ml of H_2O and added to the cell after the circuit had been opened and the system had been allowed to equilibrate. After reaction, the electrodes were removed and the anode was washed several times with CH_3OH. The combined CH_3OH and reaction mixture were evaporated to a residue which was further processed.

Preparation of 6, 8, and 10.—To an ice-cooled mixture of 2.5 g (0.014 mol) of the appropriate secondary amines,[10] 5 g of triethylamine and 100 ml of $CHCl_3$ was added, in portions, 2.5 g (0.032 mol) of acetyl chloride (within 30 min). The mixture was stirred for 2 hr at room temperature, washed with H_2O (two 20-ml portions), dried ($MgSO_4$), and evaporated to give the crude *O*,*N*-diacetyl compound as an oil. This oil was heated at 80–90° with 50 ml of 10% KOH to hydrolyze the *O*-acetyl group. The mixture was acidified with 10% HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated to give a crystalline product which was recrystallized from benzene.

Compound **6** was obtained in 71% yield and melted at 159–160°. Compound **8** was obtained in 68% yield and melted at 149–150°. Compound **10** was obtained in 68% yield and melted at 160–161°.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found for **6**: C, 65.07; H, 6.76; N, 6.08. Found for **8**: C, 65.12; H, 6.98; N, 6.24. Found for **10**: C, 65.14; H, 6.67; N, 6.36.

(21) The melting points were taken on a Kofler hot-stage apparatus and are corrected. The nmr spectra were measured on a Varian A-60 instrument in $CDCl_3$ using tetramethylsilane as an internal standard unless noted. Mass spectra were measured on an AEI MS-12 instrument. Microanalyses were carried out by Baron Consulting Co., Orange, Conn. Tlc was carried out on silica gel GF layers, and column chromatography was carried out on silica gel M (Hermann Brothers, Cologne, Germany). All of the voltages were measured against sce and were controlled with a Wenking potentiostat No. 61TR (Brinkmann Instrument Co., Westbury, N. Y.). The tetraethylammonium perchlorate and CH_3CN were commercial materials and were used without purification. The evaporations were all carried out on a rotary vacuum evaporator.

(22) The sce was placed directly in the CH_3CN, thus casting some doubt on the meaning, but not the reproducibility, of the potentials.

Table III

Oxidations in Basic CH_3CN Systems with a Graphite Anode

	Products, %[b]		
	One compartment		Two compartments
Compd[a]	Coulometric control	Tlc control	Coulometric control
4[c]	11, 40 (62.5), 2.3 hr at 0[e] V	11, 86, 3.5 hr at 0[e] V	11, 60.4 (60.4), 3.5 hr at 0[e] V
5	12,[d] 24 (37.5), 2.4 hr at 0[e] V		
6	13, 59.4 (68), 2 hr at +0.02–0.1 V	13, 43.4, 5 hr at +0.02–0.1 V	
7	18, 50.4 (62.1), 2.3 hr at −0.06–0.03 V	18, 43, 3.5 hr at −0.06–0.03 V	18, 39 (80), 3 hr at +0.1 V
8	17, 57.8 (84), 2 hr at +0.04–0.1 V	17, 44, 5 hr at +0.04–0.1 V	
9	21, 31 (51.7), 2.3 hr at +0.16 V	21, 34, 3.5 hr at +0.16 V	21, 25.8 (71), 3.5 hr at 0 V
10	20, 36 (41), 2 hr at +0.16–0.2 V	20, 31, 5 hr at +0.16–0.2 V	

[a] The phenols were oxidized as their sodium salts. [b] The figures in parentheses represent the conversion after correction for recovered starting material. [c] Traces of the C–O–C dimer **15** were seen in the reaction products by tlc. [d] Isolated as its *O,O′,N,N′*-tetracetyl derivative. [e] A potential of 0 V does not mean that there is no potential. It only means that the potential used is the same as that of the standard calomel electrode.

Oxidation of Corypalline, 4.—The oxidation of **4** in aqueous base has been described.[1a]

Corypalline hydrochloride (300 mg) was oxidized in aqueous acid at 0.72 V for 3 hr. The chloroform extract was treated as described[1a] to obtain 50 mg of **11**. The small amount of **15** observable on tlc was not isolated.

The sodium salt of **4** (from 500 mg of **4**) was oxidized in a one-compartment system at 0.0 V for 2.3 hr (coulometric control for **15**) and 3.5 hr (tlc control). The initial current was 27 mA which fell off to 24 mA after 3.5 hr. The residue was dissolved in 25 ml of H_2O and treated with 1 g of $NaBH_4$ to reduce **14** back to **11**. The mixture was kept cold for 30 min and stirred at room temperature for 3 hr. The mixture was acidified (10% HCl), basified (10% NH_4OH), and extracted with $CHCl_3$. This $CHCl_3$ extract was processed as described[1a] to yield starting material **4** (180 mg for 2.3 hr, and 0 mg for 3.5 hr) and **11** (200 mg for 2 hr and 430 mg for 3.5 hr), mp 235–237° (lit.[1a] 235–237°). A small amount of **15** observable on tlc was not isolated.

The sodium salt of 500 mg of **4** was oxidized in a two-compartment system at 0.0 V for 3.5 hr (coulometric control). The initial current was 50 mA which dropped off to 4 mA. The product was isolated as previously described[1a] to yield no **4** and 251 mg of **11**, mp 235–237°. Preparative tlc of the mother liquors yielded an additional 51 mg.

Oxidation of 5.—Oxidation of **5** in aqueous systems using a platinum anode was unsuccessful. The current at the beginning of the experiments was 20–30 mA but dropped off to 0 in a few minutes.

Compound **5** (500 mg) was oxidized in 0.1 *N* HCl on a graphite felt anode at +0.78 V for 3.5 hr. The $CHCl_3$ extract obtained as described above was evaporated to give 200 mg of syrup (crude **12**) which was heated at 50° for 1 hr with 2 ml of 37% HCHO and 20 ml of CH_3OH. The mixture was cooled, treated with 0.5 g of $NaBH_4$, neutralized with NH_4Cl, evaporated to dryness, and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract and crystallization from ethanol gave 203 mg of **11**, mp 235–237°.

Compound **5** (500 mg) was oxidized in 225 ml of 0.1 *M* $Na_2B_4O_7$–CH_3CN, 1:2, on a graphite felt anode at +0.2 V for 3.5 hr. The CH_3CN was evaporated and the aqueous residue was extracted with $CHCl_3$. Evaporation of the solvent gave 450 mg of brownish solid (crude **12**) which was acetylated with 3 g of triethylamine, 50 ml of $CHCl_3$, and 1 g of acetyl chloride, to yield, after crystallization from CH_3OH, 353 mg of **13** acetate: mp 293–294°; nmr δ 6.88 (s, 2, aromatic), 3.88 (s, 6, OCH_3), 2.00 (s, 6, $OCOCH_3$), 2.10 and 1.97 (each s, 6, $NCOCH_3$);[23] mass spectrum M^+ 524, calcd 524; ir (KBr) 1740 ($OCOCH_3$) and 1630 cm^{-1} ($NHCOCH_3$).

Anal. Calcd for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.34. Found: C, 63.75; H, 6.19; N, 5.14.

The sodium salt from 500 mg of **5** was oxidized at 0.0 V in a one-compartment system. The initial current was 30 mA and the time for coulometric control was 2.4 hr. The residue after evaporation of CH_3CN was dissolved in 25 ml of H_2O and reduced with 1 g of $NaBH_4$. The reduction mixture was kept cool in ice for 30 min and stirred for 3 hr. The mixture was treated with 5 g of NH_4Cl and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated under vacuum to a small volume, and 180 mg of starting material was removed by filtration. Acetylation of the residue from the mother liquor (200 mg) as described above for **13** gave 120 mg of **13** acetate, mp 294–295°.

Oxidation of 6.—The sodium salt of **6** (500 mg) was oxidized in a one-compartment system at +0.02 to 0.1 V for 2 hr (coulometric control) and for 5 hr (tlc control). The initial current was 30 mA at +0.02 V. The potential was raised to 0.1 V to keep the current at about 30 mA. The residue obtained as described above was dissolved in 40 ml of H_2O, washed with $CHCl_3$,[24] acidified with NH_4Cl, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated to a pale yellow syrup which was triturated with $CHCl_3$–ether to give crystals of **13**, 257 mg for the 2-hr experiment and 180 mg for the 5-hr experiment. Preparative tlc ($CHCl_3$–acetone, 1:1) of the mother liquors yielded 60 mg of **6** and an additional 40 mg of **13** from the 2.2-hr experiment and 37 mg of **13** from the 5-hr experiment. Compound **13** was recrystallized from methanol to give colorless prisms: mp 256–257°; nmr ($CDCl_3$) δ 6.72 (s, 2, aromatic), 5.70 (s broad, 2, OH), 3.90 (s, 6, OCH_3), 2.11 and 1.91 (each s, 6, $NHCOCH_3$)[23]; mass spectrum, M^+ 440, calcd 440.

Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.53; H, 6.64; N, 6.23.

Acetylation of **13** yielded the same *O,O′,N,N′*-tetracetyl derivative of **12** obtained in the oxidation of **5**.

Oxidation of 7.—The hydrochloride of **7** (300 mg) was oxidized at +0.72 V in 0.1 *N* HCl at room temperature for 3 hr. The $CHCl_3$ extract obtained as previously described was evaporated to a small volume and triturated with ethanol to give a slightly colored powder. This powder was collected, dissolved in ethanol, and treated with concentrated HCl to prepare the hydrochloride of **16**. The hydrochloride, 47 mg, mp 284–285°, was crystallized from ethanol–ether: nmr (D_2O) δ 6.85 (s, 2, aromatic), 3.85 (s, 6, OCH_3), 3.0 (s, 6, NCH_3); mass spectrum, M^+ 384, calcd 384.

Anal. Calcd for $C_{22}H_{28}N_2O_4 \cdot 2HCl \cdot H_2O$: C, 55.58; H, 6.72; N, 5.89. Found: C, 55.84; H, 6.76; N, 5.79.

Oxidation of **7** in base at +0.35 V led to no products. The

(23) Two explanations are possible for these two acetylmethyl peaks. One involves the conformation of the nitrogen ring as described by G. Fraenkel, M. P. Cava, and D. R. Dalton, *J. Amer. Chem. Soc.*, **89**, 329 (1967). The other involves the different forms of the acetyl group itself as brought about by restricted rotation of the carbon–nitrogen bond; see H. Paulsen and K. Todt, *Angew. Chem.*, **78**, 943 (1966).

(24) This $CHCl_3$ extract was evaporated to leave a noncrystalline powder (17 mg from 2-hr experiment and 45 mg from 5-hr experiment) of a still unknown structure.

current rapidly dropped off to 0 and only starting material could be seen by tlc.

The sodium salt from 500 mg of **7** was oxidized in a one-compartment system at −0.03 to +0.06 V for 2.3 hr (coulometric control) and 3.5 hr (tlc control). The current was maintained at about 30 mA by slowly raising the voltage over the range stated. The $CHCl_3$ extract obtained as described above was washed (saturated NaCl), dried ($MgSO_4$), and concentrated under vacuum to a small volume. Cooling yielded starting material, 80 mg, from the 2.2-hr experiment. Preparative tlc ($CHCl_3$–acetone–methanol–NH_4OH, 100:100:50:2.5) of the mother liquor yielded 13 mg of **7** and 252 mg of **18** from the 2.2-hr experiment and 215 mg of **18** from the 3.5-hr experiment. Compound **18**, mp 152–153°, was recrystallized from ether–hexane: nmr ($CDCl_3$) δ 6.63, 6.45, and 6.36 (each s, each 1, aromatic), 4.95–5.2 (s broad, 1, OH), 3.90 and 3.77 (each s, each 3, OCH_3), 2.52 and 2.48 (each s, each 3, NCH_3); mass spectrum M^+ 384, calcd 384.

Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.45; H, 7.46; N, 7.11.

The sodium salt from 500 mg of **7** was oxidized in a two-compartment system at +0.1 V for 3 hr. The initial current of 25 mA dropped off to 3 mA. The products were isolated as described above to yield 254 mg of starting material and 197 mg of **18**.

Oxidation of 8.—The sodium salt from 500 mg of **8** was oxidized in a one-compartment system at +0.04–0.1 V for 2 hr (coulometric control) and 5 hr (tlc control). The current was maintained at about 30 mA by slowly raising the voltage over the range stated. The $CHCl_3$ extract, obtained as previously described, was washed (saturated NaCl), dried ($MgSO_4$), and evaporated to a residue. The residue was chromatographed over a column of 35 g of silica gel, eluted with $CHCl_3$–methanol, 99:1, to yield 155 mg and 0 mg of starting material and 289 and 220 mg of **17** from the 2-hr experiment and the 5-hr experiment, respectively. Compound **17** was recrystallized from benzene to give pale yellow prisms: mp 233–235°; nmr δ 6.70 (s, 2, aromatic), 5.74 (s broad, 2, OH), 3.90 (s, 6, OCH_3), 2.17 and 2.10 (each s, 6, $NCOCH_3$);[23] mass spectrum M^+ 440, calcd 440; ir (KBr) 1620 cm^{-1} ($NCOCH_3$).

Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.17; H, 6.37; N, 6.30.

Oxidation of 9.—The hydrochloride of **9** (500 mg) was oxidized at +0.72 V in 0.1 *N* HCl for 3.5 hr. The $CHCl_3$ extract obtained as described above was evaporated to dryness and acetylated by the procedure given above for the preparation of **6**, **8**, and **10** (without the base treatment). The resulting oil was chromatographed over 25 g of silica gel using benzene–ether as an eluent. The major fraction crystallized on evaporation to yield 122 mg of the diacetate of **19**, mp 185–186°, recrystallized from ether: nmr δ 6.72 (s, 2, aromatic), 3.8 (s, 6, OCH_3); mass spectrum M^+ 468, calcd 468.

Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.46; H, 6.89; N, 5.98.

Oxidation of **9**, like **7**, in aqueous base yielded no products.

The sodium salt from 500 mg of **9** was oxidized in a one-compartment system at +0.16 V for 2.3 hr (coulometric control) and 3.5 hr (tlc control). The initial current of 30 mA dropped off to 24 mA during the experiment. The dry residue obtained as described above was washed with 300 ml of dry CH_3CN (to remove starting material) and dissolved in 25 ml of H_2O. The H_2O was acidified (10% HCl), basified (NH_4OH), and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated to dryness and separated by preparative tlc (methanol–NH_4OH, 98.5:1.5) to yield 155 mg of **21** from the 2.3-hr experiment and 170 mg from the 3.5-hr experiment. Compound **21**, as precipitated from ether with hexane, melted at 135–137°: nmr δ 6.60 (d, J = 9 Hz, 1, aromatic at C-5), 6.39 (s, 1, aromatic), 6.25 (d, J = 9 Hz, 1, aromatic at C-6), 6.18 (s broad, 1, OH), 3.77 and 3.63 (each s, each 3, OCH_3), 2.49 and 2.44 (each s, each 3, NCH_3); mass spectrum M^+ 384, calcd 384.

Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.61; H, 7.59; N, 7.03.

Starting material, 201 mg from the 2.3-hr experiment and 0 mg from the 3.5-hr experiment, was obtained by evaporating the CH_3CN wash solution to dryness.

The sodium salt from 500 mg of **9** was oxidized in a two-compartment system at 0 V for 3.5 hr at room temperature. The initial current of 50 mA dropped off to about 3 mA. The products were isolated as described above to yield 130 mg of **21** and 311 mg of starting material.

Oxidation of 10.—The sodium salt derived from 500 mg of **10** was oxidized in CH_3CN in a one-compartment system at +0.16–0.2 V for 2 hr (coulometric control) and 5.5 hr (tlc control). The current was maintained at 30 mA by slowly raising the voltage over the range given. The residue was dissolved in 25 ml of H_2O, acidified (10% HCl), and extracted with $CHCl_3$. The $CHCl_3$ extract was washed (saturated NaCl), evaporated to dryness and separated by preparative tlc ($CHCl_3$–acetone, 1:1). Starting material, 60 mg, and 180 mg of **20** were obtained from the 2.2-hr experiment, and 155 mg of **20** was obtained from the 5.5-hr experiment. Compound **20** was a noncrystalline glass: nmr δ 6.62 (s, 2, aromatic), 3.88 (s, 6, OCH_3), 2.26 and 2.18 (each s, 6, $NCOCH_3$).[23]

Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.90; H, 6.96; N, 6.49.

Oxidation of 500 mg of **10** in a two-compartment system in 0.1 *M* aqueous $Na_2B_4O_7$ at +0.9 V (platinum anode) for 3.5 hr at room temperature yielded 200 mg of **20**. Oxidation of 500 mg of **10** in a two-compartment system in a medium of 100 ml of aqueous 0.05 *M* $Na_2B_4O_7$ and 50 ml of CH_3CN at +0.2 V using a felt anode yielded, after 3 hr, 280 mg of **21**.

Registry No.—**4**, 450-14-6; **6**, 30597-81-0; **8**, 30542-00-8; **10**, 30542-01-9; **11**, 14510-48-6; **13**, 30542-03-1; **13** diacetate, 30542-04-2; **16** 2HCl, 30546-01-1; **17**, 30597-82-1; **18**, 30546-02-2; **19** diacetate, 30546-03-3; **20**, 30546-04-4; **21**, 30546-05-5.

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Synthesis and Reactions of 2,3-Diphenyl-2,5-dihydro-2-furanol

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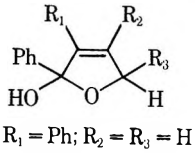
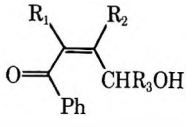
The unstable title compound **1** is the first example of a C-5 unsubstituted 2,5-dihydro-2-furanol to be prepared. In solution furanol **1** rapidly equilibrates between its cyclic and acyclic forms and slowly dehydrates to 2,3-diphenylfuran. The method of preparation of furanol **1** is general and can be adapted to positionally specific syntheses of other 2,5-dihydro-2-furanols.

In connection with our studies of the epoxidation of cyclopropenes,[2] a synthesis of 2,3-diphenyl-2,5-dihydro-2-furanol (**1**) was sought since it was a possible product of the *m*-chloroperbenzoic acid oxidation of 2,3-diphenyl-1-(hydroxymethyl)-2-cyclopropene. Several 5,5-disubstituted 2,5-dihydro-2-furanols[3] have been prepared and extensively studied, but relatively little is known about the 5-monosubstituted 2,5-dihydro-2-furanols[4] and no 5-unsubstituted 2,5-dihydro-2-furanols are known. The reported 5-monosubstituted 2,5-dihydro-2-furanols[4] were prepared by an unselective partial reduction of unsaturated 1,4 diketones to yield metastable furanols which readily dehydrated to furans, either spontaneously or under the influence of catalysts. In the monosubstituted C-5 case, **3**, most thoroughly



1, R_1 = Ph; R_2 = R_3 = H
3, R_1 = R_2 = Cl; R_3 = Ph

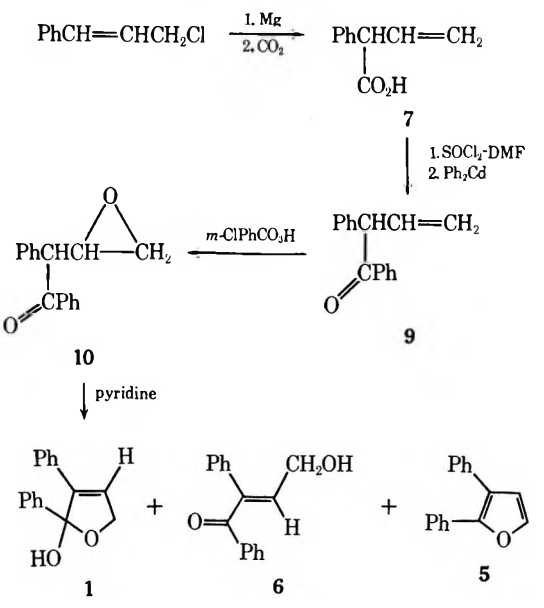


2, R_1 = Ph; R_2 = R_3 = H
4, R_1 = R_2 = Cl; R_3 = Ph

studied,[4b] no trace of the acylic form **4** was detected, although its presence was indicated by cis–trans epimerization of furanol **3**.

Synthesis.—Several straightforward routes were tried to prepare furanol **1**. Many of the simple routes which are given in the Experimental Section failed in part because of aromatization to 2,3-diphenylfuran (**5**). We, therefore, turned to the synthetic route shown in Scheme I which as expected also produced the trans isomer **6** in addition to furanol **1**. Reaction of cinnamyl chloride with magnesium followed by carbonation with Dry Ice gave an 84% yield of known phenylvinylacetic acid (**7**).[5] Thionyl chloride–dimethylformamide (DMF)[6] converted acid **7** quantitatively into acid

Scheme I



chloride **8**, which was allowed to react with diphenylcadmium to afford the β,γ-unsaturated ketone **9** in 78% yield. Epoxidation of keto olefin **9** with *m*-chloroperbenzoic acid yielded 71% of epoxide **10** as apparently one single diasteriomer.

The pyridine-catalyzed rearrangement of epoxide **10** was followed by nmr spectroscopy. The results presented in Table I show that trans–cis isomerization occurred under the reaction conditions with a slow formation of furan **5**, which after 96 hr accounted for 35% of the mixture. The trans–cis isomerization presumably occurs *via* reversible 1,4 addition of some unknown nucleophile to keto olefin **6**.[7] No epimerization of epoxide **10** was observed, which prevented the isolation

Table I

Pyridine-Catalyzed Rearrangement of 1,2-Diphenyl-3,4-epoxy-1-butanone (**10**)[a]

Time, hr	10, %	6, %[b]	1-2, %[b]
2.0	41	73	27
4.0	16	64	36
6.5	2	61	39
9.5	<1	54	46
23.5	0	27	73
28.0	0	22	78
96.0	0	15	85

[a] At 50° employing 5 ml of pyridine per 1 g of epoxide. [b] Normalized so that the sum of compounds **6** and **1**–**2** equals 100.

(1) To whom correspondence should be addressed. Financial support for this work came in part from the National Science Foundation, Grants GP-8878 and GP-20368.

(2) L. E. Friedrich and R. A. Cormier, *J. Org. Chem.*, **35**, 450 (1970).

(3) (a) V. I. Serkova, E. A. Basina, and E. D. Venus-Danilova, *J. Gen. Chem. USSR*, **37**, 1369 (1967), and preceding papers by Venus-Danilova; (b) A. Fabrycy and K. Kozlowski, *Rocz. Chem.*, **41**, 251 (1967); *Chem. Abstr.*, **67**, 33822*f* (1967); (c) A. N. Orlova and V. S. Lineva, *Zh. Org. Khim.*, **3**, 748 (1967); *Chem. Abstr.*, **67**, 43606*c* (1967); (d) C. S. Foote, M. J. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenck, and K. H. Schulte-Elte, *Tetrahedron*, **23**, 2583 (1967); (e) A. Fabrycy and R. Dobrzeniecka, *J. Gen. Chem. USSR*, **37**, 53 (1967); (f) *Zesz. Nauk. Politech. Szczecin. Chem.*, **6**, 23 (1965); *Chem. Abstr.*, **65**, 13639*h* (1966); (g) A. Fabrycy and K. Kozlowski, *J. Gen. Chem. USSR*, **33**, 3702 (1963); (h) R. E. Lutz, C. L. Dickerson, and W. J. Welstead, Jr., *J. Org. Chem.*, **27**, 3062 (1962); (i) Yu. S. Zalkind and V. K. Teterin, *J. Prakt. Chem.*, **133**, 195 (1932); *Chem. Abstr.*, **26**, 2977 (1932); (j) A. Lowenbein and G. Ulich, *Chem. Ber.*, **58B**, 2662 (1925).

(4) (a) H. H. Freedman and G. A. Doorakian, *Tetrahedron*, **20**, 2181 (1964); (b) W. K. Hankins, R. E. Lutz, E. L. Anderson, M. G. Hankins, and D. W. Boykin, Jr., *J. Org. Chem.*, **35**, 2934 (1970).

(5) A. Iliceto and G. Gaggia, *Gazz. Chim. Ital.*, **90**, 262 (1960).

(6) H. H. Bosshard, R. Mory, H. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

(7) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 344; F. M. Menger and J. H. Smith, *J. Amer. Chem. Soc.*, **91**, 4211 (1969).

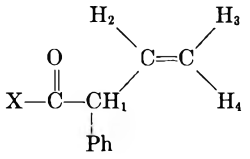
of the other diastereomer. It is therefore unknown if the two possible diastereomers may fragment to different ratios of compounds **6** and **1**–**2**. Graphical extrapolation of the **6**:**1**–**2** ratio to zero time gives a kinetic ratio of 76:24. In a typical preparative run the yield of isolated furanol **1** was 22% with large accompanying amounts of furan due to partial aromatization under the work-up conditions.

The crystalline furanol could be stored indefinitely at 0° without detectable decomposition, but at room temperature the material dehydrated to 2,3-diphenylfuran (**5**) in a week. Acetone–chloroform solutions of furanol **1** showed no dehydration after 15 hr at room temperature or after heating at 60° for *ca.* 30 min. Heating at 70° for *ca.* 30 min, however, resulted in nearly 80% dehydration. An attempt to obtain an nmr spectrum of furanol **1** in dimethyl sulfoxide solution showed only furan **5**. Similarly, attempts to chromatograph the furanol on Florisil or silica gel columns led to quantitative dehydration, whereas the reported 5-monosubstituted furanols[4b] were stable to Florisil chromatography.

Nmr Spectra.—The nmr spectra of acid **7**, its acid chloride **8**, and ketone **9** were sufficiently resolved that the straightforward use of LAOCOON III[8] gave the best values of the chemical shifts and coupling constants for these three compounds (see Table II). Similarly,

TABLE II

COMPUTER-CALCULATED NMR VALUES FOR COMPOUNDS **7**, **8**, AND **9**[a]



Proton or coupling	X = OH, **7**[b]	X = Cl, **8**[c]	X = Ph, **9**[d]
H_1	253.5	276.5	309.9
H_2	368.4	368.0	377.8
H_3	308.8	316.8	306.4
H_4	305.1	310.1	299.9
$J_{1,2}$	8.1	7.7	7.4
$J_{1,3}$	1.0	0.9	1.0
$J_{1,4}$	1.0	0.8	1.4
$J_{2,3}$	10.9	10.6	10.3
$J_{2,4}$	15.5	16.1	17.2
$J_{3,4}$	−1.3	−1.4	−1.4

[a] All values in hertz. Shifts measured downfield from TMS. [b] Root mean square error = 0.3, degrees of freedom = 13. [c] Root mean square error = 0.1, degrees of freedom = 15. [d] Root mean square error = 0.2, degrees of freedom = 8.

computer-calculated values for epoxide **10** and furanol **1** are given in Tables III and IV, respectively.

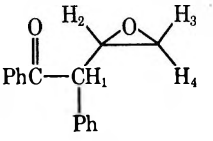
Equilibration of Furanol 1.—The solid-phase ir spectrum of furanol **1** in Nujol showed no carbonyl band the same as reported for furanol **3**.[4b] In chloroform solution, however, the ir spectrum showed a strong absorption at 1664 cm^{-1} corresponding to the carbonyl stretch of the open-form hydroxy ketone **2**.

The nmr spectrum of furanol **1** in $CDCl_3$ showed two broad singlets at δ 2.51 and 3.78 for alcohols **2** and **1**,

(8) A. A. Bothner-By and S. M. Castellano in "Computer Programs for Chemistry," Vol. 1, D. F. DeTar, Ed., W. A. Benjamin, New York, N. Y., 1968, p 10.

TABLE III

COMPUTER-CALCULATED NMR VALUES FOR EPOXIDE **10**



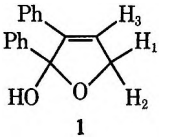
10

Proton or coupling	Frequency, Hz[a]
H_1	257.23 ± 0.06
H_2	225.62 ± 0.04
H_3[b]	169.25 ± 0.05
H_4[b]	155.25 ± 0.05
$J_{1,2}$	7.75 ± 0.07
$J_{1,3}$	0.78 ± 0.17[c]
$J_{1,4}$	0.02 ± 0.14
$J_{2,3}$	3.98 ± 0.07
$J_{2,4}$	2.77 ± 0.07
$J_{3,4}$	4.95 ± 0.08

[a] Root mean square error = 0.07; degrees of freedom = 8; all errors are standard deviations. [b] Relative assignment based on expected larger cis coupling to H_2 than trans; see L. M. Jackman and S. Sternhell in "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, p 287. [c] For large coupling across four bonds, see reference in footnote *b*, p 334.

TABLE IV

COMPUTER-CALCULATED NMR VALUES FOR FURANOL **1**



1

Proton or coupling	Frequency, Hz[a]
H_1[b]	285.94 ± 0.03
H_2[b]	292.83 ± 0.10
H_3	385.47 ± 0.03
$J_{1,2}$	−15.00 ± 0.03
$J_{1,3}$	1.68 ± 0.04
$J_{2,3}$	1.92 ± 0.13

[a] Root mean square error = 0.03; degrees of freedom = 4; all errors are standard deviations. [b] Assignment based on expected higher field shift of H_1 cis to Ph; see reference in footnote *b* of Table III, p 234.

respectively (relative area 1:4), which disappeared on exchange with D_2O. In addition, the allylic protons of furanol **1** appeared as a seven-peak multiplet at δ 4.51–5.05, whereas the allylic protons of alcohol **2** appeared as a broad doublet at δ 4.10 which sharpened to to a ringing doublet after D_2O exchange. The vinyl protons of alcohols **1** and **2** were not clearly separated and appeared as a five-peak multiplet at δ 6.21–6.42. Finally, a multiplet at δ 7.77–7.94 which was downfield from the main phenyl absorptions was assigned to the benzoyl ortho protons of alcohol **2**.

The equilibration of compounds **1** and **2** was firmly established by variable-temperature nmr studies in a 9:1 v/v $CDCl_3$–acetone-d_6 solution. The values of the calculated equilibrium constants (K = **1**/**2**) are given in Table V. The calculated values of the associated thermodynamic parameters are $\Delta H = -1.25 \pm 0.06$ kcal/mol; $\Delta S = -1.41 \pm 0.21$ cal/(deg mol).

The equilibrium appears also to be strongly dependent on the solvent. When the nmr spectrum of furanol **1** was run in pure acetone-d_6, the ratio of **1**/**2** was *ca.* 16. The origin of this solvent effect is presently un-

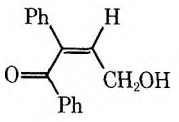
TABLE V

EQUILIBRIUM CONSTANTS FOR FURANOL 1 AND KETOL 2[a]

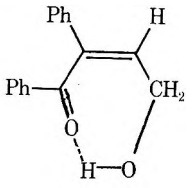
Temp, °K[b]	$K = 1/2$[c]	DF[d]
218	8.91 ± 0.28	28
229	7.45 ± 0.22	31
246	6.72 ± 0.16	15
254	5.74 ± 0.08	18
299	4.12 ± 0.04	10
333	3.20 ± 0.08	8

[a] In $CDCl_3$–acetone-d_6 solution, 9:1. [b] Error ±2°. [c] Errors are standard deviations from repetitive integration of nmr signals. [d] Degrees of freedom.

known, but presumably is not related to the possibility that ketol 2 exists primarily in an intramolecularly hydrogen bonded form, 2b. Not only does the hydroxyl



2a



2b

proton of ketol 2 absorb at a higher nmr field strength than the hydroxyl proton of furanol 1, but both the *cis*-ketol 2 and *trans*-ketol 6 have similar ir carbonyl stretches at 1664 and 1658 cm^{-1}, respectively, in $CHCl_3$ solution. Furthermore, both the nmr hydroxyl hydrogen absorptions of furanol 1 and ketol 2 were strongly temperature dependent (see Table VI). Both

TABLE VI

CHEMICAL SHIFTS[a] OF HYDROXYL PROTONS OF FURANOL 1 AND KETOL 2

Temp, °C	Furanol 1[b]	Ketol 2[c]
26	262	132
−19	309	162
−27	316	166
−44	334	179
−55	354	194

[a] In hertz downfield from TMS in $CDCl_3$–acetone-d_6 solution (9:1). [b] Slope = −1.04 Hz/deg. [c] Slope = −0.66 Hz/deg.

temperature shifts were linear as observed in other cases.[9]

These data unequivocally establish furanol 1 to be the first which exists in thermal equilibration with a measurable concentration of its open ketol form 2. Whether this feature is due to the fact that furanol 1 is also the first to be unsubstituted at C-5 is unknown. The method of synthesis *via* keto olefin 9, however, will permit other furanols to be specifically synthesized without the attending problems of other preparations.[4]

Experimental Section

General.—Nmr spectra were recorded with a Jeolco Model C60-HL spectrometer using tetramethylsilane as an internal standard. A Perkin-Elmer Hitachi RMU6E spectrometer was used to obtain mass spectra; a direct inlet probe was employed. Ir spectra were obtained with a Perkin-Elmer Model 137 spectrometer. A Cary Model 11 MS spectrophotometer was used to record uv spectra. Melting points were obtained on a calibrated Fisher–Johns melting point apparatus. Computer calculations were performed on an IBM 360/65 computer at the Computing Center of the University of Rochester. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

Phenylvinylacetic Acid (7).—The following improved preparation of cinnamylmagnesium chloride is based on a procedure reported by Young, *et al.*[10] A 72.9-g (3.00 g-atoms) portion of crushed and oven-dried magnesium turnings was placed in a 5-l., three-necked flask fitted with a dropping funnel, mechanical stirrer, reflux condenser, and nitrogen inlet. The magnesium was covered with 2.7 l. of anhydrous ether under a nitrogen atmosphere, and the reaction was initiated by addition of *ca.* 3 ml of freshly distilled cinnamyl chloride[11] and a crystal of iodine. The reaction mixture was stirred vigorously, and the remainder of the 45.9 g (0.300 mol) of cinnamyl chloride in 300 ml of anhydrous ether (total *ca.* 30.0 mol) was added at such a rate that the ether barely refluxed. The addition required 3.5 hr, and the resulting blue-gray mixture was cooled in a Dry Ice–acetone bath. The ethereal solution was decanted from the excess magnesium onto 2 kg of powdered Dry Ice contained in a 6-l. beaker. The mixture was stirred manually, and, when all of the Dry Ice had disappeared, the mixture was made strongly acidic with 400 ml of 6 *M* aqueous HCl. The aqueous layer was separated and extracted with three 200-ml portions of ether, and the combined ethereal solutions were extracted with four 200-ml portions of 10% aqueous Na_2CO_3. The combined basic extracts were washed with one 200-ml portion of ether and made strongly acidic with 400 ml of 3 *M* aqueous HCl. The resulting mixture was extracted with five 200-ml portions of ether, and the combined ethereal extracts were washed with one 200-ml portion of saturated aqueous NaCl. After drying over anhydrous Na_2SO_4 the solvent was evaporated on a rotary evaporator to yield 40.6 g (84%) of colorless, oily acid 7. This material could be used without purification. Crystallization from petroleum ether (bp 30–60°) afforded white prisms: mp 31–32° (lit.[5] mp 32–33°); uv max (95% EtOH) 249 nm (ε 850), 257 (sh, 720), and 263 (sh, 490); ir ($CHCl_3$) 2933 (broad, OH), 1704 (C=O) and 995, 930 cm^{-1} (CH=CH_2); nmr (CCl_4) δ 4.21 (d, J = 7.5 Hz, 1 H, -PhC**H**-), 4.94–5.23 (three-peak m, 2 H, -CH=CH_2), 5.88–6.45 (m, 1 H, -CH=CH_2), 7.21 (s, 5 H, aromatic protons), and 11.93 (s, 1 H, -OH). Exchange with D_2O caused the disappearance of the hydroxyl singlet at δ 11.93.

When the reaction was carried out using 72.9 g (3.00 g-atoms) of magnesium, 91.5 g (0.600 mol) of cinnamyl chloride, and 3 l. of ether, 72.8 g (75%) of acid 7 was obtained.

1,2-Diphenyl-3-buten-1-one (9).—Phenylvinylacetyl chloride (8) was synthesized by the method of Bosshard, *et al.*,[6] from the corresponding acid. The yield of pale yellow acid chloride 8 was 17.8 g (99%). This material was sufficiently pure for use in the next step. Further purification could be achieved by distillation under reduced pressure to afford a colorless liquid: bp 62–63° (1 mm); ir (CCl_4) 1764 (C=O), 1325, 1224 and 987, 935 cm^{-1} (CH=CH_2); nmr (CCl_4) δ 4.63 (d, J = 7.5 Hz, 1 H, -PhC**H**-), 5.04–5.37 (four-peak m, 2 H, -CH=CH_2), 5.89–6.47 (m, 1 H, -CH=CH_2), and 7.26 (s, 5 H, aromatic protons).

The acid chloride was converted to enone 9 by treatment with diphenylcadmium according to the procedure of Cason.[12,13] The 90% yield of crude product was dissolved in 200 ml of pentane and cooled in ice to give a reddish oil. The mother liquor was decanted from this oil and slowly cooled to −78° to yield 15.6 g (70%) of pale yellow ketone 9, mp 66–69°. Concentrating the mother liquor to *ca.* 50 ml and cooling to −78° afforded an additional 1.7 g (8%) of pale yellow ketone 9. This material was satifactory for use without further purification. Two more recrystallizations afforded the analytical sample: mp 70–71°; uv max (95% EtOH) 247 nm (ε 11,000); ir (CCl_4) 1684 (C=O), 1323, 1300, 1211 and 994, 925 cm^{-1} (CH=CH_2); nmr (CCl_4) δ 4.85–5.21 (m, 3 H, -PhC**H**-, -CH=CH_2), 6.03–6.60 (m, H, -CH=CH_2), 7.19–7.34 (m, 8 H, aromatic protons), and 7.79–7.95 (m, 2 H, benzoyl ortho protons).

(9) C. P. Rader, *J. Amer. Chem. Soc.*, **88**, 1713 (1966); ref 4b; J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 400; N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day San Francisco, Calif., 1964, p 5; J. R. Merrill, *J. Phys. Chem.*, **65**, 2023 (1961).

(10) R. H. DeWolfe, D. E. Johnson, R. I. Wagner, and W. G. Young, *J. Amer. Chem. Soc.*, **79**, 4798 (1957).

(11) H. Gilman and S. A. Harris, *Recl. Trav. Chim. Pays-Bas*, **50**, 1052 (1931).

(12) J. Cason, *J. Amer. Chem. Soc.*, **68**, 2078 (1946).

(13) H. Gilman and F. Schulze, *ibid.*, **47**, 2002 (1925).

Anal. Calcd for $C_{16}H_{14}O$ (222.27): C, 86.46; H, 6.35. Found: C, 86.53; H, 6.47.

Attempted purification of the crude reaction product by vacuum distillation or silica gel chromatography afforded a colorless oil identical with an authentic sample of (*Z*)- and (*E*)-1,2-diphenyl-2-buten-1-one.[14]

Alternate approaches to the preparation of ketone **9** were also attempted. Examination of the nmr spectrum of the crude product obtained from reacting 1,2-diphenyl-2-buten-1-one with 10 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol[15] at room temperature for 5 hr and quenching with 10% aqueous acetic acid indicated that less than 10% deconjugation had occurred. Treatment of a dimethyl sulfoxide solution of 1,2-diphenyl-2-buten-1-one with 10 equiv of sodium methoxide at room temperature for 20 hr and quenching with 2:1 benzene–acetic acid according to the procedure of Kruger[16] afforded a product whose nmr spectrum indicated a *ca.* 60% yield of ketone **9**, which could not be efficiently separated from the conjugated isomer.

1,2-Diphenyl-3,4-epoxy-1-butanone (10).—A 15.2-g (0.0750 mol) portion of 85% *m*-chloroperbenzoic acid (Aldrich Chemical Co.) was added to a solution of 16.7 g (0.0750 mol) of ketone **9** in 500 ml of methylene chloride. The reaction mixture was refluxed for 25 hr, when a starch–iodide test indicated that the peracid had been consumed. The resulting yellow solution was washed with three 100-ml portions of 5% aqueous $NaHCO_3$ and one 50-ml portion of saturated aqueous NaCl. After drying over anhydrous Na_2SO_4 the solvent was removed on a rotary evaporator to yield 17.0 g (95%) of a yellowish oil which solidified. Two recrystallizations from hexane afforded 12.6 g (71%) of white prisms: mp 104.5–106.5°; uv max (95% EtOH) 247 nm (ϵ 13,700); ir ($CHCl_3$) 1686 (C=O), 1325, 1300, 1015, 947, 886, and 837 cm^{-1} (epoxide ring); nmr ($CDCl_3$) δ 2.51–2.88 (m, 2 H, $-CHCH_2-$), 3.63–3.87 (m, 1 H, $-CHCH_2-$), 4.29 (d, J = 7.5 Hz, 1 H, $-PhCH-$), 7.27–7.42 (m, 8 H, aromatic protons), and 7.82–7.98 (m, 2 H, benzoyl ortho protons).

Anal. Calcd for $C_{16}H_{14}O_2$ (238.27): C, 80.65; H, 5.92. Found: C, 80.86; H, 6.06.

No evidence (melting point, nmr) was found for the presence of more than one of the two possible diastereomers of epoxide **10**.

2,3-Diphenyl-2,5-dihydro-2-furanol (1) and (*E*)-1,2-Diphenyl-4-hydroxy-2-buten-1-one (6).—The following rearrangement is based on the method of Crandall and coworkers[17] for the conversion of epoxides to allylic alcohols. A solution of 7.93 g (0.0333 mol) of epoxide **10** in 40 ml of pyridine was heated at 50° (bath temperature) under a nitrogen atmosphere for 7 hr. The solvent was distilled at 5 mm (bath temperature 35–40°). The residual pyridine was removed by repeatedly (*ca.* 4–5 times) dissolving the oily residue in 25 ml of benzene and distilling as before. The residue was dissolved in 450 ml of benzene–hexane (1:5) at 40° and slowly cooled to −50° to yield 1.93 g (24%) of a tan solid. Two additional recrystallizations from benzene–hexane (1:6) afforded 1.19 g (15%) of fluffy white needles of furanol **1**: mp 107.5–108.5°; uv max (95% EtOH) 248 nm (ϵ 14,800); ir (Nujol) 3333 (OH), 1238, 1093, 1057, 1031, 1014, 985, 901 (C=CH), and 755, 692 cm^{-1}; ir ($CHCl_3$) 3497, 3322 (OH), 1664 (C=O, **2**), 1229, 1176, 1063, 1011, 971, 951, and 900 cm^{-1} (C=CH); nmr ($CDCl_3$) δ 2.51 (broad s, rel area 0.2, –OH, **2**), 3.78 (broad s, rel area 0.8, –OH, **1**), 4.10 (broad d, J = 6.5 Hz, rel area 0.4, $-CH_2OH$, **2**), 4.51–5.05 (seven-peak m, rel area 1.6, $-CH_2OH$, **1**), 6.21–6.42 (five-peak m, rel area 1.0, –C=CH–, **1** and **2**), 7.05–7.56 (m, rel area 9.6, aromatic protons, **1** and **2**), and 7.77–7.94 (m, rel area 0.4, benzoyl ortho protons, **2**); exchange with D_2O caused the disappearance of the hydroxyl absorptions at δ 2.51 and 3.78 and the collapse of the broad doublet at δ 4.10 to a ringing doublet; mass spectrum (20 eV) *m/e* (rel intentsity) 238 (23.2), 220 (100), 208 (9.9), 191 (27.7), 115 (24.6), and 105 (40.1).

Anal. Calcd for $C_{16}H_{14}O_2$ (238.27): C, 80.65; H, 5.92. Found: C, 80.56; H, 5.91.

The above mother liquors were combined and evaporated on a rotary evaporator to yield 6.62 g (83%) of a brownish oil. This oil was chromatographed on 250 g of silica gel (Will Scientific, Grade 950, 60–200 mesh), *d* 3.5 cm, prepared as a slurry in benzene. Application with benzene and elution gave the following (solvent, product): benzene (1 l.), 1.65 g (21%) of colorless, oily furan **5**; 15% ether in benzene (2 l.), 1.80 g (23%) of an orange, oily mixture of furan **5**, *trans*-ketol **6** and unidentified material(s); 25% ether in benzene (1 l.) and 50% ether in benzene (1 l.), 2.75 g (35%) of pale yellow, oil *trans*-ketol **6**. The course of the chromatography was followed by tlc and nmr. Thin layer plates were prepared by dipping microscope slides into a slurry of Merck silica gel G in chloroform. Benzene was used as eluent, and the plates were developed in an iodine chamber.

Data for 2,3-diphenylfuran (**5**) follow: bp 131–133° (0.5 mm) [lit.[18] bp 173–174° (8 mm)]; uv max (95% EtOH) 230 nm (ϵ 18,300), 288 (14,500); ir (CCl_4) 1236, 1159, 1059, 1025, 943, 917, and 893 cm^{-1}; nmr (CCl_4) δ 6.43 (d, J = 2 Hz, 1 H, CH=CH) and 7.11–7.61 (m, 11 H, CH=CH and aromatic protons) [lit.[18] ir (CCl_4) 890 cm^{-1}; nmr (CCl_4) δ 6.37 (d, J = 2 Hz, 1 H), 7.16 (m, 10 H), and 7.43 (d, J = 2 Hz, 1 H)]; mass spectrum (20 eV) *m/e* (rel intensity) 220 (100) and 191 (31.8).

Data for (*E*)-1,2-diphenyl-4-hydroxy-2-buten-1-one (**6**) follow: uv max (95% EtOH) 243 nm (ϵ 15,600); ir ($CHCl_3$) 3623, 3460 (OH), 1658 (C=O), 1267, 1065, 1034, 1021, and 915 cm^{-1} (C=CH); nmr ($CDCl_3$) δ 2.27 (broad s, 1 H, –OH), 4.36 (d, J = 6 Hz, 2 H, $-CH_2OH$), 6.48 (t, J = 6 Hz, 1 H, –C=CH–), 7.20–7.58 (m, 8 H, aromatic protons), and 7.80–7.95 (m, 2 H, benzoyl ortho protons); exchange with D_2O effected the disappearance of the hydroxyl absorption at δ 2.27, mass spectrum (20 eV) *m/e* (rel intensity) 238 (74.8), 221 (41.1), 207 (44.2), and 105 (100).

Anal. Calcd for $C_{16}H_{14}O_2$ (238.27): C, 80.65; H, 5.92. Found: C, 80.60; H, 5.89.

A boiling point for (*E*)-1,2-diphenyl-4-hydroxy-2-buten-1-one (**6**) could not be obtained, since attempted distillation in a sublimation apparatus at 0.2 mm (bath temperature 150–160°) afforded a mixture of ketol **6** and furan **5** in a 2:1 ratio (nmr), respectively.

The yield of furanol **1** could be improved somewhat at the expense of ketol **6** by continuing the reaction beyond the time when all of epoxide **10** was consumed. After a reaction time of 27 hr the isolated yields of compounds **1**, **5**, and **6** were 22, 26, and 19%, respectively.

Temperature Variation of the Equilibrium between 2,3-Diphenyl-2,5-dihydro-2-furanol (1) and (*Z*)-1,2-Diphenyl-4-hydroxy-2-buten-1-one (2).—A solution of 100 mg of furanol **1** in 1 ml of 9:1 (v/v) chloroform-d_1–acetone-d_6 was prepared at room temperature in a sealed nmr tube. The equilibrium ratio was determined by a minimum of ten repetitive integrations of the methylene protons of either isomer, **1** and **2**. The nmr tube was kept at room temperature when not in the nmr probe. Methanol (−50–25°) and ethylene glycol (25–60°) were used for temperature calibration.

The most probable value of the equilibrium constant, $K = 1/2$, was determined by a weighted least squares regression analysis on the function, $K = y/x$, allowing the error in both y and x to be included. The results are given in Table V. The corresponding thermodynamic parameters were calculated by a weighted least squares regression analysis on the function, $\ln K = (\Delta S/R) - (\Delta H/RT)$, incorporating the errors determined for the equilibrium constants and the temperatures.

Unsuccessful Approaches to the Synthesis of Furanol 1 and Ketols 2 and 6. A. From (*Z*)-β-Benzoylcinnamic Acid Ethyl Ester.—According to the procedures of D'yakanov and Komendantov,[19] (*Z*)-β-benzoylcinnamic acid ethyl ester was prepared in 23% overall yield from diphenylacetylene. A 36% yield of the ester was also obtained from reaction of benzil with 1 equiv of triethyl phosphonoacetate in diglyme.[20]

Reduction of the ester with lithium monoethoxyaluminohydride,[21] aluminum hydride,[22] or lithium aluminum hydride afforded nearly quantitative yields of varying mixtures of (*Z*)-1,2-diphenyl-2-butene-1,4-diol and 1,2-diphenyl-4-hydroxy-1-butanone, which could not be separated by vacuum distillation or silver nitrate extraction.

(14) A. Padwa and R. Gruber, *J. Amer. Chem. Soc.*, **92**, 100 (1970).
(15) H. J. Ringold and S. U. Malhotra, *Tetrahedron Lett.*, 669 (1962).
(16) G. Kruger, *J. Org. Chem.*, **33**, 1750 (1968).
(17) J. K. Crandall and L. H. Chang, *ibid.*, **32**, 435 (1967); J. K. Crandall and L.-H. C. Lin, *ibid.*, **33**, 2375 (1968).
(18) A. Padwa, *Tetrahedron Lett.*, 1049 (1965); A. Padwa and R. Hartman, *J. Amer. Chem. Soc.*, **88**, 1518 (1966).
(19) I. A. D'yakanov and M. I. Komendantov, *J. Gen. Chem. USSR*, **33**, 2387 (1963).
(20) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).
(21) R. S. Davidson, W. H. H. Günther, S. W. Waddington-Feather, and B. Lythgoe, *J. Chem. Soc.*, 4907 (1964).
(22) M. J. Jorgenson, *Tetrahedron Lett.*, 559 (1962).

Attempted ketalization of the ester with a 10-mol excess of triethyl orthoformate in refluxing absolute ethanol was completely unsuccessful.

B. From β,γ-Diphenyl-γ-chloro-$\Delta^{\alpha,\beta}$-butenolide [Pseudo-(*Z*)-β-benzoylcinnamoyl Chloride].—Hydrolysis of (*Z*)-β-benzoylcinnamic acid ethyl ester with 5% methanolic KOH afforded a 71% yield of β,γ-diphenyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide [pseudo-(*Z*)-β-benzoylcinnamic acid].[19] Reaction of the hydroxybutenolide with a 2-mol excess of thionyl chloride–dimethylformamide[6] in methylene chloride gave a 92% yield of β,γ-diphenyl-γ-chloro-$\Delta^{\alpha,\beta}$-butenolide. An 82% yield of the same chlorobutenolide was obtained from treatment of the hydroxybutenolide with 1 equiv of sodium methoxide followed by 3 equiv of oxalyl chloride.[23]

Attempted reduction of the pseudo acid chloride with lithium tri-*tert*-butoxyaluminohydride[24] or sodium borohydride[25] afforded only unreacted starting chloride.

C. From α-Phenyl-$\Delta^{\alpha,\beta}$-butenolide.—Analogous to the preparation of $\Delta^{\alpha,\beta}$-butenolide from vinylacetic acid,[26] treatment of phenylvinylacetic acid with 1 equiv of performic acid followed by hydrolysis with 1.5 *M* aqueous HCl afforded a 69% yield of α-phenyl-$\Delta^{\alpha,\beta}$-butenolide.[27] Reaction of the butenolide with a 10% excess of phenyllithium analogous to the work of Pablova and coworkers[28] afforded a 75% yield of a mixture containing (nmr) 74% 2,3-diphenylfuran, 10% unreacted butenolide, and 15% of unidentified material(s).

D. From 1,2-Diphenyl-2-buten-1-one.—1-Bromo-1-phenylpropene[29] was prepared in 56% yield by reaction of propylbenzene with a 2.5-mol excess of *N*-bromosuccinimide in refluxing carbon tetrachloride followed by dehydrobromination in 10% ethanolic KOH. Treatment of the bromide with magnesium in anhydrous ether followed by condensation with benzaldehyde gave 1,2-diphenyl-1-hydroxy-2-butene[14] in 50% yield. Oxidation of this alcohol with pyridinium dichromate[30] afforded a 65% yield of 1,2-diphenyl-2-buten-1-one.[14] Attempted allylic hydroxylation of this ketone with a 10-mol excess of SeO_2 in refluxing 95% ethanol for 96 hr resulted only in cis–trans isomerization. Treatment of the ketone with 1 equiv of *N*-bromosuccinimide in refluxing carbon tetrachloride afforded a quantitative yield of 1,2-diphenyl-4-bromo-2-buten-1-one.[14] Attempted hydrolysis of this bromide with a 2-mol excess of Na_2CO_3 in 80% aqueous acetone produced only 2,3-diphenylfuran (**5**) in 70% yield.

E. From 1,2-Diphenyl-3,4-epoxy-1-butanone (10).—Rearrangement of epoxide **10** with a 10-mol excess of potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature produced a nearly quantitative yield of furan **5**. Treatment of the epoxide with a catalytic amount of triethylamine in benzene solution at room temperature for 5 hr gave no reaction.

Registry No.—**1**, 30953-21-0; **2**, 30953-22-1; **5**, 954-55-2; **6**, 30953-24-3; **7**, 30953-25-4; **8**, 30953-26-5; **9**, 30953-27-6; **10**, 30953-28-7.

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(23) R. Scheffold and P. Dubs, *Helv. Chim. Acta*, **50**, 798 (1967).
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(29) D. Y. Curtin and J. W. Crump, *J. Amer. Chem. Soc.*, **80**, 1922 (1958).
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Photolysis of Stilbene and 1,1-Diphenylethylene in the Presence of 2-Methyl-4,5-dihydrofuran

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trans-Stilbene reacts with 2-methyl-4,5-dihydrofuran on photolysis to yield two cycloaddition products. The reaction proceeds *via* the excited singlet state of stilbene. The rate constant for the quenching of *trans*-stilbene fluorescence by 2-methyl-4,5-dihydrofuran is reported and approximates the diffusion-controlled rate constant. 1,1-Diphenylethylene reacts *via* its excited triplet with 2-methyl-4,5-dihydrofuran to form two cycloaddition products in contrast to the previously reported reaction with 2,3-dihydropyran in which one cycloaddition product and two other adducts are observed.

We recently reported the results of our investigations of the photochemistry of stilbene (**1**) and 1,1-diphenylethylene (**2**) in the presence of 2,3-dihydropyran (**3**).[1] We found that stilbene gave two cycloadducts (**4** and **5**) in addition to two dimers (**6** and **7**) (Scheme I) and that this reaction could not be sensitized with triplet sensitizers.[1a] The ratio of the cycloadducts **4** and **5** was independent of the initial stilbene isomer ratio. 1,1-Diphenylethylene reacted *via* its triplet state[1b] to give one cycloadduct (**8**) and two addition products (**9** and **10**) (Scheme II), which were presumably formed in consecutive reactions initiated by hydrogen abstraction by the triplet of **2** followed by free-radical coupling.[2]

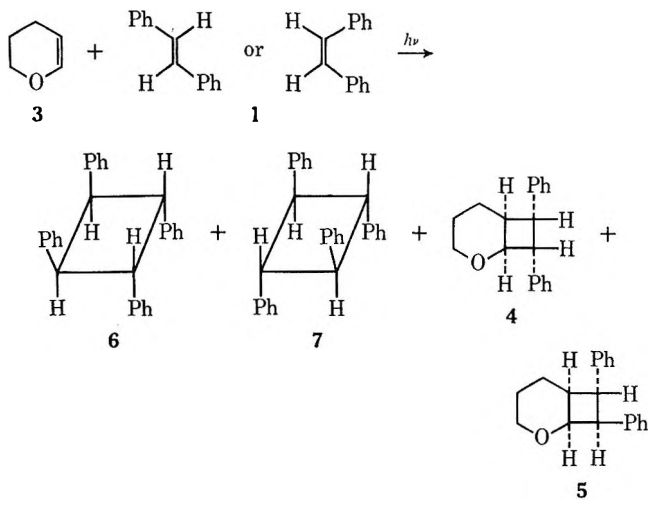
In this paper we report our results for the photolysis of **1** and **2** in the presence of 2-methyl-4,5-dihydrofuran (**11**). This study was conducted for the purpose of observing the influence of ring size of the cyclic vinyl ether substrate on the reaction.

Photolysis of Stilbene in 2-Methyl-4,5-dihydrofuran.—Solutions of *cis*- and *trans*-stilbene in 2-methyl-4,5-dihydrofuran (**11**) were photolyzed at 2537 Å. The solutions were irradiated for 48 hr in quartz vessels exposed to the atmosphere. Glpc analysis indicated that stilbene was consumed and that four products were produced whose yields were virtually independent of the stilbene isomer reactant. Two products were identified

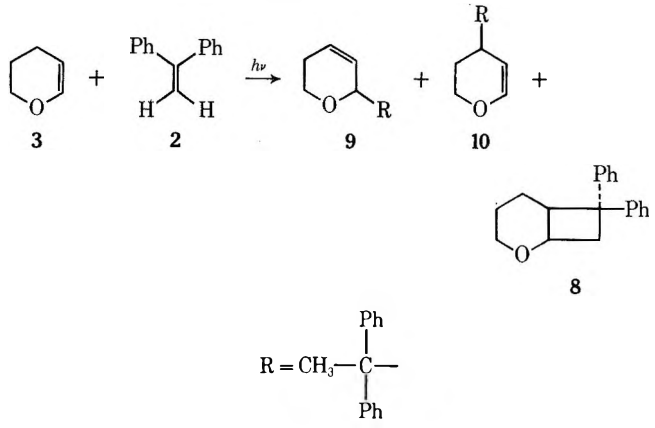
(1) (a) H. M. Rosenberg, R. Rondeau, and P. Servé, *J. Org. Chem.*, **34**, 471 (1969); (b) P. Servé, H. M. Rosenberg, and R. Rondeau, *Can. J. Chem.*, **47**, 4295 (1969).

(2) For additional examples of hydrogen abstraction by the triplet excited state of 1,1-diphenylethylene, see H. M. Rosenberg and P. Servé, *J. Amer. Chem. Soc.*, **92**, 4746 (1970), and T. S. Cantrell, *Chem. Commun.*, 1633 (1970).

SCHEME I



SCHEME II



as *cis,trans,cis*-1,2,3,4-tetraphenylcyclobutane (**6**) and *trans,trans,trans*-1,2,3,4-tetraphenylcyclobutane (**7**)[3] (combined yields 31%). The other products were characterized as 2-methyl-6,7-*cis-exo*-diphenyl-2-oxabicyclo[3.2.0]heptane (**12**, 18%) and 2-methyl-6-*exo*,7-*endo*-diphenyl-2-oxabicyclo[3.2.0]heptane (**13**, 29%).

The structural assignments of **12** and **13** were based on the following evidence (Scheme III). High-resolution mass spectra established that both products were 1:1 adducts of stilbene and **11**. Catalytic hydrogenation of 6,7-diphenyl-2-oxabicyclo[3.2.0]hept-6-ene (**14**)[4] yielded only one product whose glpc retention time and ir spectrum were identical with those of **12**. Compound **12**, on treatment with base, gave two products having similar but not identical glpc retention times. The product with the longer retention time was found to have the identical retention time with that of **13** on two different columns. A small amount of the product with the larger retention time was isolated, and its ir spectrum was identical with that of **13**. The other product (**15**) of the base isomerization was not isolated in sufficient quantity to permit positive identification. These data indicate that **12** and **13** are *cis*- and *trans*-diphenyl isomers, respectively, since catalytic hydrogen of **12** is expected to give the cis product, which should isomerize in base to the more stable trans isomers.

An attempt was made to deduce the remaining stereochemical features of **12** and **13** from their nmr spectra, details of which are given in the Experimental Section. For compound **12** the pertinent coupling constants (Hz) were found to be $J_{5,6} = 2.5$, $J_{6,7} = 7.0$, which appear to be consistent with the *cis-exo*-diphenyl structure,[5,6] although there are considerable uncertainties in basing structural assignments in cyclobutane systems on coupling constants.[6] However, the anomalously high chemical shift, *ca.* τ 7.3, for the bridgehead hydrogen H_5 suggests shielding from the phenyl substituent cis to this proton and provides support for the assigned structure.[7] Similarly, the 6-*exo*,7-*endo*-diphenyl structure proposed for **13** rests on the chemical shift, τ 7.4, of C_5,[7] in addition to its formation in the base-catalyzed isomerization of the *cis*-diphenyl isomer (*vide supra*).

Solutions of *cis*- and *trans*-stilbene (0.1 *M*) in **11** exposed to the atmosphere were irradiated at 2537 and 3000 Å. The ratio of **12** to **13** (1:1.6) remained constant throughout all reactions and was independent of the initial *cis*-stilbene:*trans*-stilbene ratio. Isomerization of stilbenes was observed and the cis:trans isomer ratios varied continuously during the course of the reactions, as shown in Table I.

SCHEME III

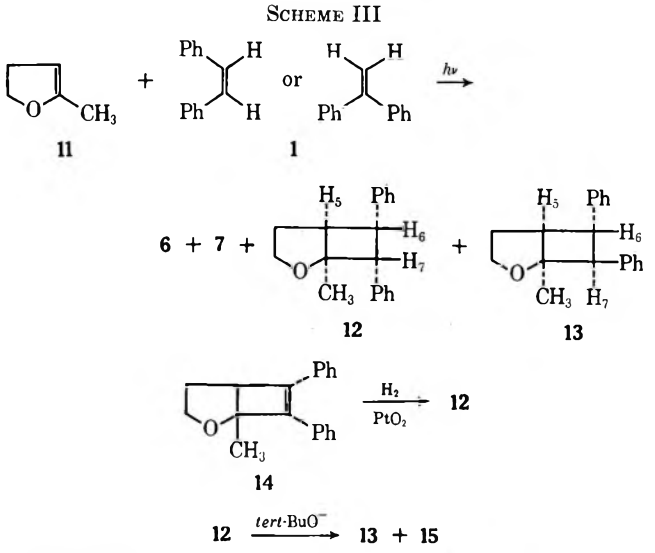


TABLE I

PHOTOLYSIS OF *cis*- AND *trans*-STILBENE IN 2-METHYL-4,5-DIHYDROFURAN AT 2537 Å

Time, min	[*cis*]/[*trans*]	Product yield, %
	cis-Stilbene	
15	26.1	6.2
30	12.8	19.8
45	7.6	24.0
75	7.0	40.1
	trans-Stilbene	
15	0.03	77.5
30	0.07	81.0
45	0.15	89.0
75	0.50	98.0

(3) H. Schecter, W. J. Link and G. V. D. Tiers, *J. Amer. Chem. Soc.*, **85**, 1601 (1963).

(4) M. P. Servé and H. M. Rosenberg, *J. Org. Chem.*, **35**, 1237 (1970).

(5) I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967).

(6) J. Krepinsky, Z. Samek, and F. Sorm, *Tetrahedron Lett.*, 3209 (1966).

(7) We are indebted to Professor L. A. Paquette, who provided us with the nmr spectrum of 2-oxabicyclo[3.2.0]heptane[8] in which the signal for H_5 was a multiplet centered at τ 6.9.

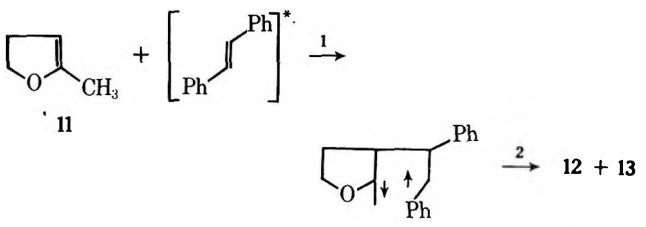
(8) L. A. Paquette, J. H. Barrett, R. P. Spitz, and R. Pitcher, *J. Amer. Chem. Soc.*, **87**, 3417 (1965).

The rate of product formation was significantly lower for the initial solution of *cis*-stilbene. Photolysis of a degassed solution of *trans*-stilbene (0.01 *M*) in **11** containing triphenylene (0.05 *M*) at 3500 Å provided evidence for sensitized isomerization of stilbene, but no sensitized formation of **12** and **13**.

The formation of cycloaddition products **12** and **13** therefore proceeds *via* the excited singlet states of stilbene. The shorter lifetime of the cis excited singlet[9] probably accounts for the lower reaction rate observed with *cis*-stilbene. The invariance of product ratio requires a common transition state or intermediate for cycloaddition reactions with *cis*- or *trans*-stilbene.

The formation of two isomeric products, in which the phenyl substituents at C_6 are exo, suggests a nonconcerted mechanism (Scheme IV). The first step appears

SCHEME IV



to involve attack by the *trans*-stilbene excited singlet to give the more stable diradical, followed by ring closure to yield products. The nonconcerted process is consistent with the concept of nonplanar excited states of olefins.[10]

A linear Stern–Volmer plot obtained for the quenching of *trans*-stilbene (10^{-4} *M*) by **11** (4×10^{-2}–2×10^{-1} *M*) in *n*-hexane is consistent with the following process.[11]

$$t^0 \xrightarrow{h\nu} t'$$

$$t' \xrightarrow{k_f} t^0 + h\nu$$

$$t' \xrightarrow{k_d} c^0 + t^0$$

$$t' + \mathbf{11} \xrightarrow{k_p} \mathbf{12} + \mathbf{13}$$

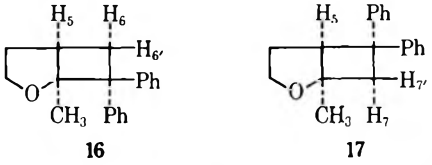
Where t and c are *trans*- and *cis*-stilbene respectively, k_f is the rate constant for fluorescence, k_d is the sum of all first-order radiationless decay processes,[13] and k_p is the bimolecular rate constant for quenching. Since the energy level of the *trans*-stilbene excited singlet is considerably lower than that of excited **11**, collisional energy transfer is unlikely and k_p may closely approximate the reaction rate constant in the absence of reversible excimer formation.

The linear plot of Φ_0/Φ *vs.* [**11**] gave slope 2.0 and intercept 1.0 in accordance with the following equation.

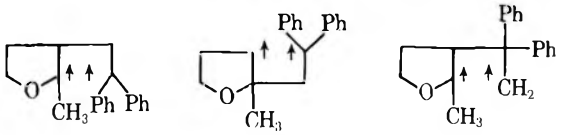
$$\Phi_0/\Phi = 1 + k_p[\mathbf{11}](k_f + k_d)$$

Using the reported values of $\Phi_0 = 0.06$[14] and $k_f = 4 \times 10^8$ sec^{-1},[15] the computed value of k_p is 1×10^{10} l. mol^{-1} sec^{-1}. It is noted that k_p closely approximates the computed diffusion-controlled rate constant for hexane, 2.0×10^{10} l. mol^{-1} sec^{-1}.[16]

Photolysis of 1,1-Diphenylethylene in 2-Methyl-4,5-dihydrofuran.—Solutions of **2** in **11** were irradiated at 2537 and 3000 Å for 48 hr. Two major products were detected by glpc in each photolysis. The products were isolated by column chromatography and were identified from spectral data as 1-methyl-7,7-diphenyl-2-oxabicyclo[3.2.0]heptane (**16**) and 1-methyl-6,6-diphenyl-2-oxabicyclo[3.2.0]heptane (**17**). The ratio of **16**:**17** was 4.5:1. Separate irradiations of **16** and **17** showed that they were not interconvertible under the reaction conditions.



16 **17**



18 **19** **20**

The parent peaks in the mass spectra of **16** and **17** corresponded to 1:1 adducts, $C_{19}H_{20}O$. The ir spectra of **16** and **17**, detailed in the Experimental Section, showed that the tetrahydrofuran ring system was still intact; both molecules also contained a methyl group and a monosubstituted phenyl. Notable by its absence was the band at 1750 cm^{-1} which was present in 2-methyl-4,5-dihydrofuran and is characteristic of an α,β-unsaturated ether.[17] The nmr spectra of **16** and **17** permitted final structure elucidations. The nmr of **16**, detailed in the Experimental Section, showed two sets of peaks each containing a doublet of doublets at τ 7.85 (J = 6.0 and 10.5 Hz) and 7.03 (J = 6.0 and 10.5 Hz). These peaks were assigned to hydrogens 6 and 6′. The nmr of **17** showed the presence of two doublets at τ 8.02 and 6.95 (J = 13 Hz); these were attributed to H_7 and $H_{7'}$. A doublet of doublets at τ 7.45 (J = 7.5 and 4.2 Hz) was assigned to H_5. Both **16** and **17** were assigned a cis ring fusion based on molecular models.

Sensitization and quenching experiments were performed in order to gain information regarding the reactive excited species. It was found that pyrene (E_T = 48.7 kcal/mol[18]) inhibited the reaction between 1,1-

(9) G. N. Lewis, T. T. Magel, and D. Lepkin, *ibid.*, **62**, 2973 (1940); D. Schulte-Frohlinde, H. Blume, and H. Gusten, *J. Phys. Chem.*, **66**, 2486 (1962); A. A. Lamola, G. S. Hammond, and F. B. Mallory, *Photochem. Photobiol.*, **4**, 259 (1964).

(10) G. S. Hammond, *Advan. Photochem.*, **7**, 377 (1969).

(11) Chapman and Lura[12] propose exciplex formation in the photolysis of *trans*-stilbene in the presence of tetramethylethylene. More complex kinetics are required for this situation and our treatment may be oversimplified.

(12) O. L. Chapman and R. D. Lura, *J. Amer. Chem. Soc.*, **92**, 6352 (1970).

(13) Stilbene dimers **6** and **7** are not formed in these reactions because of the low stilbene concentration.

(14) D. Gegiou, K. A. Muszkat, and E. Fischer, *J. Amer. Chem. Soc.*, **90**, 3907 (1968).

(15) R. H. Dyck and D. S. McClure, *J. Chem. Phys.*, **36**, 2326 (1962).

(16) A. A. Lamola and N. J. Turro, "Energy Transfer and Organic Chemistry," Interscience, New York, N. Y., 1969, p 34.

(17) L. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1966, p 119.

(18) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Amer. Chem. Soc.*, **87**, 453 (1965).

diphenylethylene (E_T = 54.5 kcal/mol[19]) and 2-methyl-4,5-dihydrofuran at 2537 Å. Equimolar concentrations of 1,1-diphenylethylene and pyrene were used. Since their molar extinction coefficients are about the same at the absorption wavelength (log ϵ 4.1 at 2537 Å[20]), quenching was attributed to triplet energy transfer rather than absorption of light by pyrene. The use of triphenylene (E_T = 66.6 kcal/mol[18]) as sensitizer for the reaction run on a degassed sample in a Pyrex vessel at 3500 Å proved successful. The product distribution in the sensitized reaction was unchanged from the unsensitized reaction run at 2537 Å. The unsensitized reaction does not occur at 3500 Å.

The sensitization and quenching experiments indicate that the reaction proceeds by way of an excited triplet state of 1,1-diphenylethylene.

The product distribution can be rationalized on the basis of the expected differences in stability of the diradical intermediates, assuming that the transition states resemble the intermediates. Thus **16** most likely proceeds from **18** whereas **17** requires **19** or **20**, both of which should be less stable than **18**.

The following differences are noted for the reaction of 1,1-diphenylethylene triplet with 2-methyl-4,5-dihydropyran and 4,5-dihydropyran: addition products involving initial hydrogen abstraction are observed only for the six-membered vinyl ether ring; both isomeric cycloaddition products occur in the reaction with the five-membered ring and only one for the six-membered ring.

Experimental Section

Melting points are uncorrected. Photolyses were conducted in a Rayonet photochemical reactor at 2537, 3000, and 3500 Å as indicated. The infrared spectra were obtained on a Perkin-Elmer Model 621 spectrophotometer. High-resolution mass spectra were obtained on a CEC-21-110 instrument. Glpc were performed on a Varian Aerograph Model 1200 HYFI on 6-ft columns packed with 10% Apiezon L on Chromosorb W or 10% SE-30 on Chromosorb W. Nmr spectra were taken on a Varian DP-60-IL instrument. An Aminco–Bowman spectrofluorimeter was used for fluorescence measurements.

Reaction of *cis*- or *trans*-Stilbene with 2-Methyl-4,5-dihydrofuran.—In a quartz vessel a solution of 5.0 g (0.02 mol) of stilbene in 70 ml of **11** was irradiated at 2537 Å in a Rayonet photochemical reactor for 48 hr. After removal of unreacted **1** under reduced pressure, the crude reaction mixture was heated with petroleum ether (bp 30–60°) and then cooled. A white, crystalline product, 2.70 g (31% based on reacted stilbene) was isolated by filtration and characterized as a mixture of *cis,trans,cis*-1,2,3,4-tetraphenylcyclobutane (**6**) and *trans,trans,trans*-1,2,3,4-tetraphenylcyclobutane (**7**): nmr ($CDCl_3$) τ 2.75, 2.94 (20 H, singlets, aromatic protons), 5.54 and 6.33 (4 H, singlets, methine protons) (lit.[3] τ 2.95 and 5.60 for **6** and 2.79 and 6.37 for **7**). The filtrate was subjected to column chromatography on alumina (80–200 mesh). Elution with petroleum ether resulted first in 2-methyl-6,7-*cis*-*exo*-diphenyl-2-oxabicyclo[3.2.0]heptane (**12**): 0.8 g (18%); mp 38–40°; parent peak 264.1481 ($C_{19}H_{20}O$); ir (thin film) 3040 (aromatic CH), 2900 (aliphatic CH), 1610, 1500 (aromatic C=C), 1050 (COC), 740 and 659 cm^{-1} (monosubstituted phenyl); nmr ($CDCl_2$) τ 2.8–3.0 (10 H, multiplet, aromatic protons), 6.05 (1 H, doublet, H_7), 6.25 (2 H, multiplet, H_3 and $H_{3'}$), 6.40 (1 H, doublet of doublets, H_6), 7.35 (1 H, multiplet, H_5), 8.4–8.6 (2 H, multiplet, H_4 and $H_{4'}$), 8.60 (3 H, singlet, CH_3), $J_{5,6}$ = 2.5, $J_{6,7}$ = 7.0 Hz. Further elution with petroleum ether resulted in the isolation of 2-methyl-6-*exo*,7-*endo*-diphenyl-2-oxabicyclo[3.2.0]heptane (**13**): 1.55 g (29%); mp 52–54°; parent peak 264.1488 ($C_{19}H_{20}O$); ir (thin film) 3040 (aromatic CH), 2930 (aliphatic CH), 1640, 1480 (aromatic C=C), 1080 (COC), 735 and 700 cm^{-1} (monosubstituted phenyl); nmr ($CDCl_3$) τ 2.8–3.0 (10 H, multiplet, aromatic protons), 6.15 (2 H, multiplet, H_3 and $H_{3'}$), 6.55 (1 H, doublet of doublets, H_6), 6.70 (1 H, doublet, H_7), 7.40 (1 H, multiplet, H_5), 8.3 (2 H, multiplet, H_4 and $H_{4'}$), 8.85 (3 H, singlet, CH_3), $J_{5,6}$ = $J_{6,7}$ = 6.5 Hz.

Hydrogenation of 2-Methyl-6,7-diphenyl-2-oxabicyclo[3.2.0]-hept-6-ene.—A solution of 2.5 g (0.01 mol) of **14** in 15 ml of anhydrous ether was hydrogenated over prereduced platinum at atmospheric pressure. After 1 equiv of hydrogen had been absorbed, the hydrogenation was stopped, the solution was filtered, and the ether was carefully removed. The remaining oil was analyzed by glpc and was found to contain only one component. The retention time of the hydrogenation product was identical with that of **12** and its ir spectrum was superimposable on that of **12**.

Isomerization of 2-Methyl-6,7-*cis*-*exo*-diphenyl-2-oxabicyclo-[3.2.0]heptane.—A mixture of **12**, 1 g, and 2 g of potassium *tert*-butoxide in 50 ml of *tert*-butyl alcohol was refluxed for 12 hr. The solvent was removed under vacuum and the residue was taken up in ether which was then washed with water and dried over anhydrous sodium carbonate. The ether solution was analyzed by glpc. The chromatograph showed two new peaks with approximately equal areas. The retention times on two different columns of the component with the longer retention time was identical with that of **13**. Chromatography on alumina resulted in the isolation of a pure sample of the component with the longer retention time and its ir spectrum was identical with that of **13**.

Reaction of 1,1-Diphenylethylene with 2-Methyl-4,5-dihydrofuran.—A solution of 1,1-diphenylethylene (2 g, 0.011 mol) in 2-methyl-4,5-dihydrofuran (25 g, 0.3 mol) was placed in a quartz vessel. The solution was degassed using three alternative freeze–thaw sequences. The solution was then irradiated at 2537 Å for 48 hr. After removal of the unreacted dihydrofuran under reduced pressure, the remaining liquid was subjected to column chromatography on alumina (80–200 mesh). Elution with petroleum ether gave 1-methyl-7,7-diphenyl-2-oxabicyclo[3.2.0]heptane (**16**): 1.6 g (63%); parent peak 264.1071 ($C_{19}H_{20}O$); ir (thin film) 3028 (aromatic CH), 2860 (aliphatic CH), 1595 (aromatic C=C), 1090 (COC), and 745 and 690 cm^{-1} (monosubstituted phenyl); nmr (C_6D_6) τ 8.8 (3 H, singlet, CH_3), 8.4–8.6 (2 H, multiplet, H_4 and $H_{4'}$), 7.85 (1 H, two doublets, J = 6.0 and 10.5 Hz, H_6 or $H_{6'}$), 7.50 (1 H, multiplet, H_5), 7.03 (1 H, two doublets, J = 6.0 and 10.5 Hz, H_6 or $H_{6'}$), 6.3–6.4 (2 H, multiplet, H_3 and $H_{3'}$), 2.8 (10 H, multiplet, aromatic H).

Further elution with petroleum ether gave 1-methyl-6,6-diphenyl-2-oxabicyclo[3.2.0]heptane (**17**): 0.29 g (12%); parent peak 264.1129 ($C_{19}H_{20}O$); ir (thin film) 3035 (aromatic CH), 2870 (aliphathic CH), 1595 (aromatic C = C), 1090 (COC), 745 and 690 (monosubstituted phenyl); nmr (C_6D_6), τ 8.9 (3 H, singlet, CH_3), 8.4–8.6 (2 H, multiplet, H_4 and $H_{4'}$), 8.02 (1 H, doublet, J = 13 Hz, $H_{7'}$), 7.45 (1 H, two doublets, J = 7.5 and 4.5 Hz, H_5), 6.95 (1 H, doublet, J = 13 Hz, $H_{7'}$), 6.2–6.4 (2 H, multiplet, H_3 and $H_{3'}$), 2.80 (10 H, multiplet, aromatic H).

Registry No.—*cis*-**1**, 645-49-8; *trans*-**1**, 103-30-0; **2**, 530-48-3; **11**, 1487-15-6; **12**, 31020-04-9; **13**, 31020-05-0; **16**, 31020-06-1; **17**, 31020-07-2.

(19) E. F. Ullman and W. A. Henderson, *J. Amer. Chem. Soc.*, **89**, 4390 (1967).

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A General Procedure for the Preparation of Deuterated and Tritiated Amino Acids by Incorporation of Solvent Isotope during Synthesis

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A convenient, specific, inexpensive, and general method for the preparation of α-deuterated and α-tritiated amino acids is described. The procedure involves incorporation of solvent isotopes of hydrogen into the α position of amino acids concomitant with decarboxylation of the substituted aminomalonate precursors, $NH_2CR(COOH)_2$. The potential use of α-tritiated amino acids to measure the extent of racemization during the synthesis of peptides is discussed. In addition, the possibilities for the specific labeling of amino acids by incorporation of hydrogen isotopes from solvent during syntheses are pointed out.

The *N*-acylaminomalonic ester synthesis (eq 1) is

$$\underset{\text{I}}{RCONHCH(COOR')_2} + R''X \longrightarrow HX + \underset{\text{II}}{RCONHCR''(COOR')_2} \xrightarrow[\Delta]{H^+} \underset{\text{III}}{NH_2CHR''COOH} + RCOOH + 2R'OH + CO_2 \quad (1)$$

where R = H, CH_3, C_6H_5, etc., and R′ = CH_3 or C_2H_5; in addition, one or both of the carboalkoxy groups in I may be replaced by CN

easily the most widely used procedure for the laboratory preparation of DL amino acids.[1] A typical amino acid synthesis employing the scheme shown in eq 1 would involve generation of the carbanion of the starting material I in strongly basic media, such as ethanolic sodium ethoxide. The carbanion is then used to effect a nucleophilic displacement of the halide from an alkyl halide, R″X, to yield the key intermediate II. This intermediate is usually hydrolyzed, deacylated, and decarboxylated in one step in boiling acid to produce the desired amino acid III.[2]

Obviously, acid-catalyzed conversion of the substituted intermediate II to the amino acid III must proceed through a symmetrical, substituted aminomalonic acid derivative IV. Equally obviously, the decarboxyl-

$$\underset{\text{IV}}{^+NH_3CR''(COOH)_2}$$

ation of the sensitive intermediate IV to the desired amino acid end product must involve the incorporation of solvent hydrogen into the α position of the resulting amino acid. This fact has been utilized to produce DL amino acids which are specifically labeled in the α position with deuterium or tritium. The method is reported herein and is demonstrated to be a convenient, general, and inexpensive method for the preparation of high-purity α-deuterium- and α-tritium-labeled amino acids.

Experimental Section

Materials. α-Methylaminomalonic Acid.[4,5]—Diethyl α-methylacetamidomalonate was prepared by the conventional alkylation procedure used in the synthesis of amino acids. Thus, a warm solution of 54.25 g of diethyl acetamidomalonate (Aldrich, 0.250 mol) in 200 ml of absolute ethanol was added dropwise with magnetic stirring to 75 ml of ethanolic sodium ethoxide (6.33 g of sodium metal, 0.275 g-atom) in a 500-ml reaction flask fitted with a condenser and drying tube. Then a solution of 48.3 g of methyl iodide (Aldrich, 0.34 mol) in 25 ml of absolute ethanol was added dropwise with stirring. The reaction mixture was refluxed for 17 hr and the solvent was removed on a rotary evaporator, leaving a yellow oil containing white crystals (NaI). This was dissolved in 50 ml of hot water and refrigerated. The resulting crystals were collected and washed with cold water, yield 39.6 g (69% of theory).

Deacetylation and hydrolysis of this product (35.0 g, 0.151 mol) was effected by refluxing in 152 ml of 5 *N* KOH for 5 days. The desired α-methylaminomalonate was isolated as the monoammonium salt employing the ion-exchange procedure described by Thanassi[6] for the preparation of the ammonium salt of aminomalonic acid, yield 14.2 g (63% of theory).

For analysis, the product was converted to the free acid by addition of cold, concentrated HCl (1 equiv) to a concentrated aqueous solution of the ammonium salt. The resulting precipitate was recrystallized from warm water and dried *in vacuo* over P_2O_5 and KOH.

Anal. Calcd for $C_4H_7NO_4$ (133.11): C, 36.09; H, 5.30; N, 10.53. Found: C, 36.20; H, 5.18; N, 10.27.

α-Deuterio-DL-alanine.—In order to remove exchangeable hydrogens, the ammonium salt of α-methylaminomalonic acid (0.50 g, 3.3 mmol) was first evaporated three times from 99.9% D_2O (Bio-Rad). Decarboxylation to the desired product was then effected by refluxing the starting material in 9.4 ml of D_2O and 0.6 ml of concentrated HCl for 3 hr. Paper chromatography showed only one ninhydrin positive spot corresponding to authentic alanine. The nmr spectrum of the product revealed that the quartet corresponding to the α hydrogen of alanine had disappeared and that the doublet for the hydrogens on the α-methyl group had merged into a singlet.

α-Deuterio-DL-phenylalanine.—2-Benzyl-2-acetamidomalonic acid was prepared according to the procedure of Albertson and Archer.[7] Deacetylation and decarboxylation to α-deuterio-DL-phenylalanine were accomplished by refluxing 2.1 g of the acetylated dicarboxylic acid precursor in 16 ml of D_2O and 0.80 ml of concentrated H_2SO_4 for 5 hr. The amino acid was isolated by isoelectric precipitation. Paper chromatography of the product in three different solvent systems showed only one ninhydrin positive spot, corresponding to authentic phenylalanine. An nmr spectrum indicated that the signals for the α hydrogen of unlabeled phenylalanine had essentially disappeared.

α-Tritio-DL-glutamic Acid.—This compound was prepared by condensing β-propiolactone (Eastman) and the sodio salt of diethyl acetamidomalonate, according to the one-step procedure described by Talbot, *et al.*,[8] except that deacetylation, hydrolysis, and decarboxylation of the oily intermediate, *N*-acetyl-2-carboethoxyglutamic acid diethyl ester (1.5 g), to the labeled amino acid were accomplished by refluxing the intermediate in 20 ml of 6 *N* HCl containing 2.5 mCi of tritiated water (New England Nuclear) for 5 hr. After removal of the radioactive solvent, the amino acid was refluxed for 95 hr in 32 ml of nonradioactive 6 *N* HCl. This was done in order to remove "semi-labile" tritium

(1) J. S. Meek, S. Minkowitz, and M. M. Miller, *J. Org. Chem.*, **24**, 1397 (1959).

(2) For detailed synthetic schemes employing this general procedure, and for numerous references to original articles, the reader is referred to Greenstein and Winitz.[3]

(3) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, Wiley, New York, N. Y., 1961.

(4) J. W. Thanassi and J. S. Fruton, *Biochemistry*, **1**, 975 (1962).

(5) G. B. Bailey, O. Chotamangsa, and K. Vuttivej, *ibid.*, **9**, 3243 (1970).

(6) J. W. Thanassi, *ibid.*, **9**, 525 (1970).

(7) N. F. Albertson and S. Archer, *J. Amer. Chem. Soc.*, **67**, 308 (1945).

(8) G. Talbot, R. Gaudry, and L. Berlinguet, *Can. J. Chem.*, **34**, 1440 (1956).

introduced into the γ position of the glutamic acid.[9] The specific radioactivity of the resulting α-tritiated DL-glutamic acid was 28% of that expected based on the specific activity of the tritium in the solvent, indicating an isotope effect of 3.6. Paper chromatography of the product in three different solvent systems showed only one spot corresponding to authentic glutamic acid.

The position of the label was confirmed with the aid of L-glutamic–oxaloacetic transaminase.[11,12] Enzyme (0.4 mg) (Boehringer), neutralized α-tritiated DL-glutamic acid (14.6 mg, 0.1 mmol), and 14.6 mg (0.1 mmol) of neutralized α-ketoglutaric acid (Boehringer) were incubated at room temperature for 1 hr in 3.0 ml of water containing 0.3 mmol of trishydroxymethylaminomethane hydrochloride buffer at pH 8.25. At the end of this time, the reaction mixture was frozen and the water collected by lyophilization into a cold finger immersed in acetone–Dry Ice. The water contained 44% of the total counts introduced into the reaction mixture as tritiated DL-glutamate; theory for the complete stereospecific enzyme-catalyzed exchange of the tritium in the L isomer with the medium is 50% of the total counts in the racemate, assuming that all of the isotope is in the desired α position.

α-Tritio-DL-aspartic Acid.—The procedure of Galat[13] was followed except that diethyl acetamidomalonate was used instead of the formamido derivative.[14] In addition, the oily intermediate, *N*-acetyl-2-carbethoxyaspartic acid diethyl ester, was hydrolyzed, deacetylated, and decarboxylated in tritiated HCl. An isotope effect of approximately 2.4 was found. Paper chromatography in three different solvent systems showed that the desired compound had been obtained. The position of the label was confirmed enzymatically as described above. All conditions were identical except that the glutamic acid was replaced by an equivalent amount of α-tritiated DL-aspartic acid. The counts released into the water amounted to 45% of the total introduced into the solution.

α-Tritio-DL-alanine and Tritioglycine.—The ammonium salts of the dicarboxylic acid precursors were dissolved in tritiated water containing 2 equiv of HCl. Decarboxylation was effected by heating at 100° for 3 hr. An isotope effect of approximately 3 was found in the decarboxylation of α-methylaminomalonic acid to α-tritio-DL-alanine.

Methods. Paper Chromatography.—The solvent systems employed were 1-butanol–acetic acid–water (4:1:1), ethanol–concentrated ammonia–water (6:3:1), and pyridine–1-butanol–water (1:1:1). Whatman No. 3 MM filter paper was used in an ascending fashion. Amino acids were visualized by spraying the paper with a ninhydrin solution in acetone.

Nmr Spectra.—These were taken on a Varian Model A-60 or a Perkin-Elmer Model R-12 nmr spectrometer; the solvent was D_2O.

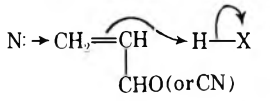
Isotope Counting.—Samples were counted in 16 ml of a solution composed of 1.0 ml of water and 15 ml of a cocktail containing, per 1200 ml, 8 g of butyl-PBD, 0.5 g of PBBO, 200 ml of Bio-Solv BBS-3, and 1000 ml of scintillation grade toluene. All materials were from Beckman Instruments, Inc. The counting efficiency for tritium was approximately 33%; counting was done on a Beckman Model LS-250 liquid scintillation counter.

Kinetics of Decarboxylation of α-Methylaminomalonic Acid.—The rate of decarboxylation of α-methylaminomalonic acid was followed by measuring the incorporation of carbon-bound tritium into the α position of the product, alanine. Aliquots (0.25 ml) of a 0.05 *M* solution of α-methylaminomalonic acid in 1.0 *M* HCl, containing tritiated water, were dispensed into 1.0-ml break-seal ampoules. The sealed ampoules were immersed in a 70° bath. After the ampoules had come to temperature, individual samples were removed at the desired times and the reaction was quenched by immersing the ampoule in ice–water. A 0.2-ml aliquot of the reaction solution was transferred to a counting vial and taken to dryness in an evacuated desiccator containing P_2O_5 and KOH pellets. Drying was repeated twice more after the addition of 0.25 ml of nonradioactive water each time in order to remove exchangeable counts. The residue was then taken up in the counting solution and the radioactivity determined. Rate constants were calculated using the conventional first-order rate equation, $k = 2.3/t \log [(\mathrm{cpm}_\infty - \mathrm{cpm}_0)/(\mathrm{cpm}_\infty - \mathrm{cpm}_t)]$, where cpm represents the observed counts per minute.

Results and Discussion

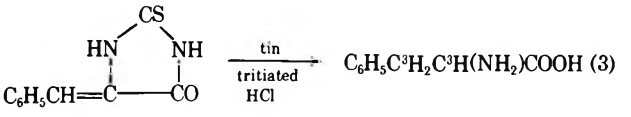
Radioactive and stable isotopes have revolutionized biological research and considerable effort and ingenuity have gone into the synthesis of compounds labeled in specific positions for use as biological tracers.[15] Inspection of the literature reveals that most, if not all, of the amino acids of biological interest can be synthesized *via* α-substituted aminomalonyl derivatives[3] and it follows that many amino acids can therefore be specifically labeled in the α position with solvent deuterium or tritium, employing procedures analogous to those presented in the Experimental Section of this paper. Thus, decarboxylation of aminomalonate precursors of amino acids in tritiated or deuterated water is a general method with wide potential use. The amount of isotope introduced into the α position during decarboxylation is directly proportional to the amount of isotope in the medium and can therefore range, depending on the medium, from a very small amount to essentially 100%, the latter figure being approached with a deuterium oxide solvent. Since tritiated water is readily available, one can synthesize in the laboratory highly radioactive amino acids for use as biological tracers at little cost.

The method of labeling amino acids by incorporation of solvent hydrogen isotopes during synthesis also has potential use in the labeling of amino acids in a number of other positions. For example, the preparations of the following amino acids can involve additions to acrolein or acrylonitrile: lysine,[16] methionine,[17] proline,[18] and ornithine[19] (eq 2). Solvent tritium incorporation



(2)

into the 2 carbon of the starting material would occur in each case.[20] Similarly, solvent–tritium incorporation could be used to prepare DL-phenylalanine labeled in the α and β positions employing the procedure of Johnson and coworkers[22,23] except that tritiated HCl would be used in the tin–HCl reduction of 5-benzalthiohydantoin to DL-phenylalanine (eq 3).



(3)

(9) Ratner, *et al.*,[10] have shown that the hydrogens on the γ carbon of glutamic acid are "semi-labile," *i.e.*, will exchange with solvent hydrogen in boiling 20% HCl, whereas the α hydrogen is stable to this treatment.

(10) S. Ratner, D. Rittenberg, and R. Schoenheimer, *J. Biol. Chem.*, **135**, 357 (1940).

(11) W. T. Jenkins and I. W. Sizer in "Methods in Enzymology," Vol. 5, S. P. Colowick and N. O. Kaplan, Ed., Academic Press, New York, N. Y., 1962, p 677.

(12) W. T. Jenkins and I. W. Sizer, *J. Biol. Chem.*, **234**, 1179 (1959).

(13) A. Galat, *J. Amer. Chem. Soc.*, **69**, 965 (1947).

(14) F. H. MacMillan and N. F. Albertson, *ibid.*, **70**, 3778 (1948).

(15) A. Murray and D. L. Williams, "Organic Synthesis with Isotopes," Interscience, New York, N. Y., 1958.

(16) O. A. Moe and D. T. Warner, *J. Amer. Chem. Soc.*, **70**, 2763 (1948).

(17) E. Rothstein, *J. Chem. Soc.*, 1560 (1940).

(18) N. F. Albertson and J. L. Fillman, *J. Amer. Chem. Soc.*, **71**, 2818 (1949).

(19) N. F. Albertson and S. Archer, *ibid.*, **67**, 2043 (1945).

(20) Frequently a nonaqueous protic solvent such as ethanol is required in these syntheses. Radioactive ethanol could easily be obtained by preparing anhydrous ethanol from a mixture of ethanol and tritiated water.[21]

(21) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 285.

(22) T. B. Johnson and B. H. Nicolet, *J. Amer. Chem. Soc.*, **33**, 1973 (1911).

(23) T. B. Johnson and W. B. O'Brien, *J. Biol. Chem.*, **12**, 205 (1912).

One of the potential problems in labeling amino acids by solvent–isotope incorporation is the danger of nonspecific incorporation into positions other than the ones desired. For example, in experiments designed to measure the extent of racemization of amino acids during hydrolysis of peptides by incorporation of solvent tritium into the α position, Manning[24] has found that nonspecific incorporation of tritium occurs, particularly in the case of glutamic and aspartic acids, histidine, phenylalanine, and tyrosine.[25] This does not appear to be a particular problem under our conditions; a stereospecific enzyme exchange assay, using L-glutamic-oxaloacetic transaminase (see Experimental Section) indicates that 90% of the radioactivity is found in the desired α position of DL-aspartic and -glutamic acids. It is probable that the relatively short reaction times used in these experiments minimize the amount of nonspecific incorporation into the product amino acids; whereas the experiments by Manning[24] involved a 22-hr heating time at 110°, the reaction times for decarboxylation in our experiments have never exceeded 5 hr. In Figure 1 are presented the rate data for the decarboxylation of α-methylaminomalonic acid in 1.0 *M* HCl and a reaction temperature of 70°. Under these conditions the rate constant for decarboxylation is 3.63×10^{-3} min^{-1}, corresponding to a half-time of 190 min. Assuming an increase in rate by a factor of 2 with every 10° rise in temperature, it can be calculated that the half-life of decarboxylation at 110° would be 11.9 min. Thus the decarboxylation in 1.0 *M* HCl at 110° would be over in about 2 hr. Preliminary experiments in this laboratory indicate that the pH–rate profile for the decarboxylation of α-methylaminomalonate resembles that of unsubstituted aminomalonate (see Thanassi[6]) and that the most sensitive species is the neutral species, $NH_3^+CCH_3(COO^-)COOH$, rather than the positively charged species, $NH_3^+CCH_3(COOH)_2$. Hence, by carrying out the decarboxylation in a buffer favoring the neutral species, the reaction time might be further decreased by a factor of 2 or 3.

(24) J. M. Manning, *J. Amer. Chem. Soc.*, **92**, 7449 (1970).

(25) Manning[24] found an isotope effect of 3.5 during the racemization of L-alanine in tritiated HCl. Similarly, Denkewalter, *et al.*,[26] found an isotope effect of 4.6 in the incorporation of tritium into the α position of amino acids during peptide synthesis. These compare with isotope effects of 2.4–3.6 found in the present study.

(26) R. G. Denkewalter, H. Schwam, R. G. Strachan, T. E. Beesley, D. F. Weber, E. F. Schoenewaldt, H. Barkemeyer, W. J. Paleveda, Jr., T. A. Jacob, and R. Hirschmann, *J. Amer. Chem. Soc.*, **88**, 3163 (1966).

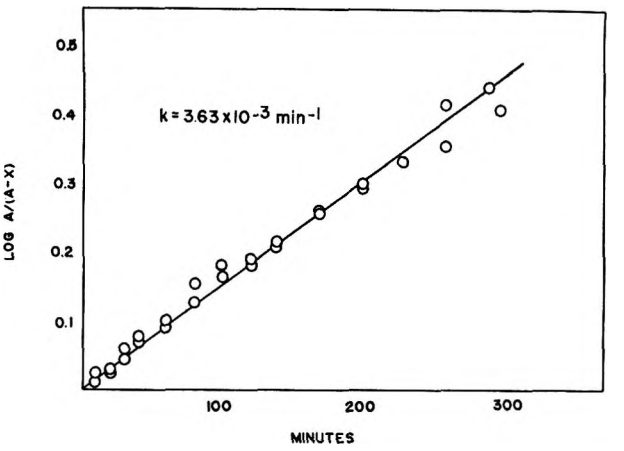


Figure 1.—First-order plot for decarboxylation of α-methylaminomalonic acid in 1.0 *M* HCl (T = 70°).

In addition to their use as metabolic tracer compounds, readily available, highly radioactive, α-tritiated amino acids can be of great help in the determination of racemization of amino acids during synthesis of peptides. The procedure would be essentially the converse of that employed by Denkewalter, *et al.*[26] That is, instead of measuring the incorporation of solvent tritium *into* the amino acids of the peptide, one would simply measure the amount of isotope coming *out* of the amino acids into the solvent. This has a considerable technical advantage in that no separations are required except the removal of the solvent in order to count it. Also the optically active L isomers of the amino acids need not be used in control syntheses carried out in order to test for the extent of racemization since those experimental conditions causing racemization of amino acids operate equally on the D and L isomers and hence will cause the release of tritium from the α positions of both isomers of the racemate into the medium.

Registry No.—α-Methylaminomalonic acid, 26767-88-4; α-deuterio-DL-alanine, 31024-91-6; α-deuterio-DL-phenylalanine, 14246-24-3; α-tritio-DL-glutamic acid, 24125-49-3; α-tritio-DL-aspartic acid, 31024-94-9; α-tritio-DL-alanine, 31024-95-0; tritioglycine, 22712-83-0.

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Amino Acids and Peptides. XXVII.[1] Synthesis of a Decapeptide Sequence (A_1–A_{10}) of Rubredoxin

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A synthesis is described for the protected N-terminal decapeptide (A_1–A_{10}) fragment of rubredoxin, methyl N^{α}-*tert*-butyloxycarbonyl-L-methionyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate.

The simplest of the nonheme iron proteins that are so important in numerous biological electron-transport reactions are the rubredoxins.[2,3] The rubredoxin from *Micrococcus aerogenes* possesses a linear array of 53 amino acid residues and contains one iron that is bound to the four cysteines in the molecule (Figure 1).[4] The chelate structure of this protein has been investigated by various methods, but the results are not definitive.[5–8] A proposed archetype correlation between the rubredoxins and the ferredoxins is of great interest,[9] particularly in view of the fundamental, evolutionary nature of the ferredoxins.[10] Thus, a synthesis of the "active-site" of rubredoxin, and, ultimately, of the complete protein would be of general value.

Rubredoxin contains glycyl residues at positions 10, 19, 27, 42, and 44; therefore, it was decided to prepare smaller fragments that could be united in these locations without fear of racemization. Alternatively, prolyl residues at positions 15, 20, 23, and 39 would provide a similar protective feature. Since two of the four cysteines occur before position 10, it is necessary to develop protecting groups on these particular residues that are compatible with the remainder of the molecule. In view of these considerations, the synthesis of the protected N-terminal decapeptide (A_1–A_{10}) of rubredoxin is now described at this time (Chart I).

Beginning at the *C*-carboxyl end, N^{α}-benzyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteine (I)[11,12] and methyl glycinate hydrochloride (II)[13] were coupled with *N*,*N*′-dicyclohexylcarbodiimide (DCCI)[14] to yield methyl N^{α}-benzyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (III). Treatment of the dipeptide III with hydrogen bromide in acetic acid cleaved the N^{α}-protecting group and furnished the corresponding hydrobromide salt IV. Next, a DCCI condensation between N^{α}-benzyloxycarbonyl-L-threonine (V)[15] and methyl L-leucinate hydrochloride (VI)[16] afforded methyl N^{α}-benzyloxycarbonyl-L-threonyl-L-leucinate (VII). Removal of the N^{α} group of dipeptide VII through catalytic hydrogenation produced oily methyl L-threonyl-L-leucinate (VIII). The second cysteinyl subunit was now introduced in the form of N^{α}-*tert*-butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteine (IX), purified as the corresponding dicyclohexylammonium salt X. This particular derivative is new and should have many applications in the peptide field. The acid IX and the amine VIII were joined by DCCI to give methyl N^{α}-*tert*-butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucinate (XI). Mild base hydrolysis of the tripeptide XI then formed the corresponding acid XII. A mixed anhydride reaction[17] between XII and IV supplied methyl N^{α}-*tert*-butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (XIII). Addition of trifluoroacetic acid to the pentapeptide XIII eliminated the N^{α} group and generated the corresponding trifluoroacetate salt XIV.

Turning to the next major subunit, methyl γ-*tert*-butyl-L-glutamate hydrochloride (XV)[18] and N^{α}-benzyloxycarbonyl-L-phenylalanine (XVI)[19] were coupled by DCCI to obtain methyl N^{α}-benzyloxycarbonyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XVII). Hydrogenolysis of the N^{α}-protecting group led to the corresponding amine XVIII. N^{α}-Benzyloxycarbonyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysine (XIX),[20,21] prepared by a different procedure and purified as the dicyclohexylammonium salt XX,[13] was incorporated into XVIII with the aid of DCCI to yield methyl N^{α}-benzyloxycarbonyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XXI). Hydrogenolysis of the N^{α} group furnished the corresponding amine XXII, which on addition of *p*-nitrophenyl N^{α}-benzyloxycarbonyl-L-glutaminate (XXIII)[22] afforded methyl N^{α}-benzyloxycarbonyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XXIV). Removal of the N^{α} group by hydrogenation produced the tetrapeptide amine XXV. A mixed anhydride reaction[17] between compound XXV

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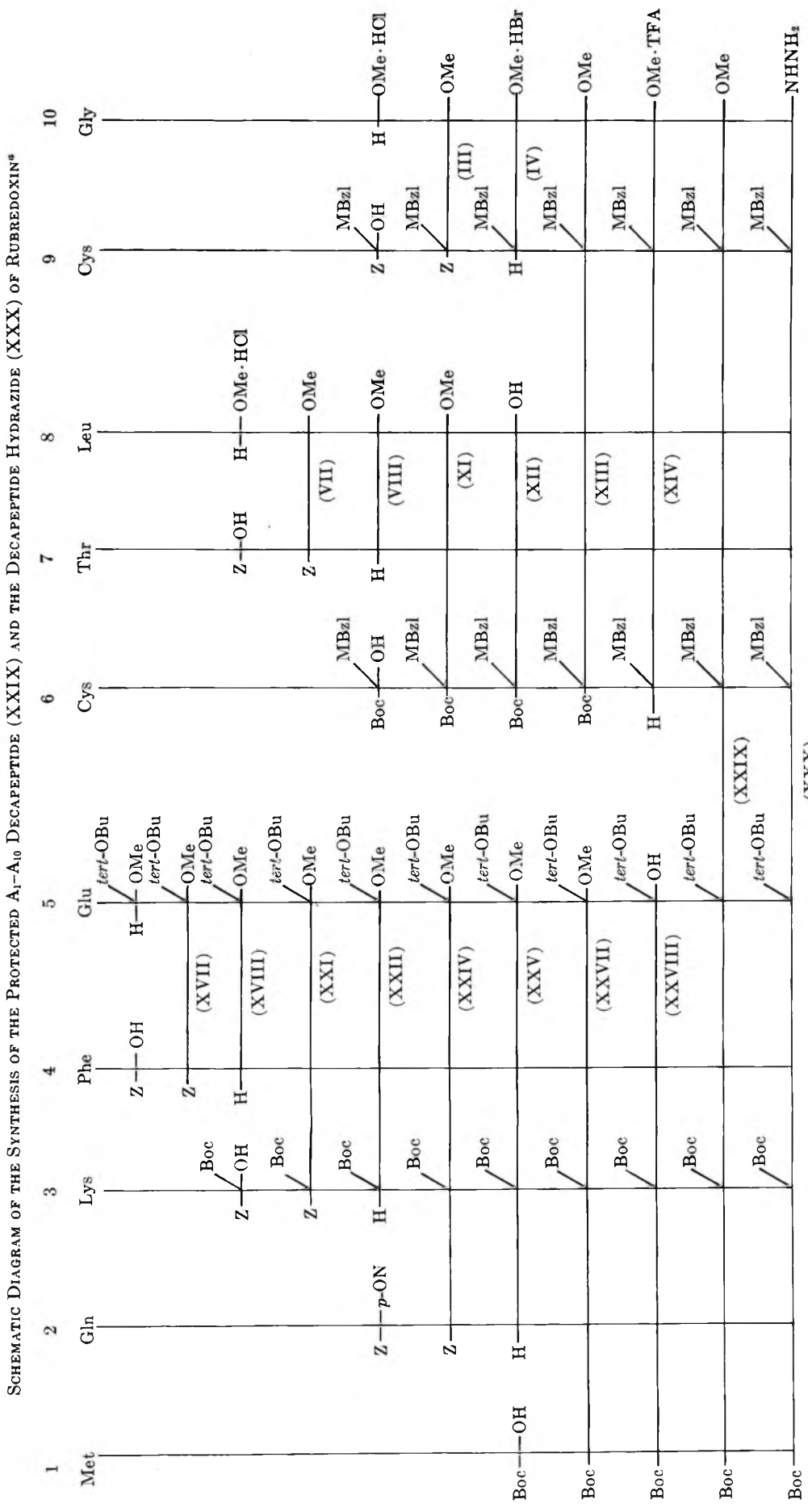
CHART I

SCHEMATIC DIAGRAM OF THE SYNTHESIS OF THE PROTECTED A_1–A_{10} DECAPEPTIDE (XXIX) AND THE DECAPEPTIDE HYDRAZIDE (XXX) OF RUBREDOXIN[a]



[a] Boc, *tert*-butyloxycarbonyl; Z, benzyloxycarbonyl; HBr, hydrobromide; HCl, hydrochloride; TFA, trifluoroacetate; MBzl, *p*-methoxybenzyl; *tert*-OBu, *tert*-butyl ester; OMe, methyl ester; $NHNH_2$, hydrazide; *p*-ON, *p*-nitrophenyl.

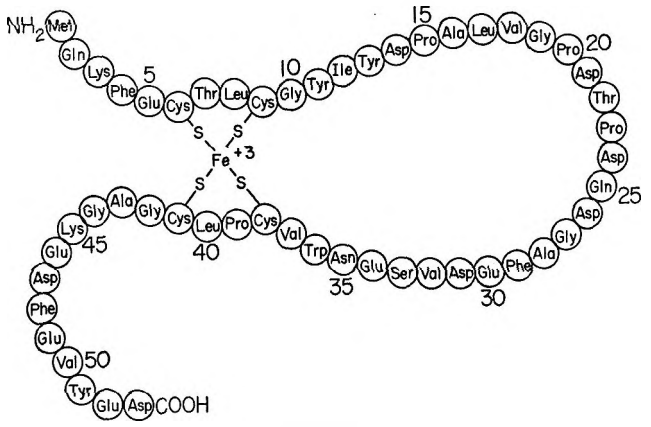


Figure 1.—The amino acid sequence of the rubredoxin from *Micrococcus aerogenes*.

and N^{α}-*tert*-butyloxycarbonyl-L-methionine(XXVI),[20,23] gave methyl N^{α}-*tert*-butyloxycarbonyl-L-methionyl-L-glutaminyl-N'-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XXVII). Mild base hydrolysis of the pentapeptide XXVII then formed the corresponding acid XXVIII.

Finally, a DCCI condensation between XXVIII and XIV in the presence of *N*-hydroxysuccinimide[24] supplied the desired decapeptide, methyl N^{α}-*tert*-butyloxycarbonyl-L-methionyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (XXIX). Addition of hydrazine to the methyl ester XXIX resulted in the formation of the corresponding hydrazide XXX. Further work in this series is in progress and will be discussed at a future date.

Experimental Section[25]

Methyl N^{α}-Benzyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (III).—N^{α}-Benzyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteine (3.75 g, 0.01 mol) and methyl glycinate hydrochloride (1.25 g, 0.01 mol) in dichloromethane (60 ml) was treated with triethylamine (1.01 g, 0.01 mol) and the solution was cooled to $-10°$. N,N'-Dicyclohexylcarbodiimide (2.06 g, 0.01 mol) was added and the resulting mixture was stirred vigorously overnight, while slowly warming to room temperature. The solvent was evaporated and the residue dissolved in ethyl acetate (200 ml). After filtration of the N,N'-dicyclohexylurea the solution was washed with dilute hydrochloric acid (1 *N*, two 60-ml portions), water (one 60-ml portion), saturated sodium bicarbonate solution (two 60-ml portions), and water (two 60-ml portions), and then dried and evaporated. The residue was crystallized from ethyl acetate–petroleum ether and recrystallized from carbon tetrachloride (4.02 g, 90%): mp 104–105°; $[\alpha]^{25.0}D$ $-57.9°$ (*c* 1.00, *N*,*N*-dimethylformamide).

Anal. Calcd for $C_{22}H_{26}N_2SO_6$ (446.53): C, 59.19; H, 5.87; N, 6.27; S, 7.17. Found: C, 59.88; H, 5.98; N, 6.24; S, 7.17.

Methyl *S*-*p*-Methoxybenzyl-L-cysteinylglycinate Hydrobromide (IV).—A solution of methyl N^{α}-benzyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (5.36 g, 0.012 mol) in acetic acid (15 ml) was mixed with 32% hydrogen bromide in acetic acid (15 ml). After 1 hr ether (300 ml) was added with swirling and the precipitated salt was collected and dried over sodium hydroxide in a vacuum desiccator for 12 hr.

Methyl N^{α}-Benzyloxycarbonyl-L-threonyl-L-leucinate (VII).—N^{α}-Benzyloxycarbonyl-L-threonine (5.07 g, 0.02 mol) and methyl L-leucinate hydrochloride (3.63 g, 0.02 mol) in dichloromethane (100 ml) was treated with triethylamine (2.02 g, 0.02 mol) and the solution was cooled to $-10°$. N,N'-Dicyclohexylcarbodiimide (4.12 g, 0.02 mol) was added and the resulting mixture was stirred vigorously overnight, while slowly warming to room temperature. The reaction was worked up in the usual fashion to obtain an oil, which solidified on standing (7.00 g, 92%): mp 48–53°; $[\alpha]^{25.0}D$ $-36.2°$ (*c* 1.25, chloroform).

Anal. Calcd for $C_{18}H_{28}N_2O_6$ (380.45): C, 59.98; H, 7.42; N, 7.36. Found: C, 60.14; H, 7.44; N, 7.22.

Methyl L-Threonyl-L-leucinate (VIII).—Oily methyl N^{α}-benzyloxycarbonyl-L-threonyl-L-leucinate (8.36 g, 0.022 mol) in methanol (300 ml) containing 10% palladium-on-charcoal catalyst (0.80 g) was hydrogenated for 5 hr. The catalyst was removed by filtration and evaporation of the solvent gave an oil (5.20 g, 96%): R_f 0.24 [acetic acid–butanol–water (1:4:1); ninhydrin positive].

N^{α}-*tert*-Butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteine (IX).—*tert*-Butyl azidoformate (21.45 g, 0.15 mol) was added dropwise over a 30-min period to a stirred suspension of *S*-*p*-methoxybenzyl-L-cysteine (24.10 g, 0.10 mol) in N,N'-dimethylformamide (350 ml) and 1,1,3,3-tetramethylguanidine (23.0 g). A clear solution was obtained on the addition of a few drops of dilute sodium hydroxide (1 *N*). After 4 days at room temperature, the solvent was evaporated and the residue was worked up in the usual fashion to obtain an oil (30.7 g, 90%).

N^{α}-*tert*-Butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteine Dicyclohexylammonium Salt (X).—A solution of N^{α}-*tert*-butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteine in ether on treatment with dicyclohexylamine yielded the corresponding dicyclohexylammonium salt. Crystallization from ethyl acetate–petroleum ether afforded white needles: mp 132°; $[\alpha]^{25.0}D$ $-14.6°$ (*c* 1.00, chloroform).

Anal. Calcd for $C_{28}H_{46}N_2SO_5$ (522.75): C, 64.34; H, 8.87; N, 5.36; S, 6.74. Found: C, 63.90; H, 8.30; N, 5.39; S, 6.58.

Methyl N^{α}-*tert*-Butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucinate (XI).—A solution of N^{α}-*tert*-butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteine (7.17 g, 0.021 mol) and freshly prepared methyl L-threonyl-L-leucinate (5.17 g, 0.021 mol) in dichloromethane (150 ml) was cooled to $-10°$ and N,N'-dicyclohexylcarbodiimide (4.33 g, 0.021 mol) was added and the resulting mixture was vigorously stirred overnight, while slowly warming to room temperature. The reaction was worked up in the usual fashion to obtain a residue, which was purified by silica gel column chromatography employing chloroform–methanol (97:3) as the developer. The resulting foam could not be crystallized (9.10 g, 76%): mp 38–42°; $[\alpha]^{25.0}D$ $-40.5°$ (*c* 1.00, chloroform).

Anal. Calcd for $C_{27}H_{43}N_3SO_8$ (569.73): C, 56.91; H, 7.61; N, 7.38; S, 5.63. Found: C, 57.17; H, 7.67; N, 7.40; S, 5.33.

N^{α}-*tert*-Butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucine (XII).—The aforementioned tripeptide (6.84 g, 0.012 mol) was treated with a solution of sodium hydroxide (1 *N*, 15 ml) in methanol (50 ml) for 30 min, and then water (40 ml) was added and the bulk of the methanol was removed by evaporation. After washing with ether (two 30-ml portions), acidification of the aqueous phase with citric acid solution precipitated an oily product. This material was taken into ethyl acetate (three 75-ml portions) and the combined organic phases was washed with water (two 75-ml portions) and dried. Evaporation gave a white solid (5.82 g, 87%).

Methyl N^{α}-*tert*-Butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucinyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (XIII).—A solution of *N*-*tert*-butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucine (5.56 g, 0.01 mol) in tetrahydrofuran (30 ml) was cooled to $-20°$ and treated in turn with *N*-methylmorpholine (1.01 g, 0.01 mol) and isobutyl chloroformate (1.37 g, 0.01 mol). After 4 min, a solution of methyl *S*-*p*-methoxybenzyl-L-cysteinylglycinate in tetrahydrofuran (40 ml) and water (5 ml), freshly prepared by dissolving the corresponding hydrobromide IV in tetrahydrofuran (20 ml) and trimethylamine (3 ml) and evaporating to dryness, was added and stirred for 30 min at $-20°$, followed by allowing the reaction to warm to room temperature over 2 hr. The solvent was evapo-

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(25) All melting points were determined on a Reichert "Thermopan" unit and are uncorrected. Evaporations were performed under reduced pressure (water pump) with a rotatory apparatus at minimum temperature, while high-boiling solvents were removed at vacuum pressure (0.2–0.5 mm). Magnesium sulfate was used for drying purposes. Acetonitrile and *N*,*N*-dimethylformamide were spectroscopic quality; other solvents were reagent grade and petroleum ether had bp 30–60°. Microanalyses were furnished by Galbraith Laboratories, Knoxville, Tenn.

rated and the residue was dissolved in ethyl acetate (300 ml) and worked up in the usual fashion. The product was purified by silica gel column chromatography employing chloroform–methanol (97:3) as the developer. The resulting foam could not be crystallized (6.63 g, 78%): mp 112–115°; $[\alpha]^{25.0}D$ −55.1° (c 1.00, chloroform).

Anal. Calcd for $C_{40}H_{59}N_5S_2O_{11}$ (850.08): C, 56.52; H, 7.00; N, 8.24; S, 7.54. Found: C, 56.59; H, 7.30; N, 8.14; S, 7.96.

Methyl *S*-*p*-Methoxybenzyl-L-cysteinyl-L-threonyl-L-leucinyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate Trifluoroacetate (XIV).—Methyl N^{α}-*tert*-butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucyl-*S*-*p*-methoxybenzyl-L-cysteineglucinate (1.36 g, 0.0016 mol) was dissolved in trifluoroacetic acid (10 ml). After 30 min at room temperature, the solution was evaporated and the residue was dried in a vacuum desiccator over sodium hydroxide for 5 hr.

Methyl N^{α}-Benzyloxycarbonyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XVII).—A solution of N^{α}-benzyloxycarbonyl-L-phenylalanine (2.99 g, 0.01 mol) and methyl γ-*tert*-butyl-L-glutamate hydrochloride (2.54 g, 0.01 mol) in dichloromethane (75 ml) was treated with triethylamine (1.01 g, 0.01 mol) and cooled to −10°. *N*,*N*′-Dicyclohexylcarbodiimide (2.06 g, 0.01 mol) was added and the resulting mixture was stirred vigorously overnight, while slowly warming to room temperature. The reaction was worked up in the usual fashion to obtain an oil, which solidified on standing (4.88 g, 98%): mp 67–68°; $[\alpha]^{25.0}D$ +10.0° (c 2.00, chloroform).

Anal. Calcd for $C_{27}H_{34}N_2O_7$ (498.59): C, 65.06; H, 6.87; N, 5.62. Found: C, 65.86; H, 7.11; N, 5.80.

Methyl L-Phenylalanyl-γ-*tert*-butyl-L-glutamate (XVIII).—A solution of methyl N^{α}-benzyloxycarbonyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (5.98 g, 0.012 mol) in methanol (250 ml) containing 10% palladium-on-charcoal catalyst (0.80 g) was hydrogenated for 2 hr. The catalyst was removed by filtration and evaporation of the solvent gave a thick oil (3.71 g, 85%): R_f 0.57 [chloroform–methanol (95:5); ninhydrin positive].

N^{α}-Benzyloxycarbonyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysine (XIX).—A mixture of N^{α}-benzyloxycarbonyl-L-lysine (28.03 g, 0.10 mol) in *N*,*N*′-dimethylformamide (220 ml) was warmed to 40° and then cooled to room temperature, and 1,1,3,3-tetramethylguanidine (23.0 g) was added, followed by *tert*-butyl azidoformate (21.45 g, 0.15 mol) dropwise over 30 min. The clear solution stood for 4 days at room temperature, after which the solvent was evaporated and the residue was partitioned between ethyl acetate (300 ml) and citric acid solution (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the combined organic phases were washed with water (three 100-ml portions), dried, and evaporated to give a thick oil (35.0 g, 92%).

N^{α}-Benzyloxycarbonyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysine Dicyclohexylammonium Salt (XX).—A sample of the aforementioned compound was treated with dicyclohexylamine in the usual fashion to obtain the corresponding salt, which was crystallized from 2-propanol: mp 154–155°.

Methyl N^{α}-Benzyloxycarbonyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XXI).—A solution of methyl L-phenylalanyl-γ-*tert*-butyl-L-glutamate (3.64 g, 0.01 mol) and N^{α}-benzyloxycarbonyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysine (3.80 g, 0.01 mol) in dichloromethane (150 ml) was cooled to −10°. *N*,*N*′-Dicyclohexylcarbodiimide (2.06 g, 0.01 mol) was added and the resulting mixture was stirred vigorously overnight, while slowly warming to room temperature. The reaction was worked up in the usual fashion and the product was crystallized from ethyl acetate–ether (5.96 g, 86%): mp 126–127°; $[\alpha]^{25.0}D$ −25.6° (*c* 1.00, chloroform).

Anal. Calcd for $C_{38}H_5N_4O_{10}$ (726.88): C, 62.79; H, 7.49; N, 7.71. Found: C, 63.21; H, 7.55; N, 7.22.

Methyl N^{ϵ}-*tert*-Butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XXII).—A solution of methyl N^{α}-benzyloxycarbonyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (7.27 g, 0.01 mol) in methanol (200 ml) containing 10% palladium-on-charcoal catalyst (0.70 g) was hydrogenated for 15 hr. The catalyst was removed by filtration and evaporation of the solvent left a residue (5.39 g, 91%): R_f 0.57 [acetic acid–butanol–water (1:4:1); ninhydrin positive].

Methyl N^{α}-Benzyloxycarbonyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XXIV).—A solution of *p*-nitrophenyl N^{α}-benzyloxycarbonyl-L-glutamine (4.42 g, 0.011 mol) and methyl N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (5.33 g, 0.009 mol) in *N*,*N*′-dimethylformamide (60 ml) was allowed to stand for 4 days at room temperature. The solvent was evaporated and the residue was crystallized from methanol (5.85 g, 76%): mp 219–221°; $[\alpha]^{25.0}D$ −26.1° (c 2.00, *N*,*N*′-dimethylformamide).

Anal. Calcd for $C_{43}H_{62}N_6O_{12}\cdot{}^1/_2H_2O$ (864.03): C, 59.75; H, 7.35; N, 9.73. Found: C, 59.75; H, 7.00; N, 9.30.

Methyl L-Glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XXV).—A solution of methyl N^{α}-benzyloxycarbonyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (5.99 g, 0.007 mol) in methanol (350 ml) containing 10% palladium on charcoal (0.80 g) was hydrogenated for 24 hr. The catalyst was removed by filtration and evaporation of the solvent left a residue (4.64 g, 92%): R_f 0.53 [acetic acid–butanol–water (1:4:1); ninhydrin positive].

N^{α}-*tert*-Butyloxycarbonyl-L-methionine (XXVI).—L-Methionine (44.70 g, 0.30 mol) was converted into N^{α}-*tert*-butyloxycarbonyl-L-methionine, following the procedure described for XIX, to afford a syrup (75.00 g, 100%).

Methyl N^{α}-*tert*-Butyloxycarbonyl-L-methionyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (XXVII).—A solution of N^{α}-*tert*-butyloxycarbonyl-L-methionine (1.60 g, 0.0064 mol) in tetrahydrofuran (30 ml) was cooled to −20° and treated with *N*-methylmorpholine (0.65 g, 0.0064 mol), followed by isobutyl chloroformate (0.87 g, 0.0064 mol). After 4 min, a solution of methyl N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (4.61 g, 0.0064 mol) in *N*,*N*′-dimethylformamide (40 ml) was added and the reaction was stirred for 30 min at −20°, then allowed to slowly warm to room temperature, and stirred for another 2 hr. The solvent was evaporated and the residue was crystallized from methanol (5.12 g, 84%): mp 223–225°; $[\alpha]^{25.0}D$ −22.5° (c 1.00, *N*,*N*′-dimethylformamide).

Anal. Calcd for $C_{45}H_{73}N_7SO_{13}$ (952.20): C, 56.76; H, 7.73; N, 10.30; S, 3.37. Found: C, 57.43; H, 7.82; N, 10.30; S, 3.01.

N^{α}-*tert*-Butyloxycarbonyl-L-methionyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamic Acid (XXVIII).—A solution of methyl N^{α}-*tert*-butyloxycarbonyl-L-methionyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamate (1.90 g, 0.002 mol) in methanol (30 ml) and sodium hydroxide (1 *N*, 2 ml) was stirred for 2 hr. After dilution with water (30 ml) the methanol was evaporated, and the mixture was acidified with citric acid solution. The precipitated product was filtered, washed, and purified from methanol–water (1.61 g, 86%): mp 212–215; $[\alpha]^{25.0}D$ −20.6° (c 1.00, *N*,*N*′-dimethylformamide).

Anal. Calcd for $C_{44}H_{71}N_7SO_{13}$ (938.17): C, 56.33; H, 7.63; N, 10.45; S, 3.42. Found: C, 55.94; H, 7.69; N, 10.35; S, 3.40.

Methyl N^{α}-*tert*-Butyloxycarbonyl-L-methionyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (XXIX).—The trifluoroacetate salt XIV was dissolved in tetrahydrofuran (15 ml), treated with trimethylamine (2.0 ml), and evaporated to dryness. Pentapeptide acid XXVIII (1.50 g, 0.0016 mol) and *N*-hydroxysuccinimide (0.28 g, 0.0024 mol) were dissolved in *N*,*N*′-dimethylformamide (20 ml), cooled to −10°, and treated with *N*,*N*′-dicyclohexylcarbodiimide (0.33 g, 0.0016 mol), followed by the above residue in *N*,*N*′-dimethylformamide (10 ml). After stirring for 1 hr at −10°, the reaction was allowed to slowly warm to room temperature followed by stirring for 4 days. The solvent was evaporated and the residue was triturated under water and washed with a saturated solution of sodium bicarbonate. Purification from methanol gave a solid (1.72 g, 64%): mp 244–246° dec; $[\alpha]^{25.0}D$ −31.1° (c 1.00, *N*,*N*′-dimethylformamide).

Anal. Calcd for $C_{79}H_{120}N_{12}S_3O_{21}$ (1670.12): C, 56.82; H, 7.24; N, 10.07; S, 5.76. Found: C, 56.52; H, 7.25; N, 9.84; S, 5.90.

N^{α}-*tert*-Butyloxycarbonyl-L-methionyl-L-glutaminyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanyl-γ-*tert*-butyl-L-glutamyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate Hydrazide (XXX).—The aforementioned decapeptide XXIX (0.251 g, 0.00015 mol) was dissolved in methanol (150 ml) and *N*,*N*′-dimethylformamide (1.5 ml) and treated with hydrazine hydrate (90%, 3 ml). The reaction was stirred for 1.5 hr and then the solvent was evaporated, and the product was precipitated with water. Crystallization from

methanol gave a solid (0.228 g, 91%): mp 248° (slow decomposition); $[\alpha]^{25.0}D$ −30.6° (*c* 0.50, *N,N'*-dimethylformamide).

Anal. Calcd for $C_{78}H_{120}N_{14}S_3O_{20}$ (1670.13): C, 56.01; H, 7.24; N, 11.74; S, 5.76. Found: C, 56.02; H, 7.19; N, 11.79; S, 5.52.

Registry No.—III, 31025-11-3; VII, 31025-12-4; VIII, 31025-13-5; X, 31025-14-6; XI, 31025-15-7; XIII, 31020-53-8; XVII, 31025-16-8; XVIII, 31025-17-9; XX, 2212-76-2; XXI, 31025-19-1; XXII, 31025-20-4; XXIV, 31020-54-9; XXV, 31020-55-0; XXVII, 31020-56-1; XXVIII, 31020-57-2; XXIX, 31020-58-3; XXX, 31020-59-4.

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Synthesis of 2-Thiouridine and 2-Thioisouridine by Mercuri Procedure[1,2]

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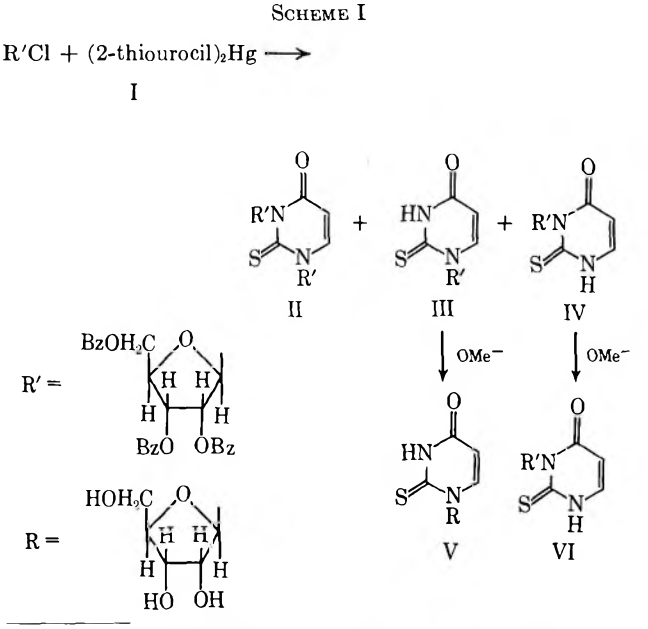
Contrary to an earlier report, (2-thiouracil)$_2$Hg (I) can be obtained from 2-thiouracil and $HgCl_2$. The compound I on treatment with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride formed one disubstituted (II) and two monosubstituted products (III and IV). The compounds III and IV on debenzoylation with sodium methoxide formed 2-thiouridine (V) and 2-thioisouridine (VI), respectively. Compounds V and VI were converted into uridine and isouridine, respectively, by cyanogen bromide. The pK_a's of both V and VI are 8.1.

The facile formation and cleavage of disulfide bonds involving 2-thio- and 4-thiopyrimidines in tRNA has been invoked on several occasions to explain biochemical mechanisms.[3-6] Although 2-thiouracil[7] and 4-thiouridine[8,9] form disulfides readily after iodine treatment, a similar oxidation of 2-thiouridine derivatives was not observed by at least two groups of workers.[10,11] It is possible that such oxidation may take place easily when 2-thiouridine moieties are parts of a macromolecule. In order to study the properties of 2-thiouridines, particularly the formation of a disulfide on oxidation, the chemical synthesis of the compound was undertaken. Of the five different methods of synthesis of 2-thiouridine,[12-16] the one reported by Lee and Wigler[16] based on mercuri condensation was reinvestigated. Several discrepancies were observed, and the characterization and properties of the intermediate blocked nucleosides and the final products are reported.

Lee and Wigler[16] were unable to prepare (2-thiouracil)$_2$Hg (I) from 2-thiouracil and $HgCl_2$ in aqueous solution by the method of Fox, *et al.*[17] In my hands, however, 2-thiouracil did form with mercuric chloride the desired (2-thiouracil)$_2$Hg in 2:1 stoichiometry and in a quantitative yield. It is noteworthy that (2-methylthiouracil)$_2$Hg was previously obtained in high yield directly from 2-methylthiouracil by Scannell and Allen.[18] However, Lee and Wigler[16] claim to have prepared I in 83% yield by prior acetylation of 2-thiouracil followed by mercuric chloride treatment: mp 282–286° dec, λ_{max} (ethanol) 294 nm. On the other hand, I have been unable to prepare 2-thiouracil·HgCl salt using equimolar amounts of 2-thiouracil and $HgCl_2$; elemental analysis of the product indicated the formation of mixtures. The addition of mercuric bromide in this mercuri condensation reaction was not essential and did not improve the yield of 2-thiouridine.

The treatment of I with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride yielded a mixture of blocked nucleosides II, III, and IV separable by chromatography on silicic acid (Scheme I). On debenzoylation with sodium methoxide in methanol, IV gave 2-thioisouridine (VI), identified by the similarities of its uv absorption spectra

SCHEME I



(1) This research was sponsored by the U. S. Atomic Energy Commission under contract with the Union Carbide Corp.

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with those of 3-ethyl-2-thiouracil.[19] On treatment with cyanogen bromide, VI was converted into isouridine. Cyanogen bromide reaction presumably goes through a thiocyanate intermediate and appears to be superior to other methods in terms of yields and mild conditions.[20] The earlier observation[16] that, unlike 2-thiouridine, 2-thioisouridine cannot be converted into isouridine by chloroacetic acid has been confirmed; this treatment results in the cleavage of the glycosyl linkage. 2-Thioisouridine has been assigned the β configuration on the basis of the "trans rule" proposed by Baker, *et al.*[21] This assignment has now been confirmed by X-ray crystallography of the compound by Einstein, *et al.*[22] The compound III, on debenzoylation with sodium methoxide in methanol, yields 2-thiouridine, identified spectrophotometrically by the published spectral data on the compound synthesized by other methods[13-15] (Figure 1). An X-ray crystallographic analysis of 2-thiouridine has been completed and will be reported shortly by Hawkinson, *et al.*, of this laboratory. Compound II has been tentatively identified as 1,3-di(2′,3′,-5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-thiouracil. Attempted hydrolysis of II by sodium methoxide in methanol led to a mixture of products among which 2-thiouridine and 2-thiouracil have been identified. No S-substituted or N-3-substituted derivative could be identified. Disubstitution on N-1 and O^4 in the case of II was eliminated as no 2-thiocytidine could be found on treatment of II with ammonia. The infrared absorption spectra of all three compounds are very similar except in the region of 1400–1550 cm^{-1}.

The total yield of blocked nucleosides by this procedure is 32% of theory based on the halogenose. This is comparable with the 30–50% yield of blocked ribothymidine by the same method.[23] For the preparation of 2-thiouridine, the recently announced silyl procedure of Vorbrüggen, *et al.*[24] appears to be the method of choice (yield 70%). The mercuri procedure has its merit in the fact that it yields also the 2-thioisouridine, which is otherwise inaccessible.

The pK_a of 2-thiouridine has been spectrophotometrically determined to be 8.1 (lit.[16] 8.8) following the procedure described by Albert and Sarjeant.[25] The same value of 8.1 was also obtained with a sample of 2-thiouridine synthesized by the silyl procedure[24] (a generous gift from Dr. Vorbrüggen, Hauptlaboratorium der Schering AG, Berlin, Germany). Lee and Wigler's preparation of 2-thiouridine may not have been pure as indicated by the considerably low value of optical rotation reported by them[16] (see Experimental Section). This may be the reason for the higher pK_a value obtained by them. In the case of 2-thiouridine, 2-thioisouridine, and uridine, there is a lowering of about

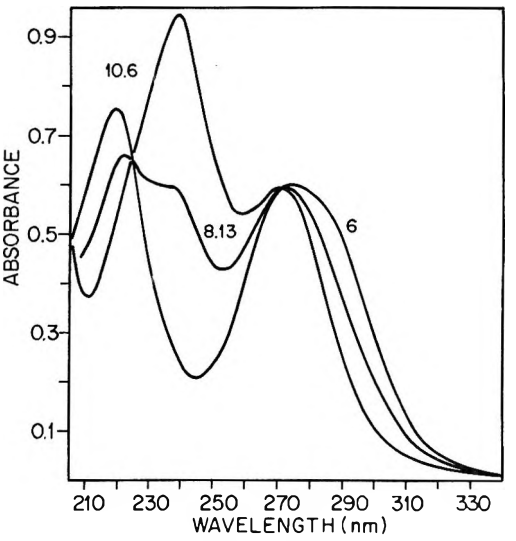

Figure 1.—Uv absorption spectra of 2-thiouridine at pH 6, 8.13, and 10.6.

0.5 in the pK_a values of the ribosyl compounds compared with their alkyl analogs, indicating the acid-strengthening effect of the ribosyl group, whereas in the case of 4-thiouridine there is practically no difference. These differences have sometimes been attributed to the possible interaction between the sugar (2′ or 5′) hydroxyl group and the O^2 of the pyrimidine ring.[26,27] However, the X-ray crystallography of 2-thiouridine and 2-thioisouridine does not shed any light on this problem.

Experimental Section

Melting points were observed in a Thomas-Hoover apparatus and are uncorrected. Thin layer chromatography was carried out on E. Merck tlc plates and descending chromatography on Whatman paper using the following solvent systems: (A) 3% ammonium chloride; (B) 0.1 *M* phosphate buffer (pH 6.8)–saturated ammonium sulfate–1-propanol (100:60:2 by volume); (C) 2-propanol–concentrated ammonia–water (60:10:30 by volume); (D) 1-butanol–water (86:14 by volume); and (E) benzene–ether (1:1 by volume). Spots on tlc silica gel plates were visualized in iodine vapor. 2-Thiouracil was purchased from Aldrich Chemical Co. and was found to be chromatographically homogeneous (Whatman 3 MM, solvent A, R_f 0.64). The ultraviolet absorption spectra were taken on a Cary recording spectrophotometer Model 14 PM. Spectra were recorded for the same solution in the same cuvette after addition of small amounts of concentrated acid, alkali, or buffer solutions to adjust the pH. Infrared spectra were recorded for 0.5% dispersions of the sample in potassium bromide pellets in a Perkin-Elmer infrared spectrophotometer Model 257. Optical rotations were determined on a Rudolph polarimeter.

Di-2-thiouracilylmercury (I).—2-Thiouracil, 12.81 g (0.1 mol), was dissolved in 100 ml of 1 *N* sodium hydroxide solution and 900 ml of warm water at 50°. A solution of mercuric chloride, 13.6 g (0.05 mol) in 125 ml of ethanol, was added rapidly with stirring. The precipitate was allowed to stand for 1 hr and then filtered with suction. It was washed with water until the filtrate was free from chloride. The residue was dried *in vacuo* over phosphorus pentoxide; the yield of di-2-thiouracilylmercury was quantitative. A sample for analysis was prepared by drying the material over P_2O_5 at 100° and 0.01 mm for 2 hr.

Anal. Calcd for $C_8H_6N_4O_2S_2Hg$: C, 21.12; H, 1.33; N, 12.32. Found: C, 21.14; H, 1.29; N, 12.43.

The compound I melts at 271° dec with darkening between 250–260°. It dissociates completely in 0.1 *N* hydrochloric acid into 2-thiouracil and Hg^{2+}, as evident from its molar extinction

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and uv absorption spectrum: ϵ_{273} in 0.1 *N* hydrochloric acid solution, 28,240 (ϵ_{273} of mercuric chloride in 0.1 *N* HCl is negligible) and ϵ_{273} of 2-thiouracil in 0.1 *N* HCl 14,180. The compound is stable at pH 12. Spectral characteristics: pH 12, max 280 nm, min 262 nm; pH 2, max 273 and 212.5 nm, min 240 nm; in ethanol, max 296 nm, min 262 nm.

Condensation of Di-2-thiouracilylmercury with 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl Chloride.—A suspension of 4.549 g (0.01 mol) of finely ground di-2-thiouracilylmercury (I) in 350 ml of dry xylene was placed in a 1-l. three-necked flask fitted with a mechanical stirrer, dropping funnel, and a distillation head. The flask was heated in an oil bath and 100 ml of xylene was distilled off. The ribosyl chloride prepared from 10.09 g (0.02 mol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose by the method of Thomas, *et al.*,[28] was added through the separatory funnel rapidly with vigorous stirring. The distillation head and the separatory funnel were replaced by a reflux condenser and a stopper, and the reaction mixture was refluxed gently for 1 hr; refluxing longer led to lower yields. The reaction mixture was cooled somewhat and filtered hot with suction. The filtrate was evaporated to about 50 ml in a rotary evaporator at 30° and treated with 500 ml of petroleum ether (bp 40–50°). It was kept at 4° for several hours. The precipitate was collected, dissolved in 50 ml of chloroform, and washed twice with 50 ml of 30% w/w aqueous potassium iodide and twice with 50 ml of water. The chloroform layer was dried with anhydrous sodium sulfate and filtered. The filtrate was evaporated to dryness in a rotary evaporator at 30°; the weight of the residue was 9.2 g.

The crude residue, 4.6 g, was chromatographed on a column of silica gel (70 × 2 cm) using a linear gradient of benzene and ether and collecting 10-ml fractions. Four chromatographically homogeneous (tlc, silica gel, solvent E) fractions were collected.

Fraction 1, tubes 23–26, 1.42 g, R_f 0.94, was devoid of nitrogen and was not examined further.

Fraction 2, tubes 29–31, 0.578 g, R_f 0.88, was characterized as 1,3-di(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-thiouracil (II): mp 99°; $[\alpha]^{22}D$ +19.5° (*c* 1.1%, chloroform); λ_{max}^{EtOH} 230 nm (ε 81,700), 274 (5700); λ_{min}^{EtOH} 210 nm (ε 26,700), 260 (3400); ir (KBr) major bands, 3410, 1725, 1600, 1440, 1370, 1260, 1120, 1090, 710 cm^{-1}.

Anal. Calcd for $C_{56}H_{44}O_{15}N_2S$: C, 66.13; H, 4.36; N, 2.755. Found: C, 66.31; H, 4.47; N, 2.67.

Fraction 3, tubes 36–43, 0.724 g, R_f 0.61, was characterized as 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-thiouracil (III): $[\alpha]^{22}D$ −33° (*c* 2.5%, in chloroform); λ_{max}^{EtOH} 232 nm (ε 47,500), 275 (14,900); λ_{min}^{EtOH} 210 nm (ε 19,900), 253 (6800); ir (KBr) major bands, 3410, 1725, 1600, 1375, 1265, 1120, 1090, 710 cm^{-1}.

Anal. Calcd for $C_{30}H_{24}O_8N_2S$: C, 62.93; H, 4.23; N, 4.89. Found: C, 63.09; H, 4.32; N, 4.65.

Fraction 4, tubes 50–59, 0.461 g, R_f 0.31, was characterized as 3-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-thiouracil (IV): mp 133°; $[\alpha]^{22}D$ +44° (*c* 3.1%, chloroform); uv λ_{max}^{EtOH} 230 nm (ε 40,760), 272 (14,820), 303 (9300); λ_{min}^{EtOH} 209 nm (ε 21,690), 254 (7140), 289 (7810); ir (KBr) major bands, 3410, 1725, 1510, 1265, 1120, 1090, 710 cm^{-1}.

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Anal. Calcd for $C_{30}H_{24}O_8N_2S$: C, 62.93; H, 4.23; N, 4.89. Found: C, 63.13; H, 4.16; N, 4.66.

1-β-D-Ribofuranosyl-2-thiouracil (2-Thiouridine) (V).—The benzoyl derivative II, 1.23 g, was treated with 8.6 ml of 1 *N* sodium methoxide in methanol at room temperature overnight. The mixture was evaporated to dryness three times in a rotary evaporator after the addition of 10-ml portions of water. It was finally taken up in 100 ml of water and treated with IR-120 (H^+), 10 g, and filtered. The filtrate was extracted with three 10-ml portions of chloroform and the aqueous layer was evaporated to dryness. The yield of practically pure 2-thiouridine V was 0.46 g (81% of theory). It crystallizes from water in large prisms, mp 208–209° (lit.[13,16] 205–207°, 214°). It is chromatographically homogeneous: R_f 0.55, tlc, solvent B; R_f 0.66, Whatman 1, solvent C; R_f 0.32, Whatman 1, solvent D; $\lambda_{min}^{H_2O}$ 219 nm (ε 17,100), 275 (14,580); $\lambda_{max}^{H_2O}$ 244 nm (ε 4800); $\lambda_{max}^{0.1\ N\ NaOH}$ 239.5 nm (ε 22,600), 271 (14,200); $\lambda_{min}^{0.1\ N\ NaOH}$ 260.5 nm (ε 13,800), 223 (16,200); spectrophotometric pK_a = 8.1 (lit.[16] 8.8); $[\alpha]^{22}D$ +38° (c 1%, in water) (lit.[14,16] +39°, +30.8°).

Anal. Calcd for $C_9H_{12}O_5N_2S$: C, 41.53; H, 4.65; N, 10.77. Found: C, 41.32; H, 4.49; N, 10.61.

3-β-D-Ribofuranosyl-2-thiouracil (2-Thioisouridine) (VI).—This was prepared by debenzoylation of IV following the procedure of making 2-thiouridine, yield 80% of theory. The product was crystallized from ethanol and was chromatographically homogeneous: R_f 0.65, tlc, solvent B; $[\alpha]^{22}D$ −24.6° (c 0.86%, water); $\lambda_{max}^{H_2O}$ 298 nm (ε 11,200), 271 (9700), 211 (15,700); $\lambda_{min}^{H_2O}$ 280 nm (ε 9300), 241 (3500), 204 (15,600); $\lambda_{max}^{pH\ 12}$ 324 nm (ε 11,700), 258 (6700); $\lambda_{min}^{pH\ 12}$ 281 nm (ε 2100), 244 (5900); spectrophotometric pK_a = 8.11.

Anal. Calcd for $C_9H_{12}O_5N_2S$: C, 41.53; H, 4.65; N, 10.77. Found: C, 41.31; H, 4.64; N, 10.65.

Attempted Debenzoylation of 1,3-Di(2′,3′,5′-tri-*O*-benzoyl-D-ribofuranosyl)-2-thiouracil (II).—(A) Attempted debenzoylation of II by sodium methoxide using the above procedure led to the decomposition of the compound; 2-thiouridine and 2-thiouracil were identified among the products. (B) Debenzoylation of II was also attempted by heating with a saturated solution of ammonia in ethanol in a sealed tube. No 2-thiocytidine could be detected among the products by tlc in solvent systems A or B.

Reaction of 2-Thiouridine V and 2-Thioisouridine VI with Cyanogen Bromide.—The compound V, 4 mg, was dissolved in 5 ml of 0.1 *M* phosphate buffer, pH 8. Cyanogen bromide, 3.26 mg, was added and the reaction mixture was heated on a steam bath for 5 min. It was concentrated in a rotary evaporator and a portion was examined by tlc on cellulose plates (solvent B); the major product (R_f 0.72) (authentic uridine, R_f 0.72) was identified spectrophotometrically as uridine.

The compound VI was also treated with cyanogen bromide in a similar manner. Isouridine, R_f 0.76, tlc, solvent B, was identified spectrophotometrically[18] as one of the products.

Registry No.—I, 12524-88-8; II, 31081-97-7; III, 21052-18-6; IV, 31120-00-0; V, 20235-78-3; VI, 21052-17-5.

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5′-Amido Analogs of Adenosine 3′,5′-Cyclic Monophosphate[1]

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5′-Amido analogs of adenosine 3′,5′-cyclic monophosphate (**7**) are reported. Synthesis may proceed *via* the unusual cyclic diester amidates **6**. The *N*-*n*-octyl-*N*-5′-deoxyadenosyl 3′,5′-cyclic phosphoramidate (**7d**) is particularly apt for biochemical testing because of its chemical stability.

Adenosine 3′,5′-cyclic monophosphate (3′,5′-AMP, c-AMP) has been found in almost all animal tissues studied. It has also been shown to be present in bacteria, slime molds, and even higher plants. c-AMP plays a key role in regulating biochemical responses of cells, tissues or organs to external stimuli on different levels of organization.[2-4] Although its significance in mediating or moderating various hormones has stimulated a large number of investigations, the detailed mechanism of c-AMP action is not yet understood.

Derivatives or analogs of c-AMP in living systems could interfere with synthesis, degradation, or activity of the cyclic nucleotide.[5,6] Distribution and rate of cleavage by phosphodiesterases of such derivatives or analogs in tissues may differ from that of the parent compound.[7] Furthermore, they could be expected to either mimic or antagonize the actions of the cyclic nucleotides[8] and may permeate membranes more easily.

Several analogs of c-AMP have been checked for activity, *e.g.*, tubercidin 3′,5′-monophosphate,[9] the 3′-methylene cyclic phosphonate analog of cyclic AMP,[10] the 5′-methylene cyclic phosphonate analog of cyclic AMP,[10] and adenosine 3′,5′-monothionophosphate.[11] An unsuccessful attempt to prepare the 5′-amido analog of adenosine 3′,5′-cyclic monophosphate was recently reported.[12]

We prepared a series of 5′-amido analogs of adenosine 3′,5′-cyclic monophosphate (**7**)[1b] starting from 5′-tosyladenosine (**1**), which by aminolysis was converted into the toluenesulfonate salts of 5′-amino-5′-deoxyadenosine (**2**).[13] The free amines were obtained either by absorption to an acidic ion exchanger, elution of *p*-toluenesulfonic acid and desorption of **3** by 1 *N* ammonia, or alternatively by treatment with potassium *tert*-butoxide in, *e.g.*, methanol.

The amino derivatives (**3**) were phosphorylated with di(*p*-nitrophenyl) phosphochloridate[14,15] to give the diaryl phosphoramidates (**4**). Sterically hindered amines like cyclohexylamino derivative **3e** resisted phosphorylation by this method.

Treatment of **4** (except **4a**) with a pyridine–concentrated ammonia–water mixture (2:5:3) or 1 *N* NaOH in methanol yielded the 5′-*N*-alkyl- and 5′-*N*-benzylamino-5′-deoxyadenosine 3′,5′-cyclic phosphoramidates (**7**) directly. Compound **4a** is much more sensitive to alkali than **4b–d**. Treatment with the pyridine–ammonia mixture or with NaOH produced a number of decomposition products.

Synthesis of **7a** could be achieved in two steps. In the first step, one *p*-nitrophenyl group of **4a** was removed with 1 *M* triethylamine in pyridine containing 1 equiv of water. The resulting monoaryl phosphoramidate (**5a**) was cyclized with 1 *M* potassium *tert*-butoxide–*tert*-butyl alcohol in dimethyl sulfoxide following Borden and Smith's procedure.[16] Ring closure of **4** to **7** probably proceeds *via* the unusual cyclic diester amide **6**.[17] After a reaction time up to 2 hr we were able to isolate **6**.

The hydrolytic stability of the c-AMP analogs **7a–d** has been examined in view of possible biochemical activity (*cf.* Experimental Section, Table II). The *n*-octyl derivative **7d** was reasonably stable in buffer systems of pH 9–6, presumably due to shielding by the coiled *n*-octyl residue. Minimum stability in this range is shown by the *N*-methyl derivative **7a**.

The newly prepared 5′-amino-5′-deoxynucleosides **3a–e** act as competitive inhibitors for adenosine kinase.[18] Tests with the enzyme adenosine deaminase[19] showed that 5′-amino-5′deoxyadenosine with a small additional substituent at the amine (*e.g.*, **3b**) are still accepted as substrates, although at a rate reduced by approximately three powers of magnitude as compared with adenosine. The derivatives **3c–e** which have bulkier substituents, are not accepted as substrates and do not act as inhibitors either. Biochemical experiments with **7** in collaboration with other research groups are under way.

Experimental Section

Uv spectra were recorded on a Cary 14 spectrophotometer. For nmr measurements, a Varian HA-100 spectrometer was used, and for mass spectra an AEI-MS-9 mass spectrometer at 70 eV was used.

Melting points (uncorrected) were determined with a Kofler hot-stage microscope apparatus. Chromatographic separations

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TABLE I.—PHYSICAL CONSTANTS AND CHROMATOGRAPHIC DATA OF COMPOUNDS PREPARED

Compd and net formula (mol wt)	No.	Mp, °C	Elemental analysis, %[h] C	H	N	S	Uv (MeOH) max, mμ	Nmr,[a] δ, ppm	Mass spectrum m/e (rel intensity)	E[b]	Rf, pc A	Rf, pc B	Rf, tlc[c] C	Rf, tlc D	Rf, tlc A
5′-Deoxyadenosylmethylammonium *p*-toluenesulfonate $C_{18}H_{24}N_6O_6S$ (453.1)	**2b**		47.58 (47.89)	5.77 (5.60)	18.49 (18.86)	7.06 (7.04)	259	2.26 (s, 3) 2.58 (s, 3) 7.11 (d, 2, J = 8 Hz) 7.46 (d, 2, J = 8 Hz)		−0.05	0.52	0.54			0.87
5′-*N*-Benzylamino-5′-deoxyadenosine $C_{17}H_{20}N_6O_3$ (356.4)	**3c**		57.29 (57.41)	5.66 (5.61)	23.58 (23.70)		259	7.28 (s, 5)	357 (<1, $M^+ + 1$) 136 (98, B + 2)[d] 135 (70, B + 1) 91 (100)	0.1	0.73	0.76		0.39	1.15
5′-*N*-*n*-Octylamino-5′-deoxyadenosine $C_{18}H_{30}N_6O_3$ (378.4)	**3d**	169	57.27 (57.36)	7.99 (8.07)	22.21 (22.33)		259	0.83 (m, 3) 1.24 (s, 12) 1.5–1.8 (m, 2)	380 (<1, $M^+ + 2$) 378 (<1, M^+) 136 (100, B + 2) 135 (40, B + 1)		0.86	0.85		0.19	1.18
5′-*N*-Cyclohexylamino-5′-deoxyadenosine $C_{16}H_{24}N_6O_3$ (348.4)	**3e**		55.15 (55.00)	6.94 (6.90)	24.11 (24.18)		259	1.0–2.0 (m, 10)	349 (<1, $M^+ + 1$) 136 (100, B + 2) 135 (50, B + 1)	0.2	0.8	0.77		0.10	1.22
Di-*O*-(*p*-nitrophenyl) *N*-(5′-deoxyadenosyl)phosphoramidate $C_{22}H_{21}N_8O_{10}P$ (588.4)	**4a**	223	44.94 (44.78)	3.60 (3.96)	18.06 (18.89)		266	7.51 (dd, 4, J = 8 Hz) 8.12 (dd, 6, J = 8 Hz)[e]				0.89	1.20	1.1	
O-(*p*-Nitrophenyl) *N*-(5′-deoxyadenosyl)-phosphoramidate $C_{16}H_{18}N_7O_8P$ (467.3)	**5a**						262 298 (shoulder) 260			0.38	0.50	0.71		0.33	0.92
Di-*O*-(*p*-nitrophenyl) *N*-methyl-*N*-(5′-deoxyadenosyl)phosphoramidate $C_{23}H_{26}N_8O_{10}P$ (602.5)	**4b**	184	45.86 (45.89)	3.85 (3.98)	18.60 (18.45)			2.83 (d, 3, J = 12 Hz) 7.41 (dd, 4, J = 8 Hz) 8.21 (dd, 4, J = 8 Hz)	139 (80, PNP)[f] 136 (65, B + 2) 135 (100, B + 1)		0.90 0.87	0.88 0.89	1.13 1.47	1.09 1.21	
Di-*O*-(*p*-nitrophenyl) *N*-benzyl-*N*-(5′-deoxyadenosyl)phosphoramidate $C_{29}H_{27}N_8O_{10}P$ (678.6)	**4c**	130	51.33 (51.19)	4.01 (4.25)	16.52 (16.36)		263	7.3 (m, 11)[g] 8.12 (m, 6)[e]	139 (100, PNP) 136 (99, B + 2) 135 (19, B + 1) 91 (78)						
Di-*O*-(*p*-nitrophenyl) *N*-*n*-octyl-*N*-(5′-deoxyadenosyl)phosphoramidate $C_{30}H_{37}N_8O_{10}P$ (700.6)	**4d**	88	51.43 (51.46)	5.33 (5.38)	16.01 (15.94)		262	0.83 (m, 3) 1.08 (s, 12) 1.5–1.8 (m, 2) 7.42 (dd, 4, J = 8 Hz) 8.11 (dd, 6, J = 8 Hz)[e]	700 (<1, M^+) 139 (80, PNP) 136 (22, B + 2) 135 (100, B + 1)		0.88	0.93	1.34	1.28	
O-(*p*-Nitrophenyl) *N*-methyl-*N*-(5′-deoxyadenosyl) 3′,5′-cyclic phosphoramidate $C_{17}H_{18}N_7O_7P$ (463.3)	**6b**	160	44.06 (43.92)	3.91 (3.99)	21.15 (21.00)		260	2.83 (d, 3, J = 12 Hz) 5.1 (q, 1, J = 5, 12 Hz) 7.52 (d, 2, J = 8 Hz) 8.11 (d, 2, J = 8 Hz)	463 (<1, M^+) 139 (40, PNP) 136 (100, B + 2) 135 (98, B + 1)		0.77	0.81	1.33	0.98	
O-(*p*-Nitrophenyl) *N*-benzyl-*N*-(5′-deoxyadenosyl) 3′,5′-cyclic phosphoramidate $C_{23}H_{22}N_7O_7P$ (539.4)	**6c**	134	51.20 (51.15)	4.11 (4.41)	18.18 (17.88)		262	5.3 (q, 1, J = 5, 12 Hz) 7.35 (m, 5) 7.5 (d, 2, J = 8 Hz) 8.11 (d, 2, J = 8 Hz)	539 (<1, M^+) 139 (99, PNP) 136 (98, B + 2) 135 (100, B + 1)		0.84	0.91	1.52	1.18	

O-(*p*-Nitrophenyl) *N*-*n*-octyl-*N*-(5′-deoxyadenosyl) 3′,5′-cyclic phosphoramidate $C_{24}H_{32}N_7O_7P$ (561.5)	6d	168	51.33 (51.17)	6.75 (6.89)	17.47 (17.56)	262	0.82 (m, 3) 1.22 (s, 12) 1.4–1.7 (m, 2) 5.28 (q, 1, J = 5, 12 Hz) 7.53 (d, 2, J = 8 Hz) 8.12 (d, 2, J = 8 Hz)	561 (<1 M^+) 139 (78, PNP) 136 (95, B + 2) 135 (100, B + 1)	0.90	0.92	1.26
N-(5′-Deoxyadenosyl) 3′,5′-cyclic phosphoramidate $C_{10}H_{13}N_6O_5P$ (328.2)	7a					260			0.46	0.31	0.43	0.06
N-Methyl-*N*-(5′-deoxyadenosyl) 3′,5′-cyclic phosphoramidate, Na salt $C_{11}H_{14}N_6O_5PNa$ (364.3)	7b		36.27 (36.31)	3.88 (4.00)	23.08 (23.21)	259			0.45	0.41	0.40	0.08
N-Benzyl-*N*-(5′-deoxyadenosyl) 3′,5′-cyclic phosphoramidate, Na salt $C_{17}H_{18}N_6O_5PNa$ (440.4)	7c					259			0.34	0.60	0.75	0.17
N-*n*-Octyl-*N*-(5′-deoxyadenosyl) 3′,5′-cyclic phosphoramidate, Na salt $C_{18}H_{28}N_6O_5PNa$ (462.5)	7d					259			0.37	0.85	0.85	0.26

[a] Nmr data are only reported for groups representative of the compound. [b] Electrophoretic mobilities refer to TMP. [c] R_f values refer to thymidine. [d] B = base. [e] *p*-Nitrophenyl and base. [f] PNP = *p*-nitrophenol. [g] *p*-Nitrophenyl, benzyl and amino groups of the base. [h] Found values in parentheses.

on paper were carried out on Schleicher and Schüll 2043 b mgl in solvent system A [1-propanol–ammonia–water (7:2:1)] or solvent system B [ethanol–1 *M* ammonium acetate (7:3)] by the descending technique.

For analytical tlc we used commercial silica plates Merck F_{254} in solvent system C [chloroform–methanol (85:15)], D [acetone–benzene–water (8:2:1)], or A. Separations on a preparative scale were carried out on silica plates Merck PF_{254} with solvents C and D or on silica gel columns, using an LKB fraction collector.

Electrophoresis was performed on Whatman 3 MM paper; buffer system: 0.1 *M* triethylammonium bicarbonate, pH 7.4 (E). DEAE cellulose was purchased from Whatman. All R_f values reported are reproducible with sufficient accuracy.

Physical constants and chromatographic data of compounds prepared are given in Table I. The yields given in the individual procedures refer to materials as described in Table I.

Derivatives of 5′-Amino-5′-deoxyadenosine (3). Reaction Procedure with Volatile Amines. 5′-Deoxyadenosylmethylammonium *p*-Toluenesulfonate (2b).—Liquid methylamine (20 ml) was condensed to 5′-*O*-tosyladenosine (1) (2.1 g, 5 mmol) in a pressure flask equipped with a safety valve. The closed system was kept at room temperature for 3 days. After evaporation of the excess methylamine, **2b** was obtained in quantitative yield as a white, hygroscopic powder.

Reaction Procedure with Liquid Amines. 5-Deoxyadenosyl-*n*-octylammonium *p*-Toluenesulfonate (2d).—To compound 1 (5 g, 11.8 mmol), *n*-octylamine (40 ml) was added and the mixture was kept at room temperature for 5 days. Ether (400 ml) was added and **2d** was filtered off, yield 4.8 g (74%). In the same way the tosylates of the following compounds were prepared: 5′-*N*-benzylammo-5′-deoxyadenosine (**3c**) in quantitative yield; 5′-*N*-cyclohexylamino-5-deoxyadenosine (**3e**), yield 80%.

Preparation of Free Amino Nucleosides (3) from 2 by an Ion Exchange Process.—The ammonium salt **2** (1 mmol) in a small volume of water was applied to a column filled with 25 ml of acidic Dowex 50 ion exchanger. *p*-Toluenesulfonic acid was washed off with distilled water, and finally the free amino nucleosides (**3**) were eluted with 1 *N* ammonia in almost quantitative yield using a fraction collector.

Preparation of Free Amino Nucleosides (3) from 2 by Treatment with Potassium *tert*-Butoxide in Methanol.—The ammonium salt **2** (1 mmol) was dissolved with stirring in anhydrous methanol (20 ml). Potassium *tert*-butoxide (1.01 mmol) was added. After approximately 5 min, anhydrous ether (40 ml) was added, and potassium *p*-toluenesulfonate was filtered off. After evaporation of the solvent the free amino nucleosides were obtained. Yields were in the range of 90%.

The amino nucleosides with lipophilic residues R are sparingly water soluble and can therefore be prepared by dissolving the ammonium tosylates in alkaline aqueous solution and filtering **3** off. The yields are somewhat lower (about 70%).

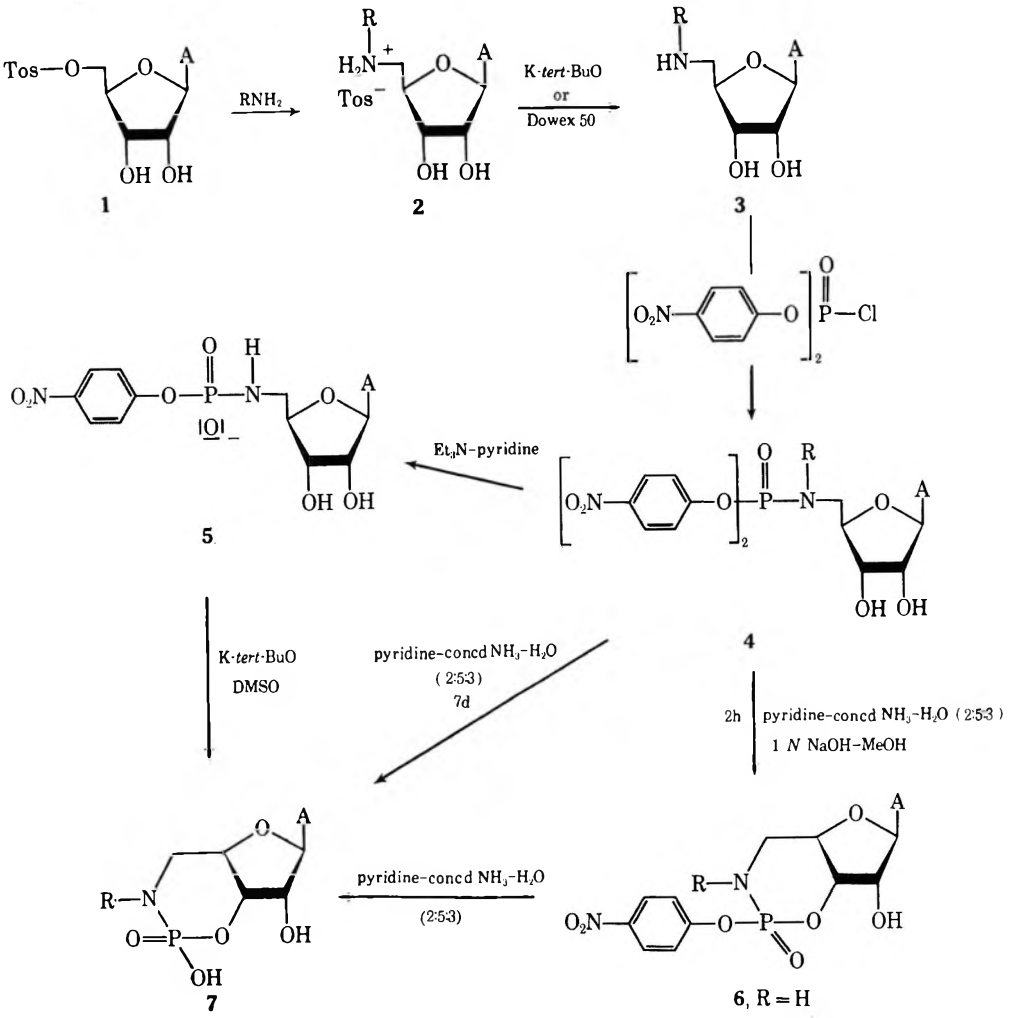
Amino nucleosides (**3**) prepared by one of the above methods were sufficiently pure for further synthetic steps. In order to obtain analytical samples, the compounds were purified on a silica gel column with solvent A.

Preparation of Hydriodides from 2.—The nucleoside ammonium tosylate (**2b**) (0.5 mmol) was dissolved in a mixture of methanol (9 ml) and acetone (20 ml), and $LiI \cdot 2H_2O$ (0.55 mmol) was added. After 20 min the solvent was evaporated and the residue was dissolved in a mixture of benzene–methanol (1:1). The first crop of crystals usually contains lithium tosylate. Indicative for tosylate is a twin peak at 260 and 254 mμ in the uv. On standing in the refrigerator **2b** crystallizes out. The hydriodide **2b** was recrystallized from benzene–methanol–petroleum ether (bp 30–60°) at 4°.

Anal. Calcd for $C_{11}H_{17}N_6O_3I$ (hydriodide of 5′-deoxymethylamino-5′-deoxadenosine[20]): C, 32.31; H, 4.29; I, 31.00. Found: C, 32.55; H, 4.39; I, 29.92.

Di(*p*-nitrophenyl) Phosphorochloridate.[15]—Diphenyl phosphorochloridate (33 g, 0.125 ml) in a three-neck flask equipped with stirrer, thermometer, dropping funnel, and drying tubes was dissolved in dry carbon tetrachloride (50 ml). A mixture consisting of 30% anhydrous nitric acid plus 70% sulfuric acid monohydrate (29 ml) was added dropwise at a rate which permits keeping the reaction mixture at 10–12°. After 4 hr stirring at 10–15° the reaction mixture was extracted with a total of 500 ml of methylene chloride with exclusion of moisture. The methylene

(20) A complete X-ray analysis of the compound was carried out by W. Saenger, *FEBS (Fed. Eur. Biochem. Soc.) Lett.*, **10**, 81 (1970).



2, 3	R
a	H
b	methyl
c	benzyl
d	*n*-octyl
e	cyclohexyl

4, 6, 7	R
a	H
b	methyl
c	benzyl
d	*n*-octyl

chloride solution was made neutral by stirring with anhydrous calcium carbonate. The solvent was removed *in vacuo* and the residue was dissolved in a little chloroform. It can be precipitated with dry petroleum ether (bp 40–60°). After the solution was refluxed shortly the compound crystallized out as greenish prisms (85%), mp 93–95° (lit.[15] mp 97–97.5°).

Di-*O*-(*p*-nitrophenyl) *N*-(5′-Deoxyadenosyl)phosphoramidate (4a).—5′-Amino-5′-deoxyadenosine (**3a**) (1 mmol)[19] in dry pyridine (10 ml) was evaporated to dryness three times. The substance was dissolved in dry pyridine (20 ml) and triethylamine (840 μl, 6 mmol). With rapid stirring at −40°, di(*p*-nitrophenyl) phosphochloridate (0.394 g, 1.1 mmol)[15] was added in portions during 1 hr. The reaction mixture was kept overnight at −20°, and after filtration the solvent was evaporated off. The residue was dissolved in dioxane–methanol (250 ml, 6:4). The solvent was reduced to 20 ml and **4a** was separated on preparative silica plates with solvent D, yield 0.265 g (45%).

***O*-(*p*-Nitrophenyl) *N*-(5′-Deoxyadenosyl)phosphoramidate (5a).**—Compound **4a** (0.294 g, 0.5 mmol) was dissolved in 1 *M* triethylamine (50 ml) in undried pyridine and kept overnight at room temperature. The reaction mixture was evaporated to dryness and **5a** separated on a DEAE cellulose column using the following conditions: DE 52-cellulose (HCO_3^- form), volume 260 ml, linear gradient water → 0.1 *M* triethylammonium bicarbonate, 3 l. each, **5a** between 0.024 and 0.031 *M*, yield 220 mg (95%).

5′-Amino-5′-deoxyadenosine 3′,5′-Cyclic Phosphoramidate (7a).—The triethylammonium salt of the *p*-nitrophenyl ester amidate (**5a**) (135 mg, 0.235 mmol) in anhydrous pyridine (10 ml) was evaporated to dryness three times and dissolved in anhydrous dimethyl sulfoxide (23 ml). After addition of 1 *M* potassium *tert*-butoxide in *tert*-butyl alcohol (2.7 ml) the reaction mixture was kept at 16° for 45 min. Then it was poured into anhydrous ether (5 l.) and kept overnight at −18°. After filtration, the residue was dissolved in a small amount of water and the cyclophosphoric ester amidate (**7a**) isolated on a DEAE cellulose column in two steps. The residue was first applied to DEAE cellulose (HCO_3^- form) (200 ml) and all inorganic substances were washed off with water, since ion exchanger Dowex 50 even as ammonium salt catalyzes decomposition of **7a**. Nucleotide material was eluted with 0.03 *M* triethylammonium bicarbonate, evaporated to dryness, and made free of triethylammonium bicarbonate by repeated evaporation of dry ethanol.

The material was fractionated in a second step on DEAE cellulose using the following conditions: DE 52-cellulose (HCO_3^- form), volume 200 ml, linear gradient water → 0.1 *M* triethylammonium bicarbonate, 2 l. each, **7a** between 0.018 and 0.023 *M*, yield 52 mg (52%).

Di-*O*-(*p*-Nitrophenyl) *N*-(5′-Deoxyadenosyl)phosphoramidates (4b–d).—The respective aminonucleosides **3b–d** (1 mmol) were made anhydrous by repeated azeotropic distillation with dry pyridine, then dissolved or suspended in a mixture of dry pyridine (10 ml) and triethylamine (840 μl, 6 mmol). With rapid stirring at −35° di-*p*-nitrophenyl phosphochloridate (0.394 g, 1.1 mmol)[15] was added in portions. The reaction mixture was kept at 4° overnight. Finally a 0.5 *M* sodium bicarbonate solution (1 ml)

was added. The mixture was evaporated to dryness. After water was added (25 ml) the residue was extracted several times with ethyl acetate. The extract was dried with anhydrous sodium sulfate and the solvent was evaporated. The substances can be purified by column chromatography or preferentially by preparative tlc on silica plates using the following solvent systems: compound **4b** in chloroform–methanol (85:15), yield 35%; **4c** and **4d** in chloroform–methanol (90:10), yield 34 and 70%, respectively.

O-(*p*-Nitrophenyl) *N*-(5′-Deoxyadenosyl) 3′,5′-Cyclic Phosphoramidates (6b–d). With Pyridine–Ammonia.—The respective diester amidate **4b–d** (1 mmol) in a mixture of pyridine–concentrated ammonia–water (2:5:3) (300 ml) was kept at 45° for 2 hr. The solvent was removed *in vacuo*, and the residue was washed with weakly alkaline (pH 9) water.

With Aqueous NaOH–Methanol.—The respective diester amidate **4b–d** (1 mmol) was dissolved in 100 ml of methanol, and after addition of 1 *N* NaOH (20 ml) the mixture was kept at room temperature for 2 hr. After neutralization with dilute acetic acid, the mixture was evaporated to dryness and some weakly alkaline water (pH 9) was added. Further work-up of the two procedures is identical; the yields are approximately the same.

Crude compounds of type **6** were purified by column chromatography or preferentially by preparative tlc on silica plates with the following solvent systems: compound **6b** in chloroform–methanol (85:15), yield 91%; **6c** and **6d** in chloroform–methanol (90:10); yield 91% each. Compound **6b** can be crystallized from methanol by adding ethyl acetate; **6c** and **6d** were obtained as a colorless powder.

Direct Synthesis of *N*-(5′-Deoxyadenosyl) 3′,5′-Cyclic Phosphoramidates (7b–d) from 4.—The respective diester amidate **4b–d** (1 mmol) was dissolved in a pyridine–concentrated ammonia–water mixture (100 ml, 3:5:2) and kept at 40° for 7 days; 1 *N* NaOH (3 ml) was added and the solvent was removed *in vacuo*. The residue was dissolved in methanol (10 ml) and filtered. After addition of acetone (300 ml), the desired cyclophosphoramidates **7b–d** precipitated. The precipitate was washed with acetone.

Further purification was carried out on a DEAE cellulose column using the following conditions for the individual compounds.

7b: DE 52 (HCO_3^- form); volume 75 ml for 3000 OD, 0.2 mmol; linear gradient water → 0.1 *M* triethylammonium bicarbonate, 2 l. each; fraction 15 ml; between fraction 58 and 70, 0.022–0.26 *M*; yield 50%.

7c: DE 52 (HCO_3^- form); volume 40 ml for 400 OD, 0.026 mmol; linear gradient water → 0.1 *M* triethylammonium bicarbonate, 1 l. each; fraction 9 ml; between fraction 21 and 39, 0.01 and 0.02 *M*; yield 55%.

7d: DE 52 (HCO_3^- form); volume 40 ml for 400 OD, 0.026 mmol; linear gradient water → 0.1 *M* triethylammonium bicarbonate, 1 l. each; fraction 9 ml; between fraction 45 and 62, 0.02–0.028 *M*; yield 53%.

Conversion of 6 into 7.—Identical conditions as described for conversion of **4** into **7** were used for converting **6** into **7**.

Stability of Compounds 7a–d in Various Buffer Solutions.—Compounds **7a–d** (20 OD each) were incubated in buffer solution (pH 5, pH 7, and pH 9, 200 μl) at 37° for 5 hr (Table II). Then the mixture was separated on paper chromatography in solvent A. The extent of cleavage was determined spectroscopically.

TABLE II
PERCENTAGE CLEAVAGE OF 7 IN BUFFER

Compd	pH 5, %	pH 7, %	pH 9, %
7a	98	15	0
7b	100	40	0
7c	90	9	0
7d	45	4	0

Registry No.—**2b**, 30765-10-7; **2b** HI, 30461-85-9; **3c**, 30765-12-9; **3d**, 30765-13-0; **3e**, 30765-14-1; **4a**, 29845-63-4; **4b**, 29845-64-5; **4c**, 30765-17-4; **4d**, 30826-38-1; **5a**, 30765-18-5; **6b**, 29845-65-6; **6c**, 30765-20-9; **6d**, 30765-21-0; **7a**, 29845-61-2; **7b** Na salt, 30765-23-2; **7c** Na salt, 30765-24-3; **7d** Na salt, 30765-25-4.

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Mobile Keto Allyl Systems. X.[1a] The Thermal Decomposition of 2-(*o*-Methylbenzal)-3-amino-4,4-dimethyl-1-tetralones[1b]

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Several 2-(*o*-methylbenzal)-3-amino-4,4-dimethyl-1-tetralones (**4**) have been prepared and those possessing a hydrogen atom α to the nitrogen in the amino moiety were found to decompose thermally to yield 2-(*o*-methylbenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (**8**). By the use of deuterium-labeling experiments, it has been shown that this α hydrogen atom is transferred to the benzylic position. Possible mechanisms are discussed.

In connection with other work, it was necessary to prepare several 2-(*o*-methylbenzal)-3-amino-4,4-dimethyl-1-tetralones and to study their thermal stability. Condensation of *o*-tolualdehyde with 4,4-dimethyl-1-tetralone yielded *trans*-2-(*o*-methylbenzal)-4,4-dimethyl-1-tetralone[2] (**1**) in high yield. Bromination[3] with *N*-bromosuccinimide gave 2-(α-bromo-*o*-methylbenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (**2**). When **2** was allowed to react with cyclohexylamine, isopropylamine, and *tert*-butylamine in solvent benzene at room temperature, two products were obtained as had been observed in a similar case.[3] Besides the corresponding 2-[α-(amino)-*o*-methylbenzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalenes (**3**), the desired 2-(*o*-methylbenzal)-3-amino-4,4-dimethyl 1-tetralones (**4**) were obtained. It is the thermal decomposition of these compounds **4** with which this paper is concerned.

Results

While compounds **3a–c** and **4c** were stable to column chromatography, compounds **4a** and **4b** decomposed.

(1) (a) For paper IX in this series, see N. H. Cromwell, K. Matsumoto, and A. D. George, *J. Org. Chem.*, **36**, 272 (1971). (b) Presented at the 1970 Midwest Regional Meeting of the American Chemical Society, Lincoln, Nebr., Oct 1970, Abstract No. 502.

(2) A. Hassner and N. H. Cromwell, *J. Amer. Chem. Soc.*, **80**, 893 (1958).

(3) N. H. Cromwell and E. M. Wu, *J. Org. Chem.*, **33**, 1895 (1968).

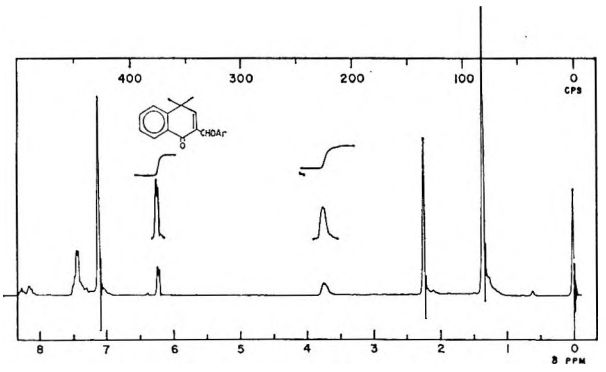
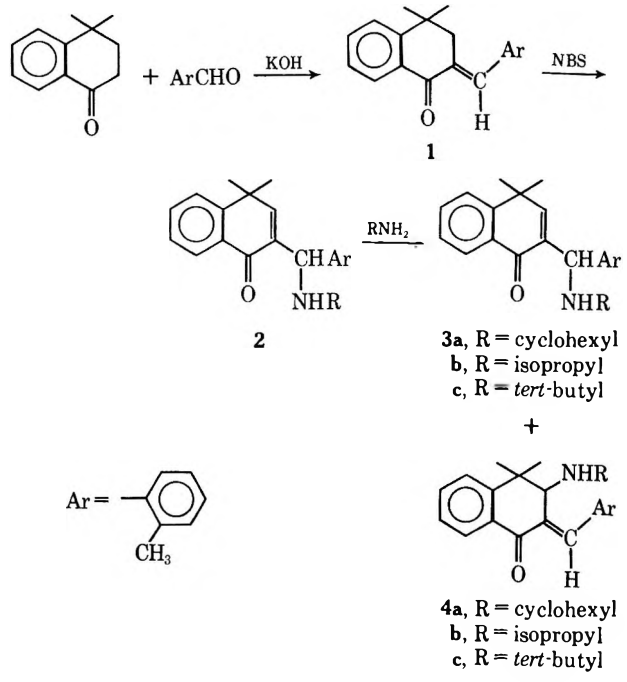
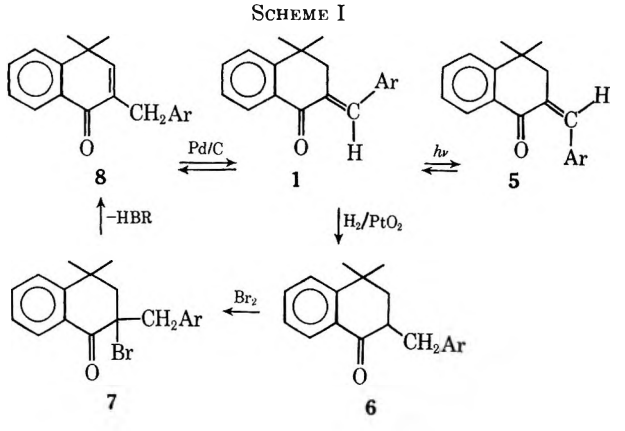


Figure 1.—Nmr spectrum of 2-(*o*-methylbenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene.



The product of decomposition was found to contain no nitrogen. From the spectral data and by comparison with *cis*-2-(*o*-methylbenzal)-4,4-dimethyl-1-tetralone[4] (5) as well as with 2-(*o*-methylbenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene[2] (8) prepared by published procedures, the isolated compound was identified as 8 (Scheme I, Figure 1).

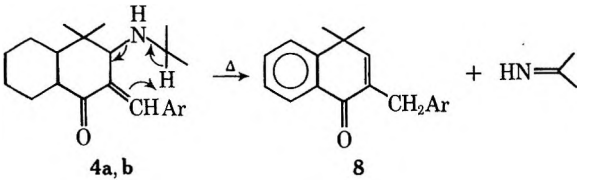
SCHEME I



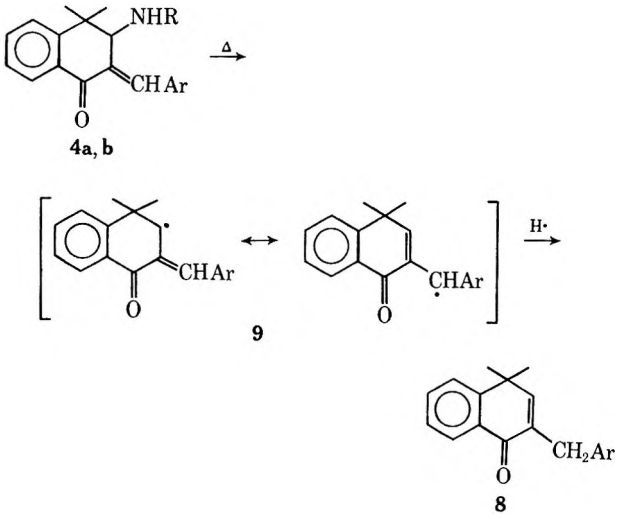
A pure sample of **4b** was obtained by precipitating it from the decomposition product **8** after column chromatography. Compound **4a** could be isolated by triturating the mixture of **3a** and **4a** and filtering the solid which formed. Because **4a** could be obtained in this manner, most of the work was done on this compound, but **4b** behaved similarly.

If **4a** or **4b** was heated to 135° in a sealed tube for 3 hr, the same product **8** could be obtained in high yield. The reaction occurred either neat or with dry benzene which had been deoxygenated with dry nitrogen. No other compounds could be readily isolated.

Two possible mechanisms come to mind immediately. The first one involves a six-membered transition state in which a ketimine and **8** are formed. This may be considered to be a retro ene reaction and can be depicted as follows.



A second mechanism is a homolytic scission of the carbon–nitrogen bond to give a radical **9** which can abstract a hydrogen atom to yield the observed product **8**.



Retro Ene Mechanism.—We have called this a retro ene reaction and have drawn a six-membered cyclic transition state only for convenience. It is recognized that the reaction may be concerted or stepwise and these possibilities are discussed later. Attempts were made to trap the imine by extraction of the decomposition solution with water and reacting the aqueous extracts with a solution of 2,4-dinitrophenylhydrazine. A small amount of the 2,4-dinitrophenylhydrazone of cyclohexanone was obtained, mp 156–157° (lit.[5] 160°), which lends support to the retro ene mechanism being operative. The small yield of cyclohexanone did not rule out the possibility that the cyclic mechanism was only a side reaction and the main reaction occurs by another pathway. The 2,4-dinitrophenylhydrazone was not of **8** since **8** did not react with 2,4-dinitrophenylhydrazine solution.

(4) D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, **29**, 1276 (1964).

(5) "Dictionary of Organic Compounds," 45h ed, Vol. 2, Oxford University Press, New York, N. Y., 1965, p 785.

Compound **4c** has no hydrogen α to the nitrogen in the amino moiety (hereafter referred to as the α hydrogen) and is stable. The retro ene reaction requires that the α hydrogen be transferred to the benzylic position. It was felt, therefore, that a deuterium labeling experiment would be of value in providing more insight into the mechanism of this decomposition. Cyclohexylamine-d_1 was prepared by the sodium and methanol-d_1 reduction[6] of cyclohexanone oxime.[7] The cyclohexylamine-d_1 was allowed to react with 2. The product **4a** was isolated by trituration of the product mixture, recrystallized, and decomposed in the normal manner. Mass spectrometric analysis showed **4a** to contain 98% atom/molecule of deuterium. The product **8** isolated after chromatography had mp 85.5–86.5°, the same as that for **8** obtained previously. The nmr spectrum (Figure 2) of **8** obtained from the decomposition of 2-(*o*-methylbenzal)-3-(1′-deuteriocyclohexylamino)-4,4-dimethyl-1-tetralone was identical with that obtained previously (Figure 1) except for the vinyl and methylene proton signals. The methylene signal appeared as a broad singlet at 229 Hz which integrated to 1.01 protons and the vinyl signal appeared as a doublet at 378 Hz (J = 1.4 Hz) and integrated to 1.00 protons. Mass spectral analysis showed **8** in this case to contain 98% atom/molecule of deuterium, and the nmr spectrum is consistent with a structure having one atom/molecule of deuterium in the benzylic position. The fact that the signal at 229 Hz is a broad singlet is probably due to unresolved coupling to the deuterium which has a spin of one and J_{CH-D} 2.4 Hz.[8]

As a control experiment, the proton on the nitrogen of **4a** was exchanged with deuterium oxide and the resultant *N*-deuterio compound containing 60% atom/molecule of deuterium by mass spectrometric analysis was decomposed. The resultant **8** showed no deuterium by nmr. The ratio of intensities of the vinyl to methylene signals was one to two and the spin–spin splitting pattern was a triplet and a doublet, respectively (Figure 1).

Radical Mechanism.—The radical produced in the homolytic scission might be expected to be relatively stable due to the high degree of resonance stabilization available to it. Therefore, attempts were made to trap and observe it. It was thought that the radical trap that offered the best possibility was 2-methyl-2-nitrosopropane.[9]

When 2-methyl-2-nitrosopropane was added to a sample of **4a** at the time it was thought to be half-decomposed and perhaps had the highest steady-state concentration of radicals present; only an esr signal due to di-*tert*-butyl nitroxide was observed. This radical is observed because 2-methyl-2-nitrosopropane decomposes to form di-*tert*-butyl nitroxide either thermally or photochemically.[10]

(6) The procedure was essentially that of W. H. Lycan, S. V. Puntambeker, and C. S. Marvel, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 318.

(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1956, p 255.

(8) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, p 1092.

(9) For recent examples of the use of 2-methyl-2-nitrosopropane as a radical trapping agent, see S. Terabe and R. Konaka, *J. Amer. Chem. Soc.*, **91**, 5655 (1969), and references therein.

(10) G. R. Chalfont, M. J. Perkins, and A. Horsfield, *ibid.*, **90**, 7141 (1968).

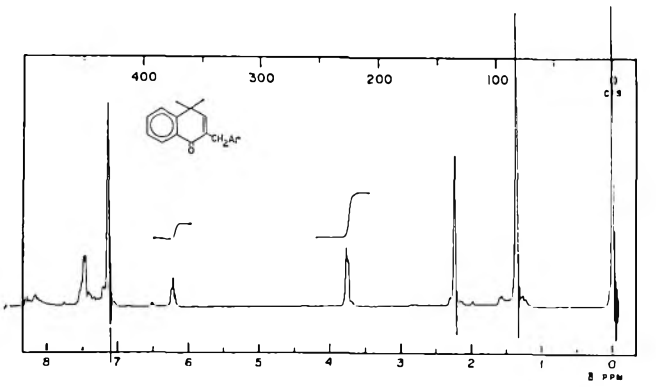
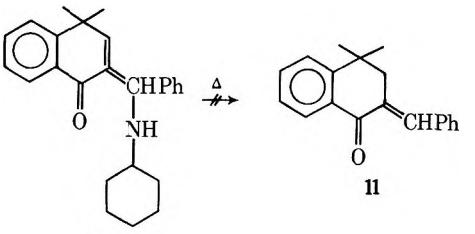


Figure 2.—Nmr spectrum of 2-(α-deuterio-*o*-methylbenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene.

Since **4a** was stable at room temperature and most radical traps decompose at elevated temperatures, no direct evidence could be obtained to support the radical mechanism.



10 **11**

In another experiment 2-[α-(cyclohexylamino)-benzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (**10**) was subjected to the same decomposition conditions for 6 hr, but nmr analysis showed no evidence of decomposition. In this case, the unsubstituted benzyl compound was used since it could be obtained more easily due to no reaction giving rearranged product, as well as the fact that **10** is a solid and **3a** is an oil.

Discussion

The complete transfer of the α deuterium to the benzylic position, the absence of deuterium transfer from the nitrogen, and the formation of cyclohexanone when water is added to the decomposition mixture argues against the radical mechanism as described above and supports the retro ene reaction as the most likely pathway. The driving force of the retro ene reaction has often been considered to be the energy gained from the formation of the new bonds minus the energy required to break the old bonds.[11] It is known that in the 4,4-dimethyl-1-tetralone system the endocyclic 2-benzyl isomer is thermodynamically more stable than the exocyclic 2-benzal isomer.[12] The greater stability of the endocyclic isomer must provide an important driving force for the decomposition of **4a** and **4b**.

By referring to this decomposition as a retro ene reaction, we do not mean to imply that the transition state is one of a truly concerted reaction. The retro ene reaction is an example of a symmetry-allowed 1,5

(11) H. M. R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).

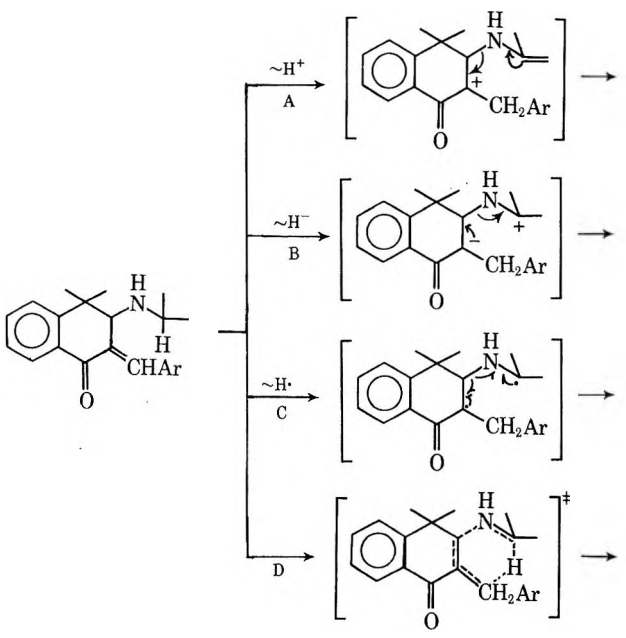
(12) N. H. Cromwell, R. P. Ayer, and P. W. Foster, *J. Amer. Chem. Soc.*, **82**, 130 (1960).

TABLE I

Compd	Mp, °C	Calcd, % C	H	N	X	Found, % C	H	N	X	Ir, cm⁻¹ C=O	C=C	Ar
1	108–109	86.92	7.29			86.71	7.47			1675	1620, 1610	1600
2	140–145 dec	67.61	5.39		22.49[a]	67.37	5.41		22.77[a]	1660	1645	1600
3a	129–131 dec[b]	68.72	7.10	3.08	17.58[a,b]	68.85	7.17	2.85	17.68[a]	1655	1640	1600
3b	236–237 dec[c]	74.67	7.62	3.78	9.58[c,d]	74.46	7.78	3.61	9.63[d]	1660	1640	1600
3c	121–122	82.95	8.41	4.03		82.66	8.45	4.03		1675	1660	1610
4a	116–117	83.60	8.37	3.75		83.38	8.35	3.69		1670	1620	1600
4b	96–97	82.84	8.16	4.20		82.70	8.25	4.36		1665	1610	1600
4c	127–128[c]	62.49[e]	5.59[e]	9.72[e]		62.72[e]	5.63[e]	9.75[e]		1675	1625	1610
	223–224[e]											
10	77.5–78.5	83.52	8.13	3.90		83.60	8.21	4.01		1660	1645	1600
5	62–64	86.92	7.29			87.15	7.32			1675	1625	1600
6	102–103	86.28	7.97			86.19	8.02			1675		1600
7	127–128	67.22	5.92		22.36[a]	66.93	5.94		22.31[a]	1680		1600
8	83–85	86.92	7.29			86.81	7.38			1660		1600

[a] Bromine. [b] Hydrobromide salt. [c] Hydrochloride salt. [d] Chlorine. [e] Picrate.

SCHEME II



hydrogen shift[13] and may be concerted, but a stepwise process cannot be excluded.[11]

There are several mechanistic extremes which may be considered and which are illustrated in Scheme II. Path A would involve a rate-determining proton transfer, path B a hydride transfer, path C a hydrogen atom transfer, while path D involves a concerted cyclic transition state. All of these possibilities would account for complete transfer of the α hydrogen as well as the products observed. The proton transfer, path A, might be unfavorable since the dipolar intermediate formed would possess a negative charge adjacent to a nitrogen atom with its lone pair and a positive charge adjacent to a carbonyl group. In contrast, the dipolar intermediate formed in path B, by the hydride transfer, would possess a negative charge stabilized by the adjacent carbonyl group as well as a positive charge adjacent to the stabilizing nitrogen atom. While the reaction may be more or less concerted, path B should have favorable energy characteristics. Thus, a concerted reaction with ionic character, *via* path B, appears to be a likely possibility. The data at hand does not allow us to exclude any of these possibilities. Kinetic experiments, particularly solvent effects and substituent effects on the rate and isotope effects, will be undertaken in order to further elucidate the mechanism of this reaction. The generality of this type of retro ene reaction is being explored.

(13) R. B. Woodward and R. Hoffman, *J. Amer. Chem. Soc.*, **87**, 2511 (1965).

Experimental Section[14]

trans-**2-(*o*-Methylbenzal)-4,4-dimethyl-1-tetralone**[15] (**1**) was prepared from 4,4 dimethyl-1-tetralone[16] and *o*-tolualdehyde according to a published procedure.[2] Recrystallization from ethanol yielded a pale yellow crystalline compound in 93% yield.

2-(α-Bromo-*o*-methylbenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (**2**)[15] was prepared by a published procedure.[3] Recrystallization from CCl_4 yielded **2** as a white crystalline compound in 78% yield. Nmr, tlc, and elemental analysis showed this compound to be pure with no aromatic bromination or bromomethyl compound present.

Reaction of 2 with Amines.[17]—All reactions were carried out in benzene solution at room temperature as previously described.[3] After 3–5 days, the solvent was removed and the residue digested with ether. The solution was then filtered free of amine hydrobromide. The ethereal solution was then saturated with dry HCl gas to precipitate the amino products. The hydrochlorides were filtered from the solution and dissolved in ethanol. The free bases were released from their salts with aqueous $NaHCO_3$ and the resulting basic solution was extracted with ether. The ether was dried over anhydrous $MgSO_4$, filtered, and evaporated to yield an oil. An nmr spectrum was taken of this oil to determine the ratio of products.

2-*o*-Methylbenzal-3-(cyclohexylamino)-4,4-dimethyl-1-tetralone (**4a**) **and 2-[α-(Cyclohexylamino)-*o*-methylbenzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene** (**3a**).[15]—The crude oil containing **3a** and **4a** in a ratio of 33 to 67 was triturated with a drop of petroleum ether (bp 30–60°) to yield a yellow solid which could be filtered after additional petroleum ether was used to dissolve the remaining oil. The yellow solid was recrystallized from ethanol to yield pure **4a** in 25% yield, mp 116–117°.

The solution remaining after the initial filtration was passed through a column of Florisil, eluting with benzene. The benzene

(14) Melting points were taken by the capillary method in a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were obtained as CCl_4 solutions using a Perkin-Elmer Model 237 spectrophotometer. Ultraviolet spectra were taken on a Cary Model 14 recording spectrophotometer. Proton magnetic resonance spectra were obtained on a Varian A-60 or A-60D spectrometer employing $CDCl_3$ solutions and are reported in hertz relative to internal TMS (0.0 Hz). Mass spectra were obtained with a Hitachi Model RMU-6D spectrometer, and electron spin resonance spectra were taken on a Joelco Model JES 3BSX spectrometer. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(15) Analytical and ir data are presented in Table I for all compounds. Nmr and uv data are presented in Table II.

(16) R. D. Campbell and N. H. Cromwell, *ibid.*, **77**, 5169 (1955).

(17) Isolated yields are not reported for all compounds since they decomposed while being isolated. Relative ratios of products given are by nmr analysis of the mixture.

TABLE II

Compd	λ_{max}	$\epsilon \times 10^{-3}$	Nmr[a,b] $(CH_3)_2C$	CH_3Ph	$-CH_2-$	CH=	-CH-	Amino
1	228 sh	6.3[c]						
	282	8.97	77	139	d, 168, J = 1.5	480		
	295	8.98						
2	245	14.1[d]	93	153		?[e]	d, 409, J = 2	
	292 sh	2.98						
	302	2.08						
3a	257	9.55[c]	84, 86	147		?[e]	322	m, 50–170, cyclohexyl
	303 sh	2.37						
3b	257	10.4[c]	83, 85	150			325	85 NH; d, 65, J = 6;[f] d, 67, J = 6;[f] m, 169, $CH(CH_3)_2$
	300 sh	2.79						
3c	258	12.0[c]	85, 88	153		?[e]	325	s, 66
	300 sh	3.86						
4a	277	12.3[c]	85, 93	142		479	236	m, 10–130
	297	11.6						
4b	275	12.6[c]	89, 94	139		m, 488–503	239	139 NH; d, 24, J = 6;[f] CH_3–; d, 40, J = 7;[f] CH_3 plus NH; m, 139, $CH(CH_3)_2$
	297 sh	11.0				503		
4c	273	11.8[c]	86, 95	138		469	250	s, 41
	302	11.6						
10	257	11.0[c]	85, 88			?[e]	308	154, NH; m, 50–130, cyclohexyl
	300 sh	3.8						
5	270	12.4[c]	85	135	d, 164, J = 1.5	m, 408		
	300 sh	8.65						
6	251	12.8[c]	75, 83	142	m, 100–240			
	292	2.06						
7	258	11.3[d]	80, 98	149	229,[g] 151			
	295	2.76						
8	255	11.0	82	134	d, 226, J = 1.5	t, 374 J = 1.5		

[a] All nmr spectra were taken in $CDCl_3$ and chemical shifts are reported in hertz relative to internal TMS. [b] All compounds exhibited a multiplet downfield of the aromatic region assigned to the ring proton β to the carbonyl [see G. Glaros and N. H. Cromwell, *J. Chem. Educ.*, 46, 854 (1969), for spectra of similar compounds] (483–504 Hz) and aromatic protons in the region 400–465 Hz. [c] 95% ethanol. [d] Isooctane. [e] Buried under aromatic protons. [f] Nonequivalent methyl on isopropyl moiety. [g] Benzylic methylene.

fraction contained **4a** which had not crystallized out of the oily mixture plus the decomposition product **6**. Elution with ethyl acetate gave **3a** in 16% yield as a white oil.

2-*o*-Methylbenzal-3-(isopropylamino)-4,4-dimethyl-1-tetralone (4b) and 2-[α-(isopropylamino)-*o*-methylbenzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (3b).[15]—The mixed hydrochlorides were obtained in 86% yield in a 50/50 ratio. Trituration of the mixture of **3b** and **4b** was unsuccessful, so the mixture was chromatographed on a column of Florisil eluting with benzene. The benzene fractions were combined and the benzene was removed under reduced pressure. Nmr analysis showed this fraction to contain **4b** and **8**. This mixture was dissolved in ether; the ethereal solution was saturated with HCl to precipitate **4b** as its hydrochloride; the hydrochloride was isolated, dissolved in ethanol, and neutralized with aqueous $NaHCO_3$. The basic solution was extracted with ether, the ether dried ($MgSO_4$), and the solvent removed to yield an oil which slowly crystallized. Recrystallization gave pure **4b**, mp 96–97°, suitable for complete analysis (Tables I and II). Further elution with ethyl acetate provided **3b** as an oil, mp (HCl salt) 236–237°.

2-*o*-Methylbenzal-3-(*tert*-butylamino)-4,4-dimethyl-1-tetralone (4c) and 2-[α-(*tert*-Butylamino)-*o*-methylbenzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (3c).[15]—The crude oil obtained in 52% yield was shown by nmr analysis to contain **3c** and **4c** in a ratio of 15 to 85. Chromatography of the crude oil on a column of Florisil eluting with benzene afforded **4c** as an oil, mp (HCl salt) 127–128°, analyzed as its picrate, mp 223–224° (Tables I and II). Further elution with ethyl acetate gave **3c**, mp 121–122°, as a white solid.

2-[α-(Cyclohexylamino)benzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (10)[15] was prepared as previously described[3] from 3.4 g (0.01 mol) of 2-(α-bromobenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene, mp 117–118 (lit.[3] 115–116°). Only one compound was detected by nmr analysis. Recrystallization from ethanol give 0.97 g (28%) pure **10**, 92–93°.

***cis*-2-*o*-Methylbenzal-4,4-dimethyl-1-tetralone (5).**[15]—Irradiation of a solution of 0.9 g (0.0033 mol) of **2** in 100 ml of methanol using a B-100A Blakray source as previously described[4] produced **5** as deep yellow plates. Recrystallization from ethanol yielded 0.55 g (62%) of **5**, mp 62–64°.

2-(*o*-Methylbenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (8).[15]—This compound could not be isolated in pure form except by decomposition of **4a** or **4b**. The following procedures yielded **8** contaminated with **1**. Column chromatography with alumina, silica gel, and Florisil, as well as tlc with silicic acid, silicic acid–$AgNO_3$, and Florisil, all failed to separate the two isomers **8** and **1**. In each case, however, the nmr spectra was the same as **1** and the decomposition product **8**.

A. Rearrangement with Palladium.—The procedure followed was that reported in the literature.[12] The product was shown by nmr analysis to contain 77% endo isomer **8** and 23% exo isomer **1**.

B. Dehydrohalogenation.—The scheme followed was that recorded in the literature.[2] Hydrogenation for 15 min at 40 psi of 2.76 g (0.01 mol) of **2** in methanol with PtO_2 yielded 2.3 g (83%) 2-*o*-methylbenzyl-4,4-dimethyl-1-tetralone (**6**), mp 102–103°.

Bromination[2] of 2.08 g (0.0075 mol) of **6** in $CHCl_3$ yielded, after the usual work-up, 2.1 g (79%) of 2-bromo-2-(*o*-methylbenzyl)-4,4-dimethyl-1-tetralone as white crystals, mp 127–128°.

Dehydrohalogenation of **7** gave a mixture of exocyclic isomer **1**, as well as endocyclic isomer **8**. This was shown by nmr when cyclohexylamine[18] or silver nitrate[12] was used as the dehydrobromination agent.

Thermal Decomposition.—The usual procedure involved adding the desired volume (2.5–5.0 ml) of benzene which had been dried over sodium to a weighed amount of **4a** in a test tube which has a constriction. This solution was deoxygenated by passing dry N_2 through it. The tube was then sealed and covered with Al foil to exclude light. The tube was suspended over boiling xylene (*ca.* 135°) for at least 3 hr. It was then opened, and the solvent was removed under reduced pressure. The product was a yellow oil which crystallized slowly and could be recrystallized from ethanol. Isolation was made easier by

(18) A. Hassner and N. H. Cromwell, *J. Amer. Chem. Soc.*, **80**, 901 (1958).

passing the decomposition solution through a small column of Florisil (2 mm × 4 cm in a small filter stem) to remove the colored material. Isolated yields were approximately 85–90% working on a scale of 40–150 mg of **4a**. Recrystallization of the solid formed gave white crystals, mp 83–85°.

Trapping Experiments. A.—The decomposition procedure described above was repeated, except that when the tube was opened, water was added and the mixture shaken well. Several extractions with water were performed and the aqueous extracts placed togenter in a flask containing freshly prepared 2,4-dinitrophenylhydrazine solution.[19] An immediate precipitate formed which was redissolved by heating the solution on a steam bath. The solution was allowed to cool and filtered to give the 2,4-dinitrophenylhydrazone, mp 156–157° (lit.[5] 160°).

B.—The decomposition tube was attached to a stopcock. After 1.5 hr, the stopcock was opened and a 1-ml sample (0.9 *M*) of 2-methyl-2-nitrosopropane in benzene was added. The tube cooled, and a sample was placed in an esr tube. The spectrum consisted of a triplet, $J \approx 15.5$ G.

2-Methyl-2-nitrosopropane was synthesized using literature methods illustrated in the reaction scheme below.

$$(CH_3)_3CNH_2 \xrightarrow{KMnO_4} (CH_3)_3CNO_2{}^{20}$$

$$(CH_3)_3CNO_2 \xrightarrow[Zn]{NH_4Cl} (CH_3)_3CNHOH{}^{21}$$

$$(CH_3)_3CNHOH \xrightarrow[OH^-]{Br_2} (CH_3)_3CNO{}^{22}$$

(19) Reference 7, p 111.
(20) N. Kornblum, *Org. React.*, **12**, 133 (1962).
(21) F. D. Greene and J. F. Pazos, *J. Org. Chem.*, **34**, 2269 (1969).
(22) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 6522 (1957).

Control Experiments.—The same decomposition conditions were applied to **3c**, **4c**, and **10**. Analysis by nmr of the crude reaction mixture showed no decomposition.

In another experiment, 100 mg of **4a** was dissolved in benzene, and the solution was extracted five times with 1 ml of D_2O. The benzene layer was dried over $MgSO_4$ and the solvent removed. The product was recrystallized from CH_3OD. Mass spectral analysis showed it to contain 60% deuterium atom/molecular. A 52-mg sample of this *N*-deuterio-**4a** was dissolved in 1 ml of benzene and decomposed as described above. The nmr spectrum of the decomposition product was identical with that obtained from normal **4a** (see Figure 1).

Registry No.—**1**, 30765-45-8; **2**, 30765-46-9; **3a** HBr, 30765-47-0; **3b** HCl, 30765-48-1; **3c**, 30765-49-2; **4a**, 30765-50-5; **4b**, 30765-51-6; **4c** HCl, 30765-52-7; **4c** picrate, 30765-53-8; **5**, 30765-54-9; **6**, 30765-55-0; **7**, 30765-56-1; **8**, 30768-30-0; **8**-*d*, 30768-31-1; **10**, 30768-32-2.

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Carbon–Sulfur Cleavage of 1-Adamantyl Sulfides[1]

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Acid-catalyzed carbon–sulfur cleavage at the bridgehead of some 1-adamantyl sulfides was encountered. β-(1-Adamantanethio)ethylamine and ε-(1-adamantanethio)pentylamine were converted by boiling hydrochloric acid to 1-chloroadamantane (80–90%) and the corresponding ω-mercaptoalkylamine. A similar cleavage was exhibited by *S*-(1-adamantyl)isothiuronium bromide and several amidine derivatives of β-(1-adamantanethio)-ethylamine. By direct contrast, 1-methyl- and 1-ethylthioadamantane were recovered quantitatively under these conditions. 1-Adamantyl alkyl ethers were converted by hydrochloric acid at 25° to 1-chloroadamantane, irrespective of the nature of the substituent in the alkyl side chain. Whereas 1-adamantanol was transformed to 1-chloroadamantane (92%) by cold concentrated hydrochloric acid, 1-adamantanethiol remained unchanged even on boiling with this acid.

During an attempted acid-catalyzed hydrolysis of the thiosulfate group in the α-amidinium Bunte salt **20** to the corresponding thiol by means of hot concentrated hydrochloric acid, cleavage of the sulfide moiety took place and 1-chloroadamantane (**1**) was isolated in 75% yield. This unexpected displacement at the 1-adamantane bridgehead prompted us to investigate this type of reaction further. In view of the facile solvolysis of 1-adamantyl ethers and sulfonates,[2–4] it was of further interest to compare the relative stability of similarly constituted 1-adamantyl ethers and sulfides and related systems toward hydrochloric acid.

The behavior of 1-adamantanol (**2**) and the corresponding thiol **12** toward hot concentrated hydrochloric acid was investigated first. Reaction of **2** furnished 1-chloroadamantane (**1**, 94%) after 0.5 hr, while **12** was recovered quantitatively even after 3 hr. This conversion of **2** to **1** appeared to be a simpler procedure than the one reported previously using thionyl chloride.[4]

Some simple ethers and thioethers in this series were examined next. It had been found that on shaking with cold concentrated hydrochloric acid for a short time, 1-methoxyadamantane (**3**) yielded **1** (96.5%),[3] but it was claimed that a similar cleavage of the ethyl analog **4** was more difficult.[3] We have found that **4**[2] was converted quantitatively to **1** by cold concentrated

(1) Support for this work by the U. S. Army Medical Research and Development Command (Contract DADA 17-69-C-9110) is gratefully acknowledged.
(2) D. N. Kevill, K. C. Kolwyck, and F. L. Weitl, *J. Amer. Chem. Soc.*, **92**, 7300 (1970).
(3) F. N. Stepanov, V. F. Baklan, and S. S. Guts, *Chem. Abstr.*, **65**, 627 (1966) [*Sint. Prir. Soedin., Ikh Analogov Fragmentov*, 95 (1965)].
(4) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).

hydrochloric acid at 25° in 10 min. In view of this facile ether cleavage, it seems logical that the ethers **5**–**11** were transformed readily to **1** by hydrochloric acid, irrespective of the nature of the side-chain substituents.

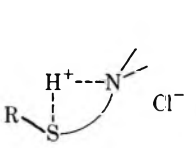
However, the methyl and ethyl thioethers **13** and **14** stubbornly resisted cleavage with boiling hydrochloric acid and were recovered unchanged. The surprising departure from this pattern was witnessed when the alkyl sulfide side chain contained a basic substituent. At 25°, β- (1-adamantanethio)ethylamine (**15**) formed a stable hydrochloride with cold concentrated hydrochloric acid but at reflux (3 hr) decomposed to **1** (90%) and β-mercaptoethylamine. The extent of this cleavage appeared to be related to the acid concentration.

For example, 6 *N* hydrochloric acid at 100° (24 hr) afforded only 34% of **1**, with 50% of **15** being recovered. This cleavage was slowed down even further when boiling 1 *N* hydrochloric acid was utilized (8 hr) when only 11% of 1-adamantanol (**2**) was isolated, together with 50% of **15**. When the amino group in **15** was converted to the benzamide **17**, the ability for C–S scission virtually disappeared. Boiling concentrated hydrochloric acid (3 hr) transformed **17** to **1** in 9% yield, with 90% of starting material being unchanged. No cleavage of the thioether group was observed at all in the sulfonamide **18** derived from **15**. It would appear that an amino function built into the side chain was essential for this substitution to take place. Addition of triethylamine to the reaction mixture containing 1-ethylthioadamantane (**14**) and hot hydrochloric acid did not induce decomposition of this sulfide.

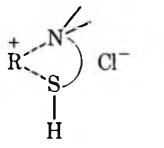
To test if the proximity of the amino group to the sulfide function was essential, ε-(1-adamantanethio)-pentylamine (**16**) was boiled with hydrochloric acid (3 hr). There were isolated **1** (83%) and ε-mercaptopentylamine (as the *N*,*S*-dibenzoyl derivative). In view of the results presented above, it is not surprising that the two amidine derivatives, based on **15**, *viz.*, **19** and **20**, were split to produce **1** in 92 and 75%, respectively.

One other interesting observation bears on this problem. When 1-bromo- or 1-chloroadamantane was allowed to react with thiourea in boiling acetic acid containing hydrobromic acid, the isothiuronium bromide **21** was isolated quantitatively. However, exposure of **21** to boiling concentrated hydrochloric acid (3 hr) seemingly reversed this displacement to form **1** in 95% yield. The conversion of **21** to **1** was only 34% complete in 0.5 hr, 43% of **21** being recovered. Interestingly enough when concentrated hydrochloric acid was replaced by a mixture of the acid and tetrahydrofuran (1:1), this displacement was prevented, 75% of **21** being recovered. The sensitivity of solvents for displacement at the 1-adamantane bridgehead is well known[5] but this aspect was not pursued further.

The amino group in the side chain appears to play an important role in this cleavage. It could exert a dual role by first assisting in the protonation of the sulfide group to form **24** and then stabilizing an ion pair, involving the 1-adamantyl carbonium ion in close contact with the nucleophilic nitrogen and sulfur atoms **25** (R = 1-adamantyl). Intrusion by chloride ion into **25** is concentration dependent and takes place in the medium employed to form the neutral 1-chloroadamantane.

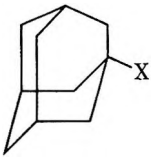


24



25

The related displacement by hydrochloric acid of the amide group in 1-acetamidoadamantane **22**, to form **1** (98%),[4] and the analogous reaction in the 3,5-dimethyl analog to produce 1-chloro-3,5-dimethyladamantane (62%),[6] bears on this problem. It is suggested that the protonated amide can function in similar fashion as outlined for **24** and **25**. The amide function is essential, since 1-aminoadamantane is recovered unchanged on boiling with hydrochloric acid. We have also found that 1-adamantyl isothiocyanate (**23**) was stable to hot concentrated hydrochloric acid.



Compd	X
1	Cl
2	OH
3	OCH_3
4	OC_2H_5
5	$O(CH_2)_2NH_2$
6	$O(CH_2)_3NH_2$
7	$OCH(CH_3)CH_2NH_2$
8	$O(CH_2)_2NHC(=NH_2^+)CH_2Cl\ Cl^-$
9	$O(CH_2)_2NHC(=NH_2^+)CH_2S_2O_3^-$
10	$O(CH_2)_3NHC(=NH_2^+)CH_2S_2O_3^-$
11	$OCH(CH_3)CH_2NHC(=NH_2^+)CH_2S_2O_3^-$
12	SH
13	SCH_3
14	SC_2H_5
15	$S(CH_2)_2NH_2$
16	$S(CH_2)_5NH_2$
17	$S(CH_2)_2NHCOC_6H_5$
18	$S(CH_2)_2NHSO_2C_6H_4CH_3$-*p*
19	$S(CH_2)_2NHC(=NH_2^+)CH_2Cl\ Cl^-$
20	$S(CH_2)_2NHC(=NH_2^+)CH_2S_2O_3^-$
21	$SC(=NH_2^+)NH_2\ Br^-$
22	$NHCOCH_3$
23	N=C=S

Experimental Section[7]

1-Adamantanethiol.—A mixture of 1-bromoadamantane[8] (10.75 g, 0.05 mol), thiourea (7.6 g, 0.1 mol), 48% HBr (25 ml), and acetic acid (50 ml) was heated under reflux for 3 hr. On cooling, **21** crystallized out (quantitatively): mp 231–232° (from ethanol); pmr (CF_3CO_2H) two broad singlets, δ 2.27 and 1.90 (adamantane H's), broad absorption due to NH between 7 and 8.

Anal. Calcd for $C_{11}H_{19}BrN_2S$: C, 45.36; H, 6.52; N, 9.62; S, 10.99. Found: C, 45.20; H, 6.50; N, 9.88; S, 11.06.

The salt (64.0 g) was stirred with 5% aqueous NaOH (400 ml) containing ethanol (100 ml) for 16 hr and the solution was acidified and extracted with ether–benzene to yield **12** (28 g, 76%): mp 102–104° (lit.[9] mp 100–102°); pmr ($CDCl_3$) two singlets showing fine splitting δ 2.05 and 1.75 (adamantane H's).

1-Ethylthioadamantane.—1-Adamantanethiol (5.04 g, 0.03 mol) was added to a stirred solution of sodium ethoxide (1.15 g of Na in 100 ml of absolute ethanol), followed by ethyl bromide (5.45 g, 0.05 mol). After 1 hr under reflux, solvents were evapo-

(5) D. N. Kevill and F. L. Weitl, *J. Amer. Chem. Soc.*, **90**, 6416 (1968).

(6) F. N. Stepanov and Y. I. Srebrodol'skii, *J. Org. Chem. USSR*, **2**, 1590 (1966).

(7) Melting and boiling points are uncorrected. Analyses were obtained by Micro-Tech Laboratories, Skokie, Ill. Analyses for N were performed by Mr. Richard Dvorak using a Model 20 Coleman nitrogen analyzer. Pmr spectra were obtained by means of a Varian A-60 instrument and are recorded in parts per million (δ) downfield from TMS.

(8) Purchased from Aldrich Chemical Co.

(9) J. R. Geigy, A. G. Belgian Patent 629,370 (Oct 21, 1963); *Chem. Abstr.*, **60**, 9167 (1964).

rated at 20 mm, and the residue was diluted with water and ether. Distillation produced the sulfide (3.65 g, 38%): bp 115–116° (0.02 mm); pmr (CCl_4) δ 2.50 (q, CH_2CH_3), 1.20 (t, CH_3), 2.27–1.60 (adamantane H's).

Anal. Calcd for $C_{12}H_{20}S$: C, 73.47; H, 10.20; S, 16.32. Found: C, 73.35; H, 10.24; S, 16.09.

1-Methylthioadamantane was synthesized in 88% yield in an analogous manner, bp 100–101° (0.01 mm) [lit.[10] bp ~70° (0.05 mm)].

β-(1-Adamantanethio)ethylamine.—1-Adamantanethiol (16.0 g, 0.1 mol) was added to sodium ethoxide solution (5.75 g of Na, 150 ml of ethanol), followed by 2-bromoethylamine hydrobromide (20.5 g, 0.1 mol). The mixture was stirred at 25° for 0.5 hr and then at the reflux for 4 hr. Solids were filtered off and the solvents evaporated *in vacuo*. The residue was diluted by water and extracted with ether–benzene (1:1), and the product was distilled (15.5 g, 77%): bp 144–148° (1.2 mm); pmr ($CDCl_3$) δ 3.08–2.48 (m, NCH_2CH_2S), 2.25–1.60 (adamantane H's). In dilute solution, a singlet at δ 1.5 was seen (NH_2).

Anal. Calcd for $C_{12}H_{21}NS$: C, 68.24; H, 9.95; N, 6.63; S, 15.16. Found: C, 68.01; H, 9.88; N, 6.48; S, 14.94.

The **hydrochloride** was prepared quantitatively in ether with HCl gas or in 75% yield when amine was added to cold concentrated HCl: mp 242–244°; pmr ($CDCl_3$) δ 3.5–2.8 (m, NCH_2-CH_2S), 2.25–1.60 (m, adamantane H's).

Anal. Calcd for $C_{12}H_{22}ClNS$: N, 5.66. Found: N, 5.52.

The amine (4.2 g) was treated with benzoyl chloride (2.8 g) in pyridine (5 ml) and benzene (50 ml) at 100° for 0.5 hr. The *benzamide* (4.6 g) was isolated in the usual fashion: mp 81–83° (from aqueous ethanol); pmr (CCl_4) δ 8.1–7.4 (arene H), 3.55 (m, CH_2N), 2.72 (t, CH_2S), 2.2–1.5 (adamantane H's).

Anal. Calcd for $C_{19}H_{25}NOS$: N, 4.44. Found: N, 4.49.

Reaction of the amine (1.05 g) with *p*-toluenesulfonyl chloride (1.14 g) in boiling pyridine (25 ml) for 1.5 hr afforded the **sulfonamide** (1.55 g), mp 86–88° (from ethanol).

Anal. Calcd for $C_{19}H_{27}NO_2S_2$: N, 3.83. Found: N, 3.69.

ε-(1-Adamantanethio)pentylamine.—1-Adamantanethiol (16.8 g) was added to sodium ethoxide solution (3.45 g of Na in 150 ml of ethanol), followed by δ-bromovaleronitrile[8] (16.2 g). After 3 hr at the reflux, the **sulfide nitrile** (25.2 g, mp 53–55°) was isolated as described for 1-ethylthioadamantane above.

A portion (15.56 g) was reduced by $LiAlH_4$ (5.7 g) in boiling ether (100 ml) over 2 hr. The reaction mixture was treated with water (40 ml) and 16 (10.3 g) was isolated from the ether extract, bp 182–186° (1.4 mm).

Anal. Calcd for $C_{15}H_{27}NS$: N, 5.72. Found: N, 5.53.

***N*-[β-(1-Adamantanethio)ethyl]chloroacetamidine Hydrochloride (19).**—To a stirred sodium methoxide solution (0.23 g of Na in 50 ml of methanol) was added chloroacetonitrile (7.5 g, 0.1 mol) in methanol (25 ml). After 0.5 hr, there was added β-(1-adamantanethio)ethylamine (16.77 g, 0.08 mol) in methanol (100 ml). The mixture was acidified by methanolic HCl to pH 4, stirred for 1 hr, filtered, and concentrated *in vacuo*. The product (17.2 g, 67%) was crystallized from 2-propanol–ether: mp 149–151°; pmr (CF_3CO_2H) δ 4.63 (s, CH_2Cl), 3.78 (m, CH_2N), 3.08 (t, CH_2S), 2.33–1.55 (m, adamantane H's).

Anal. Calcd for $C_{14}H_{24}Cl_2N_2S$: N, 8.66. Found: N, 8.63.

***S*-{*N*-[β-(1-Adamantanethio)ethyl]carboxamidiniummethyl} Thiosulfate (20).**—An aqueous solution of $Na_2S_2O_3 \cdot 5H_2O$ (10.0 g, 0.03 mol in 45 ml) was added to a solution of 19 (10.0 g, 0.03 mol) in methanol (150 ml). The mixture was stirred at 25° for 1.5 hr and then at 100° for 10 min. Solvents were removed *in vacuo*. The residue was diluted with water (20 ml) and recrystallized from ethanol–ether (1:4) to provide the product (8.35 g, 74%): mp 150–151°; pmr (CF_3CO_2H) δ 4.42 (s, $CH_2S_2O_3$), 3.75 (CH_2N), 3.67 (t, CH_2S) 2.46–1.65 (m, adamantane H's).

Anal. Calcd for $C_{14}H_{24}N_2S_3O_3$: C, 46.15; H, 6.59; N, 7.69; S, 26.37. Found: C, 45.82; H, 6.62; N, 7.66; S, 26.26.

***N*-[β-(1-Adamantanoxy)ethyl]chloroacetamidine Hydrochloride (8).**—This salt was prepared in 68% yield from β-(1-adamantanoxy)ethylamine[11] and chloroacetonitrile as described for the thio analog: mp 191–192° (from methanol–ether); pmr (CF_3CO_2H) δ 4.58 (s, CH_2Cl), 4.18 (m, CH_2O), 2.37–1.85 (m, adamantane H's).

Anal. Calcd for $C_{14}H_{24}Cl_2N_2O$: N, 9.15. Found: N, 9.31.

***S*-{*N*-[β-(1-Adamantanoxy)ethyl]carboxamidiniummethyl} Thiosulfate (9).**—Conversion of 8 to 9 was accomplished in 93% yield as described for the thio analog: mp 165; pmr (CF_3CO_2H) δ 4.70 (m, CH_2O), 3.97 (m, CH_2N), 3.80 (S, CH_2S), 2.40–1.67 (m, adamantane H's).

Anal. Calcd for $C_{14}H_{24}N_2O_4S_2$: C, 48.28; H, 6.99; N, 8.03; S, 18.39. Found: C, 48.54; H, 7.01; N, 7.94; S, 18.14.

***S*-{*N*-[β-1-(Adamantanoxy)propyl]carboxamidiniummethyl} Thiosulfate (11)** was prepared in 21% yield directly from β-(1-adamantanoxy)propylamine[11] and chloroacetonitrile without the isolation of the intermediate chloroacetamidine by the method described previously.[12] It melted at 156–158°.

Anal. Calcd for $C_{15}H_{26}N_2O_4S_2$: C, 49.72; H, 7.18; N, 7.72; S, 17.68. Found: C, 49.99; H, 7.35; N, 7.69; S, 16.87.

***S*-{*N*-[γ-(1-Adamantanoxy)propyl]carboxamidiniummethyl} Thiosulfate (10)** was prepared from γ-(1-adamantanoxy)propylamine[11] in 38% yield: mp 170°; pmr (CF_3CO_2H) δ 4.67 (m, CH_2O), 4.50 (m, CH_2N), 3.78 (s, CH_2S), 2.5–1.67 (CH_2 and adamantane H's).

Anal. Calcd for $C_{15}H_{26}N_2O_4S_2$: C, 49.94; H, 7.18; N, 7.73; S, 17.68. Found: C, 49.63; H, 7.27; N, 7.50; S, 17.48.

Cleavage of Sulfides.—The general procedure is illustrated for β-(1-adamantanethio)ethylamine (15).

The **amine** (2.0 g) was heated with concentrated HCl (40 ml) under reflux for 3 hr. 1-Chloroadamantane (1.45 g, 90%) sublimed in part into the condenser and in part remained suspended in solution. It was recovered with ether and was identified by its mp 165–166° (lit.[4] mp), and mass and pmr spectrum.[13]

The aqueous solution was made alkaline with 10% NaOH solution and treated with benzoyl chloride (3.5 g) to give *S*-(β-benzamidoethyl) thiolbenzoate (1.9 g): mp 95–96.5° (from benzene) (lit.[14] mp 96–97°); pmr ($CDCl_3$) δ 8.6–7.5 (m, arene H), 7.2 (broad s, NH), 3.85 (m, CH_2N), 3.43 (m, CH_2S).

Similar hydrolysis of ε-(1-adamantanethio)pentylamine (2.0 g) with boiling concentrated HCl (40 ml) resulted in 1-chloroadamantane (83%). On basifying the aqueous solution and addition of benzoyl chloride, there was isolated *S*-(ε-benzamidopentyl) thiolbenzoate (2.3 g): mp 72–75° (from benzene); pmr ($CDCl_3$) δ 8.4–7.4 (m, arene H), 6.8 (broad s, NH), 3.52 (m, CH_2N), 3.17 (m, CH_2S), 1.61 (broad s, three CH_2).

Anal. Calcd for $C_{19}H_{21}NO_2S$: N, 4.28. Found: N, 4.22.

Registry No.—**8**, 30771-83-6; **9**, 30771-84-7; **10**, 30771-85-8; **11**, 30771-86-9; **14**, 17233-15-7; **15**, 30771-87-0; **15** HCl, 30771-88-1; **16**, 30771-89-2; **17**, 30771-90-5; **18**, 30771-91-6; **19**, 30771-92-7; **20**, 30771-93-8; **21**, 30771-94-9; 5-(1-adamantanethio)-pentylnitrile, 30771-95-0; *S*-(ε-benzamidopentyl) thiolbenzoate, 30771-96-1.

(10) D. R. Rayner, A. J. Gordon, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4854 (1968).

(11) J. K. Chakrabarti, M. J. Foulis, and S. S. Szinai, *Tetrahedron Lett.*, 6249 (1968).

(12) A. P. Parulkar and L. Bauer, *J. Heterocycl. Chem.*, **3**, 472 (1966); J. M. Barton and L. Bauer, *Can. J. Chem.*, **47**, 1233 (1969).

(13) Identical with that reported by R. C. Fort, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).

(14) C. J. M. Stirling, *J. Chem. Soc.*, 4524 (1958).

Notes

The Reaction of Sulfur Compound Activated by Amine. II.[1] Reaction of Sulfur and Some Aliphatic Primary Amines

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The interaction of sulfur and an amino group has not been fully elucidated as some of the reaction products are unstable and none was isolated which suggests a complex reaction mechanism. Davis[2] and Hodgson[3] suggested the formation of open-chain ionic polysulfur compounds on the basis of data of several physical methods including examination of the electron spin resonance, spectra, and conductance of the solutions of sulfur in amine solvents. Although ammonia, hydrogen sulfide, and ethylenediammonium thiosulfate were detected in the reaction of sulfur with ethylenediamine (EN), the interaction of sulfur and amine was not confirmed upon a total conspectus of these reaction products.

In the present study some new reaction products have been detected, and a reaction has been postulated which is in good agreement with the yields of the products of EN with sulfur.

Immediately after the addition of sulfur to EN, generation of heat and ammonia gas was observed.[2] In the present study, yellow crystals of ethylenediamine hydrotrisulfide were obtained in 98% yield based on sulfur by diluting the reaction mixture with ethanol. Similar reactions were observed with other primary diamines, and crystalline hexamethylenediamine hydropentasulfide could be prepared. Only unstable oily hydropolysulfides from 1,3-propanediamine (PN) and diethylenetriamine (DETN) were produced, which were not characterized except by the fact that with *n*-butyl chloride they gave mixtures of higher dibutyl polysulfides. No such reaction products, however, were obtained from *n*-butylamine (BN), *n*-dibutylamine, morpholine, and tributylamine.

Addition of *n*-butyl chloride to the solutions of amine hydropolysulfide resulted in the production of dibutyl polysulfide (Table I). In the protonated amino groups such as EN, mainly dibutyl disulfide was formed, but, in dimethylformamide (DMF), dibutyl polysulfides of the sulfur chain corresponding to that of the amine hydropolysulfide were produced. Therefore, the length of the sulfur chain of amine hydropolysulfide can be determined by identifying dibutyl polysulfide obtained in DMF. Thus, ethylenediamine hydrotrisulfide (EN·H_2S_3) was confirmed to be a single compound because only dibutyl trisulfide was given in DMF.

Other amine hydropolysulfides were estimated to be mixtures, but the average of the length of the sulfur chain of dibutyl polysulfide determined by nmr analysis was almost similar to the sulfur chain length of amine hydropolysulfide by elemental analysis.

In the direct reaction of *n*-butyl chloride with the solutions of sulfur in the listed primary amines, dibutyl di- and trisulfides were selectively obtained, but no monosulfide was recovered (Table II). This was also the case with BN. Therefore, amine hydropolysulfide may be formed in BN solutions of sulfur, although not isolated. No dibutyl polysulfide was isolated with *n*-dibutylamine, tributylamine, or morpholine. Increasing the reaction time and temperature resulted in decreased trisulfide–disulfide ratios. Therefore, polysulfides, except disulfide, are desulfurized by the amines, and the sulfur chain length of dibutyl polysulfides obtained in this reaction system does not agree with that of the corresponding amine hydropolysulfides. The identification of dibutyl polysulfide is strong evidence for the formation of amine polysulfide in sulfur solution of the listed primary amine.

The amount of ammonia generated by the reaction of sulfur with excess EN was 0.322 mol per g-atom of sulfur, which approximately agrees with the calculated value (0.33 mol) from the equation which will be shown later, as well as with the result by Davis.[2] However, the amounts of ammonia formed from PN, BN, and hexamethylenediamine (HN) were smaller, *i.e.*, 0.28, 0.14, and 0.07 mol, respectively. The amount was related to the length of the sulfur chain of the corresponding amine hydropolysulfide—the shorter the sulfur chain length the more the amount of ammonia.

After separating ammonia and EN·H_2S_3 from the reaction mixture of sulfur and EN, an imino compound, probably that indicated in the following equation, was isolated by recrystallizing the neutralized residue. This unique imino compound, which will be better characterized for future publication, is of importance in understanding the interaction of sulfur and EN.

$$3NH_2CH_2CH_2NH_2 + 3S \longrightarrow NH_2CH_2CH_2NH_2 \cdot H_2S_3 + NH_3 + NH_2CH_2CH_2N{=}CHCH_2NH_2$$

Although no imino compound was isolated in the case with PN, HN, and BN, similar reactions are assumed, as amine hydropolysulfide and NH_3 were detected. It is expected that some new reaction, involving oxidation and reduction of organic compounds by polysulfide radical ions and hydropolysulfide in sulfur solution of amines as in Willgerodt reaction, will be further examined.

Experimental Section

Materials.—Sublimed sulfur was recrystallized twice from benzene. The sulfur, mp 112–113°, was free from hydrogen sulfide and sulfur dioxide. Amines were purified in a manner previously described.[2]

(1) Paper I: K. Mori and Y. Nakamura, *J. Org. Chem.*, **34**, 4170 (1969).
(2) R. E. Davis and H. F. Nakshbendi, *J. Amer. Chem. Soc.*, **84**, 2085 (1962).
(3) W. G. Hodgson, S. A. Buckler, and G. Peters, *ibid.*, **85**, 543 (1963).

TABLE I[a]

AMINE HYDROPOLYSULFIDE + n-C_4H_9Cl → $(C_4H_9)_2S_x$

Amine hydropolysulfide	g	Solvent	Reaction conditions: Temp, °C	Time, hr	Yields of $(C_4H_9)_2S_x$,[b] g: $x = 2$	$x = 3$	$x = 4$	$x = 5$	$x = 6$
EN·H_2S_3	7.9	DMF	30	2	0	6.5	0	0	0
EN·H_2S_3	7.9	DMF	50	2	0	7.5	0	0	0
EN·H_2S_3	7.9	EN	30	2	9.6	0.3	0	0	0
EN·H_2S_3	7.9	EN	50	2	10.1	0.2	0	0	0
EN·H_2S_3	7.9	BN	50	2	8.4	0.8	0	0	0
1,3-PN·H_2S_x	4.2	DMF	30	2	0	1.2[c]	1.4[c]	1.4[c]	0
HN·H_2S_5	8.8	DMF	30	2	0	0	0.4[c]	2.2[c]	0.4[c]

[a] EN, ethylenediamine; PN, propanediamine; HN, hexamethylenediamine; BN, n-buthlamine; DMF, dimethylformamide. [b] $(C_4H_9)_2S_x$ ($x = 1$) not isolated. [c] Value from nmr analysis.

TABLE II[a]

AMINE + S_8 + n-C_4H_9Cl → $(C_4H_9)_2S_x$

Amine	Reaction condition: Temp, °C	Time, hr	Yields of $(C_4H_9)_2S_x$,[b] g: $x = 2$	$x = 3$
EN	30	1	4.7	2.2
EN	30	8	9.2	0.5
EN	50	3	10.6	0.2
1,3-PN	30	1	4.2	2.5
1,3-PN	50	3	9.4	0.4
HN	60	3	9.2	0.6
DETN	30	1	3.4	2.8
DETN	50	3	8.6	0.9
XDN	50	3	5.2	2.4
BN	30	1	1.8	2.0
BN	50	3	5.9	3.6

[a] DETN, diethylenetriamine; XDN, p-xylylenediamine. [b] $(C_4H_9)_2S_x$ ($x = 1, x \geq 4$) not isolated.

Isolation of Hydropolysulfides of Amines. A. EN·H_2S_3.—A solution of 7.8 g of sulfur in 30 ml of EN was heated for about 2 hr at 50° under nitrogen until evolution of ammonia gas ceased, cooled, and diluted with 100 ml of ethanol to yield yellow, crystalline solid, which is soluble in DMF. The crystals were collected by filtration, washed with ethanol and benzene, and then dried in a desiccator: 98% yield (12.6 g) based on sulfur. The yield of the product recrystallized from EN–ethanol (1:3) was 92% (11.8 g); decomposition temperature, 116–120°; ir (KBr) SH–H_2N at 3000–3700 cm^{-1}, S–S at 480 cm^{-1}.

Anal. Calcd for EN·H_2S_3: C, 15.17; H, 6.37; N, 17.70; S, 60.76. Found: C, 15.44; H, 5.57; N, 17.33; S, 61.06.

B. HN·H_2S_5.—A solution of 7.8 g of sulfur in 30 ml of HN was heated for about 2 hr at 80° under nitrogen, and then treated in a similar manner as above. The yield of the product recrystallized from HN–ethanol (1:3) was 75% (9.1 g); decomposition temperature, 140–145°.

Anal. Calcd for HN·H_2S_5: C, 25.87; H, 6.51; N, 10.06; S, 57.56. Found: C, 25.59; H, 6.27; N, 9.67; S, 57.45.

C. Other Hydropolysulfides.—By adding 100 ml of ethanol to the reaction mixture of 7.8 g of sulfur with 30 ml of 1,3-PN or DETN, no crystalline products were obtained but a dark red oil deposited. The oily products were unable to be purified, as thermal decomposition was noted on distillation *in vacuo*. From the reaction mixtures of sulfur with BN, tributylamine, and morpholine, no reaction products were separated.

Dibutylpolysulfides from Amine Hydropolysulfides and Butyl Chloride.—Ten grams of n-butyl chloride was added dropwise to the solution of 7.9 g of EN·H_2S_3 in 50 ml of the solvent indicated in Table I. The mixture was stirred for 2 hr at the indicated temperature under nitrogen and then poured into ice–water containing an excess of sulfuric acid. The solution was extracted with benzene, and the extracts were washed with water and dried over anhydrous sodium sulfate. It was then evaporated to recover the crude product, which was distilled under a reduced pressure in a current of nitrogen. Dibutyl disulfide [bp 113–115° (15 mm),[4] ir S–S at 480 cm^{-1}] and dibutyl trisulfide [bp 73–75° (0.1 mm),[4] ir S–S at 480 cm^{-1}] were obtained, as shown in Table I.

(4) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. 3, Chemical Publishing Co., New York, N. Y., 1960, p 387.

Anal. Calcd for $(C_4H_9)_2S_2$: S, 35.95. Found: S, 35.48. Calcd. for $(C_4H_9)_2S_3$: S, 45.71; S, 45.71. Found: S, 45.29.

Similarly, dibutyl polysulfides were obtained from the hydropolysulfides of other primary diamines as summarized in Table I. Some of the dibutyl polysulfides were detected by the proton nmr spectrum analyses as previously reported.[5]

Dibutyl Polysulfides from Butyl Chloride and Amine Solutions of Sulfur.—To the solution of 5.2 g of sulfur in 50 ml of various amines, 12.5 g of n-butyl chloride was added dropwise with stirring at the temperature indicated in Table II. The mixture was cooked in a nitrogen atmosphere. The reaction mixture was treated similarly as described in the previous section and dibutyl polysulfides were isolated which are summarized in Table II.

Desulfurization of Dibutyl Trisulfide in EN.—To 20 ml of EN, 15.8 g of dibutyl trisulfide was added and the mixture was stirred for 2 hr at 30° under nitrogen. The reaction mixture was treated similarly as described previously and 9.6 g of dibutyl disulfide was obtained.

Isolation of $H_2NCH_2CH_2N{=}CHCH_2NH_2 \cdot 3HCl$.—The cooled filtrate from EN·H_2S_3 described before was neutralized with concentrated hydrochloric acid and allowed to settle the precipitates of EN·2HCl. The filtrate was then evaporated to dryness under reduced pressure, and the residue was extracted with the mixture of C_2H_5OH–H_2O (1:1). Removal of the solvent of the extracts left 2 g of colorless, crystalline product in needles which began to decompose on heating, ir (KBr) 1660 cm^{-1} (C=N).

Anal. Calcd for $H_2NCH_2CH_2N{=}CHCH_2NH_2 \cdot 3HCl$: C, 22.82; H, 6.70; N, 19.96; Cl, 50.52. Found: C, 22.56; H, 6.95; N, 20.29; Cl, 50.48.

Determination of Ammonia from Amine Solution of Sulfur.—Ammonia, generated from the mixture of 30 ml of amine and 9.6 g of sulfur at 50–80°, was determined by alkalimetry after separating amine through a trap at −10°.

Registry No.—S_8, 10544-50-0; EN·H_2S_3, 31044-74-3; HN·H_2S_5, 31044-75-4; ethylenediamine, 107-15-3; 1,3-propanediamine, 109-76-2; hexamethylenediamine, 124-09-4; diethylenetriamine, 111-40-0; p-xylylenediamine, 539-48-0; n-butylamine, 109-73-9; n-butyl chloride, 109-69-3; $H_2N(CH_2)_2N{=}CHCH_2NH_2 \cdot 3HCl$, 31044-76-5.

(5) B. D. Vineyard, *J. Org. Chem.*, **31**, 601 (1966).

Conversion of Aliphatic and Alicyclic Polyalcohols to the Corresponding Primary Polyamines

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As part of a study of complexes of transition metal ions which is presently being conducted in this labora-

tory,[1] it was found necessary to synthesize several aliphatic and alicyclic primary polyamines. Examples of four such polyamines are shown in Table I. These

TABLE I
SOME ALIPHATIC AND ALICYCLIC PRIMARY POLYAMINES. A SUMMARY OF SYNTHETIC DETAILS

Polyamine	No.	Starting material	No.	Overall yields, % This work	Overall yields, % Previously
$(CH_3)_2C(CH_2NH_2)_2$	1	$(CH_3)_2C(CH_2OH)_2$	2	64	*a*
$(CH_3)C(CH_2NH_2)_3$	3	$(CH_3)C(CH_2OH)_3$	4	76	31[b]
$C(CH_2NH_2)_4$	5	$C(CH_2OH)_4$	6	62	<23[c]
$(-CH_2CHNH_2-)_3$ (*cis,cis*)	7	$(-CH_2CHOH-)_3$ (*cis,cis*)	8	50	11[d]

[a] 2 → $(CH_3)_2C(CH)_2C(CH_2Br)_2$ (ref 2) → $(CH_3)_2C(CH_2N(CO)_2C_6H_4)_2$ (ref 2) → $(CH_3)_2C(CH_2NH_2\cdot HCl)_2$ (ref 2) → 1 (ref 3). No yields quoted. [b] 4 → $CH_3C(CH_2OSO_2C_6H_4\text{-}p\text{-}CH_3)_3$ (ref 4) → $CH_3C(CH_2N(CO)_2C_6H_4)_3$ (ref 4) → $CH_3C(CH_2NH_2\cdot HCl)_3$ (ref 4) → 3 (ref 4). [c] 6 → $C(CH_2Br)_4$ (ref *e*) → $C(CH_2NHSO_2C_6H_4\text{-}p\text{-}CH_3)_4$ (ref 5) → $C(CH_2NH_3^+)_4(SO_4^{2-})_2$ (ref 5) → 5 (ref 6). No yields quoted for last two steps. [d] $C_6H_3(OH)_3$ → $(-CH_2CNOH-)_3$ (ref *f*) → $(-CH_2CHNH_2-)_3$ *cis,trans* and *cis,cis* (ref 8) → 7 *cis,cis* (ref 9). Yield for first step = 39% (this work). [e] H. L. Herzog, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 753. [f] A. Baeyer, *Ber.*, 19, 159 (1886).

compounds have been synthesized previously (**1**,[2,3] **3**,[4] **5**,[5,6] and **7**[7-9]), but, unfortunately, the yields obtained were often quite low (see Table I) and the conditions used are inconvenient for laboratory syntheses of large quantities of material. Since the polyalcohols (**2**, **4**, **6**, and **8**) corresponding to the required polyamines are readily available (**2**, **4**, **6**,[10] and **8**[11]), it seemed desirable to design a synthetic route which would allow smooth conversion of alcohol groups to primary amine groups.

The low-yield step in the earlier syntheses of the polyamines **1**, **3**, **5**, and **7** is the introduction of a nitrogen residue, generally by nucleophilic displacement; *e.g.*, the substitution by the phthalimide moiety in these reactions requires high temperatures[2,4] for only partial conversion. Similar conditions result in only partial substitution by the *p*-toluenesulfonamido group.[5] Since the azide ion is a good nucelophile[12] and is much less bulky than either the phthalimido or *p*-toluenesulfonamido group it suggests itself as a better substrate for the introduction of nitrogen into the molecule. Also, since reduction of aliphatic azides with lithium aluminum hydride has been shown[13] to yield primary amines, we decided to test the scheme ROH → $ROSO_2C_6H_5$ → RN_3 → RNH_2 for conversion of alcohol groups into primary amines by applying it to the syntheses of compounds **1**, **3**, **5**, and **7**.

The experimental details are given below. Because of the potential hazards associated with the polyazide intermediates, they were characterized only by their ir and nmr spectra, and were used immediately in the reduction step to obtain the polyamines. Under these circumstances, no difficulties were encountered with the polyazides.

The yields resulting from this synthetic scheme are summarized in Table I, and show a marked improvement over those of earlier methods. The method is particularly useful for the cyclohexanetriamine, since it proceeds stereospecifically to yield the cis,cis isomer, as identified by the nmr of the trihydrochloride.[14] Additionally, the nmr spectrum of the tribenzenesulfonyloxy and of the triazido precursors are similar to those of the starting *cis,cis*-triol[15] and final *cis,cis*-triamine[16] and resemble those obtained for other *cis,cis*-1,3,5-trisubstituted cyclohexane compounds[16-18] (Table II).

TABLE II
COUPLING CONSTANTS FOR *cis,cis*-1,3,5-TRISUBSTITUTED CYCLOHEXANE COMPOUNDS

Compd	J_{gem}[a]	J_{aa}[a]	J_{ae}[a]	Ref
cis,cis-1,3,5-Trimethylcyclohexane	13	11	3	17
cis,cis-1,3,5-Tris(4-pyridyl)-cyclohexane	12.5	12.5	2	16
cis,cis-1,3,5-Cyclohexanetriol	11.5	11.5	4.5	14
cis,cis-1,3,5-Trichlorocyclohexane	12.7	12.4	4.3	18
cis,cis-1,3,5-Tris(benzenesulfonyloxy)cyclohexane	11	11	4.5	
cis,cis-1,3,5-Triazidocyclohexane	11	11	4	
cis,cis-1,3,5-Triaminocyclohexane	12	12	4	15

[a] In hertz.

Experimental Section

(1) **Benzenesulfonate Esters of 2, 4, 6, and 8. 1,1,1-Tris(benzenesulfonyloxymethyl)ethane** (9).—Benzenesulfonyl chloride (480 ml) was added slowly (3 hr) to a solution of **4** (126 g) in pyridine (550 ml) at 10°. After stirring for 24 hr at room temperature the product was added slowly to a mixture of water (1 l.), CH_3OH (2 l.), and concentrated HCl (800 ml). The resulting granular white precipitate was collected, washed with water and a little CH_3OH, and dried. The crude **9** (541 g, 96%) (mp 103–103.5°) on recrystallization (acetone) gave colorless needles: mp 105–106°; nmr ($CDCl_3$–TMS) τ 2.0–2.6 (m, 5, aromatics), 6.15 (s, 2, methylene), and 9.10 (s, 1, methyl).

Anal. Calcd for $C_{23}H_{24}S_3O_9$: C, 51.10; H, 4.47. Found: C, 51.04; H, 4.49.

The following were prepared in a similar manner.

2,2-Bis(benzenesulfonyloxymethyl)propane) (yield 96%) had mp 62–63°. Recrystallization (CH_3OH + little $CHCl_3$) gave colorless needles: mp 62–63°; nmr ($CDCl_3$–TMS) τ 2.0–2.6 (m, 5, aromatics), 6.20 (s, 2, methylene), and 9.12 (s, 3, methyl).

Anal. Calcd for $C_{17}H_{20}S_2O_6$: C, 53.11; H, 5.24. Found: C, 53.46; H, 5.25.

***cis,cis*-1,3,5-Tris(benzenesulfonyloxy)cyclohexane** (yield 95%) had mp 183–185°. Recrystallization (CH_3OH + little $CHCl_3$) gave fine white needles: mp 190–191°; nmr (pyridine-d_5–TMS) τ 2.0–2.8 (m, 5, aromatics), 5.12 [m, 1, methine, (axial), J_{aa}^{vic} = 11, J_{ae}^{vic} = 4.5 Hz], 7.58 [m, 1, methylene (equatorial proton), J_{ae}^{gem} = 11, J_{ae}^{vic} = 4.5 Hz] and 8.58 [m, 1, methylene (axial methylene proton), J_{ae}^{gem} = 11, J_{aa}^{vic} = 11 Hz).

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Anal. Calcd for $C_{24}H_{24}S_3O_9$: C, 52.16; H, 4.38. Found: C, 52.21; H, 4.28.

Tetrakis(benzenesulfonlyoxymethyl)methane was prepared by the method of Herzog.[19]

(2) **The Polyazide Precursors of 1, 3, 5, and 7.**—*Warning!* The handling of polyazides in large quantities may be harzardous, and the safety of the preparation described has not been fully established.

1,1,1-Tris(azidomethyl)ethane (10).—A mixture of crude 9 (73 g) and NaN_3 (44 g) in diethylene glycol (250 ml) was stirred under N_2 and maintained at 135° for 16 hr. After cooling, the mixture was poured into water (500 ml). The resulting orange-brown oil was collected, combined with a diethyl ether (100 ml) extract of the aqueous layer, and extracted with water. The ethereal solution was dried (Na_2SO_4), treated with activated charcoal and upon evaporation gave 10 an almost colorless oil (24.5 g, 93%): nmr ($CDCl_3$–TMS) τ 6.73 (s, 2, methylene) and 9.00 (s, 1, methyl); ir (neat) 2970, 2925, 2860 (CH), 2095 (vs, N_3), 1460, 1440, 1380 (CH) and 1285 cm^{-1} (vs, b, N_3).

The following were prepared in a similar manner.

2,2-Bis(azidomethyl)propane was obtained as a colorless oil (89%): nmr ($CDCl_3$–TMS) τ 6.82 (s, 2, methylene) and 9.06 (s, 3, methyl); ir (neat) 2970, 2930, 2870 (CH), 2100 (vs, N_3), 1470, 1445, 1390, 1345 (CH) and 1290 (sh), 1260 cm^{-1} (vs, b, N_3).

Tetrakis(azidomethyl)methane was prepared as colorless plates (85%): nmr ($CDCl_3$–TMS) τ 6.67 (s, methylene); ir (Nujol) 2200 (sh), 2100 (vs, N_3), and 1270 cm^{-1} (vs, b, N_3).

***cis,cis*-1,3,5-Triazidocyclohexane** was obtained (reaction mixture maintained at 100° for 6 hr) as a pale yellow oil (89%): nmr ($CDCl_3$–TMS) τ 6.58 [m, 1, methine (axial), J_{aa}^{vic} = 11, J_{ae}^{vic} = 4 Hz), 7.69 [m, 1, methylene (equatorial proton), J_{ae}^{gem} = 11, J_{ae}^{vic} = 4 Hz), and 8.71 [m, 1, methylene (axial proton), J_{ae}^{gem} = 11, J_{aa}^{vic} = 11 Hz); ir (neat) 2950, 2930, 2890 (CH), 2170 (sh), 2090 (vs, b, N_3), 1470, 1450, 1370, 1350 (sh) (CH) and 1290 (sh), 1250 cm^{-1} (vs, b, N_3).

(3) **Aliphatic and Alicyclic Primary Polyamines 1, 3, 5, and 7.**

1,1,1-Tris(aminomethyl)ethane (3).—A solution of 10 (33.6 g) in dry tetrahydrofuran (THF) (100 ml) which had been dried over molecular sieves was added slowly (2 hr) to a stirred suspension) of $LiAlH_4$ (27 g) in dry THF (500 ml). When the addition was complete the mixture was heated under reflux (18 hr). After cooling, water (27 ml), 15% NaOH solution (27 ml), and more water (81 ml) were added. The granular white solid was extracted for 24 hr in a Soxhlet thimble with THF from the refluxing motor liquor. The THF was evaporated and the resulting oil was dried by stirring with refluxing benzene (30 ml) and collecting the water in a Dean–Stark trap. Distillation gave 17.2 g (85%) of 3: bp 81° (7 mm); nmr ($CDCl_3$–TMS) τ 7.50 (s, 2, CH_2), 8.77 (s, 2, NH_2), and 9.25 (s, 1, CH_3); ir (neat) 3350, 3280 (NH), 2900, 2850 (CH), 1580 (NH), 1460 (CH), and 1370 cm^{-1} (CH). The trihydrochloride of 3 was prepared by addition of concentrated HCl to a solution of 3 in methanol.

Anal. Calcd. for $C_5H_{18}N_3Cl_3$: C, 26.51; H, 8.01; N, 18.55. Found: C, 26.88; H, 8.02; N, 18.57.

The following were prepared in a similar manner.

2,2-Bis(aminomethyl)propane (1) (75%) had bp 157–159° (lit.[3] bp 151–153°) (737 mm); nmr ($CDCl_3$–TMS) τ 7.48 (s, 2, CH_2), 8.95 (s, 2, NH_2), and 9.17 (s, 3, CH_3); ir (neat) 3380 (NH), 3300 (NH), 2950 (CH), 2870 (CH), 1600 (b, NH), 1465 (CH), 1390 (CH), and 1360 cm^{-1} (CH). The dihydrochloride of 1, recrystallized from C_2H_5OH (95%) gave white plates, mp 274–276° (lit. 256–257°,[3] 280–281°[2]).

Anal. Calcd for $C_5H_{16}N_2Cl_2$: C, 34.30; H, 9.21; N, 16.00. Found: C, 34.43; H, 9.25; N, 15.54.

Tetrakis(aminomethyl)methane (5).—The crude tetramine (80%) from the benzene azeotrope drying could not readily be distilled: nmr ($CDCl_3$–TMS) τ 7.36 (s, 1, CH_2) and 8.75 (s, 1, NH_2); ir (neat) 3370 (NH), 3290 (NH), 2910 (CH), 2860 (CH), 1600 (b, NH), 1460 (b, CH), and 1370 cm^{-1} (b, CH). The tetrahydrochloride of 5 on recrystallization from hydrochloric acid gave colorless plates, mp >300° but decomposes slowly above 250° (lit.[5] mp >300°, dec at 260°).

Anal. Calcd for $C_5H_{20}N_4Cl_4$: C, 21.60; H, 7.25; N, 20.15. Found: C, 21.74; H, 7.23; N, 19.76.

***cis,cis*-1,3,5-Triaminocyclohexane** (7) was obtained after extraction for 48 hr, yield 59%, bp 68° (0.08 mm). The trihydrochloride salt of 7 was prepared by addition of concentrated HCl to a solution of 7 in ethanol. Reprecipitation, by addition of ethanol to an ethanol–water solution of the trihydrochloride, and drying under vacuum at 100° resulted in an analytical sample of the trihydrochloride: nmr (D_2O–DSS) τ 6.45 [m, 1, methine (axial), J_{aa}^{vic} = 12, J_{ae}^{vic} = 4 Hz], 7.48 [m, 1, methylene (equatorial proton), J_{ae}^{gem} = 12, J_{ae}^{vic} = 4 Hz], 8.37 [m, 1, methylene (axial proton), J_{ae}^{gem} = 12, J_{aa}^{vic} = 12 Hz].

Anal. Calcd for $C_6H_8N_3Cl_3$: C, 30.20; H, 7.60; N, 17.61. Found: C, 30.05; H, 7.27; N, 17.40.

(19) Footnote *e*, Table I.

Registry No.—1, 29082-53-9; 3, 31044-82-3; 5, 14302-75-1; 7, 26251-48-9; 9, 31044-85-6; 10, 31044-86-7; 2,2-bis(benzenesulfonyloxymethyl)propane, 31044-87-8; *cis-cis*-1,3,5-tris(benzenesulfonyloxy)cyclohexane, 31044-88-9; 2,2-bis(azidomethyl)propane, 31044-89-0; tetrakis(azidomethyl)methane, 31107-13-8; *cis,cis*-1,3,5-triazidocyclohexane, 31044-90-3.

Acknowledgments.—This work was supported by grants from the National Science Foundation and the National Institutes of Health.

A Facile and Specific Conversion of Allylic Alcohols to Allylic Chlorides without Rearrangement[1]

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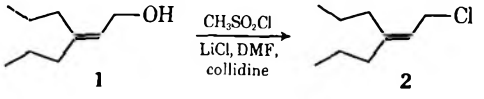
The perennial problem of converting allylic alcohols to their corresponding halides without allylic rearrangement has been the subject of considerable study.[2] In recent years several successful methods have been reported which in certain instances overcome this problem. The effort associated with the synthesis of 1,5-dienes in naturally occurring materials depends heavily upon a smooth conversion of allylic alcohols to allylic halides.[3] In connection with studies on insect pheromones, a mild and efficient technique was developed for performing this task. A considerable quantity of the allylic chloride 2 was required and in this regard various methods were investigated utilizing the allylic alcohol 1 as the precursor. It was found that the latter



1 2

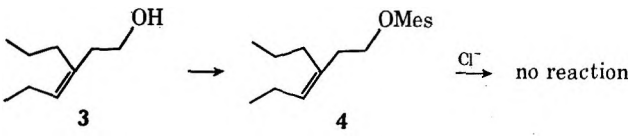
was readily transformed in excellent yield into the allylic chloride using methanesulfonyl chloride and a mixture of lithium chloride, dimethylformamide, and collidine at 0°. The product showed no contamination by rearranged chloride. An interesting feature of this process is the fact that any *nonallylic alcohol present*

(1) This study was supported by the National Institutes of Health (NIH GM-17941-01) and the National Science Foundation (NSF GP-22541).

(2) For a recent discussion of this problem, see "Advanced Organic Chemistry, Reactions, Mechanisms, and Structure," J. March, Ed., McGraw-Hill, New York, N. Y., 1968, p 270.

(3) The following articles appeared while this work was in progress: G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969); E. H. Axelrod, G. M. Milne, and E. E. van Tamelan, *J. Amer. Chem. Soc.*, **92**, 2139 (1970).

in the starting material is not converted to the allylic chloride. Thus, **1**, which was shown by vpc to contain 10% of the homoallylic alcohol **3**, gave 83% of **2** and 10% of the mesylate **4**. The mild conditions employed

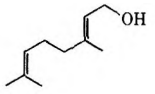
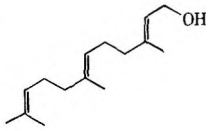
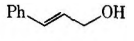
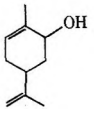


retard displacement of saturated mesylates by chloride ion, while allowing the more labile allylic mesylate to react. The use of s-collidine rather than pyridine as the hydrogen chloride scavenger is based upon the observation that its poorer nucleophilic properties fail to allow quaternization of the allylic chloride, once it is formed. When pyridine was utilized, the allylic chloride was formed, albeit in poorer yield (40–50%), the remainder of the material being lost in aqueous work-up as the *N*-allylic pyridinium salt. The function of lithium chloride was established when, in its absence, a distinct increase in the amount of rearranged chloride was noted. This indicated that the SN2 process involving chloride ion on the initially formed mesylate was giving way to a unimolecular ionization of the allylic mesylate and therefore to rearrangement. Addition of 1.0 equiv of lithium chloride in a minimum amount of dimethylformamide provided the chloride ion nucleophile in sufficient quantity to effect a clean bimolecular displacement of the mesyl group. In this fashion, the total products recovered exhibited the ratio of homoallylic mesylate to allylic chloride in close agreement to the ratio of starting homoallylic alcohol to allylic alcohol. Several different allylic alcohols were subjected to this technique and all behaved similarly under identical experimental conditions (Table I).

The method described herein allows allylic alcohols, even though they may be contaminated by their homoallylic isomers, to be converted in the same ratio as the isomeric mixture to allylic chlorides and homoallylic mesylates. The latter may be removed in a subsequent operation such as passage through silica gel if the allylic chloride is sufficiently stable. However, only relatively few allyl halides will tolerate this treatment (entry 5). The allyl chlorides were also found, as expected, to be highly sensitive toward distillation and vpc analyses, although all were quite stable at room temperature and may be utilized with the homoallylic mesylate present if the next synthetic step is sufficiently selective.

TABLE I

CONVERSION OF ALLYLIC ALCOHOLS TO ALLYLIC CHLORIDES

Entry	Alcohol	Homollylic isomer present, %[a]	Chloride, %[e]	Homollylic mesylate, %[g]
1		21[b]	87	20 ± 2
2		10[b]	84	7 ± 2
3		10[c]	83	8 ± 2
4			82	
5		10[d]	50[f]	9 ± 2[h]

[a] Isomer distribution determined by vpc (10% UC-W98, 80-100S). [b] Commercial products distilled before use. [c] Obtained by reduction of corresponding α,β-unsaturated aldehyde with sodium borohydride in aqueous ethanol (pH 7). [d] Obtained by reduction of *d*-carvone with sodium borohydride in aqueous ethanol (pH 7), bp 65° (0.3 mm). The allylic alcohol contained a mixture of geometric isomers (E. Geunther and D. Althausen, "Essential Oils," Vol. II, Van Nostrand, New York, N. Y., 1949. [e] Yield based upon per cent of allylic alcohol present in starting material. [f] Mixture of geometric isomers. [g] Determined by integration of the CH_3SO_2OR singlet in the nmr spectrum of the allyl chloride. [h] The mesylate removed by rapid elution of the crude chloride through silica gel in a hexane solution.

Experimental Section

Allylic Chlorides. General Procedure.—A stirred mixture of the allylic alcohol (0.10 mol) and s-collidine (0.11 mol) under nitrogen was treated with lithium chloride (0.10 mol) dissolved in a minimum amount of dry dimethylformamide. On cooling to 0°, a suspension was formed which was treated dropwise with methanesulfonyl chloride (0.11 mol). Stirring was continued at 0° for 1–1.5 hr, when the pale yellow reaction mixture was poured over ice–water. The aqueous layer was extracted with cold ether–pentane (1:1) and the combined extracts were washed successively with saturated copper nitrate solution. This was continued until no further intensification of the blue copper solution occurred, indicating complete removal of s-collidine. The organic extracts were dried (Na_2SO_4) and concentrated at room temperature, providing a residue of the allyl chloride. Spectral data for the allylic chlorides are given in Table II.

TABLE II

Entry	Ir, film (C=C), cm^{-1}	Nmr (CCl_4), τ
1	1675	4.43–4.8 (1, t) 4.8–5.2 (1, m) 5.9–6.1 (2, d, J = 8 Hz) 7.76–8.06 (4, m) 8.16–8.53 (9, m)
2	1675	4.4–5.15 (3, m) 5.82–6.15 (2, d, J = 8 Hz) 7.8–8.2 (8, m) 8.2–8.6 (12, m)
3	1650	4.2–4.6 (1, t, J = 5 Hz) 5.7–6.0 (2, d, J = 5 Hz) 7.7–8.1 (4, m) 8.1–8.8 (4, m) 8.8–9.3 (6, m)
4	1665	2.55–2.93 (5, m) 3.23–4.1 (2, m) 5.8–5.96 (2, d, J = 6 Hz)
5	1655	4.33–4.56 (1, m) 5.2–5.36 (2, broad s) 5.5–5.7 (1, m) 7.3–8.5 (11, m)

Registry No.—**1** chloride, 4490-10-2; **2** chloride, 6784-45-8; **3** chloride, 30808-78-7; **4** chloride, 2687-12-9; **5** chloride, 30808-80-1.

The Use of Nuclear Magnetic Resonance as a Monitor in Optical Resolutions. II. The Synthesis and Resolution of *cis*- and *trans*-2-(o-Bromophenyl)cyclohexylamines[1a]

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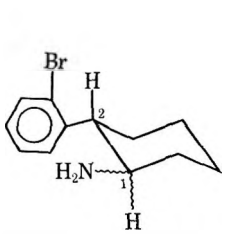
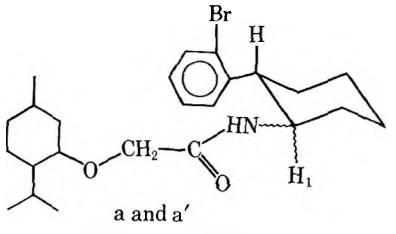
The use of nuclear magnetic resonance spectroscopy for the determination of optical purity of enantiomeric mixtures is well established. Several related approaches to this technique have been reported, all utilizing the magnetic nonequivalence of diastereotopic[2] nuclei obtained when enatiomeric compounds are either suitably derivatized with optically active reagents[3-5] or dissolved in chiral solvents.[6] In this paper we wish to report the use of the difference in the geminal nonequivalence of certain methylene hydrogens of diastereomeric (−)-menthoxyacetamides as a convenient monitor for the optical resolution of two amines. This technique was previously utilized to follow the resolution of the *cis*- and *trans*-2-*o*-tolylcyclohexanols through their (−)-menthoxyacetates[5] and we have now demonstrated this to be a useful method for (−)-methoxyacetamides as well. The attractiveness of this method is that the diastereotopic nuclei are on the resolving agent, thus allowing nmr to be used as a convenient monitor for following the separation of the diastereomers, and therefore the resolution of the enantiomers, without the need of intermediate chemical steps.

The enantiomers of *trans*- and *cis*-2-(*o*-bromophenyl)-cyclohexylamine (**1** and **2**) were resolved through their diastereomeric (−)-menthoxyacetamides. These amines were prepared by the stereospecific scheme described by Trager and Huitric[7] for the synthesis of other 2-arylcyclohexylamines and the (−)-menthoxyacetamides of **1** (**3** and **4**) and of **2** (**5** and **6**) were obtained



1, NH_2 equatorial; H axial
2, NH_2 axial; H equatorial



a and a′

3 and **4**, H_1 axial
5 and **6**, H_1 equatorial

quantitatively from the reaction of the racemic amines with (−)-menthoxyacetyl chloride (**7**) in pyridine. The trans diastereomers **3** and **4** were separated by repeated fractional crystallization and column chromatography while the cis amides **5** and **6** were separated simply by fractional crystallization. The details of the separations are described in the Experimental Section.

Figure 1 shows the nmr spectra of the methylene hydrogens (a and a′) on the acetamide portion of the diastereomeric (−)-menthoxyacetamides. Spectra A, B, D, and E are of the four diastereomeric amides **3**–**6**, while spectra C and F are of 50:50 mixtures of the two trans and the two cis amides, respectively. In both of the trans diastereomers, **3** and **4**, these methylene hydrogens are magnetically nonequivalent, and the signal of each hydrogen appears as a skewed doublet with geminal coupling of 15 Hz. However, the nonequivalence is not the same in the two diastereomers, being 0.15 ppm in **3** and 0.49 ppm in **4**.[8] Only one of the diastereomeric cis amides shows this geminal nonequivalence, the methylene protons of **5** having a difference in chemical shift of 0.41 ppm while those of **6** are equivalent, producing a sharp singlet. This large difference in nonequivalence allows the members of each diastereomeric pair to be readily distinguished by nmr spectroscopy, and thus by following the changing peaks intensities in the nmr spectra of these amides a complete assessment of the progress of the separation of diastereomers was possible. This was particularly useful in monitoring the separation of the trans diastereomers by column chromatography, since the individual fractions from the column could be readily analyzed by nmr.

The very large geminal nonequivalence seen in **4** and **5** is significantly greater than that observed for the corresponding hydrogens of diastereomeric (−)-menthoxyacetate esters of 2-arylcyclohexanols[5], which show a maximum geminal nonequivalence of 0.15–0.20 ppm. This large geminal nonequivalence in the amides is most reasonably accounted for by preferred time-average conformations in which the methylene hydrogens are dissymmetric about the amide function, but the anisotropy of the aromatic ring could also have an important effect.[4c] It is of interest that the nmr spectra of the acetamide methylene protons of these amides remain practically unchanged in a variety of solvents including chloroform, carbon tetrachloride, benzene, acetonitrile, pyridine, and trifluoroacetic acid (TFA), except that the pair of highly skewed doublets of **3** collapse to a broad singlet in TFA. This would indicate the preferred time-average conformations of these molecules about the amide function are essentially the same in these solvents.

The enantiomeric amines obtained upon acidic hydrolysis of the trans amides **3** and **4** gave optical rotations of equal magnitudes and opposite signs as did their crystalline hydrochloride salts. A similar hydrolysis of the two cis amides **5** and **6** afforded the enantiomeric cis amines, also having rotations of equal magnitudes and opposite signs.

An improved procedure for the synthesis of (−)-menthoxyacetic acid, in which the lithium salt of (−)-menthol is formed in THF rather than the sodium salt in toluene,[9] leads to a more facile procedure of higher

(1) (a) This investigation was supported in part by Research Grant 5-RO1-N508329 from the National Institutes of Health, U. S. Public Health Service. (b) NIH Predoctoral Fellow, 1968–1970.

(2) For a discussion of this terminology, see M. Raban and K. Mislow, *Top. Stereochem.*, **1**, 19 (1967).

(3) M. Raban and K. Mislow, *ibid.*, **2**, 216 (1967).

(4) (a) J. P. Casey, R. L. Lewis, and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 2789 (1969); (b) J. Jacobus and M. Raban, *J. Chem. Educ.*, **46**, 351 (1969); (c) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968).

(5) D. R. Galpin and A. C. Huitric, *J. Org. Chem.*, **33**, 921 (1968).

(6) W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **91**, 5150 (1969).

(7) W. F. Trager, F. F. Vincenzi, and Alain C. Huitric, *J. Org. Chem.*, **27**, 3006 (1962).

(8) The nonequivalence values are based on the calculated centers of gravity of the signals of the AB systems.

(9) A. W. Ingersoll, *Org. React.*, **2**, 376 (1944).

yield. The details are described in the Experimental Section.

Experimental Section[10]

trans-*o*-*β*-**Nitrostyrene.**—In the manner described by Gairaud and Lappin[11] a solution of 30 g (0.16 mol) of *o*-bromobenzaldehyde, 19.5 g (0.32 mol) of nitromethane, and 12.5 g (0.16 mol) of ammonium acetate in 100 ml of glacial acetic acid was heated in a 100° oil bath for 2 hr and then poured onto 2 l. of crushed ice. The resulting orange precipitate was collected and recrystallized from 95% EtOH to give 21 g (57%) of dark yellow crystals, mp 86–87° (lit.[12] 86°). Steam distillation of the neutralized aqueous filtrate afforded an additional 3 g (8%) of the styrene.

trans-**4-Nitro-5-(*o*-bromophenyl)cyclohexene.**—Employing the method of Wildman and Wildman,[13] a mixture of 29 g (0.128 mol) of *trans*-*o*-bromo-*β*-nitrostyrene, 30 g (0.56 mol) of condensed butadiene, and 100 mg of hydroquinone in 100-ml of dry toluene was heated at 108° in a heavy steel bomb for 7 days. Evaporation of the toluene yielded a brown oil which was crystallized from isopropyl alcohol to give 30 g (82%) of colorless crystals, mp 90–90.8°.

Anal. Calcd for $C_{12}H_{12}NO_2Br$: C, 51.09; H, 4.09; N, 4.96. Found: C, 51.26; H, 4.38; N, 4.75.

trans-**2-(*o*-Bromophenyl)nitrocyclohexane.**—Catalytic hydrogenation of *trans*-4-nitro-5-(*o*-bromophenyl)cyclohexene over 10% palladium on carbon in ethyl acetate at 30 psi for 1 hr afforded an oil which was crystallized from an isopropyl alcohol–hexane mixture to give colorless crystals, mp 82–83°.

Anal. Calcd for $C_{12}H_{14}NO_2Br$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.61; H, 5.02; N, 4.74.

cis-**2-(*o*-Bromophenyl)nitrocyclohexane.**—Using the method described by Zimmerman and Nevins,[14] a solution of 6 g (0.0216 mol) of *trans*-2-(*o*-bromophenyl)nitrocyclohexane and 25 ml of 10% ethanolic KOH in an additional 15 ml of ethanol was stirred for 30 min and then added to 600 ml of a buffer solution of the following composition: 600 ml of 95% EtOH, 45 g of sodium acetate trihydrate, and 5 ml of glacial acetic acid. After standing for 15 min the solution was diluted with 2 l. of water and extracted with three 300-ml portions of ether. The ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give an oil which was crystallized from hexane affording 5 g (83%) of blocky crystals, mp 82–83° (sublimes).

Anal. Calcd for $C_{12}H_{14}NO_2Br$: C, 50.72; H, 4.97; N, 4.93. Found: C, 51.16, H, 4.92; N, 4.67.

This compound could be recoverted to its trans isomer by refluxing in 95% EtOH with a catalytic amount of Na_2CO_3, as reported by Zimmerman.[14]

trans-**2-(*o*-Bromophenyl)cyclohexylamine** (1).—In the manner outlined by Kornblum and coworkers,[15] finely powdered hydrogen reduced iron (18 g, 0.32 g-atom) was washed with 25 ml of 5% HCl, rinsed with 25 ml of glacial acetic acid, and then added to a stirred solution of 9 g (0.032 mol) of *trans*-2-(*o*-bromophenyl)-nitrocyclohexane in 100 ml of glacial acetic acid. This mixture was stirred at gentle reflux for 5 hr and then filtered while hot through a sintered glass funnel. The solid was rinsed with 50 ml of hot acetic acid and the combined acidic filtrates were made strongly basic by the careful addition of 50% NaOH, while cooling in an ice bath, and then diluted with water to a volume of 1 l. and extracted with 1 l. of ether in three portions. The ethereal solution was washed with water, dried (Na_2SO_4), concentrated, and distilled to give 6.3 g (78%) of colorless oil: bp 98–100° (0.1 mm); ir (neat) 2.97 and 3.03 μ (N–H). The hydrochloride salt was prepared by bubbling HCl gas through an absolute EtOH solution of 1, evaporating the solution to dryness, and recrystallizing the solid from ethyl acetate–1,2-dichlorethane (10:1), mp 199–201°.

(10) Melting points were determined on a Kofler micro hot stage and are corrected. Specific rotations were measured at ambient temperature with a Rudolph polarimeter using a sodium lamp and a 2-dm tube. Infrared spectra were obtained on a Beckman IR-5-A spectrophotometer and nmr spectra on a Varian A-60 spectrometer using TMS as an internal reference. Elemental analyses were performed by Huffman Laboratories, Wheatridge, Colo.

(11) C. B. Gairaud and G. R. Lappin, *J. Org. Chem.*, **18**, 1 (1953).

(12) N. Campbell, W. Anderson, and J. Gilmore, *J. Chem. Soc.*, 446 (1940).

(13) W. C. Wildman and R. B. Wildman, *J. Org. Chem.*, **17**, 581 (1952).

(14) H. E. Zimmerman and T. E. Nevins, *J. Amer. Chem. Soc.*, **79**, 6559 (1957).

(15) N. Kornblum, W. D. Burowitz, H. O. Larson, and D. E. Hardies, *ibid.*, **82**, 3099 (1960).

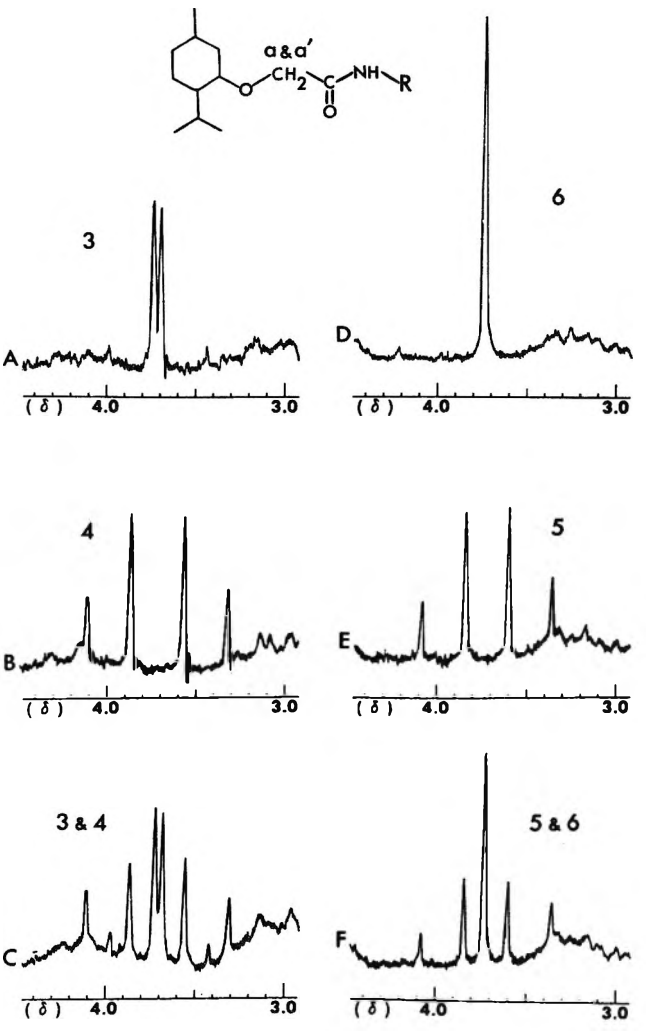


Figure 1.—Portions of the 60-MHz nmr spectra of the diastereomeric (−)-menthoxyacetamides measured in chloroform at 37°.

Anal. Calcd for $C_{12}H_{17}NBrCl$: C, 49.59; H, 5.90; N, 4.82. Found: C, 49.81; H, 6.05; N, 4.83.

cis-**2-(*o*-Bromophenyl)cyclohexylamine** (2).—This compound was prepared in a 66% yield from *cis*-2-(*o*-bromophenyl)nitrocyclohexane by the method described for obtaining 1: bp 106° (0.2 mm); ir (neat) 2.98 and 3.05 μ (N–H). The hydrochloride salt was crystallized from isopropyl alcohol–hexane (2:1), mp 254–256°, sublimes.

Anal. Calcd for $C_{12}H_{17}NBrCl$: C, 49.59; H, 5.90; N, 4.82. Found: C, 49.63; H, 5.77; N, 4.78.

(−)-**Menthoxyacetic Acid.**—To a solution of 156 g (1 mol) of menthol, $[\alpha]_D$ −50° (c 10, 95% EtOH), in 500 ml of anhydrous THF under nitrogen was added 8 g (1.15 g-atoms) of lithium metal ribbon cut into small pieces and this mixture was stirred at gentle reflux for 4 hr. The unreacted lithium was mechanically removed, a solution of 42.5 g (0.45 mol) of dry monochloroacetic acid in 125 ml of anhydrous THF was slowly added, and the resulting solution was stirred at gentle reflux for 20 hr. Following the addition of 300 ml of water the THF and menthol were steam distilled from the yellow aqueous suspension, which was then cooled in an ice bath, and the solid lithium salt was collected on a Büchner funnel and washed with cold water. The free acid was liberated upon acidification of an ether suspension of the salt with 10% HCl and the resulting ethereal solution was washed with water, dried (Na_2SO_4), concentrated, and distilled to give 84 g (88%) of clear oil: bp 124–126° (0.4 mm); $[\alpha]_D$ −92.7° (*c* 10, 95% EtOH) [lit.[9] bp 134–137° (2 mm); $[\alpha]_D$ −91.5° (c 2, EtOH)].

The acid chloride was prepared in thionyl chloride as described by Ingersoll[9] and distilled, bp 85–87° (0.4 mm) [lit.[9] bp 132° (10 mm)].

Synthesis of the Mixture of Diastereomers 3 and 4.—To a solution of 4.2 g (0.0165 mol) of 1 in 15 ml of dry pyridine was added 4.0 g (0.017 mol) of freshly distilled (−)-menthoxyacetyl

chloride and the resulting mixture was allowed to stand at room temperature for 2 days and then diluted with 100 ml of ether. The ethereal solution was washed with water, 10% HCl, 10% Na_2CO_3, and water, dried (Na_2SO_4), and concentrated to give 7 g (96%) of a brown oil.

Isolation of (−)-*trans*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (3).—This amide was obtained by crystallization of the crude mixture of diastereomers from a concentrated hexane solution at Dry Ice–isopropyl alcohol bath temperature. The amide was collected by filtration and washed with cold hexane but melted upon warming to room temperature. This material was recrystallized six times at refrigerator temperature to give a viscous oil (at room temperature): $[\alpha]_D$ −14° (*c* 5, chloroform); ir (neat) 2.92 (N–H), 6.00 μ (C=O). The nmr spectrum indicated the presence of only one diastereomer.

Isolation of (+)-*trans*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (4).—This diastereomer was isolated by column chromatography of the residual amide mixture remaining after the isolation of **3**. Typically, 4 g of the oil mixture was chromatographed on 125 g of neutral alumina (Merck), eluting with petroleum ether followed by increasing concentrations of benzene–petroleum ether mixtures. The eluted oil was collected in approximately 200-mg portions and analyzed by nmr spectroscopy. The desired diastereomer **4** eluted first and the pure fractions from several columns were combined and crystallized from hexane to give colorless crystals: mp 70.5–71.5°; $[\alpha]_D$ −73° (*c* 5, chloroform). The nmr spectrum indicated the presence of only one diastereomer.

Anal. Calcd for $C_{24}H_{36}NO_2Br$: C, 63.99; H, 8.06; H, 3.11. Found: C, 63.72; H, 8.03; N, 3.15.

Synthesis of the Mixture of Diastereomers 5 and 6.—The mixture of diastereomeric amides was obtained as an oil in a 98% yield from the reaction of **2** with (−)-menthoxyacetyl chloride in pyridine as described for the synthesis of **3** and **4**.

Isolation of (+)-*cis*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (5).—This diastereomer was obtained by fractional crystallization of the crude amide mixture in hexane at refrigerator temperature to give colorless crystals: mp 121–122.5°; $[\alpha]_D$ +86° (*c* 5, methanol); ir (Nujol) 2.94 (N–H), 5.99 μ (C=O). The nmr spectrum indicated the presence of only one diastereomer.

Anal. Calcd for $C_{24}H_{36}NO_2Br$: C, 63.99; H, 8.06; N, 3.11. Found: C, 64.06; H, 8.08; N, 3.08.

Isolation of (−)-*cis*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (6).—The residual amide mixture remaining after the isolation of **5** was crystallized from hexane at Dry Ice–isopropyl alcohol bath temperature and the crude solid was recrystallized from hexane by slow evaporation of solvent at room temperature. The fine needle crystals which formed recrystallized from hexane: mp 104.5–105.5°; $[\alpha]_D$ −174° (*c* 4, methanol). The nmr spectrum indicated the presence of only one diastereomer.

(−)-*trans*-2-(*o*-Bromophenyl)cyclohexylamine.—To a solution of 0.45 g of **3** in 8 ml of glacial acetic acid was added 5 ml of concentrated HCl and the resulting solution was heated in a 105° oil bath for 40 hr, cooled, and diluted with 30 ml of water. This solution was extracted with three 25-ml portions of ether and then carefully basified to pH 11 with 50% NaOH, while cooling in an ice bath. The resulting cloudy solution was extracted with 100 ml of ether in three portions and the ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give 0.23 g (91%) of a yellow oil, $[\alpha]_D$ −56° (*c* 2, methanol). The ir and nmr spectra were identical with those of **1**. The hydrochloride salt was prepared as for **1**: mp 217–219°; $[\alpha]_D$ −46° (*c* 5, methanol).

(+)-*trans*-2-(*o*-Bromophenyl)cyclohexylamine.—This compound was obtained upon an identical acidic hydrolysis of **4**, $[\alpha]_D$ +56° (*c* 2, methanol). The hydrochloride salt was prepared as for **1**: mp 217–219°; $[\alpha]_D$ +46° (*c* 4, methanol).

(+)-*cis*-2-(*o*-Bromophenyl)cyclohexylamine.—This compound was obtained as an oil upon an acidic hydrolysis of **5**, as previously described for the hydrolysis of **3**, $[\alpha]_D$ +109° (*c* 3, methanol). The ir and nmr spectra were identical with those of **2**. The hydrochloride salt was prepared as for **2**: mp 240–242°, sublimes extensively; $[\alpha]_D$ +123° (*c* 4, methanol).

(−)-*cis*-2-(*o*-Bromophenyl)cyclohexylamine.—This compound was obtained as an oil upon the acidic hydrolysis of **6**, $[\alpha]_D$ −110° (*c* 2, methanol). The hydrochloride salt was prepared as for **2**: mp 240–242°, sublimes extensively; $[\alpha]_D$ −122° (*c* 4, methanol).

Registry No.—**1**, 30808-81-2; **1** HCl, 30808-95-8; **2**, 30808-82-3; **2** HCl, 30808-96-9; **3**, 30808-83-4; **4**, 30808-84-5; **5**, 30808-85-6; **6**, 30808-86-7; *trans*-4-nitrc-5-(*o*-bromophenyl)cyclohexene, 30808-87-8; *trans*-2-(*o*-bromophenyl)nitrocyclohexane, 30808-88-9; *cis*-2-(*o*-bromophenyl)nitrocyclohexane, 30896-88-9; (−)-*trans*-2-(*o*-bromophenyl)cyclohexylamine, 30808-89-0, 30808-93-6 (HCl); (+)-*trans*-2-(*o*-bromophenyl)cyclohexylamine, 30808-90-3, 30808-97-0 (HCl); (+)-*cis*-2-(*o*-bromophenyl)cyclohexylamine, 30808-91-4, 30808-98-1 (HCl); (−)-*cis*-2-(*o*-bromophenyl)cyclohexylamine, 30808-92-5, 30808-94-7 (HCl).

Acknowledgment.—The authors wish to thank Mr. W. A. Edwards for technical assistance in the synthesis of the amines.

The Mechanism of the Base-Catalyzed Conversion of Nitriles to Amides by Hydrogen Peroxide

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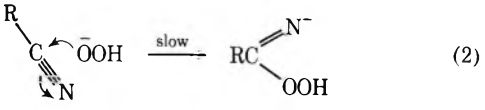
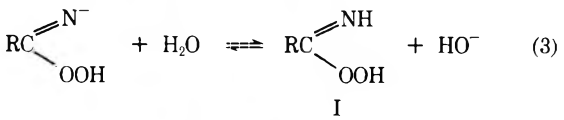
The conversion of nitriles to amides by alkaline solutions of hydrogen peroxide is a well-known preparative procedure.[1] Wiberg[2] has investigated the mech-

$$RC{\equiv}N + 2\,H_2O_2 \xrightarrow{HO^-} RC(=O)NH_2 + O_2 + H_2O \qquad (1)$$

anism of this reaction in the pH range 7–8. Our interest in the nucleophilic reactivity of peroxy anions[3] and the α effect[4] led us to a reinvestigation of this reaction. Wiberg's mechanism,[2] eq 2–4, involves rate-

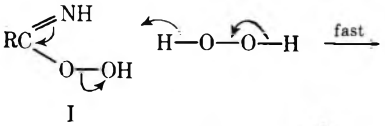


(2)

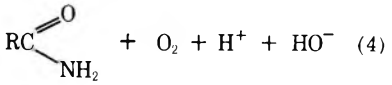


(3)

I



I



(4)

(1) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 469.

(2) K. B. Wiberg, *J. Amer. Chem. Soc.*, **75**, 3961 (1953); K. B. Wiberg, *ibid.*, **77**, 2519 (1955).

(3) J. E. McIsaac, Jr., H. A. Mulhausen, and E. J. Behrman, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, ORGN 70.

(4) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

determining nucleophilic attack of the anion of hydrogen peroxide on the nitrile carbon followed by a rapid reaction of the intermediate peroxycarboximidic acid I with hydrogen peroxide.

In order to obtain rate data for eq 2 in aqueous solution, we chose to study the reaction using *p*-cyanobenzoic acid as the substrate. We were, however, unable to obtain satisfactorily reproducible kinetics for the reaction in carbonate buffers. EDTA (ethylenediaminetetraacetic acid) was added as a sequestering agent to suppress metal ion catalyzed decomposition of hydrogen peroxide. Representative data under pseudo-first-order conditions in the region of pH 10 are given in Table I. Rate data were also obtained under second-order conditions in 0.5 M NaOH and 8.5×10^{-5} M EDTA by following the production of oxygen. These experiments confirmed the stoichiometry of eq 1 with respect to oxygen and yielded rate constants of approximately 1 M^{-1} min^{-1} in rough agreement with the data of Table I. However, both second-order and first-order plots exhibited significant curvature.

TABLE I

KINETIC DATA FOR THE REACTION OF HYDROGEN PEROXIDE AND *p*-CYANOBENZOIC ACID AT 25° [a]

pH	[Nitrile], M	$t_{1/2}$, min	k_{HOO^-}, M^{-1} min^{-1} [b]
9.79	2.5×10^{-2}	200	1.35
10.00	5.0×10^{-2}	102	0.82
10.00	5.0×10^{-2}	71	1.15
10.07	2.5×10^{-2}	162	0.90

[a] Initial $[H_2O_2] = 2 \times 10^{-3}$ M. Carbonate buffers contained 8.5×10^{-5} M EDTA; $\mu = 1.0$ M with KCl in deionized water. [b] Calculated using a pK_a for H_2O_2 of 11.37[3] and statistically and stoichiometrically corrected.

These data and the well-documented susceptibility of peroxide reactions to metal ion catalysis led us to carry out a series of kinetic experiments in carbonate buffers in which all solutions were prepared from the same bottles in order to evaluate the effects of EDTA. Figure 1 demonstrates that in the presence of EDTA, hydrogen peroxide alone is stable but that it disappears rapidly in the presence of the nitrile. In the absence of EDTA, the disappearance of hydrogen peroxide is roughly five times faster when the nitrile is present. This figure also shows the complex kinetics by the evident curvature of the plots. A study of the effects of EDTA concentration indicates that EDTA itself, or its complexes with metal ions, is involved in reaction with some species in solution (perhaps the intermediate peroxycarboximidic acid).

In phosphate buffers, however, EDTA has no observable effect, perhaps because phosphates themselves are good sequestering agents. In agreement with Wiberg,[2] we find that under these conditions second-order plots are linear and show no evidence of metal ion involvement. At 50° and pH 6.77 in 0.1 M phosphate buffer we find $k_{HOO^-} = 4.1 \times 10^1$ M^{-1} min^{-1};[5] this compares with Wiberg's[2] value of $k_{HOO^-} = 4.4 \times 10^2$ M^{-1} min^{-1} for benzonitrile in 50% acetone–water. The addition of allyl acetate to the system in phosphate buffer halves the rate of loss of hydrogen peroxide;

(5) Initial $[H_2O_2] = 0.1$ M, initial [nitrile] $= 5.0 \times 10^{-2}$ M; in the presence of 1×10^{-3} M EDTA; calculated using a pK_a for H_2O_2 at 50° of 10.98.[3]

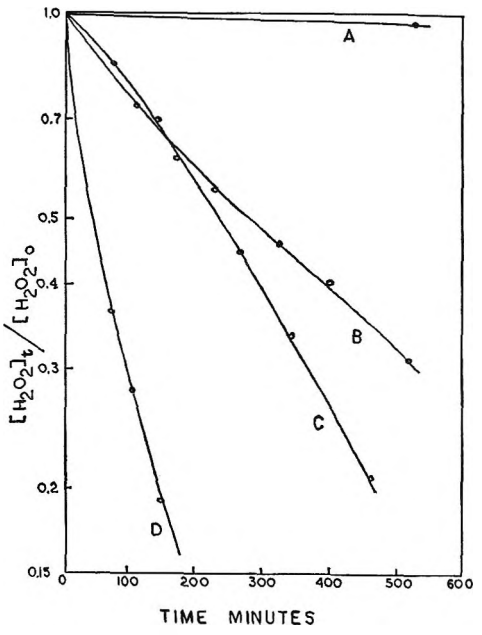


Figure 1.—First-order plots demonstrating the effect of EDTA and *p*-cyanobenzoic acid on the rate of loss of H_2O_2. Initial $[H_2O_2] = 3.5 \times 10^{-3}$ M in 0.3 M carbonate buffer at pH 9.75; $\mu = 1.0$ with KCl; $T = 25°$. A, [EDTA] $= 8.5 \times 10^{-5}$ M, no nitrile; B, no EDTA, no nitrile; C, [EDTA] $= 8.5 \times 10^{-5}$ M, [nitrile] $= 2.5 \times 10^{-2}$ M; D, [nitrile] $= 2.5 \times 10^{-2}$ M, no EDTA.

this is expected on the basis of the work of Payne[6] and his colleagues on the epoxidation of olefins by peroxycarboximidic acids.

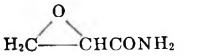
We conclude that Wiberg's[2] mechanism is substantially correct for the system he investigated, but at higher pH under the usual preparative conditions,[1] in the absence of EDTA or phosphates, there can be a significant contribution to the rate of loss of hydrogen peroxide by a metal-catalyzed free-radical reaction.[7]

As a test for the proposed mechanism[2] of the fast step, eq 4, we have carried out a double-isotope-labeling experiment[9] at pH 7.4. Wiberg's mechanism predicts that for doubly labeled hydrogen peroxide H–^{18}O–^{18}O–H, 100% of the double label will be retained, appearing as $^{36}O_2$ (no scrambling). An experiment was performed in which 16% of the hydrogen peroxide was doubly labeled; 81% of the original double label appeared as $^{36}O_2$ in the product oxygen. The data are listed in Table II. This suggests that Wiberg's mechanism cannot be operating exclusively, but that another mechanism must also be involved.

Edwards and coworkers[10-13] have shown that per-

(6) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **26**, 651 (1961); G. B. Payne, P. H. Deming, and P. H. Williams, *ibid.*, **26**, 659 (1961).

(7) This is consistent with the observation that acrylonitrile in carbonate buffer yields only "resinous products,"[8] whereas at pH 7.0–7.5 70% yields of the epoxyamide are isolated.[6]



(8) J. V. Murry and J. B. Cloke, *J. Amer. Chem. Soc.*, **56**, 2749 (1934); see also M. F. Shostakovskii and A. B. Bogdanova, *Chem. Abstr.*, **46**, 1961*f* (1952).

(9) J. O. Edwards and P. D. Fleischauer, *Inorg. Chem. Acta, Rev.*, **2**, 53 (1968).

(10) E. Koubek, G. Levy, and J. O. Edwards, *Inorg. Chem.*, **3**, 1331 (1964).

(11) E. Koubek, M. L. Haggett, C. J. Battaglia, K. M. Ibne-Rasa, H. Y. Pyun, and J. O. Edwards, *J. Amer. Chem. Soc.*, **85**, 2263 (1963).

(12) R. E. Ball, J. O. Edwards, M. L. Haggett, and P. Jones, *ibid.*, **89**, 2331 (1967).

(13) E. Koubek and J. E. Welsch, *J. Org. Chem.*, **33**, 445 (1968).

TABLE II

MASS SPECTRAL ANALYSIS OF OXYGEN GAS

	Mole fractions		
	$^{32}O_2$	$^{34}O_2$	$^{36}O_2$
H_2O_2[a]	0.826	0.014	0.160
Reaction[b]	0.834	0.037	0.129

$$\text{Per cent unscrambled} = \frac{0.129}{0.160} \times 100 = 81\%$$

[a] Oxygen liberated by oxidation with Ce(IV) in 20% H_2SO_4 at 25°.[12] [b] In 0.1 *M* phosphate buffer containing 1×10^{-3} *M* EDTA at pH 7.4 in deionized water; T = 50–52°.

oxycarboxylic acids may decompose simultaneously *via* two distinctly different paths: (1) involving nucleophilic attack by the peroxy acid anion upon the carbonyl carbon of the peroxy acid (no scrambling) and (2) involving nucleophilic attack of the peroxy acid anion upon the outer oxygen of the peroxy acid (scrambling). For example, peroxyacetic acid decomposes 83% *via* path 1 and 17% *via* path 2.[11] When the carbonyl site is sterically hindered, as in the case of peroxypivalic acid, the results are reversed, 24% *via* path 1 and 76% *via* path 2.[13]

Because of the similarity in structure between I and peroxycarboxylic acids, we suggest that the fast step of the reaction can best be described by eq 5–7. Equation 5 predicts no scrambling, eq 7 predicts complete scrambling, and eq 6 predicts 50% scrambling. Edwards' work with peroxycarboxylic acids indicates that the transition states for paths 1 and 2 must be of similar energy; however, sp^2 carbon is the preferred site for attack.[14] In our case, since scrambling occurs, either eq 6 or eq 7 or both must be operative. We therefore conclude that eq 5 accounts for the major portion of the oxygen produced at pH 7.4. Under these conditions, if scrambling occurs only by eq 6, eq 5 will account for 62% of the reaction. If scrambling occurs only by eq 7, eq 5 will account for 81% of the reaction. Since the pK_a values of the peroxycarboximidic acid is probably in the vicinity of 8 (by analogy with peroxycarboxylic acids),[15] we expect that eq 7 will increase in importance at the expense of eq 5 and 6 at higher pH values. However, the complexity of the reaction at higher pH values, *vide ante*, would make the interpretation of double-labeling experiments in carbonate buffer or in sodium hydroxide solutions equivocal.

(14) The anion of hydrogen peroxide is an extremely powerful nucleophile toward the sp^2 carbon.[3]

Experimental Section

Kinetics were followed by monitoring the rate of loss of H_2O_2 by iodometric titration in the usual manner. A Warburg apparatus was used in those experiments for which the product of oxygen was followed.

Doubly labeled $H_2{}^{18,18}O_2$ was prepared by passing ^{18}O enriched H_2O (98 atom % ^{18}O, Miles-Yeda Ltd., Lot No. 18W97U) through an electric discharge tube.[16] The product $H_2{}^{18,18}O_2$ was rinsed from the cold traps with normal 30% H_2O_2 (Mallinkrodt, Lot WPBP) such that the resulting peroxide solution had an isotopic enrichment of 16 atom % of ^{18}O.

The *p*-cyanobenzoic acid (Aldrich Chemical Co., Lot No. 070671) was recrystallized twice from deionized water and treated with decolorizing charcoal. Deionized water was obtained by passing distilled water through a Barnsted mixed-bed ion exchange column. The mono- and dibasic potassium phosphate salts and the mono- and dibasic sodium carbonate salts used for buffer solutions were reagent grade. The disodium salt of EDTA was obtained from Eastman Organic Chemicals (Lot 681 A).

The reaction of the nitrile with hydrogen peroxide was carried out at 50–52°. Gas samples were collected at 2-hr intervals at a pressure of approximately 200 Torr at room temperature. Mass spectrometric analyses were performed on a Hitachi Perkin-Elmer RMU-6D instrument.

Registry No.—Hydrogen peroxide, 7722-84-1; *p*-cyanobenzoic acid, 619-65-8.

Acknowledgments.—This work was supported by the National Science Foundation (GB-7998, GB-21267) and the Department of Chemistry, Western New England College. We also wish to thank J. O. Edwards and Brown University for the use of the mass spectrometer and the discharge tube.

(15) J. F. Goodman, P. Robson, and E. R. Wilson, *Trans. Faraday Soc.*, **86**, 1846 (1962).

(16) R. E. Ball, J. O. Edwards, and P. Jones, *J. Inorg. Nucl. Chem.*, **28**, 2458 (1966).

Nitrile Synthesis *via* the Acid–Nitrile Exchange Reaction

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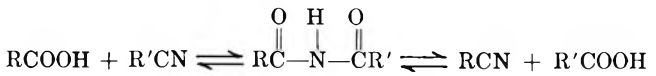
Organic nitriles traditionally have been synthesized from the corresponding carboxylic acids by ultimate dehydration of the amide. Occasionally, the acid–nitrile exchange reaction has been used to accomplish direct conversion of carboxylic acids to nitriles by reaction with acetonitrile at high temperatures.[1,2] Apparently

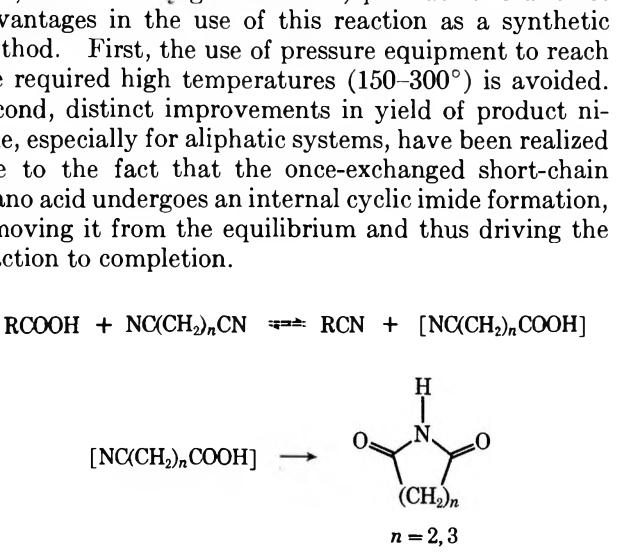
(1) D. J. Loder, U. S. Patent 2,377,795 (1945).

(2) French Patent 1,525,498 (1968).

an equilibrium exists which proceeds through an imide addition product, the equilibrium being displaced toward the side of the weaker carboxylic acid.[3]

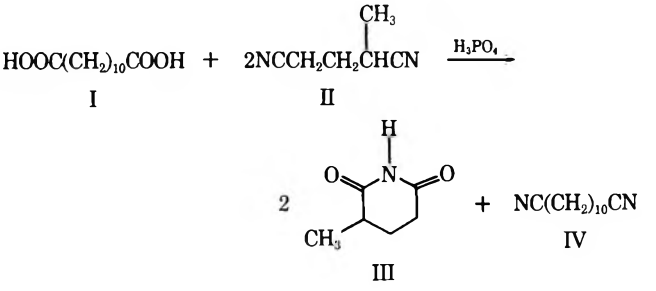


We have found that replacing acetonitrile with short-chain dinitriles (specifically succinonitrile, glutaronitrile, and α-methylglutaronitrile) provides two distinct advantages in the use of this reaction as a synthetic method. First, the use of pressure equipment to reach the required high temperatures (150–300°) is avoided. Second, distinct improvements in yield of product nitrile, especially for aliphatic systems, have been realized due to the fact that the once-exchanged short-chain cyano acid undergoes an internal cyclic imide formation, removing it from the equilibrium and thus driving the reaction to completion.



Although the reaction proceeds uncatalyzed, there are apparent advantages in adding 0.5–1.0 wt % of compounds such as sulfonic, sulfuric, or phosphoric acids or their various salts.

We have used this method for the synthesis of aliphatic dinitriles. Reaction of 1,12-dodecanedioic acid (I) with 2 molar equiv of α-methylglutaronitrile (II) afforded a 98% recovered yield of α-methylglutarimide (III) and a 97% recovered yield of 1,12-dodecanedinitrile (IV). Azelaonitrile similarly was prepared in 87% recovered yield from azelaic acid.



Conversion of I into IV also was accomplished in high yield by refluxing with 2 molar equiv of glutaronitrile or succinonitrile. The products glutarimide, mp 158–159°, and succinimide, mp 126–127°, were purified by recrystallization from chloroform and characterized by infrared, proton magnetic resonance, and elemental analyses.

Experimental Section

A typical reaction involved refluxing (*ca.* 285°) a mixture of 1150 g (5.0 mol) of dodecanedioic acid (I) and 1150 g (10.65 mol) of α-methylglutaronitrile (II) containing 11.6 g of 85% H_3PO_4 for 18 hr. The resulting black solution was cooled and vacuum distilled to give 1246 g (98% of theoretical) of tan solid α-methylglutarimide (III), bp 137° (7 mm), and 929.7 g (97% of theoretical) of yellow liquid dodecanedinitrile (IV), bp 193° (8 mm). Aqueous NaOH washing and redistillation afforded colorless liquid IV, mp 21–22°.

Anal. Calcd for $C_{12}H_{20}N_2$: C, 75.00; H, 10.42; N, 14.58. Found: C, 74.95; H, 10.52; N, 14.54.

Redistillation and recrystallization from 1:1 benzene–cyclohexane afforded white, crystalline III, mp 98.5–99°.

Anal. Calcd for $C_6H_9NO_2$: C, 56.69; H, 7.09; N, 11.02. Found: C, 56.44; H, 7.14; N, 11.00.

Proton magnetic resonance and infrared spectra of III were consistent with the proposed cyclic imide structure.

Registry No.—I, 693-23-2; III, 29553-51-3; IV, 4543-66-2.

(3) F. Becke and T. F. Burger, *Justus Liebigs Ann. Chem.*, **716**, 78 (1968).

Ionization Scheme for the *N*,*N*-Di(carboxymethyl)anilines

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It is well known that aliphatic amino acids exist in aqueous media in the form of dipolar molecules (zwitterions). In fact, the equilibrium between the neutral form and the dipolar form favors the dipolar form by a factor of several tens of thousands.[1] However, if the basicity of the nitrogen is reduced by interaction with an aromatic ring, then the neutral form and dipolar form can have comparable stabilities in aqueous media. For example, the *o*-, *m*-, and *p*-aminobenzoic acids have dipolar molecule–neutral molecule ratios of 0.2, 2.5, and 0.17.[2] Infrared work in D_2O and D_2O–dioxane mixtures[3] demonstrated that the three pyridinecarboxylic acids existed largely as dipolar molecules in aqueous media, but the neutral form was present to a nonnegligible extent.

The purpose of this work was to decide whether or not dipolar molecules or ions were important species in the ionization scheme of the *N*,*N*-di(carboxymethyl)anilines. Two complementary studies on five of these acids (unsubstituted and the para-substituted chloro, fluoro, methyl, and methoxy acids) led to the conclusion that dipolar molecules or ions are not involved to any appreciable extent in the ionization scheme of these acids.

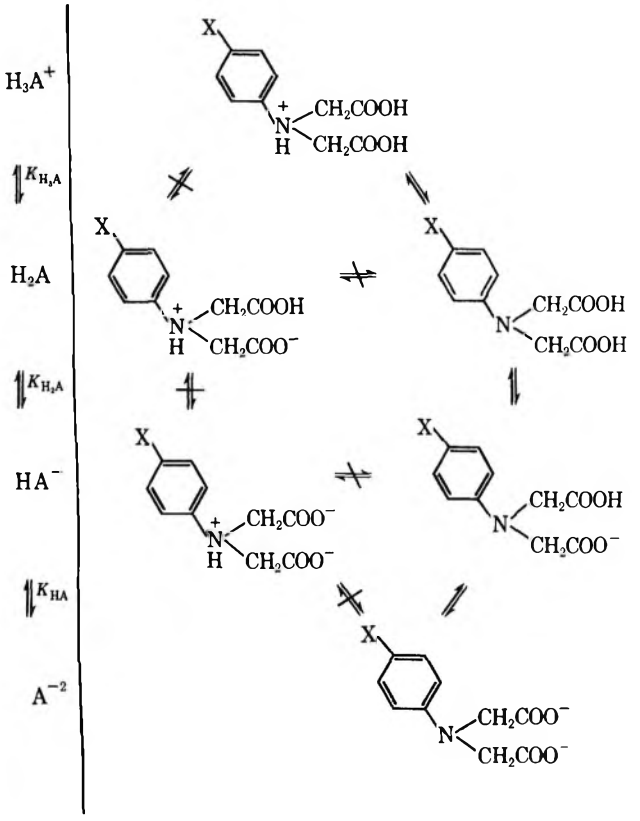
The ionization scheme is presented in Scheme I. It can be seen that H_2A and HA^- can both exist in either a dipolar form or a neutral form, *i.e.*, protonated or nonprotonated on the nitrogen. H_2A^+ represents the fully protonated species. Since thermodynamics does not discriminate between the possible forms, the three experimental p*K*'s which completely describe the ionization scheme for any one acid are actually composite p*K*'s. However, using nonthermodynamic experiments and reasoning, it has been possible to demonstrate

(1) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, Wiley, New York, N. Y., 1961, p 447.

(2) J. J. Christensen, D. P. Wrathall, R. M. Izatt, and D. O. Tolman, *J. Phys. Chem.*, **71**, 3001 (1967).

(3) J. F. Wojcik and T. H. Stock, *ibid.*, **73**, 2153 (1969).

SCHEME I



that the pathway connected by solid arrows is the major pathway for these acids.

Ultraviolet Spectroscopy.—The ultraviolet spectra of the five acids studied here were measured as a function of pH. A peak was observed for all of the acids around 300 nm in basic and weakly acid solution. This peak disappeared as the pH was lowered below about 2. Using these data, the pK data determined in this work, and an iterative computer program, the molar extinction coefficients were determined for all possible species for all of the acids at the proper maxima. These data are given in Table I. The extinction coefficient for H_3A^+ is far smaller than that for the other species for all five acids in the 300-nm region. The extinction coefficients for H_2A and HA^- represent composites made up from contributions from dipolar and neutral forms in the proportion that these make up H_2A and HA^-. Now aniline compounds are known to absorb in the ultraviolet region around 300 nm. However, the anilinium ions do not absorb here; protonation shifts the absorption to lower wavelengths. Thus, it is expected that the extinction coefficients of H_2A and HA^- represent a contribution from the neutral form only. The ratios of the extinction coefficient for A^{2-} to that for HA^- are 1.17, 0.99, 1.16. 1.09, and 1.17 for the chloro, fluoro, unsubstituted methyl, and methoxy compounds, respectively. The same ratios for A^{2-} and H_2A are 1.10, 0.98, 1.12, 1.11, and 1.06. It would be expected that either of these ratios would increase across the series if a dipolar form were important for either HA^- or H_2A. This would be so because the dipolar form in each case would make the extinction coefficient for that species smaller, the effect being greater as the dipolar form contributed more to the structures of H_2A and HA^-. The increase across the series would be expected because the basicity of the nitrogen increases across the series. This would make the dipolar form more important for the methoxy compound than the others. The absence of such an increase supports the ionization pathway proposed. Both sets of data can be used to estimate an upper limit to the concentration of dipolar species in the methoxy case. Assuming a 10% uncertainty in all the extinction coefficients, it is estimated that the amount of dipolar species in the methoxy case must be less than 15% in order to account for the approximate constancy of all of the ratios. The per cent dipolar species would be less than 15% for the other compounds.

TABLE I

MOLAR EXTINCTION COEFFICIENTS[a]

Substituent	Registry no.	H_2Y λ_{max}	H_2Y ϵ	HY^- λ_{max}	HY^- ϵ	Y^{2-} λ_{max}	Y^{2-} ϵ
p-Cl	30042-69-4	305	2000	308	2100	312	2300
p-F	31045-00-8	302	2500	308	2600	312	2500
p-H	1137-73-1	293	2200	297	2200	301	2500
p-CH_3	28444-51-1	298	2200	304	2100	308	2300
p-CH_3O	30042-67-2	309	2300	314	2600	318	2700

[a] λ values are in nm, ϵ values are in M^{-1} cm^{-1}.

Dissociation Constants.—The three different acid dissociation constants for each of the five acids are tabulated in Table II. Each of the three pK's was analyzed in terms of a Hammet $\sigma\rho$ plot.[4] It is expected that the pK (or pK's) which involves the ionization of the proton off the nitrogen will be most sensitive to substituent effects. The ρ value for the first ionization was 3.5, that for the second 0.0, and that for the third 0.8. It is seen that the first ionization is by far the most sensitive to substituent effects. This ρ value compares favorably with the value of 3.56 for the ionization of N,N-dimethylanilinium ions.[5]

TABLE II

pK VALUES OF THE N,N-DI(CARBOXYMETHYL)ANILINES[a]

Substituent	pK_{H_3Y}	pK_{H_2Y}[b]	pK_{HY}[b]
p-Cl	0.5 ± 0.2	2.38 ± 0.02	4.84 ± 0.02
p-F	0.2 ± 0.2	2.43 ± 0.02	4.90 ± 0.02
p-H	−0.4 ± 0.2	2.34 ± 0.03[c]	5.04 ± 0.02[c]
p-CH_3	−0.3 ± 0.2	2.21 ± 0.13	5.24 ± 0.02
p-CH_3O	−1.3 ± 0.2	2.41 ± 0.05	5.16 ± 0.02

[a] All averages based on five determinations. [b] Data for *m*-SO_2H and *p*-SO_2H agree reasonably well with these data depending on what σ values are used (L. G. Sillen and A. E. Martell, "Stability Constants," 2nd ed, The Chemical Society, London, 1964, p 648). [c] Compare with 2.40 ± 0.1 and 4.96 ± 0.1 and 20° [G. Schwarzenbach, G. Anderegg, W. Schneider, and H. Senn, *Helv. Chim. Acta*, **38**, 1147 (1955)].

Conclusions

The results presented here can be extended to other ring-substituted compounds. The σ value for the *p*-methoxy compound is one of the most negative of the σ values and suggests that the nitrogen in the methoxy compound would be the most basic of all aniline com-

(4) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 173.

(5) P. R. Wells, "Linear Free Energy Relationships," Academic Press, London, 1968, p 12.

pounds. This would then be the most likely possibility for the observation of a dipolar species. Since it is not conclusively observed in this case, no substituent of those commonly investigated would be expected to produce dipolar species.

Experimental Section

The acids were synthesized from the parent anilines using the procedure outlined by Pettit and Irving.[6] Neutralization equivalents were determined for all of the acids and found to agree with the theoretical value within 1%. The neutralization equivalent of the *p*-methoxy compound was that for a monohydrate. Microanalysis for this compound confirmed the result. Microanalyses were carried out by Galbraith Laboratories.

Anal. Calcd for *N,N*-di(carboxymethyl)aniline ($C_{10}H_{11}NO_4$): C, 57.41; H, 5.30; N, 6.70. Found: C, 57.49; H, 5.17; N, 6.57.

Anal. Calcd for *N,N*-di(carboxymethyl)-4-chloroaniline ($C_{10}H_{10}NO_4Cl$): C, 49.29; H, 4.14; N, 5.75. Found: C, 49.48; H, 4.08; N, 5.60.

Anal. Calcd for *N,N*-di(carboxymethyl)-4-fluoroaniline ($C_{10}H_{10}NO_4F$): C, 52.86; H, 4.44; N, 6.17. Found: C, 52.74; H, 4.25; N, 5.99.

Anal. Calcd for *N,N*-di(carboxymethyl)-4-methylaniline ($C_{11}H_{13}NO_4$): C, 59.18; H, 5.87; N, 6.28. Found: C, 59.96; H, 6.09; N, 6.21.

Anal. Calcd for *N,N*-di(carboxymethyl)-4-methoxyaniline ($C_{11}H_{13}NO_5 \cdot H_2O$): C, 51.36; H, 5.88; N, 5.45. Found: C, 51.51; H, 6.04; N, 5.44.

Nmr spectra of all of the acids were run in NaOD solutions on a Varian A-60. All of the compounds gave the expected aromatic chemical shifts around 6.72–6.92 relative to 3-(trimethylsilyl)-propanesulfonate. The methylene chemical shifts fell between 3.82 and 3.89. The methyl chemical shift in the *p*-methyl compound was 2.22. The methyl shift in the *p*-methoxy compound was at 3.70. Integrated results confirmed the molecular formulas.

The ultraviolet spectra were run on a Beckman DK-2 at 25°. A stock solution of the acid was prepared in dilute sodium hydroxide solution and then added to the final buffer solution. Buffers were chosen which did not absorb in the wavelength region of interest. The reference cell contained buffer. pH measurements were made on a Beckman Research pH meter. Buffer pH's were in steps of one between 1.00 and 10.00. In order to obtain the best set of extinction coefficients an iterative procedure was used. Based on the pH value and the pK's of the acids the concentration of each species was measured. With these values, extinction coefficients were chosen which best fit the absorption change with pH.

The pK values for H_2A and HA^- were determined from buffer solutions of these acids at 25° and an ionic strength of 0.100 using KCl as the added electrolyte. A glass electrode–calomel electrode system was used to determine the pH of the solution. The pH meter was calibrated against an acetate buffer and 0.01 M HCl. The hydrogen ion concentrations of these buffer solutions are known and the pH reading for the unknown solutions was converted to hydrogen ion concentration. Thus the pK values are concentration constants. In some cases the pH of the solution drifted. This was attributed to an acid-catalyzed decarboxylation of the acids. All pH readings were measured as a function of time and extrapolated back to time of mixing. The correction was negligible for the chloro and fluoro compounds and was greatest for the methoxy. However, the pH drift was small and easily measured.

The pK of H_3A^+ was determined spectrophotometrically. The acidity of the solutions were adjusted with HCl and the ionic strength was kept constant at the value of 3.0 with KCl. Decomposition proceeded more rapidly at these acidities and all spectra were measured as a function of time. This constant is also a concentration constant.

Acknowledgments.—The authors wish to acknowledge support from the National Science Foundation under Research Grant GP-9034.

(6) L. D. Pettit and H. M. N. J. Irving, *J. Chem. Soc.*, 5336 (1964).

The Reaction of Ionic Thiocyanates with Diacyl Peroxides. The Formation of Thiocyanogen

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The thermolysis[1] and photolysis[2] of acyl peroxides represent convenient modes for the production of alkyl radicals, *e.g.*

$$RCOOCR \longrightarrow 2R\cdot + 2CO_2 \quad (1)$$

However, complications due to ionic processes can arise by rearrangement to carboxylic carbonic anhydrides involving carboxy inversion.[3] Acyl peroxides are also susceptible to a variety of nucleophiles (Nuc)[4] and the acyloxy intermediate **1** has been shown in a number of

$$RCOOCR + Nuc \longrightarrow \underset{\mathbf{1}}{R{-}C{-}O{-}Nuc^+} + RCO^- \quad (2)$$

cases to be involved further in competing heterolytic and homolytic processes.[5] Thus, benzoyl hypochlorite, an intermediate in the reaction of benzoyl peroxide and ionic chloride, is capable of electrophilic and free-radical chlorinations.[6]

$$PhCOOCPh + Cl^- \longrightarrow PhCOCl + PhCO^- \quad (3)$$

We wish to report a similar facile reaction when diacyl peroxides are exposed to ionic thiocyanates. Thus, a solution of 0.040 M valeryl peroxide and 0.080 M potassium thiocyanate in acetonitrile afforded thiocyanogen and potassium valerate according to eq 4 after 5 hr at

$$(n\text{-}C_4H_9CO\text{-})_2 + 2KSCN \longrightarrow 2n\text{-}C_4H_9COK + (SCN)_2 \quad (4)$$

room temperature. Less than 3% carbon dioxide and no butyl thiocyanate were detected.[7]

(1) See A. G. Davies, "Organic Peroxides," Butterworths, London, 1961; E. Hawkins, "Organic Peroxides, Their Formation and Reactions," E. and F. Spon, London, 1961; C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957; W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966.

(2) R. A. Sheldon and J. K. Kochi, *J. Amer. Chem. Soc.*, **92**, 4395 (1970).

(3) (a) F. D. Greene, H. S. Stein, C. C. Chu, and F. M. Vane, *ibid.*, **86**, 2081 (1964); (b) C. Walling, H. N. Moulden, J. H. Waters, and R. C. Neuman, *ibid.*, **87**, 518 (1965); (c) H. Hart and D. Wyman, *ibid.*, **81**, 4891 (1959); (d) J. K. Kochi, *ibid.*, **85**, 1958 (1963); (e) R. C. Lamb and J. R. Sanderson, *ibid.*, **91**, 5034 (1969); (f) S. Oae, T. Kashiwagi, and S. Kozuka, *Chem. Ind. (London)*, 1964 (1965); (g) D. B. Denney and N. Sherman, *J. Org. Chem.*, **30**, 3760 (1965); (h) D. S. Tarbell, *Accounts Chem. Res.*, **2**, 296 (1969).

(4) J. O. Edwards, "Peroxide Reaction Mechanisms," Interscience, New York, N. Y., 1962, p 67 ff.

(5) (a) F. D. Greene, W. Adam, and J. E. Cantrill, *J. Amer. Chem. Soc.*, **83**, 3461 (1961); F. G. Greene and W. Adam, *J. Org. Chem.*, **28**, 3550 (1963); **29**, 136 (1964); (b) Y. Ogata and I. Tabushi, *Bull. Chem. Soc. Jap.*, **31**, 962 (1958); (c) L. Horner and E. Schwenk, *Angew. Chem.*, **61**, 411 (1949); L. Horner and B. Anders, *Chem. Ber.*, **95**, 2470 (1962); C. Walling and N. Indictor, *J. Amer. Chem. Soc.*, **80**, 5814 (1958); C. Walling and R. B. Hodgson, *ibid.*, **80**, 228 (1958); C. Sato and T. Otsu, *Chem. Ind. (London)*, 125 (1970).

(6) (a) J. K. Kochi, B. M. Graybill, and M. Kurz, *J. Amer. Chem. Soc.*, **86**, 5257 (1964); (b) N. J. Bunce and D. D. Tanner, *ibid.*, **91**, 6096 (1969).

(7) C. L. Jenkins and J. K. Kochi, *J. Org. Chem.*, in press.

The kinetics of reaction 4 was monitored by following the disappearance of the carbonyl absorption at 1780 cm^{-1} after careful calibration of the system. The reaction between valeryl peroxide and potassium thiocyanate followed clean second-order kinetics (first order in each component) to beyond 80% reaction. The second-order rate constants listed in Table I were invariant

TABLE I

REACTION OF VALERYL PEROXIDE WITH POTASSIUM THIOCYANATE

$(BuCO_2)_2$, $M \times 10$	KSCN, $M \times 10$	Temp, °K	k, M^{-1} sec^{-1}
2.00	4.00	273	1.36×10^{-4}
2.00	0.80	298	1.95×10^{-3}
2.00	2.00	298	1.92×10^{-3}
2.00	1.20	306	3.86×10^{-3}

with changes in the concentration of each reactant. From the temperature dependence of these second-order rate constants the activation parameters were determined at 25° as $\Delta G^{\pm} = 20.6$ kcal/mol, $\Delta H^{\pm} = 15.6$ kcal/mol, and $\Delta S^{\pm} = -16.8$ eu.

We deduce from these results that the reaction is a multistep process, and the following mechanism is formulated in which the first step (eq 5) is rate-determining.

$$(n\text{-}C_4H_9CO)_2 + KSCN \longrightarrow \underset{\mathbf{2}}{n\text{-}C_4H_9COSCN} + n\text{-}C_4H_9COK \quad (5)$$

$$n\text{-}C_4H_9COSCN + KSCN \longrightarrow n\text{-}C_4H_9COK + (SCN)_2 \quad (6)$$

Nucleophilic attack by thiocyanate on valeryl peroxide represented by eq 5 compares with the oxidation in aqueous solution of thiocyanate by hydrogen peroxide in which the rate-limiting step was represented[8] as

$$HOOH + SCN^- \longrightarrow \underset{\mathbf{3}}{HOSCN} + HO^- \quad (7)$$

The activation parameters for reaction 7 at 25° are $\Delta H^{\pm} = 14.9$ kcal/mol and $\Delta S^{\pm} = -25$ eu. These values are similar to those obtained for reaction 5 above, and both sets of activation parameters lie in the range $\Delta H^{\pm} = 12$–16 kcal/mol and $\Delta S^{\pm} = -15$ to -30 eu, observed for a variety of other nucleophilic displacements on peroxidic oxygen.[9]

Despite the similarity in (a) the kinetics, (b) the rate-determining steps, and (c) the intermediates, the stoichiometries of the reactions between thiocyanate ion and hydrogen peroxide or valeryl peroxide are markedly different. Thus, thiocyanogen was the exclusive product of the oxidation of thiocyanate by valeryl peroxide (eq 4), whereas none was detected when hydrogen peroxide was the oxidant. The stoichiometry of the latter oxidation was represented by the rather complex eq 8.[8]

$$4H_2O_2 + SCN^- \longrightarrow HSO_4^- + HOCN + 3H_2O \quad (8a)$$

$$HOCN + 2H_2O \longrightarrow NH_4^+ + HCO_3^- \quad (8b)$$

Following the rate-limiting formation of HOSCN, the postulation of several simultaneous and consecutive reactions involving facile oxidation of the intermediate **3** by hydrogen peroxide was necessitated. The formation of thiocyanogen from the metastable n-$C_4H_9CO_2SCN$ is most readily accommodated by nucleophilic attack on **2** by thiocyanate ion (eq 6). This lability of the oxygen–sulfur bond is analogous to the situation in acyl hypochlorites, in which molecular chlorine is readily formed (eq 9) in the presence of ionic chloride under similar conditions.[6]

$$PhCOCl + Cl^- \longrightarrow PhCO^- + Cl_2 \quad (9)$$

The analogy with acyl hypochlorite is somewhat limited, since the Hunsdiecker product[10] derived by homolysis (eq 10) was not represented. The unimportance of such a pathway could be due either to the slow homolysis (eq 10) or the facility of reaction 6 relative to decomposition.[11]

$$n\text{-}C_4H_9COSCN \longrightarrow n\text{-}C_4H_9CO\cdot + \cdot SCN \quad (10)$$

$$n\text{-}C_4H_9CO\cdot \longrightarrow CO_2 + n\text{-}C_4H_9\cdot \xrightarrow{C_4H_9CO_2SCN} n\text{-}C_4H_9SCN \quad (11)$$

In the present study, the reaction of diacyl peroxide with thiocyanate ion has been studied in an inert medium to determine the reactivity and fate of the intermediate **2** in the absence of other reagents. However, this intermediate, RCO_2SCN, represents a potentially active agent for thiocyanation,[12] and reactions with other nucleophiles such as alkenes and arenes would be of interest.

Experimental Section

Materials.—Valeryl peroxide was prepared as described previously.[13] Potassium thiocyanate, n-butyl thiocyanate, and n-butyl isothiocyanate (Eastman Organics) were commercial samples. Acetonitrile was redistilled from phosphorus pentoxide before use.

A solution of thiocyanogen in 75 ml of acetonitrile was prepared by treating 0.0187 mol of bromine in 50 ml of acetonitrile with 0.0218 mol of lead thiocyanate in 25 ml of acetonitrile. The unreacted $Pb(NCS)_2$ and $PbBr_2$ were removed by filtration and the concentration of thiocyanogen was determined by iodometric titration[14] to be 0.246 M.

Analysis.—Valeryl peroxide showed a doublet absorption at 1780 and 1800 cm^{-1} in the infrared region characteristic of diacyl peroxides. The absorbances of the bands were carefully measured in acetonitrile and calibration curves were constructed over the range of relevant concentrations. Valeryl peroxide was also assayed by iodometric titration using ferric chloride (0.02% solution) as a catalyst.[15]

Carbon dioxide was measured by quantitative gas chromatography using the internal standard method with ethane as the marker.[13] Sodium valerate was neutralized and determined quantitatively by gas chromatography on a FFAP column. Thiocyanogen was measured by gas chromatography and iodometric titration.

Kinetics.—Standard solutions of valeryl peroxide and potassium thiocyanate in acetonitrile were mixed in the appropriate ratios

(8) I. R. Wilson and G. M. Harris, *J. Amer. Chem. Soc.*, **82**, 4515 (1960); **83**, 286 (1961).

(9) R. Curci and J. O. Edwards, "Organic Peroxides," Vol. I, D. Swern, Ed., Interscience, New York, N. Y., p 199 ff (1970).

(10) *Cf.* F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Amer. Chem. Soc.*, **90**, 5793 (1968); C. V. Wilson, *Org. Reactions*, **9**, 332 (1957); R. G. Johnson and R. K. Ingham, *Chem. Rev.*, **56**, 219 (1956).

(11) See J. K. Kochi and R. V. Subramanian, *J. Amer. Chem. Soc.*, **87**, 1508 (1965).

(12) Compare with the electrophilic chlorination using benzoyl hypochlorite reported in ref 6a.

(13) J. K. Kochi, *J. Amer. Chem. Soc.*, **85**, 1950 (1963).

(14) A. I. Vogel, "Quantitative Inorganic Analysis," 3rd ed., Wiley, New York, N. Y., p 343 ff.

(15) L. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).

to obtain several concentrations of reactants. The reactions were carried out in standard volumetric flasks which were placed in a constant-temperature bath. Samples were removed periodically and analyzed for the extent of reaction. The kinetic runs were carried out under conditions in which the relative concentrations of valeryl peroxide and potassium thiocyanate were varied. Second-order kinetics were followed in each case to beyond 80% reaction.

Registry No.—Thiocyanogen, 505-14-6; valeryl peroxide, 925-19-9; potassium thiocyanate, 333-20-0.

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tert-Alkylnitroso Compounds. Synthesis and Dimerization Equilibria

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Kahr and Berther[1] showed that sodium tungstate catalyzed hydrogen peroxide oxidation of primary amines containing an α hydrogen gives oximes. With an amine containing no α hydrogen, this oxidation should give the nitroso compound. In this way we have prepared 2-methyl-2-nitrosopropane in 24% yield.[2] This simple one-step preparation from the inexpensive *tert*-butylamine is more convenient than the previous routes such as $KMnO_4$ oxidation of *tert*-butylamine to the nitro compound[3] followed by Zn–HCl reduction to the hydroxylamine[4] and finally bromine oxidation.[5] The nitroso compound has also been prepared on a small scale by oxidation of *tert*-butylamine vapor with solid *m*-chloroperbenzoic acid.[6] The other product of the H_2O_2 oxidation is 2-methyl-2-nitropropane. Using more H_2O_2 the yield of this nitro compound is 70%. This is a rapid and convenient alternative to permanganate oxidation.

$$RNH_2 + H_2O_2 \xrightarrow{Na_2WO_4} RNO \longrightarrow RNO_2$$

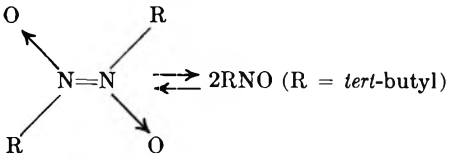
R = *tert*-butyl or 1,1,3,3-tetramethylbutyl

The method functions as well with water-insoluble amines such as 1,1,3,3-tetramethylbutylamine which gives the nitroso compound in 36% yield.

Unhindered aromatic nitroso compounds are monomeric in solution while aliphatic nitroso compounds are dimeric in solution.[7,8] For example, nitrosobenzene is 100% dissociated at 20° in benzene (0.1 *M*) while nitrosocyclohexane is only 0.088% dissociated.[8] The title compounds are exceptions to this. The high steric hindrance of a *tert*-alkyl group favors the monomeric form. For example, we have found that solutions of 2,4,4-trimethyl-2-nitrosopentane in CCl_4 (0.5 *M*) are >99% dissociated by nmr analysis. The equilibrium constants for the *tert*-butyl compound were measured at several temperatures; these and the thermodynamic values are given in Table I.

TABLE I

EQUILIBRIUM CONSTANTS AND THERMODYNAMIC VALUES



K_c = [monomer]²/[dimer]

Temp, °C (±0.5°)	K_c	$\Delta G°$, cal
35.0	4.85	−968
26.5	2.77	−609
20.0	1.92	−381
9.0	1.06	−33
4.0	0.57	309
0.5	0.43	458

$\Delta H° = 11.8 \pm 0.3$ kcal/mol
$\Delta S° = 41.5 \pm 1.0$ cal/(deg mol)

The $\Delta H°$ is 9 kcal/mol smaller than that for nitrosocyclohexane (20.6 kcal/mol),[8] probably due to the steric bulk of the *tert*-butyl group causing a large amount of crowding in the dimer. This is the opposite of the effect of steric hindrance on aromatic compounds. Ortho substitution favors dimerization; for example, nitrosomesitylene is about 69% dimer. This was explained[9] as steric hindrance to resonance in the monomer which destabilizes the monomer with respect to dimerization.

The per cent dissociation was measured by nmr integration. The spectra of the dimers were obtained by rapid scanning of solutions freshly prepared from the crystalline dimers. These solutions were pale blue but after a few minutes they were deep blue and the spectra showed mostly monomer.

2,4,4-Trimethyl-2-nitrosopentane is thermally unstable. Heating a sample at 150° for 10 min causes complete decomposition giving a variety of products including diisobutylenes and the nitro compound.

Experimental Section

2-Methyl-2-nitrosopropane.—A solution of *tert*-butylamine (36.6 g, 0.50 mol) and $Na_2WO_4 \cdot 2H_2O$ (4.0 g) in 50 ml of water was cooled in an ice bath. Hydrogen peroxide (170 g of 21%, 1.0 mol) was added dropwise over 1.3 hr at 15–20° with stirring.[10]

(1) K. Kahr and C. Berther, *Chem. Ber.*, **93**, 132 (1960).

(2) 2-Methyl-2-nitrosopropane is frequently used as a trap for free radicals where the resulting nitroxyl radical can be examined by esr: M. J. Perkins, P. Ward, and A. Horsfield, *J. Chem. Soc. B*, 395 (1970); P. Tordo, M. P. Bertrand, and J.-M. Surzur, *Tetrahedron Lett.*, 3399 (1970).

(3) N. Kornblum, R. J. Clutter, and W. J. Jones, *J. Amer. Chem. Soc.*, **78**, 4003 (1956); N. Kornblum, *Org. Reactions*, **12**, 133 (1962).

(4) F. D. Greene and J. F. Pazos, *J. Org. Chem.*, **34**, 2269 (1969).

(5) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 6522 (1957).

(6) R. J. Holman and M. J. Perkins, *J. Chem. Soc. C*, 2195 (1970).

(7) P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, p 358.

(8) V. v. Keussler and W. Lüttke, *Z. Elektrochem.*, **63**, 614 (1959).

(9) R. R. Holmes, *J. Org. Chem.*, **29**, 3076 (1964); see also R. Okazaki, T. Hosogai, E. Iwadore, M. Hashimoto, and N. Inamoto, *Bull. Chem. Soc. Jap.*, **42**, 3611 (1969).

(10) Stop H_2O_2 addition temporarily whenever 20° is reached. More rapid addition can cause accumulation of H_2O_2, leading to higher temperatures.

Stirring was continued for 30 min more at 20–25°. About 3 g of NaCl was added to break the emulsion and the blue organic layer was separated. This was washed with dilute HCl and dried ($MgSO_4$). Distillation gave 10.2 g (24%) of the dark blue nitroso compound, bp 50–55°, which rapidly solidified to a colorless solid, mp 74–75° (sealed capillary, variable according to how long the sample is in the bath) (lit.[4,6] mp 66–67° or 79–81°). The distillate should be kept in an ice bath until it solidifies, since the heat of dimerization–crystallization can boil off some of the monomer.

Continued distillation gave 21.2 g (41%) of the nitro compound, bp 126–127°.

2-Methyl-2-nitropropane.—A solution of *tert*-butylamine (36.6 g, 0.50 mol), $Na_2WO_4 \cdot 2H_2O$ (4.0 g), and 25 ml of water was cooled in an ice bath. Hydrogen peroxide (255 g of 21%, 1.50 mol) was added dropwise over a 2-hr period with stirring. The first 100 g was added at 15–20°,[10] 100 ml of methanol was then added, and the H_2O_2 addition was continued at 25–35°. This was stirred for an additional hour at 25°. The organic layer was separated and the water layer was extracted with three 25-ml portions of ether. The combined organic layer and extract was dried ($MgSO_4$) and distilled to afford 35.9 g (70%), bp 126–127° (lit.[3] bp 126–127°), $\delta_{TMS}^{CCl_4}$ 1.60.

2,4,4-Trimethyl-2-nitrosopentane.—Hydrogen peroxide (0.40 mol, 65 g of 21%) was added over a 30-min period to a mixture of 2.0 g of $Na_2WO_4 \cdot 2H_2O$, 25 ml of water, and 25.9 g (0.20 mol) of 1,1,3,3-tetramethylbutylamine with stirring. A temperature of 18–22° was maintained by occasional ice bath cooling. The blue mixture was stirred for an additional 3.5 hr at 18–22°. The organic layer was separated with 25 ml of pentane and then extracted with excess dilute HCl. The blue organic layer was then dried (K_2CO_3) and distilled to give 10.24 g (36%) of the nitroso compound, bp 90–92° (130 mm), a blue liquid which slowly crystallized. Pressing the pale blue crystals on filter paper gives white solid, mp 63–65° (lit.[5] mp 63–64°).

Continued distillation gave 2,4,4-trimethyl-2-nitropentane (6.57 g, 21%): bp 80–85° (15 mm) [lit.[11] bp 83–86° (18 mm)]; $\delta_{TMS}^{CCl_4}$ 0.95 (9 H), 1.60 (6 H), 1.98 (2 H).

A sample of the crystalline nitroso dimer was dissolved in CCl_4 (pale blue solution) in an nmr tube and scanned rapidly. The dimer showed $\delta_{TMS}^{CCl_4}$ 0.96 (9 H), 1.52 (6 H), 2.06 (2 H). Within a few minutes the solution was deep blue and no trace of the dimer was detectable. The spectrum now showed only monomer: $\delta_{TMS}^{CCl_4}$ 0.82 (9 H), 1.04 (6 H), 2.34 (2 H).

Equilibrium Measurement.—A solution of 0.0563 g of 2-methyl-2-nitrosopropane per gram of CCl_4 was analyzed by nmr integration using a variable-temperature probe. The solution was held at each temperature until a constant peak ratio was obtained. The molar concentrations were calculated using a

Temp, °C	Wt % monomer	Temp, °C	Wt % monomer
35.0	76.5	9.0	51.1
26.5	67.6	4.0	40.9
20.0	61.5	0.5	36.8

correction for the density of CCl_4 at each temperature.[12] The ΔH° was obtained by a least-squares treatment.

The signal assignments were made as follows. A sample of the crystalline dimer was dissolved in CCl_4 in an nmr tube (pale blue solution) and rapidly scanned. This gave a large peak at δ 1.51 (dimer). After a few minutes this peak was small and the peak at δ 1.20 became the larger (monomer) and the solution became deep blue.[13]

Registry No.—2-Methyl-2-nitropropane, 917-95-3, 31107-20-7 (dimer); 2-methyl-2-nitropropane, 594-70-7; 2,4,4-trimethyl-2-nitrosopentane, 31044-98-1; 2,4,4-trimethyl-2-nitropentane, 5242-78-9.

(11) G. B. Bachman and K. G. Strawn, *J. Org. Chem.*, **33**, 313 (1968).

(12) J. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Elsevier, New York, N. Y., 1950, p 226.

(13) These peaks were previously assigned: J. P. Freeman, *J. Org. Chem.*, **28**, 2508 (1963).

Di-*tert*-butyluretidinedione[1]

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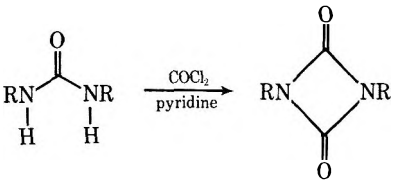
Diaryluretidinediones (1,3-diaryl-1,3-diazetidinediones) are well-known compounds and are readily available by trialkylphosphine-catalyzed dimerization of isocyanates.[2] Little is known of dialkyluretidinediones.[3,4] Treatment of aliphatic isocyanates with the phosphine catalysts gives trimers in good yield.[5] At low conversion small amounts of aliphatic isocyanate dimers may be formed along with the trimers.[3]

We have prepared an aliphatic uretidinedione by a different route. Treatment of *N,N'*-di-*tert*-butylurea with pyridine–phosgene[6] gives the ring compound in 50–60% yield.



R = *tert*-butyl

Previous workers have found that phosgenation of ureas under various conditions gave a variety of products including isocyanates, chloroformamidines, and allophanoyl chlorides.[7] An allophanoyl chloride is a likely intermediate; a recent report describes the preparation of uretidinediones (a series of diaryl and the dimethyl derivative) from allophanoyl chlorides.[4] In our case the choice of *tert*-butyl substituents, which are known to stabilize small rings,[8] allowed synthesis in one operation from the urea. The only by-product was the easily removable carbodiimide.[8c]

Di-*tert*-butyluretidinedione gives one peak in the nmr at δ 1.37 and shows a carbonyl absorption in the infrared at 1760 cm^{-1}. For comparison, β-lactams absorb

(1) Financial support from the National Science Foundation is gratefully acknowledged.

(2) J. A. Moore, "Heterocyclic Compounds with Three- and Four-membered Rings," Part II, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, p 965.

(3) (a) French Patent 1,532,054 (1968); *Chem. Abstr.*, **71**, 81328 (1969); (b) D. M. Parker and M. E. Johnson, Abstracts, Deuxième Congrès International de Chimie Hètérocyclique," 1969, p 91.

(4) H. Helfert and E. Fahr, *Angew. Chem., Int. Ed. Engl.*, **9**, 372 (1970).

(5) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Rev.*, **57**, 47 (1957); J. H. Saunders and R. J. Slocombe, *ibid.*, **43**, 203 (1948).

(6) Acylpyridinium salts are more potent acylating agents than acid chlorides: R. A. Barnes, "Pyridine and Its Derivatives," Part I, E. Klingsberg, Ed., Interscience, New York, N. Y., 1960, p 39.

(7) D. F. Gavin, W. J. Schnabel, E. Kober, and M. A. Robinson, *J. Org. Chem.*, **32**, 2511 (1967), and references cited therein.

(8) (a) See F. D. Greene, J. C. Stowell, and W. R. Bergmark, *ibid.*, **34**, 2254 (1969), and references cited therein. (b) A. Berndt, *Angew. Chem., Int. Ed. Engl.*, **7**, 637 (1968). (c) For a study on the synthesis and reactions of allophanoyl chlorides, including information on carbodiimide formation, see H. Ulrich, J. N. Tilley, and A. A. R. Sayigh, *J. Org. Chem.*, **29**, 2401 (1964).

at 1730–1760 cm^{-1}, diphenyluretidinedione absorbs at 1775 cm^{-1}, di-*tert*-butyldiazetidinedione absorbs at 1813 cm^{-1},[9] and 2,4-azetidinediones absorb at 1725–1750 cm^{-1}.[10]

It is interesting to note that treatment of *tert*-butylamine with phosgene–pyridine gives *tert*-butyl isocyanate[11] and only small amounts of the urea and the uretidinedione. Treatment of *tert*-butylamine with phosgene in the absence of pyridine gives the urea in good yield. No tri-*tert*-butyl isocyanurate was found in these reactions.

The ring compound is quite stable. At 200° it readily cleaves to give 2 mol of *tert*-butyl isocyanate in high yield.[12] Infrared analysis of a sample which had been heated at 200° showed isocyanate and remaining dimer but no trimer. The convenience of this preparation of *tert*-butyl isocyanate is comparable with other good methods.[13] The ring is rapidly opened by sodium methoxide in methanol to give methyl *N,N'*-di-*tert*-butylallophanate.

Photolysis of the di-*tert*-butyluretidinedione gave only *tert*-butyl isocyanate. Di-*tert*-butyldiaziridinone[8a] was not detected[14] and was shown to be stable to the photolysis conditions.

Comparison of the photochemical and mass spectra results are of interest. The principal ions in the mass spectrum are M −15 (loss of CH_3), M −15 − 56 (loss of CH_3 and of C_4H_8), and M − 15 − 99 (the base peak, loss of CH_3 and of C_4H_9NCO). These fragmentations are similar to those observed with acyclic ureas.[15] Completely absent are *m/e* 99 (cleavage of molecular ion into two *tert*-butyl isocyanates), 170 (decarbonylation), and 142, 141 (loss of isobutylene, loss of *tert*-butyl).

Experimental Section

Di-*tert*-butyluretidinedione.—A solution of 4.05 g (0.0410 mol) of phosgene in 50 ml of benzene was added dropwise with stirring and ice-bath cooling to 25 ml of pyridine, giving a yellow precipitate. *N,N'*-Di-*tert*-butylurea (6.43 g, 0.0373 mol) was added at once, giving a thick yellow mixture. This was stirred for 1 hr at room temperature, during which it became more fluid and the yellow color faded. Water (200 ml) was added and the benzene layer was separated. No solid was present, and infrared analysis showed carbodiimide (2095 and 2130 cm^{-1}) and the uretidinedione. The water layer was extracted with pentane and the combined pentane and benzene solution was extracted with 50 ml of dilute HCl to remove the pyridine and to hydrate the carbodiimide. The precipitated *N,N'*-*tert*-butylurea was filtered. The solvent was distilled and the residue taken up in 50 ml of pentane. Filtration gave the remainder of the urea (total 1.70 g, representing a 26% yield of di-*tert*-butylcarbodiimide). The pentane was evaporated and the residue sublimed at 15 mm and 75° to give 3.84 g (52%) of white crystals, mp 87–90°. Recrystallization from a small amount of pentane gave mp 89–90°; ir (CCl_4) 1760 cm^{-1}; nmr (CCl_4) 1.37 (singlet); uv (cyclohexane) 240 nm (ε 96); mass spectrum (70 eV) *m/e* (rel intensity) 198 (M, 2.8), 183 (16.5), 127 (21), 85 (5.9), 84 (100), 70 (4.4), 57 (23), 56 (11.3), 55 (3.8).

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.57; H, 9.15; N, 14.13. Found: C, 60.37; H, 9.14; N, 14.14.

***tert*-Butyl Isocyanate.**—Di-*tert*-butyluretidinedione (1.00 g) was placed in a distilling flask with a boiling stone and heated at 200°. For about 30 min the colorless liquid isocyanate distilled (0.95 g, 95%): ir (neat) 2251 cm^{-1}, nmr (CCl_4) 1.37 (singlet).

Photolysis of Di-*t*-butyluretidinedione.—A solution of 452 mg (2.28 mmol) of the uretidinedione in 4.0 ml of cyclohexane in a quartz tube was placed in a quartz flask filled with methylene chloride (to cut out radiation below 230 mm) and irradiated with a Hanovia mercury lamp for 25 hr. Glc and infrared analysis showed *tert*-butyl isocyanate (11%) and unchanged starting material (88%). Di-*tert*-butyldiaziridinone[8a] was not detected.

Control Experiment on Irradiation of Di-*t*-butyldiaziridinone.—A solution of 0.808 g of the diaziridinone[8a] in 20 ml of cyclohexane was irradiated for 20 hr under the conditions described above. The course of the photolysis was followed by ir, which showed an undiminishing diaziridinone carbonyl band and the appearance at the end of two very small bands, one at 2250 cm^{-1} assignable to *tert*-butyl isocyanate and one at 1680 cm^{-1}. Fine needles, 18 mg (2% yield), mp 240–241°, of di-*tert*-butylurea were collected by filtration and identified by mixture melting point and infrared spectrum.

Methyl *N,N'*-Di-*tert*-butylallophanate.—Di-*tert*-butyluretidinedione (1.00 g, 5.05 mmol) was dissolved in 10 ml of methanol, and about 50 mg of sodium was added. After 5 min the solution was poured into 100 ml of water. The resulting precipitate was filtered, washed with water, and dried to give 0.396 g (34%) of white solid. Recrystallization from cyclohexane followed by sublimation at 0.15 mm and 40° gave mp 132–133°; nmr (CCl_4) 1.32 (9 H), 1.40 (9 H), 3.65 (3 H), 5.2 (1 H, broad); ir (CCl_4) 1710, 1730, 3423 cm^{-1}.

Anal. Calcd for $C_{11}H_{22}N_2O_3$: C, 57.36; H, 9.63; N, 12.17. Found: C, 57.05; H, 9.57; N, 12.06.

Registry No.—Di-*tert*-butyluretidinedione, 30885-14-4; *tert*-butyl isocyanate, 1609-86-5; methyl *N,N'*-di-*tert*-butylallophanate, 30885-16-6.

(9) J. C. Stowell, *J. Org. Chem.*, **32**, 2360 (1967).

(10) A. Ebnöther, E. Jucker, E. Rissi, J. Rutschmann, E. Schreier, R. Steiner, R. Süess, and A. Vogel, *Helv. Chim. Acta*, **42**, 918 (1959).

(11) Carbamoyl chlorides are known to react with pyridine to give isocyanates: R. J. Slocombe, E. E. Hardy, J. H. Saunders, and R. L. Jenkins, *J. Amer. Chem. Soc.*, **72**, 1888 (1950).

(12) Diphenyluretidinedione also gives phenyl isocyanate, while triphenyl isocyanurate gives CO_2 and diphenylcarbodiimide: R. Stollé, *Ber.*, **41**, 1125 (1908).

(13) H. Ulrich and A. A. R. Sayigh, *Angew. Chem., Int. Ed. Engl.*, **5**, 724 (1966).

(14) Photolysis of 1,3-cyclobutanediones effects successive decarbonylation to the corresponding cyclopropanones and olefins: N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).

(15) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 503–506.

On the Dehydration of Bicyclo[2.2.1]-2-heptanols in the Mass Spectrometer

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The mass spectra of bicyclo[2.2.1]-2-heptyl derivatives have been reported in a number of papers. The behavior under electron impact was studied in order to find methods for structure elucidations[1] and also in connection with the investigation of some well-known reactions in the gas phase and solutions as Wagner–Meerwein rearrangement,[2] retro-Diels–Alder reaction,[3] and the classical–nonclassical controversy. In these studies deuterium labeling was often necessary to get precise information regarding the fragmentation in the mass spectrometer and structures of obtained fragments. Kwart and Blazer[3] recently published an

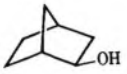
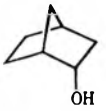
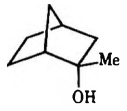
(1) D. D. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 410, 2087, 2735 (1967).

(2) C. A. Bunton and T. W. Del Pesco, *Org. Mass Spectrom.*, **2**, 81 (1969).

(3) H. Kwart and T. A. Blazer, *J. Org. Chem.*, **35**, 2726 (1970).

TABLE I

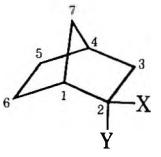
DEHYDRATION OF BICYCLO[2.2.1]-2-HEPTANOL DERIVATIVES BY ELECTRON IMPACT

Compd	No.		Relative intensities[a] [M − 17]	[M − 18]	[M − 19]	[M − 20]	Deuterium contents, %	HOD loss, %
	I		10	100	5			
I-3-3-d_2		Expt[b]	11	97	8		97 D_2	<1
		Calcd[c]	10	97	8		3 D_1	
	II		9	100	5.5			
II-2-d_2		Expt[b]	9	99	6.5		99.5 D	<1
		Calcd[c]	9	99	6			
II-3,3-d_2		Expt[b]	10	95	9.5		96 D_2	<1
		Calcd[c]	9.5	96	9		4 D_1	
	III		10	100	3			
III-7,7-d_2		Expt[b]	8	22	50	33	3 D_3 21 D_2	>5
		Calcd[c]	5	26	55	26	52 D_1 24 D_0	
	IV		10	100	4			
IV-7,7-d_2		Expt[b]	7.5	21	51	33	3 D_3 21 D_2	>5
		Calcd[c]	5	26	54	28	50 D_1 26 D_0	
IV-*endo*-5,6-d_2		Expt[b]	13	63	33	5	4 D_3	~25
		Calcd[c]	13	87	13	1	86 D_2 10 D_1	
	V		16	100	6			
V-*exo*-5,6-d_2		Expt[b]	19	80	23		4 D_3	~2
		Calcd[c]	17	83	21		80 D_2 16 D_1	

[a] Including ^{13}C; accurate within 1%. [b] Normalized to the corresponding undeuterated compound. [c] Assuming that only H_2O is lost; normalized as "b".

analysis of mass spectral fragmentation patterns in various bicyclic alcohols, where bicyclo[2.2.1]-2-heptanol was examined employing the deuterium-labeling technique. It was stated that the alcohols undergo dehydration *via* the formation of an intermediate carbonium ion which then experiences extensive scrambling of hydrogen (and deuterium) atoms on the skeleton before completing elimination of water.

We have also studied the mass spectral behavior of bicyclo[2.2.1]-2-heptanols using a number of specifically deuterated compounds. The results indicate that



bicyclo[2.2.1]-*exo*-2-heptanol (I), X = OH; Y = H
bicyclo[2.2.1]-*endo*-2-heptanol (II), X = H; Y = OH

the dehydration of the molecular ion is a stereospecifically preferred 1,3 (and possibly 1,4) single-step elimination process which occurs prior to hydrogen scrambling.

The mass spectra of bicyclo[2.2.1]-2-heptanol, *exo*- (I) and *endo*- (II), 1-methylbicyclo[2.2.1]-2-heptanol, *exo*- (III) and *endo*- (IV), 2-methylbicyclo[2.2.1]-*endo*-2-heptanol (V), as well as of I-3,3-d_2, II-2-d, II-3,3-d_2, III-7,7-d_2, IV-7,7-d_2, IV-*endo*-5,6-d_2, and V-*exo*-5,6-d_2 have been measured. A survey of the results concerning the loss of water from bicyclo[2.2.1]-2-heptanols is given in Table I. Unfortunately, not all deuterium-labeled compounds were deuterated to a high degree and some calculations were necessary in order to get the distribution of HOD–H_2O. Assuming that only H_2O is lost from the partially deuterated molecules (*i.e.*, [M′ − 17], [M′ − 18], and [M′ − 19] ions obtained; M′ being molecular mass of the species) and regarding the water loss from the undeuterated analog, a pattern for [M − 17], [M − 18], [M − 19], and [M − 20] ions (M′ being the molecular mass according to formula) was calculated and is given in Table I. This pattern is compared with the experimentally obtained

pattern. An increase in abundancy of lower masses [M − 19] and [M − 20] accompanied by a simultaneous decrease in higher masses [M − 17] and [M − 18] gives then the extent of HOD loss. A loss of HOD (*m/e* 19) was found with III-7,7-d_2, IV-*endo*-5,6-d_2, IV-7,7-d_2, and V-*exo*-5,6-d_2. All other deuterated compounds lost only H_2O (*m/e* 18). Deuterium randomization would require a ratio of ions [M − HOD]/[M − H_2O] of about 1:10 for monodeuterated and of about 1:5 for the dideuterated compounds, respectively, regardless of the position of deuteration. The fact that I-3,3-d_2, II-2-*d*, and II-3,3-d_2 do not lose HOD at all rules out a 1,1 and 1,2 elimination process. However, a 1,2 elimination including H from position 1 cannot be excluded on the basis of these results, but it seems unlikely to occur for steric reasons (Bredt's rule). The difference in HOD elimination from IV-*endo*-5,6-d_2 and V-*exo*-5,6-d_2 (which can be 1,3 as well as 1,4 elimination) confirms the stereospecificity of the dehydration. A similar result was obtained in the 1,4 elimination of cyclohexane-1,4-diol-1,4-d_2 where the loss of HOD from the molecular ion was due to 1,4 elimination, the proportion of ion yield associated with the [M − HOD] peak in the spectrum of trans compound being eight times greater than the corresponding peak from the spectrum of cis compound.[4] The loss of HOD in IV-*endo*-5,6-d_2 of 25% indicates that hydrogens from other positions are also contributing to the elimination. No evidence is available whether one or both hydrogens in positions 5 and 6 are involved in dehydration.

A substantial loss of HOD (>5%) was observed in the case of III-7,7-d_2 and IV-7,7-d_2. These compounds were 50% deuterated but these results are good indications that hydrogens from position 7 are involved in dehydration. On the other hand, it is interesting that in these compounds no difference between exo and endo position of the hydroxyl group was found.

The lack of contribution from hydrogens in position 3 in the case of I-3,3-d_2 and II-3,3-d_2 compared with substantial contribution from hydrogens in position 7 is an additional proof that positions 3 and 7 are not equivalent as one would expect in the case of involvement of nonclassical carbonium ion in the process of dehydration.

Experimental Section

Technique.—All spectra were recorded under identical operating conditions with a CEC 21-110C mass spectrometer at about 100° with 70 eV, using a direct inlet (rod).

Origin of Samples.—The samples III, IV, V, III-7,7-d_2, IV-7,7-d_2, IV-*endo*-5,6-d_2, and V-*exo*-5,6-d_2 were prepared in the Physical Organic Chemistry Laboratory, Institute "Rudjer Bošković," by Dr. J. Jerkunica, whereas I, II, I-3,3-d_2, and II-3,3-d_2 were prepared as described earlier.[5]

Registry No.—I, 497-37-0; I-3,3-d_2, 10503-35-2; II, 497-36-9; II-2-*d*, 24867-16-1; II-3,3-d_2, 10503-34-1; III, 766-25-6; III-7,7-d_2, 30469-68-2; IV, 3588-21-4; IV-7,7-d_2, 30469-70-6; IV-*endo*-5,6-d_2, 30469-71-7; V, 3212-16-6; V-*exo*-5,6-d_2, 30469-72-8.

(4) C. G. Macdonald, J. S. Shannon, and G. Sugowdz, *Tetrahedron Lett.*, **13**, 807 (1963).

(5) J. P. Shaefer, M. J. Dagani, and D. S. Weinberg, *J. Amer. Chem. Soc.*, **89**, 6938 (1967).

Condensation Cyclization Reactions of Electron-Deficient Aromatics. III. *N*-Bromosuccinimide Oxidation of Bicyclic Dinitropropenides to Isoxazoline *N*-Oxides

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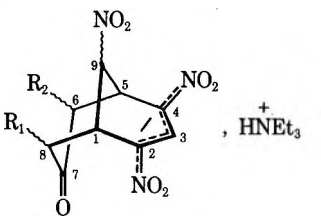
We have previously reported the preparation of a new class of stable bicyclic anions **1** which form spontaneously from appropriately structured Meisenheimer complexes.[1-5] We report here the unusual NBS oxidation of these anions to isoxazoline *N*-oxides and a detailed pmr analysis which provides evidence for the proposed structures.



1a, $R_1 = R_2 = C_6H_5$ (cis)
b, $R_1 = EtO_2C$; $R_2 = H$

Reaction of 2 equiv of NBS with 1 equiv of **1a**[3] or **1b**[3] in methanol solution at 25° results in immediate disappearance of the intense dinitropropenide absorption at 500 nm.[1] Two equivalents of NBS are required, as the first reacts with $HNEt_3^+$ (*vide infra*).[6] Quenching the yellow methanolic solution in a large excess of distilled water yields a voluminous white precipitate, which when filtered and recrystallized from ethanol gives colorless crystals of the oxidation product (*ca.* 50% yield).

The oxidation product obtained from NBS treatment of **1a** melts at 211–213° and analyzes correctly for $C_{21}H_{15}N_3O_7$. This corresponds to a formal loss of hydrogen and triethylamine from **1a**, and is consistent with the parent peak of 421 in the mass spectrum. The product readily forms a dinitrophenylhydrazone, mp 184–185°, rapidly decolorizes permanganate, but does not add bromine. It shows a broad band from 235 to to 290 nm (ϵ 6 × 10^3) in the uv and strong carbonyl and weak olefinic absorption at 1721 and 1653 cm^{-1} in the ir. Base treatment with alcoholic hydroxide or methoxide yields a solution with an intense absorption at 500 nm, indicating that the dinitropropenide function has probably been regenerated. These chemical and spectral properties, coupled with the observed disappearance of one of the benzylic proton resonances and induced nonequivalence of the phenyl groups in the pmr

(1) Previous papers: M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Conner, *J. Org. Chem.*, **35**, 383 (1970); H. Schran and M. J. Strauss, *ibid.*, **36**, 856 (1971).

(2) M. J. Strauss and H. Schran, *J. Amer. Chem. Soc.*, **91**, 3974 (1969).

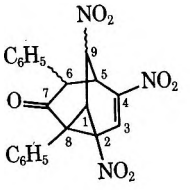
(3) M. I. Foreman, R. Foster, and M. J. Strauss, *J. Chem. Soc. C*, 2112 (1969).

(4) R. Foster, M. I. Foreman, and M. J. Strauss, *Tetrahedron Lett.*, 4949 (1968).

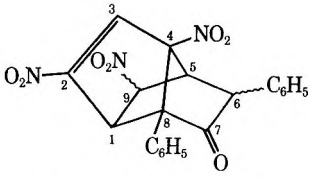
(5) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

(6) This was established by pmr analysis of the reaction of $HNEt_3^+$, Br^-, and NBS.

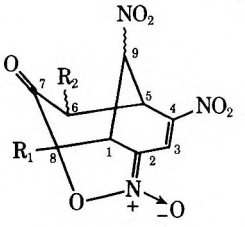
spectrum on conversion of **1a** to the oxidation product (*vide infra*), lead to the conclusion that a bond has formed between one of the benzylic centers, C-6 (C-8), and a constituent atom of the propenide function. The structures **2**, **3**, and **4a** reflect such possibilities, as each could result from initial NBS bromination at C-6 (C-8) of **1a**, followed by intramolecular displacement of bromide by the formal negative charge on C-2 (C-4) or a propenide NO_2 group.



2



3



4a, $R_1 = R_2 = C_6H_5$
b, $R_1 = CO_2Et$; $R_2 = H$
c, $R_1 = H$; $R_2 = CO_2Et$

The carbonyl stretching frequency of the product is more consistent with **2** or **4a** than **3**, but the cyclopropyl C–H absorption near 3000 cm^{-1} anticipated for **2** could not be detected in the presence of the aromatic absorption. The 100-MHz pmr spectrum (Table I) provides

TABLE I

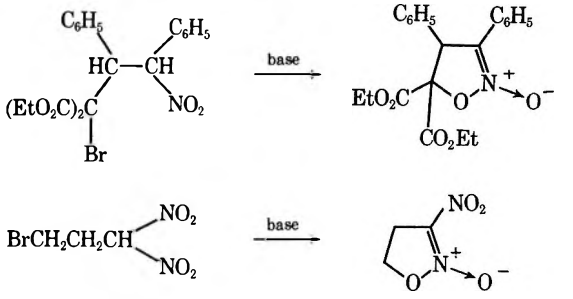
CHEMICAL SHIFTS (δ VALUES) AND SPLITTING[a] OF PROTONS IN THE ISOXAZOLINE *N*-OXIDES **4a** AND **4b** (IN ACETONE-d_6)

	Protons				
Compd	H-1	H-3	H-5	H-6	H-9
4a[e]	4.88 (m)	8.62 (d)	4.96 (m)	4.72 (d)	6.48 (t)
	irr[b]	d	*c*	d	d
	t[d]	irr[b]	*c*	d	t
	m	s	irr[b]	s	d
	m	d	*c*	irr[b]	t
	d[d]	d	*c*	d	irr[b]
	irr[b]	s	irr[b]	s	s
4b[f]	4.41 (m)	8.38 (d)	4.65 (br)	3.12 (dd)	6.09 (t)
	irr[b]	s	irr[b]	q	s
	t[d]	irr[b]	m	dd	t
	s, br	d	br	dd	irr[b]

[a] s = singlet; t = triplet; q = quartet or two droplets; m = multiplet; br = broad; dd = doublet of doublets. [b] Irradiated. [c] Simplified multiplet. [d] Poorly resolved. [e] R_1, δ 7.56 (m, 2 H), 7.38 (m, 3 H); R_2, [a] 7.24 (br, 5 H); spectrum measured at 100 MHz. [f] R_1, δ 1.2 (t, 3 H), 4.2 (q, 2 H); spectrum measured at 60 MHz.

substantive evidence for **4a**, however. The similarity of the H-5 and H-1 chemical shifts might be expected for **3** and **4a**, but not **2**. A cyclopropyl proton, even on a nitrocyclopropane, should resonate at higher field.[7] Since H-3 and H-6 are both strongly coupled to H-5, structure **3** seems unlikely. In addition, the triplet observed for H-9 requires that $J_{1,9} = J_{5,9}$. This would be expected if the dihedral angle between H-1 and H-9 is approximately equal to that between H-5 and H-9, a requirement which is met by **4a** and **2** but clearly not by **3**, regardless of the configuration at C-9. On the basis of the decoupling experiments, the following coupling constants have been determined: $J_{5,6} \cong 3.5$, $J_{1,9} \cong J_{5,9} \cong 2.5$, $J_{3,5} = 2.0$, and $J_{1,5} \cong 2.6$ cps. These values are accurate to about 0.15 cps. Using these coupling constants and the chemical shifts noted above, the calculated spectrum agrees well with that determined experimentally. Three recrystallizations from CH_3OD results in H-9 and H-6 resonances of diminished intensity owing to partial deuterium exchange. Thus, both these protons are relatively acidic, as expected.

The pmr evidence for **4a** is supported by the ir and uv spectra, which are characteristic of isoxazoline *N*-oxides [uv, 280–290 nm (ε 6000); ir, 1610–1660 cm^{-1} (C=N$^+$)][8] and by analogous internal displacement reactions proposed to occur through nitronate intermediates.[8,9]



The bicyclic anion **1b** was treated with NBS in order to confirm the generality of the reaction. In this case, the two isomeric products **4b** and/or **4c** could form, since C-6 and C-8 are no longer equivalent as in **1a**. As expected on the basis of a bromination–internal displacement mechanism for the formation of these isoxazolines, only **4b** was obtained, corresponding to initial bromination of the most reactive site, C-8. The compound melts at 170–173° and analyzes correctly for $C_{12}H_{11}N_3O_9$. The pmr (Table I) and ir spectra of the material are consistent only with **4b**.

Both **4a** and **4b** could suffer base attack at C-8 with concomitant cleavage of the C-8–O bond to regenerate the dinitropropenide function. This is a reasonable explanation for the strong maximum at 500 nm observed in basic solutions of **4**. Attempts to isolate dinitropropenide products have been unsuccessful, as a complex isomeric mixture is formed.

The oxidation of compounds like **1** with NBS occurs generally, and does not require electron delocalizing or withdrawing substituents on C-6 and/or C-8. The instantaneous decolorization of other anions **1** ($R_1 = R_2 = CH_3$; $R_1 = R_2 = H$; $R_1 = CH_3CO$, $R_2 = H$; $R_1 = R_2 = CH_3O_2C$) readily occurs on treatment with NBS.

Experimental Section

The isoxazoline *N*-oxides, **4**, were prepared by adding 2 equiv of NBS to 1 equiv of the appropriate salt, **1**, in a minimum amount of dry methanol. The intense orange color of **1** immediately disappeared and the resulting yellow solution was stirred

(7) J. Smidt and Th. J. de Boer, *Recl. Trav. Chim. Pays-Bas*, **79**, 1235 (1960).

(8) A. Nielsen in "The Chemistry of the Nitro and Nitroso Groups," H. Feuer, Ed., Wiley, New York, N. Y., 1969.

(9) V. A. Tartakovskii, B. G. Gribov, I. A. Savost'yanova, and S. S. Novikov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1644 (1965); *Chem. Abstr.*, **64**, 2080 (1966).

for 5 min and poured into ten times its volume of distilled water. The resulting white precipitate was filtered, dried, and recrystallized twice from dry ethanol to yield pure **4** (~30–50% yield). *Anal.* Calcd for $C_{21}H_{15}N_3O_7$ (**4a**): C, 59.86; H, 3.59; N, 9.97. Found: C, 59.78; H, 3.69; N, 9.81. Calcd for $C_{12}H_{11}N_3O_9$ (**4b**): C, 42.24; H, 3.25; N, 12.31. Found: C, 42.20; H, 3.22; N, 12.17.

Registry No.—NBS, 128-08-5; **4a**, 30388-22-8; **4a** 2,4-DNP, 30388-23-9; **4b**, 30338-24-0.

Acknowledgments.—The authors wish to thank the Army Research Office at Durham, the National Aeronautics and Space Administration, and the Research Corporation for partial support of this work. Thanks are also due to Mr. Robert Martin of Jeolco, Mr. Robert Travis of Varian, and Mr. James Hannon of Perkin-Elmer for use of the Jeolco Minimar-100, Varian X-L-100, and PE R-20B nmr instrumentation.

Pyrolysis of Phenylalkenylidenecyclopropanes[1]

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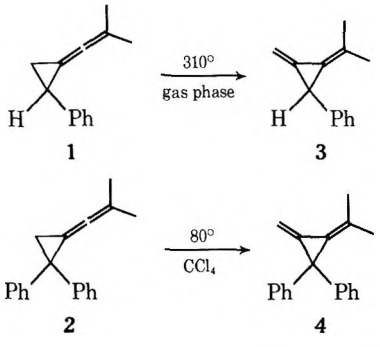
Dimethylenecyclopropanes have been found to be the products of the thermal rearrangement of alkenylidenecyclopropanes in both the parent[3] and methylated[4] systems. Because of the nature of the substitution of these compounds, little or no choice exists in the substitution pattern of the products. To probe this question, we have heated the mono- and diphenylalkenylidenecyclopropanes **1** and **2** and find that the phenyl groups

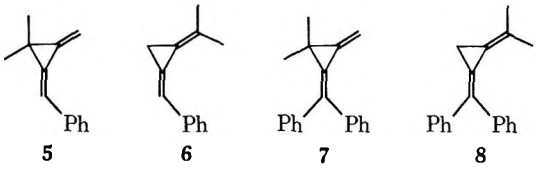


always remain on the cyclopropane ring and do not migrate to the double bonds.[5]

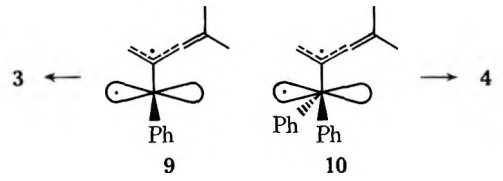
Pyrolysis of **1**[6] in a flow system at 310° under vacuum gives only **3** and starting material in the ratio 2.6:1. Compound **3** was identified by its elemental analysis and nmr spectrum in CCl_4: multiplets at δ 1.82 (3 H, methyl), 1.94 (3 H, methyl), 2.85 (1 H, benzyl cyclopropyl), 5.11 (1 H, vinyl), 5.34 (1 H, vinyl), and 6.9–7.2 (5 H, aryl). The chemical shift of the methyl signals leaves no doubt that it is the double bond and not the three-membered ring that bears the methyl groups. A broad band in the infrared spectrum at 1795 cm^{-1} confirms the methylenecyclopropane structure.[7,8]

Compound 2 is less volatile than **1** *and was therefore* rearranged to **4** in CCl_4 solution at 80°. **2** was made by an adaptation of the method of Hartzler[6] and was identified by its mass spectrum and nmr spectrum in CCl_4: singlets at δ 1.82 (6 H, methyls) and 2.13 (2 H, cyclopropyls) and a multiplet at 7.1–7.5 (10 H, aryl). A band in the infrared spectrum at 2005 cm^{-1} is appropriate for an allene.[9] Compound **4** was similarly identified by its mass spectrum and nmr spectrum in CCl_4: broad singlets at δ 2.09 (6 H, methyls), 5.50 (1 H, vinyl), and 5.64 (1 H, vinyl) and a multiplet at 7.2–7.7 (10 H, aryl). Again, a band in the infrared spectrum at 1795 cm^{-1} is typical of methylene cyclopropanes.[7,8]

The potential products **5–8** are not formed in significant amounts, as appropriate signals do not appear in the nmr spectra of the crude products. At first glance



this may seem strange, but, if the mechanism of these changes involves perpendicular diradicals, as is generally thought,[10,11] it is understandable. The diradicals **9** and **10** should be the most stable ones available, and



they must lead to **3** and **4**, and cannot give the others. At higher temperatures many other compounds are formed, and we hope to report on these at a later time.

Experimental Section

General.—Nmr and infrared spectra were recorded on Varian Associates A-60A and Perkin–Elmer 237B instruments, respectively. Mass spectra were measured on an AEI MS-9 mass spectrometer.[12] Gas chromatographic analyses were performed on a Varian Aerograph A-90P instrument using a 5-ft 10% Dow-Corning 550 silicone oil on 60–80 mesh Chromosorb P column operated at 150° with a He flow rate of 100 ml/min.

Pyrolysis of 1.—Compound **1**, 1-(2-methylpropenylidene)-2-phenylcyclopropane, was prepared by the method of Hartzler[6] and purified by bulb-to-bulb distillation immediately before use. The pyrolysis apparatus consisted of a 20-cm length of 14-mm quartz tube heated by chromel wire. Temperatures in the tube varied by a maximum of 6° over its length. The temperature reported is the maximum in the tube. In a typical run

(1) We thank the National Science Foundation for support of this work through Grant GP-12759.

(2) National Science Foundation Predoctoral Fellow, 1967–1971.

(3) R. Bloch, P. LePerchec, and J.-M. Conia, *Angew. Chem.*, **82**, 910 (1970).

(4) D. R. Paulson, J. K. Crandall, and C. A. Bunnell, *J. Org. Chem.*, **35**, 3708 (1970).

(5) The rearrangement of **1** to **3** at 130° in solution has been noted by T. B. Patrick, E. C. Haynie, and W. J. Probst, *Tetrahedron Letters*, 423 (1971), and, in passing, by I. H. Sadler and J. A. G. Stewart, *Chem. Commun.*, 1588 (1970).

(6) H. D. Hartzler, *J. Amer. Chem. Soc.*, **83**, 4990 (1961).

(7) J. T. Gragson, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *ibid.*, **75**, 3344 (1953).

(8) R. F. Bleiholder and H. Shechter, *ibid.*, **86**, 5032 (1964).

(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958.

(10) W. von E. Doering and H. D. Roth, *Tetrahedron*, **26**, 2825 (1970).

(11) J. J. Gajewski, *J. Amer. Chem. Soc.*, **90**, 7178 (1968).

(12) We thank the National Science Foundation for providing the funds for the purchase of this instrument through Grant GP-5200.

80 μl of 1 was placed in a reservoir at the cold end of the tube and a 0.1-mm vacuum was applied through a trap cooled to −78°. Gentle warming was applied to the sample to facilitate distillation into the hot tube. Collection of the major product gave a colorless liquid: ir 3070, 3060, 3015, 2960, 2915, 2895, 2835, 1795, 1745, 1600, 1490, 1360, 855, and 690 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.53; H, 8.17.

Synthesis of 2.—To a slurry of 6.12 g (0.054 mol) of potassium *tert*-butoxide and 18 g (0.1 mol) of 1,1-diphenylethylene in 75 ml of *n*-pentane held at −10° was added dropwise a solution of 5.12 g (0.054 mol) of 3-chloro-3-methyl-1-butyne[13] in 20 ml of *n*-pentane. Following the addition the slurry was allowed to warm to room temperature and 100 ml of water was added. The layers were separated and the organic material was washed with five 150-ml portions of water, dried over anhydrous sodium sulfate, and concentrated at the water pump to give 21 g of a red oil. Chromatography of 2.0 g of the oil on silica gel using hexane as eluent led to the recovery of 1.5 g of 1,1-diphenylethylene and 0.3 g of 2. A value of 246.140713 was obtained in a precise mass measurement (calcd for $C_{19}H_{18}$: 246.140844).

Pyrolysis of 2.—2 (100 mg) was dissolved in 500 μl of CCl_4 and sealed in a medium-walled nmr tube under nitrogen. Heating the sample at 80° for 19 hr caused complete rearrangement to **4**, which was purified by chromatography on a 1 ft × 0.5 in. column of basic alumina: ir 3080, 3060, 3030, 2970, 2930, 2905, 1795, 1600, 1490, 1440, 1365, 1095, 1070, 855, 775, 750, and 685 cm^{-1}. A value of 246.140713 was obtained in a precise mass measurement.

Registry No.—**1**, 4544-23-4; **2**, 30800-74-9; **3**, 30896-86-7; **4**, 30800-58-9.

(13) W. J. Bailey and C. R. Pfeifer, *J. Org. Chem.*, **20**, 95 (1955).

Mononitration of Methyl Abieta-8,11,13-trien-18-oate

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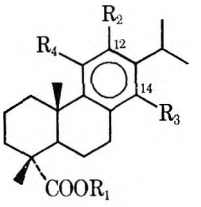
Aromatic substitution reactions on abieta-8,11,13-trien-18-oic acid, dehydroabietic acid (**1a**), and the corresponding methyl ester **1b** have been the subject of a number of investigations. Although monosulfonation at C-12,[1-3] monobromination at C-12,[4] and monoacetylation[2,5] at C-12 and at C-14 (75% C-12) have been reported, attempted mononitration has failed to produce the desired results, yielding instead the 12,14-dinitro derivative **1c**[6] and **1d**.[7] Also an attempt to produce a mononitro derivative *via* nitration of the 12-sulfonic acid and subsequent hydrolysis of the sulfonic acid group failed at the second step.[4] The 14-nitro derivative **1e** has been prepared from methyl 12,14-dinitroabieta-8,11,13-trien-18-oate (**1d**) by selective reduction of the 12-nitro group to the amine **1f** followed by deamination[4,8] and by nitration of the 12-amino compound **1g** followed by deamination.[4,9]



1

	R_1	R_2	R_3	R_4
a	H	H	H	H
b	CH_3	H	H	H
c	H	NO_2	NO_2	H
d	CH_3	NO_2	NO_2	H
e	CH_3	H	NO_2	H
f	CH_3	NH_2	NO_2	H
g	CH_3	NH_2	H	H
h	CH_3	NO_2	H	H
i	CH_3	H	H	NO_2

The work cited indicates that the 12 position is more reactive than the 14 position. We, therefore, decided to investigate anew the feasibility of direct mononitration of methyl abieta-8,11,13-trien-18-oate (**1b**). We hoped to obtain the 12-nitro derivative **1h**, which we believe would be a useful synthetic intermediate. We were encouraged also by the advent of positionally selective nitration procedures in recent years. Acetic acid, for instance, is the solvent of choice for positionally selective nitrations of fluoranthene[10] and naphthalene[11] (mixed acids), acenaphthene[12] (nitric acid), and octaethylporphyrin[13] (fuming nitric acid). Nitric acid in nitromethane is also positionally selective.[11] Mechanistic considerations have been discussed[11,14] but will not be reviewed here.

We attempted mononitration of **1b** with the above procedures and found, uniformly, that under the usual mild conditions no reaction occurred. By increasing time or temperature complex mixtures were obtained which were relatively free of both starting material and the desired product, as shown by the aromatic region of their nmr spectra. The conclusion reached was that the substrate **1b** was not sufficiently reactive toward these reagents under the usual conditions.

The more reactive but still selective[15,16] nitrating agent acetyl nitrate provided a procedure which yields a mixture of the 12-nitro and 14-nitro derivatives, **1h** and **1e**, respectively. A convenient separation of the mixture by one fractional crystallization in methanol gave a first fraction of almost pure 14-nitro derivative **1e** (20% yield). The 14-nitro derivative **1e** was identical with a sample prepared by the method of Zeiss.[8] This one-step synthesis (20%) compares well in terms of con-

(1) Numbering systems used in the past have been translated into the presently accepted system.

(2) L. F. Fieser and W. P. Campbell, *J. Amer. Chem. Soc.*, **60**, 2631 (1938).

(3) T. Hasselstrom and J. D. McPherson, *ibid.*, **60**, 2340 (1938).

(4) W. P. Campbell and M. Morgana, *ibid.*, **63**, 1838 (1941).

(5) L. F. Fieser and W. P. Campbell, *ibid.*, **61**, 2528 (1939).

(6) L. F. Fieser and W. P. Campbell, *ibid.*, **60**, 159 (1938).

(7) E. S. Hansen and H. H. Zeiss, *ibid.*, **77**, 1643 (1955).

(8) H. H. Zeiss, U. S. Patent 2,803,645 (1957); *Chem. Abstr.*, **52**, 2921 (1958).

(9) The assignment of one nitro group of the dinitro compound (**1c** and **1d**) at C-12 was unambiguous.[2,4] Locating the second nitro group at C-14 was based on the expectation of normal meta orientation. Hansen and Zeiss[7] have pointed out that this assignment is reasonable but not beyond question.

(10) A. Streitwieser, Jr., and R. C. Fahey, *J. Org. Chem.*, **27**, 2352 (1962).

(11) P. G. E. Alcorn and P. R. Wells, *Aust. J. Chem.*, **18**, 1377 (1965).

(12) A. Davies and K. D. Warren, *J. Chem. Soc. B*, 873 (1969).

(13) R. Bonnett and G. F. Stephenson, *J. Org. Chem.*, **30**, 2791 (1965).

(14) G. A. Olah, S. J. Kuhn, S. H. Flood, and J. C. Evans, *J. Amer. Chem. Soc.*, **84**, 3687 (1962).

(15) G. Powell and F. R. Johnson, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1955, p 449.

(16) M. L. Scheinbaum, *Chem. Commun.*, 1235 (1969).

venience with the best three-step synthesis (43%).[8] The nmr spectrum supports the assigned structure. The aromatic region contains an AB quartet with J_{AB} = 9 Hz and $\Delta\nu$ = 9.4 Hz.[17] The coupling constant is satisfactory for ortho protons[18] and $\Delta\nu$ is consistent for two protons meta and para to a nitro group, respectively.[19] Alternative structure **1i** is clearly not allowed by these data.

Concentration of the methanol gave a second fraction which is *ca.* 80% 12-nitro **1h** and 20% 14-nitro **1e** (by nmr). The total material represented a 45% yield of the 12 isomer. Pure 12-nitro **1h** was obtained on further fractional crystallization. The structure of the 12-nitro derivative **1h** was established by nitration to the known 12,14-dinitro derivative **1d**[9] and by catalytic hydrogenation to the known 12-amine **1g**.[4]

The nmr spectrum of **1h** has the methine proton of the isopropyl group downfield from its position in **1b**, **1d**, and **1e**. In view of the known long-range shielding effect of the nitro group[13] we assume that the isopropyl group is in some conformation in which the methine proton is out of the area shielded by the nitro group. The methyls of the isopropyl side chain in both **1h** and **1e** appear as doublets (J = 2 Hz) of a doublet (J = 7 Hz). Decoupling experiments to determine the source of the weaker coupling were not conclusive, but suggested that the $ArCH_2$ protons were responsible.

With the two pure isomers in hand it was shown that the 12-nitro compound **1h** underwent catalytic reduction to the amine **1g** smoothly, while the 14-nitro compound **1e** did not react under the same conditions. This is in accord with the selective catalytic reduction of the 12,14-dinitro compound **1d** cited above.[4,8] These data suggested a separation scheme based on selective reduction from the crude mixture of the 12-nitro compound. This was realized and direct catalytic hydrogenation of the crude mixture of products yielded the 12-amine **1g** in 32% yield and the unreacted 14-nitro compound **1e** in 20% yield.

Experimental Section[20]

Nitration.—To a solution of 3.14 g (0.01 mol) of methyl abieta-8,11,13-trien-18-oate (**1b**) in 30 ml of acetic anhydride at 25° was added dropwise with stirring over 15 min a solution of 0.90 ml of fuming nitric acid (90%) in 1.80 ml of acetic anhydride also at 25°. After the addition was completed the mixture was stirred for 1 hr and poured onto ice. The solid, collected by filtration after hydrolysis of the solvent, was washed with water and air dried to 3.48 g. This crude product had four relatively large peaks in the aromatic region of the nmr spectrum (CCl_4) and at least five smaller peaks in the same region. Integration indicated approximately 27% 14-nitro **1e** and 47% 12-nitro **1h** in the crude product.

Isolation of Methyl 14-Nitrodehydroabietate (1e).—The crude product was dissolved in 125 ml of methanol and the first crop, collected after 1 day at room temperature, weighed 0.75 g,[21] mp 187–190°, 185–190°, 185–189°. One recrystallization from methanol gave 0.61 g,[21] mp 193–194.5°. Concentration of the mother liquor yielded a second crop of less pure material, 0.06 g,[21] mp 184–188°, total yield 19% (lit. mp 194–195°,[4] 192–193.5°;[8] authentic sample prepared by the method of Zeiss[8] had mp 192.5–194.5°). The mixture melting point of authentic sample and sample prepared by one-step mononitration was 193–194.5°. The ir and nmr spectra were identical: ir (CCl_4) 5.8 (C=O), 6.5, 7.3 μ (NO_2); nmr ($CDCl_3$) δ 7.30 (AB quartet, $\Delta\nu_{AB}$ = 9.4 Hz, J_{AB} = 9 Hz, 2 H, Ar), 3.67 (s, 3 H, $-OCH_3$), 2.75 (m, 3 H, $ArCH_2$, ArCH), 1.27 (s, CH_3), 1.22 (s, CH_3), 1.22 [d, J = 6 Hz, $CH(CH_3)_2$, both peaks are further split, J = 2 Hz]. Decoupling (difference frequency = −97 Hz) caused the methyl region to collapse to two peaks at δ 1.22 and 1.27.

Isolation of Methyl 12-Nitrodehydroabietate (1h).—The mother liquor from which the 14-nitro compound **1e** had been obtained was concentrated to 25 ml. After cooling, the precipitate was collected and washed with cold alcohol. The air-dried solid weighed 1.65 g,[21] mp 116–126°, 107–125°, 120–129° (*ca.* 80% 12-nitro by integration of nmr aromatic region). Recrystallization from 95% ethanol yielded 1.13 g[21] (*ca.* 90–95% pure by nmr), mp 123–131°, yield 31%. Three more layers of fractional recrystallization from 95% ethanol afforded pure material (0.63 g) in the head fraction and an additional 0.26 g of material 70+% pure by nmr, mp 123–134°, next to the head fraction. Two more recrystallizations of the head fraction afforded the analytical sample: mp 134.5–136°; ir (KBr) 5.8 (C=O), 6.6, 7.5 μ (NO_2); nmr (CCl_4) δ 7.57 (s, 1 H, Ar), 7.07 (s, 1 H, Ar), 3.63 (s, 3 H, OCH_3), 3.53, 3.42, 3.30, 3.18 (four peaks observed of $-CH(CH_3)_2$ septuplet, 1 H, J = 7 Hz), 2.93 (t, 2 H, $ArCH_2$, J = 6 Hz), 1.25 (s, CH_3), 1.22 (s, CH_3), 1.25 [d, J = 7 Hz, $CH(CH_3)$, both peaks are further split, J = 2 Hz). Decoupling (difference frequency = −126 Hz, methine H) caused the methyl region to collapse to two peaks at δ 1.25 and 1.22. With a difference frequency of −110 Hz ($ArCH_2$) the methyl region collapsed to four peaks at δ 1.20, 1.23, 1.25, and 1.32.

Anal. Calcd for $C_{21}H_{29}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.19; H, 8.12; N, 3.82.

Nitration of Methyl 12-Nitrodehydroabietate (1h).—Methyl 12-nitrodehydroabietate (1h), 0.50 g (*ca.* 85% pure), was nitrated with mixed acids (dinitration procedure of Fieser[6] and of Zeiss[7]). Recrystallization of the crude product from ether afforded a first crop of 0.17 g: mp 188–189° (lit. mp 189–190°,[8] 189–189.5°,[6] 190–191°[7]), mmp 188–189° (authentic sample prepared by method of Hansen and Zeiss[7] had mp 188–189°); ir ($CHCl_3$) 5.8 (C=O), 6.5, 7.35 μ (NO_2) (identical with spectrum of authentic methyl 12,14-dinitrodehydroabietate); nmr ($CDCl_3$) δ 7.58 (s, Ar), 3.68 (s, OCH_3), 2.83 (m, ArCH, $ArCH_2$), 1.32 [d, J = 7 Hz, $CH(CH_3)_2$], 1.27 (s, CH_3), 1.25 (s, CH_3).

Concentration of the mother liquor gave a second crop of 0.13 g, mp 186.5–188°.

Catalytic Reduction of Methyl 12-Nitrodehydroabietate (1h).—Methyl 12-nitrodehydroabietate (1h), 0.50 g (*ca.* 90% pure), in 20 ml of ethyl acetate and 2 ml of acetic acid with 0.09 g of 83% platinum oxide was treated with hydrogen at room temperature and atmospheric pressure (selective reduction procedure of Zeiss[8]). The crude solid recovered by filtration and evaporation was dissolved in ether and treated with dry hydrogen chloride. The hydrochloride salt was treated with dilute aqueous base to yield 0.34 g (65%) of methyl 12-aminodehydroabietate (1g): mp 135–137° (lit.[5] mp 137–137.5°); ir (KBr) 2.85, 2.95 (NH_2), 5.8 (C=O), 6.1, 6.35, 6.65 μ (Ar); nmr ($CDCl_3$) δ 6.80 (s, 1 H, Ar), 6.58 (s, 1 H, Ar), 3.65 (s, 3 H, OCH_3), 3.50 (broad, 2 H, NH_2), 2.83 (m, 3 H, ArCH, $ArCH_2$), 1.27 (s, CH_3), 1.23 [d, J = 7 Hz, $CH(CH_3)_2$], 1.18 (s, CH_3).

Under the same conditions the 14-nitro isomer 1e did not consume hydrogen.

Catalytic Hydrogenation of Crude Nitration Mixture.—A solution of 1.00 g of crude nitration mixture in 40 ml of ethyl acetate and 4 ml of acetic acid with 0.10 g of 83% platinum oxide was treated as above.

The crude hydrochloride salt of methyl 12-aminodehydroabietate (1g) was isolated in the usual manner and converted to the free amine 1g, 0.33 g,[21] mp 135–137° (32% yield from methyl dehydroabietate).

The ether mother liquor was concentrated and crude methyl 14-nitrodehydroabietate was recovered, 0.20 g,[21] mp 186–189° (20% yield from methyl dehydroabietate), ir identical with ir of authentic sample.

Registry No.—**1b**, 1235-74-1; **1g**, 30885-12-2; **1h**, 30885-13-3.

(17) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 203.

(18) Reference 17, p 183.

(19) Reference 17, p 175.

(20) Infrared spectra were obtained on a Perkin–Elmer Model 137 spectrophotometer and nmr spectra were obtained from dilute solutions with tetramethylsilane as internal standard using a Varian A-60 spectrometer equipped with a Model V6058A spin decoupler. Melting points were determined in open capillary tubes with a Büchi melting point apparatus and are corrected. Microanalysis was by Scandinavian Microanalytical Laboratory, Box 25, 2730 Herlev, Denmark.

(21) Data given are average for three similar experiments.

Acknowledgment.—We wish to express our thanks to Dr. Horace F. White for helpful discussion of the nmr spectra and to the Portland State University Research Committee for support.

Three-Step Synthesis of Methyl Sterculate[1a]

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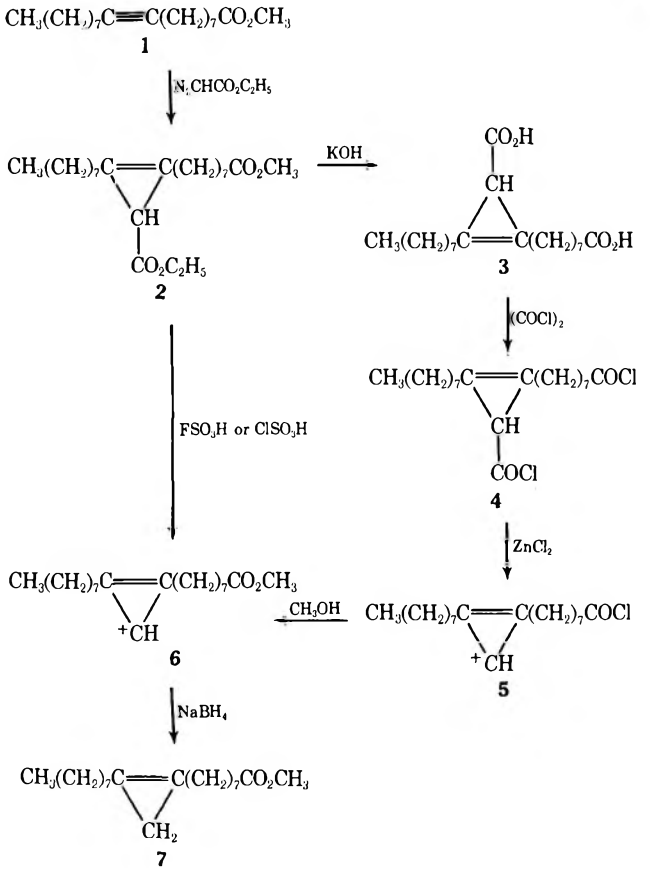
Received March 4, 1971

Studies to elucidate details of the metabolism[2,3] of the physiologically important cyclopropenoic acids have made the availability of these acids highly desirable. Several devised syntheses have provided possible routes but the low overall yield realized in these procedures offered no satisfactory solution to the problem.[4-7] Recently, however, Gensler and his associates[7,8] published a method for the synthesis of methyl sterculate with an overall yield in the order of 30%. A vital sequence in their synthesis was the decarbonylation of **2** to **7** *via* the corresponding biacid chloride **4**.



We have now developed an alternate method (reaction 2 → 7) for a direct decarbonylation of **2** by employing either fluorosulfonic or chlorosulfonic acids[9] and we have arrived at the final methyl sterculate **7** in a three-step synthesis (60–65% yield). Fluorosulfonic acid in methylene chloride reacted upon 9,10-(carbethoxymethano)-9-octadecenoate and the reaction proceeded with gas evolution and formation of cyclopropenium cation ester **6**. The obtained yield as a function of the amount and the concentration of the reagent are given in Table I.

TABLE I

DETERMINATION OF THE PER CENT DECARBONYLATION OF THE CYCLOPROPENIUM CARBONYL BY FLUOROSULFONIC ACID AT ROOM TEMPERATURE[a]

Amount of FSO_3H, mmol	FSO_3H in CH_2Cl_2, *M*	Cyclopropeniod diester, mmol	Decarbonylation,[b] %
5.25	0.28	5.25	
5.25	0.53	5.25	
5.25	1.72	5.25	10
34.58	1.72	5.25	25
43.74	4.37	5.25	20
43.74	17.50	5.25	100

[a] The extent of decarbonylation was followed by monitoring the disappearance of the cyclopropenium carbonyl absorption at 1730 cm^{-1} after complete work-up of the solution. [b] Reaction time 1 hr.

The analogous reaction with a solution of chlorosulfonic acid in methylene chloride was difficult to predict. In that respect, the difference in performance between chlorosulfonic and fluorosulfonic acids may be due to the high ionizing power and low nucleophilicity of the latter.[10] However, when chlorosulfonic acid was added without any previous dilution it performed better than fluorosulfonic acid and the reaction proceeded and afforded cyclopropenium cation ester. We elected to use fluorosulfonic acid in methylene chloride as our standard decarbonylation reagent.

Experimental Section

Melting points and boiling points are uncorrected. Elementary analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill. Infrared analyses were made in CCl_4 solution on a Beckman 1R-7 spectrophometer. All nmr spectra were taken on a Varian A-60A instrument as saturated solutions in chloroform-*d*, using tetramethylsilane as the internal standard. Chemical shifts are reported in τ units (τ 10.00 for tetramethylsilane). Glpc analyses were carried out on a Barber-Coleman Model 5000 equipped with a flame ionization detector. The column (6 ft × 1/8 in. glass) was packed with 10% EGS on Chromosorb W 60–80 mesh. The temperature was 175° and the helium flow was 45 ml/min.

Methyl Stearolate (1).—Stearolic acid, mp 45.5–46.0°, was synthesized according to the method of Butterfield and Dutton.[11] Methyl stearolate prepared with diazomethane gave a single peak on glpc with a relative retention time of 1.90 (methyl stearate 1.00).

(1) (a) Abstracted in part from a thesis submitted by J. L. Williams to the University of Illinois, Aug 1970, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) Tuskegee Institute, School of Veterinary Medicine, Tuskegee Institute, Ala. 36088.

(2) P. K. Raju and R. Reiser, *J. Biol. Chem.*, **242**, 379 (1964).

(3) S. V. Pande and J. F. Mead, *ibid.*, **246**, 1856 (1970).

(4) D. G. Booke and J. C. Smith, *Chem. Ind. (London)*, 1580 (1957).

(5) S. D. Andrews and J. C. Smith, *ibid.*, 1636 (1966).

(6) E. R. Altenburger, J. W. Berry, and A. J. Deutschman, Jr., *J. Amer. Oil Chem. Soc.*, **47**, 77 (1970).

(7) W. J. Gensler, M. B. Floyd, R. Yanase, and K. W. Pober, *J. Amer. Chem. Soc.*, **91**, 2397 (1969).

(8) W. J. Gensler, M. B. Floyd, R. Yanase, and K. W. Pober, *ibid.*, **92**, 2472 (1970).

(9) Decarbonylation with sulfur trioxide in sulfuric acid, fluorosulfonic acid, or chlorosulfonic acid was demonstrated for several short aliphatic and aromatic cyclopropenium carbonyls [D. G. Farnum, G. Mehta, and R. G. Silberman, *ibid.*, **89**, 5048 (1967)]. Also, the possibility that this kind of decarbonylation could be applied to their compounds was suggested by Gensler, Floyd, Yanase, and Pober (see ref 8).

(10) A. Diaz, I. L. Reich, and S. Winstein, *ibid.*, **91**, 5637 (1969).

(11) R. O. Butterfield and H. J. Dutton, *J. Amer. Oil Chem. Soc.*, **45**, 635 (1968).

Preparation of 9,10-(Carbethoxymethano)-9-octadecenoate (2).—Ethyl diazoacetate (3.4 g, 29.3 mmol) in the presence of 0.2 g of powdered copper bronze[12] was allowed to react with 5.9 g (20 mmol) of methyl stearolate to form the corresponding cyclopropenoid diester 2 as previously described.[8] Subsequently it was cooled to room temperature, filtered to remove the catalyst, and distilled *in vacuo*, bp[4] 174–176° (0.05 mm). The desired diester 2 was obtained in this way as a yellowish oil (3.9 g, 15.4 mmol, 77% yield).

Preparation of the Fluorosulfonic Acid Decarbonylation Reagent.—This reagent was prepared by mixing 2.5 ml of fluorosulfonic acid in 2.5 ml of methylene chloride at room temperature. The resulting 50% (v/v) solution contained 43.7 mmol of fluorosulfonic acid (17.5 *M*).

Decarbonylation of 9,10-(Carbethoxymethano)-9-octadecenoate (2).—Throughout the experiment a current of argon blanketed the reaction mixture. Decarbonylation was accomplished by slowly dropping 5 ml of the 17.5 *M* fluorosulfonic acid solution on 5.25 mmol of cyclopropenoid ester over a 0.5-hr interval at room temperature. After the solution had stood for an additional 0.5 hr, 20 ml of cold (−78°) methylene chloride was added and 5 g of type 4A or 5A molecular sieves.[18] The cold solution with the molecular sieves was allowed to stand for 1 hr under argon.

Preparation of the Sodium Borohydride Reducing Solution.—A three-necked round-bottomed flask equipped with a magnetic bar stirrer was placed in a Dry Ice–trichloroethylene bath maintained at −50°. Sodium borohydride (1 g) was charged in the flask followed by 25 ml of a stock solution of methanol saturated with sodium hydroxide. The reaction was blanketed by argon all the time and the solution was stirred and allowed to stand at −50°. This solution was designated as a 1.05 *M* sodium borohydride reducing reagent.

Methyl Sterculate (7).—Under a blanket of argon, the cyclopropenium cation solution was slowly dropped into the 1.05 *M* sodium borohydride reducing reagent. The mixture was stirred for 20 min at −50°. After stirring for an additional 10 min, the reaction mixture was allowed to warm to room temperature. During the reduction of the brown cyclopropenium cation solution, gas evolved and the solution was placed in a separatory funnel containing 10 ml of cold (−78°) petroleum ether (bp 55–60°) and 50 ml of saturated sodium bicarbonate. The ethereal layer was removed and further extraction was accomplished with two 50-ml portions of petroleum ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate at room temperature for 2 hr. The dry petroleum ether solution was filtered and the solvent was evaporated under reduced pressure. The residual yellow oil in a small volume of petroleum ether was placed on top of a 1.2 × 100 cm column of 200–325 mesh silicic acid (Unisil)[14] prepared as a slurry in petroleum ether under a blanket of argon and water jet pump vacuum. A total of 750 ml of petroleum ether was passed through the column. Fractions of 50 ml were collected and the elutions were monitored by using silica gel G tlc and a solvent system consisting of petroleum ether–diethyl ether (95:5, v/v). All eluates which furnished a compound with the same R_f value as a reference methyl sterculate were combined. Evaporation of the solvent under vacuum at room temperature yielded a colorless oil (1.03 g, 65%).

The synthetic methyl sterculate (*Anal.* Calcd for $C_{20}H_{36}O_2$: C, 77.82; H, 11.76. Found: C, 77.72; H, 11.61) gave a positive Halphen test. In infrared absorption spectra it showed peaks at 1750 (carbonyl), 1880 (cyclopropene), and 1020 cm^{-1} (cyclopropene). In the last case, the vibration given by cyclopropenes normally at 1010 was shifted to 1020 cm^{-1} due to the way the spectra were taken. Masson[15] also reported a value of 1020 cm^{-1} for methyl sterculate when its infrared spectrum was taken in carbon tetrachloride. A check using pure methyl sterculate prepared from natural sources[16] verified this observation.

In nmr is showed signals at 9.23 (s, 2 H, cyclopropenyl CH_2), 9.10 (m, 3 H, distal terminal CH_3), 8.63–8.71 (m, 22 H, internal CH_2), 7.61–7.78 (diffuse m, 6 H, α to cyclopropenyl and $-CO_2-CH_3$), and 6.32 ppm (s, 3 H, methyl ester CH_3). Generally, the spectra were identical with those obtained with pure methyl sterculate obtained from *sterculia foetida*. Furthermore, the synthetic and natural materials gave single spots with the same R_f value on thin layer plates and identical gas chromatographic curves.[17]

Registry No.—2, 30689-71-5; 7, 3220-60-8.

Acknowledgments.—This work was supported in part by Research Grant HE-10779-04 from the National Institutes of Health, U. S. Public Health Service. We would like to thank Dr. W. T. Gensler and his associates for valuable discussions and for communication of their method to us prior to its detailed publication. Generous gifts of *sterculia foetida* seeds from Mr. J. L. Utleg, Assistant Director of Forestry, Manila, Phillippines, and *sterculia foetida* oil from Dr. Sheeham, University of Arizona, were greatly appreciated.

(12) Purchased from The British Drug House, Poole, England.

(13) Linde Division of Union Carbide Corp., Chicago, Ill.

(14) Clarkson Chemical Co., Inc., Williamsport, Pa.

(15) J. C. Masson, Ph.D. Thesis, University of Arizona, and University Microfilms, Ann Arbor, Mich., 59-3048 BB (1957).

(16) Pure methyl sterculate isolated from *sterculia foetida* seeds by the method of H. W. Kircher, *J. Amer. Oil Chem. Soc.*, **41**, 4 (1964).

(17) E. L. Schneider, S. P. Loke, and D. T. Hopkins, *ibid.*, **45**, 585 (1970).

Absolute Configuration of the Phenyl-2-piperidylcarbinols

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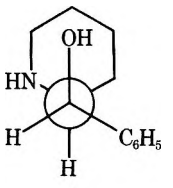
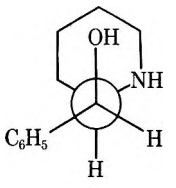
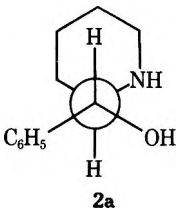
The Cotton effect associated with the $^1L_b \pi \rightarrow \pi^*$ transition[2] has been reported to be a reliable guide to the absolute configuration of both the ephedrine and the chloramphenicol stereoisomers.[3] This ^1L_b absorption band, as measured *via* circular dichroism (CD), is now used to assign the absolute configuration of the phenyl-2-piperidylcarbinols (**1** and **2**).



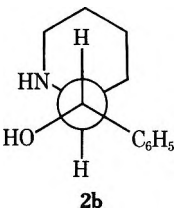
1a



1b



2a



2b

The diastereomeric carbinols (**1** and **2**) were prepared *via* the reduction of phenyl 2-pyridyl ketone with Brown catalyst,[4] which is a modification of the method of Crook and McElvain,[5] and separated *via* fractional crystallization. Diastereomers **1** and **2** were demonstrated to be erythro and threo, respectively, by acyl migration studies.[6] This conclusion is confirmed by

(1) To whom correspondence should be addressed.

(2) J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949).

(3) L. A. Mitscher, F. Kautz, and J. LaPidus, *Can. J. Chem.*, **47**, 1957 (1969).

(4) H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **84**, 2827 (1962).

(5) K. E. Crook and S. M. McElvain, *ibid.*, **52**, 4006 (1930).

(6) A. Dudas and I. Weisz, *Chem. Ber.*, **94**, 412 (1961).

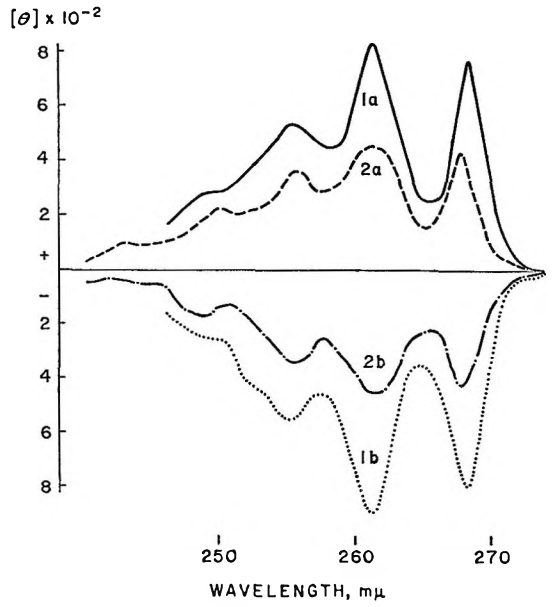


Figure 1.—Circular dichroism curves of the four isomeric phenyl-2-piperidylcarbinols.

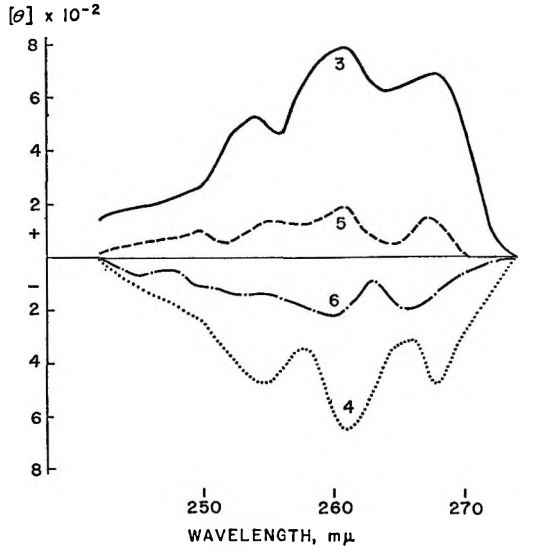


Figure 2.—Circular dichroism curves of the four isomeric ephedrines: (1*R*,2*S*)-ephedrine hydrochloride (**3**), (1*S*,2*R*)-ephedrine hydrochloride (**4**), (1*R*,2*R*)-pseudoephedrine hydrochloride (**5**), and (1*S*,2*S*)-pseudoephedrine hydrochloride (**6**).

noting that **1a** and **1b** give CD curves of larger amplitude than **2a** and **2b** (Figure 1), as would be expected,[3] and by noting that $J_1 = 3.3$ and $J_2 = 9.3$ cps, as would be expected.[7]

Resolution of **1** and **2** was accomplished with mandelic acid and di-*p*-toluoyltartaric acid, respectively. Comparison of the CD curves of the stereoisomers of phenyl-2-piperidylcarbinol (Figure 1) with the CD curves of the stereoisomers of ephedrine (Figure 2) allows us to assign the 1*R*,2*S* configuration to the erythro-(−) enantiomer (**1a**) which has the positive CD curve and the 1*S*,2*R* configuration to the erythro-(+) enantiomer (**1b**) which has the negative CD curve. Likewise, the 1*R*,2*R* configuration is assigned to the threo-(−) enantiomer (**2a**) which has the positive CD curve and the 1*S*,2*S* configuration to the threo-(+) enantiomer (**2b**) which has the negative CD curve.

Experimental Section

General.—Melting points were determined in open capillaries on a Thomas–Hoover Uni-Melt apparatus and are uncorrected. The CD measurements were carried out using a Durrum–Jasco Model ORD/UV-5 instrument equipped with a CD attachment operating at ambient temperature.

Phenyl-2-piperidylcarbinols (1 and 2).—Brown catalyst was generated *in situ* in a Brown hydrogenator (Delmar)[8] from a 0.2 *M* ethanolic chloroplatinic acid solution (2 ml) and activated charcoal (2.0 g) according to the method of Brown.[4] To this was added phenyl 2-pyridyl ketone (Matheson Coleman and Bell) (9.15 g, 0.05 mol) dissolved in 50% ethanol–concentrated hydrochloric acid (20 ml) and the reaction was allowed to proceed until no further hydrogen uptake was observed. The reduction required 10 hr and 45.8 ml of sodium borohydride was consumed (theoretical 50.0 ml). The catalyst was removed *via* filtration and the solvent removed *in vacuo*, leaving a tacky oil which was fractionally crystallized according to the method of Crook and McElvain,[5] giving **1**, yield 1.5 g (16%), mp 140–142° (lit.[5] 141–142°), and **2**, yield 1.1 g (12%), mp 170–173° (lit.[5] 171–173°).

Resolution of *erythro*-Phenyl-2-piperidylcarbinol (1).—A solution of **1** (2.0 g) and (+)-mandelic acid (Aldrich) (1.2 g) in hot 95% ethanol (8 ml) was allowed to slowly cool to room temperature. The crystals which separated were removed *via* filtration and the mother liquor was set aside as solution A. The crystals were recrystallized twice from 95% ethanol (4 ml), mp 145–146°. A solution of these crystals in water (25 ml) was made basic with 10% potassium hyroxide, extracted with ether (four 20-ml portions), and dried ($MgSO_4$). The ether volume was reduced to about 20 ml and made acidic with gaseous hydrogen chloride. The resultant hydrochloride salt (**1b** HCl) was collected *via* filtration: yield 0.278 g (11.6%), mp 213.5–215°, $[\alpha]^{25}D$ +23.1° (water).

Solution A was taken to dryness and the free base was regenerated as described above. The resultant free base was combined with (−)-mandelic acid (Aldrich) (1.2 g) in hot 95% ethanol (4 ml). The solution was allowed to cool slowly to room temperature and the crystals were removed *via* filtration and recrystallized twice from 95% ethanol (4 ml), mp 144–146°. The free base was regenerated and converted to the hydrochloride salt (**1a** HCl) as described above: yield 0.464 g (22.3%), mp 213.5–215°, $[\alpha]^{25}D$ −22.0°.

Resolution of *threo*-Phenyl-2-piperidylcarbinol (2).—A solution of **2** (1.0 g) and (+)-di-*p*-toluoyltartaric acid (Aldrich) (1.3 g) in hot ethanol (2.0 ml) was allowed to come slowly to room temperature. The crystals which formed were removed *via* filtration and the mother liquor was set aside as solution B. The crystals were recrystallized five times from 50% butanol–ethanol, mp 185–186°. The free base was regenerated as above, the ether volume was reduced to about 20 ml, and the free base (**2a**) was precipitated (the hydrochloride salt could not be prepared): yield 0.118 g (11.8%), mp 149–151°, $[\alpha]^{25}D$ −15.9° (ethanol).

Solution B was taken to dryness and the free base was regenerated as above. The resultant solid and (−)-di-*p*-toluoyltartaric acid (Aldrich) (0.845 g) were dissolved in hot ethanol (2.0 ml). The crystals which formed upon cooling slowly to room temperature were removed *via* filtration and recrystallized five times from 50% butanol–ethanol, mp 185–186°. The free base was regenerated as above (**2b**): yield 0.132 g (13.2%), mp 149–151°, $[\alpha]^{25}D$ +16.2° (ethanol).

Circular Dichroism Measurements. (1*R*,2*S*)-**Phenyl-2-piperidylcarbinol (1a).**—CD measurements were made at 5.23×10^{-5} *M* (ethanol): $[\theta]_{273}$ 0, $[\theta]_{268}$ 757, $[\theta]_{266}$ 252, $[\theta]_{261}$ 821, $[\theta]_{258}$ 442, $[\theta]_{255}$ 537, $[\theta]_{250}$ 284, $[\theta]_{248}$ 252, $[\theta]_{246}$ 158.

(1*S*,2*R*)-**Phenyl-2-piperidylcarbinol (1b).**—CD measurements were made at 5.23×10^{-5} *M* (ethanol): $[\theta]_{274}$ 0, $[\theta]_{268}$ −789, $[\theta]_{265}$ −347, $[\theta]_{261}$ −884, $[\theta]_{257}$ −442, $[\theta]_{255}$ −537, $[\theta]_{250}$ −252, $[\theta]_{246}$ −158.

(1*R*,2*R*)-**Phenyl-2-piperidylcarbinol (2a).**—CD measurements were made at 6.55×10^{-6} *M* (ethanol): $[\theta]_{274}$ 0, $[\theta]_{268}$ 434, $[\theta]_{265}$ 152, $[\theta]_{261}$ 455, $[\theta]_{257}$ 283, $[\theta]_{256}$ 354, $[\theta]_{251}$ 202, $[\theta]_{250}$ 222, $[\theta]_{245}$ 91, $[\theta]_{243}$ 101.

(7) A. A. Larsen, W. A. Gould, H. R. Roth, William T. Comer, R. H. Uloth, K. W. Dungan, and P. M. Lish, *J. Med. Chem.*, **10**, 462 (1967).

(8) H. C. Brown, K. Sivasankaran, and C. A. Brown, *J. Org. Chem.*, **28**, 214 (1963).

(1*S*,2*S*)-**Phenyl-2-piperidylcarbinol (2b).**—CD measurements were made at 6.55×10^{-5} *M* (ethanol): $[\theta]_{274}$ 0, $[\theta]_{268}$ −414, $[\theta]_{265}$ −222, $[\theta]_{261}$ −455, $[\theta]_{258}$ −253, $[\theta]_{255}$ −333, $[\theta]_{251}$ −121, $[\theta]_{249}$ −162, $[\theta]_{242}$ −30, $[\theta]_{240}$ −40.

Registry No.—**1a**, 5583-31-3; **1a** HCl, 5583-32-4; **1b**, 5583-35-7; **1b** HCl, 5583-36-8; **2a**, 31002-84-3; **2b**, 30882-77-0.

Anomalous Diborane Reductions of Benz[c]acridines[1]

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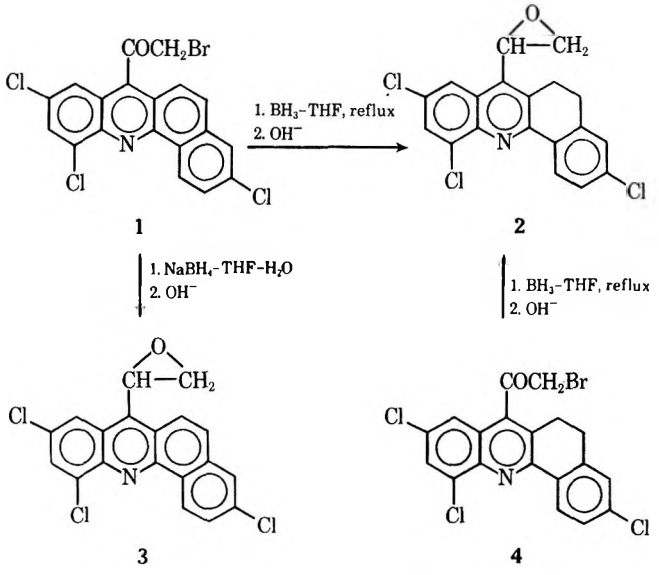
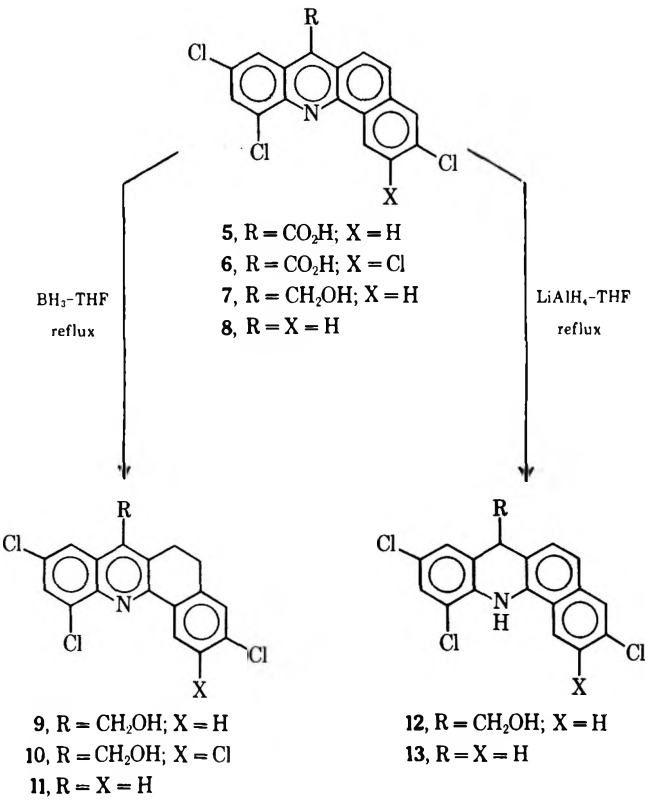
Received April 13, 1971

During the course of our work on the synthesis of benz[*c*]acridinemethanols as potential antimalarials,[2] we encountered an unusual diborane reduction of the benz[*c*]acridine ring system. Treatment of 7α-bromoacetyl-3,9,11-trichlorobenz[*c*]acridine (**1**) with diborane in refluxing tetrahydrofuran, followed by an alkaline work-up, unexpectedly yielded the 5,6-dihydro epoxide **2** instead of the desired aromatic product **3**. The identity of **2** was established beyond doubt by comparison with an authentic specimen prepared by reduction of the 5,6-dihydro bromomethyl ketone **4**.[2] Reduction of **1** with sodium borohydride in aqueous tetrahydrofuran at room temperature afforded the aromatic epoxide **3**.[2,3]



When diborane reduction in refluxing tetrahydrofuran was carried out with 3,9,11-trichlorobenz[*c*]acridine-7-carboxylic acid (**5**) or the 2,3,9,11-tetrachloro analog **6** (Scheme I), attack at the 5,6 double bond occurred again, with formation of alcohols **9** and **10**, respectively. Reduction of **5** with diborane at room temperature, on the other hand, afforded the aromatic alcohol **7** only, whereas reduction with lithium aluminum hydride in refluxing tetrahydrofuran yielded the 7,12-dihydro alcohol **12**.

SCHEME I



While it is well known that acridines can undergo reduction of the hetero ring upon treatment with metal hydrides[4] or diborane,[5] there appears to be no precedent in the literature for reduction of a carbocyclic aromatic ring by diborane. We considered the possibility that 5,6-dihydro compounds such as **2**, **9**, and **10** were perhaps being formed *via* reduction to the 7,12-dihydro compounds, which could then undergo rearrangement during work-up. This appeared feasible, at first, because alkaline conditions were used in the work-up of these compounds. However, inasmuch as reduction of **5** to **9** also proceeded with a neutral work-up, we were led to conclude that diborane is able to attack the double bond directly.[6]

Further evidence militating against the intermediacy of 7,12-dihydro compounds in the formation of 5,6-dihydro products was obtained by deliberate prolonged treatment of **12** with alkali. Two products were isolated, 7-methyl-3,9,11-trichlorobenz[*c*]acridine (**14**) and 3,9,11-trichlorobenz[*c*]acridine (**8**); however, no

(1) This investigation was supported in part by Research Contract DA-49-193-MD-3008 from the U. S. Army Medical Research and Development Command, Office of the Surgeon General. This is publication No. 871 from the Army Research Program on Malaria.

(2) A. Rosowsky, M. Chaykovsky, S. A. Yeager, R. A. St. Amand, M. Lin, and E. J. Modest, *J. Heterocycl. Chem.*, in press.

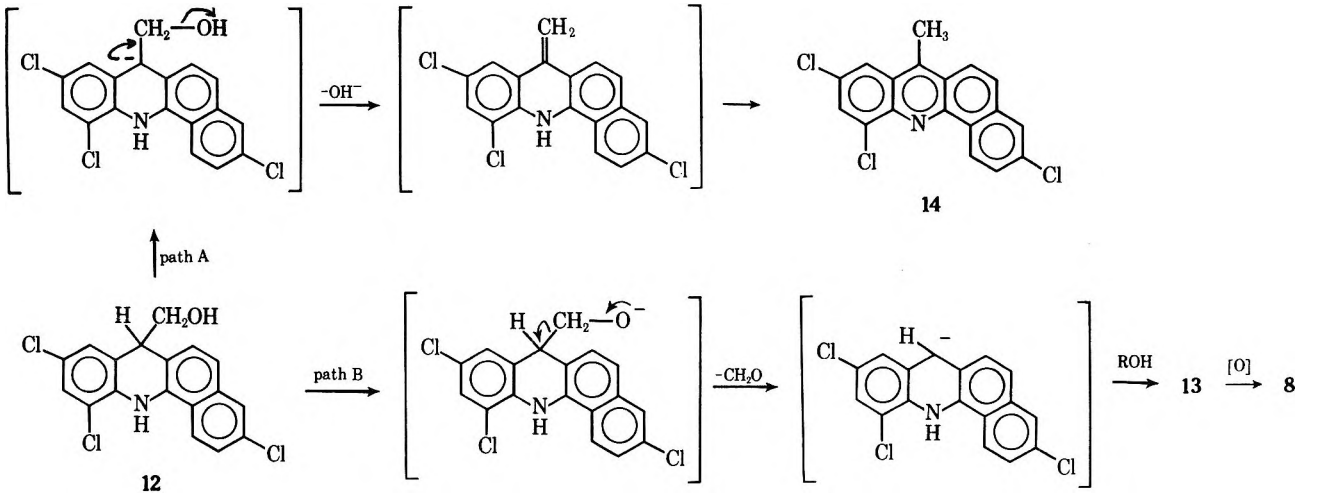
(3) It is of interest to note that reduction of 7α-bromoacetyl-2,3,9,11-tetrachlorobenz[*c*]acridine with sodium borohydride under these same conditions resulted in reduction of the hetero ring to give the 7,12-dihydro epoxide.[2]

(4) A. Campbell and E. N. Morgan, *J. Chem. Soc.*, 1711 (1958).

(5) W. J. Wechter, *J. Org. Chem.*, **28**, 2935 (1963).

(6) During the reduction of **5** to **9** with diborane, thin layer chromatography of samples of the reaction mixture on silica gel (2:2:1 benzene–cyclohexane–acetone) showed the formation of **9** with no evidence for the formation of the faster moving **12**. Apparently, partial hydrolysis of the boron intermediate can occur on the tlc plate. The ease of hydrolysis of the boron intermediates involved in 5,6 reduction by aqueous alkali is probably a consequence of the benzylic nature of the boron–carbon bond in these intermediates. The high reactivity of allylic boron derivatives has been reported; see H. C. Brown and H. Nambu, *J. Amer. Chem. Soc.*, **92**, 1761 (1970).

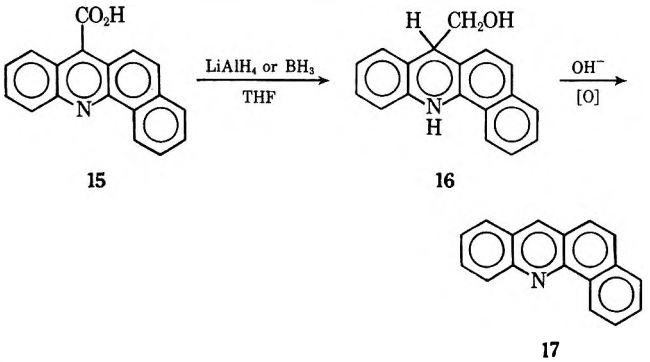
SCHEME II



trace of **7** or **9** could be detected. A plausible pathway for the formation of **14** and **8** is depicted in Scheme II.

In order to determine whether the unexpected diborane reductions observed with compounds **1**, **5**, and **6** might be associated in some fashion with the presence of a side chain at the 7 position, we also investigated the action of reducing agents on **8**. Reduction with lithium aluminum hydride in refluxing tetrahydrofuran or with sodium borohydride in refluxing aqueous tetrahydrofuran afforded the expected 7,12-dihydro product **13**. On the other hand, reduction with diborane in refluxing tetrahydrofuran led once again to the formation of the 5,6-dihydro derivative **11** with only a trace of **13** present. No reaction occurred at room temperature. This evidence tended to rule out the possibility that reduction of the 5,6 double bond involves participation by some intermediate species in which boron is covalently bound to a functional group in the side chain.

It was of interest to determine whether reduction of the 5,6 double bond is related to the presence of halogen atoms, especially at the 11 position. A chlorine substituent at this position would be expected to decrease the basicity of the neighboring ring nitrogen by virtue of its electron-withdrawing effect and also to impede the approach of a Lewis acid such as diborane by virtue of its steric bulk (an example of Brown's F-strain[7]). Such a phenomenon would reduce the ability of nitrogen to serve as an electron sink[5] in the addition of hydride at C-7. In fact, reduction of benz[*c*]acridine-7-carboxylic acid (**15**) did turn out to follow a somewhat different course from the reduction of the halogenated analogs. Like lithium aluminum hydride, diborane effected reduction only in the hetero ring, with formation of 7,12-dihydro-7-hydroxymethylbenz[*c*]acridine (**16**) both at room temperature and at reflux. Prolonged treatment with alkali only yielded benz[*c*]acridine **17** (according to path B, Scheme II).



It is significant that diborane treatment at room temperature sufficed to reduce both the carboxyl function and the hetero ring in **15**, but reduced only the carboxyl function in the 3,9,11-trichloro analog **5**, and effected no reduction in **8**. We believe that these findings are consistent with the view that the 11-chloro substituent retards diborane reduction for reasons stated above. Apparently, reduction of the 5,6 double bond of **1**, **5**, **6**, and **8** with diborane at the reflux temperature of tetrahydrofuran is seen because "normal" reduction of the hetero ring is energetically unfavorable.

Finally, in this connection, we became interested in the effect of lithium ions on the course of diborane reduction of the 11-chloro substituted compounds. We anticipated that the small size of the lithium cation would allow it to penetrate the steric barrier of the 11-chloro substituent and to coordinate with the ring nitrogen, thus facilitating hydride addition at C-7 and promoting reduction of the hetero ring. In fact, reduction of **8** with diborane in the presence of lithium iodide (1:3:3) yielded a mixture of reduced products consisting of about 40% of the 7,12-dihydro isomer and 60% of the 5,6-dihydro isomer. Increasing the amount of lithium iodide (1:3:6) led to a mixture containing about 60% of the 7,12-dihydro isomer. Thus, lithium cations lower the energy barrier for the "normal" diborane reduction of **8** sufficiently to allow the 7,12-dihydro isomer to become the predominant product.

Experimental Section[8]

Starting Materials.—The synthesis of compounds **1**, **5**, **6**, and **15** has been described.[2] Compound **8** was prepared by heating **5** to its melting point (280°) for several minutes to effect decarboxyla-

(7) H. C. Brown and R. B. Johannesen, *J. Amer. Chem. Soc.*, **85**, 16 (1953).

(8) Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were taken in potassium chloride disks with a Perkin–Elmer Model 137B double-beam recording spectrophotometer. Nmr spectra were determined on a Varian A-60 instrument, with tetramethylsilane as the internal reference. Melting points were measured in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Mass.) and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Werby Laboratories, Boston, Mass.

tion; recrystallization from benzene gave pale yellow needles, mp 228–230°.

Anal. Calcd for $C_{17}H_8Cl_3N$: C, 61.38; H, 2.42; N, 4.21; Cl, 31.98. Found: C, 61.32; H, 2.42; N, 4.07; Cl, 32.06.

5,6-Dihydro-3,9,11-trichloro-7-benz[*c*]acridinyloxirane (2).—A solution of borane in tetrahydrofuran[9] (60 ml, 0.06 mol) was added to a slurry of bromomethyl ketone 1 (12.0 g, calculated by nmr to contain 0.0208 mol of bromomethyl ketone and 0.0069 mol of methyl ketone) in dry tetrahydrofuran[10] (200 ml). After 2 hr of refluxing, the mixture was cooled to room temperature, and a solution of potassium hydroxide (15.7 g, 0.28 mol) in water (50 ml) and ethanol (150 ml) was added slowly. After 15 min of stirring, water (200 ml) was added, and after another 15 min the mixture was poured into cold water (400 ml). The precipitated solid was filtered, washed with water, and dried, yield 6.8 g, mp 228–231° dec. The solid was chromatographed on silica gel (250 g), with benzene as eluent. The oxirane **2** was eluted in the first few fractions, the more polar alcohols being retained on the column: yield 4.5 g (58% based on bromomethyl ketone); light tan solid, mp 234–240° dec. This product proved to be identical (ir, mixture melting point) with the compound obtained by borane reduction of 4.[2] The nmr spectrum ($CDCl_3$) showed a pair of multiplets centered at δ 2.95 and 3.30 (total of 6 H) and a multiplet centered at δ 4.26 (1 H).

5,6-Dihydro-7-hydroxymethyl-3,9,11-trichlorobenz[*c*]acridine (9).—A solution of borane in tetrahydrofuran (2.34 ml, 2.34 mmol) was added to a solution of **5** (220 mg, 0.585 mmol) in tetrahydrofuran (10 ml). The solution was refluxed for 3 hr and cooled to room temperature, and a solution of potassium hydroxide (336 mg, 6.0 mmol) in water (5 ml) was added slowly. After 20 min, water (40 ml) was added and the precipitated solid was filtered, washed with water, and dried: yield 160 mg (75.1%); mp 220–224° dec. Recrystallization from benzene gave almost colorless plates, mp 222–224° dec. The same compound was produced by borane reduction of the 5,6-dihydro-7-carboxylic acid:[2] nmr (deuteriopyridine) A_2B_2 multiplet centered at δ 3.0 (4 H), 5.25 (s, CH_2OH).

Anal. Calcd for $C_{18}H_{12}Cl_3NO$: C, 59.28; H, 3.32; N, 3.84; Cl, 29.17. Found: C, 59.45; H, 3.28; N, 3.79; Cl, 29.01.

5,6-Dihydro-7-hydroxymethyl-2,3,9,11-tetrachlorobenz[*c*]acridine (10).—Reduction of **6** (205 mg, 0.5 mmol) with borane in tetrahydrofuran (2.0 mmol) and treatment with KOH (280 mg, 5.0 mmol) as described above yielded 10 (163 mg, 81.6%), mp 235–239° dec. Recrystallization from benzene gave almost colorless needles, mp 245–248° dec. This compound was identical with the product formed on borane reduction of the 5,6-dihydro-7-carboxylic acid:[2] nmr (deuteriopyridine) A_2B_2 multiplet centered at δ 3.0 (4 H), 5.28 (s, CH_2OH); uv λ_{max} (95% EtOH) 222 mμ (ϵ 37,670), 268 (33,400), 276 (48,300), 312 (9780), 327 (11,800), 341 (16,110), 356 (17,500).

5,6-Dihydro-3,9,11-trichlorobenz[*c*]acridine (11).—Reduction of **8** (166 mg, 0.5 mmol) with borane in tetrahydrofuran (1.5 mmol) and treatment with KOH (280 mg, 5.0 mmol) as described above yielded 11 (155 mg, 93%); mp 221–223° dec. Tlc analysis (silica gel, 1:1 benzene–hexane) showed only a trace of compound **13**. Recrystallization from benzene gave pale yellow needles, mp 243–246° dec. The same compound was formed by decarboxylation of the 5,6-dihydro-7-carboxylic acid[2] by heating to 280°. The nmr spectrum ($CDCl_3$) showed a multiplet at δ 3.02 ($-CH_2CH_2-$).

Anal. Calcd for $C_{17}H_{10}Cl_3N$: C, 61.01; H, 3.01; N, 4.19; Cl, 31.79. Found: C, 61.20; H, 2.96; N, 4.12; Cl, 31.61.

7-Hydroxymethyl-3,9,11-trichlorobenz[*c*]acridine (7).—When **5** was reduced with borane in tetrahydrofuran for 3 hr at room temperature by the standard procedure, compound 7 was formed (84%), mp 225–235° dec. Recrystallization from benzene gave yellow needles: mp 247–250° dec; nmr (deuteriopyridine) δ 5.70 (s, CH_2OH).

Anal. Calcd for $C_{18}H_{10}Cl_3NO$: C, 59.61; H, 2.78; N, 3.86; Cl, 29.33. Found: C, 59.24; H, 2.61; N, 3.68; Cl, 29.25.

7,12-Dihydro-7-hydroxymethyl-3,9,11-trichlorobenz[*c*]acridine (12).—Compound **5** (735 mg, 2.0 mmol) was added in portions to a mixture of lithium aluminum hydride (228 mg, 6.0 mmol) in tetrahydrofuran (30 ml). The mixture was refluxed for 2 hr, cooled to room temperature, and treated dropwise with saturated aqueous sodium chloride (2.0 ml). The mixture was filtered and the filtrate was evaporated to leave a red oil which was dissolved in methylene chloride, washed with 5% aqueous sodium hydroxide, rinsed with water, dried over sodium sulfate, and evaporated. Recrystallization of the yellow solid from benzene gave almost colorless prisms (520 mg, 71.4%): double mp 168–170° and 189–190°; nmr (deuteriopyridine) δ 3.95 (d, CH_2OH) and 4.30 (quartet, CH); uv λ_{max} (EtOH) 263 mμ (ϵ 24,300), 283 infl (15,800), 290 infl (12,970), 343 (9940), 385 (1400).

Anal. Calcd for $C_{18}H_{12}Cl_3NO$: C, 59.28; H, 3.32; N, 3.84; Cl, 29.17. Found: C, 59.11; H, 3.55; N, 3.59; Cl, 29.18.

7,12-Dihydro-3,9,11-trichlorobenz[*c*]acridine (13). A. By $LiAlH_4$ Reduction.—A mixture of **8** (998 mg, 3.0 mmol) and lithium aluminum hydride (228 mg, 6.0 mmol) in dry tetrahydrofuran (30 ml) was refluxed for 3 hr. The mixture was cooled and saturated aqueous sodium chloride (2.0 ml) was added slowly, followed by dilution with tetrahydrofuran (30 ml) and filtration. Evaporation of the filtrate left a yellow solid which was recrystallized from benzene: yield 550 mg (55%); yellow needles, mp 210–213°. A second recrystallization gave the analytical sample: mp 214–215°; nmr (deuteriopyridine) δ 4.08 (s, CH_2); uv λ_{max} (EtOH) 263 mμ (ϵ 23,100), 280 infl (13,740), 287 infl (12,540), 345 (9100), 365 infl (7390), 383 infl (2400).

Anal. Calcd for $C_{17}H_{10}Cl_3N$: C, 61.01; H, 3.01; N, 4.19; Cl, 31.79. Found: C, 61.08; H, 2.97; N, 4.12; Cl, 31.92.

B. By $NaBH_4$ Reduction.—A mixture of **8** (166 mg, 0.5 mmol), sodium borohydride (280 mg, 5.0 mmol), tetrahydrofuran (10 ml), and water (3 ml) was refluxed for 6 hr, cooled, and treated with potassium hydroxide (280 mg, 5.0 mmol) in water (5 ml). After 20 min, water (30 ml) was added and the precipitated solid was filtered, washed with water, and dried, yield 150 mg (95.2%), mp 200–204°. Two recrystallizations from benzene gave the pure compound, mp 214–215°.

Reduction of 8 with Borane in the Presence of Lithium Iodide.—To a solution of **8** (166 mg, 0.5 mmol) and anhydrous lithium iodide (201 mg, 1.5 mmol) in tetrahydrofuran (15 ml) was added borane in tetrahydrofuran (1.5 ml, 1.5 mmol). The mixture was refluxed for 3 hr, cooled to room temperature, and treated slowly with potassium hydroxide (280 mg, 5.0 mmol) in water (5 ml). After 20 min, water (30 ml) was added and the precipitated yellow solid was filtered, washed with water, and dried, yield 155 mg, mp 198–220°. Thin layer chromatography (silica gel, 1:1 benzene–hexane) showed the presence of **11** and **13** (the latter being the faster moving spot). Nmr analysis (deuteriopyridine) showed bands at δ 2.87 ($-CH_2CH_2-$ in **11**) and 4.08 ($-CH_2-$ in **13**). The amount of **13** was calculated to be about 40 mol %. When the reaction was run again under the same conditions but with twice the amount of lithium iodide (402 mg, 3.0 mmol) a product was isolated, mp 195–200°, which contained about 60% **13** and 40% **11**.

7,12-Dihydro-7-hydroxymethylbenz[*c*]acridine (16).—To a solution of **15** (2.73 g, 10 mmol) in tetrahydrofuran (20 ml) was added dropwise a solution of borane in tetrahydrofuran (30 ml, 30 mmol) with slight external cooling. After 3 hr of stirring at room temperature, 4 *N* hydrochloric acid (20 ml) was added slowly. The tetrahydrofuran was removed under vacuum, water (20 ml) was added, and the pH of the mixture was adjusted to 7 with concentrated aqueous potassium hydroxide. The mixture was extracted with methylene chloride and the extracts were washed with 5% aqueous potassium hydroxide, rinsed with water, dried over sodium sulfate, and evaporated. Recrystallization of the brown solid from benzene–hexane (charcoal) yielded **16** (1.9 g, 73.4%) as light tan crystals, mp 153–156°. Almost identical results were obtained when the reaction was carried out at reflux. The pure compound had mp 157–159° and was identical (ir, mixture melting point) with the product obtained on lithium aluminum hydride reduction of **15**.

Benz[*c*]acridine (17).—A solution of **16** (1.30 g, 5.0 mmol) and potassium hydroxide (1.12 g, 20 mmol) in absolute ethanol (45 ml) was stirred at room temperature in an open flask for 24 hr (after about 2 hr a precipitate began to form). The mixture was concentrated to about 20 ml under vacuum and filtered, and the solid was washed with dilute aqueous ethanol and dried, yield 860 mg (75%), mp 105–108°. Recrystallization from ethanol gave **17** as yellow needles, mp 107–108° (lit.[11] mp 108°).

(9) A 1.0 *M* solution of "borane" in tetrahydrofuran was supplied by Alfa Inorganics, Inc., Beverly, Mass.

(10) Matheson Coleman and Bell tetrahydrofuran was dried over molecular sieves (Linde 3A) and used without distillation.

(11) A. Albert, "The Acridines," 2nd ed, Edward Arnold, London, 1966, p 279.

Anal. Calcd for $C_{17}H_{11}N$: C, 89.05; H, 4.83; N, 6.11. Found: C, 89.02; H, 4.64; N, 5.87.

7-Methyl-3,9,11-trichlorobenz[c]acridine (14).—A solution of 12 (364 mg, 1.0 mmol) and potassium hydroxide (561 mg, 10 mmol) in absolute ethanol (60 ml) was refluxed for 3 hr. After about 1 hr a precipitate began to form. The mixture was cooled and the solid was filtered, washed with water, and dried, yield 300 mg, mp 208–213°. Two recrystallizations from benzene gave pale yellow needles, mp 234–237°, nmr (deuteriopyridine) δ 2.82 (s, CH_3).

Anal. Calcd for $C_{18}H_{10}Cl_3N$: C, 62.36; H, 2.91; N, 4.04; Cl, 30.69. Found: C, 62.17; H, 21.87; N, 3.93; Cl, 30.45.

The mother liquor from the first recrystallization, upon standing, deposited 20 mg of crystals, mp 215–220°. Further recrystallization from benzene gave pale yellow needles, mp 227–230°. This proved to be **8** (ir and mixture melting point).

Registry No.—**2**, 30885-38-2; **7**, 30885-39-3; **8**, 30885-40-6; **9**, 30885-41-7; **10**, 30885-42-8; **11**, 30885-43-9; **12**, 30885-44-0; **13**, 30885-45-1; **14**, 30953-15-2; **16**, 30885-46-2.

A New Method for the Controlled Hydroxymethylation of Ketones

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Received May 3, 1971

The attachment of a single hydroxymethyl substituent adjacent to a ketone or other electron-withdrawing function is most often accomplished by base-catalyzed aldol condensation of the active methylene compound and formaldehyde. Unfortunately, the process is usually difficult to control at the monoalkylation stage, resulting in complex mixtures containing polycondensation products as well as Cannizzaro-type reduction products.[1]

One well-used alternative to this process is the Mannich Reaction[2] which results in formation of the β-amino carbonyl derivative.

We now report a convenient two-step procedure capable of performing the desired transformation selectively and in high yield. The reaction sequence is illustrated by the conversion of 4-*tert*-butylcyclohexanone to 2-hydroxymethyl-4-*tert*-butylcyclohexanone.

Treatment of the ketone with sodium hydride and excess ethyl formate in dry dimethoxyethane (25°, 3–5 hr) gave the 2-hydroxymethylene derivative in 95% yield. This material was reduced, without further purification, by a method based on that suggested by Brown in his studies of aluminum hydride.[3] Generation of the sodium enolate by reaction with sodium hydride in tetrahydrofuran, followed by reaction with a tetrahydrofuran solution of aluminum hydride, furnished the desired 2-hydroxymethyl ketone in 90% yield. This material could be further purified by preparative layer chromatography on silica gel or short-path distillation.

The procedure may be varied by the substitution of dimethyl carbonate for ethyl formate, but there seems to be no particular advantage in this change. In fact, in some cases, only the more reactive formate was capable of acylating hindered ketones.

Experimental Section

Acylation with Ethyl Formate.—4-*tert*-Butylcyclohexanone (0.16 g, 1.04 mmol) in 2 ml of dry dimethoxyethane (distilled from lithium aluminum hydride) was added to a slurry of 4.1 mmol of sodium hydride (0.19 g of 55% mineral oil dispersion, washed three times with petroleum ether) in 3 ml of dry, alcohol-free ethyl formate (dried over potassium carbonate, distilled from phosphorus pentoxide) at 25° under argon. Ethanol (0.010 ml) was added, and the mixture was stirred for 5 hr and then poured into half-saturated aqueous ammonium chloride. Extraction with ether and drying of the ethereal extracts over sodium sulfate, followed by evaporation of the solvent, gave 0.18 g (95%) of the hydroxymethylene ketone: nmr (CCl_4) δ 0.92 (s, CH_3, 9 H), 1.0–2.6 (m, 7 H), 8.65 (s, olefinic, 1 H), 14.1 (m, OH, 1 H); ir $\lambda_{max}^{CCl_4}$ 2.7–4.0 (OH), 6.0–6.3 μ (keto enol ether).

Aluminum Hydride Reduction to 2-Hydroxymethyl-4-*tert*-butylcyclohexanone.—The hydroxymethylene ketone (0.17 g, 0.95 mmol) in 4 ml of tetrahydrofuran (distilled from lithium aluminum hydride) was added to a slurry of 1.07 mmol of sodium hydride (0.051 g of 55% mineral oil dispersion, washed three times with petroleum ether) in 2 ml of tetrahydrofuran. After 20 min at room temperature, 1.4 ml (1.05 mmol) of 0.75 *M* aluminum hydride in tetrahydrofuran (prepared from lithium aluminum hydride and 100% sulfuric acid by the method of Brown[3]) was added. After 1.25 hr the reaction mixture was poured into a mixture of ether and half-saturated aqueous ammonium chloride and filtered through Celite. Ether extraction of the filtrate, followed by drying (sodium sulfate) and evaporation of the solvent, gave 0.16 g (90%) of the desired hydroxymethyl ketone: nmr (CCl_4) δ 0.93 (s, CH_3, 9 H), 1.0–2.6 (m, 9 H), 3.65 (m, CH_2OH, 2 H); ir $\lambda_{max}^{CCl_4}$ 2.8 (OH), 5.85 μ (C=O). An analytical sample was prepared by bulb-to-bulb distillation at 90° (0.01 mm).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.58; H, 10.86.

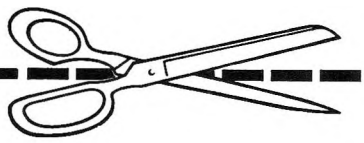
Registry No.—Ethyl formate, 109-94-4; 2-hydroxymethylene-4-*tert*-butylcyclohexanone, 22252-96-6; 2-hydroxymethyl-4-*tert*-butylcyclohexanone, 31354-38-8.

Acknowledgment.—This work was supported by the National Science Foundation.

(1) *Cf.* H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 230.

(2) F. F. Blicke, *Org. React.*, **1**, 303 (1942).

(3) N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 2927 (1968).



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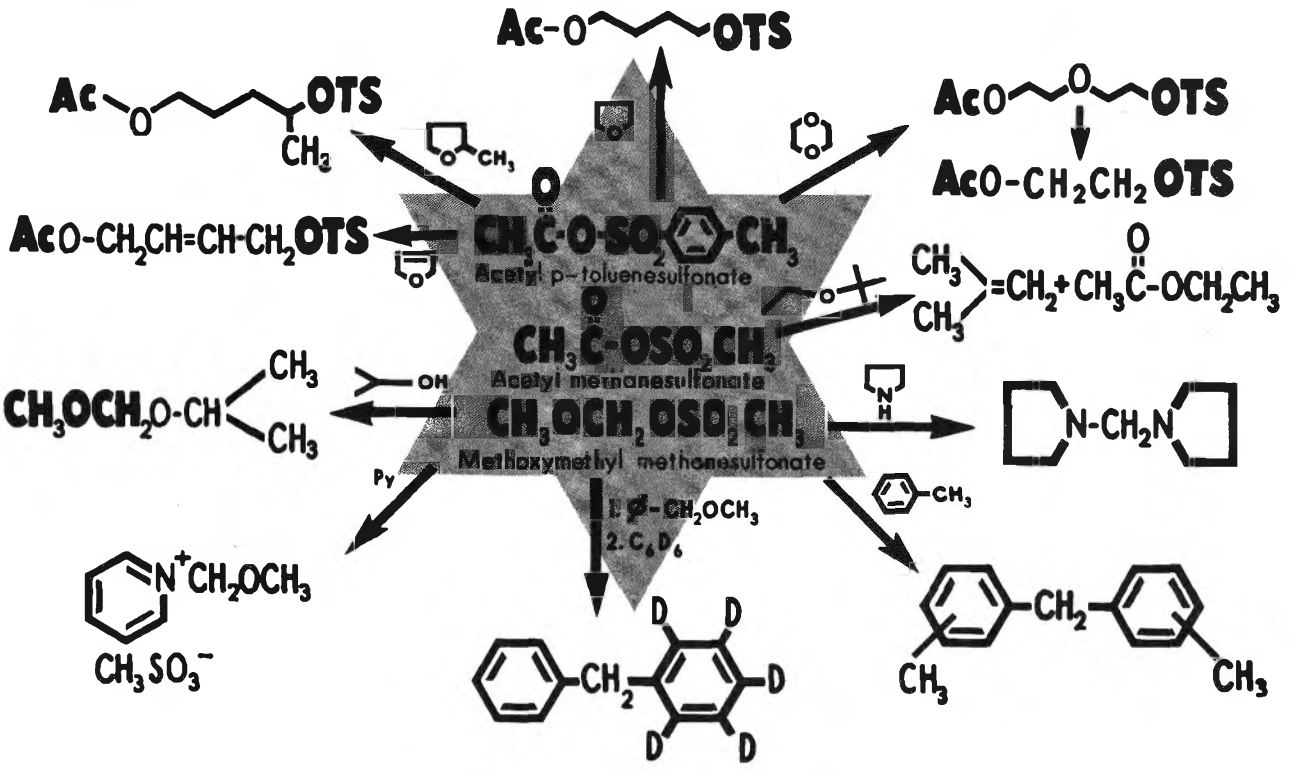
Recent publications by Karger and Mazur of the Weizmann Institute of Science have greatly extended the utility of the acetyl sulfonates and have introduced a *new* reagent, methoxymethyl methanesulfonate (MMM).



ACETYL p-TOLUENESULFONATE and ACETYL METHANESULFONATE are members of a class of mixed sulfonic-carboxylic anhydrides[1] which function as acylating agents. The aromatic carboxylic-sulfonic anhydrides were shown[2] to acylate phenols, anilines and alcohols and the acetyl sulfonates have been used[3] in the Friedel-Crafts reaction. The acetyl sulfonates are such *powerful acylating agents* that simple, mixed and cyclic *ethers are cleaved*[4] *in high yield* without Lewis acid catalysis at 25°C in most cases. THF has been cleaved[5] to butane-1,4-diol acetate with acetic anhydride-$ZnCl_2$ at 230°C over many hours but acetyl *p*-toluenesulfonate gives the diester[4] in just 3 hours at 25°C. Also *unsymmetrical ethers*[4] are cleaved with a high degree of *specificity* so that 2-methylTHF gives only a single product as a consequence of the SN1 nature of the cleavage step, further exemplified by the cleavage of *t*-butyl ethyl ether. Cleavage of 1,4-dioxane under stringent conditions[6] (acetyl chloride; $SnCl_4$; 30 hrs at 200°C) gave very poor results whereas acetyl *p*-toluenesulfonate gives 87% of the diester.[4] This diester at higher temperatures will give[4] ethylene glycol acetate tosylate as the only product, again a result of the SN1 nature of the reaction with neighboring group participation. Such mixed acetate sulfonate diesters should be useful alkylating agents.

METHOXYMETHYL METHANESULFONATE is a powerful *alkylating agent*.[7] Primary and secondary alcohols react with it within 5 min at 25°C to yield *mixed acetals*, and this reagent should find extensive use as a *protecting group* which can be removed by acid treatment. *tert*-Amines yield[7] *quaternary salts* quantitatively within 5 min at 0°C. *sec*-Amines yield[7] *aminals* which can be used in α-aminoalkylations as in the Mannich reaction.[8] Even ethers are cleaved, although in low yield (ethylene oxide at 0°C and THF after extended reflux), but this property accounts for methoxymethyl methanesulfonate's unique behavior[7] toward benzene derivatives. Alkylation first takes place to give readily the intermediate methyl benzyl ether which is further cleaved to a benzyl carbonium ion, which in turn reacts with the aromatic starting material to yield substituted diphenylmethanes.[7]

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